**National Immunization Schedule, India replaces TT with Td vaccine: Why not Tdap?**

**Title page**

**Title of article:**National Immunization Schedule, India replaces TT with Td vaccine: Why not

Tdap?

**Running title:**Why not Tdap instead of Td?

**Category:**Perspective

**Authors:**

1.Dr Akanksha Rathi, MD: Asisstant Professor, Department of Community Medicine, Dr

Baba Saheb Ambedkar Medical College, Delhi

2.Dr Nidhi Bhatnagar, MD: Asisstant Professor, Department of Community Medicine,

Maulana Azad Medical College, Delhi

3.Dr Satyavir Singh, MD: Director Professor & Head, Department of Community

Medicine, Dr Baba Saheb Ambedkar Medical College, Delhi

**Contribution of authors:**AR did the literature search and wrote the manuscript. NB conceived

the idea and did literature search. SVS gave important insights, edited and finalized the

manuscript.

**Name of department and institution to which the work should be attributed:**Department of

Community Medicine, Dr Baba Saheb Ambedkar Medical College, Delhi

**Corresponding author details:**

Dr Nidhi Bhatnagar, MD: Asisstant Professor, Department of Community Medicine, Maulana

Azad Medical College, Delhi, Ph-+91-8750647995, email id- bhatnagarnidhi.mamc@gmail.com

**Source of support/ funding:**Nil

**Conflict of interest:**None

**Word count:**1459

**Abstract (150 words)**

On 2018 Aug 14, India announced a change in the Universal Immunization Program (UIP), replacing Tetanus (TT) booster dose, currently being given to adolescent of 10 and 16 years and pregnant females, with Tetanus-Diphtheria (Td) vaccine. Just like diphtheria, epidemiology of pertussis has changed with adolescents and adults acting as disease reservoirs. Need to improve adult population immunity against pertussis is felt. Indian Academy of Pediatrics (IAP) recommends offering Tdap vaccine instead of Td/TT vaccine to all children/ adolescents who can afford to use the vaccine at the age of 10-12 yrs. Administering Tdap to pregnant women with the aim of intensifying the transfer of antibodies to the child also seems appropriate. Apart from the cost of Tdap vaccine, shortage of good quality sero-surveillance studies in Indian settings, are barriers to its introduction in the national immunization schedule.

**Keywords**

TT, Td, Tdap, Pertussis, Newer vaccine

**Introduction of newer vaccines**

Immunization has been the most cost effective public health measure to curb morbidity and mortality, not just among children, but all age groups. India has seen some major changes in its immunization schedule in the last few years owing to the introduction of newer vaccines. Based on the guidelines of WHO-UNICEF to determine vaccine priority, few vaccines were recently included in the list as high priority vaccines, which are pentavalent vaccines (DTP-hepatitis B-Hib), mumps, measles, rubella vaccines (MMR), the rotavirus vaccine, pneumococcal vaccine, injectable polio and monovalent Type 1 oral polio vaccine [1]. On 2018 Aug 14, India announced another change in the Universal Immunization Program (UIP), by declaring to replace Tetanus (TT) booster dose currently being given to adolescent of 10 and 16 years and pregnant females, with Tetanus-Diphtheria (Td) vaccine, acting on the recommendation of National Technical Advisory Group on Immunization (NTAGI) [2].

**Tetanus, diphtheria and pertussis**

TT vaccine has been a blessing for a country like India where tetanus was once very prevalent. To ensure 100% efficacy, WHO has recommended 5 doses of tetanus toxoid for childhood immunization: the primary series of 3 doses of DTP (DTwP or DTaP) in infancy (age <1 year), with a booster dose of a tetanus toxoid-containing vaccine ideally at age 4-7 years and another booster in adolescence, e.g. at age 12-15 years.  However, it has also advised a sixth dose in early adulthood to provide added assurance of protection throughout the childbearing years, and possibly for life [3]. Since antibodies to tetanus decline over time, boosters are needed to maintain an adequate level of antibodies against tetanus in the advent of an infection or exposure. Similarly, for diphtheria, the average duration of protection is about 10 years following a primary series of 3 doses of diphtheria toxoid [4].  Therefore, revaccination of adults against diphtheria and tetanus every 10 years may be necessary to sustain immunity in some epidemiological settings [5].

