Is it time to administer acellular pertussis vaccine to childbearing age/pregnant women in all areas using whole-cell pertussis vaccination schedule?

Abdouleza Esteghamati, Shirin Sayyahfar, Yousef Alimohamadi, Sarvenaz Salahi and Mahmood Faramarzi

Abstract

Background: Whole-cell pertussis (wP) vaccine administration is still advocated for children under 7 years of age in Iran. However, there is no recommendation for the administration of a dose of tetanus, diphtheria, and acellular pertussis (Tdap) vaccine to childbearing age/pregnant women in the Iranian vaccination program and it has increased the risk of infection through waning immunity during women’s childbearing age life. The study aimed to assess the levels of anti-\textit{Bordetella pertussis} antibodies in childbearing age women of different ages in Iran.

Methods: A cross-sectional study was conducted on a total number of 360 childbearing age women divided into six age groups, with 5-year intervals from 15 to 45 years old, in 2018–2019. Then, the levels of immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) antibodies against \textit{B. pertussis} were evaluated using enzyme-linked immunosorbent assay (ELISA). The IBM SPSS Statistics software (version 16.0) (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results: The mean age of the participants was 30.01 $\pm$ 8.35 years (range 14–45 years). All the cases were IgM negative, but two IgA-positive individuals (in the age groups of 14–19 and 30–34 years) were reported. Overall, 239 (66.4%) cases were IgG positive. The mean age of IgG-positive cases was 30.37 $\pm$ 8.37 years. The IgG-positive cases were mostly in the age groups of 30–34 and 35–39 years [43 (71.1%)]. The odds of IgG positivity were 1.97. The highest odds of IgG positivity were seen in 30–34 and 35–39 years groups (2.52) and the lowest odds were seen in the 20–24 and 25–29 years groups [1.60]. Using the Jonckheere–Terpstra test, the increasing trend of IgG changes in different age groups was not statistically significant ($T_\pi=5.78, p=0.09$).

Conclusion: The infants of women of childbearing age might be prone to pertussis in countries using the wP vaccination schedule. It is suggested to administer a dose of Tdap to women before or during pregnancy to increase the immunity of their infants against this disease during early infancy.

Keywords: acellular pertussis vaccine, immunization, pertussis, vaccine, whole-cell vaccine

Introduction

Currently and despite extensive and global vaccination, the prevalence rate of pertussis is rising steadily so that all age groups can be affected with the severe clinical consequences of this contagious respiratory disease.\(^1\) The life-threatening
presentations of pertussis are particularly prevalent among infants.\textsuperscript{2,3} Although waning immunity has been reported with both vaccines, several outbreaks of pertussis in countries using acellular pertussis (aP) vaccine have been associated with its lower effectiveness.\textsuperscript{4} Therefore, some countries such as Iran and India are still recommending whole-cell pertussis (wP) vaccination for children aged under 7 years. While the extended program of immunization (EPI) of Iran suffices for the administration of wP, the Indian Academy of Pediatrics recommends a dose of aP vaccine to pregnant women to augment levels of maternal antibodies and to provide more protection for newborns.\textsuperscript{5} Brazil is also one of the countries that has included both wP and aP vaccines in the vaccine schedule.\textsuperscript{6,7} Lack of such a guideline and recommendation in the Iranian vaccination program has made infants vulnerable to pertussis through waning immunity during women’s childbearing age life.

Newborns cannot be vaccinated against pertussis and according to the EPI of Iran, the youngest age to administer the first dose of this vaccine is at 6 weeks of age, so infants are left unprotected or partially protected until they are at least 6 months old. Therefore, passive transfer of antibodies from mother to fetus (passive immunization) remains the mainstay of protection of newborn and infants against pertussis in early infancy.\textsuperscript{8,9} The maternal immunoglobulin G (IgG) can thus pass through the placenta. However, the levels of antibodies rapidly decrease within the first months of life after birth.\textsuperscript{10} For that reason, the Centers for Disease Control and Prevention (CDC) recommends tetanus, diphtheria, and acellular pertussis (Tdap) vaccine administration for women during the second or third trimesters of pregnancy.\textsuperscript{11}

In Iran, infants are vaccinated at 2, 4, and 6 months of age using the pentavalent formulation containing diphtheria, tetanus, \textit{Haemophilus influenzae} type B, hepatitis B and wP vaccines.

