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Effectiveness of prenatal tetanus toxoid immunization against neonatal tetanus in a rural area in India

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Background. **Neonatal tetanus is the cause of 23 to 73% of neonatal deaths in developing countries and continues to be an important killer in many parts of India.**

Methods. **In this nonrandomized cohort study in a rural area in India, tetanus toxoid immunization status was recorded for 1688 pregnant women. Liveborn children were followed up for 30 days for the occurrence of neonatal tetanus. Nonimmunized and partially immunized women were asked their reasons for not receiving tetanus toxoid vaccine.**

Results. **Complete prenatal immunization with tetanus toxoid during pregnancy (two doses 1 month apart) was associated with an 88% reduction in the risk of neonatal tetanus among the newborn children [95% confidence interval (CI) 59 to 98%]. In multivariable analysis only complete immunization and the use of clean instruments for cutting the umbilical cord were independently associated with a reduction in risk of neonatal tetanus. Registration by the health care provider before 29 weeks of gestation, being 5 km or less from the vaccination facility, having two or more contacts with the health provider and having some school education were independently associated with complete immunization.**

Conclusions. **Immunization of pregnant women with tetanus toxoid was the single most effective intervention against neonatal tetanus independent of other interventions.**

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Key words: Neonatal tetanus, prenatal immunization, tetanus toxoid, barriers to vaccination, India.

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INTRODUCTION

In developing countries, including India, neonatal tetanus continues to be an important killer in childhood. More than 400 000 deaths occur annually, with ~20% of these occurring in India.[1, 2] Neonatal tetanus is the cause of 23 to 73% of all neonatal deaths,[3–7] and accounts for 25 to 30% of deaths in the first year of life.[8–10] In 1989 the World Health Organization (WHO) set a goal of eliminating neonatal tetanus by 1995.[11]

Prenatal immunization of pregnant women with two doses of tetanus toxoid and promotion of aseptic care of the umbilical cord were the two main elements of the elimination strategy.

In India the effectiveness of prenatal tetanus toxoid immunization has not been previously evaluated with a well-designed field-based study. The present study was designed to assess the effectiveness of a community-based intervention against neonatal tetanus in a rural area in Rajasthan. This is a report of vaccination effectiveness and factors influencing tetanus toxoid immunization coverage during pregnancy.

METHODS

This was a nonrandomized cohort study supplemented by a retrospective survey using in person interviews.

Population. This project was undertaken in the Phagi block of the Jaipur district in Rajasthan by the Indian Institute of Health Management Research (IIHMR). The project area included 44 villages with a population of >30 000. All pregnant women were identified by auxiliary nurse midwives, traditional birth attendants and field investigators during monthly household visits in each village. These women were then invited to attend the maternal and child health clinics at the health center. Women failing to attend were recontacted at home. Details of delivery and pregnancy outcome were recorded. For this study live-born children born between June, 1988, and May, 1990, were followed for 30 days after delivery. We identified 1760 pregnant women who gave birth during this period, of whom 1688 (95.9%) were included in the study.

Vaccination protocol and immunization status. In this integrated Maternal and Child Health Care Project, each woman was offered a detailed antenatal checkup, including periodic examination and identification of high risk pregnancy, immunization with tetanus toxoid and iron supplementation. Tetanus toxoid vaccine (10 limes flocculation units), produced at the Central Research Institute, Kasauli, India, was given intramuscularly as a single booster dose to those who had received two doses in the preceding 3 years and in two doses at a 1-month interval to those who had no previous history of tetanus toxoid immunization or who were previously only partially immunized.

Women who received two doses of tetanus toxoid at least 4 weeks apart or a booster dose were considered to be completely immunized. Women who received one dose of tetanus toxoid either during the current pregnancy or in the past 3 years were considered to be partially immunized. Women who had not received any tetanus toxoid in the past 3 years were considered to be nonimmunized.

Definition of neonatal tetanus. The following criteria[12] were used to define a case of neonatal tetanus: history of normal suckling and crying for the first 2 days of life; onset of illness/death of a child within 3 to 30 days of birth following generalized spasm of muscles and stiffness; convulsions; and cessation of the child sucking milk with the onset of illness.

