

# Safety of tetanus toxoid in pregnant women: a hospital-based case-control study of congenital anomalies

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*Reported are the results of the Latin American Collaborative Study of Congenital Malformations (ECLAMC), a hospital-based case-control study of 34 293 malformed and 34 477 matched non-malformed newborn controls. No statistical differences were found between the malformed and control groups, exposed or not exposed to tetanus toxoid.*

## Introduction

Globally, about 0.5 million deaths from neonatal tetanus still occur annually. Infants who die from neonatal tetanus are born to women considered to be high-risk mothers for the condition: they live in a periurban or rural area, deliver at home, and are unprotected by vaccine.

By the 1960s the efficacy of tetanus toxoid (TT) in preventing neonatal tetanus had been established (1–3) and the immunization of pregnant women became mandatory worldwide. Subsequently, it was realized that the major burden of this strategy lay in contacting high-risk mothers and vaccinating them during the recommended period of pregnancy.

The fear of potentially deleterious effects to the fetus if TT is not administered during the recommended period has been one of the reasons for missed opportunities in vaccinating women of child-bearing age.<sup>a</sup> Because high-risk mothers are hard to reach, every opportunity for vaccination should be considered unique. Nevertheless, it is not an easy decision for a physician to make, especially since there is very limited information on the safety of TT administered during early pregnancy.

The present article provides data on the use of TT during early pregnancy in Latin America.

## Materials and methods

Information on 34 293 malformed neonates and 34 477 controls was obtained by the Latin American Collaborative Study of Congenital Malformations (ECLAMC) from physical examinations of 1 282 403 neonates in 173 hospitals in 105 cities throughout nine countries in South America (4). Although the study began in 1967, the hospitals that comprise ECLAMC joined at different times; therefore, the periods covered by the data provided by ECLAMC hospitals are not identical.

ECLAMC represents a hospital-based case-control study of congenital anomalies and their associated risk factors in South America. The working definitions were determined in advance. Before being accepted, monthly data collected from participating hospitals are checked for compliance with quality control standards. Following procedures provided to them in an instruction manual, paediatricians document detailed descriptions of all congenital anomalies observed; they also maintain records on antenatal, perinatal, and family history data. This practice ensures the consistency of the data and of the hospitals recording and reporting births and malformations. The information collected was obtained from a physical examination of the newborn and a history taken from the mother within 2 days after delivery. For each malformed newborn, an identical record was kept for a nonmalformed baby of the same sex, born in the same hospital immediately after the birth of the malformed child. This approach provided a one-to-one matched control group paired by sex, time, and place of birth with the cases.

The case distribution was calculated per year and by country. Information on the vaccines received by the mothers during the first 3 months of preg-

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nancy was among that on 50 risk factors regularly ascertained for cases and controls. Exposure to TT was recorded as "yes", "no" or "not specified". The data presented here refer to those countries included in ECLAMC. Details about the ECLAMC methodology have been published elsewhere (4, 6).

Of 300 distinct or generic diagnostic categories that were recorded for the 34 293 malformed infants in this sample, those that had a low frequency were excluded from the statistical analyses.

The odds ratios and 95% confidence limits were calculated for TT exposure. Only those malformations that had at least 1000 cases-control pairs were analysed. A total of ten types of malformation fulfilled this criterion. Use of such large sample sizes enabled us to determine whether there was a true difference in relative risk — the risk for cases was required to be three times larger than that for controls (7, 8). For the analysis of the aggregated data for cases and controls, a probability of 95%, a power test of 80%, and an exposure rate of 9 per 1000 were used in testing the TT risk factor.

An  $\alpha$  value of 0.01 was used to compare the ten most frequent malformation types (9, 10).<sup>b</sup>

Statistical significance was determined using McNemar's test (7) with a  $\chi^2$  test (1 degree of freedom).

<sup>b</sup> Application of the significance test once with  $\alpha = 0.05$  means that the chance of not finding an association is 0.95. If the significance test is applied 10 times, the chance of not finding an association decreases from 0.95 to 0.59 ((0.95)<sup>10</sup>), which is too small to be used in the present study. We therefore used  $\alpha = 0.01$  with the chance of not finding any association being 0.90 = (0.99)<sup>10</sup>.

Table 1: Malformation among cases and controls of mothers exposed to tetanus toxoid, South America, 1967-89

Exposed to tetanus toxoid	No. malformed	No. of controls	Total
Yes	317	261	578
No	33 976	34 216	68 192
Total	34 293	34 477	68 770

## Results

A total of 69 751 mothers of cases and controls were interviewed during the puerperal period. The number of cases ( $n = 34\ 908$ ) and controls ( $n = 34\ 843$ ) were not equal because cases who were stillborn did not have matched controls. Furthermore, since TT data were missing for 615 cases and 366 controls, the effective totals were 34 293 cases and 34 477 controls (Table 1).

The average TT exposure rate was 9.24/1000 live births (confidence interval (CI) = 8.23 – 10.26) for cases and 7.57/1000 live births (CI = 6.64 – 8.50) for controls. The aggregate data analysis revealed no significant difference in exposure rate between cases and controls at an  $\alpha$  value of 5%.

