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Original Research Article

# Are Early Infants Adequately Protected against Pertussis: An Experience from a Tertiary Care Centre in India

**Niranjan Sahoo[1], Ritu Agarwal[2], Gururaja R[3], Deeksha Katoch[4]**

[1]Graded Specialist Pediatrics, Military Hospital Bhopal, Madhya Pradesh, India
[2]Professor and HOD, Department of Pediatrics, Military Hospital, Dehradun, India
[3]Assistant Professor, Department of Pediatrics, Command Hospital, Lucknow, India
[4]Paediatric Haematology/Oncology/BMT, Yale School of Medicine, New Haven, Connecticut, USA

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**Corresponding Author: Dr. Niranjan Sahoo**
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**Abstract:**

**Introduction:** Infants younger than 6 months are the most vulnerable to severe pertussis. Efforts at national level have been aimed to reduce the infant mortality associated with pertussis. We aimed to determine the proportion of infants who have protective levels of serum anti-Pertussis IgG antibody levels at birth.

**Methodology:** We conducted a cross-sectional observational study at the Department of Pediatrics at Base Hospital, New Delhi using cord blood of term babies, weighing 2.5 kgs or more to measure anti-pertussis antibody levels. Based on antibody titer, neonates were classified as fully protected (titer > 100 IU/ml), some protection (40 to 100 IU/ml) and no protection (< 40 IU/ml). We also collected data on maternal vaccination history and other variables.

**Results:** The mean anti-pertussis antibody level was 39.93 ± 12.27 IU/ml, ranging from 0 to 280.7 IU/ml. Only 11% of the neonates were fully protected (> 100 IU/ml), 21.5% had some level of protection (40 to 100 IU/ml) and 67.5% were not protected at all (< 40 IU/ml). Among fully protected neonates, mothers of 86.4% had a history of Tdap immunization, and the rest 13.6% had a history of TT immunization. Mean anti-pertussis antibody levels were 117.42 ± 46.38 IU/ml, ranging from 77.38 to 280.7 IU/ml in neonates whose mothers received Tdap immunization, which were significantly higher than neonates of mothers who did not receive Tdap.

**Conclusion:** We concluded that most of the infants had nil to minimal levels of IgG anti-pertussis antibody making them susceptible to severe pertussis infection before the first dose of vaccination. Tdap vaccination of mothers should be promoted and should be included in the national immunization schedule of India. Future studies assessing maternal sera and cord blood pairs are required to show that maternal antibody is actively transferred thereby significantly elevating newborn levels.

**Keywords:** Maternal vaccination, Tdap in pregnancy, Pertussis.



## Introduction

Pertussis is an underdiagnosed bacterial respiratory infection affecting all age groups. Infants have the highest rates of hospitalization and deaths due to pertussis with the majority occurring in infants less than 3 months. [1,2,3] Incidence of pertussis is on rise despite high vaccine coverage. Many strategies are being implemented to reduce the burden including immunization of pregnant women with acellular pertussis vaccine (aP). Till the infant is immunized, this TdaP vaccination provides protection to the neonate through passive transport of maternal IgG anti pertussis antibodies.

During an outbreak in California in 2015, a comparison was done between 53 fatal and 183 non-fatal hospitalized cases and risk factors for fatal pertussis in infants were analysed. [4] Fatal cases had significantly younger gestational age, lower birth weight, earlier disease onset and high lymphocyte counts. To ascertain the pathogenesis of fatal pertussis in young infants, an autopsy series of 15 infants revealed intra-alveolar hemorrhage, necrotizing bronchiolitis and fibrinous edema in the lungs.[5]

There has been a resurgence of pertussis in India as well. 145,486 cases of pertussis were reported globally and 11,875 cases from India in 2019. [6,7] Better modalities of surveillance and more sensitive diagnostic lab tests like ELISA and PCR, can be attributable for this resurgence. Most widely available diagnostic pertussis PCR assays are not species-specific, as they use only fewer targets.[8] This resurgence also indicates that current immunization schedules are not sufficient to provide immunity against the disease due to waning

immunity, along with deficient natural boosting because of termination of wild organism circulation in high vaccine coverage areas. As the earliest immunisation is at 6 weeks of age, infants do not form their own antibodies against pertussis until nearly 2 months of age. [9] This period becomes vulnerable for young infants, many of whom may get transmitted serious pertussis infections from primary caregivers and family members. [10]

