A reassessment of risk factors for neonatal tetanus

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A hospital-based case–control study was conducted to further examine the risk factors for neonatal tetanus (NNT) in the North-west Frontier Province of Pakistan. Three control infants were concurrently evaluated for each of 102 consecutively diagnosed NNT cases hospitalized over an 8-week period. Application of clarified butter (ghee) during the first few days of life was shown to be a significant risk factor, confirming our previously reported finding. However, the risk appeared to be limited to ghee made in the home from cow's milk. The tool used to cut the umbilical cord was again refuted to be a risk factor; application of topical antibiotics conferred significant protection. Multivariate analysis of the matched data showed that delivery by persons with academic training (physicians, nurses, and lady health visitors) was also protective. Mothers with a past history of NNT babies were shown to have a significantly increased risk, and accounted for more than one-third of all cases in the present study. The findings suggest possible ways to augment the effectiveness of NNT elimination programmes.

Introduction

Neonatal tetanus (NNT), which currently causes over 780 000 deaths every year,¹ is a problem occurring almost exclusively in the developing countries. The main strategy for prevention is the provision of passive immunity to newborns through prior immunization of their mothers with tetanus toxoid. The “virtual elimination” of neonatal tetanus, which is defined as a reduction in incidence to less than 1 case per 1 million live births, by the year 2000 has been adopted as an objective by The Task Force for Child Survival (3); and the World Health Assembly adopted a resolution to “eliminate” neonatal tetanus by 1995.⁴ The ability to achieve such reductions will be greatly facilitated in the future by current successes in immunizing young girls, but many women of childbearing age at present have not been immunized with tetanus toxoid. Indeed, only about 25% of pregnant women in the developing nations of the world are at present estimated to have been fully immunized with tetanus toxoid,⁴ despite ongoing efforts of WHO’s Expanded Programme on Immunization which has achieved coverage in excess of 70% for other antigens in childhood. One factor contributing to low coverage is that most pregnant women in rural areas of the developing world are delivered at home, and many never come in contact with the medical establishment throughout pregnancy and delivery. Better systems to improve coverage of pregnant women and women of childbearing age in such areas are needed. Meanwhile, there will be a continuing and complementary role for reducing the risk of NNT through the promotion of practices that reduce the risk of contamination of the umbilical cord wound with tetanus spores by maintaining cleanliness throughout delivery and during transection of the umbilical cord, and by not applying unhygienic substances to the umbilical cord wound.

Several descriptive studies of the risk factors for neonatal tetanus have been reviewed (4–9); these and similar studies raise but do not test hypotheses. Relatively few analytic studies (11–15) have been undertaken to elucidate risk factors for NNT, a surprising finding in view of the magnitude of the continuing problem of NNT globally. None of these have specifically assessed exposure after delivery and during the first several days of life, and none employed multivariate analysis to control for confounding variables. Also, infants born to immunized mothers were included as controls in some of them.

In a case–control study we previously reported (I), commonly held beliefs about neonatal tetanus were refuted. Specifically, the instrument used to cut the umbilical cord and the method of preparing the tool for use could not be confirmed as risk factors. However, the application of clarified butter, ghee, to the umbilical wound during the first several days of life was shown to pose an important but previously undocumented risk among cases in North-west Frontier Province. We undertook the present hospital-based, matched, case–control study with

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multivariate analysis to further evaluate the risk factors for NNT.

Methods

Case ascertainment. A total of 102 consecutive NNT cases were prospectively identified among admissions to the Infectious Disease Hospital in Peshawar, North-west Frontier Province, Pakistan, from October to December 1989. Each case had been diagnosed by a physician as neonatal tetanus and had all the following symptoms and signs: the infant sucked normally at birth but became unable to suckle as the disease progressed; became unable to open the jaw; manifested clenched fists and dorsiflexed feet; experienced generalized spasms that could be triggered by physical stimuli and showed generalized rigidity as the disease progressed. A standard questionnaire, which included information based on interviews with the child's mother and other family members, was completed for each case. Interviews were conducted in the local language.

