Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

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To cite this article: Giovanni Gabutti, Chiara Azzari, Paolo Bonanni, Rosa Prato, Alberto E Tozzi, Alessandro Zanetti & Gianvincenzo Zuccotti (2015) Pertussis, Human Vaccines & Immunotherapeutics, 11:1, 108-117, DOI: 10.4161/hv.34364

To link to this article: https://doi.org/10.4161/hv.34364

Published online: 01 Nov 2014.

RESEARCH PAPER

Human Vaccines & Immunotherapeutics 11:1, 108–117; January 2015; © 2015 Landes Bioscience

Pertussis

Current perspectives on epidemiology and prevention

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Keywords: pertussis, epidemiology, prevention, vaccination, immunization strategies

Abbreviations: FHA, filamentous haemagglutinin; FIM, fimbiae; PRN, pertactin; PT, pertussis toxin; AC, adenylate cyclase; TCT, tracheal cytotoxin; CMI, cell-mediated immunity; WHO, World Health Organization; EPI, Expanded program on immunization; DTP, diphtheria-tetanus-pertussis vaccine; USA, United States of America; dTap, diphtheria-tetanus-acellular pertussis low-antigen vaccine; VC%, vaccine coverage rate; HHE, hypotonia-hyporesponsiveness; PAMPs, pathogen-associated molecular patterns; IL, interleukin; Th, T helper; KPNC, Kaiser Permanente Northern California; PCR, polymerase chain reaction; DTaP, diptheria-tetanus-acellular pertussis vaccine; ACIP, Advisory Committee on Immunization Practices

Pertussis continues to be an important public-health issue. The high immunization coverage rates achieved, mainly in industrialized countries, have certainly decreased the spread of the pathogen. However, as immunity wanes, adolescents and adults play an important role in the dynamics of the infection. The surveillance system has several limitations and the underestimation of pertussis in adolescents, young adults and adults is mainly related to the atypical clinical characteristics of cases and the lack of lab confirmation. The real epidemiological impact of pertussis is not always perceived. The unavailability of comprehensive data should not hamper the adoption of active prophylactic measures designed to avoid the impact of waning immunity against pertussis. Different immunization strategies have been suggested and/or already adopted such as immunization of newborns, pre-school and school children, adolescents, adults, healthcare workers, childcare workers, pregnant women, cocoon strategy. Prevention of pertussis requires an integrated approach and the adoption of different immunization strategies, with the objective of achieving and maintaining high coverage rates.

Introduction

Pertussis is an airborne respiratory infection, caused by *Bordetella pertussis*, a Gram-negative, strictly aerobic, capsulate, non-motile, non-spore-forming bacillus. The bacterium attaches to the cilia of the respiratory tract epithelium through adhesins and exerts its pathogenic action by producing toxins.[1] Pertussis is highly contagious,[2,3] and susceptible people who come in close contact with infected subjects have a high likelihood of acquiring the infection.

The disease affects subjects of all age groups, but mainly affects children. Today it still is one of the main causes of death in children aged less than 1 year.[4]

After an incubation period of approximately 7–10 days, the typical clinical course of pertussis is divided into three stages of about 2 weeks each: the catarrhal (the most contagious period), paroxysmal and convalescent phases. If untreated, an infected person can spread pertussis for up to 3 weeks or more after cough onset. The clinical features are related to the age of acquisition of the infection, to immunity level and to antibiotic therapy.[5] The severity of the disease is inversely related to the age of the patient. In unvaccinated children pertussis has a typical course; symptoms may be severe and result in complications. The prognosis can be particularly severe in the first and second year of life, when incidence, as well as hospitalizations and death rates are particularly high (case fatality rate: 0.2% and 4% in developed and developing countries, respectively).[4] Serious complications (neurological, respiratory and nutritional), albeit relatively rare, can be fatal. Encephalitis, which is relatively rare, is particularly alarming since it is associated with death or permanent sequelae. Pulmonary complications are in absolute terms the most frequent (approximately 10% of cases) and are associated with most of the deaths. Nutritional deficiencies due to vomiting are an important issue, especially in developing countries. Minor complications (abdominal hernias, prolapses, otitis, sinusitis, conjunctival

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Submitted: 06/11/2014; Accepted: 06/17/2014; Published Online: 08/12/2014
http://dx.doi.org/10.4161/hv.34364

hemorrhage) are more frequent in absolute terms, but clinically less serious.[6]

In immunized children, adolescents and adults, the disease may have a mild and non-specific course; for this reason, in these subjects, pertussis is usually not diagnosed and may be a major source of infection for children, particularly for infants during their first year of life, when they have not started or completed the primary vaccination cycle.[7] From a practical point of view, the spreading of infection can be stopped only by achieving high immunization coverage in the population (>92%).[8]

