Determining the role of circumcision and other traditional surgeries in neonatal tetanus (NNT) is complicated, since it is difficult to be confident in any single case whether the illness derived from the umbilical wound or another wound. Though male circumcisions have been reasonably suggested as the basis for the preponderance of male NNT in some community-based studies, we could identify no case-control studies that actually documented its risk. Perhaps as a consequence, strategies specifically designed to prevent circumcision-derived NNT have not been given much attention. Indeed, circumcision wounds are not even identified as a source of NNT in the global plan for eliminating NNT.

In an earlier community-based study, we noted that circumcisions in the neonatal period paradoxically appeared protective. It was recognized that this was related to the selection criteria for the boy controls, who were required to survive the neonatal period and were thus at risk of circumcision throughout this time, whereas cases most often became ill and died early in the neonatal period. Sokal et al. also noted that circumcision in boys and ear piercing in girls were significantly protective against NNT, and speculated that these traditional surgeries may have been avoided in infants who were ill.

Circumcision and neonatal tetanus: disclosure of risk and its reduction by topical antibiotics

John Bennett, Catherine Breen, Hector Traverso, S Bano Agha, Jennifer Macia and John Boring

Background Previous case-control studies have paradoxically suggested that circumcisions protect against neonatal tetanus (NNT), but these observations have not been adjusted for differences in the length of survival of cases and controls.

Methods Boy cases (n = 133) and their sex-matched controls (n = 399) were extracted from a population-based study of NNT undertaken in Punjab Province, Pakistan. In the resulting file, circumcisions were censored such that analysis was restricted to only those that occurred before onset in cases or before age of onset in the matched case for controls. The effect of topical antibiotics in circumcision wounds was then evaluated.

Results After adjusting for confounders, circumcision before onset posed a significant risk for NNT (matched odds ratio [OR] = 3.1, 95% CI: 1.2–8.0). The risk of NNT in those circumcised before onset and treated with topical antibiotics did not differ significantly from the referent group who had not been circumcised before onset (matched OR = 1.1, 95% CI: 0.2–6.8), whereas the lack of topical use was associated with significant risk (matched OR = 4.2, 95% CI: 1.4–12.6). This suggests that topical antibiotics are likely to be highly effective in preventing NNT from circumcision wounds. We estimated an overall risk of about 16 fatal NNT cases per 1000 live boy births with circumcision wounds that were not protected by topical antibiotics, and that circumcision and umbilical wounds each accounted for about half of this overall risk in these boys.

Conclusions Topical antibiotics should be routinely applied to all wounds created by traditional circumcisions, to prevent NNT and sepsis from these frequently unsterile procedures.

Keywords Neonatal, tetanus, circumcision, topical, antimicrobials, prevention, case-control

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Bundling, a traditional practice in the Northern areas of Pakistan whereby the umbilical wound becomes exposed at various ages of the child to dried cow dung, also appeared paradoxically protective on initial analysis. It was recognized that a survival bias in the controls was also involved in these findings. The real risk became evident after censoring the bundling exposures of controls to those that took place before the onset of illness in their matched case.6

In a large unpublished case-control study involving 229 cases and 687 matched controls that was conducted in Punjab Province in 1990, it was again recognized that boy controls were more likely to be circumcised during the neonatal period than boy cases, thus again seemingly indicating protection. However, use of topical antibiotics on the circumcision wound also appeared to protect against NNT, creating a puzzling predicament—if circumcision is not risky, then how could topical antibiotics provide protection?

In order to study delivery and cord care practices related to NNT and avoid bias from circumcision-derived cases, all cases in this data set who had been circumcised before onset of their NNT, along with their matched controls, were excluded and the emended data set used for analysis. Published findings indicated that protection was conferred by topical antimicrobial agents applied to umbilical wounds at delivery and after the delivery day, hand washing by the delivery attendant, and delivery by a medically trained attendant; conversely, applying animal dung or ash to the wound, exposing mothers to clarified butter (ghee) on skin or intravaginally, and delivery on a surface contaminated by dried cow dung were risky.7 Subsequent analysis also showed that delivery on surfaces other than a clean cloth, plastic sheet or bed was also risky.

