Duration of Protective Immunity Conferred by Maternal Tetanus Toxoid Immunization: Further Evidence from Matlab, Bangladesh

ABSTRACT

Objectives. Although maternal tetanus immunization has been shown to be highly effective in the prevention of neonatal tetanus, unresolved questions remain concerning the required minimum number of doses and the resulting duration of effective immunity. This study examined the duration of effective immunity against neonatal tetanus provided by maternal tetanus immunization.

Methods. A randomized, double-blind cholera vaccine trial of 41 571 children and nonpregnant adult women carried out in 1974 in the Matlab comparison area of rural Bangladesh provided a unique opportunity to address dose and immunity issues.

Results. Children of women who received either 1 or 2 injections of tetanus toxoid experienced 4- to 14-day mortality levels consistently lower than those of children of unimmunized mothers. Analysis of neonatal-tetanus–related mortality showed that 2 injections of tetanus toxoid provided significant protection for subsequent durations of up to 12 or 13 years.

Conclusions. The data demonstrate that a limited-dose regimen of maternal tetanus toxoid provides significant and extended protection against the risk of neonatal tetanus death. (*Am J Public Health.* 1998; 88:903–907)

Michael A. Koenig, PhD, Nikhil Chandra Roy, MA, Thomas McElrath, PhD, Md. Shahidullah, PhD, and Bogdan Wojtyniak, ScD

Introduction

Neonatal tetanus remains a major public health problem in many parts of the developing world.[1] Most commonly resulting from infection of the newborn through unhygienic dressing of the umbilical cord at the time of delivery, the disease, once contracted, is fatal in a high percentage of cases.[2] Prevention of neonatal tetanus has been most commonly achieved through vaccination of women of childbearing age. The effectiveness of this approach in reducing neonatal tetanus mortality has been conclusively demonstrated in a number of studies from developing countries.[3–6]

Important and unresolved questions remain, however, regarding both the number of tetanus vaccination doses required to achieve immunity against neonatal tetanus and the duration of effective immunity. Two doses of maternal tetanus immunization have generally been shown to provide significant protection against neonatal tetanus for periods of as long as 4 years.[3–5] Findings with respect to 1 dose of tetanus toxoid have been less consistent, with some studies reporting protective effects for limited durations from a single dose, particularly when administered with a high toxoid concentration,[3,4,7–9] and others reporting a single dose to be of little or no protective value.[5,6,10]

Longitudinal data from the Matlab demographic surveillance area in rural Bangladesh provided a unique opportunity to further investigate these issues. By examining the mortality experience of subsequent births to mothers who participated in a 1974 cholera vaccine trial in which tetanus toxoid was given as the placebo, it was possible to evaluate the extent to which 1 and 2 doses of maternal tetanus immunization provide extended protective immunity against the risk of death from neonatal tetanus.

Data and Methods

Since 1966, the International Centre for Diarrhoeal Disease Research, Bangladesh, has carried out demographic surveillance at its field site in Matlab, a rural riverine area situated approximately 50 km southeast of Dhaka, the capital. The program consists of continuous surveillance of vital events (births, deaths, migration, and changes in marital status) on a 2-week basis and has resulted in a high level of accuracy and completeness in the recording of vital events for the large population under surveillance. At the time of the 1974 census, the surveillance area consisted of 233 villages with a total population of 277 000. The study area was subsequently reduced in 1978 to 149 villages with a population of 175 000.

In July and August of 1974, the International Centre for Diarrhoeal Disease Research carried out a cholera vaccine trial in the entire Matlab area that included male and female children 1 to 14 years of age and nonpregnant women 15 years of age or older.[3,11] Participants received, on a double-blind basis, either 1 or 2 doses of 0.5 mL of cholera toxoid or 0.5-mL adult-dose aluminum-phosphate–adsorbed tetanus–diphtheria toxoids as

Michael Koenig is with the Ford Foundation, New Delhi, India. Nikhil Chandra Roy is with the International Centre for Diarrhoeal Disease Research, Bangladesh. Thomas McElrath is with Harvard Medical School, Boston, Mass. Md. Shahidullah is an independent consultant in Canberra, Australia. Bogdan Wojtyniak is with the National Institute of Hygiene, Warsaw, Poland.

Requests for reprints should be sent to Michael Koenig, PhD, The Ford Foundation, 55 Lodi Estate, New Delhi 110003, India.

