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Protective Effects of Topical Antimicrobials against Neonatal Tetanus

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Background. Case-control studies previously conducted in Pakistan suggested that topical antimicrobials might provide protection against neonatal tetanus (NNT) when applied to the umbilical cord wound during the first several days of life. The present case-control study, the largest such study yet reported, was undertaken in Punjab Province, Pakistan and afforded further opportunities to evaluate such effects.

Methods. A population-based, matched, case-control study was undertaken to assess topical antimicrobials and other factors related to NNT risk in rural parts of Punjab Province.

Results. Continuous use of antimicrobial agents (antibiotics and antiseptics) at delivery and during the first few days after delivery was highly protective in univariate testing (matched odds ratio 0.2 [95% confidence interval : 0.11–0.64], $P = 0.003$), and remained significantly protective when other delivery and cord care practices were controlled. In contrast, applying nothing to the wound was risky compared with antimicrobial exposures. Hand washing and delivery by a trained birth attendant appeared protective. Application of animal dung or ash to the umbilical wound was hazardous. Similarly, predelivery cutaneous or intravaginal exposure of mothers to ghee (clarified butter) and delivery on a surface prepared with dried cow dung were risky, with significant interaction noted between them. Mortality and NNT were far more likely among previous births to mothers of cases.

Conclusions. Topical antimicrobials offer a new, effective and inexpensive means to prevent NNT, and could usefully complement maternal immunization with tetanus toxoid in controlling the disease. Special prevention efforts should be directed towards mothers of NNT cases.

Keywords: neonatal, tetanus, topical, antimicrobials, prevention, case-control

Neonatal tetanus (NNT) is one of the most lethal infectious diseases of man, and was responsible for more than half a million deaths during 1993 in the developing world.[1] It occurs after contamination of the umbilical wound with spores of *Clostridium tetani* at the time of delivery or during the first few days of life. Circumcisions have been suspected to contribute to NNT in boys, but have paradoxically appeared 'protective' in epidemiological studies.[2,3]

Neonatal tetanus can be prevented by transplacental transfer of antibodies from mothers immunized with tetanus toxoid (TT), by parenteral injections of tetanus immune globulin to unprotected newborns, and by sterile cord care of infants born to unimmunized mothers. However, several factors have limited progress in controlling this disease in the developing world. First, vaccination coverage of pregnant women with TT remains disappointingly low; only about 45% of women were appropriately immunized at the time of delivery in 1993.[1] Also, tetanus immune globulin of human origin is far too expensive for routine use, and the safety of injections of the less expensive equine product is a concern. Unsafe umbilical care practices at delivery persist, especially in areas where most deliveries occur at home and delivery attendants are untrained. Finally, proper cord care during the first several days of life has received little emphasis in prevention programmes.

Global 2000, Inc., and The Task Force for Child Survival and Development, The Carter Center, in collaboration with UNICEF, the World Health Organization (WHO) and the Ministry of Health, undertook a series of case-control studies from 1989 to 1991 in rural areas

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of Pakistan to identify maternal factors and birth and cord care practices related to the risk of NNT.

The first case-control study was conducted in North West Frontier Province.[2] The application of antiseptics to the umbilical wound after delivery was more common among controls (7%) than cases (3%), though this was not statistically significant. Topical antibiotics could not be meaningfully evaluated in this study, since the absence of such exposure was a selection criterion for two-thirds of the controls, and topical antibiotics were used in only two cases and one control of those not subjected to this restriction.

The second case-control study[4] was based at the Infectious Disease Hospital in North West Frontier Province. Antiseptics were applied in equal frequency (2%) to the umbilical wounds of cases and controls. However, topical antibiotics were significantly protective, and were applied after delivery in 29% of the controls but in only 13% of the cases (odds ratio [OR] = 0.35, 95% confidence interval [CI] : 0.18–0.66, $P = 0.001$).

A third case-control study[5] provided suggestive evidence of protection from antiseptics at delivery (OR = 0.21, 95% CI : 0.06–0.75) and topical antibiotics used after delivery (OR = 0.57, 95% CI : 0.22–1.29). However, neither was statistically significant when the influence of other factors was controlled in multiple logistic regression.