As young infants are entirely dependent on maternal antibodies due their inability to mount a cell-mediated immunity, vaccination of pregnant women with Pertussis during pregnancy has recently been recommended to provide protection to infants from Pertussis until they get their first dose of immunization. In June 2011, the Advisory Committee on Immunization Practices recommended that pregnant women should receive a single dose of Tdap, [11] following which Indian Academy of Pediatrics (IAP) in 2014 recommended immunization of pregnant women with a single dose of Tdap in each pregnancy. [12] The present study was done to assess the anti-Pertussis antibody levels in infants at birth and to assess the proportion of neonates having protective immunity against pertussis.

## Material and Methods

The study was an observational cross-sectional study which was done in the Department of Paediatrics of a teaching hospital of the Armed Forces of India. All the babies born in the period from June 2019 till May 2021 were taken into consideration. 200 term neonates born weighing more than 2.5 kgs were included in the study. Exclusion criteria included all preterms, low birth weight, sick babies requiring resuscitation at birth, having birth defects, any underlying neurological, cardiac, renal, or pulmonary disease in either mother or neonate.

Maternal data included age, parity, blood group with Rh, previous history of any neonatal deaths, history of infection and history of any comorbidities like Gestational Hypertension, Gestational Diabetes or Hypothyroidism, history of TdaP/TT immunization in this pregnancy and COVID status of mother during delivery (during the pandemic period). Neonatal data like sex, birth weight, gestational age and APGAR score were also noted.

After taking written informed consent from the parents, the mother was observed during the delivery. Soon after delivery of the neonate, umbilical cord was clamped and a sterile umbilical cord clamp was clamped 2-3 cm from the abdomen and umbilical cord was cut. 3 ml of cord blood was collected in a sterile vacutainer and sent for sampling.

The anti-pertussis antibody levels were calculated from the cord blood using ELISA technique. Serum Anti Pertussis IgG level of more than 40 IU/ml was taken as positive that is protective immunity status in the newborn against pertussis. It is based on the instruction manual provided by the manufacturer of the SeroPertussis™ Toxin IgG kit, Savyon Diagnostics Ltd. For this study, we considered the following cut-offs for protection levels:

Fully protected: > 100 IU/ml

Some protection: 40 to 100 IU/ml

No protection: < 40 IU/ml

### Statistical Analysis

The study involved examining the characteristics of patients based on various maternal and neonatal clinical factors along with laboratory parameters. Descriptive analysis of quantitative parameters was summarized using means and standard deviation, while ordinal data were presented as absolute numbers and percentages.

All neonates were divided based on their anti-pertussis protection level in their cord blood. Cross tables were generated and chi square or Fisher's exact test was used for testing of associations. Student t test was used for comparison of means.

Comparison of three or more means was done using analysis of variance test (ANOVA), with post hoc Bonferroni test. A p-value < 0.05 is considered statistically significant. All analyses were done using SPSS software, version 24.0.

## Results

**Table 1: Distribution of patients according to anti-pertussis antibody protection level**

| Anti-pertussis antibody protection level | Frequency | Percent |
|---|---|---|
| Fully protected (> 100 IU/ml) | 22 | 11 |
| Some protection (40 to 100 IU/ml) | 43 | 21.5 |
| No protection (< 40 IU/ml) | 135 | 67.5 |
| Total | 200 | 100 |

In the present study, 200 neonates were included. The mean anti-pertussis antibody level was 39.93 ± 12.27 IU/ml, ranging from 0 to 280.7 IU/ml. Based on the cut-offs, it was found that 11% of the neonates were fully protected (> 100 IU/ml), 21.5% had some level of protection (40 to 100 IU/ml) and 67.5% were not protected at all (< 40 IU/ml).