Selection of controls. The village of origin of each case was visited, and three control infants were selected from the same village or (if needed) the nearest neighbouring village; the controls were of the same sex and their birth dates were as close as possible to the date of birth of the matching case. Potential control infants were rejected if their mothers had a history of appropriate immunization with tetanus toxoid. All control infants were followed up to ensure that they remained well throughout the neonatal period. A standard questionnaire was completed, as described above, for each control infant.

Sex matching was undertaken to control for the possible impact of circumcision on the risk of NNT in males, while village matching was designed to minimize the effect of village-to-village differences in delivery practices. Matching by date of birth was designed to assure equivalent degree of recall among mothers of cases and controls. Finally, only babies of mothers were not appropriately immunized were accepted as controls, so that the risk factors were not obscured by passive immunity transferred from mother to child.

Data analysis. Data were tabulated in dBase III plus. Standard \( \chi^2 \) and Fisher's tests were used to test the significance of differences involving dichotomous variables in unmatched data, using two-tailed tests. Univariate analysis of matched data employed Mantel-Haenszel \( \chi^2 \) for multiple matched controls per case as described by Fleiss (16). Multivariate analysis of matched data employed the PECAN procedure (2).

Results

Compared with their matched cases, 23.7% and 63.7% of the controls were born within 1 week and 1 month, respectively, of the date of birth of the matched case. Only 1 control was born more than 2 months from the birth date of its matched case. Males comprised 82 of the 102 hospitalized cases. A higher proportion of female cases (25%) than male cases (8.0%) was admitted more than 3 days after the onset of symptoms (\( P = 0.037 \) by Fisher's exact test). The mean age at onset was 6.1 days (range, 3–10 days).

Predelivery practices administered by attendants to the mothers, including the frequency of enemas and cleaning of the perineum, did not differ significantly between cases and controls. Almost all deliveries were attended by either relatives (52.8%) or traditional birth attendants (TBAs) (32.9%) and took place at home (92.5%). No significant differences were seen between the mothers of cases and controls in regard to delivery by any specific category of attendant. However, when grouped into those with formal academic training that encompassed obstetrics (physicians, nurses and lady health visitors*) versus those without this background (TBAs, relatives, self-delivered, etc.), the academically trained group was associated with a decreased risk of NNT on univariate analysis (O.R. 0.28; 95% confidence limits, 0.08 to 1.0).

Mothers of cases and controls were similar in average age and total live births. Overall, the average number of live births was 4.3 with a range from 1 to 15. However, the case mothers gave a history of NNT among former live births more frequently than the control mothers; 27 former NNT cases were reported among 355 previous children of mothers of cases (7.6%), compared with 42 NNT cases among 1000 previous children of mothers of controls (4.2%) \( (\chi^2 = 5.60, P = 0.018) \).

Of the 171 current and previous NNT cases reported among case mothers and control mothers in this study, 65 (38.0%) were born to 28 mothers who already had a child with NNT (Fig. 1). Thirty-two (10.5%) mothers of control infants had histories of 1 or more previous NNT cases; and 8 (2.6%) of these mothers had multiple cases that accounted for 18 (42.9%) of the total of 42 previous cases born to control mothers. Of the 102 mothers of current cases, 20 had a history of multiple cases that accounted for 47 (36.4%) of the total of 129 cases (Fig. 1).

* Lady health visitors are high-school graduates with two years of training in maternal and child health at a school of public health.
About 44.3% of cases and 26.3% of controls reported the use of a new razor to transect the umbilical cord. Non-academically trained birth attendants were responsible for 116 of the total of 117 instances where new razors were used. Thus, the risk of use of a new razor could not be separated from the risk of being delivered by non-academically trained birth attendants. Academically trained attendants almost always used scissors.