This paper was accepted October 6, 1997.

Editor's Note. See related editorial by Glezen (p 871) in this issue.

the placebo (with an interval of 42 days between the first and second injections).

In late 1977, the International Centre for Diarrhoeal Disease Research launched an experimental maternal and child health/family planning program in half of the Matlab study area, with the other half remaining as a comparison area. In the intervention area, maternal and child health services were gradually and carefully phased in over time; maternal tetanus immunization was one of the first interventions introduced.[12] Tetanus immunization coverage levels rose rapidly, reaching near universal levels by the early 1980s.

Following the experimental design of the Matlab project, outreach health services in the comparison area were purposefully limited to those provided through the regular government program.[12] Vaccine trial participants from the comparison area were unlikely to have received additional tetanus immunizations prior to late 1988, when tetanus toxoid was introduced into the comparison area as part of the Bangladesh government's national immunization program. While no data exist on levels of maternal tetanus immunization coverage in the comparison area, these levels were very low prior to intensification of the national immunization program. Results from a 1989 national survey indicate that the maternal tetanus immunization coverage rate for rural Bangladesh as a whole remained at 5% or lower through 1984 and was still only 12% in 1986, rising significantly only toward the end of the decade.[13] Other evidence indicates that levels of health service coverage in the Matlab comparison area during this period are unlikely to have exceeded those for Bangladesh as a whole.[14]

The present study was restricted to data from the Matlab comparison area. A total of 21 041 individuals received either 1 or 2 injections of cholera toxoid, and an additional 5464 and 15 066 individuals received 1 and 2 doses of tetanus–diphtheria toxoid, respectively, in the villages that subsequently comprised the comparison area. Since each individual in the study area was assigned a unique identification number, subsequent birth and death records could be linked for all women who participated in the 1974 cholera vaccine trial. Information on 4- to 14-day and neonatal mortality was obtained by matching birth and death records for births to comparison area women who participated in the original trial. The study followed the subsequent mortality experience of children of female vaccine trial participants through 1987, using this cutoff date to minimize the potentially confounding effects of tetanus immunization from sources other than the vaccine trial.

Information on neonatal-tetanus–related mortality rates was obtained in 2 independent assessments of causes of childhood death. The first consisted of a special study of causes of neonatal and postneonatal mortality in the Matlab study area in 1982/83; this study undertook retrospective semistructured interviews with the mother or closest kin of the deceased child to ascertain the sequence of symptoms experienced prior to death and to assign a specific cause of death, including neonatal tetanus.[15] These histories were reviewed, and a probable cause of death was assigned by a public health physician. The second data source, from 1986 onward, was a more rigorous system of cause-of-death assignment implemented throughout the entire Matlab study area, in recognition of the limitations of the previous system with respect to causes of death such as neonatal tetanus. A special questionnaire was administered by trained female interviewers to the families of all infants who died between the 4th and 21st days of life. The main criteria for neonatal tetanus death included no apparent complications at birth, good suckling and crying patterns during the initial 48 hours of life, difficulty in suckling and lockjaw as initial symptoms, spasms of the neck and body, rigidity, and signs of umbilical stump infection.[16] All death records were reviewed, and a cause of death was assigned by independent reviewers (initially a team of physicians and subsequently a specially trained medical assistant). In both assessments, cause of death was assigned according to the World Health Organization's *International Classification of Diseases*.[17,18]

Results

Table 1 presents data on the characteristics of the 3 vaccine groups. It is evident that the 3 groups were highly similar in terms of age and socioeconomic indicators such as household area and level of maternal education. Similar conclusions were reached in comparing the characteristics of specific birth cohorts; maternal age and parity were similar for the 3 vaccine groups for births occurring during 1985/86 as well as for other birth cohorts (data not shown). On the whole, these results provide strong support for the integrity of the randomized design of the 1974 vaccine trial.