Moreover, the trivalent formulation is administered at 18 months of age and 4–6 years old containing diphtheria, tetanus and whole-cell pertussis (DTP) vaccines.\textsuperscript{12}

Therefore, each woman of childbearing age is vaccinated for the last time before 7 years of age based on the EPI of Iran. As pertussis is typically acquired from a family member in newborns and infants younger than 12 months, protecting infants \textit{via} vaccination of close contacts (namely, cocooning)\textsuperscript{13} can be an effective preventive method.

The levels of immunity against pertussis in childbearing age women have thus far been evaluated in a limited way in Iran.\textsuperscript{14} Due to lack of similar studies, the current study aimed to assess the levels of anti-pertussis antibodies in Iranian childbearing age women.

**Methods**

**Study design and patient selection**

This cross-sectional study was conducted on a total number of 360 women of childbearing age referred to a laboratory for performing check-ups from 2018 to 2019. The study was approved by the ethics committee of Iran University of Medical Sciences, Iran (no. IR. IUMS.REC139528934) and then informed consent forms were signed by all participants.

The cases were then divided into six age groups with 5-year intervals from 15 to 45 years old. The exclusion criteria were a history of confirmed or probable diagnosis of pertussis over the past 6 months, any primary or secondary immunodeficiency, unknown history of immunization against pertussis, and a history of not receiving wP vaccine.

After filling in the written consent forms by the participants, a checklist indicating demographic characteristics data and medical history was completed. The history of vaccination against pertussis was further asked. Afterwards, 5 mL of venous blood was taken from each case, collected in a tube containing sodium heparin, and transferred to the laboratory of PIRC where the tubes were centrifuged and plasma supernatants were collected, frozen, and stored at \textdegree{}80\textdegree{}C. Ultimately, the levels of immunoglobulin A (IgA), immunoglobulin M (IgM), and IgG antibodies against \textit{Bordetella pertussis} were evaluated using enzyme-linked immunosorbent assay (ELISA) (IBL International GmbH, Hamburg, Germany). Bordetella-specific antigens including pertussis toxin (PT), filament hemagglutinin (FH) and pertussis lipopolysaccharide (LPS) were
measured. Moreover, levels of IgG antibodies higher than 20 U/ml were considered positive\(^5\) (positive and negative were defined as anti-pertussis antibodies above and below the mentioned limit, respectively).

**Statistical analysis**

The study results were presented as mean ± standard deviations and geometric mean concentration (GMC) with 95% confidence intervals (CIs) of IgG in different age groups and then summarized by absolute frequencies and percentages for categorical variables. Also the odds of IgG positivity were calculated in all age groups using \(\frac{p}{1-p}\). In this formula \(p\) was the probability of event occurrence while \(1-p\) was the probability of event non-occurrence.

The Kruskall–Wallis test was used to assess the null hypothesis or equal GMC in different age subgroups. Also the Jonckheere–Terpstra test was used to determine the statistically significant trend between different age groups. A \(p\)-value less than 0.05 was considered as a statistically significant level. IBM SPSS Statistics software (version 16.0) (SPSS Inc., Chicago, IL, USA) was used for data analysis.

**Results**

The mean age of cases was 30.01 ± 8.35 years (range 14–45 years). Overall, 239 (66.4%) cases were IgG positive and 121 (33.6%) cases were IgG negative. The mean age of IgG-negative and positive cases was 29.23 ± 8.39 and 30.56 ± 8.28 years, respectively.

Overall, the GMC (95% CI) of IgG was 34.30 (31.15–37.76). The lowest GMC (95% CI) of IgG was seen in the 14–19 years age group [27.90 (21.94–35.49)] and the highest was seen in the 40–45 year group [38.35 (29.97–49.08)]. According to the IgG GMC values, the difference between the age groups was not statistically significant (\(p=0.47\)). More details have been shown in Table 1 and Figure 1.

All of the cases were IgM negative and the IgG-positive cases were mostly in the age groups of 30–34 and 35–39 years [43(71.1%)].