A fourth study using similar methods was conducted in the Northern Areas.[6] Too few children had been exposed to antimicrobial substances to permit a reliable evaluation; only two cases and eight controls were exposed to antimicrobial agents at delivery, while only three cases and five controls were exposed after delivery.

We could identify no other case-control studies of NNT that evaluated the effects of topical antiseptics or antibiotics.

In 1990, the largest case-control study of NNT ever undertaken was conducted in Punjab Province, Pakistan. This provided an opportunity to test further the effect of topical antimicrobials and other factors affecting the risk of NNT.

STUDY DESIGN

Case Ascertainment

In August 1990, a 60-cluster survey of 23 670 live births in rural areas of Punjab Province was conducted, using WHO cluster survey techniques.[7] All births reported in the year before 30 June 1990 were included, so that complete neonatal death information was available at the time of interviews for all infants. Women students in training at schools of public health to become lady health visitors were selected and trained to administer a structured questionnaire in the local language. The questionnaire encompassed both demographic data and TT immunization details, as well as delivery and perinatal practices. Detailed questions were included about substances applied to umbilical and circumcision wounds. Pilot tests were conducted in the field with each interview team before actual data collection began. Supervisors of each team of interviewers randomly selected the first house in the cluster, and interviewers then proceeded to the next nearest house and village(s), if needed, to reach their live-birth targets of 400 per cluster.

A special form for recording details of illnesses, focusing on signs and symptoms of NNT, was completed on each child who was alive at birth but died in the neonatal period. A total of 229 definite and 46 probable NNT deaths were detected (incidence 11.6/1000 live births). Overall NNT accounted for 64% of all neonatal deaths. Cases were considered to be definite NNT cases if their fatal illnesses began in the neonatal period and included both muscle rigidity and spasms. Only definite cases were included in case-control analysis. Other characteristics of the definite cases included triggering of spasms by touch or environmental stimuli (89%), cessation of suckling at onset (97%), and normal appearance and behaviour at birth (94%). Tetanus had been diagnosed by an attending physician in 134 cases. The mean age at onset was 5.5 days. Boys accounted for 55% of the cases in this data set.

Eighteen of the 229 definite cases had been circumcised before onset of NNT. They and their matched controls were excluded from analysis in the following case-control studies, since circumcision proved to be a significant risk factor for boys (Bennett J, Malooly C, Traverso H, *et al.*; unpublished data); excluding such cases permitted the effects of umbilical exposures to be studied among the remaining 211 cases independent of circumcision.

Control Selection

Three controls who survived the neonatal period were selected for each case. Potential control infants were rejected if their mothers had a history of ever receiving TT, so that risk factors for NNT would not be concealed by passive protection from antibodies transferred from mother to child. Controls were matched to cases by date of birth, sex, and cluster. Birth-date matching was undertaken to equalize recall difficulties for mothers of cases and controls, and cluster matching was used to control for potential geographical variability in delivery practices. In all, 81% and 100% of the controls were born within 7 days or 25 days, respectively, of the date of birth of their matched case. Controls who were circumcised

TABLE 1 *Maternal variables*

Variable	Cases	Controls
Mean age of mother in years (range)	27.8 (18–42)	28.3 (15–45)
Mean number of live births (range)	3.6 (1–13)	3.9 (1–13)
Proportion of multiparas with		
One or more previous NNT cases*	15% (26/177)	1% (6/526)
Death in the preceding live birth*	19% (34/175)	3% (18/523)
Proportion appropriately immunized at delivery		
By personal history	7% (15/211)	0% (0/633)
By card document	2% (4/211)	0% (0/633)

* $P < 1 \times 10^{-8}$ by χ^2.

were not excluded since their circumcision was not related to the use of antimicrobials on umbilical wounds. Therefore, there should be no selection bias.

Data Analysis

Data were initially tabulated by members of Global 2000's Islamabad-based staff in 'dBase III +' (Ashton-Tate). The data set was converted into Epi Info 6.0[8] for editing and subsequent analysis.

Separate dichotomous variables were created for all exposure variables, including all those previously found significantly associated with NNT in our studies. Substances applied to the umbilical cord after it was cut during delivery were defined as 'initial' applications, while post-delivery applications were designated 'subsequent' applications. 'Continuous' refers to substances applied both initially and subsequently.