Cases and controls did not differ significantly in use of other tools—kitchen knives were used for 35% of cases and 47% of controls; scissors for 15.5% cases and 21.0% controls; an old razor for 6.9% cases and 1.8% controls; and farm tools for 0% cases and 1.8% controls.

Only six case infants had substances applied to the umbilical wound immediately after the cord was transected, and no significant differences in such exposure were noted between cases and controls. Ghee was applied initially to 2 case infants, both of whom also had subsequent ghee applications. Table 1 summarizes the substances applied to the umbilical wound subsequent to the initial dressings.

The frequencies of exposure to both ghee and antibiotics differed significantly on univariate analysis between cases and controls. Exposure to ghee irrespective of its origin conferred an enhanced risk of NNT (O.R. 1.72; 95% confidence intervals, 1.03 to 2.87), while topical antibiotics were significantly protective (O.R. 0.34; 95% confidence intervals, 0.18 to 0.65). A wide variety of topical antibiotics were used; products containing neomycin, bacitracin and nitrofurazone, separately or in combinations, were most common. None of the other substances differed significantly between cases and controls.

Several different types of ghee were used, and each type was separately analysed. Commercially available ghee of vegetable origin was used on approximately equal proportions of cases and controls, while cases were actually exposed less frequently to ghee from water buffalo’s milk than controls; these differences were not significant. However, cases were exposed significantly more frequently to ghee made in the home from cow’s milk (O.R. 2.93; 95% confidence intervals, 1.69 to 5.08 by univariate test).

The home-made cow’s ghee was almost invariably heated before use on both cases and controls (97.5% and 97.1%, respectively). Both cases and controls averaged about two applications of cow’s ghee daily. Controls had longer average exposures to ghee than cases since exposures were curtailed when the case was admitted with neonatal tetanus.

Fig. 2 depicts the frequencies of the four factors that were investigated and found to be significantly different between cases and controls. Matched data for cow’s ghee, delivery attendant and topical anti-

### Table 1: Substances subsequently applied to umbilical wounds

<table>
<thead>
<tr>
<th>Substance</th>
<th>Cases (n = 102)</th>
<th>Controls (n = 306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghee, by source:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sources</td>
<td>62(60.8)*</td>
<td>152(49.7)</td>
</tr>
<tr>
<td>Vegetable origin</td>
<td>9(8.8)</td>
<td>31(10.2)</td>
</tr>
<tr>
<td>Water buffalo milk</td>
<td>19(18.8)</td>
<td>79(25.8)</td>
</tr>
<tr>
<td>Cow milk</td>
<td>42(41.2)</td>
<td>72(23.5)</td>
</tr>
<tr>
<td>Turmeric</td>
<td>36(35.3)</td>
<td>130(42.5)</td>
</tr>
<tr>
<td>Oil</td>
<td>27(26.5)</td>
<td>82(26.8)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>13(12.7)</td>
<td>88(28.8)</td>
</tr>
<tr>
<td>Surma</td>
<td>12(11.8)</td>
<td>19(6.2)</td>
</tr>
<tr>
<td>Surkay</td>
<td>12(11.8)</td>
<td>40(13.1)</td>
</tr>
<tr>
<td>Disinfectant</td>
<td>2(2.0)</td>
<td>6(2.0)</td>
</tr>
<tr>
<td>Ash</td>
<td>1(1.0)</td>
<td>4(1.3)</td>
</tr>
<tr>
<td>Earth</td>
<td>1(1.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Cow dung</td>
<td>0(0.0)</td>
<td>2(0.7)</td>
</tr>
</tbody>
</table>

* Figures in parentheses are percentages.
biotics were also subjected to multivariate analysis (17). Each remained significant after controlling for the influence of the other factors, with the following odds ratios: home-made cow’s ghee, O.R. 1.94 (1.07 to 3.53); non-academically trained delivery attendant, O.R. 3.90 (1.02 to 14.88); and topical antibiotics, O.R. 0.37 (0.25 to 0.74). These results thus confirmed those found with univariate testing.

