HUMAN VACCINES & IMMUNOTHERAPEUTICS
2017, VOL. 13, NO. 4, 744–756
http://dx.doi.org/10.1080/21645515.2016.1259780

Taylor & Francis
Taylor & Francis Group

REVIEW

# Immune persistence after pertussis vaccination

Zhiyun Chen[a] and Qiushui He[a,b]

[a]Department of Medical Microbiology and Research Centre of Microbiome, Capital Medical University, Beijing, China; [b]Department of Medical Microbiology and Immunology, University of Turku, Turku, Finland

**ABSTRACT**

Pertussis is one of the most prevalent vaccine-preventable diseases worldwide. The true infection rate is significantly higher than the reported incidence rate. An increased prevalence of pertussis in older populations has been found, mainly caused by waning immunity after vaccination. Vaccine-induced immunity differs due to variation in vaccine content, schedule and coverage. Protection following acellular pertussis vaccines has been suggested to wane faster than whole cell pertussis vaccines. However, long-term immune persistence of whole cell pertussis vaccines may be confounded by a progressive acquisition of natural immunity. The World Health Organization has recommended that a switch from whole cell to acellular pertussis vaccines for primary immunization in infants should only be considered if additional periodic boosters or maternal immunization can be ensured and sustained in the national immunization schedules. In this review, we present data on immune persistence after different pertussis vaccinations and compare the findings from countries with different vaccination strategies. Future aspects in serological studies are briefly discussed.

**ARTICLE HISTORY**
Received 3 August 2016
Revised 20 October 2016
Accepted 8 November 2016

**KEYWORDS**
acellular pertussis vaccines; immune persistence; pertussis; vaccination; whole cell pertussis vaccines

## Introduction

Despite high vaccination coverage, a resurgence of pertussis (whooping cough) has been observed during the past few decades. Estimated by World Health Organization (WHO) in 2011, pertussis caused 50 million cases and 300 000 deaths every year.[1] Recently increased incidence of pertussis has been observed in both developed and developing countries. In Argentina, the incidence of the disease rose from 1.8/100,000 in 2003, 5.7/100,000 in 2005 to 8.3/100,000 in 2011.[2, 3] In China, a total of 3408 and 6658 pertussis cases were notified in 2014 and 2015, whereas the corresponding number of notified cases ranged from 1612 to 2517 during the period of 2008–2013.[4] In England and Wales, the total number of confirmed cases was 9741 in 2012, 10 times higher than the number of 902 reported in 2008.[5] In 2012, the number of reported cases in USA was 48,277, the highest in the past 50 y in this country.[6] Clearly pertussis has become one of the most prevalent vaccine-preventable diseases throughout the world.[4] Furthermore, based on recent seroprevalence studies estimated infection rates ranged from 1% to 12% in industrialized countries and from 5% to 50% in developing countries.[7]

Whooping cough is most dangerous in neonates who are too young to be immunized and in infants who have not completed their primary vaccinations. The incidence rate, hospitalizations and deaths are particularly high in children younger than 2 y (reported case fatality rate: 0.2% and 4% in developed and developing countries, respectively).[8,9] A shift in the epidemiologic profile of pertussis to older age groups has been found.[10-12] In developed countries, pertussis is one of the most common causes of prolonged cough illnesses in adults, ranging from 2.9% to 32%.[13] The increased prevalence of pertussis in older populations is mainly due to the waning of immunity against Bordetella pertussis (B. pertussis).[14] Today, adults and adolescents are recognized as the most notable source of transmission of infant pertussis.[15-17]

The duration of immunity against pertussis after infection or vaccination was reported to be 7–20 y and 4–12 years.[14,18] Compared to a natural infection, the duration of protection after vaccination appears to be shorter, especially after the vaccination with acellular pertussis (aP) vaccines.[19] Since the 1990s, aP vaccines have replaced whole cell (wP) vaccines in most of industrial countries. However, this change has not been able to control the circulation of B. pertussis. One of the possible reasons is that protection provided by aP vaccines is less enduring than previously thought, raising the possibility that the switch from wP vaccines to aP vaccines may have aggravated the pertussis problem. [20-22]

Estimates of vaccine-induced immunity are often difficult to make because vaccine efficacy (primary vaccine failure) and waning immunity (secondary vaccine failure) are confounded, and potentially affected by variation in vaccine strategies used in different countries.[23] In this review, we present data on immune persistence after pertussis immunizations with wP and aP vaccines, and compare the findings from countries with different vaccination strategies. In addition, future aspects in serological studies are briefly discussed. To better understand the

**CONTACT** Qiushui He qiushui.he@utu.fi Department of Medical Microbiology, Capital Medical University, No 10 Xitoutiao, Youanmenwai, Fengtai District, Beijing 100069, China.

**Table 1.** Terms used in this study.

| Term | Definition | Reference |
|---|---|---|
| Cell-mediated immune response | Host defenses that are mediated by antigen-specific T cells. | 130 |
| Correlate of protection | An immune marker statistically correlated with vaccine efficacy (equivalently predictive of vaccine efficacy) that may or may not be a mechanistic causal agent of protection | 131 |
| Humoral immune response | Host defenses that are mediated by antibody present in the plasma, lymph, and tissue fluids. It protects against extracellular bacteria and foreign macromolecules. | 130 |
| Immune response | The outcome of pathogen recognition, which is an intracellular or extracellular cascade of events that ultimately leads to the labeling and destruction of the pathogen | 130 |
| Immunity | Is the state of protection against foreign pathogens or antigens | 130 |
| Protection | Host defenses that protect against infection | 130 |
| Seropositivity | Significant presence of antibodies in the blood against a particular pathogen | This study |
| Susceptibility | Altered risk to be infected by certain pathogens due to genetic factors or lack of protection e.g., from vaccination | 130 |

content in this review, definitions of common terms used have been listed in Table 1.

## Pertussis vaccination

### *Pertussis vaccines*

At present, 2 types of pertussis vaccines are being used, wP vaccines and aP vaccines. Most of them are combined with diphtheria and tetanus toxoids (DTwP or DTaP), while some are also combined with other vaccines routinely administered during infancy, such as Haemophilus influenzae type b (Hib), hepatitis B (HBV) and/or inactivated poliovirus (IPV). Vaccines containing reduced concentrations of pertussis antigens and diphtheria toxoid (Tdap) have been used for booster immunizations. Thus there are various B. pertussis containing vaccines, but no stand-alone pertussis vaccines available worldwide.[24]

wP vaccines are made of bacterial suspensions of one or more strains of killed whole B. pertussis bacteria. In the latest recommendations for wP vaccines,[25] the World Health Organization (WHO) has developed a set of requirements for the production, standardization, and quality control of wP vaccines. For example, strains of B. pertussis used in preparing vaccines should be identified by a full record of their history and be well characterized; since the vaccines may be prepared from more than one strain, the bacterial concentration should be determined by comparison with the 10 IU of WHO opacity standard before killing and detoxification, making the number of bacteria in a single human dose of the final bulk be equivalent to having an opacity of no more than 20 IU; thiomersal or other preservatives should be added for multidose presentations while aluminum used as adjuvant should not exceed an upper limit of 1.25 mg per single human dose; the potency of a passed vaccine should not be less than 4.0 IU per single human dose, with a lower fiducial limit of the estimated potency being no less than 2.0 IU; and vaccines containing wP must not be frozen but instead should be stored at 2–8°C.[25] Despite the standardized procedure of vaccine production, manufacturers use different strains of B. pertussis, and the methods used for production also vary. Whole-cell pertussis vaccine induces complex immune responses to many bacterial antigens, including those included in the aP vaccines.[26] The varying amounts of biologically active components are unclear, hence the wP vaccines are relatively heterogeneous, which complicates the comparisons of immunogenicity, efficacy and effectiveness of different vaccines in different studies. A systematic review reported that the pooled efficacy of wP vaccines against pertussis in children was 78%, but efficacy varied significantly among vaccines.[27] For example, DTwP vaccines manufactured by Pasteur Mérieux, Behring, Wyeth-Lederle, and SmithKline Beecham had efficacies of 92% to 98%, but a DTwP vaccine from Connaught Laboratories had an extremely low efficacy of 40% when it was used in vaccine trials in the 1990s. The vaccine was also a licensed wP vaccine having passed recommended potency assays.[28] The potency of wP vaccines is still being tested by the mouse intracerebral challenge, which does not work for aP vaccines.

aP vaccines contain 1 to 5 highly purified B. pertussis antigens, including pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and serotypes 2 and 3 fimbriae (FIM2, FIM3). The latest recommendations to ensure the quality, safety and efficacy of aP vaccines were issued by the WHO in 2013. However, there is as yet no consensus about the antigenic composition of an ideal aP vaccine. Currently licensed vaccines contain either detoxified PT alone or detoxified PT in combination with FHA, with or without PRN and FIM 2 and 3. Not only the number, but concentrations of antigen components also vary in different aP vaccines, with different degrees of adsorption to different adjuvants. Table 2 shows some worldwide licensed pertussis vaccines. However, there is no internationally agreed upper limit for active PT in aP vaccines. In addition, different strains of B. pertussis, purifying methods, and detoxification agents used for individual antigen preparation also vary among manufacturers.[29] Therefore, direct comparison of the protection provided by various aP vaccines is difficult. Infanrix (GSK) and Pediacel (Sanofi-Pasteur MSD) induced comparable short-term efficacy in clinical trials performed in Sweden.[30] Difference in vaccine effectiveness (VE) following vaccination with different Tdap brands (Boostrix/Adacel) was also found in a study conducted in the USA.[31] However, there is no sufficient amount of evidence to establish any significant difference in VE of the aP vaccines.[24] Several sources of evidence revealed the differing capacity to induce immune responses among different brands of aP vaccines. Higher levels of antibodies and B. pertussis antigen-specific memory B cells were induced in mice immunized with Infanrix vaccine, suggesting the longer persistence of protection observed with the vaccine.[32] Whereas, compared with Tetravac (Sanofi Pasteur MSD), Infanrix-vaccinated preterm children had a persistently lower specific cell-mediated immune response.[33] Two parallel studies performed in the same cohort of children showed that a longer persistence of IgG-PT and

