




IJCRR
Section: Healthcare
ISI Impact Factor
(2019-20): 1.628
IC Value (2019): 90.81
SJIF (2020) = 7.893

Copyright@IJCRR

Public Health Measures for Pertussis Immunization in Pregnancy- A Rationalized Study

Sahoo PK¹, Sahoo G², Kar B³, Kar D⁴, Bhuyan R^{4,5}

¹Senior Consultant in Pediatrics, Laxmi Hospital, Vyasagar, Jajpur Road, Odisha, India; ²Dean IMS and SUM Hospital, Sikhsha O Anusandhan (Deemed to be) University Bhubaneswar, Odisha, India; ³Department of Medicine, IMS and SUM Hospital, Sikhsha O Anusandhan (Deemed to be) University Bhubaneswar, Odisha, India; ⁴Department of Medical Research Health Sciences, IMS and SUM Hospital, Sikhsha O Anusandhan (Deemed to be) University Bhubaneswar, Odisha, India; ⁵Department of Oral Pathology & Microbiology, IMS and SUM Hospital, Sikhsha O Anusandhan (Deemed to be) University, Bhubaneswar, Odisha, India.

ABSTRACT

Introduction: Pertussis (Whooping Cough) is a serious disease having the highest incidence and severe, potentially life-threatening complication rates among young infants. Death due to pertussis occurs mostly in infants of < 3 months of age. Unfortunately, infants are unable to build their protection until they get vaccinated at 6-8 weeks of birth. Thus they remain unprotected in the first months of life and during this time they are at the greatest risk of contracting the disease and falling very sick. On one hand, the babies don't have immunity of their own and on the other hand, they come in contact with individuals in the older age group whose immunity has decreased over time and get infected. Immunization strategy to a particular group such as infant caregivers and family members (Cocooning Strategy) achieved some success. Pertussis vaccination to pregnant ladies protects infants under the passive and active transplacental transfer of maternal antibodies giving protection to the infants till they build their immune system through vaccination. Studies demonstrate that acellular pertussis vaccination ensures safety both for mother and infant. The efficient transplacental transmission of maternal pertussis antibodies effectively prevents pertussis in young infants during the first months of life.

Objective: A study reported higher pertussis antibody concentrations in the period between birth and administration of the first dose of vaccine in infants born to mothers immunized with Tdap vaccine during pregnancy. Besides Cocooning and neonatal immunization, vaccination of pregnant women offers hope to prevent the incidence of pertussis in infants of < 3 months of age. The best timing of pertussis vaccination in pregnancy is yet to be determined.

Conclusion: The American College of Obstetricians and Gynaecologists (ACOG) recommends administering the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) to pregnant women during each pregnancy in the 27-36 week gestational period or with at least 2 weeks before the expected date of delivery.

Keywords: Acellular pertussis vaccine (aP), Maternal immunization, Pertussis, GMC (Geometric Mean Concentration), Safety and immunogenicity, Serious adverse event (SAD), Tdap vaccine, Whole-cell pertussis vaccine (wP).

INTRODUCTION

Globally pertussis (Whooping Cough) is acknowledged as a significant cause of morbidity and mortality in young infants. A significant number of morbidity and mortality due to pertussis infection is noticed in infants of < 3 months of age.¹ Despite being a vaccine-preventable disease and the existence of high coverage of effective immunization programmes, the disease continues to be one of the least controlled infections affecting all age groups and also a public health concern.²

As per the estimate of the World Health Organisation (WHO) 50 million cases and 30,000 deaths approximately

occur throughout the world every year.² The disease burden was reported to be the greatest in early infancy (among both unvaccinated and under-vaccinated infants) and teenagers.³⁻⁵ An estimated 5.1 million pertussis cases occurred globally in 2014 in infants resulting in 85,900 deaths. Low and middle-income countries having low vaccination coverage were worst affected with more than 80% of cases and 95% of deaths.^{5,6} Due to a less robust surveillance system, the true picture of disease burden in these countries is not estimated perfectly. However, despite > 95% vaccine coverage in resource-rich nations, pertussis is still a very poorly controlled vaccine-preventable disease.⁷⁻¹⁰

Corresponding Author:

Prof. Dr Ruchi Bhuyan, Department of Oral Pathology & Microbiology, IMS and SUM Hospital, Sikhsha O Anusandhan (Deemed to be) University, Bhubaneswar, Odisha, India; Email: ruchibhuyan@soa.ac.in

ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 30.09.2020

Revised: 15.11.2020

Accepted: 14.12.2020

Published: 25.04.2021

Pertussis, caused by the bacterium *Bordetella pertussis*, is endemic in all countries. Despite effective vaccination programmes and high vaccine coverage achievement, epidemic cycles do occur every 2-5 years (typically 3-4 years).¹¹ The reported rate of pertussis incidence in early infancy (below 3 months) per 1 lakh infants was 235 in the USA in 2017, 1368 in Pakistan and 4800 in South Africa in 2016.^{4,5,12} Out of reported 15,662 cases in 2019 in the USA, 1202 cases occurred under 6 months of age and age incidence per 1 lakh cases was 62.5, the highest in all age groups.¹³ Incidence and death rates due to Pertussis Outbreaks which occurred in California and Canada in 2010, Washington State in 2012 and Italy in 2012 and 2014 were highest in early infancy.¹⁴ Death due to pertussis almost exclusively occur in infants below the age of 3 months and out of these 76% of deaths are in the age group of < 2 months.^{15,16}

In India, during the year 1987, 2011 and 2017 the reported incidence of pertussis cases were 1,63,000, 39,091 and 23,779 respectively. In 2017, states like MP, Jharkhand, Assam, UP, West Bengal and UT Dadra & Nagar Haveli reported the maximum cases and 6 deaths only.¹⁷ Due to under-reporting the actual number will be much more taking into consideration of low vaccination coverage with primary and booster doses of diphtheria, pertussis and tetanus (DPT) vaccine in the country. The data on pertussis infection and disease are very much deficient in adolescents and adults. Actual *Bordetella pertussis* infection rates in the community, causing typical pertussis disease in infants and children, is not available.¹⁸

PATHOGEN

Bordetella pertussis is a tiny, fastidious Gram-negative coccobacillus and infects the ciliated epithelial cells of the respiratory tract in human beings. Adjusting to the environmental conditions the *Bordetella* species alter their phenotype and express virulence factors like pertussis toxin (PT), pertactin (PRN) filamentous haemagglutinin (FHA), fimbriae (FIM) type 2 and type 3, lipooligosaccharide (LPS), adenylate cyclase toxin (ACT) and tracheal cytotoxin (TCT). Though the pathogenesis of pertussis is not clear, FHA, PRN and FIM facilitate attachment to the epithelial cells and PT, TCT and ACT permit evasion of host immune factors destroying the epithelial cells.²

The available data suggest the evolution of strains with time with different isolates in the pre and post-vaccination era. Moderate changes have been detected in the genomic sequences of PT, FIM and PRN in the circulating strains.² Circulation of antigen-deficient isolates of PRN has been observed in areas where aP vaccine is used.¹⁹ However, to date there is no evidence of less effectiveness of vaccines against different *B. pertussis* allelic variants.²

MODE OF TRANSMISSION

Through droplets transmission, pertussis spreads from infected to healthy individuals. In its early catarrhal stage, the organism is very much contagious with a secondary attack rate of almost 90% in non-immune household contacts.¹² Though infectivity diminishes rapidly after the catarrhal stage, the possibility of transmitting infection for 3 weeks or more, persists following the onset of typical coughing attacks. Adolescents and adults are the remarkable sources of transmission to unvaccinated young infant contacts. In a systematic review of the identified source of infection in infants below the age of 6 months, it was observed that the contacts in the family contributed 74%-96% of cases.²⁰ The pooled analysis demonstrated that out of the household contact cases, 39% (95% CI: 33%-45%) were mothers, 16% (95% CI: 12%-21%) were fathers and 5% (95% CI: 2%-10%) were grandparents.²