The conditional logistic regression program in EGRET was used to determine matched OR and the statistical significance of single variables using the Wald statistic.[9] Analyses were also undertaken to identify potential confounders, and to assess interaction between the variables. To model the data, we used conditional logistic regression with EGRET,[9] and c LOGISTIC.[10] Use of continuous topical antibiotics, antiseptics and antimicrobials on the umbilical wound were considered the main exposures of interest.

RESULTS

Maternal Factors

Mothers of cases were statistically similar to those of controls in age and number of live births (Table 1). However, multiparous mothers of cases were 15 times as likely to report NNT in previous children. For multiparous mothers for whom the survival status of the immediately preceding live birth was known, mothers of cases were also far more likely to report a death than mothers of controls. The lack of TT immunization in the controls was the expected consequence of selection criteria.

Delivery Variables

Traditional birth attendants (TBA) delivered nearly all cases (97%) and controls (94%). The training backgrounds of TBA were not ascertained. No significant differences were found in the frequency of deliveries of cases and controls by different types of delivery attendants.

Ghee (clarified butter) was commonly applied intravaginally (46%), and to the abdomen (44%) and perineum (42%) of the mothers of NNT cases, and each of these practices was associated with significant risk. However, these uses of ghee were very highly correlated with each other for both case and control mothers, which obviated a valid assessment of the contributions of each practice. A composite variable, 'maternal ghee', encompassing exposure to any of these three practices, was significantly risky (OR = 1.9, 95% CI : 1.4–2.8, $P < 0.0003$).

Reported washing of hands by the delivery attendant was highly protective against NNT (OR = 0.44, 95% CI : 0.29–0.67, $P < 0.0002$).

Enemas were uncommonly given and appeared unrelated to NNT risk.

Delivery on a surface that had been prepared with dried cow dung appeared to be a risk factor for NNT. However, a significant interaction was noted between pre-delivery applications of ghee to mothers and delivery on a surface prepared with dried cow dung. Such a delivery surface was risky for NNT only when ghee was also used on the mother, while maternal ghee was significantly risky only when cow dung was present on the delivery surface. An interaction term composed of these two variables was highly risky (OR = 5.8, $P = 0.0001$).

Delivery on bamboo mat, straw, dirt, plastic sheet, cots and beds did not affect risk significantly.

Tools Used to Cut the Umbilical Cord

No significant associations were found for use of old or new razor blades, kitchen knives, sharp stones, sharp-edged leaves or tree bark and NNT. Use of a farm tool initially appeared risky. However, eight of 12 infants whose umbilical cord had been cut with a farm tool were cases, and six of the eight also had ash or animal dung applied (see below). When stratified for these exposures, use of a farm tool no longer remained significant. The use of scissors to cut the umbilical cord was protective (OR = 0.47, 95% CI : 0.32–0.69, $P < 0.001$), and strongly correlated with trained attendants.

TABLE 2 *Substances applied to umbilical wounds, Pakistan, 1990*

	At delivery				Post delivery			
	Frequency among		Matched odds ratio (CI)	*P*	Frequency among		Matched odds ratio (CI)	*P*
	Cases	Controls			Cases	Controls		
1. antiseptic	2%	5%	0.4 (0.12–1.0)	0.057	1%	4%	0.2 (0.05–0.98)	0.048
2. antibiotic	3%	7%	0.4 (0.18–1.0)	0.059	3%	8%	0.4 (0.18–0.94)	0.034
3. antimicrobials	5%	12%	0.4 (0.19–0.77)	0.007	4%	11%	0.4 (0.17–0.73)	0.005
4. ash	13%	5%	3.0 (1.7–5.2)	<0.001	9%	3%	3.6 (1.8–7.1)	< 0.001
5. animal dung	5%	0.3%	28.1 (3.6–220)	<0.001	6%	0.4%	18.0 (4.1–80.4)	< 0.001
6. ghee	22%	22%	1.0 (0.7–1.6)	0.83	35%	29%	1.4 (0.95–1.9)	0.096
7. turmeric	3%	3%	1.0 (0.4–2.3)	0.91	4%	5%	0.7 (0.31–1.6)	0.44
8. Surma	39%	41%	0.9 (0.7–1.3)	0.69	48%	46%	1.1 (0.8–1.5)	0.63
9. oil	6%	8%	0.7 (.4–1.4)	0.30	11%	13%	0.8 (0.5–1.4)	0.45
10. nothing	23%	20%	1.3 (0.8–1.8)	0.25	14%	11%	1.4 (0.9–2.2)	0.13