**Table 2.** Licensed aP and wP vaccines in the world.*

| type | Brand® | Manufacturer | Contents of pertussis antigens per dose | Adjuvant (mg-$Al^{3+}$ content) | Reference |
|---|---|---|---|---|---|
| DTap | Hexavac | Sanofi Pasteur | PT 25 $\mu$g; FHA 25 $\mu$g | aluminum hydroxide 0.3 mg | 34,132,133 |
| | Tetravac(DTap-IPV) Pentaxim (DTaP-IPV//PRP-T) | | | | |
| | Infanrix/Pediarix | GlaxoSmithKline Biologicals | PT 25 $\mu$g; FHA 25 $\mu$g; PRN 8 $\mu$g | aluminum hydroxide 0.5 mg | 34 |
| | Pediacel/Pentacle (DTap-IPV-Hib) | Sanofi Pasteur | PT 20$\mu$g; FHA 20 $\mu$g; PRN 3 $\mu$g; FIM 2/3 5 $\mu$g | aluminum phosphate 1.5 mg | 134,135 |
| | Quadracel (DTap-IPV) | | | | |
| | Daptacel | Sanofi Pasteur | PT 10 $\mu$g; FHA 5 $\mu$g; PRN 3 $\mu$g; FIM 2/3 5 $\mu$g | aluminum phosphate 0.33 mg | 28,136 |
| | Tripacel | | | | |
| Tdap | Boostrix | GlaxoSmithKline Biologicals | PT 8 $\mu$g; FHA 8 $\mu$g; PRN 2.5 $\mu$g | Aluminum hydroxide $\leq$ 0.39 mg (US) or 0.5 mg (rest of world) | 34,137 |
| | Adacel, Triaxis Covaxis(Tdap+OPV) Repevax (Tdap-IPV) | Sanofi Pasteur FHA 5 $\mu$g; PRN 3 $\mu$g; FIM 2/3 5 $\mu$g | PT 2.5 $\mu$g; | Aluminum phosphate 0.33 mg | 132,136,137 |
| | diTeKiBooster | Serum Institute of India Ltd. | PT 20 $\mu$g | Aluminum hydroxide 0.5 mg | 136 |
| wP | Triple Antigen Pentavac (DTwP-HepB+Hib) | Serum Institute of India Ltd. | Whole-cell *B. pertussis* $\geq$ 4 IU | aluminum phosphate $\leq$ 1.25 mg | 28,138 |
| | DT-COQ | Sanofi Pasteur | Whole-cell *B. pertussis* $\geq$ 4 IU | aluminum hydroxide 0.6 mg | 28 |
| | Quinvaxem | Crucell-Janssen | Whole-cell *B. pertussis* $\geq$ 4 IU | aluminum phosphate 0.3 mg | 28 |
| | DTwP | GlaxoSmithKline Biologicals | Whole-cell *B. pertussis* $\geq$ 2 IU | | 137 |

*The table does not represent all worldwide licensed pertussis vaccines.

IgG-PRN antibody levels after the pre-school booster was observed in Infanrix-primed children than in Hexavac (Sanofi Pasteur)-primed children, while cell-mediated immune responses were significantly higher in the children primed with Hexavac than in those who received the Infanrix vaccine. The 2 vaccines seemed to behave differently in terms of induction of humoral and cell-mediated immune responses. However, there was no evidence that the 2 types of immune responses are in anyway correlated.[34,35]

## Pertussis vaccination schedules

The main aim of a pertussis vaccination is to reduce the risk of severe pertussis in infancy. At least 90% coverage of infants with 3 doses of high quality pertussis vaccines remains the priority of the immunization program worldwide, particularly in countries where pertussis still poses a serious health problem in infants and young children. wP vaccines were first introduced widely in industrialized countries in the mid-20th century. Since 1974 they have been included in the WHO Expanded Program of Immunization (EPI). Associated with significantly fewer adverse reactions than wP vaccines, DTaP was first introduced in Japan in 1981 and then replaced DTwP in the 1990s in many industrial countries. According to the WHO, during 2015, about 86% (116 million) of infants worldwide received 3 doses of the diphtheria-tetanus-pertussis (DTP3) vaccine, with 126 countries having reached at least 90% coverage of the DTP3 vaccine.[36] However, there are also many countries that are still using wP vaccines, including Serbia and Poland in Europe, as well as low- and middle- income countries (LMICs) in Africa, the Middle East, South America and Asia.[7]

To protect infants who are at the highest risk of pertussis, WHO recommends a 3-dose primary series in childhood, with the first dose administered at the age of 6 weeks; subsequent doses should be given 4–8 weeks apart, at the age of 10–14 weeks and 14–18 weeks, or so that the last dose be administrated by the age of 6 months. A booster dose is recommended for children aged 1–6 years, preferably during the second year of life, and should be given $\geq$6 months after the last primary dose.[24] More than 80 different pertussis vaccination schedules are used globally. In general, only aP vaccines are now used for both primary and booster vaccination in most of developed countries[7] and in some developing countries such as China,[37] Malaysia[38] and Turkey.[39] In countries like Belgium, Canada, Germany, Israel, the Netherlands, Spain, USA and Turkey, a 5-dose childhood series of the DTaP vaccine was used, while a 3-dose series is recommended in many other European countries, typically at 2, 3 and 4 months; 2, 4 and 6 months; or 3, 5 and 11 months of age, usually followed with a booster vaccine for school-aged children aged 4–9 y.[7,40,41] In some countries including Argentina,[42] India,[43] Mexico,[44] Poland, and Serbia,[45] both wP and aP vaccines are used. Children or adolescents are boosted by aP vaccines after 3 to 5 doses of wP vaccines. In Mexico, however, 4 doses of aP vaccines are first given and then 1 booster dose of wP vaccine is

used. Many LMICs only provide wP vaccines.[26,46-49] In the majority of countries where wP vaccines are used, 3 primary doses are administered at various intervals within the first year of life, followed by one or 2 boosters between 15 months and 5 y of age. Two primary immunization schedules are most commonly used. In the first, all 3 doses are given at approximately equal intervals of 4–8 weeks (3p), while in the other, 2 doses are given at a short interval of about 2 months, with a longer interval (4–6 months) before the third dose ((2+1)p).[50]

## Immune persistence after vaccination with aPs

### *Persistence of immunity after DTaP immunization in children*

Although the aP vaccine provides a lower degree of protection than the highly effective DTwP, the immunity after the aP vaccinations was once considered durable.[51-53] However, the resurgence of pertussis in many industrial countries suggests unsatisfying duration of immunity after aP vaccinations.

In a clinical follow-up study, Gustafsson et al. reported increased incidence among 7- to 8-year-olds, suggesting that protection wanes some 5–7 y after 3 doses of an aP vaccination in infancy.[54] Even after the immunization with a 5 dose series, a case-control study conducted in California, USA indicated that after the fifth dose of DTaP, the odds of acquiring pertussis increased by an average of 42% per year. The increased odds were consistent with a relative decline of 27% in estimated VE from less than 1 y to 5 y or longer.[55,56] Moreover, the results of this cohort study showed that protection decreases in a period of 5 y after the fifth DTaP dose at the age of 5–6 years, and incidence rates and the risk of pertussis have increased substantially in the 6 y. This rise is likely attributable in part to waning immunity from DTaP vaccines, which is suggested to occur before the recommended adolescent booster dose at 11 to 12 y of age.[57] A similar conclusion was made by a recent meta-analysis of duration of immunity after DTap vaccination. However, no significant difference in duration of protective immunity was found between a childhood immunization series with 3 and 5 doses of DTaP. For every additional year after the last dose of DTaP, the odds to get pertussis increased by 1.33 times. The estimated average duration of protection from DTaP is ~3 to 4 years, and only 10% of the children vaccinated with DTaP would be protected by 8.5 y after the last dose.[40] Indeed, among 132 pediatric patients, there was a notable increase in cases from ages 8–12 y with the highest positive testing rate among those aged 12 y. The VE for children aged 8–12 y was the lowest (24%) compared with that of 2–7 y and 13–18 y (41% and 79%, respectively).[58]

Results from recent serosurvey studies on the duration of antibody responses also support waning immunity after aP vaccination in children. With a recent cross-sectional serological study in Zhejiang province of China, where only DTaP was administered after 2010, 63% of children aged 3 y (1 y after the booster dose by aP vaccine) had undetectable IgG-PT antibodies, indicating an increased risk of susceptibility to pertussis at the population level.[59] Maria Carollo et al. found that no matter which kind of aP vaccines were used, 5 y after primary vaccination, the percentage of children with IgG-PT antibodies (>20 EU/ml) reduced to below 50% in non-boosted children, which was restored above 50% after the use of a pre-school booster dose.[34] Whereas, after the booster dose of around 4 y of age, a recent follow-up study in UK children vaccinated with 3 different aP-containing vaccines showed that antibodies to PT became undetectable (PT ≤5 IU/ml) in 49% of children at the 5-year follow-up visit.[60]

Thus, with a preschool booster offered for children aged 4–6 years, it is suggested that most children over the age of 10 y would lose protection against pertussis, signaling the need for an earlier adolescent Tdap booster.