Immunological Overview

B. pertussis has a complex antigen structure. The agent attaches to the cilia of respiratory epithelium through adhesins (filamentous hemagglutinin [FHA], fimbriae [FIM 1, 2 e 3], pertactin [PRN],) and exerts its pathogenic effects by producing toxins (pertussis toxin [PT], adenylate cyclase [AC], dermonecrotic toxin, tracheal cytotoxin [TCT]). Adhesins and toxins (TCT excluded) are highly immunogenic.[9] Immunity against pertussis, both natural or acquired by vaccination, is not lifelong and immunity protection tends to wane over a period ranging from 4 to 10 years. This is confirmed by the occurrence of outbreaks especially in adolescents and adults, even in geographical areas where vaccine coverage is high.[10] Although antibodies produced against *B. pertussis* antigens are thought to play a crucial role in protecting against the disease (since they neutralize bacterial toxins that inhibit the destruction of bacteria by macrophages and neutrophils), the antibody levels against a single antigen or a combination of antigens that can certainly be associated with clinical protection are not currently known.[11] Moreover, it is well known that cell-mediated immunity (CMI) plays a crucial role in protecting against *B. pertussis* infection by contributing to microorganism clearance.[12] Over the last few years, spreading of *B. pertussis* strains with particular antigenic features has been reported and this seems to be suggestive of an evolution of the pathogen related to the immunologic pressure of vaccination. This may be the reason for epidemic outbreaks in settings with high vaccine coverage.[13-16]

Epidemiology

Pertussis is a worldwide endemic/epidemic infectious disease, with outbreaks usually every 3–5 years and a Summer-Autumn seasonality. In the pre-antibiotic and pre-immunization era, both incidence and case fatality rates were very high and the disease mainly affected children aged less than 5 years. The adoption of both antibiotic therapy and immunization has had an extremely positive impact with a clear reduction in the number of cases as well as in mortality. Immunization against pertussis (combination vaccines against also tetanus and diphtheria) has been included in World Health Organization (WHO)'s Expanded Program on Immunization (EPI) in 1974 and, according to data provided for 2008, the estimated worldwide rate of newborns immunized with three doses of anti-pertussis vaccine was about 82%. Nevertheless, WHO estimates that during 2008 approximately 16 million cases of pertussis occurred worldwide, 95% of which in developing countries, causing approximately 195 000 deaths in children. In the same year, the vaccination program against pertussis prevented approximately 680 000 deaths.[4] The latest worldwide estimates report 200 868 notified cases, 89 000 deaths (in 2008) and an estimated vaccine coverage with 3 doses of diphtheria-tetanus-pertussis vaccine (DTP) of 83%.[17] In the last few years in the developed countries, an increasing number of cases among adolescents and adults have occurred.[18] This proves that the epidemiology of this infectious disease is changing as a consequence of the immunologic pressure of vaccination. In the United States of America (USA) after the introduction of immunization in the 1940s, the incidence has progressively declined; however, since the 1980s notifications have started to increase again and in 2010 over 27 000 cases were reported. Data referring to 2012 report 48 277 cases and 20 pertussis-related deaths.[19] Similarly to reports for the period 1990–2013, final data for 2012 show that children aged less than 1 year were the group with the highest incidence rate (126.7/100 000) and that the role played by children aged 7–10 years was significant (58.5/100 000).[20] One of the last epidemic outbreaks in the USA occurred in the State of Washington where in the period from January 1 to June 16 2012, 2520 cases were notified (37.5 per 100 000 inhabitants) with an increase in incidence of 1,300% as compared to data from the same period in 2011. During this outbreak, a high incidence rate was reported in adolescents (13–14 years), notwithstanding a high vaccine coverage rate and the recent adoption of a booster with low-antigen dose vaccines (dTap), suggesting the need for implementing and maximizing vaccine interventions.[21] As highlighted also during previous epidemic outbreaks (Delaware 2004–2005, Illinois 2006–2007, California 2010),[22-24] 2012 data show that most of the burden is on infants. Of the 20 deaths, 16 involved subjects aged less than 1 year (15 aged <3 months and 1 aged between 3 and 11 months). In Europe, in the 2003-2007 period 43,482 cases were notified (incidence of 4.1/100 000; 35.5/100 000 in subjects aged less than 1 year), 2777 hospitalizations (82/1000 cases of pertussis) and 30 deaths (0.8/1000 cases of pertussis); 87% of deaths involved infants.[25] In 2010, in Europe 15 749 cases of pertussis (3.7/100 000 inhabitants) were reported overall, with particularly high incidence rates in Norway and Estonia. Case stratification by age groups shows that 5%, 7%, 9%, 21%, 17%, 5%, 4%, and 33% of reports involved <1 year, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, and >30 years age groups, respectively. The highest incidence rates were observed in infants (15/100 000) and in the group including children aged 10–14 years (13/100 000). Eighteen percent of cases were notified in unimmunized subjects, 2% in subjects who received 1 dose only and 61% in subjects who received at least 2 doses (18% immunized with an undefined number of doses). Among unimmunized subjects, 25% were infants and 51% adults aged >20 years. The overall hospitalization rate was 87/1000 cases of pertussis; 35% of hospitalizations involved infants and 18% children aged 10–14 years. In 2010, 3 deaths were notified (Denmark, UK, and Austria); two cases involved