ACELLULAR PERTUSSIS VACCINE

The use of whole-cell pertussis (wP) vaccine caused a decline in morbidity and mortality of pertussis. Public anxiety regarding the safety of wP vaccines and increased concerns on the frequently encountered local side-effects forced the researchers to develop acellular pertussis (aP) vaccines in Japan in 1981. Later in 1986, the vaccine was licensed in the US and at present is in use in developed countries.²¹ wP vaccines were replaced by vaccines due to the added advantage of significant lesser side-effects. The reproducible production process, use of purified antigens and removal of lipopolysaccharides (LPS) and other parts of the bacterial cell wall during purification of soluble antigenic material, is another significant added advantage. These vaccines contain one or more of the separately purified antigens like pertussis toxin (PT), pertactin (PTN), fimbrial hemagglutinins 2 and 3 (FIM type 2 and type 3), filamentous hemagglutinin (FHA). Vaccines differ from one another both in the number and quantity of antigen components and the bacterial clone used for primary antigen production, purification and detoxification methods, incorporated adjuvants and the use of preservatives like thiomersal.² The efficacy and duration of protection offered by Tdap vaccines are similar to that of whole-cell vaccines.¹⁸

EVOLUTION OF PERTUSSIS VACCINATION IN PREGNANCY

Most of the morbidity and mortality, on account of pertussis disease, occurs in infants below the age of 3 months.¹ Vaccination of neonates with pertussis vaccine starts at 2 months of age when 1st dose of DTaP/DTwP vaccination is initiated,

the earliest possible vaccination being at 6 weeks of age in developing countries.²² Thus a window of significant vulnerability to contract infections from family members and care givers does exist.¹⁹⁻²³ The infant would be protected against pertussis infection during the first months of life through the effective transplacental transmission of maternal antibodies against pertussis disease. Ordinarily, these transplacentally acquired antibodies are detected at least up to 6-8 weeks of birth when the 1st dose of immunization is usually started but the antibody concentration required to protect against pertussis infection is not known.¹⁸ Cocooning approach to vaccinating previously unimmunised family members, caregivers and women in the postpartum period with Tdap vaccine to provide a protective cocoon of immunity around the neonate was initiated following the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommendations in 2006.^{24, 25} However, the cocooning approach with high coverage which requires multiple doses for parents and family members as a minimum proved challenging and was not cost effective.² Studies demonstrate the inherent limitations in adopting the cocooning approach as a stand-alone prevention strategy against pertussis in infants. However, it is still a recommended component in the multi-prong strategy to lessen pertussis disease burden.²⁵ To provide protection both for the mother and the neonate during the earliest weeks of life, in June 2011, the ACIP recommended administering a dose of Tdap to all pregnant women after 20 weeks of gestation.²⁶ ACIP, again in 2013, issued its updated recommendation that irrespective of prior history of vaccination with Tdap vaccine, one dose of Tdap vaccine must be administered during each pregnancy, the timing being between 27-36 weeks of gestation. However, maternal immunization may safely be executed at any time during pregnancy, if the situation warrants conditions like wound management, pertussis outbreaks or other life-threatening circumstances where the protection requirement supersedes the benefit of immunization during 27-36 weeks of gestation.²⁷ From 2013, other reported evidence suggest in favour of Tdap vaccination during the later part of the second or early part of the third trimester with at least 2 weeks gap between vaccination and delivery.²⁸

The rationale of pertussis vaccination in pregnancy

Definite evidence exists regarding the effectiveness of maternal pertussis immunization in reducing infection in infants in first few months after birth, the most vulnerable high risk period of pertussis morbidity and mortality. First, maternal immunization is recognized as an ideal dual strategy offering direct protection of the infant through maternal antibody induction and transplacental transfer to infants for protection from birth in one hand and indirect infant protection through prevention of infection and transmission

of maternal infection on the other. Second, theoretically Tdap, being an inactivated vaccine can pose no concern on safety in pregnant ladies. Third, pertussis is not identified to create more morbidity in women during pregnancy. So Tdap can be administered in the later part of pregnancy thus avoiding concerns regarding interference with fetal development or associated pregnancy loss, much common in the 1st trimester. Another added advantage of vaccination towards the later part of pregnancy is that maternal antibodies are highest due to highly efficient placental transport from approximately 34 weeks of gestation. Theoretically, this timing optimizes maternally derived antibodies level in neonate for more sustained protection. Fourth, Tdap induces the production of maternal antibodies of the immunoglobulin G₁ subclass which in turn are transported transplacentally both actively and passively to the neonate. Fifth, these antibodies are required to persist for a short period only in the neonate for protection against fatal and severe infant disease till the first dose of the primary series vaccination is administered and the infant builds his immune system.²⁹ Sixth, in situations where maternal immunization is not fully protective, infants born to Tdap vaccinated pregnant women demonstrated significantly less morbidity, including risk of hospital and intensive care unit admission if they suffer from pertussis.²⁷