### *Persistence of immunity after booster immunization of Tdap in adolescents and adults*

The primary goal of Tdap vaccination was to reduce the growing burden of pertussis among adolescents and adults and to reduce the transmission of the disease to infants. Persistence of immunity after aP booster immunizations was once thought to be extended beyond 5 y. Within a prolonged follow-up of a cohort, the persistence of pertussis-specific antibody and cell-mediated immunity (CMI) after booster immunization in adolescents were assessed at one month, 3 y and 5 y after a Tdap (Boostrix) booster vaccination in adolescents aged 11–13 y in Finland.[61-63] During the 5-year follow-up, 28% of the study subjects had undetectable anti-PT IgG antibodies, whereas IgG antibodies to FHA and PRN were well preserved. CMI levels to each of the 3 antigens also persisted above the prebooster levels measured 5 y earlier. In most studies, long-term persistence of antibodies is considered main indicator for the assessment of immune persistence induced by Tdap vaccines. Since there are no universally accepted antibody correlates of protection for pertussis, seropositivity was evaluated by determining the proportion of individuals having antibody levels at or above the limit of quantitation (LOQ), or 4 times higher than the LOQ (LOQ×4).[64,65] According to these studies conducted during the follow-up of 1–10 y after a Tdap vaccination, the majority of subjects were still seropositive for one or more pertussis-specific antibodies, of which the concentration remained higher than pre-vaccination levels.[64-69] Therefore, it has been suggested that 10 y could be an optimal interval for Tdap vaccine booster doses to reduce the reservoir of pertussis, which could help protect young infants.[64,68,69] A second Tdap booster has been found highly immunogenic and well tolerated in adults who have received one Tdap dose 10 y previously.[70,71]

Field evaluations conducted shortly after the introduction of the Tdap vaccine among adolescents revealed 66% to 78% effectiveness.[72,73] In the USA, shortly following the introduction of Tdap vaccines in 2005, reported rates of pertussis among targeted adolescents aged from 11- to 18-years decreased more quickly than all of the other age groups the years immediately following Tdap introduction, suggesting that the targeted use of Tdap reduced the burden of pertussis preferentially in the adolescent age group.[74] However, beginning in 2010, this trend was reversed. Once again, the incidence of disease among adolescents increased at a faster rate than the other age groups, similar to what was observed before the introduction of Tdap in the United States but at a much steeper incline.[75] It should be noted that pertussis is cyclic disease and

outbreaks can occur every 2–5 y.[24] Therefore, in some cases one does not know whether the outbreak is caused by resurgence or due to the next cycle of pertussis. Another matched case-control study conducted during the 2012 pertussis epidemic in Washington showed that among adolescents who received all acellular vaccines, Tdap vaccine effectiveness declined from 73% within 1 y to 34% at 2 to 4 y post vaccination, suggesting that protection induced by Tdap declined even faster than ever thought. The lack of long-term protection after Tdap vaccination is likely contributing to increases in pertussis among adolescents in this country.[76]

### *Persistence of immunity after maternal immunization*

Efficient placental transfer of specific pertussis antibodies has been shown after maternal immunizations with aP vaccines.[77,78] The first recommendation for a routine pertussis vaccination in pregnancy was given by the CDC in 2011.[79] After that, some other countries, like the UK, Australia, New Zealand, Israel and Belgium, adopted this recommendation successively.[7,80] In a simulative decision and cost-effectiveness analysis, Tdap vaccination during pregnancy could avert more infant cases and deaths at a lower cost than postpartum vaccination, even when postpartum vaccination is combined with additional cocooning doses.[81] Concentrations of vaccine-induced pertussis antibodies in sera from infants born to mothers immunized with Tdap during pregnancy were significantly higher at birth and at the age of 2 months than in infants whose mothers were immunized postpartum.[82] Ideally, maternal antibodies should offer protection until the primary vaccination schedule starts to confer protection. Recent studies in the UK demonstrated that maternal antibodies can provide more than a 90% protection against infection with B. pertussis in infants younger than 2 months, and lead to lower prevalence rates in the study cohorts.[80,83] However, maternal antibodies wane rapidly. Although maternal vaccination status was not available, Smallenburg et al. found that in children with a IgG-PT concentration >30 U/ml in their umbilical cord blood, the mean IgG-PT concentration declined to levels around the concentration needed for protection against pertussis (>20 U/ml) in the first 2 months of life.[84] In a recent Spanish study, in infants whose mothers received Tdap between 21 and 38 weeks of gestation a decline in geometric mean antibody titers (GMTs) of IgG-PT between peripartum and follow-up levels were presented, 52.7 IU/ml versus 7.5 IU/ml at 2 months of age. The median half-life of maternal antibodies to PT was 47 d.[85]

It is known that protection provided by transferred maternal antibodies depends on the maternal antibody concentration, which is mainly influenced by timing of maternal immunization. Immunizing pregnant women during the third or late second trimester (after 20 weeks of gestation), preferably at 27–36 weeks of gestation is recommended.[79,86] In the randomized clinical trial conducted by Munoz et al., maternal immunization given at gestation of 30–32 weeks with Tdap resulted in concentrations of IgG-PT in the infants dropping from 68.8 EU/ml at birth to 20.6 EU/ml at the age of 2 months, which is a relatively high concentration of pertussis antibodies in infants during the first 2 months of life.[82] Whereas, compared with 31–36 weeks and >36 weeks, women immunized at gestation of 27–30 weeks conveyed the highest IgG-PT and IgG-FHA antibodies from umbilical cord blood, suggesting an optimal timing for maternal Tdap immunization.[87] It is difficult, however, to know how often the vaccine would be needed to be given during childbearing age to confer protection to infants. Whether vaccination is needed in every pregnancy, irrespective of pregnancy spacing is still controversial. In a previous study, 24 non-pregnant women received a Tdap booster vaccine between 2 consecutive pregnancies. The mean interval between the vaccination with Tdap and the next delivery was 12.7 (range 8–18.4) months. Although decreasing steeply in the first year after vaccination (for example, GMT of IgG-PT in vaccinated women declined between vaccination and the next delivery, 53.7 EU/ml vs. 12.1 EU/ml), antibody concentrations of the cord blood remained above baseline in the next pregnancy (GMT of cord serum IgG-PT in second born children after the maternal booster dose was 19.0 EU/ml, compared with 6.1 EU/ml in the sibling born before the vaccination). However, the protective threshold is uncertain.[88] On the contrary, Healy et al. studied cord blood anti-pertussis antibody levels in 105 pregnant women who received Tdap sometime in the past 2 y before delivery. No difference was found in GMTs for pertussis-specific IgG in maternal delivery or infant cord sera for women immunized before or during early pregnancy. The estimated GMT of PT-IgG was <5 EU/ml in infants aged 2 months, a level which is definitely insufficient to provide protection against infection. The finding indicated that although pertussis-specific IgG concentrations in delivering women were high, maternal antibodies waned quickly, even in women immunized during the first and second trimester, suggesting that Tdap may need to be administered during the late stages of each pregnancy.[89] Recent research has also highlighted the importance of repeated Tdap immunizations for each pregnancy. Raya et al. measured pertussis-specific antibodies 9–15 months after delivery in women immunized with Tdap after the 20th week of their recent pregnancy. All the detected antibodies including IgG-PT, IgG-FIM and IgG-PRN exhibited a significant decline between the peripartum and follow-up levels in Tdap-immunized women.[90]

The Advisory Committee on Immunization Practices of the CDC has recommended the immunization of all pregnant women with Tdap in each pregnancy, irrespective of their immunization status and the interval between pregnancies.[86] However, these recommendations were based primarily on studies in which Tdap was administered before pregnancy or the timing of maternal vaccination could not be ascertained.[87]

Moreover, it has been reported that maternal antibodies may interfere antibody development in infant after primary vaccination. Antenatal pertussis immunization results in high antibody concentrations in infant before primary immunization, but may blunt subsequent antibody responses to some vaccine antigens.[91,92] Further researches are needed to evaluate the interference effect on immune response and persistence in infants after primary immunization.

## Immune persistence after vaccination with wPs

As mentioned previously, considerable variation has been noted in the antigenic content of different wP vaccines.

Therefore, it is difficult to directly compare the complex immunogenicity of different wP vaccines. Also, the differences in immunogenicity may not be translated into different clinical effectiveness because of the absence of any known correlate of protection.

The schedules of 3 primary doses are typically completed between ages 4 to 6 months, whereas the 3rd dose in (2 + 1)p schedules is given later at 11–13 months. According to those early studies, after both kinds of schedules, decline in VE started between 1–2 y after the third dose, and the duration of immunity acquired after wP vaccination is estimated to range from 4–12 y.[26] The most dramatic decline was reported in data from Gustafsson et al. with a drop of VE from ~75% to ~34% in 2 y after the 3p schedule, and this was suggested to be due to the lower efficacy induced by a particular Connaught vaccine.[93] In other studies, however, VE was mostly showed with a modest decline and good protection was found in children up to the age of 5 y.[94-99] Some of the observational studies in the UK even showed high effectiveness (ranging from 70% to 90%) beyond 10 y.[97-99] Although most studies above are relatively old, with limitation, and the majority of them were conducted in high income countries where whole cell pertussis vaccines are no longer used, the data are consistent with waning protection overtime since wP vaccination. For the vaccines currently in use, wP vaccination was indicated to have a maximum annual loss of protection of 13% and a minimum loss of 2% following a primary series.[24] But the actual rate of decline in VE remains unclear. It could be due to waning in vaccine-derived protection, or by a progressive acquisition of natural immunity in the unvaccinated population.

There is little data on the duration of protection after a wP vaccination from LMICs. However, the prevalence of pertussis has been found to be increased in adolescents and adults with prolonged cough in many LMICs.[46,100,101] Asymptomatic pertussis infections are also common in school children aged 7–15 y old, as showed in a recent Chinese study.[102] Similar to the findings in developed countries,[103] although reported incidences are mostly <1/100 000, true incidences estimated by seroprevalence studies are much higher, especially in adolescents and adults populations.[7] Seropositivity rates even reached 40%~50% in adolescents and adults in Mexico and Iran, indicating high circulation of pertussis in these countries where wP vaccines are in use.[44,104,105] In Gambia, in children aged between 6 and 10 y without serological evidence of recent pertussis infection, overall concentrations of IgG-PT antibodies were lower but the seropositivity rate was higher compared with the younger age group, suggesting waning of vaccine-induced immunity and evidence for increased susceptibility to natural infection. Increased age was associated with increased infection risk (1.9% yearly increase), implying that childhood vaccination with wP vaccine or disease may not be sufficient to provide long-term immunity.[47] Recent data from seroprevalence studies conducted in China might shed light on the persistence of immunity to wP vaccines. In Beijing, the proportion of subjects with undetectable IgG-PT levels (<5 IU/ml) was found to increase significantly during the first 7 y after vaccination with the peak of 84.6% in 7 y olds.[106] In another study performed in Beijing, only 13.8% of adults who were at a childbearing age of 20–39 y did not have detectable anti-PT antibodies (<5 IU/ml).[12] Although China has recommended the use of wP or aP vaccines since 2007, the vaccination schedule (3, 4, 5, 18–24 months) has remained unchanged, no booster dose is given to children after 2 y of age. Protection induced by wP vaccination might have declind in 5 y since the booster dose given at 2 y.