Only one case was circumcised. This circumcision occurred one day after onset of NNT symptoms.

None of the mothers of cases had been appropriately immunized with tetanus toxoid before admission of their child with NNT. In accord with the study design, no mothers of controls had received two or more doses of TT before delivery of the control infant.

Overall, 40.7% of all mothers reported receipt of injections in association with labour and delivery; 61% of mothers delivered by traditional birth attendants reported such injections. The most common reason for injection, when specified, appeared to be prolonged labour and placental retention.

### Discussion

The results of this case–control study confirm and extend those reported earlier (1). Application of ghee to the umbilical wound during the first several days of life was again shown to be a significant risk factor for NNT. Ghee has been traditionally accepted as a dressing for the umbilical cord wound (9). Detailed questioning revealed that only ghee made at home from the milk of cows was associated with increased risk. Microbiological studies are now being carried out on samples from cases and controls associated with home-made cow’s ghee to assess intrinsic and in-use contamination. The results of these studies will be reported elsewhere. The involvement of only one type of ghee would seem to indicate the presence of an undisclosed and possibly unique aspect involved in its preparation or use.

Only one previous case–control study specifically assessed the exposure to ghee as a risk factor (10). This study did not reveal a difference in the frequency of exposure of cases and controls to ghee, but the matched controls were delivered by the same traditional birth attendant who delivered the case, and the substances applied by mothers were not tabulated.

Optimal control of neonatal tetanus requires that attention be given to practices involving the umbilical wound during the first several days of life, not just clean practices at the time of delivery. Mothers and other adult household members will need to be educated to avoid unsanitary substances.

As with our previous study, none of the specific tools used to cut the umbilical cord, including kitchen knives, appeared to increase the risk for NNT. We concluded that the association of new razors with disease was most likely due to lack of education and training among the attendants who used them, which is supported by the observation that other tools more likely to be contaminated with tetanus spores posed no risk. Baxter-Grillo and co-authors (11) found no significant difference in the cutting tools used on cases and hospitalized controls. Yusuf et al. (12) reported a higher NNT mortality rate where bamboo knives had been used rather than scissors, but the actual numbers involved were not given and statistical tests of significance were not reported.

Topical antibiotics were not significantly protective in our earlier case–control study based on cluster surveys of live births in rural areas, but only a few infants received such treatment. In contrast, topical antibiotics were both commonly used and significantly protective in the current urban, hospital-based study.

Other analytic studies have also evaluated the risk of substances applied to the umbilical wound. In the study of Baxter-Grillo et al. (11), the frequencies of exposures to different substances did not differ significantly between cases and the control group. Yusuf et al. (12) noted that the NNT mortality rate was higher among babies exposed to traditional substances, such as kitchen ash or sirih leaf mixture, than among babies exposed to “antiseptic” substances, but neither the actual numbers nor results of statistical tests of significance were given. Sokol et al. (13) found traditional cord care, defined as use of dressings with oil from nuts of a local tree, plant leaves, and/or cotton wool, was significantly more common among cases than controls. However, the birth dates of cases were closer to the interview date than the birth dates of controls, thus making recall of substances used on the umbilical wound more difficult for the control mothers. Stroh et al. (14) reported that for areas with low TT immunization of pregnant women (8%) about one-third of cases and one-third of all deliveries had been exposed to potentially infectious dressings, which were defined as primarily saffron, sesame oil and “indigenous medicine”. In the comparison area with high coverage (66%), 4 of 11 cases (36.4%) and 48 of 3000 (16%) deliveries (P = 0.085) had been so exposed. Thus, these substances could not be incriminated in a univariate analysis.

Although physicians, nurses and lady health visitors used more topical antibiotics and less ghee than other delivery attendants, a protective effect persisted after controlling for the influence of other variables.
in the multivariate analysis of the matched case-control pairs. Though not studied here, handwashing may well have been a factor underlying this observation.