Substances Applied to Umbilical Wound

Table 2 presents information on exposures of the umbilical wounds of cases and controls to various substances, both initially and subsequently. Antiseptics and antibiotics produced similar results, each giving borderline protection when used initially, but providing significant protection when used subsequently. The combination of these two types of substances into an 'antimicrobial variable' resulted in highly significant protection when used either initially or subsequently. Antiseptics and antibiotics were rarely used together. Greatest protection occurred (OR = 0.27, $P = 0.003$) when antimicrobial substances were used continuously (i.e. both initially and subsequently), which occurred in 9.8% of the controls and 2.9% of the cases.

Ash, presumably often incompletely burned cow dung fuel, and animal dung were very risky, whether used initially or subsequently. Very few controls were exposed to animal dung. An umbilical exposure to either of these types of substances initially or subsequently was combined into one variable, 'dirty cord' (OR 4.3, 95% CI : 2.5–7.2, $P < 0.001$).

Ghee (clarified butter) did not appear risky when used initially but had an elevated OR and borderline statistical significance when used subsequently.

Applying nothing to the umbilical wound, 'dry cord care', either at delivery or thereafter, was not protective. When the sample was restricted to only those infants who had continuous antimicrobials or dry cord care both initially and subsequently, continuous antimicrobials remained protective (OR = 0.2, 95% CI : 0.06–0.58, $P = 0.001$).

Multivariate Analysis

Umbilical ghee, scissors, dirty cord, and maternal ghee were all determined to be confounders, and were thus included in all logistic regression models. Handwashing by the delivery attendant was not a confounder, and models with and without handwashing were evaluated.

A large number of records were missing information about the delivery surface, and inclusion of a cow dung delivery surface and its interaction term with maternal ghee resulted in a substantial loss of power. Thus, models with and without a cow dung delivery surface and its interaction term were also evaluated.

Continuous antimicrobial use proved significantly protective in all four of these models. The best fitting model excluded both the interaction term and handwashing, and resulted in the following matched OR and likelihood ratio *P*-values for the variables included: continuous antimicrobials 0.38, $P = 0.026$; umbilical ghee 1.3, $P = 0.17$; scissors 0.58, $P = 0.008$; dirty cord 4.2, $P = < 0.001$; and maternal ghee 1.6, $P = 0.014$.

Similar results were found when this model was subjected to unconditional logistic regression, where a highly satisfactory Hosmer-Lemeshow goodness of fit was observed ($P = 0.57$).

The component parts of continuous antimicrobials (initial and subsequent use) were not individually significant when used to replace continuous antimicrobials in the best fitting model. However, subsequent and continuous exposures always showed greater protection and had more highly significant results than initial antimicrobials.

Further analysis by logistic regression was undertaken to determine the comparative effects of topical antimicrobials and dry cord care after controlling for risky practices (ghee, dung, and ash exposures). The risks of NNT increased more than twofold for infants with dry cord care compared with infants who had non-hazardous substances including antimicrobials applied (OR = 2.5, 95% CI : 1.3–4.7, $P = 0.005$).

DISCUSSION

This study documents significant protection against NNT by the topical use of antimicrobials on the umbilical stump at delivery and thereafter. This confirms our earlier studies, which reported protection from topical antibiotics or disinfectants (antiseptics).[4,5] These hospital-based studies had larger percentages of subjects exposed to antiseptics and antibiotics than the present rural, population-based study, and the number of treated children in the current study was not large enough to produce statistically significant associations for antibiotics and disinfectants separately. However, their combination into the biologically relevant variable 'antimicrobial' provides a clear picture of their significant protection.

One major shortcoming of the present study is the lack of detailed information on the identity of the topical antimicrobial substances. The interview form did not provide for the systematic collection of this detailed information. Based on notes spontaneously entered by interviewers on the form, 'Dettol', appeared to be the most frequent antiseptic agent; Furacin (nitrofurazone) ointment was specifically noted as an antibiotic several times. There were too few observations of use of either substance to permit a meaningful assessment of their specific effectiveness. Dettol is a liquid household product containing a phenolic derivative (chloroxylenol), pine oil, and isopropyl alcohol that is intended for use as a disinfectant.[11] It has also been studied as a handwashing agent.[12] Its label identifies the substance as an 'antiseptic-germicide' and advises use for 'cuts' and 'midwifery'.

