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Review

Epidemiological and immunological reasons for pertussis vaccination in adolescents and adults☆

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ABSTRACT

The resurgence of pertussis has been the subject of considerable debate. Hypotheses to explain increased reporting in developed countries have focused mainly on three aspects: (1) increased recognition of the disease in adolescents and adults; (2) waning of vaccine-induced immunity and (3) loss of vaccine efficacy due to an antigenic shift of *Bordetella pertussis*. Waning immunity after vaccination or natural infection combined with the absence of regular boosters either in the form of vaccine boosters or natural exposure to *B. pertussis* – due to the low circulation of the bacterium in well-immunized populations – has been suggested to explain this shift in the age distribution of pertussis. The highest incidence of the disease is currently reported among adolescents and adults who may additionally serve as the source of infection for susceptible infants. Immunological and epidemiological data indicates the need for a universal booster vaccination against pertussis for adolescents and adults.

1. Introduction

Pertussis is an infectious disease sustained by gram-negative bacteria *Bordetella pertussis* and transmitted through droplets. The bacteria produces multiple antigenic and biologically active products: pertussis toxin (PT), which favors bacterial colonization and is responsible for cell toxicity; filamentous hemagglutinin (FHA), fimbriae (agglutinogens), and pertactin (PRN) or 69-kDa* protein, which are involved in attaching to ciliated respiratory mucosa and in adenylate cyclase-inhibiting phagocytosis; endotoxin which induces fever; and tracheal cytotoxin, which causes paralysis of cilia (Cherry, 1996; Wood and McIntyre, 2008). The incubation period for pertussis is 7–10 days. Humans are the only sources of the bacteria. Pertussis is highly contagious: a 90% transmission rate is observed among susceptible household contacts and 50–80% transmission rates in school environments (de Greeff et al., 2012). The basic reproductive number (Ro), which represents the number of secondary cases caused by each primary case in a population of fully-susceptible subjects, is estimated to be high (approximately 10–14) (de Greeff et al., 2012). The course of typical pertussis comprises three phases: a catarrhal phase lasting 1–2 weeks characterized by the presence of coryza, lacrimation, low grade fever, and mild cough; a paroxysmal phase lasting 4–6 weeks with symptoms like: paroxysmal cough (>10 coughs in 1 single expiration, 'whoop' upon inspiration), post-tussive vomiting, cyanosis, neck vein distension, bulging eye, tongue protrusion; a convalescent phase (lasting 1–3 months) characterized by a gradual disappearance of coughing. Clinical manifestations vary with age and vaccination status. In neonatals and early infancy, pertussis has a severe prognosis with the incidence of hospitalizations, complications and deaths being particularly high. In unvaccinated infants and young children, pertussis has a typical course; while in neonates the only symptoms of pertussis may be cyanosis, apnea, and respiratory insufficiency. In immunized children, adolescents and adults, pertussis usually has a mild and unspecific course, but complications may occur. Complications of pertussis may be classified into several categories: respiratory (pneumonia, otitis media), neurological, nutritional, and others (Castagnini and Munoz, 2010).

2. Current epidemiology of pertussis

Pertussis is a global endemic–epidemic infectious disease. In the pre-antibiotic and pre-vaccine era, the disease mainly affected

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children under 5 and the incidence and mortality were high (Marconi et al., 2012). In Poland before 1960, when a mandatory and universal vaccination against pertussis, combined with a vaccination against tetanus and diphtheria, was introduced, the incidence rate was 350/100,000 inhabitants and about 1400 deaths were reported annually (mainly among infants), while in 2010 the incidence rate was 3.3/100.000 inhabitants and no deaths have been reported since 2004 (Gzyl et al., 2004; NIPH-NIH, 2010).

According to EUVAC Net data, in 2010, there were 15,749 cases of pertussis reported in 28 European countries and the incidence rate for this region was 3.7/100.000 inhabitants; the highest incidence rates were observed in Norway, Estonia, and Slovakia. In Europe, the incidence was highest among infants (15/100,000) and children aged 10–14 (13/100,000) (ECDC, 2010). In Slovakia, an increase of 200% in the crude incidence was observed. In 2010, in Lithuania a 10-fold decrease in the incidence was noted as compared with 2009. Three cases of deaths due to perstussis were reported in European countries in 2010: one in Austria, one in Denmark and one in United Kingdom (ECDC, 2010).

The epidemiology of pertussis is changing in developed countries with a high coverage rate among infants and school children. The incidence of the disease is currently increasing in adolescents or adults who have lost their immune protection after vaccination and in infants, mainly those under 6 months, who have not begun or completed their primary immunisation schedule (Celentano et al., 2005). The health burden of pertussis in adults and adolescents is deemed to be underestimated. The proportion of cases reported by the CDC among patients aged >10 years increased from 15.1% in the late 1970s to 26.9% in the early 1990s and to 49% in the early 2000s (CDC, 2005).