unimmunized infants aged 4 and 6 weeks and one involved an adult aged >30 years.[26] Overall, these data clearly show that the burden of pertussis in terms of incidence and hospitalization rate mainly involves infants and confirms that *B. pertussis* spreads in the European population involving also age groups that were not considered to be a target before. This has already been highlighted by the Network ESEN (European Sero-epidemiology Network),[27,28] and, more recently, in a study carried out in 5 European countries (Finland, Germany, Italy, The Netherlands, and UK).[3] In Italy, it is also possible to distinguish, from an epidemiological point of view, a pre- and a post-vaccination period.[29] According to the ICONA 2008 coverage study, that year vaccine coverage rate (VC%) reached 96.6% in children aged 12–24 months and 45.6%, 26.7% and 14.1% in adolescents with 3, 4, and 5 doses, respectively.[30] The impact of the increasing vaccine coverage is very clear when different periods with a low (1971–1989), intermediate (1990–1996) and high (1998–2002) VC% are compared. The achievement of high VC% led to a considerable reduction in the incidence of pertussis in children aged less than 10 years. The comparison of the period 1971–1989 (low VC%) with the period 1998–2002 (high VC%) shows that the percent distribution of cases has changed remarkably, declining by half in the 0–4 year age group, while increasing by 1.5-fold in the 5–9 year age group and three-fold in the 10–14 year age group.[29] Therefore, pertussis epidemiology is changing in Italy, too, with a lower incidence in children and an increased incidence in adolescents and adults.[31,32] Both national and international notification data show that pertussis continues to be an important public-health issue. From an epidemiological point of view, a major role is played by adolescents and adults, who are a significant source of infection for unvaccinated or incompletely immunized newborns/infants in whom the severity of the disease can be serious.[33-36] Notification-based surveillance of pertussis is affected by a number of limitations that are inherent in passive surveillance systems, including under or delayed reporting and under-diagnosis. Cases involving adolescents and adults are certainly underestimated as are mild/asymptomatic cases in immunized subjects.[37] In the light of available data, an innovative approach to pertussis epidemiological surveillance should be adopted, including a comprehensive systematic evaluation of surveillance, laboratory and vaccine coverage data, as well as the use of contact matrices, the conduction of specific studies on adolescents and adults/elderly, increased use of molecular tests, the consequent evaluation of molecular epidemiology and the use of mathematical modelling.[33,38]

Prevention: Currently Available Vaccines

The most recent data seem to show a significant increase in the epidemiological impact of pertussis; it is confirmed that this infectious disease is widespread and is relevant in terms of morbidity, complications, sequelae, hospitalizations and mortality.[39]

WHO suggests that the primary objectives of immunization are the reduction in the risk of severe disease in infants and the minimum level of vaccine coverage required (90%) to be achieved with 3 doses in newborns.[4] More recently, in addition to the objective of preventing the disease in infants as well as the related severe forms, authorities have focused on infection control. WHO points out that the wide immunization campaign carried out in the 1950–60s enabled the achievement of a reduction in incidence and mortality in industrialized countries. Also the most recent data support the importance of immunization which historically has been achieved by using two vaccines: cellular (old generation) and acellular (new generation) vaccines.[4]

Both types have been mainly used as components of combination products and the basic vaccine schedule consisted of 3 doses. WHO reports that the best old and new generation vaccines have similar excellent efficacy/effectiveness profiles against severe pertussis. However, it is clear that the results obtained in different studies and/or clinical trials are inconsistent and this makes comparison among the products available on the market very difficult.

