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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*

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Immunization of non-pregnant women in rural Bangladesh with two doses of aluminium-adsorbed tetanus-diphtheria toxoids reduced neonatal mortality by one-third during a period of 9–32 months after vaccination. The reduction in mortality rate was attributable almost entirely to a 75% lower mortality rate among 4–14-day-old infants, when tetanus was the predominant cause of death.

In the period up to 20 months following vaccination, the reduction in deaths among 4–14-day-old infants after a single dose of tetanus-diptheria toxoids was about the same as that after two doses. However, beyond 20 months a single dose did not appear to provide protection.

Tetanus, particularly among neonates, continues to be an important problem in most developing countries. In some, it is the primary cause of death among children up to 1 year of age and it is estimated that nearly 10% of deaths among live-born infants are due to tetanus (*1*, *2*).

Tetanus toxoid given to pregnant women prevents neonatal tetanus; however, in many developing countries health services are not yet available to all pregnant women (*2–4*). Immunization of all women of reproductive age has been considered as an alternative but this may not be practicable since two doses of tetanus toxoid must be given for the primary immunization. Thus, efforts have been made to develop a vaccine that will provide durable protection after a single dose without excessive side effects (*5–7*). Reports indicate that one dose of aluminium phosphate-adsorbed tetanus toxoid may provide substantial, though transient, protection against neonatal tetanus (*3*, *5*, *6*). If this protection could be confirmed and its duration determined, it might be possible to simplify immunization programmes in many developing countries.

In 1974, a group of subjects was vaccinated with a cholera toxoid with a view to evaluating its efficacy. Concomitantly, aluminium phosphate-adsorbed tetanus and diphtheria (Td) toxoids were given to a randomly-assigned group of subjects who served as controls. We determined the protection from neonatal tetanus afforded by one or two doses of Td toxoids by retrospectively analysing the data on neonatal mortality among infants born to the subjects in the two groups 9–32 months after immunization.

METHODS

During July and August 1974, the protective effect of a glutaraldehyde-treated cholera toxoid was evaluated in the Matlab field study area of the International Centre for Diarrhoeal Disease Research (ICDDR), Bangladesh (formerly the Cholera Research Laboratory) (*8*). Children between the ages of 1 and 14 years and non-pregnant women at least 15 years old were vaccinated after their informed consent had been obtained. On a double-blind basis, volunteers received 0.5 ml of cholera toxoid or 0.5 ml of adult-dose aluminium phosphate-adsorbed Td toxoids (Wyeth Laboratories, Inc.) by intramuscular injection from a Ped-O-Jet[a] injector. Attempts were

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[a] Use of trade names is for identification only and does not constitute endorsement by the Public Health Service US Department of Health, Education and Welfare.

Table 1. Mortality in two birth cohorts[a] by vaccine status of mother

Interval between vaccination and birth	Immunization status of mother[b]										
	Cholera toxoid (1 or 2 injections)			Tetanus diphtheria toxoids (1 injection)				Tetanus diphtheria toxoids (2 injections)			
	Deaths	Births	Rate	Deaths	Births	Rate	*P* value[c]	Deaths	Births	Rate	*P* value[c]
Neonatal mortality[d]											
9–20 months	113	1652	68.4	18	536	33.6	< 0.01	46	1044	44.1	< 0.025
21–32 months	149	2734	54.5	36	729	49.4	NS	73	1946	37.5	< 0.025
Mortality on days 4–14[e]											
9–20 months	52	1652	31.5	4	536	7.5	< 0.01	8	1044	7.7	< 0.001
21–32 months	58	2734	21.2	13	729	17.8	NS	16	1946	8.2	< 0.001

[a] Born April 1975–March 1976 and April 1976–March 1977.

[b] Vaccinated July–August 1974.

[c] Significance level compared with cholera toxoid group, based on chi-square test; NS = not significant at $P < 0.05$.

[d] Deaths per 1000 live births in first 28 days.

[e] Deaths per 1000 live births on days 4–14 after birth.

made 42 days later to give all those vaccinated a second injection of the same vaccine, and 74% actually received a second dose. One or two injections of cholera toxoid were given to 46 443 persons, one injection of Td toxoids was given to 13 220 persons, and two injections of Td toxoids were given to 33 175 persons.

Since 1966, the ICDDR has maintained a demographic surveillance system in the Matlab field area, which had a population of 277 000 in 1974. The surveillance involves carrying out cross-sectional censuses (the last census was carried out in 1974 immediately before the vaccine field study) and keeping records of vital statistics and migration (*9*).