However, it is not possible to distinguish between antibodies induced by wP vaccination or infection using current ELISAs, as the observed anti-PT antibodies may result from "silent" natural boosting. New assays capable of distinguishing between vaccine- and infection-induced antibodies are in need to be developed. Active surveillance and long-term follow-up studies of vaccine trials are essential to establishing the duration of protection. As recommended by the WHO, the optimal immunization schedule and the appropriate time for a booster dose of DTwP vaccine should be assessed in individual national programmes, taking into account the current epidemiological situation.[24]

## Comparison of immune persistence after vaccinations with wPs and aPs

It is suggested that wP vaccines provide a significantly better and longer protection compared with aP vaccines.[21] A cohort study in Australia compared relative risk among children who were vaccinated with all doses of DTwP, all doses of DTaP, or a mixed series in the same period during a pertussis outbreak of 2009 to 2011. Adolescents who received all doses of DTaP had a 3.3-fold more likely chance to be diagnosed with pertussis compared with children vaccinated with only DTwP.[107] Similarly, among teenagers born during the transition period of 1994–1999 in the USA, a decreasing number of DTwP doses was significantly associated with an increased risk of getting pertussis.[108] Even with a first DTwP priming, in all scenarios (3 or 5 primary doses, or with a Tdap booster ≥10 years), the reported rates of pertussis were significantly lower among children who had started the vaccination process with DTwP than among those who were primed by DTaP.[109]

Increasing evidence supports that wP vaccines induce longer-lasting immune responses than aP vaccines. In a previous German study, adolescents aged at 10–14 y were primed with a different schedule: 5 doses of a 2-component aP vaccine (last dose given at age of 4–6 years), 4 doses of the aP vaccine (last dose given at age of 18–24 months), or 4 doses of wP (last dose given at age of 18–24 months), and all boosted with a Tdap vaccine. Although the interval since the last dose was longer, IgG-PT levels in the wP-primed group were higher than those of both pre- and post-boosters in the aP-primed groups.[110] Another study compared the B. pertussis-specific T cell responses in Belgian children of 9–12 y olds primed with wP or aP vaccines. They all received an aP booster between 5.5 and 8.2 y of age. The time since the booster was significantly longer for wP compared with aP vaccinated children (4.8 y vs. 2.7 y). But the proliferation capacity in response to antigen stimulation was comparable, and more children had a detectable cytokine response after wP, compared with an aP vaccination.[111] However, higher pertussis-specific antibodies and better B cell memory responses were noticed in children who received aP vaccines in infancy, compared with those who were primed

with a wP vaccine up to 2 y after a booster vaccine in Dutch studies. As stated by the authors, the observation that children who received aP vaccines in infancy and had higher pertussis antibodies were possibly due to the use of non-optimal Dutch wP vaccines.[112,113] Thus care should be taken not to generalize the findings to all wP vaccines.

## Evaluation of protective immunity after pertussis vaccination in human

It has been shown that wP and aP vaccines direct the host immune responses differently. wP vaccines favor a T-helper 1 (Th1) response, whereas aP vaccines drive the immune responses to a mixed Th2/Th1 profile, and thus induce high antibody titers against vaccine antigens.[114] As already shown by clinical trials performed in the 1990s, antibodies against vaccine antigens such as PT, FIM and PRN correlate with protection.[115,116] Thus measurement of serum antibodies to these antigens is a classical approach to evaluate immune persistence after immunization. Since PT is an essential virulence factor and a protective antigen, level of IgG-PT antibodies is usually taken as the most important parameter.[117-119] However, levels of IgG-PT antibodies were already found to wane sharply within a few years after the vaccination.[120] When comparing IgG antibodies to FHA and PRN, IgG-PT antibodies usually decreased fastest,[63,121] possibly because PT is the most specific antigen of B. pertussis while other antigens are usually involved in cross-reaction.[122] However, serum antibodies, especially IgG-PT, were considered to be insufficient to represent a correlate of protection, and immunized population with waning antibodies could be still protected by presence of CMI. CMI induced by vaccination are also believed to be important for the evaluation of protection against pertussis.[35,123-125] However, complex T- and B- cell responses to pertussis were reported in different studies.[124] Until now, the immune mechanism(s) of protection for pertussis are still not fully understood. Further research is needed to better understand the type of immune responses that yield optimal, long-lasting protection and the mechanisms responsible for this protection.

Another limitation needs to be noted. There is no unified standard for evaluation of pertussis protection and vaccine effectiveness. In serologic studies, seropositivities of pertussis-specific antibodies were compared based on different cutoffs. Most of the data on CMI mainly rely on identifying the capability of pertussis-specific cytokine production or cell proliferation. Which immune response—level of antibodies, level of functional antibodies, or T-cell responses—would be the most meaningful measure of the effectiveness, is still to be queried.[19] In observational studies, the defining loss of immunity also varied. The incidence of pertussis was compared for every year since the vaccine was administered with the use of various case definitions of pertussis. Symptoms, culture or polymerase chain reaction (PCR) were used solely or in combination. Some of the studies used the confirmed/suspected case definition from official documents. These varying definitions of pertussis likely contributed to the observed heterogeneity between the studies.[40]

## Conclusion and future perspective

Pertussis resurgence is believed to happen due to waning vaccine-induced immunity. It has been suggested that wP vaccines could provide a more effective and a longer duration of protection than aP vaccines,[126] although the precise rate of VE decline and the related mechanisms are unclear. A recent study of a baboon model has clearly shown that aP vaccines can protect against disease, but had limited impact on protection from infection or transmission. A possible mechanism seems to be due to the lower Th1/Th17 responses induced by aP vaccines.[127] Indeed, all of the wP vaccines tested in the baboon model can clear B. pertussis much faster than aP vaccines.[28] Since there is a more rapid waning of immunity and possibly a reduced impact on transmission, with aP relative to wP vaccines, the overall goal of the national immunization program needs to be carefully contemplated when considering a switch from wP to aP vaccines for the primary vaccination series. In LMICs, the scarcity of up-to-date data about the disease burden will probably ensure that the focus will remain on the maximisation of coverage for infants by wP vaccines. In high-income countries with longstanding pertussis immunization and high coverage, efforts to reduce severe morbidity (especially death) from pertussis in infants before they receive the first dose should be taken.[128] Maternal pertussis vaccination therefore is considered the most cost-effective strategy and more effective than cocooning.[129] But these findings are not necessarily applicable to LMICs. Therefore, as recommended by the WHO, a switch from wP to aP vaccines for primary infantile immunization should only be considered if the inclusion in the national immunization schedules of additional periodic boosters or maternal immunization can be ensured and sustained. National immunization program currently administering wP vaccines should continue to use wP vaccines for primary vaccination series; while others who currently using aP vaccines should consider the need for additional booster doses and maternal immunization to prevent early childhood mortality and the resurgence of pertussis.[24]

Several issues in this field need to be investigated in the future. First of all, pertussis vaccines induce various immune responses that typically are measured as serum antibodies or CMI assays, but we do not know what they really mean in regard to protection against re-infection on the mucosal surface. Furthermore, the methods by which especially CMI is measured are poorly standardized. Further research is needed to better understand the type of immune responses that yield optimal, long-lasting protection and the mechanisms responsible for this protection. Since many factors may intervene, such as quality of the initial immune response related to the vaccine type, vaccination schedules, and the acquisition of natural immunity as a consequence of high or low vaccine coverage, the magnitude and timing of the protective immunity after vaccination are difficult to predict and should continue to be evaluated. Mechanisms that are related to the waning of antibodies are as yet unclear. As the most widely used parameter, standardization of the cutoffs for IgG-PT levels is urgent for the evaluation of protection efficacy, as well as for surveillance of pertussis.

It should be kept in mind that pertussis is rather unique in that the same antibody to pertussis antigens may be measured for diagnostic purposes, for performing seroepidemiological studies and for measuring vaccine responses as well as for estimating susceptibility to infection. The specific humoral immune responses induced by vaccines cannot be clearly distinguished from those induced after infection. Therefore, except for PT, new protective and specific antigens are needed to be explored and used for surveillance, diagnosis and vaccine evaluation. Ideally, antibodies to these new antigens should be capable of distinguishing the vaccination from natural infection. Apart from waning immunity, the reasons of decline in observed vaccine effectiveness and the mechanisms involved are ambiguous, and need to be studied further. Factors for this could be the loss of functional antigenic epitopes during the treatment of the antigens e.g. detoxification, or genetic changes in circulating B. pertussis populations, like a dramatic increase in PRN-deficient strains in some countries.[126]

## Abbreviations

| | |
|---|---|
| aP | acellular pertussis vaccines |
| B. pertussis | Bordetella pertussis |
| CMI | cell-mediated immunity |
| DTaP | tetanus toxoid, diphtheria toxoid and acellular pertussis vaccines |
| DTwP | whole cell pertussis vaccines combined with diphtheria and tetanus toxoids |
| EPI | Expanded Program of Immunization |
| FHA | filamentous hemagglutinin |
| FIM2 | serotype 2 fimbriae |
| FIM3 | serotypes 3 fimbriae |
| GMTs | geometric mean antibody titers |
| HBV | hepatitis B virus |
| Hib | Haemophilus influenzae type b |
| IPV | inactivated polio virus |
| LMIC | low- and middle- income country |
| LOQ | limit of quantitation |
| PRN | pertactin |
| PT | pertussis toxin |
| Tdap | tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines |
| VE | vaccine effectiveness |
| WHO | World Health Organization |
| wP | whole cell pertussis vaccines. |

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

## Acknowledgment

We thank Tom Hamilton for the English language review.

## Funding

Z.C. was supported by the Beijing Excellent Researcher Award Program from Beijing Municipal Party Committee Organization Department (2014000020124G154) and Capital Medical University Young Teachers Research Funding (2014PY44). Q.H. was supported by a research grant from the Collaborative Innovation Center of Infectious Diseases, Capital Medical University (PXM 2015_014226_000058).