Moreover, two cases were IgA positive (in the age groups of 14–19 and 30–34 years). According to Table 2, the odds of IgG positivity in total cases was 1.97. The highest odds of IgG positivity were seen in the 30–34 and 35–39 years groups (2.52) and the lowest odds were seen in the 20–24 and 25–29 years groups (1.1.60). More details based on age groups are shown in Table 2 and Figure 2.

Using the Jonckheere–Terpstra test, the trend of IgG changes in different age groups was not statistically significant (\(T π = 5.78, p = 0.09\)).

**Discussion**

Iran is among the countries that still recommend wP vaccine administration in children under 7 years of age. As this type of vaccine is not given...
after this age, it is of utmost importance to know the serological status against *B. pertussis* in childbearing age women because the level of protection against pertussis in early infancy is completely dependent on maternal antibodies which are transplacentally transferred to the newborns. In this study, the levels of anti-*B. pertussis* antibodies were thus measured among women of childbearing age (14–45 years old) and then compared between six age groups to determine the necessity of adding a dose of Tdap at pregnancy/childbearing age.

According to the results of this study, the levels of IgG were negative in about 33.6% of the cases of childbearing age. Lack of sufficient levels of antibodies against *B. pertussis* could put infants at risk of pertussis. Therefore, a dose of Tdap might
reduce the risks of pertussis and better protect the newborns against pertussis. In addition, using the Jonckheere–Terpstra test, the trend of IgG changes in different age groups was not statistically significant.

In addition to the potential effectiveness of Tdap administration during pregnancy, available data do not support any association between Tdap vaccination during pregnancy and any adverse maternal, fetal, or infant outcomes.16

It seems that childbearing age women living in areas with the wP vaccine strategy may not transfer adequate antibodies to their newborns, while most cases of morbidity and mortality due to pertussis occur in children under 3 months of age.9

The current recommendation by the CDC and the Advisory Committee on Immunization Practices (ACIP) is to administer Tdap to all pregnant women between 27 and 36 gestational weeks regardless of prior Tdap history.9

In this study, 66.4% of the cases with a mean age of 30.56 years old were IgG positive against B. pertussis. This means that 33.6% of the women who might become pregnant did not have adequate antibodies to transfer to the fetus at the time of this study. In the report by Hashemi et al., 35.8% of the pregnant women living in the city of Hamadan, western Iran, with a mean age of 27.5 ± 6 years were IgG positive.14

Several studies from all around the world have correspondingly recommended a single dose of Tdap during every pregnancy.17,18 However, none of the previous studies have evaluated the level of anti-pertussis antibodies among women of child-bearing age in different age groups in order to make decisions about pertussis vaccination in countries with the wP vaccination schedule.

In this respect, Saffar et al. conducted a study in Iran to determine the effect of Tdap on the serum titer of anti-pertussis antibodies in women with planning for pregnancy. In this study, 114 childbearing age women planning for pregnancy were vaccinated with a single dose of Tdap. Maternal blood samples were further collected before and after vaccination at 1, 12, 28 and 43 months. Blood samples were also collected at birth. The results of this study established that the seroprevalence rate and mean concentration antibody (MCA) were 69.3% and 68.19 EU/ml before vaccination and then increased to 93.8% and 152.82 EU/ml following vaccination, respectively.19

Regarding the impact of maternal pertussis vaccination on infants’ immune response to pertussis vaccination during infancy, Wanlapakorn et al. performed a study.20 The authors showed more interference of the infant immune response to wP compared to aP vaccines. They concluded that countries introducing Tdap vaccination of pregnant women and vaccinating their infants with wP-containing vaccines should monitor their infants carefully.20

Whether this interference is clinically significant needs surveillance of pertussis disease, especially in infants of these countries.21

Figure 2. The linear trend of odds of immunoglobulin G (IgG) positivity in different age groups.
Although there is no accepted relationship with regard to serological protection, a dose of pertussis vaccine during pregnancy increases the levels of maternal antibodies and thus transfers passive immunity to newborns within the first months of life.22–25

There are several studies reflecting on the safety and efficacy of Tdap administration during pregnancy. For example, Donegan et al. found no evidence of an increased risk of any adverse effects associated with pregnancy in pregnant women receiving pertussis vaccination in the third trimester. In particular, there was no evidence of a growing risk of stillbirth.26

The results of a case–control study in the United Kingdom had additionally revealed that maternal pertussis vaccination was effective in preventing this infection in infants younger than 8 weeks of age.27

In addition, there are some seroprevalence studies available in the literature from countries that still have wP vaccines in their national immunization schedules. The studied cases were from different age groups while we studied only childbearing age women.28–31 However, all evaluated studies recommended a Tdap booster dose when the waning of vaccine-elicited immunity supported the need for a booster dose at that age.