We were unable to determine from interviews with mothers whether the TBAs in attendance had been trained and whether trained TBAs followed the academic pattern. In earlier unpublished studies of the TBA's knowledge and practices in this province conducted by us, trained TBAs were significantly more likely to use disinfectants and less likely to use ghee on umbilical cord wounds. The importance of delivery attendants' practices has also been evaluated by others. Olive et al. (15) noted that untrained TBAs had attended deliveries where a higher proportion of babies died with NNT than from other causes in the neonatal period, but they did not investigate the proportion of deliveries by untrained TBAs where the babies survived the neonatal period. Yusuf et al. (12) reported only 5 NNT deaths among 954 (0.5%) babies delivered by doctors and midwives, compared with 77 NNT deaths among 2794 (2.8%) deliveries by traditional birth attendants. Stroh et al. (14) reported that delivery by trained birth attendants reduced the risk of neonatal tetanus.

Clustering of cases among babies of the same mothers, whether of cases or controls, which had not previously been noted in the epidemiology of NNT, may be due to the same risky practices being continued with the later offspring of the same mother. Repeated NNT cases born to the same mother accounted for more than one-third of all cases reported in our study; these could have been prevented by immunization of the mother after the recognized occurrence of her first case of NNT. Based on the data presented in Fig. 1, immunization of the 102 mothers of current cases immediately after their first case could have prevented at least 27 cases among 20 women, and immunization of the 32 mothers of controls after their first case could have prevented at least 10 cases among 8 women. The number of NNT cases prevented would increase with further pregnancies of these mothers, if delivery practices and immunization status remain unchanged. Therefore, this strategy could potentially prevent about 1 case of NNT for every 3 mothers so immunized. Overall neonatal tetanus rates could potentially be reduced by as much as one-third if all mothers known to have an earlier case were specially targeted for immunization in accord with their increased risk.

More than 90% of NNT cases in the present study area do not come to the attention of the medical care system (1) and those cases detected through clinical facilities would identify only a fraction of the mothers with this special indication for immunization. However, immunization of mothers of currently hospitalized cases, which can be carried out through hospital-based programmes, is likely to be highly cost-effective in preventing further cases. Since most women in this study environment are delivered at home, more complete reporting of NNT cases as well as the identification of the mothers of these cases would require more intensive surveillance, which could be achieved by expanding the roles of the trained TBAs.

Earlier surveys in this province revealed 52% of live births and 59% of NNT cases to be male (I), whereas about 80% of NNT cases in our hospital-based study were male. These observations suggest that male cases were more quickly hospitalized after the onset of symptoms because of local societal values. We did not collect sufficient data to determine whether case fatality ratios differed significantly by sex.

Our data on just over 100 cases of NNT collected in an 8-week period are probably a small fraction of the actual NNT cases occurring in the study area. Clearly, tetanus remains a major infection contributing to neonatal and infant mortality in Pakistan and other areas of the developing world. While the main intervention must be immunization with TT, the coverage rates in pregnant women remain unacceptably low in developing countries. Achievement of the global goal of elimination of NNT will require improved control strategies, including the training and retraining of TBAs who are potentially useful for control efforts including reporting of all cases of NNT, and systematic referral of mothers for TT injections (or TBAs themselves immunizing the mothers with TT, since a high proportion of trained TBAs already give injections during labour and delivery). TBAs should be instructed to avoid the use of ghee on the umbilical cord wound and to advise mothers and other family members against this practice; instead, they could use topical antibiotics which were shown to be significantly protective in this study. Additionally, the development of systems to immunize mothers known to be associated with an NNT case should be considered. This group is at much higher risk for further cases, and TBAs could be particularly useful in identifying such women.

The role and importance of TBA practices and TT coverage in controlling NNT have often been debated. Both approaches are clearly complementary in attacking this major, still unsolved public health problem of the developing world.