After a development phase carried out in the early 19th century, a vaccine consisting of inactivated whole bacteria was marketed in the USA in 1914. After World War II (1948), the vaccine was marketed in combination with tetanus and diphtheria anatoxins, and was absorbed on aluminum salts. Basic manufacturing procedures are similar, however vaccines elicit very diverse antibody responses against different *B. pertussis* antigens.[40]

The clinical efficacy of the different whole-cell vaccines was evaluated in a number of experimental studies leading to extremely variable results (36–96%) and this wide variability, associated with high reactogenicity, was the main limitation to the use of this type of vaccine.[41-43] Cellular vaccines were evaluated in controlled clinical trials that demonstrated their impact in terms of reduction of incidence and mortality rates whenever they were used on a large scale. Moreover, the effects of stopping immunization programs in some settings have also been reported, as well as the lower rates of cough in immunized children in comparison to partially immunized/unimmunized subjects during epidemic outbreaks.[44] The duration of protection resulting from the use of these products is directly related to the type of vaccine injected, to the number of doses administered, to the vaccine schedule adopted and to possible natural boosters. The evaluation of immunization efficacy is also very dependent on case definition during the evaluation of results.

Since the manufacturing cycle of whole-cell vaccine does not allow the elimination of the bacterial components responsible for adverse reactions (e.g., endotoxin), the use of whole-cell vaccine can be associated with relatively frequent adverse reactions (26–40% of the doses) including fever, irritability, reactions at the injection site, or rare reactions including hypotonia-hyporesponsiveness (HHE; 1 case every 1500–2000 doses).[4,45]

In the 1970s, a possible relationship between whole-cell vaccine and permanent neurological damage was reported, especially in the United Kingdom, and this considerably reduced compliance to this vaccine and encouraged research on less reactogenic products. Later studies concluded that there is no evidence of brain damage or neurological complications resulting from the use of whole-cell vaccine.[46] On the other hand, it has been confirmed that the percentage of local reactions tends to

increase with increasing age and number of administered doses; for these reasons, cellular vaccines are not recommended in adolescents and adults.[4] Today a greater amount of data on the mechanisms of immune responses induced by these vaccines is available. Whole-cell vaccines contain particular molecules, such as lipopolysaccharides which act as pathogen-associated molecular patterns (PAMPs) that activate the production of a number of interleukins (IL-1, IL-6, IL-12, IL-23) by dendritic cells and macrophages. These pro-inflammatory cytokines promote the induction of (T helper) Th1 and Th17 cells from naive T cells. Whole-cell vaccines induce an immune response similar to what happens following natural *B. pertussis* infection.[11]

In the 1980s, researchers succeeded to design and develop new pertussis vaccines with the same efficacy of whole-cell vaccines, but significantly lower reactogenicity. The crucial step in the development of new generation acellular vaccines was the identification of cellular components that are important for the induction of protective response: pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM).[7,11] The first new generation vaccines were manufactured and used in Japan in the early 1980s; during the manufacturing phase, approximately 90% of endotoxin was eliminated and pertussis toxin was used in its formaldehyde-detoxified form. Later on, detoxification of pertussis toxin was also obtained by gene engineering techniques and a number of vaccines were put on the market worldwide, which differed in terms of number and quantity of antigens, type and quantity of adjuvants and type of excipients as well as the method of purification and detoxification used.[47] Antibody responses to FHA and PRN seem to be proportional to the antigen amount, while response to PT seems to depend also on the inactivation method (the response is higher to genetically detoxified PT).

With regard to infections caused by *B. pertussis*, antibody levels against a single antigen or a combination of antigens that can be related with certainty to clinical protection are not currently known. Clinical studies have not provided certain and definitive evidence on the protective role of antibodies against PT, FHA, PRN, or FIM and on the existence of a serologic correlate of protection against pertussis. Conversely, other studies seem to suggest that antibodies against PT, PRN and FIMs remain high in adults and are related to long-term immunity following the administration of both whole-cell and acellular vaccines. Therefore, a high level of antibodies against these antigens would be associated to a lower likelihood of acquiring pertussis. The strongest relationship observed was with PRN, while the weakest was with PT. Clinical trials with acellular vaccines against pertussis, consisting of three or five components, have shown that subjects with high levels of antibodies against PT, PRN, and FIM are less likely to develop overt disease when they are exposed to pertussis.[9,48-50] No clear relationship is deemed to exist between the levels of antibodies against FHA and protection from the disease; however, the inclusion of FHA in the composition of vaccines was associated with a reduction in the disease rate when it was administered together with PRN or PRN/FIM. For example, the first Swedish efficacy study on the acellular vaccine against pertussis showed that PT/FHA was better than vaccines containing PT alone.[51]

Taken together, these observations show that in order to evaluate a vaccine it is necessary to resort to clinical efficacy data. Studies aimed at evaluating antibody kinetics, which show a relatively rapid decline of the antibody level, are not reliable, since it is not possible to establish with certainty a cut-off value below which the subject is susceptible to the infection.