Vaccination safety in pregnancy

Several studies regarding the safety and immunogenicity of vaccines in different age groups have established better tolerance and lower adverse event rate than wP vaccines. Studies conducted on Tdap vaccination in pregnancy did not reveal increased adverse events in any form including pregnancy loss or poor neonatal outcome.²⁹ In 2011, the US adopted to vaccinate Tdap unvaccinated pregnant women, with Tdap vaccine irrespective of the interval from prior tetanus toxoid containing vaccine administration.³¹ Later this was updated to administer Tdap during the third trimester of every pregnancy.²⁷ After a pertussis epidemic, causing several infant casualties, the United Kingdom adopted Tdap vaccination in pregnancy in 2012 and other countries followed later.²⁹

Since the original US recommendation of 2011, several studies reported on the evaluation of Tdap maternal immunization safety. Munoz FM et al. in a randomized, double-blind, placebo-controlled study, demonstrated no Tdap-associated serious adverse events in mothers and infants.³⁰⁻³² A similar predominantly short-lived post-vaccination adverse event was reported in 52 women who received Tdap and 51 women who received TT during pregnancy in a randomized control study in Vietnam by Hoang HT et al. without any occurrence of Tdap-associated SAE.³³⁻³⁶ In an observational cohort study. Donegan et al reported no evidence of increased risk of early or late stillbirth in Tdap vaccinated pregnant women after vaccination.³⁴ Concomitant administration of influ-

enza vaccination with Tdap in pregnancy did not result in the increased incidence of adverse events or untoward birth outcome.³⁵ Tdap being a combination vaccine with tetanus and diphtheria toxoids, concern arose that frequent use of TT may cause adverse events. However, Sukumaran et al. In a retrospective cohort study did not find any significant differences in rates of adverse events or poor birth outcomes.³⁶

THE IMMUNE RESPONSE FOLLOWING IMMUNIZATION

The Us Phase 1-2 study demonstrated that Tdap immunization was immunogenically resulting in 5.6-fold greater GMC of pertussis toxin (PT) antibodies both in mothers and infants at birth with pregnant ladies, vaccinated with Tdap during pregnancy than those who did not receive the vaccine.³³ In another cohort study, infant cord samples at delivery taken from 312 women, vaccinated with Tdap during 3rd trimester of pregnancy as per the required norm, reported GMC to PT to be 47.3 IU/ml whereas in 314 women without Tdap vaccination in pregnancy it was 12.93 IU/ml only ($P < 0.001$).³⁷

The possibility of vaccination to pregnant women interfering with the induction of antibody production in infants after their primary immunization is a factor of concern. However, the up to date available critical evaluation of the immunological data suggests that induction of high antibodies in infants at delivery for sustenance through the critical first months of life is of paramount benefit in the prevention of mortality due to pertussis in infants rather than possible mild interference with infant immune response that can be taken care of by booster immunization after 12 months of age.³⁸

Effectiveness of maternal immunization in preventing pertussis in infants

Two studies conducted recently in United Kingdom provide clear cut evidence regarding pertussis vaccination to pregnant women protecting infants at very young age. Amirthalingam et al demonstrated that vaccine effectiveness was 91% (95% CL 84% to 95%) in preventing pertussis in infants below the age of three months in case the pregnant woman received vaccination at least 7 days prior to delivery.³⁹ Dabrera et al. also found similar results in a case control study of infants with pertussis in England and Wales.⁴⁰

CONCLUSION

In spite of various strategies, pertussis still remains a public health concern and is a significant life-threatening problem for young infants infected with pertussis. Vaccinating pregnant women is most likely the best cost-effective strategy for disease prevention in infants, too young to be immunized. Probably it is more effective and favourable than cocooning

which may have some impact in preventing disease in particular settings to achieve significant coverage in a phased and timely manner. Although the optimal timing of maternal immunization is still debatable (there is a lack of consensus for the vaccination timing in pregnancy) and whether the observed immune interference in infants (correlation between the presence of antibodies and immunity to pertussis) has any clinical relevance, this strategy has shown safety, immunogenicity and effectiveness in preventing disease in young infants in countries using aP vaccine.⁴¹ The benefit of this strategy needs to be further evaluated in women, receiving primary vaccination with aP vaccine in childhood and also, evaluation should be carried out in resource-poor countries where wP vaccine is used in National immunization schedule. It is desired that efforts should continue to optimize pertussis vaccine uptake by pregnant women. ACOG advises obstetrician-gynaecologists and obstetric caregivers to strongly recommend Tdap vaccination to all pregnant women in each pregnancy between 27-36 weeks of gestational age. Along with other strategies the development of a robust maternal pertussis vaccination program can eradicate infant pertussis-associated deaths globally.