Kurova et al. demonstrated that Russian children became susceptible to pertussis infection at or soon after entering school.28 Taye et al. observed declining trends in the protective effectiveness of wP vaccine 6 years after vaccination and highly recommended a booster dose to optimize pertussis prevention and control strategies.29

A booster dose of acellular pertussis vaccine was also suggested to be considered by Sigera et al. in Sri Lanka.30 Sera of 385 asymptomatic individuals aged 4–24 years were used for this study. The majority of the study population, especially the 8–11 years age group had low anti-pertussis toxin IgG levels.30

In our study, we checked IgA and IgM in addition to IgG. IgA and IgM measurement may be useful for laboratory confirmation of clinical pertussis in adults.28 In addition, primary vaccinations with wP induce IgM and IgG antibodies but do not induce IgA antibodies.32

In our study, there were two cases of IgA positivity in the age groups of 14–19 and 30–34 years. It might be secondary to post-vaccination natural infection after the decline of immunity against B. pertussis overtime because IgA might remain positive for several months (about 7.2 months) after infection.33

To identify which age group should be targeted for a booster dose, Wanlapakorn et al. investigated the seroprevalence of antibodies to pertussis toxin among healthy people across all ages in the population.31 The authors concluded that a booster dose during adolescence should be considered in order to reduce the incidence of pertussis disease.31

In conclusion, and according to the results of this study, the women of childbearing age might have declining levels of anti-pertussis IgG. It could be beneficial to add maternal Tdap vaccination to the immunization program of Iran and other countries with the same EPI to increase the immunity against pertussis during early infancy.

As Iranian infants are administered wP vaccine, further studies are needed to determine any clinical interference of maternal Tdap vaccination and infantile wP vaccination.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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References

1. Centers for Disease Control and Prevention (CDC). Pertussis – United States, 1997–2000. MMWR Morb Mortal Wkly Rep 2002; 51:73–76.

2. Winter K, Zipprich J, Harriman K, et al. Risk factors associated with infant deaths from pertussis: a case–control study. Clin Infect Dis 2015; 61: 1099–1106.

3. Abu-Raya B, Bettinger JA, Vanderkooi OG, et al. Burden of children hospitalized with pertussis in Canada in the acellular pertussis vaccine era, 1999–2015. J Pediatric Infect Dis Soc 2020; 9: 118–127.

4. Zerbo O, Bartlett J, Goddard K, et al. Acellular pertussis vaccine effectiveness over time. Pediatrics 2019; 144: e20183466.

5. Vashishtha VM, Bansal CP and Gupta SG. Pertussis vaccines: position paper of Indian Academy of Pediatrics (IAP). Indian Pediatr 2013; 50: 1001–1009.

6. SBIM. Vacinação. Calendário SBIM. http://www.svim.org.br/vacinacao/ (2014; accessed 26 April 2021).

7. Borba RCN, Vidal VM and Moreira LO. The re-emergency and persistence of vaccine preventable diseases. An Acad Bras Cienc 2015; 87 (2 Suppl.): 1311–1322.

8. Abu-Raya B, Maertens K, Edwards KM, et al. Global perspectives on immunization during pregnancy and priorities for future research and development: an international consensus statement. Front Immunol 2020; 11: 1282.

9. Swamy GK and Wheeler SM. Neonatal pertussis, cocooning and maternal immunization. Expert Rev Vaccines 2014; 13: 1107–1114.

10. Firth MA, Shewen PE and Hodgins DC. Passive and active components of neonatal innate immune defenses. Anim Health Res Rev 2005; 6: 143–158.

11. Sawyer M, Liang JL, Messonnier N, et al. 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: 131–135.

12. Moradi-Lakeh M and Esteghamati A. National Immunization Program in Iran: whys and why nots. Hum Vaccin Immunother 2013; 9: 112–114.

13. Clark TA and Bobo N. CDC update on pertussis surveillance and Tdap vaccine recommendations. NASN Sch Nurs 2012; 27: 297–300.