Just like Tetanus and Diphtheria, Pertussis is another vaccine-preventable disease that demands our due attention. Not only the epidemiology of the disease has changed with adolescents and adults acting as reservoirs [6], but also the high rate of serious disease and death in young infants, and the repeated outbreaks of pertussis even in highly-vaccinated populations is a matter for grave concern [7]. Adult and adolescent infection not only results in loss of healthy life years but it also is responsible for transmitting the disease to the susceptible neonates and infants. Family members have been implicated as important sources of pertussis for unprotected neonates who are at highest risk of complications and death [8-11]. Data from industrialized countries shows that despite high coverage of population with pertussis vaccine, disease continues to circulate in all populations and most often affects very young, unimmunized or incompletely immunized infants, with a rising incidence in adolescents and adults [8,9]. Waning immunity is a concern with almost all vaccines, but the drop in immunity is significant in case of pertussis vaccine over time as it has been reported that routine Tdap vaccination does not prevent pertussis outbreaks as the immunity acquired by Tdap vaccination wanes in 2-4 years [12,13]. Young infants infected with pertussis, experience the highest morbidity and mortality from this infection, specially infants younger than 6 weeks who are generally not protected against pertussis in the absence of maternal immunization [14-16]. Recent estimates suggest that approximately 50% of infected infants require hospitalization and of these, nearly 2% die [17]. Many countries like United States of America (USA), have included Tdap in their immunization schedules. In 2012, the US Advisory Committee on Immunization Practices (ACIP) recommended that acellular pertussis vaccine (Tdap) be given to any person likely to be in contact with young infants under the age of 12 months, including pregnant women regardless of previous Tdap vaccination [18]. Administering the vaccine to pregnant women is advised because it not only protects the mother from pertussis but also induces antibodies that are passed to the infant prior to birth which provide protection for the first weeks of life [18].

**Effectiveness of Tdap in preventing neonatal pertussis**

Maternal antibodies with half-life of approximately 6 weeks, if boosted to sufficiently high levels may provide time-limited, passive protection for newborn infants prior to their first childhood immunizations [19,20]. A review done by Campbell H et al [21] reported that current evidence supports effectiveness of maternal pertussis immunization to protect neonates in settings where pertussis burden is high. However, good epidemiological data are key prior to the introduction of such programmes. A study done by Sartori AMC et al [22] from Brazil, indicate that universal maternal immunization with Tdap is a cost-effective intervention for preventing pertussis cases and deaths in infants in Brazil. One study found that only 37% of pregnant women had anti-pertussis antibodies but after a dose of Tdap, this figure rose to 90% [23], and almost 95% of newborns were born with antibodies. Vaccinating pregnant women appears to be an effective and safe intervention for protecting young infants [24,25].

**Tdap vaccine and its concerns**

The introduction of Tdap in the immunization schedule particularly raises some concerns as a highly vulnerable population is at the receiving end i.e. the pregnant females. ACIP acknowledged that the safety of Tdap immunisation during pregnancy has not been systematically studied, with the only data available coming from small studies, postmarketing surveillance and the US Vaccine Adverse Event Reporting System (VAERS) [26]. The study done by Petousis-Harris et al [27], reveals that the vaccine is safe and is not likely to cause a serious adverse event in pregnancy. Another study reported that birth weight, gestational age at birth, congenital anomalies or infant growth of a birth cohort born to mothers receiving Tdap vaccine was not different from that of the baseline population and in addition no cases of pertussis occurred in this cohort despite high rates of disease in the community [28]. A study by Desilva M et al [29], concluded that despite of an observed association between maternal Tdap vaccination and maternal chorioamnionitis, there were no clinically significant infant outcomes associated with maternal chorioamnionitis. Other studies have also reported that the Tdap vaccine does not raise any safety concerns [26,30-33].

