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REDUCTIONS IN NEONATAL MORTALITY ACHIEVED THROUGH A TETANUS IMMUNIZATION PROGRAM IN MATLAB, BANGLADESH
I. IMPACT OF THE 1974 VACCINE TRIAL

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ABSTRACT

In the Matlab demographic surveillance area in 1974, aluminium-adsorbed tetanus toxoid was provided as a placebo to a randomly assigned group of non-pregnant women during a field trial of cholera toxoid vaccine. This paper examines the reduction in neonatal mortality associated with one and two doses of tetanus toxoid, compared with a control group who were not immunized. The results demonstrate that two doses of tetanus toxoid result in a statistically significant reduction in neonatal mortality. The results of a logistic regression, controlling for the effects of other potentially confounding variables, shows that among the children whose mothers received two doses of tetanus toxoid, the risk of neonatal mortality and 4-14 day mortality were 34 and 68 percent lower, respectively, than for the unimmunized control group. Lower mortality risks were also evident among the group of births whose mother received only one tetanus toxoid dose, although this relationship was somewhat weaker.

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Introduction

Neonatal tetanus is a major cause of infant death throughout much of the developing world [1]. Neonatal tetanus most commonly results from infection of the newborn through unhygienic dressing of the umbilical cord at the time of delivery. Once contracted during infancy, it is fatal in a very high percentage of cases. Symptoms typically become manifest in the latter part of the first week of life, with the majority of tetanus deaths occurring between the fourth and fourteenth days of life.

Prevention of neonatal tetanus is most commonly achieved through immunization of women of childbearing age. The efficacy of tetanus toxoid immunization in reducing neonatal mortality has been demonstrated in a wide variety of settings [2-5]. While there is little debate about the merits of tetanus immunization programs, important questions remain concerning the effectiveness of different dose regimens and immunization strategies. Important unresolved questions include: What reductions in neonatal and infant mortality might realistically be achieved through an effective tetanus immunization program? What are the relative merits of strategies which target only pregnant women as opposed to all reproductive-aged women? What number of doses is sufficient to provide immunity against the contraction of tetanus? What is the maximum duration of effective immunity against tetanus conferred by immunization? These questions are of paramount policy relevance given the frequent limitations of service delivery systems in settings where tetanus remains a major public health problem.

Data from the Demographic Surveillance System in Matlab, Bangladesh permit more detailed investigation of the impact of a tetanus immunization program upon neonatal mortality. In the present study-- the first in a series on the tetanus immunization program-- we examine the impact upon subsequent neonatal mortality of the provision of one and two doses of tetanus toxoid to mothers, delivered as a placebo in a cholera vaccine trial.

Data and Methods

Data from an experimental pilot project in rural Bangladesh provide a unique opportunity to address many of these issues. Since 1963, the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) has maintained a field site in Matlab, a rural riverine area situated approximately 45 kilometers southeast of Dhaka, the capital of Bangladesh. At the time of the 1982 census, this area consisted of 149 villages containing a total population of approximately 190,000. A key feature of this study area is the existence of the Demographic Surveillance System (DSS), a system which maintains continuous surveillance of vital events (births, deaths, migration, marriage and divorce) on a fortnightly basis throughout the entire study area. This system has resulted in a level of accuracy and completeness in the registration of vital events such as births and deaths -- the subject of interest in the present study-- which is likely unique for a rural, traditional population [6].

In October of 1977, the ICDDR,B launched an experimental MCH and family planning program in roughly half of the Matlab area.

The remaining villages served as a comparison area, with services limited largely to those provided by the regular government program. While services were initially limited to family planning, over time the range of services offered was expanded to include immunization, oral rehydration therapy, and safe delivery practices. Although the tetanus immunization program was formally added as a component of the service program in June of 1978, a significant number of women had in fact already received tetanus immunizations prior to the introduction of the formal program.

In July and August of 1974, the ICDDR,B fielded a cholera vaccination trial of children aged 1-14 years and non-pregnant women aged 15 and over in the entire study area. As the placebo, these individuals received either one or two doses of 0.5 ml aluminum phosphate-adsorbed tetanus toxoid. As a result of this trial, in addition to the 46,442 individuals receiving either one or two injections of cholera vaccine, 33,175 individuals received two tetanus toxoid injections, and an additional 13,220 individuals received one dose of tetanus toxoid [7]. Thus, a significant proportion of the Matlab general population, and reproductive-aged women specifically, may have received at least some protection against tetanus prior to the immunization program introduced in 1978 as part of Matlab service program in the treatment area.

In this paper, we explore the reduction in neonatal mortality attributable to the tetanus toxoid immunization placebo administered to treatment area women as part of the 1974 cholera

vaccine trial. In order to obtain information on important covariates, our analysis is based upon births to the 15,636 mothers who were present during the initial baseline survey in the treatment area carried out in December of 1977. Analysis is further restricted to only births to these women which occurred prior to their receiving additional tetanus toxoid doses through the subsequent formal immunization program (which began in 1978), in order to avoid the confounding effects of subsequent tetanus toxoid vaccination. These criteria result in a total of 11,546 births in the present analysis; 80 percent of whom were born to mothers who received no tetanus doses, 14 percent to mothers who received two doses, and the remaining 6 percent to mothers who received only one dose as part of the 1974 cholera vaccine trial.