**Table 2: Distribution of patients according to anti-pertussis antibody protection level according to maternal and neonatal risk factors**

| | Risk factors | Total (n=) | Protective Anti Pertussis Ab levels | | | P value |
|---|---|---|---|---|---|---|
| | | | Fully protection | Some protection | No protection | |
| **A** | **Maternal Factors** | | | | | |
| 1 | Maternal Age | | | | | |
| | Up to 20 | 8 | 2 | 2 | 4 | 0.42 |
| | 21 to 30 | 157 | 16 | 35 | 106 | |
| | 31 to 40 | 33 | 3 | 6 | 24 | |
| | More than 40 | 2 | 1 | 0 | 1 | |
| 2 | Gravida of mother | | | | | |
| | Primigravida | 91 | 10 | 17 | 64 | 0.66 |
| | Multigravida | 109 | 12 | 26 | 71 | |
| 3 | Blood group of mother | | | | | |
| | A | 41 | 3 | 9 | 29 | 0.32 |
| | AB | 20 | 4 | 3 | 13 | |
| | B | 67 | 7 | 10 | 50 | |
| | O | 72 | 8 | 21 | 43 | |
| 4 | Rh status of mother | | | | | |
| | Negative | 25 | 2 | 4 | 19 | 0.62 |
| | Positive | 175 | 20 | 39 | 116 | |
| 5 | Maternal History of Neonatal death | | | | | |
| | No | 170 | 20 | 37 | 113 | 0.66 |
| | Yes | 30 | 2 | 6 | 22 | |
| 6 | Maternal history of infection | | | | | |
| | No | 184 | 20 | 39 | 125 | 0.91 |
| | PROM | 16 | 2 | 4 | 10 | |
| 7 | Maternal co-morbidities (GHTN,GDM,Hypothyroidism) | | | | | |
| | No | 112 | 14 | 23 | 75 | 0.72 |
| | Yes | 88 | 8 | 20 | 60 | |
| 8 | Maternal immunisation | | | | | |
| | TdaP | 30 | 19 | 11 | 0 | <0.001 |
| | TT | 162 | 3 | 32 | 127 | |
| | Unknown history | 8 | 0 | 0 | 8 | |
| 9 | COVID Status of mother | | | | | |
| | Negative | 180 | 22 | 41 | 117 | 0.06 |
| | Positive | 20 | 0 | 2 | 18 | |
| B | **Neonatal Factors** | | | | | |
| 1 | APGAR Score at 1 min | | | | | |
| | 4 to 6 | 4 | 1 | 3 | 0 | <0.05 |
| | 7 to 10 | 196 | 21 | 40 | 135 | |
| 2 | APGAR Score at 5 min | | | | | |
| | 4 to 6 | 0 | 0 | 0 | 0 | NA |
| | 7 to 10 | 200 | 22 | 43 | 135 | |
| 3 | Gender of neonate | | | | | |
| | Female | 98 | 8 | 19 | 71 | 0.28 |
| | Male | 102 | 14 | 24 | 64 | |

In this study, 15% of the mothers had received Tdap, 81% had received TT and 4% were not aware of their immunization history.

It was observed that among fully protected neonates (n=22), mothers of 86.4% had a history of Tdap immunization, and the rest 13.6% had a history of TT immunization.

Among neonates with some level of anti-pertussis protection (n=43), mothers of 25.6% had a history of Tdap immunization, and the rest 74.43% had a history of TT immunization. Among 30 mothers who received Tdap, 63.3% of their neonates developed full protection (anti-pertussis antibody level > 100 IU/ml) and 36.7% developed some protection with anti-pertussis antibody (40 to 100 IU/ml). Among those mothers who received TT immunization, only 1.85% of neonates developed

full protection, while 19.7% developed some level of protection and 78.3% developed no protective antibody levels.

