

Risk factors for mortality in neonatal tetanus: a 15-year experience in Sagamu, Nigeria

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Background: Neonatal tetanus (NNT) is a major cause of newborn deaths especially in the developing world. While efforts aimed at eradicating NNT should be sustained, it is equally imperative to reduce death among affected infants. Therefore, the factors associated with mortality rate in this condition need to be studied.

Methods: The records of infants with NNT over a 15-year period (1991-2005) were reviewed. A statistical comparison of the survivors and fatalities for relevant clinical characteristics was done, and the determinants of fatality rate were also determined using logistic regression.

Results: Ninety-six of 151 newborns with NNT died, giving a mortality rate of 63.6%. The case fatality rate during the study period varied between 33.3% and 100%. More deaths occurred in the infants with low birth weight ($P=0.004$) within 1 day at the onset of symptoms ($P<0.001$), whose mothers aged 18 years or less ($P=0.001$) belonged to socio-economic class V ($P=0.001$). Determinants of mortality in these infants with NNT included low socio-economic class ($P=0.002$), no anti-tetanus vaccination ($P=0.006$), presentation with spasms ($P<0.001$), and non-administration of anti-tetanus serum during treatment ($P=0.013$).

Conclusions: The mortality rate in infants with NNT remains significantly high in Nigeria. Improved maternal anti-tetanus vaccination and timely recognition and treatment of affected infants may jointly reduce the incidence and fatality rate of NNT.

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Introduction

Neonatal mortality is a major contributor to infant mortality in Nigeria like in most other parts of the developing world.^[1,2] The leading causes of neonatal mortality include preterm birth, low birth weight, perinatal asphyxia, and infections.^[3] Studies have also shown the role of neonatal tetanus (NNT) in neonatal mortality.^[4,5] Similarly, the case fatality rate (CFR) of NNT has been high in most centres in the developing world.^[6-8] Therefore, the efforts taken to reduce infant and childhood mortality rates in the developing countries should necessarily include the reduction of incidence and mortality associated with NNT. Despite of several international and regional efforts aimed at eradicating NNT,^[9] physicians in the developing countries still face the challenge of managing infants with NNT. Worse still, the CFR in most of these countries remains high. NNT deaths have been reduced in a few centres using intensive care in the developing countries,^[10] but such facilities are still not available in most of the developing countries where the incidence of this disease is high. Therefore, it may be cost-effective for such less-privileged economies in the developing world to apply epidemiological approach in lowering NNT deaths. A study of the factors which predispose to mortality in NNT will also be useful to improve the management of NNT.

This study aimed to determine the pattern and risk factors for mortality in infants with NNT in Nigeria.

Methods

The records were reviewed of all neonates managed for tetanus at the Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, Nigeria between January 1991 and December 2005. The study was approved by the Ethics Committee of the hospital. The hospital provided general pediatric specialist and neonatal services to infants delivered in the hospital and those referred from other government-owned or privately-owned health facilities based in at least three states of the nation. Data extracted included age at presentation, sex, body weight, maternal age and parity, details of

antenatal care and anti-tetanus vaccination, and places of delivery. The details and duration of symptoms were also documented. Parental occupation and educational qualification were used to categorize socioeconomic status.^[11] Socioeconomic classes I to III formed the upper class while classes IV and V constituted the lower class.

Infants with NNT were routinely treated with a combination of three muscle relaxants (phenobarbitone, diazepam and chlorpromazine) administered initially intravenously and subsequently orally according to the standard protocol. Phenytoin was not routinely used to treat NNT cases because it was not readily available. Parenteral crystalline penicillin was the main antibiotic of choice but gentamicin was empirically added whenever septicemia was suspected depending on antibiotic sensitivity reports. Anti-tetanus serum at a dose of 5000 units was also administered both intravenously and intramuscularly. Other supportive treatments included maintenance fluid therapy (8% dextrose-in-5th saline infusion or expressed breast milk feeding via nasogastric tubes), frequent nasopharyngeal suction, and oxygen therapy as indicated.