Table 2 shows neonatal mortality and vaccine efficacy rates for births to mothers from the 3 vaccine groups in 2-year groups (with the exception of 1987). No significant differences in neonatal mortality were evident during the 1973/74 period (effects from the vaccine trial would not have been evident prior to 1975). However, infants born to mothers who received 2 injections of tetanus–diphtheria toxoid experienced significantly lower neonatal mortality levels

TABLE 1—Characteristics of Female Participants in the Cholera Vaccine Trial: Matlab, Bangladesh, 1974

	Cholera Toxoid (1–2 Injections)	Tetanus–Diphtheria Toxoid (2 Injections)	Tetanus–Diphtheria Toxoid (1 Injection)
	1974 vaccine trial		
No.	8413	6550	1964
Age, y, %			
0–4	17.1	17.2	16.9
5–14	36.9	37.8	33.5
15–44	46.0	45.0	49.6
Mean household area, sq ft	263	270	260
Education level of 15- to 44-year-old women, y, %			
(No.)	(3872)	(2951)	(975)
0	80.7	82.2	79.0
1–5	16.5	15.5	18.5
6+	2.8	2.3	2.5
	1985/86 birth cohort		
No.	1342	1007	307
Maternal age, y, %			
<20	13.1	14.4	12.7
20–34	72.9	74.2	76.2
35+	14.0	11.4	11.1
Parity, no., %			
0	21.8	23.8	18.2
1–5	73.6	72.4	76.9
6+	4.6	3.8	4.9

TABLE 2—Neonatal Deaths, by Year of Birth and Maternal Tetanus Immunization Status: Matlab, Bangladesh, 1973 through 1987

Period and Birth Year	Cholera Toxoid (1–2 Injections)			Tetanus–Diphtheria Toxoid (2 Injections)					Tetanus–Diphtheria Toxoid (1 Injection)				
	Births	Deaths	Rate[a]	Births	Deaths	Rate[a]	Vaccine Efficacy Rate	95% Confidence Interval	Births	Deaths	Rate[a]	Vaccine Efficacy Rate	95% Confidence Interval
Prevaccine													
1973/74	994	69	69.4	740	55	74.3	. . .	. . .	237	17	71.7	. . .	. . .
Postvaccine													
1975/76	1130	89	78.8	767	36	46.9[b]	40	13, 59	329	18	54.7	31	−14, 58
1977/78	1192	90	75.5	893	47	52.6[c]	30	2, 50	332	14	42.2[c]	44	3, 68
1979/80	1435	104	72.5	988	48	48.6[b]	33	7, 52	360	23	63.9	12	−36, 43
1981/82	1393	99	71.1	1041	50	48.0[b]	32	6, 51	357	23	64.4	9	−41, 42
1983/84	1313	92	70.1	945	46	48.7[c]	31	2, 51	338	16	47.3	32	−13, 60
1985/86	1342	74	55.1	1007	49	48.7	12	−25, 38	307	9	29.3	47	−5, 73
1987	647	33	51.0	503	19	37.8	26	−29, 57	170	7	41.2	19	−79, 64

[a]Per 1000 live births.
[b]Significantly different from the cholera toxoid control group at $P < .01$.
[c]Significantly different from the cholera toxoid control group at $P < .05$.

than control group infants whose mothers received cholera toxoid through 1983/84, a period of 10 years postvaccination. While neonatal mortality rates among the 1-injection group were also consistently lower than those for the control group, these differences largely failed to attain statistical significance.

Differences across vaccine groups are even more pronounced when 4- to 14-day mortality—the primary risk period for neonatal tetanus—is considered (Table 3). Among infants of mothers who received 2 injections of tetanus–diphtheria toxoid, 4- to 14-day mortality levels during the subsequent 10-year period were significantly lower, at levels roughly one half those for the control group. Among the 1-injection group, 4- to 14-day mortality rates were significantly lower than those for the control group during the 4 years immediately following the vaccine trial (1975 through 1978). Although subsequent mortality rates were also lower than those for the control group, these differences failed to attain statistical significance.

Previous research has shown that more than half of all 4- to 14-day deaths in the Matlab area are attributable to causes other than neonatal tetanus.[19] We therefore also considered neonatal-tetanus–related mortality rates for those years in which reliable data on cause of death were available from special studies (1982/83 and 1986/87) (Table 4). Two injections of tetanus toxoid provided significant protection against death from neonatal tetanus in both the 1982/83 and 1986/87 birth cohorts (3.8 vs 14.4 deaths per 1000 live births and 2.0 vs 10.0 deaths per 1000 live births), and the differences were highly significant. Neonatal-tetanus–related mortality rates were also discernibly lower among the 1-injection group in both the 1982/83 and 1986/87 birth cohorts and comparable to rates for the 2-injection group (5.6 vs 14.4 deaths per 1000 live births and 3.3 vs 10.0 deaths per 1000 live births), although both differences failed to attain statistical significance.