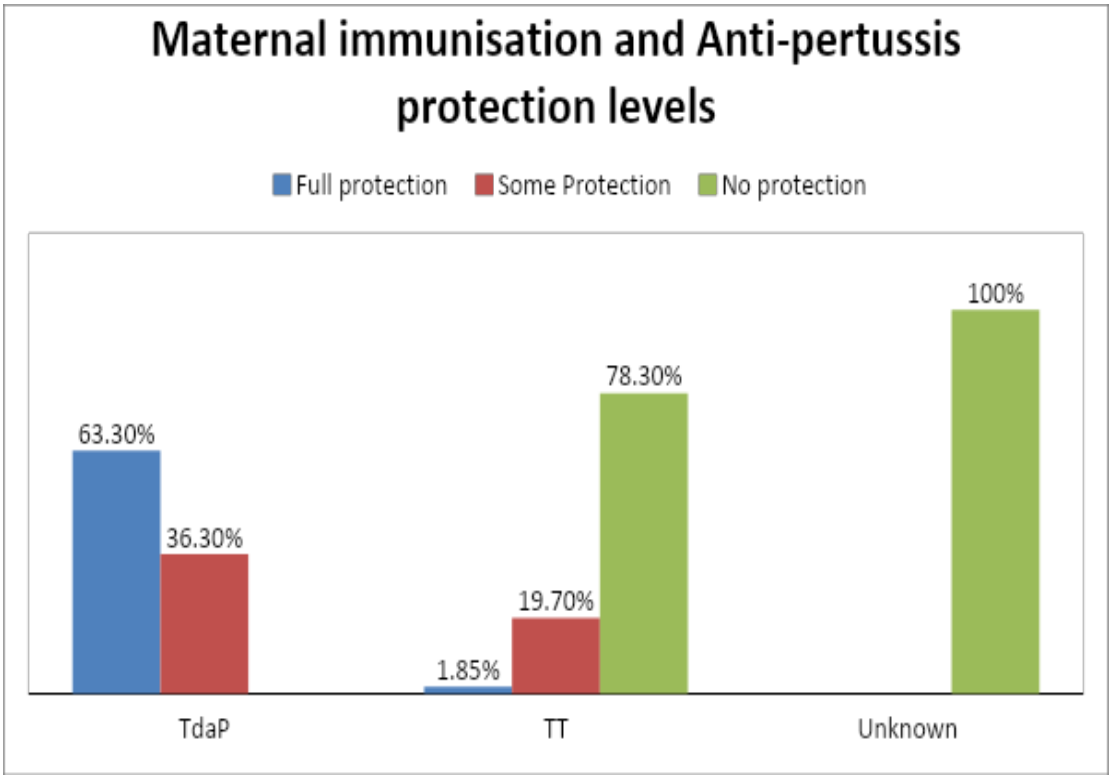


**Figure 1: Maternal immunisation and anti-pertussis protection levels**

The association between Tdap immunization of mother and neonate developing protective anti-pertussis antibody level was statistically highly significant (p value < 0.001).

**Table 3: Mean anti-pertussis antibody levels according to maternal immunization status**

| Immunization status | Mean antibody (IU/ml) | Std. Deviation | 95% CI for Mean | | Minimum | Maximum | p value* |
|---|---|---|---|---|---|---|---|
| | | | Lower Bound | Upper Bound | | | |
| Tdap | 117.42 | 46.38 | 100.11 | 134.74 | 77.38 | 280.70 | < 0.001 |
| TT | 27.18 | 21.98 | 23.77 | 30.59 | 0.00 | 103.10 | |
| Unknown | 7.63 | 2.21 | 0.00 | 15.33 | 0.00 | 23.59 | |
| Total | 39.93 | 42.27 | 34.04 | 45.83 | 0.00 | 280.70 | |

## Discussion

The findings of our study provide valuable insight into immunization status of pregnant mothers and the resulting antibodies levels in neonates in the Indian context. Our results indicate that in the antenatal period, a considerable proportion of mothers (81%) is still receiving tetanus toxoid vaccination only. Since 2011, the American College of Physicians (ACIP) has recommended immunization of pregnant women with Tdap vaccine in each pregnancy preferably in early third trimester. [13] In 2013, in their position paper on pertussis vaccines, the Indian Academy of Pediatrics (IAP) also reiterated the ACIP recommendations with maternal immunization with Tdap in the third trimester as an effective approach to protect neonates from pertussis. [12] Despite longstanding recommendations, Tdap immunization remains low, with the Centers of Disease (CDC) reporting only 44% of women receiving Tdap in the 2021-22 seasons. [14] Data for maternal immunization are not available for the Indian population, but our study shows similar findings albeit in a smaller sample size. A major factor for the poor uptake of Tdap vaccination could be that the national program for immunization in India still recommends tetanus-diptheria (Td) immunization for pregnant women. It is worth noting that 4% of mothers in our study were unaware of their immunization history, highlighting the importance of improving awareness and documentation of immunization records.

Our study utilized the anti-pertussis IgG cutoff

levels for pertussis protection as provided by SeroPertussisTM Toxin IgG kit by Savyon Diagnostics Ltd. [15] Similar cut-offs were used by Meng and colleagues in their study to determine level of protective immunity against preventable diseases using paired maternal and cord blood sera (n= 194). [16] Using these cutoffs in a Women and Children's Hospital in Beijing, the authors found that 97.4% infants had no protection against pertussis.