CMI also plays a crucial role in protecting against *B. pertussis* infection. Some authors have demonstrated that proliferation of peripheral blood mononucleated cells in response to *B. pertussis* antigens (PT, FHA, and PRN) is inversely related to clinical manifestation of the disease.[52-54]

New generation vaccines do not contain any PAMPs. They contain adjuvant aluminum salts that stimulate the production of IL-1 and Th17 cells. The latter have the function of recruiting and activating neutrophils which capture and kill *B. pertussis*. Acellular vaccines induce a predominantly Th2 response.[11] With regard to reactogenicity and safety, acellular vaccines are less reactogenic than cellular vaccines. During clinical trials, the frequency of adverse events following the primary cycle with acellular vaccines was the same as the frequency observed in the control group.[4,55]

After the primary cycle (3 doses), local reactions due to additional doses tend to increase both in frequency and severity. In particular, cases of transient, sometimes extensive, non-painful swelling, were reported after administration of booster doses of acellular vaccines; these cases resolved spontaneously without any sequelae.[4]

Based on the considerations above, acellular vaccines with low antigen content included in combination products have been developed and marketed with the purpose of having a formulation with excellent profile in terms of immunogenicity, tolerability and safety that can also be used in adolescents and adults.[45,56]

WHO points out that the adoption of a vaccination primary cycle with whole-cell or acellular vaccines can lead to protection against severe forms of pertussis in newborns and infants. According to WHO, although local and systemic reactogenicity is more commonly associated with the products containing whole-cell vaccines, both vaccines (cellular and acellular) have an excellent safety profile in terms of serious adverse events. Acellular vaccines are significantly more costly than whole-cell vaccines and this may restrict their use in a number of countries. Wherever the higher incidence of non-serious adverse events induced by the use of old generation vaccines (cellular) may hinder the achievement of high coverage rates, acellular vaccines can and should be included in the national pediatric immunization programs, for the primary cycle as well as for the booster dose.

The evaluation of effectiveness was carried out in several settings. Historically, the first study of this type was performed in Sweden;[57-59] studies followed in Denmark,[60,61] USA,[62,63] Austria,[64] and the Netherlands.[65] Overall effectiveness was high and exceeded 92–95% in subjects treated with three doses of acellular vaccine; however, while a decline in the incidence in the target age groups of vaccine intervention was observed in the various settings, the overall average incidence increased in unimmunized children aged 0–2 months, in children aged over 9 years, in adolescents and adults.

The effectiveness of immunization with low-antigen products (dTap) in adolescents and adults was evaluated in a case-control study carried out at Kaiser Permanente Northern California (KPNC). Effectiveness was 53% and 64% when the two control groups (negative [polymerase chain reaction] PCR and KPNC) were considered, thus suggesting moderate effectiveness of dTap immunization in preventing cases of PCR-confirmed pertussis in adolescents and adults.[66]

KPNC was also used to verify whether there are any differences in the risk of pertussis in subjects aged 10–17 years who receive whole-cell or acellular vaccines. After the epidemic outbreak that occurred in California in 2010–2011, young people (10–17-y-old) immunized with cellular vaccine resulted to have greater protection than those who received acellular vaccine.[67]

In conclusion, the availability of old and new generation vaccines, having adequate levels of efficacy, effectiveness, safety and tolerability, was crucial in planning extensive primary prevention interventions. As demonstrated by interventions adopted in industrialized countries, the high rates of vaccine coverage achieved have certainly reduced the spreading of the etiologic agent. However, the lack of long-term persistence of immunity protection implies that a major role is played by adolescents and adults, who are a significant source of infection for unimmunized or incompletely immunized infants.[68] However, it is important to bear in mind that the use of marketed vaccines worldwide has resulted in the achievement and maintenance of high rates of vaccine coverage which, regardless of the type of vaccine used and the number of its components, is the key factor for a successful vaccine intervention against pertussis.

Strategies for the Prevention of Pertussis

The introduction of acellular pertussis vaccines characterized an era during which there was a progressive increase in vaccine coverage in most of the Western countries as well as a strong containment of the incidence of the disease. However, as reported above, since the early 2000s, the incidence of pertussis has started to return back to previous levels in several geographical areas where vaccine coverage has been high for a long time (e.g., USA, Australia, UK).[69]

This return of the disease is to be related to reduced ability of currently used pertussis vaccines to induce long-term protection, especially in areas where natural exposure levels have been low for several years.[70-72] Thus, there is the need for identifying an immunization strategy designed to prevent the spreading of the infection in all age groups and, above all, that enables the prevention of the disease in infants, who suffer from the most serious complications of the disease, including death.