Discussion

The 1974 cholera vaccine trial undertaken in the Matlab study area provided a unique opportunity to assess the duration and magnitude of mortality effects resulting from maternal tetanus immunization. Because tetanus toxoid was provided as the placebo as part of a double-blind trial randomized on an individual basis, the results are free from the problems of selection bias commonly associated with evaluations of health interventions such as immunization. Several potential limitations of the present study should nevertheless be noted. First, the possibility of error in the assignment of cause of neonatal tetanus death cannot be ruled out. While there has been a concerted effort to strengthen cause of childhood death assignment in the Matlab area over the last decade, cause of death data based on lay reporting invariably remain subject to a certain degree of classification error.[20] In the present study, however, since cause-of-death assignments were made independently of knowledge of the mother's 1974 tetanus vaccination status, any classification error that did occur should have been randomly distributed across all 3 vaccination groups. Misclassification of cause of death would therefore not account for any of the observed differences in mortality among vaccination groups.

Second, it is possible that the results reported were influenced by the confounding effects of tetanus vaccination from sources other than the 1974 cholera vaccine trial. One possible source was cholera vaccine trials held by the International Centre for Diarrhoeal Disease Research during the 1960s, in which tetanus toxoid was also used as a placebo.[21,22] An earlier study conducted in Matlab, however, found that the proportion of women in the 1974 cholera vaccine trial who received tetanus toxoid through participation in the earlier vaccine trials was very small (only 6%).[3] Acceptance of tetanus vaccination from other sources following the 1974 vaccine trial—most notably, through the national immunization program—represents a second and potentially more serious source of bias. By limiting the prospective period of our study to 1987, when tetanus coverage levels nationally and in the Matlab comparison area still remained very low, we sought to minimize the extent of bias introduced by tetanus vaccination from sources other than the 1974 trial. Moreover, given the double-blind design of the 1974 cholera vaccine trial, any subsequent acceptance of tetanus vaccination could be expected to take place largely independently of 1974 vaccination status and, therefore, to be randomly distributed across all 3 vaccination groups. To the extent that subsequent acceptance of maternal tetanus vaccination did occur, unvaccinated mothers would also be expected to have disproportionately benefited, as children of mothers who received tetanus toxoid during the 1974 trial would continue to experience significant levels of residual protection against the risk of neonatal tetanus. Our results may thus somewhat understate the protective effects

TABLE 3—Four- to 14-Day Mortality, by Year of Birth and Maternal Tetanus Immunization Status: Matlab, Bangladesh, 1973 through 1987

Period and Birth Year	Cholera Toxoid (1–2 Injections)			Tetanus–Diphtheria Toxoid (2 Injections)					Tetanus–Diphtheria Toxoid (1 Injection)				
	Births	Deaths	Rate[a]	Births	Deaths	Rate[a]	Vaccine Efficacy Rate	95% Confidence Interval	Births	Deaths	Rate[a]	Vaccine Efficacy Rate	95% Confidence Interval
Prevaccine													
1973/74	994	30	30.2	740	23	31.1	. . .	. . .	237	9	38.0	. . .	. . .
Postvaccine													
1975/76	1130	36	31.9	767	5	6.5[b]	80	48, 92	329	3	9.1[b]	71	8, 91
1977/78	1192	39	32.7	893	13	14.6[b]	56	17, 76	332	1	3.0[b]	91	33, 99
1979/80	1435	46	32.1	988	16	16.2[b]	49	11, 71	360	8	22.2	31	–46, 67
1981/82	1393	47	33.7	1041	17	16.3[b]	52	16, 72	357	8	22.4	34	–39, 68
1983/84	1313	35	26.7	945	13	13.8[c]	48	3, 73	338	4	11.8	56	–24, 84
1985/86	1342	28	20.9	1007	19	18.9	10	–61, 49	307	2	6.5	69	–30, 93
1987	647	15	23.2	503	7	13.9	40	–46, 75	170	3	17.6	24	–160, 78

[a]Per 1000 live births.
[b]Significantly different from the cholera toxoid control group at $P < .01$.
[c]Significantly different from the cholera toxoid control group at $P < .05$.