14. Hashemi SH, Zamani M, Mamani M, et al. Seroprevalence of Bordetella pertussis antibody in pregnant women in Iran. J Res Health Sci 2014; 14: 128–131.

15. Versteegen P, Pinto MV, Barkoff AM, et al. Responses to an acellular pertussis booster vaccination in children, adolescents, and young and older adults: A collaborative study in Finland, the Netherlands, and the United Kingdom. EBioMedicine 2021; 65:103247.

16. Vyggen-Bonnet S, Hellenbrand W, Garbe E, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. BMC Infect Dis 2020; 20: 136.

17. Maertens K, Caboré RN, Huygen K, et al. Pertussis vaccination during pregnancy in Belgium: results of a prospective controlled cohort study. Vaccine 2016; 34: 142–150.

18. Abu-Raya B, Giles ML, Kollmann TR, et al. The effect of timing of tetanus-diphtheria-acellular pertussis vaccine administration in pregnancy on the avidity of pertussis antibodies. Front Immunol 2019; 10: 2423.

19. Saffar M, Ajami A, Moslemi-zadeh N, et al. Prepregnancy pertussis immunization: effect on materno-neonatal antibody titers and infant immune response to whole-cell pertussis vaccination. J Vaccines Vaccin 2012; 3: 1–5.

20. Wanlapakorn N, Maertens K, Yongpun sawad S, et al. Quantity and quality of antibodies after acellular versus whole-cell pertussis vaccines in infants born to mothers who received tetanus, diphtheria, and acellular pertussis vaccine during pregnancy: a randomized trial. Clin Infect Dis 2020; 71: 72–80.

21. Abu-Raya B and Edwards KM. Interference with pertussis vaccination in infants after maternal pertussis vaccination. Pediatrics 2020; 146: e20193579.

22. Abu Rayaab B, Srugo I, Kessel A, et al. 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: 5787–5793.
23. Healy CM, Rench MA, Swaim LS, et al. Association between third-trimester Tdap immunization and neonatal pertussis antibody concentration. *JAMA* 2018; 320: 1464–1470.

24. Naidu MA, Muljadi R, Davies-Tuck ML, et al. The optimal gestation for pertussis vaccination during pregnancy: a prospective cohort study. *Am J Obstet Gynecol* 2016; 215: 237.e1–237.e6.

25. Abu-Raya B and Edwards KM. Optimizing the timing of vaccine administration during pregnancy. *JAMA* 2019; 321: 935–936.

26. Donegan K, King B and Bryan P. Safety of pertussis vaccination in pregnant women in the UK: observational study. *BMJ* 2014; 349: g4219.

27. Dabrera G, Amirthalingam G, Andrews N, et al. 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: 333–337.

28. Kurova N, Timofeeva EV, Guiso N, et al. A cross-sectional study of *Bordetella pertussis* seroprevalence and estimated duration of vaccine protection against pertussis in St. Petersburg, Russia. *Vaccine* 2018; 36: 7936–7942.

29. Taye S, Tessema B, Gelaw B, et al. Assessment of pertussis vaccine protective effectiveness in children in the Amhara regional state, Ethiopia. *Int J Microbiol* 2020; 2020: 8845835.

30. Sigera S, Perera J, Rasarathinam J, et al. Seroprevalence of *Bordetella pertussis* specific immunoglobulin G antibody levels among asymptomatic individuals aged 4 to 24 years: a descriptive cross-sectional study from Sri Lanka. *BMC Infect Dis* 2016; 16: 729.

31. Wanlapakorn N, Ngaovitunvong V, Thongmee T, et al. Seroprevalence of antibodies to pertussis toxin among different age groups in Thailand after 37 years of universal whole-cell pertussis vaccination. *PLoS One* 2016; 11: e0148338.

32. van der Zee A, Schellekens JFP and Mooi FR. Laboratory diagnosis of pertussis. *Clin Microbiol Rev* 2015; 28: 1005–1026.

33. Mertens PLJM, Stals FS, Steyerberg EW, et al. Sensitivity and specificity of single IgA and IgG antibody concentrations for early diagnosis of pertussis in adults: an evaluation for outbreak management in public health practice. *BMC Infect Dis* 2007; 7: 53.