A re-analysis of our earlier study,[4] where the identity of antibiotics was frequently recorded, may provide some indication of the likely identity of the agents used in the present study. A wide variety of topical antibiotics were noted in the earlier study, including nitrofurazone, bacitracin, penicillin, sulfonamides, tetracycline, neomycin and gentamicin. Except for one instance of initial application, all applications were subsequent ones. Subsequent antibiotics had been used in 90 controls; for 53 of these, agents were specifically identified. 'Cicatrin', a combination of bacitracin and neomycin (n = 22, 42%), and Furacin (n = 16, 30%) were most common. When compared to those who received no other topical antibiotics subsequently, Cicatrin, Furacin, and both combined all showed some evidence of protection: OR = 0.33, $P = 0.08$; OR undefined, $P = 0.02$; OR = 0.19, $P = 0.007$, respectively. (No cases had Furacin applied, thus its OR could not be defined.)

Another deficiency of the current study is the lack of data on the frequency and extent of subsequent use of antimicrobials. Subsequent, post-delivery use could conceivably mean one wipe of an alcohol swab a few hours after delivery or the application of an antibiotic several times daily for many days. The subsequent use of such agents was almost always initiated by the mothers, and a wide variety of topical antibiotics were readily available to them in pharmacies. Labelling instructions accompanying topical antibiotics usually advise that the product be used several times daily for several days, but it is unknown how many mothers followed such patterns. Detailed data were collected on subsequent use of ghee, however, and its most common usage pattern was twice daily for 7 days. This and information about the patterns of use of antibiotics inserted by interviewers on a few forms suggest that similar application patterns may have been followed.

Subsequent exposure to antimicrobials appeared relatively more important than initial exposure. In the present study, subsequent and continuous exposures always had more protective and significant OR than initial exposures. Other studies have shown significant protection from only subsequent use of antibiotics,[4] significant risk from only subsequent ghee,[2] and significant risk when dried cow dung came in contact with umbilical wounds anytime during the first 3 days of life.[6] These observations, and repeated instances of NNT in babies born under presumed aseptic hospital conditions,[2,13–17] imply that the risk of contamination and the subsequent development of NNT continue after delivery as the wound heals during the first few days of life. The observation that use of nothing on the umbilical wound is risky, after controlling for other risky delivery practices, also supports this conclusion and indicates that proactive efforts to protect the umbilical wound are needed in environments where animals and animal dung exist in close proximity to living areas and frequent exposure to environmental sources of *Cl. tetani* is likely. It is clear that clean delivery alone will not optimally reduce the global morbidity and mortality of NNT.

It is also clear that topical antimicrobials offer important incremental benefits to NNT control programmes based on TT immunization. Universal childhood immunization targets of 80% coverage with standard

Expanded Programme for Immunization vaccines in children under one year of age in developing countries were reached only after more than a decade of intensive concerted efforts by WHO, UNICEF, developing countries, and others.[18] It seems doubtful, in the absence of such concerted efforts, that global coverage of women of childbearing ages with TT will increase from its present levels of 45%[1] to 80% or more in the near future. Also, actual in-the-field effectiveness of TT in the developing world is unknown but several observations suggest it is less than perfect. For one, potent amounts of tetanus toxins can overcome 'protective levels of antibodies'.[19] Also, TT produced and used in developing countries has not infrequently been shown to be defective in potency.[20,21] Finally, TT efficacy of only 83% was noted for non-Punjab areas of Pakistan we studied (unpublished observations based on immunization card records). If 80% coverage of women of childbearing ages can be achieved with TT assumed to be 90% effective, about 37.5 million unprotected births will still occur annually among the 125 million annual births in the developing world. With 10 or more NNT deaths/1000 live births to unimmunized mothers, as observed in the present study, 375 000 or more NNT deaths would continue to be expected annually under these circumstances. Current data suggest that a substantial portion of these deaths that are not expected to be prevented by TT might be preventable annually by topical antimicrobials.