For the retrospective analysis of neonatal mortality data, two birth cohorts, April 1975–March 1976 and April 1976–March 1977, were selected for study. Since pregnant women were intentionally excluded from vaccination, records for the first birth cohort begin 9 months after the immunization campaign. With data from vital records, births during these periods were matched with deaths during the 28 days following birth. With records from the 1974 field study, neonatal mortality and mortality on days 4–14 were calculated for children of women who had been given cholera toxoid or one or two injections of Td toxoids.

Some of the people in this area had participated in field tests of cholera vaccines in 1966–67 and 1968–69, when tetanus toxoid was also used for the control group. In order to determine whether earlier immunization with tetanus toxoid could bias this analysis, we reviewed the vaccination records of women who had received one injection of Td toxoids in 1974 and had given birth to a child sometime in the period of the first birth cohort.

RESULTS

In the first birth cohort (births 9–20 months after the immunization programme), the neonatal mortality rate for children of mothers who had been given cholera toxoid was 68.4 per 1000 births. The mortality rate for children of mothers who had been given one or two injections of Td toxoids was significantly lower (see Table 1). The numbers of deaths on days 4–14 were likewise significantly smaller for infants whose mothers had had one or two injections of Td toxoids.

In the second birth cohort, the rates for neonatal mortality on days 4–14 were significantly lower for children of women who had received two doses of Td toxoids than for children of women who had received cholera toxoid. However, during this period the mortality rate for children of women who had received only one injection of Td toxoids 21–32 months earlier was not different from that for children whose mothers had received cholera toxoid.

Of the 536 women who received one injection of Td toxoids in 1974 and whose child was included in our first birth cohort, 33 (6%) had been immunized in an earlier trial. Two of those 33 children died in the neonatal period, but not between days 4 and 14.

When data from the two birth cohorts were combined, the neonatal mortality rate for children whose mothers had had two injections of tetanus toxoid was 20 per 1000 births less than the rate for the children whose mothers had had cholera toxoid, representing a one-third reduction in neonatal mortality. As illustrated in Fig. 1, this difference was seen almost entirely as reduced mortality on days 4–14.

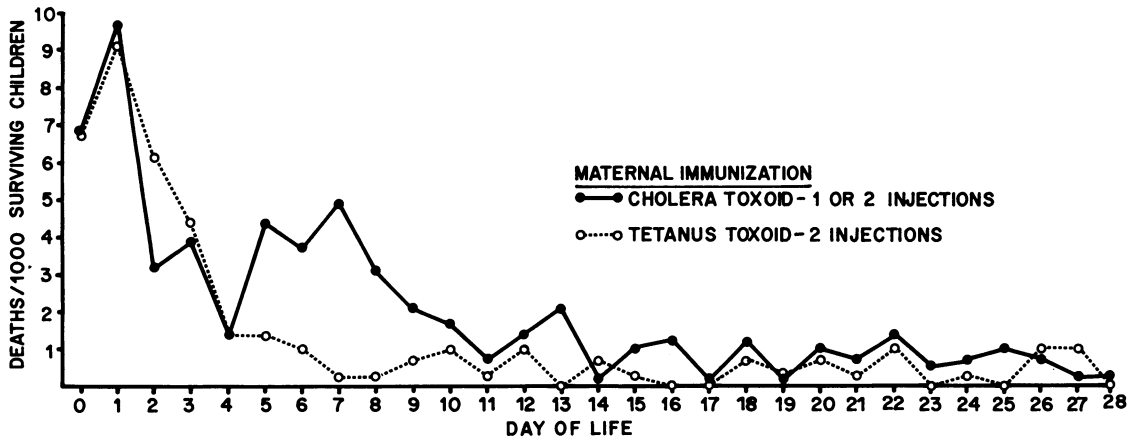

Fig. 1. Neonatal death rates by age of death following maternal immunization with one or two doses of cholera or two doses of tetanus/diphtheria toxoids.

DISCUSSION

We have used neonatal mortality, and more precisely mortality on days 4–14, as indicators of neonatal tetanus. Earlier studies of unimmunized populations indicate that in some countries tetanus is responsible for one-fourth to one-third of all neonatal deaths (*1*). Furthermore, deaths between days 4 and 14 after birth should be a good indicator of tetanus, since studies have demonstrated that over 90% of neonatal deaths caused by tetanus, but only 25% of neonatal deaths from other causes, would occur in this period (*3*).