## References

[1] Pan American Health Organization. Vaccinate your family, Protect your community. Final report of the XIX Technical Advisory Group (TAG) Meeting on Vaccine-preventable Diseases of the Pan American Health Organization. Buenos Aires, Argentina; 2011 July 6–8. [accessed 2016 Sep 15]. http://www.paho.org/hq/index.php?option=com_content&view=article&id=1862&Itemid=1674

[2] Gentile A. Bordetella pertussis infection. Arch Argent Pediatr 2010; 108:78-81; PMID:20204244; http://dx.doi.org/10.1590/s0325-00752010000100020

[3] Falleiros Arlant LH, de Colsa A, Flores D, Brea J, Avila Aguero ML, Hozbor DF. Pertussis in Latin America: epidemiology and control strategies. Exp Rev Anti-infect Therapy 2014; 12:1265-75; PMID:25139010; http://dx.doi.org/10.1586/14787210.2014.948846

[4] World Health Organization. WHO vaccine-preventable disease: monitoring system. 2016 global summary. [accessed 2016 Sep 15]. http://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=CHN

[5] UK Government Web Archive. Confirmed pertussis in England and Wales: data to end-December 2012. Health Protection Report 2013; 7(5). [accessed 2016 Sep 15]. http://www.hpa.org.uk/hpr/archives/2013/news0513.htm#prtsss

[6] Centers for Disease Control and Prevention. 2012 Final pertussis surveillance report. Notice to readers: Final 2012 Reports of Notifiable Diseases. MMWR Morb Mortal Wkly Rep 2013; 62(33): 669–82; PMID: 24133698 [accessed 2015 Aug 11]. http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2012.pdf

[7] Barkoff AM, Grondahl-Yli-Hannuksela K, He Q. Seroprevalence studies of pertussis: what have we learned from different immunized populations. Pathog Dis 2015; 73(7): pii:ftv050; PMID:26208655; http://dx.doi.org/10.1093/femspd/ftv050

[8] de Greeff SC, Mooi FR, Westerhof A, Verbakel JM, Peeters MF, Heuvelman CJ, Notermans DW, Elvers LH, Schellekens JF, de Melker HE. Pertussis disease burden in the household: how to protect young infants. Clin Infect Dis 2010; 50:1339-45; PMID:20370464; http://dx.doi.org/10.1086/652281

[9] Gabutti G, Rota MC. Pertussis: A Review of Disease Epidemiology Worldwide and in Italy. Int J Environmental Res Public Health 2012; 9:4626-38; PMID:23330226; http://dx.doi.org/10.3390/ijerph9124626

[10] Zepp F, Heininger U, Mertsola J, Bernatowska E, Guiso N, Roord J, Tozzi AE, Van Damme P. Rationale for pertussis booster vaccination throughout life in Europe. Lancet Infect Dis 2011; 11:557-70; PMID:21600850; http://dx.doi.org/10.1016/s1473-3099(11)70007-x

[11] Huygen K, Rodeghiero C, Govaerts D, Leroux-Roels I, Melin P, Reynders M, Van Der Meeren S, Van Den Wijngaert S, Pierard D. Bordetella pertussis seroprevalence in Belgian adults aged 20-39 years, 2012. Epidemiol Infect 2014; 142:724-8; PMID:24073712; http://dx.doi.org/10.1017/s0950268813002458

[12] Chen Z, Zhang J, Cao L, Zhang N, Zhu J, Ping G, Zhao J, Li S, He Q. Seroprevalence of pertussis among adults in China where whole cell vaccines have been used for 50 years. J Infect 2016; 73(1):38-44; http://dx.doi.org/10.1016/j.jinf.2016.04.004

[13] Siriyakorn N, Leethong P, Tantawichien T, Sripakdee S, Kerdsin A, Dejsirilert S, Paitoonpong L. Adult pertussis is unrecognized public health problem in Thailand. BMC Infect Dis 2016; 16:25; PMID:26809648; http://dx.doi.org/10.1186/s12879-016-1357-x

[14] Mooi FR, Van Der Maas NA, De Melker HE. Pertussis resurgence: waning immunity and pathogen adaptation - 2 sides of the same coin. Epidemiol Infect 2014; 142:685-94; PMID:23406868; http://dx.doi.org/10.1017/s0950268813000071

[15] Bisgard KM, Pascual FB, Ehresmann KR, Miller CA, Cianfrini C, Jennings CE, Rebmann CA, Gabel J, Schauer SL, Lett SM. Infant

pertussis: who was the source? Pediatr Infect Dis J 2004; 23:985-9; PMID:15545851

[16] Wendelboe AM, Njamkepo E, Bourillon A, Floret DD, Gaudelus J, Gerber M, Grimprel E, Greenberg D, Halperin S, Liese J, et al. Transmission of Bordetella pertussis to young infants. Pediatr Infect Dis J 2007; 26:293-9; PMID:17414390; http://dx.doi.org/10.1097/01.inf.0000258699.64164.6d

[17] Wiley KE, Zuo Y, Macartney KK, McIntyre PB. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine 2013; 31:618-25; PMID:23200883; http://dx.doi.org/10.1016/j.vaccine.2012.11.052

[18] Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against Pertussis after natural infection or vaccination. Pediatric Infect Dis J 2005; 24:S58-S61; PMID:15876927

[19] Burns DL, Meade BD, Messionnier NE. Pertussis resurgence: perspectives from the Working Group Meeting on pertussis on the causes, possible paths forward, and gaps in our knowledge. J Infect Dis 2014; 209 Suppl 1:S32-5; PMID:24626870; http://dx.doi.org/10.1093/infdis/jit491

[20] Ausiello CM, Cassone A. Acellular pertussis vaccines and pertussis resurgence: Revise or replace? mBio 2014; 5:e01339-14; PMID:24917600; http://dx.doi.org/10.1128/mBio.01339-14

[21] Gambhir M, Clark TA, Cauchemez S, Tartof SY, Swerdlow DL, Ferguson NM. A change in vaccine efficacy and duration of protection explains recent rises in pertussis incidence in the United States. PLoS Comput Biol 2015; 11:e1004138; PMID:25906150; http://dx.doi.org/10.1371/journal.pcbi.1004138

[22] Warfel JM, Edwards KM. Pertussis vaccines and the challenge of inducing durable immunity. Curr Opin Immunol 2015; 35:48-54; PMID:26091979; http://dx.doi.org/10.1016/j.coi.2015.05.008

[23] Wearing HJ, Rohani P. Estimating the duration of pertussis immunity using epidemiological signatures. PLoS Pathog 2009; 5: e1000647; PMID:19876392; http://dx.doi.org/10.1371/journal.ppat.1000647

[24] World Health Organization. Pertussis vaccines: WHO position paper -August 2015. Weekly Epidemiological Record 2015; 35 (90):433-60. Available at: http://www.who.int/wer/2015/wer9035.pdf

[25] WHO Expert Committee on Biological Standardization. WHO Technical Report Series, No. 941 - Fifty-sixth report, Annex 6: Recommendations for whole-cell pertussis vaccine, 301–33. WHO HQ, Geneva, 2007. Available at: http://apps.who.int/medicinedocs/en/cl/CL7.13/clmd,50.html

[26] World Health Organization. Whole Cell Pertussis Vaccines: Summary of evidence relevant to schedules. SAGE meeting of April 2015; EB room, WHO HQ, Geneva; 2015 Apr 14–16. [accessed 2016 Jun 6]. http://www.who.int/immunization/sage/meetings/2015/april/2_wP_summary_WG_23Mar2015_submitted.pdf?ua=;

[27] Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. Vaccine 2003; 21:2003-14; PMID:12706690

[28] Warfel JM, Zimmerman LI, Merkel TJ. Comparison of 3 whole-cell pertussis vaccines in the baboon model of pertussis. Clin Vaccine Immunol 2016; 23:47-54; http://dx.doi.org/10.1128/cvi.00449-15

[29] WHO Expert Committee on Biological Standardization. WHO Technical Report Series, No. 979 - Sixty-second report, Annex 4: Recommendations to assure the quality, safety and efficacy of acellular pertussis vaccines, pages 187–260. WHO HQ, Geneva, 2013. Available at: http://apps.who.int/medicinedocs/en/m/abstract/Js21093en/

[30] Olin P, Gustafsson L, Barreto L, Hessel L, Mast TC, Rie AV, Bogaerts H, Storsaeter J. Declining pertussis incidence in Sweden following the introduction of acellular pertussis vaccine. Vaccine 2003; 21:2015-21; PMID:12706691

[31] Koepke R, Eickhoff JC, Ayele RA, Petit AB, Schauer SL, Hopfensperger DJ, Conway JH, Davis JP. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. J Infect Dis 2014; 210:942-53; PMID:24903664; http://dx.doi.org/10.1093/infdis/jiu322

[32] Morel S, Denoel P, Godfroid F, Cortvrindt C, Vanderheyde N, Poolman J. Induction of Bordetella pertussis-specific immune memory by DTPa vaccines. Vaccine 2011; 29:3449-55; PMID:21382483; http://dx.doi.org/10.1016/j.vaccine.2011.02.062

[33] Vermeulen F, Dirix V, Verscheure V, Damis E, Vermeylen D, Locht C, Mascart F. Persistence at one year of age of antigen-induced cellular immune responses in preterm infants vaccinated against whooping cough: comparison of 3 different vaccines and effect of a booster dose. Vaccine 2013; 31:1981-6; PMID:23429006; http://dx.doi.org/10.1016/j.vaccine.2013.02.004

[34] Carollo M, Pandolfi E, Tozzi AE, Buisman A-M, Mascart F, Ausiello CM. Humoral and B-cell memory responses in children 5 years after pertussis acellular vaccine priming. Vaccine 2014; 32:2093-9; PMID:24556506; http://dx.doi.org/10.1016/j.vaccine.2014.02.005

[35] Palazzo R, Carollo M, Bianco M, Fedele G, Schiavoni I, Pandolfi E, Villani A, Tozzi AE, Mascart F, Ausiello CM. Persistence of T-cell immune response induced by 2 acellular pertussis vaccines in children 5 years after primary vaccination. New Microbiol 2016; 39:35-47; PMID:26922984

[36] World Health Organization. Data on pertussis cases, estimated deaths and vaccination coverage. 2017. Available at: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/