In a separate investigation, Healy et al. determined the levels of anti-pertussis toxin antibodies in cord blood samples taken from newborns whose mothers have received Tdap vaccination during pregnancy, comparing them to those born to mothers who had not been vaccinated. [17] The study encompassed 626 neonates, with 312 born to Tdap-vaccinated mothers and 314 born to unvaccinated mothers. The findings demonstrated that infants born to Tdap-vaccinated mothers exhibited anti-pertussis toxin antibodies concentrations of 15 IU/mL or more, surpassing the levels born to Tdap-unvaccinated mothers.

Using similar cut-offs in an Indian setting, James et al also reported only 14.3% newborns (23/160) to have full protective antibody levels against pertussis while 58.8% had anti-pertussis toxin (PT) levels less than 40 U/ml. [18] In their study, however, maternal immunization data were not provided.

We also observed that among fully protected neonates (n=22), 86.4% had maternal history of Tdap immunization while 13.6% had a history of TT immunization. The association between Tdap immunization of mother and neonate developing protective anti-pertussis antibody level was statistically highly significant (p value < 0.001). The mean anti-pertussis antibody levels were 117.42 ± 46.38 IU/ml in neonates whose mothers received Tdap immunization. There is a definite role of natural infection and herd immunity that might explain infants fully protected against pertussis despite maternal immunization with TT only.

Among 30 mothers who received Tdap, 36.7% infants developed only some protection with anti-pertussis antibody (40 to 100 IU/ml). We did not have data on gestational age at maternal immunization; however immunizations in early trimesters could have been a reason of low levels of protective level of antibodies in these infants. Conversely, among neonates with some level of anti-pertussis protection, a larger proportion of mothers had received TT (74.43%) compared to Tdap (25.6%). This reflects the wide uptake of TT immunization in maternal immunization however, it is difficult to determine whether equivocal levels of anti-pertussis protection (in our study, between 40-100 U/ml) will provide clinically significant levels of immunity to infants.

Other strategies to prevent neonatal pertussis transmission have also been studied. Cocooning involves administering Tdap to the mother and all close contacts of the infant before hospital discharge. There is limited evidence for cocooning to decrease transmission and logistical and cost barriers add to the challenges of its widespread implementation especially in low and middle income countries.[19] [20] There have also been concerns that a birth dose of DTaP could suppress the effect of a subsequent infant and childhood vaccination doses. [21] Maternal immunization with Tdap offers a cost-effective approach to protecting newborns < 3 months from pertussis.

Gall et al determined whether tetanus– diphtheria–pertussis vaccination (Tdap) in pregnancy provides newborn antibodies against pertussis when compared to mothers who did not receive Tdap. [22] In their study, there was a significant increase in the odds that newborns from mothers who received Tdap during pregnancy were protected against pertussis based on anti-PT (88.5% vs 40.4%; OR, 11.32; 95% CI, 4.10–31.24; p value < 0.0001) compared to newborns from mothers who did not receive Tdap during pregnancy.

Our results also highlight the potential benefits of maternal Tdap immunization in conferring robust anti-pertussis protection to neonates. The higher proportion of neonates with full protection and the lower percentage of neonates with no protective antibody levels among mothers who received Tdap impress upon the superiority of Tdap in stimulating a more effective immune response.

While the results provide valuable insights, it is important to acknowledge certain limitations of this study. This was a single center study with a relatively small sample size, which may limit the generalizability of the findings. Additionally, the study did not include maternal sera as well as gestational age at maternal immunization. Long term follow-up of infants is also required to assess the disease frequency in fully and partially protected infants. Future studies with larger sample sizes and more robust methodologies, such as serological confirmation of maternal immunization status, would be beneficial to expand upon our findings.

## Conclusion

Our study concludes that maternal immunization with Tdap is an effective measure to boost protective levels of anti-pertussis antibody in neonates. As the adherence to COVID masking and isolation measures wanes, we can anticipate a surge in pertussis incidence. We must urgently prioritize the widespread adoption of the IAP's position paper on maternal immunization with a single dose of Tdap during the third trimester to decrease neonatal pertussis transmission.

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