The results from several studies indicated that between 12% and 32% of adults and adolescents with a coughing illness for at least 1 week are infected with *B. pertussis* (Crawfort and Pebody, 2006). Sero-epidemic studies have been performed in many countries, and widespread pertussis infection, primarily unrecognised, among adolescents and adults has been confirmed (Wood and McIntyre, 2008). An interesting finding is a description of unrecognized pertussis infection among healthcare workers: the yearly infection rate, as determined by rises in anti-PT antibodies, varies between 4% and 16% (Deville et al., 1995).

In a serologic surveillance study of 100 individuals aged 65 or over in a 3-year period, 10% had serologic proofs of infection; between one third and half of them were asymptomatic. This pool of frequently undiagnosed pertussis cases in adolescents and adults provides a source of potentially serious infections in young infants (Hodder et al., 2000).

3. Resurgence of pertussis

The resurgence of pertussis has been the subject of considerable debate. The hypotheses to explain increased reporting in developed countries have focused mainly on three aspects: (1) increased recognition of the disease in adolescents and adults; (2) waning of vaccine-induced immunity and (3) loss of vaccine efficacy due to an antigenic shift of *B. pertussis* (Mooi et al., 2001).

The spreading of the disease can only be halted by achieving significant immunization coverage in the general population (>92%). Immunization against pertussis was included in the WHO's Expanded Program on Immunization in 1974. The estimated rate of infants immunized with 3 doses of the vaccine against pertussis was about 82% in 2008, while 16 million cases were reported all over the world (90% of them in developing countries) with 195,000 deaths occurring. It is worth pointing out that in the same year, immunization helped avoid around 680,000 deaths) (WHO, 2010).

4. Explanations for the disease shifting to older age groups

In the pre-vaccination era, the majority of pertussis cases occurred in children who also represented the major source of transmission. In adults, their immunity was regularly boosted by recurrent exposure in the population. Protection was then passed from mothers to their infants through the placental transfer of specific antibodies. As maternal antibodies waned, infants became vulnerable to infection. This pattern is still observed in developing countries, where not all children are adequately immunized during infancy (Hewlett and Edwards, 2005).

After the universal use of the pertussis vaccine has been established, the newly immunized pediatric group is protected. As a result of widespread vaccine use, the circulation of *B. pertussis* within the community is reduced and adolescents and adults are less regularly boosted by natural infection. Therefore, an increasing proportion of cases occur in adolescents and adults, who have lost their vaccine-induced immunity, and in infants, who receive fewer passive antibodies than infants did in the pre-vaccination era and who are too young to be immunized (Hewlett and Edwards, 2005).

The waning immunity after vaccination or natural infection combined with the absence of regular 'boosters' either in the form of vaccine boosters or natural exposure to *B. pertussis* – due to the low circulation of the bacterium in well-immunized populations – has been suggested to explain this shift in the age distribution of pertussis (Celentano et al., 2005).

The increasing awareness of the occurrence of adult pertussis among physicians, as well as the improvement in diagnostic methods, may also account for this change in the disease's epidemiology. Finally, we should consider the potential contribution of genetic changes in circulating strains of *B. pertussis*, which have occurred over time in three *B. pertussis* antigens – pertussis toxin, pertactin, fimbriae (Wood and McIntyre, 2008). Several studies have suggested that genetic changes (strain polymorphis) have led to vaccine failures, but this problem is still questionable (Raya et al., 2012).

5. Waning of vaccination-acquired immunity

There are various vaccinations against pertussis: (a) a combined vaccine against diphtheria, tetanus and pertussis containing an inactivated whole cell pertussis component and three bacteria serotypes (DTwP), (b) combined diphtheria, tetanus and pertussis vaccines containing a high dose of the acellular pertussis component and including up to five antigens: PT, PHA, PRN, and two different fimbrial proteins (DTaP, used in infants and pre-school children) and (c) combined vaccines against diphtheria, tetanus and pertussis, containing a low dose of the acellular pertussis component (Tdap, used in adolescents and adults). Additionally, DTaP vaccines may be combined with vaccines against *Haemophilus influenzae*, poliomyelitis or hepatitis B (Wood and McIntyre, 2008).

Many developed countries had already switched from DTwP to DTaP for infant and childhood vaccinations, because DTaP vaccines are considered less reactogenic and safer than DTwP vaccines (Wood and McIntyre, 2008; Higgs et al., 2012). The mechanism of immunity to pertussis after natural infection or immunization is complex and not fully understood. Antibodies to different pertussis antigens – PT, PRN, FHA, fimbrial proteins, and whole microorganisms appear following natural infection. Immunity has been shown to wane 7–20 years after natural infection (Aguas et al., 2006; Wearing and Rohani, 2009).

Increases in anti-PT IgG and anti-FHA IgG are measurable in over 90% of infections, anti-PRN IgG in 30–60%, anti-PRN IgA in 20–24%, anti-PT Ig in 20–40% and anti-FHA IgA in 30–50% of infected people. However, the antibody cut-off that defines a diagnosis of pertussis is debatable and somewhat test-dependent (Muller et al., 1997).