Acknowledgements

We thank the Bank of Credit and Commerce International, London, the BCCI Foundation, Pakistan, and Global
Résumé

Réévaluation des facteurs de risque de tétanos néonatal

Le tétanos néonatal est responsable de plus de 780 000 décès chaque année dans le monde. Si la vaccination de la totalité des femmes par l'anatoxine tétanique est la méthode préventive de choix, le taux de couverture chez les femmes enceintes des pays en développement ne dépasse guère 25%. Les raisons de ce phénomène sont que dans bien des endroits la plupart des accouchements ont lieu à domicile et que la mère n’a parfois aucun contact avec le personnel médical ou de santé publique, que ce soit pendant la grossesse, pendant le travail ou pendant l’accouchement.

Une étude cas-témoin en milieu hospitalier a été réalisée pour réexaminer les facteurs de risque de tétanos néonatal dans la province pakistanaise de la Frontière du Nord-Ouest. Trois nourrissons restés en bonne santé dans la période néonatale ont été examinés dans le même temps et pris comme témoins pour chacun des 102 cas consécutifs de tétanos néonatal diagnostiqués et hospitalisés sur une période de huit semaines. Les témoins, choisis parmi des nourrissons nés de mères sans vaccination antérieure par l’anatoxine tétanique, ont été appariés aux cas sur la date de naissance, le sexe et le village.

Une analyse multivariée a été faite sur ces données appariées. L’application de beurre clarifié (ghee) pendant les premiers jours qui suivent la naissance paraît être un facteur de risque important, ce qui confirme les résultats obtenus par nous précédemment. Il semble, cependant, que le risque soit limité à la préparation domestique faite à partir de lait de vache. Ce beurre clarifié est une préparation largement répandue et couramment utilisée en Asie méridionale pour faire le pansement ombilical. Si l’on veut lutter contre le tétanos néonatal, il faut considérer également les substances appliquées pendant les premiers jours de la vie sur la plaie de section du cordon, et pas seulement l’hygiène des gestes au moment de l’accouchement.

L’instrument de section du cordon n’apparaît pas comme un facteur de risque, tandis que l’application locale d’antibiotiques confère une protection significative. La présence à l’accouchement d’un médecin, d’une infirmière ou d’une visiteuse de santé, est également protectrice. Un risque de tétanos néonatal significativement augmenté s’observe pour les naissances antérieures quand la mère a un enfant qui est un cas actuel de tétanos néonatal: 7,6% des naissances antérieures ont eu un tétanos néonatal quand la mère a un nourrisson qui est un cas actuel, contre 4,2% quand le nourrisson est un témoin actuel. D’après les données de l’étude, la vaccination de toutes les mères après la survenue du premier cas devrait pouvoir prévenir près d’un tiers des cas de tétanos néonatal. On se propose donc, afin d’éliminer cette augmentation du risque, de réaliser des vaccinations ciblant particulièrement ces mères.

Si l’élimination du tétanos néonatal est envisagée à l’échelle mondiale, les stratégies de lutte devront être améliorées. Il faut notamment envisager la formation et le recyclage des accoucheuses traditionnelles qui ont leur place dans les actions de lutte, qu’il s’agisse de notifier les cas de tétanos néonatal, de diriger les mères vers un centre où elles pourront se faire vacciner par l’anatoxine tétanique, ou de les vacciner elles-mêmes. Les accoucheuses traditionnelles recevront pour instruction de ne pas employer de beurre clarifié pour le pansement ombilical, et de déconseiller cette pratique aux mères et aux autres membres de la famille. Les antibiotiques topiques paraissent protecteurs et peuvent être recommandés.

L’importance relative des pratiques des accoucheuses traditionnelles et de la couverture par l’anatoxine tétanique dans la lutte contre le tétanos néonatal est souvent l’objet de débats. Il va de soi que le traitement de ce problème de santé publique, majeur et encore non résolu dans les pays en développement, doit recourir à ces deux approches, de toute évidence complémentaires.

References

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