Results

The results presented in Table 1 demonstrate a significantly lower neonatal mortality rate among all births to mothers who received two tetanus toxoid injections compared to births whose mothers were unimmunized during the 1974 trial - 46 vs. 70 per thousand live births. This difference represents 34 percent reduction in neonatal mortality, and is statistically significant ($p < .01$). Neonatal mortality rates for births whose mothers received only one dose of tetanus toxoid were comparable to risks for the two dose group (45 vs. 46 per 1000). The difference between risks for the one dose and the unvaccinated group is also statistically significant ($p < .05$).

To examine the possibility of declining protective immunity over time, this relationship was also considered by birth year cohort. Larger proportional mortality reductions are observed for births which occurred shortly after the 1974 vaccine trial (1974-76) than from 1977 onward (50 and 47 percent vs. 25 and 28 percent). The reduction in mortality relative to the unimmunized group is statistically significant for both the two dose ($p < .01$) and the one dose ($p < .05$) groups in the earlier birth cohort (1974-76). However, among the later birth cohort (1977 onward), these differences had declined in significance for both the two dose ($p < .05$) and the one dose (not significant) groups. The impact of vaccination on neonatal mortality is almost the same for the two dose and one dose groups in both birth cohorts.

Table 2 presents the effect of vaccination status upon mortality during 4-14 days of life, the period when tetanus deaths are most prevalent [8]. The results show even more pronounced effects of vaccination upon mortality, with 4-14 day mortality reduced by almost two-thirds compared to the unimmunized group. As in the case of neonatal mortality, the effects of one and two doses are comparable and are highly statistically significant ($p < .01$). More detailed breakdowns by birth cohort, however, reveal a somewhat less consistent picture. Two doses of tetanus toxoid result in a reduction in 4-14 day mortality which is statistically significant ($p < .01$) in both the 1974-76 and 1977+ birth cohorts. This effect is particularly pronounced for the cohort born closest to the vaccination date (1974-76 births), with 4-14 day mortality

reduced by 82 percent relative to the unvaccinated group. Findings for the group receiving only one dose, however, are more ambiguous. While the mortality reduction associated with only one tetanus dose is non-significant for the earlier birth cohort, this reduction is highly significant among the group born from 1977 onward ($p < .01$).

While vaccination doses were randomly assigned during the 1974 vaccine trial, the unvaccinated group also contained a significant number of births whose mothers entered the treatment area study population through marriage or in-migration after the 1974 trial. It is possible that these women differed substantially from mothers present at the 1974 trial in terms of their demographic or socioeconomic characteristics. We therefore present in Table 3 the results of multiple logistic regression models of the effects of tetanus vaccination upon both neonatal and 4-14 day mortality, controlling for the effects of other potentially confounding socio-demographic covariates. The control variables include maternal age and parity (at time of childbirth), maternal education, area of household, post-1974 vaccine trial birth order (i.e., whether the reference birth was the first, second, or higher order birth to the mother following the 1974 vaccine trial), and year of birth. Maternal age, maternal education, and area of household were not statistically significant in the initial models, and were therefore not retained in the final models.

As shown in Table 3, the effect of two doses of tetanus toxoid remains highly significant for both the neonatal and 4-14

day mortality models ($p < .01$), even after controlling for the effects of these other covariates. A single dose of tetanus toxoid is also associated with lower mortality in both models, although at a lower level of statistical significance ($p < .05$). Parity is a significant predictor of mortality for the neonatal model only, with lower mortality risks for parities 1-4 and higher mortality risks for parities 5+. The absence of a significant association between parity and 4-14 day mortality is perhaps not surprising, given the predominance of tetanus as a cause of death during this period and previous findings which failed to demonstrate a relationship between parity and tetanus detaths [9]. Post- 1974 vaccine trial birth order is significant in both models, indicating that the first child born following vaccination of the mother is likely to benefit most in terms of protective immunity from tetanus. Several different interaction terms were considered-- vaccination status by birth year and by birth order-- but none proved significant for either the neonatal or 4-14 day models, and were therefore not included in the final models shown in Table 3.

Table 4 presents the estimated odds ratios and 95% confidence intervals of neonatal and 4-14 day mortality and tetanus vaccination status, based on the final multiple logistic regression models shown in Table 3. After controlling for other covariates, the risk of neonatal mortality to births whose mothers received two doses of tetanus vaccination was 34 percent lower than the unvaccinated group [(1.00 - .66) X 100]. The reduction in neonatal mortality for the one dose group is

comparable, although it is evident that confidence intervals are much wider than those of the two dose group, indicating that the estimate for the one dose group is less reliable. Table 4 also shows that the impact of tetanus toxoid upon 4-14 day mortality, is particularly pronounced, with two doses and one dose associated with mortality reductions of 68 percent and 60 percent, respectively.