Data analysis was carried out with the SPSS 15.0 software. The data of the infants who were prematurely discharged against medical advice were excluded from statistical analysis. Socio-clinical characteristics of the survivors and the fatalities were compared using odds ratio (OR) and 95% confidence interval (CI). Logistic regression analysis was made to determine the risk factors of mortality. *P* values less than 0.05 and 95%CI values excluding 1 are accepted as significant.

Results

A total of 175 infants with NNT were admitted to this hospital but 151 were studied after the exclusion of 24 infants who were prematurely discharged against medical advice. The 151 infants comprised 94 (62.3%) boys and 57 (37.8%) girls, aged from 2 to 14 days with a mean of 8.65 ± 4.5 days. Four infants (2.6%) were <3 days, 69 infants (45.7%) 3 to 7 days, and 78 infants >7 days (51.7%). The mean (SD) admission weight was 2.7 ± 0.5 kg (range: 1.8 to 3.9 kg). Forty-four (29.1%) infants were low-birth-weight while the remaining 107 (70.9%) weighed 2.5 kg or more. Only one (0.7%) baby was post-term but the remaining 20 (13.2%) and 130 (86.1%) infants were preterm and full-term respectively.

Nine (6.0%) mothers were 18 years or below while the remaining 142 (94.0%) were more than 18 years. Most of the mothers (83, 55.0%) were primiparous but 68 (45.0%) were multiparous. Only 30 (19.9%) mothers belonged to socioeconomic class III and the remaining 48 (31.8%) and 73 (48.3%) belonged to classes IV and V respectively.

The outcomes of hospitalization were as follows: 55 (36.4%) survived and 96 (63.6%) died. Thus, the overall CFR was 63.6%. The CFR in boys and girls was similar [59/94 (62.8%) vs 37/57 (64.9%); OR=0.91, 95%CI=0.43-1.91]. The annual numbers of NNT cases and CFR are shown in Table 1. The CFR fluctuated remarkably between 33.3% and 100.0%.

Most of the deaths (40, 41.7%) occurred between 72 hours and 1 week after admission. The durations of hospitalization in deaths were as follows: <24 hours (22, 22.9%), 24 to 72 hours (24, 25.0%), and >1 week (10, 10.4%).

Comparison of NNT survivors and deaths (Table 2)

Neonatal characteristics

A significantly higher proportion of the deaths compared to the survivors were low birth weight infants ($P=0.004$) and NNT presented within 7 days after birth ($P=0.001$). Similarly, a significantly higher proportion of the deaths presented within 1 day after the onset of symptoms ($P=0.039$) with generalized spasms ($P<0.001$) and they did not have anti-tetanus serum during the treatment ($P<0.001$).

The proportion of the male survivors (35, 67.6%) and the male deaths (59, 61.5%) was similar (OR=1.10, 95%CI=0.52-2.31). A higher proportion of the deaths (41, 42.7%) compared with the survivors (21, 38.2%) had co-morbidities (like severe anemia, septicemia, hypoglycemia and asphyxia) at presentation, but this difference was not statistically significant (OR=0.83, 95%CI=0.40-1.72).

Maternal characteristics

A significantly higher proportion of mothers of the

Table 1. Yearly pattern of number of neonatal tetanus infants and case fatality rates

Year	Number of cases	Deaths (n)	Case fatality rates (%)
1991	17	16	94.1
1992	7	6	85.7
1993	8	6	75.0
1994	14	6	42.9
1995	17	10	58.8
1996	16	4	25.0
1997	9	3	33.3
1998	7	3	42.9
1999	6	4	66.7
2000	7	6	85.7
2001	9	9	100.0
2002	11	11	100.0
2003	12	4	33.3
2004	4	4	100.0
2005	7	4	57.1
Total	151	96	63.6

Table 2. Comparison of the clinical characteristics of the survivors and the deaths