In a random subsample of about 900 of the 23 670 survey records, a slight excess of antimicrobial use was noted in newborns whose mothers gave positive rather than negative histories for having received TT doses before delivery (10.3% versus 7.2%). Thus, by excluding from our control group mothers who had received TT doses before delivery, we may have introduced a small bias towards the null, and underestimated the full impact of topical antimicrobials.

Bandages are not currently recommended for umbilical cord care in developed countries because the cord separates more quickly when exposed to air.[22] Further, dry cord care has not been considered to be safe, and routine use of topical antimicrobials has been recommended for infants in nurseries.[23] In a randomized trial involving the application of agents that are commonly used for this purpose (triple dye [brilliant green, proflavine hemisulfate and gentian violet], povidone-iodine ointment, silver sulfadiazine, and bacitracin ointment), daily applications of these substances by nurses and mothers to the umbilical stump and adjacent skin until the cord separated produced no significant differences in the incidence of colonization with any organism.[24] Povidone iodine was preferred by nurses because of its cleanliness and ease of use, and it also was associated with the shortest average time until the stump separated (about 10 days). Triple dye was poorly tolerated and was judged 'messy' to use. All of these agents as well as nitrofurazone, chloroxylenol, and isopropyl alcohol are active against Gram-positive organisms and, with the possible exception of sulfadiazine, might be expected to have activity against vegetative cells of *Cl. tetani*. Indeed, the widespread and routine use of topical antimicrobials may be a factor underlying the rarity of NNT in the USA and other countries of the developed world.

The most promising of these agents for use in developing countries, based on epidemiological findings and the above considerations, appear to be nitrofurazone, bacitracin and povidone-iodine ointments, which are all approved for topical use. Dettol may be less suitable for topical use on umbilical wounds, since the risk of sensitization to chloroxylenol is enhanced when it is applied to damaged skin,[24] and cross sensitization may occur to other over-the-counter products containing related substances, including certain baby powders.[25] Topical nitrofurazone could produce sensitization to systemically administered nitrofurans, although the latter are not widely used therapeutically. Both bacitracin and povidone iodine may induce sensitivity on topical use. Transient hypothyroidism of newborns from topical use of iodine-containing antiseptics is also a concern, although only two published studies have dealt with short-term topical exposures of the umbilical stump in healthy neonates. In one of these,[26] transient hypothyroidism without clinical findings was noted in 2.7% of a combined group of newborns delivered vaginally and by caesarian section. They had received once daily povidone-iodine for 3 days (vaginal deliveries) or 5–7 days (caesarian sections); elevated thyroid stimulating hormone levels were noted in about 2% of those treated for 3 days and 15% of those treated for 5–7 days. In the second study,[27] despite elevation of plasma iodine, no alteration in thyroid function in a small sample of newborns was noted 3 days after a single application. Potential adverse effects of all topical agents must be balanced against the potential benefits of inexpensively preventing a highly fatal disease that is the most common cause of neonatal death in many endemic areas.

A prophylactic course of treatment with one of the above ointments should be inexpensive, and the risk of superinfection with resistant organisms should be minimal on short-term use, especially in babies delivered at home. Administration costs are also likely to be nominal since tubes containing small quantities sufficient for a few days of use could be routinely included in delivery kits for developing countries or be given by TBA and others to mothers to apply at home. In addition to

the effects on NNT, the impact of topical antimicrobials on neonatal morbidity and mortality from omphalitis and sepsis should also be evaluated in developing country settings.

The results of this study offer public health practitioners the promise of another useful and highly cost-effective strategy in the arsenal against NNT. We believe topical antimicrobials should be routinely applied to the umbilical stump at all deliveries, and that field trials should now be undertaken to evaluate optional care after the day of delivery (antimicrobials vs. undisturbed dressings).

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REFERENCES

[1] Centers for Disease Control and Prevention. Progress toward the global elimination of neonatal tetanus, 1989–1993. *MMWR* 1994; **43:** 885–87, 893–94.

[2] Traverso H P, Bennett J V, Kahn A J *et al.* Ghee applications to the umbilical cord: a risk factor for neonatal tetanus. *Lancet* 1989; **i:** 486–88.

[3] Sokal D C, Imboua-Bogui G, Soga G *et al.* Mortality from neonatal tetanus in rural Cote d'Ivoire. *Bull World Health Organ* 1988; **66:** 69–76.