Based on the results of a number of available studies, it seems that an effective strategy for pertussis control should rest on the combination of several approaches.[73]

One the first issues to focus on is the spreading dynamics of pertussis and the need to protect newborns.

Most of the scientific studies published focus on the source of infection. They demonstrate that parents, family members and cohabitants frequently are the source of infection in infants,[74] and suggest that oligo- and asymptomatic patients play an important role in spreading the infection.[75,76] The role of adults in spreading the infection is reinforced by the difficulty in identifying symptoms in this age group; the diagnosis of pertussis is rarely considered in adult patients.[77] Moreover, it should be borne in mind that, besides the mode of transmission, infection dynamics also depends on the number of contacts among individuals in a given population and this parameter is population specific.[78]

In the current situation and with the existing tools for infection control, it is not possible to take pertussis eradication into consideration. Therefore, strategies implemented in the various countries aim specifically at reducing its incidence and containing the circulating pathogen, as well as, above all, protecting infants who are not old enough to benefit from the protective effect of immunization and who would suffer from the most serious complications in case of infection.

According to WHO immunization should be started at 6 weeks of age and the three-dose schedule should be completed within 6 months. In relation to the local situation and schedule, a booster dose is recommended at 1–6 years of age.[79] The solutions adopted by the various countries for the implementation of the primary vaccination cycle often depend on tradition and local decisions made for immunization against other diseases. In any case, at least 3 vaccine doses are to be administered during the first 12 months. The schedule can vary, ranging from 3 doses at 2, 3, and 4 months to 3 doses at 3, 5, and 12 months.[80] It is evident that early immunization is associated with a more rapid completion of the primary cycle, after which excellent protection against pertussis is obtained.[81] It has been estimated that the protection efficacy afforded by a single dose of vaccine against pertussis is about 60%.[82] Based on this observation, it is important to start immunization against pertussis early and that the immunization cycle starts at 6–8 weeks of age.[4,83] A similar approach seems to be associated with a reduction in the number of hospitalizations and deaths due to pertussis.[84,85]

Most of the countries that include vaccination against pertussis in their schedule, plan a booster dose at pre-school or school age (between 3 and 7 years of age). The administration period is usually decided according to available epidemiological data. In the Netherlands, in 2001 a booster dose at the age of 4 years led to a significant reduction in the incidence among pre-school children.[86] In Sweden, following the conduction of clinical trials on acellular vaccines in the 1990s, local epidemiology suggested the need to introduce a booster dose in pre-school children.[87] Pertussis surveillance under the European project EUVAC-NET, between 1998 and 2002, disclosed high incidence of pertussis in the age group from 5 to 14 years in a number of countries that had not included a booster dose in pre-school children in their vaccination schedule.[88] An epidemiological study carried out in Germany before re-unification showed similar results; the lack of booster dose at school age was clearly associated with a high incidence in the >5-y-age-group.[89] In the light of these data, it is clear that a booster dose at pre-school or school age should be included in pertussis vaccination schedules and that efforts should be made to achieve vaccine coverage in this age group.[90]

The pre-school booster dose consolidates herd immunity, prolongs protection and prevents pertussis transmission to infants by siblings in this age group. A further integration in the immunization approach against pertussis is the introduction of a booster dose in adolescents who represent the age group in which the issue of waning immunity starts to appear. Since adolescence is a significant source of infection in the epidemiology of this disease,[91] immunization in this age group has an indirect impact on the protection of infants. The introduction of a booster dose in adolescents has been suggested to be one of the strategies with the greatest impact on pertussis infection control for a long time. However, there are a number of barriers to the implementation of adolescent immunization, including the difficulty to achieve a high coverage rate and the need to implement specific strategies, possibly based on administration at school.[92] Even in these conditions, it does not seem feasible to achieve high vaccine coverage rates,[92] and it is necessary to take advantage of any possible opportunity to increase compliance to vaccine booster dose (missed opportunities strategy).[93] Only a few European countries (Italy, Germany, Czech Republic, Austria, France, Greece, Liechtenstein, United Kingdom) have introduced adult immunization with a specific recommendation.[94] In this age group, disease diagnosis is difficult due to non-specific symptoms and probably also to the fact that the healthcare staff perceives this disease as rare in older subjects;[77] however, the proportion of pertussis cases in adults is high.[95,96] Offering adult immunization is not an easy strategy to implement nor is the rapid achievement of vaccine coverage. A booster dose should be administered taking into consideration the time that has elapsed from the previous dose. In general, the most feasible solution seems to be the administration of a Tdap vaccine every time a tetanus-diphtheria vaccine is indicated in adults, including tetanus prophylaxis, as in the USA,[97] in the attempt to administer at least one booster dose in this period of life.