TABLE 4—Neonatal Tetanus Mortality Rates, by Year of Birth and Maternal Tetanus Immunization Status: Matlab, Bangladesh, 1982/83 and 1986/87

Birth Year	Cholera Toxoid (1–2 Injections)			Tetanus–Diphtheria Toxoid (2 Injections)					Tetanus–Diphtheria Toxoid (1 Injection)				
	Births	Deaths	Rate[a]	Births	Deaths	Rate[a]	Vaccine Efficacy Rate	95% Confidence Interval	Births	Deaths	Rate[a]	Vaccine Efficacy Rate	95% Confidence Interval
1982/83	1392	20	14.4	1058	4	3.8[b]	74	23, 91	357	2	5.6	61	–66, 91
1986/87	1301	13	10.0	1003	2	2.0[b]	80	12, 95	303	1	3.3	67	–152, 96

[a]Per 1000 live births.
[b]Significantly different from the cholera toxoid control group at $P < .01$.

of 1 and 2 injections of tetanus toxoid relative to unimmunized births.

A final concern relates to the fact that no special effort was made to subsequently trace original cholera vaccine trial participants and provide additional immunizations. This decision is most likely explained by the limited efficacy of the cholera vaccine tested,[11] the absence of persuasive evidence on an extended duration of protection afforded by maternal tetanus information (data on the effects of maternal tetanus immunization indicating a protective duration of up to 32 months were not published until 1980[3]), and the existence of a strict experimental design within the Matlab project area that precluded formal intervention in the comparison area by the International Centre for Diarrhoeal Disease Research.

The results of our study provide strong evidence that maternal tetanus toxoid vaccination confers significant protection against the risk of neonatal tetanus for a much longer duration than previously documented. Our analysis has shown that children whose mothers received 2 injections of tetanus toxoid in the 1974 vaccine trial experienced consistently lower 4- to 14-day mortality risks than children of unimmunized mothers during the 10-year period postvaccination. A single tetanus toxoid injection was shown to provide significant protection for 4 subsequent years. Even more conclusive evidence on the extended duration conferred by maternal tetanus immunization is provided by the findings with respect to neonatal-tetanus–related mortality levels. Children whose mothers received 2 doses of tetanus toxoid experienced significantly lower risks than children of unimmunized mothers for periods of up to 12 to 13 years following initial vaccination. Vaccination with a single dose of maternal tetanus toxoid also resulted in lower neonatal-tetanus–related mortality levels during the subsequent period, although this difference failed to attain statistical significance, owing perhaps to small sample sizes.

Our findings have important implications for current maternal tetanus immunization policies and programs in developing countries. Current World Health Organization guidelines indicate that 4 doses of maternal tetanus toxoid provide protection against the risk of tetanus for 10 years and that lifetime protection can be achieved through the administration of 5 doses.[23] Although the present study did not specifically address the issue of the number of doses required for complete immunity, our findings do demonstrate that significant and extended protection against the risk of neonatal tetanus can be achieved through the administration of a more limited sched-

ule of maternal tetanus toxoid. From the standpoint of immunization strategy in settings such as South Asia, where immunization coverage levels remain low and health infrastructures are weak, our findings argue strongly for according highest priority to the goal of universal coverage of all reproductive-aged women with a minimum of 2 tetanus toxoid injections. Our results also suggest that initiating programs to reach young women with 2 doses of tetanus toxoid prior to the onset of childbearing (and even during adolescence) would confer a high degree of protection against the risk of neonatal tetanus throughout most, if not all, of the primary reproductive years. □

Acknowledgments

This research was supported by the International Centre for Diarrhoeal Disease Research, Bangladesh. The centre is supported by countries and agencies that share its concern about the impact of diarrhoeal diseases and the related issues of nutrition and fertility in the developing world. The Matlab Demographic Surveillance System was supported by the United Nations Fund for Population Activities until 1983 and has been supported by the Canadian International Development Agency since 1984. Research for the present paper was made possible by funding from the United States Agency for International Development.

We are grateful to V. Fauveau, A. de Francisco, A. Galazka, G. Hlady, J. Rohde, and M. Strong for helpful comments on earlier versions of this paper; to G. Curlin for his invaluable assistance in tracking down information on the tetanus vaccine provided in the 1974 trial; and to W. H. Mosley for originally suggesting the idea for this study.