[4] Traverso H P, Kamil S, Rahim H *et al.* A reassessment of risk factors for neonatal tetanus. *Bull World Health Organ* 1991; **69:** 573–79.

[5] Bennett J, Azhar N, Rahim F *et al.* Further observations on ghee as a risk factor for neonatal tetanus. *Int J Epidemiol* 1995; **24:** 643–47.

[6] Bennett J, Schooley M, Traverso H *et al.* Bundling, a newly identified risk factor for neonatal tetanus: implications for global control. *Int J Epidemiol* 1996; **25:** 879–84.

[7] Galazka A, Stroh G. Neonatal tetanus guidelines on the community-based survey on neonatal tetanus mortality. *WHO Document EPI.GEN*; **86:** 8.

[8] Dean A G, Dean J A, Burton A *et al. Epi Info, Version 6.0: A Word Processing, Database and Statistics Program for Epidemiology on Microcomputers*. Atlanta, Georgia: Centers for Disease Control and Prevention, 1994.

[9] EGRET: Epidemiological graphics, estimation, and testing package; analysis module (PECAN), version 0.26.6. Copyright 1985–1991, SERC and CYTEL.

[10] Dallal G E. c LOGISTIC: a conditional logistic regression program for the IBM-PC. *Am Statistician* 1989; **43:** 125.

[11] Chan T, Critchley J. Is chloroxylenol nephrotoxic like phenol? A study of patients with Dettol poisoning. *Vet Hum Toxicol* 1994; **36:** 250–51.

[12] Ansari S, Sattar S, Springthorpe V *et al.* In vivo protocol for testing efficacy of hand-washing agents against viruses and bacteria: experiments with rotavirus and *Escherichia coli*. *Appl Environ Microbiol* 1989; **55:** 3113–18.

[13] De Silva A. Neonatal tetanus problems in Sri Lanka. *Pak Pediatr J* 1982; **6:** 214–27.

[14] Radha Krishnam V B, Saini L, Gupta S. A study of tetanus in children. *Arch Child Health* 1975; **17:** 65–73.

[15] Stroh G, Kyu U A, Thaung U *et al.* Measurement of mortality from neonatal tetanus in Burma. *Bull World Health Organ* 1987; **65:** 309–16.

[16] Suleman O. Mortality from tetanus neonatorum in Punjabi (Pakistan). *Pak Pediatr Jl* 1982; **6:** 152–83.

[17] Kumar V, Kumar R, Mathur V N *et al.* Neonatal tetanus mortality in a rural community of Haryana. *Ind Pediatr* 1988; **25:** 167–69.

[18] UNICEF. *The State of the World's Children 1992*. New York: Oxford University Press, 1993.

[19] Maselle S Y, Matre R, Moise R *et al.* Neonatal tetanus despite protective serum antitoxin concentration. *FEMS Microbiol Immuno* 1991; **3:** 171–75.

[20] Hlady W G, Bennett J V, Samadi A R *et al.* Neonatal tetanus in rural Bangladesh: risk factors and toxoid efficacy. *Am J Public Health* 1992; **82:** 1365–69.

[21] World Health Organization. Tetanus toxoid quality assessment: an update. *Wkly Epidemiol Rec* 1994; **19:** 137–39.

[22] Cunningham F G, MacDonald P, Gant N, Levens K, Gilstrap U (eds). *The Newborn Infant*. Williams Obstetrics, 19th edn. Norwalk, CT: Appleton and Lange, 1993, pp. 443–57.

[23] Brann A W, Cepulo R C (eds). *Guidelines for Perinatal Care.* Evanston, IL: American Academy of Pediatrics, 1983, pp. 443–57.

[24] Gladstone I M, Clapper L, Thorp J W *et al.* Randomized study of six umbilical cord-care regimens. *Clin Pediatr* 1988; **27:** 127–29.

[25] Caro I. Iatrogenic dermatitis. *Med Clin North Am* 1981; **65:** 1083–89.

[26] Arena J, Eguileor I, Emparanza J. Repercussion of the application of povidone-iodine to the umbilical stump on thyroid function of the neonate at term. *An Esp Pediatr* 1985; **23:** 562–68.

[27] Pyati S, Ramamurthy S, Kraus M T *et al.* Absorption of iodine in the neonate following topical use of povidone iodine. *Pediatrics* 1977; **91:** 825–28.

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