Conflict of interest: Nil

Financial support: Nil

Author Contribution:

Prasanna Kumar Sahoo, Gangadhar Sahoo and Ruchi Bhuyan conceived, planned, designed the manuscript. Prasanna Kumar Sahoo drafted the manuscript. Bhagirathi Kar and Dattatrey kar collected the materials, edited and revised the manuscript.

REFERENCES

1. Van Rie A, Wendelboe AM, Englund JA. Role of maternal pertussis antibodies in infants. *Pediatr Infect Dis J* 2005;24(5): S62-5.
2. World Health Organization. Pertussis vaccines: WHO position paper—August 2015. *Weekly Epidemiological Record. Revue Epidém Hebd* 2015;90(35):433-58.
3. Smith BM. Determining sequence types of circulating Bordetella pertussis strains isolated from South African infants (Doctoral dissertation). https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=3.%09Smith+BM.+Determining+sequence+types+of+circulating+Bordetella+pertussis+strains+isolated+from+South+African+infants+%28Doctoral+dissertation%29.&btnG=
4. Masseria C, Martin CK, Krishnarajah G, Becker LK, Buikema A, Tan TQ. Incidence and burden of pertussis among infants less than 1 year of age. *Pediatr Infect Dis J* 2017;36(3): e54.
5. Omer SB, Kazi AM, Bednarczyk RA, Allen KE, Quinn CP, Aziz F, et al. Epidemiology of pertussis among young Pakistani infants: a community-based prospective surveillance study. *Clinic Infect Dis*. 2016;63(4):S148-53.
6. Worz C, Martin CM, Travis C. Vaccines for Older Adults. *Consult Pharm* 2017;32(9):6-13.