Another concern about Tdap is vaccine cost ($64 per dose of Tdap as compared to $0.01 per dose of TT). However, cost effective analysis in varied settings have shown vaccination with Tdap in adolescence and pregnancy saves money in terms of DALYs being averted or QALYs being saved [34,35].

**Pertussis burden in India and way forward**

Data on exact burden and incidence of pertussis in the developing countries including India is sparse. A study done by Koh MT et al [36] on seroprevalence of pertussis in Asian countries like Malaysia, Taiwan and Thailand reported that more than 5% of patients having chronic cough had pertussis and it should be considered an etiology in such patients in absence of other diseases. A study done by Son S et al [37] reported that there is significant circulation of B. pertussis amongst Asian children and adolescents, with one in 20 having serologic evidence of recent infection regardless of vaccination background. A study done in a premier institute in Delhi, limited by a small number of study subjects, demonstrated ongoing circulation of *B. pertussis* in India [38]. Although few data are available describing the epidemiology of pertussis disease in Asian countries, the available evidence suggests that, as in other countries with high pertussis vaccine coverage in infants and young children, pertussis continues to circulate in adolescents and adults [39]. In Mexico City, 32.8% of adolescents who had a cough for more than 14 days tested positive for pertussis, with the potential to transmit the disease [40]. Around 22,616 cases of pertussis were reported in India in 2006 [30]. This probably reflects a fraction of actual disease incidence as DPT3 coverage in India is only 55% and coverage with the 1st and 2nd booster is even lower [41]. There is no data on incidence of adolescent and adult pertussis in India.

There is definitely a need for larger serosurveys among adults defining the disease burden [42].

Indian Academy of Pediatrics (IAP) recommends offering Tdap vaccine instead of Td/TT vaccine to all children/ adolescents who can afford to use the vaccine at the age of 10-12 yrs [43]. Administering Tdap to pregnant women with the aim of intensifying the transfer of antibodies to the child also seems appropriate [44,45]. The Global Pertussis Initiative recommends that acellular pertussis immunization in pregnancy should be implemented as a priority in all lower and middle income countries if resources allow, given that protection against disease and death due to pertussis in neonates is a key priority [46]. However, good quality serosurveillance studies should be conducted before introducing Tdap in India.

**Key messages:** Pertussis is a vaccine-preventable disease that demands our due attention as it is a major cause of mortality in neonates. The epidemiology of the disease has changed with adolescents and adults acting as reservoirs, and there is evidence of high rate of serious disease and death in young infants. The repeated outbreaks of pertussis even in highly-vaccinated populations are also a matter for grave concern. Administering Tdap to adolescents and pregnant women seems appropriate.