[37] National Health and Family Planning Commission of the People's Republic of China. Implementation plan for the national Expanded Programme of Immunization. 2008 Feb 18. [accessed 2015 April 4]. http://www.nhfpc.gov.cn/zwgkzt/pzxgzgh/200804/33518.shtml

[38] Koh MT, Liu CS, Chiu CH, Boonsawat W, Watanaveeradej V, Abdullah N, Zhang X, Devadiga R, Chen J. Under-recognized pertussis in adults from Asian countries: a cross-sectional seroprevalence study in Malaysia, Taiwan and Thailand. Epidemiol Infect 2016; 144:1192-200; PMID:26468043; http://dx.doi.org/10.1017/s0950268815002393

[39] Turkoglu E, Sonmez C, Kurugol Z, Coplu N, Koturoglu G. Pertussis Serosurveillance Study in Izmir, Turkey. J Trop Pediatr 2014; 61(1):32-6; PMID:25424662; http://dx.doi.org/10.1093/tropej/fmu062

[40] McGirr A, Fisman DN. Duration of Pertussis immunity after DTaP immunization: A Meta-analysis. Pediatrics 2015; 135:331-43; PMID:25560446; http://dx.doi.org/10.1542/peds.2014-1729

[41] European Centre for Disease Prevention and Control. Vaccine Schedule. [accessed 2016 Jul 3]. http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

[42] Ministry of Health of the Nation. National vaccination calendar of the Argentine Republic. [accessed 2016 Jul 3]. http://119.90.25.22/www.msal.gob.ar/images/stories/ryc/graficos/0000000628cnt-2016_calendario_vacunacion.pdf

[43] Vashishtha VM, Choudhury P, Kalra A, Bose A, Thacker N, Yewale VN, Bansal CP, Mehta PJ. Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years-India, 2014 and updates on immunization. Indian Pediatr 2014; 51:785-800; PMID:25362009

[44] Conde-Glez C, Lazcano-Ponce E, Rojas R, DeAntonio R, Romano-Mazzotti L, Cervantes Y, Ortega-Barria E. Seroprevalence of Bordetella pertussis in the Mexican population: a cross-sectional study. Epidemiol Infect 2014; 142:706-13; PMID:23734968; http://dx.doi.org/10.1017/s0950268813001313

[45] Heininger U, Andre P, Chlibek R, Kristufkova Z, Kutsar K, Mangarov A, Meszner Z, Nitsch-Osuch A, Petrovic V, Prymula R, et al. Comparative Epidemiologic Characteristics of Pertussis in 10 Central and Eastern European Countries, 2000–2013. PLoS One 2016; 11:e0155949; PMID:27257822; http://dx.doi.org/10.1371/journal.pone.0155949

[46] Koh MT, Liu C-S, Chiu C-H, Boonsawat W, WatanaVeeradej V, Abdullah N, Zhang X, Devadiga R, Chen J. Under-recognized pertussis in adults from Asian countries: a cross-sectional seroprevalence study in Malaysia, Taiwan and Thailand. Epidemiol Infect 2016; 144:1192-200; PMID:26468043; http://dx.doi.org/doi:10.1017/S0950268815002393

[47] Scott S, van der Sande M, Faye-Joof T, Mendy M, Sanneh B, Barry Jallow F, de Melker H, van der Klis F, van Gageldonk P, Mooi F, et al. Seroprevalence of pertussis in the Gambia: evidence for continued circulation of bordetella pertussis despite high vaccination rates. Pediatr Infect Dis J 2015; 34:333-8; PMID:25764094; http://dx.doi.org/10.1097/inf.0000000000000576

[48] Vaz-de-Lima LR, Martin MD, Pawloski LC, Leite D, Rocha KC, de Brito CA, Vaz TM, Martins LM, Alvarenga DP, Ribeiro AF, et al. Serodiagnosis as adjunct assay for pertussis infection in Sao Paulo, Brazil. Clin Vaccine Immunol 2014; 21:636-40; PMID:24599531; http://dx.doi.org/10.1128/cvi.00760-13

[49] Saffar MJ, Khalilian AR, Rafee AR, Parsaei MR, Imanikhani S, Shojaei J, Saffar H. Bordetella pertussis IgG and IgA antibodies seroprevalence among 1–35 y-old population: the role of subclinical pertussis infection. Indian J Pediatr 2012; 79:353-7; PMID:22105235; http://dx.doi.org/10.1007/s12098-011-0593-8

[50] World Health Organization. Report from the SAGE Working Group on Pertussis vaccines, 26–27 August 2014, meeting, Geneva, Switzerland. SAGE meeting of April 2015; EB room, WHO HQ, Geneva; 2015 Apr 14–16. [accessed 2015 Oct 7]. http://www.who.int/immunization/sage/meetings/2015/april/1_Pertussis_report_final.pdf?ua=1;

[51] Simondon F, Preziosi MP, Yam A, Kane CT, Chabirand L, Iteman I, Sanden G, Mboup S, Hoffenbach A, Knudsen K, et al. A randomized double-blind trial comparing a 2-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine 1997; 15:1606-12; PMID:9364690

[52] Salmaso S, Mastrantonio P, Tozzi AE, Stefanelli P, Anemona A, Ciofi degli Atti ML, Giammanco A. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience. Pediatrics 2001; 108:E81; PMID:11694665

[53] Lugauer S, Heininger U, Cherry JD, Stehr K. Long-term clinical effectiveness of an acellular pertussis component vaccine and a whole cell pertussis component vaccine. Eur J Pediatrics 2002; 161:142-6; PMID:11998910; http://dx.doi.org/10.1007/s00431-001-0893-5

[54] Gustafsson L, Hessel L, Storsaeter J, Olin P. Long-term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5, and 12 months of age indicates the need for a Booster Dose at 5 to 7 years of age. Pediatrics 2006; 118:978-84; PMID:16950988; http://dx.doi.org/10.1542/peds.2005-2746

[55] Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, Clark TA, Martin SW. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA 2012; 308:2126-32; PMID:23188029; http://dx.doi.org/10.1001/jama.2012.14939

[56] Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 2012; 367:1012-9; PMID:22970945; http://dx.doi.org/10.1056/NEJMoa1200850

[57] Tartof SY, Lewis M, Kenyon C, White K, Osborn A, Liko J, Zell E, Martin S, Messonnier NE, Clark TA, et al. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics 2013; 131:e1047-52; PMID:23478868; http://dx.doi.org/10.1542/peds.2012-1928

[58] Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. Clin Infect Dis 2012; 54:1730-5; PMID:22423127; http://dx.doi.org/10.1093/cid/cis287

[59] He H, Yao P, Zhou Y, Deng X, Pan J. Is Pertussis infection neglected in China? Evidence from a Seroepidemiology survey in Zhejiang, an Eastern province of China. PLoS One 2016; 11: e0155965; PMID:27223467; http://dx.doi.org/10.1371/journal.pone.0155965

[60] Voysey M, Kandasamy R, Yu LM, Baudin M, Sadorge C, Thomas S, John T, Pollard AJ. The predicted persistence and kinetics of antibody decline 9 years after pre-school booster vaccination in UK children. Vaccine 2016; 34(35):4221-8; http://dx.doi.org/10.1016/j.vaccine.2016.06.051

[61] Tran Minh NN, He Q, Ramalho A, Kaufhold A, Viljanen MK, Arvilommi H, Mertsola J. Acellular vaccines containing reduced quantities of pertussis antigens as a booster in adolescents. Pediatrics 1999; 104:e70; PMID:10586004

[62] Edelman KJ, He Q, Makinen JP, Haanpera MS, Tran Minh NN, Schuerman L, Wolter J, Mertsola JA. Pertussis-specific cell-mediated and humoral immunity in adolescents 3 years after booster immunization with acellular pertussis vaccine. Clin Infect Dis 2004; 39:179-85; PMID:15307026; http://dx.doi.org/10.1086/421943

[63] Edelman K, He Q, Makinen J, Sahlberg A, Haanpera M, Schuerman L, Wolter J, Mertsola J. Immunity to pertussis 5 years after booster immunization during adolescence. Clin Infect Dis 2007; 44:1271-7; PMID:17443462; http://dx.doi.org/10.1086/514338

[64] Tomovici A, Barreto L, Zickler P, Meekison W, Noya F, Voloshen T, Lavigne P. Humoral immunity 10 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine. Vaccine 2012; 30:2647-53; PMID:22353673; http://dx.doi.org/10.1016/j.vaccine.2012.02.013

[65] McIntyre PB, Turnbull FM, Egan AM, Burgess MA, Wolter JM, Schuerman LM. High levels of antibody in adults 3 years after vaccination with a reduced antigen content diphtheria-tetanus-acellular pertussis vaccine. Vaccine 2004; 23:380-5; PMID:15530684; http://dx.doi.org/10.1016/j.vaccine.2004.05.030

[66] Turnbull FM, Heath TC, Jalaludin BB, Burgess MA, Ramalho AC. A randomized trial of 2 acellular pertussis vaccines (dTpa and pa) and a licensed diphtheria-tetanus vaccine (Td) in adults. Vaccine 2000; 19:628-36; PMID:11090714

[67] Barreto L, Guasparini R, Meekison W, Noya F, Young L, Mills E. Humoral immunity 5 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine. Vaccine 2007; 25:8172-9; PMID:17945400; http://dx.doi.org/10.1016/j.vaccine.2007.09.031

[68] Bailleux F, Coudeville L, Kolenc-Saban A, Bevilacqua J, Barreto L, André P. Predicted long-term persistence of pertussis antibodies in adolescents after an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine, based on mathematical modeling and 5-year observed data. Vaccine 2008; 26:3903-8; PMID:18555563; http://dx.doi.org/10.1016/j.vaccine.2008.04.089

[69] Embree J, Law B, Voloshen T, Tomovici A. Immunogenicity, safety, and antibody Persistence at 3, 5, and 10 years postvaccination in adolescents randomized to booster immunization with a combined tetanus, diphtheria, 5-component acellular pertussis, and inactivated poliomyelitis vaccine administered with a Hepatitis B Virus vaccine concurrently or 1 month apart. Clin Vaccine Immunol 2015; 22:282-90; PMID:25540274; http://dx.doi.org/10.1128/cvi.00682-14