A nationally representative, retrospective sample survey of infant mortality conducted by the World Health Organization in Bangladesh in the period 1975–77, indicated that neonatal tetanus caused 25 deaths per 1000 live births. We found that for children whose mothers had had two tetanus injections 9–32 months before delivery, the neonatal death rate was 20 per 1000 live births lower than the rate for children whose mothers were in the control group. Since approximately 6% of mothers in the area had received one or more doses of tetanus toxoid in earlier vaccine trials, the incidence of neonatal tetanus in the study area was slightly lower than that in most of the rest of Bangladesh, where almost no immunizations had been carried out. The estimated neonatal tetanus death rate of 25 per 1000 live births for Bangladesh is consistent with our findings.

In this study we found that two doses of aluminium-adsorbed Td toxoids given to non-pregnant women reduced the neonatal mortality by approximately one-third. The reduction in deaths for days 4–14 is even more marked—i.e., the mortality rate being less than 25% of the rate among the non-immunized group. This lowered mortality probably reflects the elimination of neonatal tetanus.

Earlier reports on the protection afforded by one dose of adsorbed tetanus toxoid are contradictory. Some studies based on antitoxin levels suggest that one injection does not provide protective levels for a substantial number of women (*5*, *10*), while others show that one dose of adsorbed toxoid provides adequate levels for periods up to 1 year (*6*, *11*, *12*). In one study a single dose appeared to protect against neonatal tetanus for 4–24 months after immunization (*3*); however, since the difference in tetanus rates was not statistically significant, this protective effect has remained in doubt.

Our analysis gives further support to the conclusion that one dose of adsorbed tetanus toxoid has a protective effect for a minimally immunized population. This apparent protection from neonatal tetanus was evident only up to 20 months after immunization. This durable protection with one dose was probably not a result of earlier tetanus immunization, since only 6% of women in our one-dose group had had a previous tetanus toxoid injection. However, the single-dose injection may have served as a booster for women who had already had asymptomatic infection with *Clostridium tetani* and had thus been exposed to tetanus toxin. Other reports have suggested this explanation for antitoxin titres and booster-type responses to toxoid for unimmunized populations (*7*).

In countries with a high rate of neonatal tetanus and with little or no prenatal care, mass tetanus toxoid immunization of all females of reproductive age may be indicated. The finding that one injection of aluminium-adsorbed Td toxoids protects against

neonatal tetanus for 20 months indicates that the two initial immunizations could be safely scheduled one year apart in areas where more closely spaced visits would not be feasible and that these injections could be delivered by jet injector as was previously suggested (*13*). To ensure prevention of neonatal tetanus, given the limited duration of transplacental protection, booster doses of tetanus toxoid are recommended at subsequent three-year intervals. With this approach, or by immunizing all pregnant women, it may be possible in Bangladesh and similar developing countries to reduce neonatal mortality from tetanus by one-third.

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RÉSUMÉ

DIMINUTION DU TÉTANOS NÉONATAL GRÂCE À UNE VACCINATION DE MASSE DES FEMMES NON ENCEINTES: DURÉE DE LA PROTECTION FOURNIE PAR UNE OU DEUX DOSES D'ANATOXINE TÉTANIQUE ADSORBÉE SUR ALUMINIUM

Au cours d'une évaluation de l'efficacité d'un vaccin anticholérique, effectuée en 1974, de l'anatoxine tétanique et diphtérique (DT) adsorbée sur phosphate d'aluminium a été administrée à des sujets désignés au hasard pour servir de groupe témoin aux sujets vaccinés contre le choléra . La protection contre le tétanos néonatal assurée par une ou deux doses d'anatoxine DT a été déterminée par une analyse rétrospective de la mortalité néonatale chez les enfants des femmes de ces groupes, 9 à 32 mois après le programme de vaccination.

Deux doses d'anatoxine DT ont abaissé d'un tiers la mortalité néonatale pendant une période de 9 à 32 mois suivant la vaccination. La différence dans les taux de mortalité est attribuable à un abaissement de 75% du taux de mortalité parmi les nourrissons de 4 à 14 jours, âge où le tétanos est la principale cause de décès. Une dose unique d'anatoxine DT réduisait les décès des nourrissons de cet âge approximativement dans la même mesure que deux doses pendant une période allant jusqu'à 20 mois après la vaccination, mais au-delà de ce temps une dose unique ne semblait pas fournir de protection.

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