In the present analysis, which is focused on circumcision, all and only the 133 boy cases and their 399 matched controls from the Punjab case-control study were selected for analysis.

Study Design
Basic aspects
The case ascertainment, data collection methods and case definitions for detecting NNT deaths in this population-based survey of 23,670 live births have been described previously.7 Each detected NNT death was then matched with three controls by birth date, sex, and cluster. Controls were required to survive the neonatal period, and their mothers were required to have no histories of TT injection. Maternal factors, delivery variables, tools used to cut the umbilical cord and substances applied to the umbilical wound have been detailed elsewhere.6

During the survey, trained women interviewers were asked to determine from the mother whether the baby was circumcised and, if so, the age in days when the procedure was performed and who did the circumcision. They were also asked to indicate which of the following list of substances had been used to dress the wound: surma, ash, disinfectant, camel dung, cow dung, earth, antibiotic, turmeric, ghee, surkhay, and oil. Space was provided to write in other substances that were used. Many of these substances are traditionally used on umbilical wounds.

Data analysis
Data from questionnaires were originally entered into a Data Base III + file, which was subsequently converted into an EpilInfo 6.0 file for analysis.6 Using the EpilInfo export function, the file was converted into EGRET (Epidemiological Graphics, Estimation and Testing Package) format, and logistic regression analysis was performed using the PECAN module of EGRET.9 Another program, cLogistic, was also used for the conditional analysis.10 Statistical Analysis Software (SAS) was used to calculate Pearson correlation coefficients. Breslow-Day $\chi^2$ was used to evaluate possible interactions.

The number of missing, or ‘don’t know’ responses varied by questionnaire item. Most fields had a few missing responses, but it ranged from none for birth date to 46 records missing data for the delivery surface. In the following text, results are based on the number of records with information for a given variable, not on the total number of subjects in the study.

Results
General findings
In the population-based live birth surveys from which the present data set is derived, 51.3% of the births were male (12,126 of 23,618 live births). Among the 229 NNT deaths identified, 58.1% (133) were male. This difference in proportions is statistically significant ($z = 2.059, P = 0.042$).

Within the case-control data set, all circumcised cases and 96% of those in controls had been performed by barbers; doctors circumcised five controls.

Substances applied to circumcision wounds
A variety of traditional substances were commonly applied to the circumcision wound. Figure 1 shows frequencies of exposures to substances among cases and controls in decreasing order of frequency of use in cases. Antibiotics appeared protective. Antiseptics had been used with low frequency (4%) for both cases and controls. Surma, cow dung, urine treatments, ash, and ghee were all applied more often to cases than controls.

Risk of circumcision
Before accounting for survivor bias, circumcision appeared to be protective—about 20% of the cases and 39% of the controls

![Figure 1](https://example.com/figure1.png)
had been circumcised (matched OR = 0.37, 95% CI: 0.22–0.60), including 12 controls whose circumcisions occurred after the neonatal period. Circumcision during the neonatal period (matched OR = 0.44, 95% CI: 0.27–0.73) was also significantly more common among controls (35%) than cases (20%). However, when circumcisions were censored to include only those performed before onset of illnesses in cases or, for controls, before the age at onset of NNT in their matched case, circumcision before onset became significantly risky with 18 cases (14%) and 30 controls (8%) circumcised before onset time (matched OR = 2.35, 95% CI: 1.12–4.92).

The mean age at onset of illness for NNT was 10.6 days for those circumcised before onset, and 4.9 for cases not circumcised before onset (P < 0.0001, Mann-Whitney U). In a random subsample of records from the live birth file, the mean circumcision age for boys circumcised in the neonatal period was 9.0 days. The average length of illness was similar for those circumcised and not circumcised before onset, 4.7 and 4.8 days, respectively.