References

1. Stanfield JP, Galazka A. Neonatal tetanus in the world today. *Bull World Health Organ.* 1984;62:647–669.
2. Foster SO. Immunizable and respiratory diseases and child mortality. *Pop Dev Rev.* 1984;10(suppl):119–140.
3. Black RE, Huber DH, Curlin GT. Reduction of neonatal tetanus by mass immunization of non-pregnant women: duration of protection provided by one or two doses of aluminium-adsorbed tetanus toxoid. *Bull World Health Organ.* 1980;58:927–930.
4. Newell KW, Lehmann AD, Leblanc DR, et al. The use of toxoid for the prevention of tetanus neonatorum: final report of a double-blind controlled field trial. *Bull World Health Organ.* 1966;35:863–871.
5. Rahman M, Chen LC, Chakraborty J, et al. Use of tetanus toxoid for the prevention of neonatal tetanus, I: reduction of neonatal mortality by immunization of non-pregnant and pregnant women in rural Bangladesh. *Bull World Health Organ.* 1982;60:261–267.
6. Schofield FD, Tucker VM, Westbrook GR. Neonatal tetanus in New Guinea: effect of active immunization in pregnancy. *BMJ.* 1961;2:785–789.
7. Hardegree MC, Barile MF, Pittman M, et al. Immunization against neonatal tetanus in New Guinea, II: duration of primary antitoxin response to adjuvant and plain toxoids and comparison of booster responses to adjuvant and plain toxoids. *Bull World Health Organ.* 1970;43:439–451.
8. Kielmann AA,Vohra SR. Control of tetanus neonatorum in rural communities: immunization effects of high-dose calcium phosphate-adsorbed tetanus toxoid. *Ind J Med Res.* 1977;66:906–916.
9. Breman JG, Wright GG, Levine L, et al. The primary serological response to a single dose of adsorbed tetanus toxoid, high concentration type. *Bull World Health Organ.* 1981;59: 745–752.
10. Stanfield JP, Gail D, Bracken PM. Single-dose antenatal tetanus immunisation. *Lancet.* 1973; 1:215–219.
11. Curlin GT. *Immunological Aspects of a Cholera Toxoid Field Trial in Bangladesh.* Dhaka, Bangladesh: International Centre for Diarrhoeal Disease Research; 1978. Scientific report 8.
12. Koenig M, Strong M. Assessing the mortality impact of an integrated health program: lessons from Matlab, Bangladesh. In: Rashad H, Gray R, Boerma JT, eds. *Evaluation of the Impact of Health Interventions.* Liege, Belgium: Derouaux Ordina Editions; 1994: 361–395.
13. Huq MN, Cleland J. *Bangladesh Fertility Survey 1989: Main Report.* Dhaka, Bangladesh: National Institute of Population Research and Training; 1990.
14. Koenig MA, Rob U, Khan MA, et al. Contraceptive use in Matlab, Bangladesh in 1990: levels, trends, and explanations. *Stud Fam Plann.* 1992;23:352–364.
15. Bhatia S. Patterns and causes of neonatal and postneonatal mortality in rural Bangladesh. *Stud Fam Plann.* 1989;20:136–146.
16. Fauveau V, Wojtyniak B, Chowdhury HR, Sarder AM. Assessment of cause of death in the Matlab Demographic Surveillance System. In: Fauveau V, ed. *Matlab: Women, Children, and Health.* Dhaka, Bangladesh: International Centre for Diarrhoeal Disease Research; 1994: 65–86.
17. *International Classification of Diseases,* 1975 revision. Geneva, Switzerland: World Health Organization; 1977;1.
18. *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death.* 9th revision. Geneva, Switzerland: World Health Organization; 1977.
19. Koenig MA. Mortality reductions from health interventions: the case of immunization in Bangladesh. *Pop Dev Rev.* 1991;17:87–104.
20. Gray RH, Smith G, Barss P. *The Use of Verbal Autopsy Methods to Determine Selected Causes of Death in Children.* Liege, Belgium: International Union for the Scientific Study of Population; 1990. Paper no. 3.
21. Benenson AS, Mosley WH, Fahimuddin M, et al. Cholera vaccine field trials in East Pakistan, II: effectiveness in the field. *Bull World Health Organ.* 1968;38:359–372.
22. Mosley WH, Aziz KMA, Rahman ASMM, et al. Report of the 1966–67 cholera vaccine trial in rural East Pakistan. *Bull World Health Organ.*1972;47:229–238.
23. *Prevention of Neonatal Tetanus through Immunization.* Geneva, Switzerland: World Health Organization; 1986. WHO/EPI/GEN/86/9.