Characteristics	Survivors, n=55 (%)	Fatalities, n=96 (%)	Statistics
Age ≤7 days at presentation	17 (30.9)	56 (58.3)	OR=3.13, 95%CI=1.47-6.72
Preterm	4 (7.3)	16 (16.7)	OR=0.39, 95%CI=0.10-1.35
Onset of symptoms <1 day	4 (7.3)	19 (19.8)	OR=0.32, 95%CI=0.09-1.07, P=0.039
Presence of spasms	25 (45.5)	88 (91.7)	OR=0.08, 95%CI=0.03-0.20, P<0.001
Non-administration of anti-tetanus serum	4 (7.3)	53 (55.2)	OR=0.06, 95%CI=0.02-0.20, P<0.001
Maternal primiparity	36 (65.5)	47 (49.0)	OR=1.98, 95%CI=0.94-4.16
Maternal age <18 years	1 (1.8)	22 (22.9)	OR=0.06, 95%CI=0.0-0.46
Socioeconomic class V	22 (40.0)	64 (66.7)	OR=0.33, 95%CI=0.16-0.70, P=0.001
Lack of antenatal care	38 (69.1)	79 (82.3)	OR=0.48, 95%CI=0.21-1.12
No tetanus toxoid vaccination	31 (50.4)	75 (78.1)	OR=0.36, 95%CI=0.17-0.79, P=0.005
Delivery outside health facilities	43 (78.2)	86 (89.6)	OR=0.42, 95%CI=0.15-1.14

Table 3. Multivariate analysis of risk factors for mortality in neonatal tetanus using logistic regression

	B*	P value	Exp (B)†	95% CI	
				Lower	Upper
Age ≤7days	1.821	<0.001	6.176	2.471	15.436
Low birth weight‡	1.048	0.069	2.852	0.922	8.824
Maternal age <18 years	-0.113	0.834	0.893	0.312	2.557
Socioeconomic class V	1.484	0.002	4.410	1.731	11.236
No anti-tetanus vaccination in pregnancy	1.497	0.006	4.468	1.531	13.037
Onset‡	0.772	0.282	2.163	0.530	8.827
Spasms§	2.616	<0.001	13.679	4.919	38.038
ATS	1.309	0.013	3.701	1.316	10.413
Constant	-4.547	<0.001	0.011		

*: regression coefficient; †: exponential value of coefficient; ‡: presentation within 1 day of onset of symptoms; §: generalized spasms present at presentation; ||: lack of anti-tetanus serum administration.

deaths compared with the survivors were ≤18 years ($P=0.001$). None of the mothers of the survivors was grand multiparous compared with 8 (8.3%) of the mothers of the deaths, but this difference was not statistically significant (OR=0.0, 95%CI=0.0-1.31).

The proportion of the mothers of the deaths who belonged to the lowest socioeconomic class (class V) was significantly higher than that of the survivors ($P=0.001$). Similarly, a significantly higher proportion of the mothers of the fatalities took no dose of tetanus toxoid vaccine during the index pregnancy compared with the survivors ($P=0.005$).

The proportions of mothers of the deaths and survivors who received clinically-based antenatal care and delivered their infants outside health facilities were similar (OR=0.48, 95%CI=0.21-1.12; OR=0.42, 95%CI=0.15-1.14).

Multivariate analysis of potential determinants of mortality

The potential risk factors for mortality in NNT as identified in the aforementioned comparison were entered into a binary logistic regression model as

independent variables to determine their contributions to mortality in the infants. The significant determinants of mortality in these infants with NNT included age at presentation <7 days ($P<0.001$), low socioeconomic status ($P=0.002$), lack of tetanus toxoid vaccination ($P=0.006$), presence of spasms at presentation ($P<0.001$), and non-administration of anti-tetanus serum during management ($P=0.013$) (Table 3). On the contrary, low birth weight, young maternal age (<18 years) and presentation within a day after the onset of symptoms were not significant determinants of mortality in these infants.