[70] Mertsola J, Van Der Meeren O, He Q, Linko-Parvinen A, Ramakrishnan G, Mannermaa L, Soila M, Pulkkinen M, Jacquet J-M. Decennial administration of a Reduced antigen content Diphtheria and Tetanus Toxoids and Acellular Pertussis vaccine in young adults. Clin Infect Dis 2010; 51:656-62; PMID:20704493; http://dx.doi.org/10.1086/655825

[71] Booy R, Van Der Meeren O, Ng S-P, Celzo F, Ramakrishnan G, Jacquet J-M. A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix™) is immunogenic and well tolerated in adults. Vaccine 2010; 29:45-50; PMID:20974302; http://dx.doi.org/10.1016/j.vaccine.2010.10.025

[72] Rank C, Quinn HE, McIntyre PB. Pertussis vaccine effectiveness after mass immunization of high school students in Australia. Pediatr Infect Dis J 2009; 28:152-3; PMID:19106780; http://dx.doi.org/10.1097/INF.0b013e318185608e

[73] Wei SC, Tatti K, Cushing K, Rosen J, Brown K, Cassiday P, Clark T, Olans R, Pawloski L, Martin M, et al. Effectiveness of adolescent and adult tetanus, reduced-dose diphtheria, and acellular pertussis vaccine against pertussis. Clin Infect Dis 2010; 51:315-21; PMID:20578875; http://dx.doi.org/10.1086/653938

[74] Skoff TH, Cohn AC, Clark TA, Messonnier NE, Martin SW. Early impact of the US Tdap vaccination program on pertussis trends.

Arch Pediatr Adolesc Med 2012; 166:344-9; PMID:22213608; http://dx.doi.org/10.1001/archpediatrics.2011.1093

[75] Skoff TH, Martin SW. Impact of Tetanus Toxoid, reduced diphtheria toxoid, and acellular pertussis vaccinations on reported pertussis cases among those 11 to 18 years of age in an Era of Waning Pertussis Immunity: A follow-up analysis. JAMA Pediatr 2016; 170:453-8; PMID:27018748; http://dx.doi.org/10.1001/jamapediatrics.2015.4875

[76] Acosta AM, DeBolt C, Tasslimi A, Lewis M, Stewart LK, Misegades LK, Messonnier NE, Clark TA, Martin SW, Patel M. Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic. Pediatrics 2015; 135:981-9; PMID:25941309; http://dx.doi.org/10.1542/peds.2014-3358

[77] Healy CM, Munoz FM, Rench MA, Halasa NB, Edwards KM, Baker CJ. Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. J Infect Dis 2004; 190:335-40; PMID:15216470; http://dx.doi.org/10.1086/421033

[78] Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol 2011; 204:334 e1-5; http://dx.doi.org/10.1016/j.ajog.2010.11.024

[79] CDC. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged. MMWR Morb Mortal Wkly Rep 2011; 60:1424-6; PMID:22012116

[80] Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, Fry NK, Miller E, Ramsay M. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014; 384:1521-8; PMID:25037990; http://dx.doi.org/10.1016/s0140-6736(14)60686-3

[81] Terranella A, Asay GR, Messonnier ML, Clark TA, Liang JL. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis. Pediatrics 2013; 131:e1748-56; PMID:23713104; http://dx.doi.org/10.1542/peds.2012-3144

[82] Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, Walter EB, Jackson LA, Englund JA, Edwards MS, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA 2014; 311:1760-9; PMID:24794369; http://dx.doi.org/10.1001/jama.2014.3633

[83] Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Fry NK, Ramsay M. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clin Infect Dis 2015; 60:333-7; PMID:25332078; http://dx.doi.org/10.1093/cid/ciu821

[84] Smallenburg LC, van Welie NA, Elvers LH, van Huisseling JC, Teunis PF, Versteegh FG. Decline of IgG pertussis toxin measured in umbilical cord blood, and neonatal and early infant serum. Eur J Clin Microbiol Infect Dis 2014; 33:1541-5; PMID:24756212; http://dx.doi.org/10.1007/s10096-014-2110-2

[85] Vilajeliu A, Ferrer L, Munros J, Gonce A, Lopez M, Costa J, Bayas JM. Pertussis vaccination during pregnancy: Antibody persistence in infants. Vaccine 2016; 34:3719-22; PMID:27265448; http://dx.doi.org/10.1016/j.vaccine.2016.05.051

[86] CDC. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women-Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep 2013; 62:131-5; PMID:23425962

[87] Abu Raya B, Srugo I, Kessel A, Peterman M, Bader D, Gonen R. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels-a prospective study. Vaccine 2014; 32:5787-93; http://dx.doi.org/10.1016/j.vaccine.2014.08.038

[88] Leuridan E, Hens N, Peeters N, de Witte L, Van der Meeren O, Van Damme P. Effect of a prepregnancy pertussis booster dose on maternal antibody titers in young infants. Pediatr Infect Dis J 2011; 30:608-10; PMID:21206396; http://dx.doi.org/10.1097/INF.0b013e3182093814

[89] Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. Clin Infect Dis 2013; 56:539-44; PMID:23097585; http://dx.doi.org/10.1093/cid/cis923

[90] Abu Raya B, Srugo I, Kessel A, Peterman M, Vaknin A, Bamberger E. The decline of pertussis-specific antibodies after tetanus, Diphtheria, and Acellular Pertussis immunization in late pregnancy. J Infect Dis 2015; 212:1869-73; PMID:26160743; http://dx.doi.org/10.1093/infdis/jiv324

[91] Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, Waight PA, England A, Matheson M, Bai X, Findlow H, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. Clin Infect Dis 2015; 61:1637-44; PMID:26374816; http://dx.doi.org/10.1093/cid/civ695

[92] Hoang HT, Leuridan E, Maertens K, Nguyen TD, Hens N, Vu NH, Cabore RN, Duong HT, Huygen K, Van Damme P, et al. Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during pregnancy. Vaccine 2016; 34:151-9; PMID:26529073; http://dx.doi.org/10.1016/j.vaccine.2015.10.098

[93] Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a 2-component acellular, a 5-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996; 334:349-55; PMID:8538705; http://dx.doi.org/10.1056/nejm199602083340602

[94] Bassili WR, Stewart GT. Epidemiological evaluation of immunisation and other factors in the control of whooping-cough. Lancet 1976; 1:471-4; PMID:55731

[95] Jenkinson D. Duration of effectiveness of pertussis vaccine: evidence from a 10 year community study. Br Med J (Clin Res Ed) 1988; 296:612-4; PMID:3126927

[96] Ramsay ME, Farrington CP, Miller E. Age-specific efficacy of pertussis vaccine during epidemic and non-epidemic periods. Epidemiol Infect 1993; 111:41-8; PMID:8348931

[97] White JM, Fairley CK, Owen D, Matthews RC, Miller E. The effect of an accelerated immunisation schedule on pertussis in England and Wales. Commun Dis Rep CDR Rev 1996; 6:R86-91; PMID:8664929

[98] Van Buynder PG, Owen D, Vurdien JE, Andrews NJ, Matthews RC, Miller E. Bordetella pertussis surveillance in England and Wales: 1995–7. Epidemiol Infect 1999; 123:403-11; PMID:10694150

[99] Campbell H, Amirthalingam G, Andrews N, Fry NK, George RC, Harrison TG, Miller E. Accelerating control of pertussis in England and Wales. Emerg Infect Dis 2012; 18:38-47; PMID:22260989; http://dx.doi.org/10.3201/eid1801.110784

[100] Karagul A, Ogunc D, Midilli K, Ongut G, Ozhak Baysan B, Donmez L, Daglar D, Kuskucu MA, Bingol A, Ozbudak O, et al. Epidemiology of pertussis in adolescents and adults in Turkey. Epidemiol Infect 2015; 143:2613-8; PMID:25524454; http://dx.doi.org/10.1017/s0950268814003483

[101] Pimentel AM, Baptista PN, Ximenes RA, Rodrigues LC, Magalhaes V, Silva AR, Souza NF, Matos DG, Pessoa AK. Pertussis may be the cause of prolonged cough in adolescents and adults in the interepidemic period. Braz J Infect Dis 2015; 19:43-6; PMID:25452019; http://dx.doi.org/10.1016/j.bjid.2014.09.001

[102] Zhang Q, Yin Z, Li Y, Luo H, Shao Z, Gao Y, Xu L, Kan B, Lu S, Zhang Y, et al. Prevalence of asymptomatic Bordetella pertussis and Bordetella parapertussis infections among school children in China as determined by pooled real-time PCR: a cross-sectional study. Scand J Infect Dis 2014; 46:280-7; PMID:24520981; http://dx.doi.org/10.3109/00365548.2013.878034

[103] Sealey KL, Belcher T, Preston A. Bordetella pertussis epidemiology and evolution in the light of pertussis resurgence. Infect Genet Evol 2016; 40:136-43; PMID:26932577; http://dx.doi.org/10.1016/j.meegid.2016.02.032

[104] Hashemi SH, Ranjbar M, Hajilooi M, Seif-Rabiei MA, Bolandi M, Moghimi J. Seroprevalence of Immunoglobulin G antibodies against pertussis toxin among asymptomatic medical students in the west of Iran: a cross sectional study. BMC Infect Dis 2009; 9:58; PMID:19426546; http://dx.doi.org/10.1186/1471-2334-9-58

[105] Pourakbari B, Moradi B, Mirzaee F, Mahmoudi S, Teymuri M, Mamishi S. Seroprevalence of antibodies to diphtheria, tetanus and pertussis among healthy adolescents and adults in Iran. Roum Arch Microbiol Immunol 2013; 72:250-4; PMID:24923108

[106] Li X, Chen M, Zhang T, Li J, Zeng Y, Lu L. Seroepidemiology of diphtheria and pertussis in Beijing, China: A cross-sectional study. Hum Vaccin Immunother 2015; 11:2434-9; PMID:26177302; http://dx.doi.org/10.1080/21645515.2015.1062954

[107] Sheridan SL, Ware RS, Grimwood K, Lambert SB. Number and order of whole cell pertussis vaccines in infancy and disease protection. JAMA 2012; 308:454-6; PMID:22851107; http://dx.doi.org/10.1001/jama.2012.6364