Each of the variables used in the following conditional logistic regression analysis was also found to be significantly related to NNT in the companion paper that focused on delivery and cord care risks. However, variables for medically trained attendant and hand washing by the delivery attendant were dropped because of their high correlations and collinearity with the variables that were included. The following variables were included: use of scissors to cut the cord; pre-delivery application of clarified butter (ghee) to mother’s perineum, abdomen or intra-vaginally; dirty delivery surface (straw, cow dung, dirt, floor, etc. i.e. any surface other than clean cloth, plastic sheet or a bed); use of antimicrobials (antibiotics or antiseptics) on the umbilical wound at and after the day of delivery, and dirty cord treatments (cow dung or ash).

Circumcision before onset remained significantly related to NNT (matched OR = 3.1, 95% CI: 1.2–8.0; P = 0.017 by likelihood ratio statistic) after controlling for these confounding variables.

Effects of topical antibiotics
The impact of antibiotics on the risk of circumcision before onset was then assessed by creating two design (indicator) variables. The referent group was those who had not been circumcised before onset, and thus had only umbilical wounds as a potential source. Those who had been circumcised before onset were then coded for either the use or non-use of topical antibiotics.

In the 446 records complete for all variables, circumcision without antibiotics posed a substantial and significant risk for NNT, (OR = 4.1, 95% CI: 1.4–12.0; P = 0.005 by likelihood ratio statistics), after controlling for the five variables mentioned above. In contrast, no significant increase in risk relative to the referent group was seen in those treated with topical antibiotics (OR = 1.1, 95% CI: 0.2–6.8; P = 0.90 by likelihood ratio statistics). Findings were basically unchanged when antimicrobials (antibiotics and antiseptics) were substituted for antibiotics (OR = 4.2, 95% CI: 1.4–12.6 without antimicrobials, OR = 1.5, 95% CI: 0.3–7.1 with antimicrobials).

The reduction in NNT risk associated with topical antibiotics did not reach statistical significance when analysis was restricted to the 44 boys who were circumcised before onset (OR = 0.26, P = 0.09 by Fisher’s one-tailed test). Confidence intervals were very wide (0.03–1.6), reflecting the small sample sizes involved in this direct comparison.

Discussion
The preponderance of evidence presented in this study supports the conclusion that circumcisions are an important source of NNT in the study area. It specifically implicates circumcision performed without antibiotics as a risk factor. This conclusion is also consistent with the observed significantly higher frequency of NNT in boys relative to their proportion among all births, and by the highly significantly later age at onset for boy cases who were circumcised before onset.

Some estimates can be made of the possible magnitude of this problem in the study area. If the risk of NNT is the same in girls and uncircumcised boys, and no circumcisions had been performed, then only 101 (96 girl cases × 1.055) total boy cases would have occurred after accounting for the excess male live births. The observed 133 cases in boys is 32 cases in excess of this number, and the excess would be attributable to circumcisions. In a random subsample of more than 900 records from the live birth file, 50% of boys had been circumcised in the neonatal period, and topical antibiotics had been applied to 30% of the circumcisions. Thus, it can be estimated that these 32 circumcision-attributed cases occurred among an estimated 6063 (50% of the total 12 126 male live births) circumcised boys. This corresponds to a risk of 5.3/1000 circumcisions, which is more than half as large in itself as the risk seen in girls (96 fatal cases/11 492 live births, or 8.4/1000) and expected in uncircumcised boys. Based on our findings, however, this overall risk would be much less in those treated with topical antibiotics and much higher in those not so treated. If it is assumed that all 32 excess male fatal cases occurred among the 4244 (70% of 6063) circumcised boys who were not protected by topical antibiotics, then the risk of dying from circumcision-attributable NNT in this group would be 7.5/1000; this is roughly equivalent to the risk of dying from umbilical wound derived NNT (8.4/1000), and would produce an overall risk of about 16/1000 in this group of boys. These circumcision related risks are of special concern, since the data suggest they may be almost completely preventable with topical antibiotics that are inexpensive and they involve a wound from an elective procedure, whereas umbilical wounds are unavoidable.