Data collection. A computer-based information system was developed to maintain the records of pregnant women and the children born to them in each village. This record was updated at each visit.

An in person interview was conducted with women at their homes during January, 1993, to April, 1993. A questionnaire was used to verify information abstracted from the information system and to ask nonimmunized and partially immunized women their reasons for not receiving complete vaccination.

Statistical analysis. The data were analyzed using Epi-Info 5.0®[13] and SPSS IV® statistical software packages.[14] The relative risk of neonatal tetanus associated with immunization was calculated as (Iv/Iu), where Iv and Iu were the incidence of neonatal tetanus among children born to immunized and unimmunized women, respectively. Vaccine effectiveness was calculated as $(Iu - Iv)/Iu$, which is equivalent to $1 - (Iv/Iu)$. Multivariable logistic regression was used to estimate the effect of tetanus toxoid immunization on the risk of neonatal tetanus controlling for other delivery practices and also to examine which factors were associated with complete immunization.

RESULTS

Table 1 provides a comparison of the characteristics for completely immunized, nonimmunized and par-

TABLE 1. Characteristics of completely immunized, nonimmunized and partially immunized pregnant women in a rural area of Rajasthan, India, 1988 to 1990

Characteristics	Completely Immunized	Nonimmunized	Partially Immunized	P*
No. of women	762	696	230	
Av. age (yr)	25.37 ± 0.18†	25.58 ± 0.21	26.18 ± 0.38	>0.05
Mean parity	1.65 ± 0.06	1.74 ± 0.07	1.96 ± 0.13	>0.05
Av. family income (Rupees × 1000)	14.69 ± 0.39	11.48 ± 0.23	12.79 ± 0.76	>0.05
No school education (%)	73.8	89.4	91.7	<0.01
Delivery by midwife/doctor (%)	20.0	13.6	9.1	<0.01
Delivery at health center/hospital (%)	12.3	8.6	3.9	<0.05

* P value for comparison of completely immunized with nonimmunized. See text for definitions of immunization status.

† Mean ± SE.

tially immunized women. The completely immunized women had significantly higher proportions of deliveries conducted by the midwife or doctor, deliveries at the health center or hospital and women with some school education. The partially immunized group was more similar to the nonimmunized group than to the completely immunized group.

Effectiveness of tetanus toxoid. Tetanus toxoid immunization during the antenatal period was highly protective against neonatal tetanus (Table 2). Effectiveness, calculated as the proportion of neonatal tetanus prevented attributable to tetanus toxoid vaccine, was 88% (95% CI, 59% to 98%) for complete immunization and 59% (95% CI −37% to 88%) for partial immunization. The risk of neonatal tetanus among children born to women who received any dose of tetanus toxoid was one-fifth of that for children born to nonimmunized mothers.

For completely immunized women the length of time between vaccination and delivery was examined. Among completely immunized women the average interval between the first dose and delivery was significantly greater for women whose children did not develop neonatal tetanus than for women whose children did develop the disease (91.5 days compared with 41.7 days). Similarly the interval between second dose and delivery was also significantly longer (49.7 days compared with 4.7 days). However, the average interval between the first and second doses was very similar for the two groups (39.0 days compared with 41.3 days).

Effectiveness of other interventions. Logistic regression was carried out to evaluate the effectiveness of the other interventions, namely: delivery by trained personnel; institutional deliveries; use of clean tools for cutting the umbilical cord; and hand washing before conducting the delivery. These interventions were associated with reduced risk of neonatal tetanus; however, the protection offered was not statistically significant except for the use of clean cutting tools. The effectiveness of using clean cutting tools was 61% (95% CI, 12% to 83%).

Next multivariable logistic regression was carried out adjusting for all interventions simultaneously, because this more closely represents the conditions under which immunization may be given (table 3). Completed prenatal tetanus toxoid vaccination was still strongly associated with a reduction in risk of neonatal tetanus (relative risk, 0.13; 95% CI, 0.04 to 0.44). Thus the adjusted relative risk is almost identical with the unadjusted estimate. There was no evidence of interaction between tetanus toxoid and other interventions. In the multivariable analysis use of clean cutting tools was significantly associated with a reduction in risk of neonatal tetanus (relative risk, 0.25).