Conclusions

The findings reported here, which indicate that significant reductions in neonatal mortality can be achieved through tetanus immunization programs, are largely consistent with previous studies of this issue in rural Bangladesh and other similar developing settings. A clear association between tetanus immunization and lower mortality was demonstrated. While effects were evident for neonatal mortality as a whole, the association was especially pronounced for 4-14 day mortality, a period generally recognized as having the highest risk of tetanus death. Both one dose and two doses of tetanus toxoid appear to contribute to reduce mortality risks, although the effect of two doses was more highly statistically significant.

Our findings indicate that tetanus immunization in Matlab has the potential to reduce neonatal mortality by about one-third. Whether the data presented here represent realistic estimates of gains in mortality from a tetanus immunization program in rural Bangladesh remains an unresolved question, particularly in light

of the knowledge that some women in our study may have also received tetanus toxoid as a placebo in an even earlier vaccine trial [10]. In any event, our findings suggest that while tetanus immunization thus represents an important intervention to improve child survival, tetanus represents only one of the causes of neonatal mortality, and thus a broader intervention strategy will be required if substantial reductions in neonatal and infant mortality are to be achieved in settings such as rural Bangladesh.

Table 1. Birth year and Tetanus Vaccination Status of Births in the Analysis

	Tetanus Vaccination Status			
Year of Birth	No Doses	1 Dose	2 Doses	Total
1974	881	4	2	887
1975	1307	126	201	1634
1976	1930	188	459	2577
1977	2221	173	398	2792
1978	1406	100	261	1767
1979	1055	81	215	1351
1980	295	24	49	368
1981	35	5	10	50
1982	69	6	13	88
1983+	27	2	3	32
Total:	9226	709	1611	11546

Table 2. Neonatal Mortality by Mother's 1974 Vaccination Status nd Birth Year of Infant

Vaccination Status	No. of births	No. of deaths	Deaths/ 1000 live birth	Percent Mortality Reduction: Vaccinated vs. Not Vaccinated Group
All births	11546	758	66	
2 doses	1611	75	46 **	34
1 dose	709	32	45 *	36
Not vaccinated	9226	651	70	
1974-1976 births:				
2 doses	662	22	33 **	50
1 dose	318	11	35 *	47
Not vaccinated	4118	270	66	
1977+ births:				
2 doses	949	53	56 *	25
1 dose	391	21	54 NS	28
Not vaccinated	5108	381	75	

** P<.01
* P<.05
NS = Not significant.

Table 3. 4-14 Day Mortality by Mother's 1974 Vaccination Status and Birth Year of Infant

Vaccination Status	No. of births	No. of deaths	Deaths/ 1000 live birth	Percent Mortality Reduction: Vaccinated vs. Not Vaccinated Group
All births	11546	312		
2 doses	1611	17	10 **	68
1 dose	709	8	11 **	65
Not vaccinated	9226	287	31	
1974-1976 births:				
2 doses	662	3	5 **	82
1 dose	318	6	19 NS	32
Not vaccinated	4118	114	28	
1977+ births:				
2 doses	949	14	15 **	56
1 dose	391	2	5 **	85
Not vaccinated	5108	173	34	

** $P<.01$
* $P<.05$
NS = Not significant.

Table 4. Estimates of the Final Multiple Logistic Regression Models of Neonatal and 4-14 Day Mortality

Effects	Neonatal mortality Regression Coefficient	Neonatal mortality S.E.[a]	4-14 day mortality Regression Coefficient	4-14 day mortality S.E.[a]
Vaccination Status (VS):				
Not vaccinated	RC[b]	-	RC	-
2 doses	-0.420**	0.126	-1.146**	0.269
1 dose	-0.425*	0.186	-0.913*	0.363
Birth Year (BYR):				
1974-76	RC	-	RC	-
1977+	-0.0002	0.089	0.050	0.160
Parity:				
0	RC	-	RC	-
1-4	-0.790**	0.103	-0.344	0.203
5+	0.473**	0.116	0.063	0.216
Post-1974 Vaccine Trial Birth Order:				
1	RC	-	RC	-
2+	0.408**	0.101	0.455**	0.170

[a] SE = Standard Error.

[b] RC = Reference category

** p <.01

* p <.05

Table 5. Estimated Odds Ratio and Confidence Intervals for Multiple Logistic Regression Models of the Effects of Tetanus Vaccination Status on Neonatal and 4-14 Day Mortality

	Neonatal Mortality		4-14 Day Mortality	
Effects	Odds Ratio	95% CI of Odds Ratio	Odds Ratio	95% CI of odds Ratio
<u>Vaccination Status:</u>				
Not vaccinated	RC[a]	-	RC	-
2 doses	0.66	0.51-0.84	0.32	0.19-0.54
1 dose	0.65	0.45-0.94	0.40	0.20-0.82

[a] RC = Reference category

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