These estimates may underestimate the problem, however, since non-fatal cases of NNT were not included in our studies, fatal cases with onset in the neonatal period but dying thereafter would have been missed by our study design, and septic deaths from these frequently unsterile procedures were not studied. On the other hand, more complete recall of the deaths of boys by parents may have had an opposite effect. If such recall bias also contributed to the excess male deaths, then the disease burden from circumcision would be reduced.

Disclosure of the real influence of circumcision proved challenging. The analytical approach, which restricted analysis of circumcisions to those occurring before onset in cases or matched cases for controls, clearly helped to successfully remove the effects of survivor bias in the controls. With control for confounding, the odds ratio for circumcision before onset increased from 2.4 to 3.1. This risk reflects the combined effects of both clean and dirty circumcisions before onset. When exposure was separated
into circumcision with and without antibiotics, the odds ratio for those without antibiotics increased further to 4.1, while the odds ratio for boys treated with topical antibiotics was 1.1 in reference to uncircumcised boys.

Conditional logistic regression findings were basically unchanged when antimicrobials (antibiotics and antiseptics) were substituted for antibiotics. However, antibiotics accounted for nearly all antimicrobials, and the use of antiseptics was too infrequent (n = 7) to reliably assess their independent effects.

The identity of the topical antibiotics that were used is unknown; this information was not solicited in the questionnaire. Further, the frequency and duration of use is also unknown. These are important shortcomings in this data set. If similar to umbilical wound treatments with antibiotics in these areas,7 then nitrofurazone (Furacin) ointment and ointments containing bacitracin alone or in combination with other agents were perhaps most commonly used.

Although this study is a large case-control study conducted in an NNT endemic area where neonatal circumcisions are common, the sample size was still small for some aspects of analysis. Only 48 (9%) of the cases and controls were circumcised before onset. Antibiotic exposures were known for only 44 of them, of whom 12 had been treated and 32 not treated with topical antibiotics. Thus, the finding of elevated risk in boys untreated with topical antibiotics should be accorded greater confidence than the absence of risk in treated boys. While NNT risk in treated and untreated boys did not differ significantly in a direct comparison, the finding of elevated risk from untreated circumcisions was still clearly and significantly established against the referent group of 467 uncircumcised boys, whose only presumed potential source for NNT was the umbilical site. Similarly, a protective effect of treatment could be inferred from the close similarity in odds ratios for treated boys (1.1) and the referent group (1.0), coupled with the remote probability that these odds ratios really differed significantly from each other.

Preventing NNT from circumcision wounds is made difficult by deeply ingrained traditional practices. Traditional circumcisions are common in Islamic societies such as our study area, and religious leaders could play an effective and useful role in promoting prevention strategies.

Passive transfer of antibodies from immunized mothers to their babies is an important and effective way to reduce risks of NNT from all wounds. Subsequent protection should last until most infants have been actively immunized with three doses of DPT, which often occurs by 14 weeks of age in developing countries. There is clearly a need for prevention strategies complementary to maternal immunization, however, since several hundred thousand NNT deaths might continue to occur annually in the developing world if underlying risks remain unchallenged, despite optimistic estimates of achievable coverage and vaccine effectiveness.7

Specific additional strategies to prevent NNT from circumcisions can be recommended. Circumcision under aseptic conditions should be promoted. We believe topical antibiotics should be routinely applied to every circumcision wound, whether a traditional procedure or not, and topical application of all other substances avoided. Circumcision wounds that are not directly contaminated with applied substances are still at risk for contamination with tetanus spores from hands, cutting tools, and other environmental sources, and risk of acquiring NNT from such contamination probably persists for the first few days after the procedure, as suggested by other observations.5 Thus, it would seem prudent to recommend daily applications for 3–5 days after the procedure. Delaying circumcision until the infant has received three doses of DPT could prevent both neonatal and later onset tetanus cases; topical agents would complement such immunization in preventing tetanus. Topical agents are likely to be highly effective in preventing NNT from circumcision wounds, and may also be highly beneficial in preventing septic complications from these frequently unsterile traditional procedures.

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