Barriers to immunization. Despite high vaccine efficacy the effectiveness of a tetanus toxoid immunization program may be seriously limited unless most women receive the vaccine. Results of univariate and multivariable analyses to determine which factors were associated with vaccine coverage are presented in Table 4.

Four factors were independently associated with being more likely to receive complete immunization with tetanus toxoid (compared with receiving incomplete or no immunization with tetanus toxoid): registration of the pregnant woman by the health care provider before 29 weeks of gestation; being 5 km or less from the vaccination site; having two or more contacts with the health provider; and having some school education. Higher family income was not independently associated with receiving complete immunization.

Reasons reported by nonimmunized women for not receiving the vaccine included lack of awareness of the need for vaccination (44%), lack of information about the time and place of immunization session (29%) and fear of side effects (17%). Program-related reasons were long distance to the vaccination site (16%), inconvenient time of vaccination sessions (16%) and long waiting time (11%). Similar program-related reasons were given by the partially immunized women for not completing the required dosage schedule. In addition 30% said that they did not remember, were not aware of the need for a second dose or were not aware of the need for a booster dose.

DISCUSSION

The 88% effectiveness of tetanus toxoid found in this study is close to that observed in other studies, which

TABLE 2. Incidence and relative risk of death from neonatal tetanus among children born to completely immunized, partially immunized and nonimmunized women in a rural area of Rajasthan, India, 1988 to 1990

Immunization Status	Live Births	Deaths from Neonatal Tetanus	Incidence/1000 Live Births	RR of NNT*	Vaccine Effectiveness* (%)
Completely immunized	762	3	3.93	0.12 (0.02–0.41)†	88 (59–98)
Partially immunized	230	3	13.04	0.41 (0.12–1.37)	59 (−37–88)
Nonimmunized	696	22	31.60	Reference group	Reference group
Overall	1688	28	16.58		

* Compared with nonimmunized group.
† Numbers in parentheses, 95% CI.
NNT, neonatal tetanus; RR, relative risk.

TABLE 3. Multivariable logistic regression analysis of risk factors for neonatal tetanus death, in a rural area of Rajasthan, India, 1988 to 1990

Variable	Odds Ratio for NNT Death	95% CI	*P*
Complete immunization (*vs.* no immunization)	0.13	0.04–0.44	0.001
Partial immunization (*vs.* no immunization)	0.38	0.11–1.30	0.124
Delivery at home (*vs.* health center/hospital)	1.52	0.17–13.72	0.704
Traditional birth attendant (*vs.* midwife/doctor)	1.18	0.50–2.75	0.696
Hand washing	2.37	0.80–6.90	0.087
Use of clean cutting tools	0.25	0.08–0.75	0.013

NNT, neonatal tetanus.

range from 81% to 90%[15, 16] (IIHMR/UNICEF. Estimates of incidence of neonatal tetanus in Rajasthan, personal communication, 1993). Realistic assessment of vaccine efficacy under field conditions can be derived by observational epidemiologic studies provided the vaccinated and unvaccinated populations have similar underlying risk of disease.[17–20] However, observational studies are often subject to problems associated with lack of comparability between immunized and nonimmunized groups, problems of case definition, ascertainment of cases and validity of immunization records.

In this study the immunized and nonimmunized groups were similar with respect to demographic characteristics. Furthermore other studies suggest that unimmunized mothers do not differ from immunized mothers in terms of other behaviors that might predispose their children to having a higher risk of neonatal tetanus.[21] In the present study ascertainment of cases was nearly complete as a population-reporting system was in place. The completeness of ascertainment is supported by the finding that the incidence rate of neonatal tetanus was similar to that reported in India and similar countries in special studies based on cluster surveys.[3–7] Also the proportion of neonatal deaths caused by neonatal tetanus in this study (32.8%) was almost identical with that reported in a country-wide survey[4] (32.2%). A comparison of the case definition of this study with cause of death based on verbal autopsy.[22–24] during the in person interview and on review of medical records found that the case definition of this study was 100% sensitive and specific.

Misclassification of immunization status was minimized by using the immunization records at the health centers and the mother's health card and by verifying this information during the in person interview. In addition tetanus toxoid was not available in the area to provide immunization outside this program. However, such misclassification may arise in a normal program setting in developing countries due to inadequate records. The possibility of misclassification because tetanus toxoid had been given during the mother's childhood or while she was not pregnant is remote, given that the effective implementation of the immunization program in India took place after 1985 and women were asked about immunization from 1985 onward.