7. Cherry JD. Epidemic pertussis in 2012—the resurgence of a vaccine-preventable disease. *N Engl J Med* 2012; 367(9):785-7.
8. Chiappini E, Stival A, Galli L, De Martino M. Pertussis re-emergence in the post-vaccination era. *Bri Med Con Infect Dis.* 2013; 13(1): 1-2.
9. Guiso N, von König CH, Forsyth K, Tan T, Plotkin SA. The Global Pertussis Initiative: report from a round table meeting to discuss the epidemiology and detection of pertussis. *Vaccine* 2011;29(6):1115-1121.
10. Mooi FR, de Greeff SC. The case for maternal vaccination against pertussis. *Lancet Infect Dis* 2007; 7(9): 614-624.
11. Edwards KM, Decker Md. Pertussis vaccines. In: Plotkin S, Orenstein W, Offit P. eds. *Vaccines*, 6th ed. Philadelphia, Saunders, 2013: 447-492.
12. Gkentzi D, Katsakiori P, Marangos M, Hsia Y, Amirthalingam G, Heath PT, et al. Maternal vaccination against pertussis: a systematic review of the recent literature. *Arch Dis Child-Fetal and Neonatal Edition.* 2017; 102(5):F456-463.
13. Tan T, Dalby T, Forsyth K, Halperin SA, Heininger U, Hozbor D, et al. Pertussis across the globe: recent epidemiologic trends from 2000 to 2013. *Pediatr Infect Dis J* 2015;34(9): e222-232.
14. Chiappini E, Berti E, Sollai S, Orlandini E, Galli L, de Martino M. Dramatic pertussis resurgence in Tuscan infants in 2014. *Pediatr Infect Dis J* 2016; 35(8): 930-931.
15. National Vaccine Advisory Committee. The National Vaccine Advisory Committee: Reducing patient and provider barriers to maternal immunizations. *Pub Health Rep* 2015:10-42.
16. IAP Guidebook on Immunization 2018-19 by Advisory Committee on Vaccines & Immunization Practices (ACVIP), 3rd edition;134.
17. Vashishtha VM, Bansal CP, Gupta SG. Pertussis vaccines: position paper of Indian Academy of Pediatrics (IAP). *Ind Pediatr* 2013;50(11):1001-1009.
18. Hegre N, Guiso N. Bordetella pertussis and pertactin-deficient clinical isolates: lessons for pertussis vaccines. *Expert Rev Vacc* 2014;13(9):1135.
19. 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. *Vaccines* 2013; 31(4): 618-625.
20. IAP Guidebook on Immunization 2018-19 by Advisory Committee on Vaccines & Immunization Practices (ACVIP), 3rd edition; p-137.
21. Robinson CL, Romero JR, Kempe A, Pellegrini C, Advisory Committee on Immunization Practices. Advisory Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger—United States, 2017. *MMWR. Morb Morta Weekly Rept.* 2017; 66(5):134.
22. 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(11):985-989.
23. Skoff TH, Kenyon C, Cocoros N, Liko J, Miller L, Kudish K, Baumbach J, Zansky S, Faulkner A, Martin SW. Sources of infant pertussis infection in the United States. *Pediatrics* 2015; 136(4): 635-641.
24. Murphy TV, Slade BA, Broder KR, Kretsinger K, Tiwari T, Joyce MP, Iskander JK, Brown K, Moran JS. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants. *Morbidity Mortal Week Rep* 2008;57:1-51.
25. Healy CM, Baker CJ. Infant pertussis: what to do next? *Clin Infect Dis* 2012; 54(3):328-330.
26. Canters for Disease Control and Prevention (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. Morbidity Mortal Week Rep* 2011; 60(41): 1424-1426.
27. Updated recommendation for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. Centers for Disease Control and Prevention (CDC). *Morbidity Mortal Week Rep.* 2013; 62: 131-135.
28. Update on Immunization and Pregnancy: Tetanus, Diphtheria and Pertussis Vaccination. Committee on Obstetric Practice and Immunization and Emerging Infections Expert Group, No. 718, September 2017, .
29. Tessier E, Campbell H, Ribeiro S, Fry NK, Brown C, Stowe J, et al. Impact of extending the timing of maternal pertussis vaccination on hospitalized infant pertussis in England, 2014-2018. *Clin Infect Dis.* 2020: doi: 10.1093/cid/ciaa836.
30. Winter K, Cherry JD, Harriman K. Effectiveness of prenatal tetanus, diphtheria, and acellular pertussis vaccination on pertussis severity in infants. *Clin Infect Dis.* 2016; 64(1): 9-14.
31. Sawyer M, Liang JL, Messonnier N, Clark TA. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices. *Morbidity Mortal Week Rep* 2013; 62(7): 131.
32. Hoang HT, Leuridan E, Maertens K, Nguyen TD, Hens N, Vu NH, et al. Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial. *Vaccine* 2016;34:151-159.
33. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. *Br Med J* 2014;349:4219
34. Sukumaran L, McCarthy NL, Kharbanda EO, McNeil MM, Naleway AL, Klein NP, et al. Association of Tdap vaccination with acute events and adverse birth outcomes among pregnant women with prior tetanus-containing immunizations. *J Am Med Assoc* 2015;314(15):1581-1587.
35. Healy CM, Swaim L, Rench M, Harrison M, Martin M, Baker CJ. Third-Trimester Tdap Immunization Elicits Substantial Pertussis Toxin Immunoglobulin G in Neonates. In *Open Forum Infectious Diseases* 2015 Dec 1 (Vol. 2, No. suppl_1). Oxford University Press.
36. Cherry JD. Editorial commentary: the effect of Tdap vaccination of pregnant women on the subsequent antibody responses of their infants. *Clin Infect Dis* 2015;61(11):1645-1647.
37. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014;384(9953):1521-1528.
38. Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, 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(3):333-337.
39. Eberhardt CS, Blanchard-Rohner G, Lemaître B, Boukrid M, Combescure C, Othenin-Girard V, et al. Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. *Clin Infect Dis* 2016; 62(7): 829-836.
40. van den Biggelaar AH, Poolman JT. Predicting future trends in the burden of pertussis in the 21st century: implications for infant pertussis and the success of maternal immunization. *Expert Rev Vacc* 2016;15(1):69-80.