**References:**

1. Jayakrishnan T. Newer vaccines in the Universal Immunisation Programme. Indian  
   J Med Ethics. 2011 Apr-Jun;8(2):107-12.
2. Jayachandran N. India moves to Tetanus-Diphtheria vaccine, instead of only Tetanus, on WHO guideline. The News Minute: Vaccines [newspaper on the internet]. 2018 Aug 15 [cited 2019 Jan 2]. Available from: <https://www.thenewsminute.com/article/india-moves-tetanus-diphtheria-vaccine-instead-only-tetanus-who-recommendation-86614>
3. World Health Organization. Tetanus vaccine: WHO position paper. Weekly Epidemiol Rec. 2006;81:198-207.
4. World Health Organization. Diphtheria vaccine: WHO position paper. Weekly Epidemiol Rec. 2006;81:24-32.
5. Vashishtha VM. Tetanus Vaccine in UIP in India-Reply. Indian Pediatr. 2012 Jan 16;49:70-1.
6. Villarreal Pérez JZ, Ramírez Aranda JM, de la O Cavazos M, Zamudio Osuna MJ,  
   Perales Dávila J, Ballesteros Elizondo MR, et al. Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. Hum Vaccin Immunother. 2017 Jan 2;13(1):128-35.
7. Mehta PN. Protection against Pertussis. Indian Pediatr. 2016;53:679-83.
8. Edwards KM. Overview of pertussis: focus on epidemiology, sources of infection, and long term protection after infant vaccination. Pediatric Infectious Disease Journal 2005; 24 (6 Suppl.): S104–8.
9. Winter K, Harriman K, Zipprich J, Schechter R, Talarico J, Watt J, et al.  
   California pertussis epidemic, 2010. J Pediatr. 2012 Dec;161(6):1091-6.
10. de Greeff SC, de Melker HE, Westerhof A, Schellekens JF, Mooi FR, van Boven M.  
    Estimation of household transmission rates of pertussis and the effect of  
    cocooning vaccination strategies on infant pertussis. Epidemiology. 2012  
    Nov;23(6):852-60.
11. Kwon HJ, Yum SK, Choi UY, Lee SY, Kim JH, Kang JH. Infant pertussis and  
    household transmission in Korea. J Korean Med Sci. 2012 Dec;27(12):1547-51.
12. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap Effectiveness in  
    Adolescents. Pediatrics. 2016 Mar;137(3):e20153326.
13. Acosta AM, DeBolt C, Tasslimi A, Lewis M, Stewart LK, Misegades LK, et al. Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic. Pediatrics. 2015 Jun;135(6):981-9.
14. Walls T, Graham P, Petousis-Harris H, Hill L, Austin N. Infant outcomes after   
    exposure to Tdap vaccine in pregnancy: an observational study. BMJ Open. 2016 Jan  
    6;6(1):e009536.
15. Dempsey AF, Brewer SE, Sevick C, Pyrzanowski J, Mazzoni S, O'Leary ST. Tdap  
    vaccine attitudes and utilization among pregnant women from a high-risk  
    population. Hum Vaccin Immunother. 2016 Apr 2;12(4):872-8.
16. Tanaka M, Vitek CR, Pascual FB, Bisgard KM, Tate JE, Murphy TV. Trends in pertussis among infants in the United States, 1980–1999. JAMA 2003;290:2968–75.
17. Centers for Disease Control and Prevention Pertussis: Clinical Complications. 2015. Acced on 2019 Jan 31. Available from: <https://www.cdc.gov/pertussis/clinical/complications.html>
18. Centers for Disease Control and Prevention 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.
19. van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis 1990;161:487–92.
20. Healy CM, Baker CJ. Prospects for prevention of childhood infections by maternal immunization. Curr Opin Infect Dis 2006;19:271–6.
21. Campbell H, Gupta S, Dolan GP, Kapadia SJ, Kumar Singh A, Andrews N,  
    et al. Review of vaccination in pregnancy to prevent pertussis in early infancy. J Med Microbiol. 2018 Oct;67(10):1426-56.
22. Sartori AMC, de Soárez PC, Fernandes EG, Gryninger LCF, Viscondi JYK, Novaes  
    HMD. Cost-effectiveness analysis of universal maternal immunization with  
    tetanus-diphtheria-acellular pertussis (Tdap) vaccine in Brazil. Vaccine. 2016  
    Mar 18;34(13):1531-9.
23. Vilajeliu A, Goncé A, López M, Costa J, Rocamora L, Ríos J, et al. Combined tetanus-diphtheria and pertussis vaccine during pregnancy: transfer of maternal pertussis antibodies to the newborn. Vaccine. 2015;33:1056-62.
24. 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;60:333-7.
25. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway A, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA. 2014;312:1897-904.