Vaccination with tetanus toxoid was the single most effective intervention against neonatal tetanus, independent of all other interventions. Inclusion of other interventions in the regression models did not alter the estimates of its effectiveness. Deliveries attended by trained personnel, cutting umbilical cord with clean tools and proper hand washing, are all components of WHO's complementary strategy of elimination of neonatal tetanus. Although these were associated with reduced risk, only the use of clean tools was statistically significant in the multivariable model. Interventions such as hand washing, for which correct procedures are neither understood nor practiced, and for which reports may be somewhat subjective, are subject to misclassification. With the lack of water and soap in rural areas, it is difficult to visualize proper hand washing. Furthermore in rural areas delivery conducted at a health center or by trained birth attendants does not ensure asepsis because sterile gloves and other necessary materials may not be available.

The finding that a single dose of tetanus toxoid during pregnancy for women not previously immunized was associated with a reduced risk of neonatal tetanus that is not statistically significant has been reported in other studies.[25, 26] However, studies by Black et al.[27] and Koenig[28] provide evidence of the benefit of one dose of tetanus toxoid in reducing neonatal tetanus mortality.

An important finding is that women registered in the first 28 weeks of pregnancy were more likely to receive complete immunization. In rural settings such as this, identification of pregnant women is a major program constraint; a national survey[29] found that 60% of pregnant women at most receive antenatal care with fewer than one-third receiving care in the first trimester. In this study the median gestational age at first contact was >20 weeks. The study revealed that the likelihood of receiving immunization was significantly reduced with increased distance to the health facility/vaccination site. Low frequency of contact with the health provider was a critical factor given that those with fewer than two contacts were at least 30 times less likely to receive immunization than those with two or more contacts. It is essential to utilize each opportunity for improving the coverage. On average the unimmunized women had about two contacts with the health provider, but this opportunity to immunize them was not used. A low awareness of prenatal immunization was reported by nonimmunized women. Various surveys of immunization coverage have re-

TABLE 4. Factors associated with complete immunization in a rural area of Rajasthan, India, 1988 to 1990, with univariate and multivariable logistic regression

Factors	Univariate		Multivariable*	
	OR	95% CI	OR	95% CI
Weeks of gestation at registration				
≤20	1.48	1.15–1.89	3.36	2.24–5.03
21–24	2.01	1.56–2.58	4.00	2.66–6.00
25–28	2.80	2.31–3.56	4.92	3.41–7.09
29+	1.00		1.00	
5 km or less from health center	3.33	2.22–5.00	2.50	1.43–4.35
2 or more contacts with health provider during pregnancy	50.0	33.3–100.0	33.3	25.0–50.0
Any school education	3.23	4.35–2.44	2.50	1.70–3.70
Family income >10 000 Rupees	1.39	1.15–1.70		

* Each variable adjusted for the effects of the other variables shown.
OR, odds ratio.

ported similar findings.[30–32] (IIHMR/UNICEF. Immunization coverage evaluation surveys in 11 districts in Rajasthan, unpublished reports, 1989, Rajasthan, Jaipur).

These results have important implications for intervention programs aimed at the elimination of neonatal tetanus. Efforts are being made to provide facilities for institutional deliveries in the rural areas. However, this is a nearly impossible task to achieve in the immediate future. There are cultural barriers to deliveries by trained personnel, as well as low accessibility to the health centers. Thus, establishing this practice is a long drawn out process. Presently tetanus toxoid vaccination is the only and the most effective, operationally feasible intervention against neonatal tetanus. It is also the least expensive of the available alternatives. Immunization strategies should be evolved for improving the coverage with tetanus toxoid through improving access, increasing awareness and information dissemination and minimizing missed opportunities. Continuing immunization of pregnant women is more effective than a mass immunization campaign[33]; however, identification of pregnant women sufficiently early during the gestation period is critical for the program to be effective. Prenatal tetanus toxoid immunization should be an integral part of mother and child health care services with an emphasis on early registration of pregnant women and effective communication to create awareness and improve utilization of services.

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