A worldwide debate has been ongoing for some time regarding other immunization strategies against pertussis, and, in particular, about cocoon strategy and infant immunization, during the pre-conception period or during pregnancy. Immunization of contacts, and therefore of potential sources of infection of infants has been an interesting strategy for a long time, with a number of possibilities.[74] One natural approach is the post-partum vaccination of mothers. However, the problem of this approach is that vaccination should induce protection very rapidly to achieve a protective effect on infants. Several cases of pertussis in which mothers were the source of infection are characterized by the onset of symptoms in the pregnant woman before delivery.[98] Moreover, maximal response to immunization in terms of antibody levels does not occur until 14 days after administration of a booster dose, thus leaving a potentially uncovered time window.[99] Finally, besides mothers, several other family members are also potential sources of infection.[91] In fact, post-partum immunization alone does not seem to be sufficient to reduce pertussis incidence in newborns.[100] While post-partum immunization can be logistically affordable if entrusted to the staff providing assistance to delivery, the immunization of other family members can be a problem. Even if delivery could be a good opportunity to reach all family members, this strategy should include provision of accurate information.[101] In terms of cost-benefit balance, it is clear now that reaching high levels of coverage in all family members is a difficult target to achieve and that the use of cocooning strategy should be evaluated according to the local situation.[102] However, this option requires careful consideration,[103] especially when it is not possible to immunize mothers during pregnancy. The possibility of protecting newborns directly, immediately after delivery, is the most intuitive strategy to induce protection in the first months of life. Evidence collected so far suggests that immunization in this age group enables the achievement of high antibody levels, but that after the first 6 months the protection could also decline on account of the other vaccines administered concomitantly.[104] To make this strategy even more complex, it should also be considered that today a monovalent pertussis vaccine formulation is not available. In one of the first studies published on this issue, the administration of a 3-component acellular vaccine at birth with 3 subsequent doses at 3, 5, and 11 months induced a reduction in antibody response after the first dose, but was effective in priming; however, at 12 months antibody levels against PT were low.[105] An additional study demonstrated a reduced response to *B. pertussis* antigens after diptheria-tetanus-acellular pertussis vaccine (DTaP) administration at birth and a dose at 2, 4, 6, and 17 months as compared to a schedule that did not include the administration of a dose at birth.[106] Another study showed that the administration of a monovalent vaccine at birth seemed to accelerate the production of antibodies until it overlapped at the age of 7 months with the level obtained with a schedule that did not include an administration at birth;[107] this study did not show any interference with subsequent vaccinations. The administration of a second dose of monovalent pertussis vaccine at 1 month after birth further increases immunization response and does not interfere with subsequent DTaP doses.[108] Based on published study results, although this approach is promising, infant immunization does not seem to be able to induce complete protection in the very early phases of life. Moreover, one has to take into consideration the time needed for a response after administration and that this approach is not currently possible due to the unavailability of a monovalent formulation of pertussis vaccine. Finally, it is possible that early DTaP immunization induces a polarization of Th2 immune response with a potential risk for allergic diseases.[109]

A possible alternative option designed to reduce the likelihood of infant infection in its early months of life is immunization of the mother. This approach could enable the achievement of transmission of the immunity induced by immunization through the placenta and could prevent the mothers from becoming possible sources of infection for their infants. The debate on this approach has actually been re-opened by the possibility of considering immunization during pregnancy. Since there is no protection correlate for this disease, it is difficult to verify the efficacy of this intervention based on serological criteria. Moreover, some studies also showed a rapid reduction in antibody levels in children whose mothers received a booster dose in the pre-conception period or in the initial 2–3 months of pregnancy; their antibody levels were presumably inadequate for ensuring protection