[108] Klein NP, Bartlett J, Fireman B, Rowhani-Rahbar A, Baxter R. Comparative Effectiveness of Acellular Versus Whole-Cell Pertussis Vaccines in Teenagers. Pediatrics 2013; 131:e1716-e22; PMID:23690518; http://dx.doi.org/10.1542/peds.2012-3836

[109] Liko J, Robison SG, Cieslak PR. Priming with whole-cell versus acellular pertussis vaccine. N Engl J Med 2013; 368:581-2; PMID:23388023; http://dx.doi.org/10.1056/NEJMc1212006

[110] Rieber N, Graf A, Belohradsky BH, Hartl D, Urschel S, Riffelmann M, Wirsing von Konig CH, Liese J. Differences of humoral and cellular immune response to an acellular pertussis booster in adolescents with a whole cell or acellular primary vaccination. Vaccine 2008; 26:6929-35; PMID:18852002; http://dx.doi.org/10.1016/j.vaccine.2008.09.064

[111] Smits K, Pottier G, Smet J, Dirix V, Vermeulen F, De Schutter I, Carollo M, Locht C, Ausiello CM, Mascart F. Different T cell memory in preadolescents after whole-cell or acellular pertussis vaccination. Vaccine 2013; 32:111-8; PMID:24176499; http://dx.doi.org/10.1016/j.vaccine.2013.10.056

[112] Schure RM, Hendrikx LH, de Rond LG, Ozturk K, Sanders EA, Berbers GA, Buisman AM. Differential T- and B-cell responses to pertussis in acellular vaccine-primed versus whole-cell vaccine-primed children 2 years after preschool acellular booster vaccination. Clin Vaccine Immunol 2013; 20:1388-95; PMID:23825195; http://dx.doi.org/10.1128/cvi.00270-13

[113] Hendrikx LH, Berbers GA, Veenhoven RH, Sanders EA, Buisman AM. IgG responses after booster vaccination with different pertussis vaccines in Dutch children 4 years of age: effect of vaccine antigen content. Vaccine 2009; 27:6530-6; PMID:19729085; http://dx.doi.org/10.1016/j.vaccine.2009.08.052

[114] Higgs R, Higgins SC, Ross PJ, Mills KHG. Immunity to the respiratory pathogen Bordetella pertussis. Mucosal Immunol 2012; 5:485-500; PMID:22718262

[115] Cherry JD, Gornbein J, Heininger U, Stehr K. A search for serologic correlates of immunity to Bordetella pertussis cough illnesses. Vaccine 1998; 16:1901-6; PMID:9796041; http://dx.doi.org/10.1016/S0264-410X(98)00226-6

[116] Storsaeter J, Hallander HO, Gustafsson L, Olin P. Levels of anti-pertussis antibodies related to protection after household exposure to Bordetella pertussis. Vaccine 1998; 16:1907-16; PMID:9796042; http://dx.doi.org/10.1016/S0264-410X(98)00227-8

[117] Giammanco A, Taormina S, Chiarini A, Dardanoni G, Stefanelli P, Salmaso S, Mastrantonio P. Analogous IgG subclass response to pertussis toxin in vaccinated children, healthy or affected by whooping cough. Vaccine 2003; 21:1924-31; PMID:12706678

[118] Taranger J, Trollfors B, Lagergård T, Sundh V, Bryla DA, Schneerson R, Robbins JB. Correlation between pertussis toxin IgG antibodies in postvaccination sera and subsequent protection against Pertussis. J Infect Dis 2000; 181:1010-3; PMID:10720524; http://dx.doi.org/10.1086/315318

[119] Storsaeter J, Hallander HO, Gustafsson L, Olin P. Low levels of anti-pertussis antibodies plus lack of history of pertussis correlate with susceptibility after household exposure to Bordetella pertussis. Vaccine 2003; 21:3542-9; PMID:12922081

[120] Hallander HO, Gustafsson L, Ljungman M, Storsaeter J. Pertussis antitoxin decay after vaccination with DTPa: Response to a first booster dose - years after the third vaccine dose. Vaccine 2005; 23:5359-64; PMID:16051400; http://dx.doi.org/10.1016/j.vaccine.2005.06.009

[121] Riffelmann M, Littmann M, Hülße C, Wirsing von König CH. Antibody decay after immunisation of health-care workers with an acellular pertussis vaccine. Eur J Clin Microbiol Infect Dis 2009; 28:275-9; PMID:18797942; http://dx.doi.org/10.1007/s10096-008-0625-0

[122] Prince HE, Lieberman JM, Cherry JD. Age-related differences in patterns of increased Bordetella pertussis antibodies. Clin Vaccine Immunol 2012; 19:545-50; PMID:22357646; http://dx.doi.org/10.1128/cvi.05725-11

[123] Grondahl-Yli-Hannuksela K, Kauko L, Van Der Meeren O, Mertsola J, He Q. Pertussis specific cell-mediated immune responses 10 years after acellular pertussis booster vaccination in young adults. Vaccine 2016; 34:341-9; PMID:26643932; http://dx.doi.org/10.1016/j.vaccine.2015.11.049

[124] Hendrikx LH, Ozturk K, de Rond LG, Veenhoven RH, Sanders EA, Berbers GA, Buisman AM. Identifying long-term memory B-cells in vaccinated children despite waning antibody levels specific for Bordetella pertussis proteins. Vaccine 2011; 29:1431-7; PMID:21187178; http://dx.doi.org/10.1016/j.vaccine.2010.12.033

[125] de Rond L, Schure RM, Ozturk K, Berbers G, Sanders E, van Twillert I, Carollo M, Mascart F, Ausiello CM, van Els CA, et al. Identification of pertussis-specific effector memory T cells in preschool children. Clin Vaccine Immunol 2015; 22:561-9; PMID:25787136; http://dx.doi.org/10.1128/cvi.00695-14

[126] Sheridan SL, Frith K, Snelling TL, Grimwood K, McIntyre PB, Lambert SB. Waning vaccine immunity in teenagers primed with whole cell and acellular pertussis vaccine: recent epidemiology. Expert Rev Vaccin 2014; 13:1081-106; PMID:25093268; http://dx.doi.org/10.1586/14760584.2014.944167

[127] Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. Proc Natl Acad Sci U S A 2014; 111:787-92; PMID:24277828; http://dx.doi.org/10.1073/pnas.1314688110

[128] McIntyre PB, Clark TA. Pertussis vaccine in pregnancy-first dose for every infant? Lancet 2014; 384:1484-6; PMID:25037989; http://dx.doi.org/10.1016/s0140-6736(14)60977-6

[129] Rivero-Santana A, Cuellar-Pompa L, Sanchez-Gomez LM, Perestelo-Perez L, Serrano-Aguilar P. Effectiveness and cost-effectiveness of different immunization strategies against whooping cough to reduce child morbidity and mortality. Health Policy 2014; 115:82-91; PMID:24444703; http://dx.doi.org/10.1016/j.healthpol.2013.12.007

[130] Owen JA, Punt J, Stanford SA. Kuby Immunology 7th ed. New York: W. H. Freeman and Company; 2013

[131] Plotkin SA, Gilbert PB. Nomenclature for immune correlates of protection after vaccination. Clin Infect Dis 2012; 54:1615-7; PMID:22437237; http://dx.doi.org/10.1093/cid/cis238

[132] John T, Voysey M, Yu LM, McCarthy N, Baudin M, Richard P, Fiquet A, Kitchin N, Pollard AJ. Immunogenicity of a low-dose diphtheria, tetanus and acellular pertussis combination vaccine with either inactivated or oral polio vaccine compared to standard-dose diphtheria, tetanus, acellular pertussis when used as a preschool booster in UK children: A 5-year follow-up of a randomised controlled study. Vaccine 2015; 33:4579-85; PMID:26165918; http://dx.doi.org/10.1016/j.vaccine.2015.06.105

[133] Plotkin SA, Liese J, Madhi SA, Ortiz E. A DTaP-IPV//PRP∼T vaccine (Pentaxim$^{TM}$): a review of 16 years' clinical experience. Exp Rev Vaccin 2011; 10:981-1005; PMID:21749196; http://dx.doi.org/10.1586/erv.11.72

[134] Langley JM, Halperin SA, Rubin E, White C, McNeil S, Mutch J, Mackinnon-Cameron D, Smith B. Safety and immunogenicity of 2 mixed primary infant immunization schedules of pentavalent diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, and Haemophilus influenzae Type B vaccines at 2, 4, and 6 months of age: a randomized controlled trial. Pediatr Infect Dis J 2012; 31:189-92; PMID:22173143; http://dx.doi.org/10.1097/INF.0b013e318242462a

[135] Liang J, Wallace G, Mootrey G. Licensure of a diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine and guidance for use as a booster dose. MMWR Morb

Mortal Wkly Rep 2015; 64:948-9; PMID:26334944; http://dx.doi.org/10.15585/mmwr.mm6434a5

[136] Carlsson RM, Gustafsson L, Hallander HO, Ljungman M, Olin P, Gothefors L, Nilsson L, Netterlid E. Two consecutive randomized controlled pertussis booster trials in children initially vaccinated in infancy with an acellular vaccine: The first with a 5-component Tdap vaccine to 5-year olds and the second with 5- or monocomponent Tdap vaccines at age 14–15 years. Vaccine 2015; 33:3717-25; PMID:26057135; http://dx.doi.org/10.1016/j.vaccine.2015.05.079

[137] McCormack PL. Reduced-antigen, combined diphtheria, tetanus and acellular pertussis vaccine, adsorbed (Boostrix(R)): a review of its properties and use as a single-dose booster immunization. Drugs 2012; 72:1765-91; PMID:22931522; http://dx.doi.org/10.2165/11209630-000000000-00000

[138] Dalvi S, Kulkarni PS, Phadke MA, More SS, Lalwani SK, Jain D, Manglani M, Garg BS, Doibale MK, Deshmukh CT. A comparative clinical study to assess safety and reactogenicity of a DTwP-HepB+Hib vaccine. Hum Vaccin Immunother 2015; 11:901-7; PMID:25933183; http://dx.doi.org/10.1080/21645515.2015.1010953