The various types of malformation presented in Table 2 identify only the ten commonest specific types. Analyses of these data failed to find any significant difference for a mean odds ratio of 3 and a  $\chi^2$  test (1 degree of freedom) at an  $\alpha$  value of 1%.

Table 2: Exposure rates to tetanus toxoid for the 10 most frequent malformation types, South America, 1967-89

Malformation type	Exposed case/ unexposed control	Unexposed case/ exposed control	Effective No. of pairs	Mean odds ratio	$\chi^2$ test
Cleft lip	9	4	1 056	2.25 (0.69–7.30) <sup>a</sup>	1.92
Pes equinovarus	19	15	1 648	1.27 (0.64–2.49)	0.47
Postaxial polydactyly	31	17	1 697	1.82 (1.00–3.29)	4.08
Hip subluxation	18	13	2 049	1.38 (0.67–2.82)	0.81
Haemangioma	10	16	1 621	0.63 (0.28–1.37)	1.38
Periauricular tag	33	26	3 339	1.27 (0.75–2.12)	0.83
Fistula auris	17	10	1 869	1.70 (0.77–3.71)	1.81
Pigmented naevus	28	30	4 346	0.93 (0.55–1.56)	0.07
Other skin defects	10	5	1 581	2.00 (0.68–5.85)	1.67
Multiple malformed	19	19	2 664	1.00 (0.52–1.88)	0

<sup>a</sup> Figures in parentheses are the 99% confidence interval.

## Discussion

In calling for the elimination of neonatal tetanus by 1995, the World Health Assembly in 1989 paved the way to overcoming political and administrative obstacles to achieving this goal (11). At the practical level, changes also need to be made, mainly in avoiding missed opportunities to vaccinate women of childbearing age, pregnant or not.

It has been stated that there is no convincing evidence that immunizing a pregnant woman with TT poses any risk to the fetus (12, 13); however, there have been no in-depth studies to verify the validity of this statement. Over the past 50 years there have been two studies of the use of TT and the occurrence of neonatal malformations (14, 15).

In the study reported by Freda, two groups of pregnant women were observed, those exposed to TT and those who were not (14). The frequency of complications of pregnancy in the two groups were the same; the limiting factor in this study was the small sample size of 107 subjects in each group.

In the second study, conducted by Heinonen et al., 50 282 mother-child pairs were followed up, of whom 337 pairs of mothers were analysed for their exposure/nonexposure to immunizing agents during the first 4 months of pregnancy. Crude relative risk and standardized relative risks (SRR) were obtained using the Mantel-Haenszel procedure. The 337 children exposed to TT *in utero* during the first 4 months had SRRs of 1.36 and 1.60, for major and minor malformations, respectively. Polydactyly among Blacks had a SRR of 2.32. These findings for polydactyly were considered to be due to chance because of its strong association with African Black ethnicity; polydactyly is strongly influenced by socioeconomic confounders (5). Also, postaxial polydactyly is the most heritable common congenital anomaly, having an etiology involving at least four different genes (6). Further investigation was recommended. The polydactyly in Blacks reported by Heinonen et al. is equivalent to the postaxial polydactyly identified in our study.

In the present study, analysis of each of the 10 most frequent malformations and the aggregated data for 68 770 infants failed to find any statistical association for comparisons of cases and controls either exposed or not exposed to TT.

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## Résumé

### Innocuité de l'anatoxine tétanique chez la femme enceinte: étude cas-témoins hospitalière des anomalies congénitales

Au niveau mondial, près d'un demi-million de décès dus au tétanos néonatal surviennent encore chaque année malgré l'usage généralisé de l'anatoxine tétanique (AT) chez la femme enceinte. La principale stratégie pour éviter ces décès consiste à prendre contact avec les mères les plus exposées et à les vacciner pendant la période recommandée au cours de la grossesse. Les mères fortement exposées sont celles qui habitent des régions rurales et des zones périurbaines, accouchent à domicile et ne sont pas vaccinées. La crainte d'effets préjudiciables possibles pour le fœtus si l'anatoxine tétanique est administrée au cours du premier trimestre de la grossesse est une des raisons qui explique les occasions manquées de vaccination des femmes en âge de procréer.

Le présent article contient des données relatives à l'utilisation de l'AT pendant les premiers mois de grossesse, réunies dans le cadre de l'étude collective latino-américaine des malformations congénitales (ECLAMC), étude cas-témoins des anomalies congénitales et des facteurs de risque associés menée en milieu hospitalier en Amérique du Sud. Les données portent sur un total de 34 293 nouveau-nés malformés et 34 477 témoins appariés. Sur 300 catégories de diagnostic distinctes ou génériques retrouvées chez les 34 293 nouveau-nés malformés de l'échantillon, on a éliminé des analyses statistiques celles qui revenaient le moins fréquemment. La signification statistique a été déterminée au moyen du test de McNemar assorti d'un  $\chi^2$  (1 degré de liberté). L'analyse des données n'a permis de déceler aucune différence significative dans l'incidence des dix malformations les plus fréquentes entre les cas et les témoins, exposés ou non à l'AT (odds ratio moyen de 3,  $\chi^2$ , 1 degré de liberté;  $\alpha = 1\%$ ).

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