26. Zheteyeva YA, Moro PL, Tepper NK, Rasmussen SA, Barash FE, Revzina NV, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol. 2012 Jul;207(1):59.e1-7.
27. Petousis-Harris H, Walls T, Watson D, Paynter J, Graham P, Turner N. Safety of  
    Tdap vaccine in pregnant women: an observational study. BMJ Open. 2016 Apr  
    18;6(4):e010911.
28. Walls T, Graham P, Petousis-Harris H, Hill L, Austin N. Infant outcomes after   
    exposure to Tdap vaccine in pregnancy: an observational study. BMJ Open. 2016 Jan  
    6;6(1):e009536.
29. DeSilva M, Vazquez-Benitez G, Nordin JD, Lipkind HS, Klein NP, Cheetham TC,  
    et al. Maternal Tdap vaccination and risk of infant morbidity. Vaccine. 2017 Jun  
    22;35(29):3655-60.
30. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway  
    AL, et al. Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007-2013. Vaccine. 2016 Feb 10;34(7):968-73.
31. Shakib JH, Korgenski K, Sheng X, Varner MW, Pavia AT, Byington CL. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: pregnancy and infant health outcomes. J Pediatr 2013; 163:1422-6
32. Layton JB, Butler AM, Li D, Boggess KA, Weber DJ, McGrath LJ, Becker-Dreps S.   
    Prenatal Tdap immunization and risk of maternal and newborn adverse events.  
    Vaccine. 2017 Jul 24;35(33):4072-8.
33. Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, 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 May 7;311(17):1760-9.
34. Hoshi SL, Seposo X, Okubo I, Kondo M. Cost-effectiveness analysis of pertussis  
    vaccination during pregnancy in Japan. Vaccine. 2018 Aug 16;36(34):5133-40.
35. Kamiya H, Cho BH, Messonnier ML, Clark TA, Liang JL. Impact and  
    cost-effectiveness of a second tetanus toxoid, reduced diphtheria toxoid, and  
    acellular pertussis (Tdap) vaccine dose to prevent pertussis in the United  
    States. Vaccine. 2016 Apr 4;34(15):1832-8.
36. 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 Apr;144(6):1192-200.
37. Son S, Thamlikitkul V, Chokephaibulkit K, Perera J, Jayatilleke K, Hsueh PR,  
    et al. Prospective multinational serosurveillance study of Bordetella pertussis infection among 10- to 18-year-old Asian children and adolescents. Clin Microbiol Infect. 2018 Apr 22. pii: S1198-743X(18)30351-3.
38. Dahiya S, Kapil A, Kabra SK, Mathur P, Sood S, Lodha Ret al. Pertussis in  
    India. J Med Microbiol. 2009 May;58(Pt 5):688-9.
39. Chiu TF, Lee CY, Lee PI, Lu CY, Lin HC, Huang LM. Pertussis seroepidemiology  
    in Taipei. J Formos Med Assoc. 2000 Mar;99(3):224-8.
40. Sandoval PT, Arreola L del P, Quechol GR, Gallardo HG.. [Bordetella pertussis em estudantes adolescentes da Cidade do México]. Rev Saúde Publica 2008; 42:679-683.
41. Sirivichayakul C, Chanthavanich P, Limkittikul K, Siegrist CA, Wijagkanalan W,  
    Chinwangso P, et al. Safety and immunogenicity of a combined Tetanus, Diphtheria, recombinant acellular Pertussis vaccine (TdaP) in healthy Thai adults. Hum Vaccin Immunother. 2017 Jan 2;13(1):136-43.
42. Kulkarni PS, Raut SK, Dhorje SP, Barde PJ, Koli G, Jadhav SS. Diphtheria,  
    tetanus, and pertussis immunity in Indian adults and immunogenicity of td  
    vaccine. ISRN Microbiol. 2011 Dec 28;2011:745868.
43. Vashishtha VM, Choudhury P, Kalra A, Bose A, Thacker N, Yewale VN, Bansal CP, Mehta PJ; Indian Academy of Pediatrics. Indian Academy of Pediatrics (IAP)recommended immunization schedule for children aged 0 through 18 years--India, 2014 and updates on immunization. Indian Pediatr. 2014 Oct;51(10):785-800.
44. Center for Disease Control and Prevention, CDC Feature. Diseases. Help Protect Babies from Whooping Cough. Accesed on 2019 Jan 31. Available from: <http://www.cdc.gov/Features/Pertussis/>
45. Centers for Disease Control and Prevention . 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. (CDC). MMWR Morb Mortal Wkly Rep 2013; 62:131-5.
46. Forsyth KD, Tan T, von König CW, Heininger U, Chitkara AJ, Plotkin S.  
    Recommendations to control pertussis prioritized relative to economies: A Global   
    Pertussis Initiative update. Vaccine. 2018 Nov 19;36(48):7270-5.