against pertussis.[110,111] Immunization during pregnancy has not been taken into serious consideration for some time since it is difficult to verify its efficacy and safety. Recently this possibility has been reconsidered, since the rationale for this strategy is well known and it plays a key role in the prevention of other neonatal diseases, including tetanus and influenza. One of the issues concerning immunization against pertussis during pregnancy is the likelihood of inducing an interference that could jeopardize the full response to the primary immunization cycle in the first year of life.[112] The most sensitive aspect of immunization during pregnancy is the scarcity of data on safety and teratogenic potential. However, a number of reports suggest that there are no potentially serious adverse events in mothers and fetuses exposed to vaccination during pregnancy.[113] During recent pertussis outbreaks in USA, Canada, Australia, and UK, where a significant rate of cases occurred in infants with a number of deaths, the hypothesis of vaccination use during pregnancy became current again and in 2012 the UK Department of Health actively started to offer immunization against pertussis during the third trimester of pregnancy,[83] and the Advisory Committee on Immunization Practices (ACIP) in the USA offered immunization to pregnant women from 27 to 36 weeks of gestation.[114] The administration of pertussis vaccine with acellular products during the last months of pregnancy determines a significant increase in the number of antibodies in infants.[115] In the light of the experience of countries that have introduced immunization for this category, immunization during the third trimester of pregnancy seems to be one of the key strategies in preventing the disease in infants. This applies until the results of clinical trials carried out in those countries where immunization during pregnancy has been introduced are available, especially those with the aim of determining any interferences with the response to the primary immunization cycle. In addition to the strategies discussed so far, it is necessary to give the immunization of healthcare staff careful consideration, as it is especially important in the light of the potential spread of pertussis to patients with co-morbidities that can involve a more serious evolution of the disease. Notwithstanding this, vaccine coverage for this immunization, as well as for others in this category, is modest.[116] Pertussis transmission in hospitals is widely documented,[117,118] and the consequences associated with outbreaks described in the medical literature are important. Immunization of healthcare staff aims at preventing outbreaks within the hospital setting as well as ensuring functioning of healthcare staff also in case of emergency.[116] It should be borne in mind that, as for other infectious diseases, the prevention of secondary cases requires timely antibiotic treatment of the index case and antibiotic prophylaxis in secondary cases. Prophylaxis in contacts is indicated regardless of immunization status, age and history of pertussis.[119]

Expert Conclusions and Recommendations

Pertussis is an infectious disease that continues to be an important public health issue. The high immunization rates achieved, especially in industrialized countries, have certainly contributed to infection control. Moreover, adolescents and adults play a crucial role in the transmission dynamics due to decline in their immune protection. The fact that adolescents and adults may be a source of infection, often unrecognized due to the non-specific features of the clinical pattern in these age groups, requires measures to prevent *Bordetella pertussis* from infecting subjects at high risk of developing potentially fatal, severe and/or complicated pertussis, i.e. especially infants in their first months of life who have not started or completed their immunization cycle. In the light of available data, effective prevention of pertussis requires the combination of several strategies that can have a significant impact on the reduction of the burden of this disease only when they are adopted together.

However, there are some aspects that deserve consideration, including:

1) identification of the best schedule to adopt in the first year of life;
2) increased use of booster in pre-schoolers;
3) compliance with adult immunization;
4) compliance with healthcare staff immunization;
5) in-depth analysis of pharmacoeconomic issues;
6) better definition of aspects concerning tolerability and safety;
7) better definition of the interventions to adopt taking into consideration the population mixing patterns.

It is also clear that successful immunization strategies against pertussis should also include high coverage rates of target groups. Since in some cases, e.g. adolescents and adults, the achievement of high coverage rates is often complex, it is useful to bear in mind that standard recommendations in order to increase immunization coverage rates, e.g. reminders, training interventions, introduction of immunization certificates to access communities and reduction of vaccination costs should always be included and reinforced.

Disclosure of Potential Conflicts of Interest

Gabutti G received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, and Pfizer for taking part in advisory boards, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.

Azzari C. during the last two years took part in boards and/or congresses organized/supported by vaccine producers (Sanofi Pasteur MSD, Novartis, Pfizer, GlaxoSmithKline Biologicals SA)

Bonanni P received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, and Pfizer for taking part in advisory boards, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as promoter of epidemiological studies partially supported by vaccine producers

Prato R received grants and travel expenses from Pfizer, Novartis, GlaxoSmithKline Biologicals SA, and Sanofi Pasteur MSD to take part to advisory boards and expert meetings, to be a speaker in conferences, and to act as principal investigator

in studies supported by unrestricted funding from vaccine manufacturers

Tozzi AE received research grants from Pfizer, Sanofi Pasteur MSD, and GlaxoSmithKline Bilogicals SA

Zanetti A received consulting and speaker honoraria from GlaxoSmithKline Biologicals SA, and Sanofi Pasteur MSD.

Zuccotti GV received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, and Pfizer for taking part in advisory boards, expert meetings, being a speaker or an organizer of congresses/conferences.

Acknowledgements

This paper reports the technical and scientific independent opinion of the group of experts involved in the Advisory Board on vaccination in the first year of age, promoted by the Sanofi Pasteur MSD Medical and Scientific Department with the purpose of issuing a summary comprehensive report of all available evidence and expert opinions on pertussis.

The Board would like to thank Marco Ercolani and Luigi Fuiano of Sanofi Pasteur MSD Medical Department for their scientific support and active cooperation.

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