Discussion

This study shows that mortality in NNT remains very high in this Nigerian center. The overall CFR in a 15-year period in this study was higher than 43.8% reported from Ilesha, Nigeria^[7] but comparable to 57.7% reported from Ile-Ife, Nigeria^[12] and 52% from Turkey.^[13] Interestingly, it was lower than 66.3% reported from North Bengal, India.^[8] The variability in NNT-related CFR in different centers in the same country or in different countries may be attributed to the differences in severity of the disease and the quality of care offered to affected infants. It is important to note that a Turkish study reported a decline in the NNT-related CFR from 88.5% to 56.3% over a 4-year period following an intervention program in terms of improved intensive care for NNT cases.^[10] The annual CFR in the present study ranged from 33.3% to 100%; the wide range cannot be readily explained since no specific intervention was carried out during this period and infants with NNT were still managed without intensive care. Nevertheless, most of the deaths in this study occurred within the first 7 days of admission. This may be attributed to persistent actions of the tetanus toxins bound to tissues, difficulty in controlling spasms and difficulty in achieving adequate fluid and caloric

balance during this period. Therefore, the first week of hospitalization is a critical period in the management of NNT and efforts targeted at improved management should focus on this critical period.

Univariate analysis in this study suggested significantly higher death rates among infants who presented within the first 7 days of life and weighed less than 2.5 kg on admission. This is consistent with previous reports that outcome in NNT was worse when affected infants presented within the first week of life.^[7,12-14] This may be related to the relationship between the response of the immune system and the toxin load at this age compared to infants who are relatively older. It is also attractive to speculate that this same principle may explain the higher fatality rate among low-birth-weight infants whose immune system may be easily overwhelmed by the toxin load considering their relatively poor immune response. Indeed, transplacental transfer of antibodies has been shown to be directly related to gestation and fetal growth.^[15]

The relatively earlier presentation of the fatal cases should have been advantageous if the illness is mild. However, most cases do not present until the disease has progressed to either inability to suck or generalized spasticity.^[16] Therefore, the early presentation observed in these cases may reflect a short period of onset which connotes poor prognosis.

The infants of mothers who were adequately vaccinated against tetanus in pregnancy had been shown to be protected against the disease.^[17] Even when the disease occurs in such infants, studies have shown better survival in them.^[18] This highlights the important role of anti-tetanus vaccination of mothers in the prevention of NNT and reduction of associated fatality. Therefore, it is desirable to improve tetanus toxoid vaccine coverage particularly in a high-risk population.^[19]

With the exception of low-birth-weight, young maternal age and early presentation in the hospital, multivariate analysis confirmed that age of 7 days or less, presentation with spasms, low maternal socioeconomic classification, lack of anti-tetanus vaccination during pregnancy and non-administration of anti-tetanus serum during the treatment were determinants of mortality in NNT. Therefore improved quality and accessibility of ante-natal care will ensure better anti-tetanus vaccination and better protection of infants against fatal tetanus. Health education is also desirable for early presentation of sick infants in the hospitals equipped for specialized care.

In conclusion, the CFR in NNT in our center remained high over a 15-year period. We acknowledge the pivotal role of health education, adequate maternal anti-tetanus vaccination and clean deliveries in

reducing the incidence of NNT.^[20] However, improved case management (muscle paralysis with mechanical ventilation and parenteral nutrition) may be the best tool for drastically reducing the CFR in NNT. This is important since most of the identified determinants of mortality, apart from lack of anti-tetanus vaccination, may not be out rightly amenable to prevention. Advocacies should be put in place for the provision of neonatal intensive care facilities in the developing countries.

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Ethical approval: The Ethical Committee of the hospital approved the study since the identity or safety of the subjects was not at stake.

Competing interest: None.

Contributors: Fetuga BM conceived and designed the study while Ogunlesi TA and Adekanmbi FA analyzed and interpreted the data. All the authors drafted the manuscript and approved the final version of the manuscript.

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