Tetanus toxoid immunization to reduce mortality from neonatal tetanus

Hannah Blencowe,1 Joy Lawn,2,3 Jos Vandelaer,4 Martha Roper5 and Simon Cousens1

1London School of Hygiene and Tropical Medicine, London, UK, 2Saving Newborn Lives/Save the Children-USA, Cape Town, South Africa, 3Health Systems Strengthening Unit, Medical Research Council, Cape Town, South Africa, 4UNICEF, Health Section, New York, USA and 5WHO, Department of Immunisation, Vaccines and Biologicals, Geneva, Switzerland.

Corresponding author. Simon Cousens, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK.
E-mail: simon.cousens@lshtm.ac.uk

Background

Neonatal tetanus remains an important and preventable cause of neonatal mortality globally. Large reductions in neonatal tetanus deaths have been reported following major increases in the coverage of tetanus toxoid immunization, yet the level of evidence for the mortality effect of tetanus toxoid immunization is surprisingly weak with only two trials considered in a Cochrane review.

Objective

To review the evidence for and estimate the effect on neonatal tetanus mortality of immunization with tetanus toxoid of pregnant women, or women of childbearing age.

Methods

We conducted a systematic review of multiple databases. Standardized abstraction forms were used. Individual study quality and the overall quality of evidence were assessed using an adaptation of the GRADE approach. Meta-analyses were performed.

Results

Only one randomised controlled trial (RCT) and one well-controlled cohort study were identified, which met inclusion criteria for meta-analysis. Immunization of pregnant women or women of childbearing age with at least two doses of tetanus toxoid is estimated to reduce mortality from neonatal tetanus by 94% [95% confidence interval (CI) 80–98%]. Additionally, another RCT with a case definition based on day of death, 3 case–control studies and 1 before-and-after study gave consistent results. Based on the consistency of the mortality data, the very large effect size and that the data are all from low/middle-income countries, the overall quality of the evidence was judged to be moderate.

Conclusion

This review uses a standard approach to provide a transparent estimate of the high impact of tetanus toxoid immunization on neonatal tetanus.

Keywords

neonatal mortality, newborn care, neonatal tetanus, tetanus toxoid, immunization

Background

Neonatal tetanus was estimated to be responsible for over half a million neonatal deaths globally in early 1980s.1 Estimates suggest that these deaths have been reduced, but that still some 130 000 babies died around the year 2004 from this very preventable disease.2 Despite this impressive progress, two global elimination target dates have been missed, most recently in 2005, to a rate of ‘less than 1 case per 1000 livebirths in every district of every country’. Most of the remaining deaths from neonatal tetanus...
TETANUS TOXOID IMMUNIZATION

Objective

The objective of this article is to provide an estimate of the effect on neonatal tetanus mortality of immunization of pregnant women, or women of childbearing age, with two or more doses of tetanus toxoid for use in the LiST tool.

Methods

We systematically reviewed the published literature to identify studies of tetanus toxoid immunization of women for the prevention of neonatal tetanus mortality for use in the LiST model. In the model, increases in coverage of an intervention results in a reduction of one or more cause-specific deaths. The review and the GRADE process used were designed to develop estimates of the effect in reducing neonatal mortality. For more details on the review methods, the adapted grade approach or the LiST model see other articles in this supplement.

We searched PubMed, EMBASE, Cochrane Libraries and all World Health Organization Regional Databases and included publications in any language. Combinations of the following search terms were used: ‘neonatal tetanus, tetanus toxoid, neonatal mortality and women’.

Inclusion/exclusion criteria

We applied the PICO format (Patient, Intervention, Comparison and Outcome) to define the studies to be included as follows. The ‘population’ of interest were neonates, and the ‘intervention’ was at least two tetanus toxoid vaccine doses, given at least 4 weeks apart, with the last dose given during the current pregnancy. The comparison group were those neonates born after pregnancies without tetanus toxoid immunization. The outcome of interest was mortality from neonatal tetanus (Box 1). We considered both randomized trials and observational studies meeting these criteria (Figure 1). We excluded studies not fulfilling the inclusion criteria, studies reporting serological outcomes only and any duplicate reports of trials or studies (Figure 1).
Abstraction, analyses and summary measures

All studies meeting the inclusion/exclusion criteria were abstracted onto a standardized abstraction form for each outcome of interest. Each study was assessed and graded according to the CHERG adaptation of the GRADE technique. The evidence was summarized by outcomes including qualitative assessment of study quality. CHERG Rules for Evidence Review were applied to the collective evidence to provide an estimate for reduction in neonatal tetanus mortality. We conducted a meta-analysis using STATA version 10.0 statistical software and reported the Mantel–Haenszel pooled relative risk and corresponding 95% confidence interval (CI).

Results

The literature search identified 1358 papers (Figure 2). After initial screening of the title or abstract, we reviewed the full text of 54 papers. Thirty-two of these papers were not abstracted as they contained no mortality data. Data were abstracted from 22 papers. Expert review of the studies abstracted identified two further relevant studies. The following

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Figure 1 Synthesis of study identification in the review of the effect of tetanus toxoid immunization on mortality from neonatal tetanus.

BOX 1

Cause-specific mortality effect and quality grade of the estimate for the effect of tetanus toxoid immunization.

- **Cause-specific mortality to act on:** Neonatal tetanus.
- **Cause-specific effect and range:** 94% (80–98%).
- **Quality of input evidence:** Moderate (one RCT and one cohort study in low/middle-income countries; mortality data consistent; and very large effect, hence quality upgraded from low to moderate).
  Supported by low-quality evidence from one RCT, three case–control studies and one before and after study.
- **Proximity of the data to cause-specific mortality effect:** High (cause-specific mortality).
- **Limitations of the evidence:** Only two studies are included in the effect size estimate, one of which was an RCT.
studies were excluded at this stage: 10 observational studies and 5 case–control studies which made no attempt to control for confounding and 1 study with multiple concurrent interventions where it was impossible to separate the effect of tetanus toxoid from the other interventions and 1 study which had used sub-potent vaccine (Supplementary Table 1). Where studies reported effects of one dose and of two doses, we restricted analysis to the effect of two doses.

Seven studies were included in the final database (Supplementary Table 1). We identified two studies of high/moderate-quality reporting neonatal tetanus mortality. One was a high-quality randomised controlled trial (RCT) and the second a cohort study which was well designed with adjustment for confounding in its analysis. There was no strong evidence of heterogeneity between the two studies ($P = 0.16$). Hence, the data were combined in one meta-analysis giving an estimate of effect of relative risk (RR) = 0.06 (95% CI 0.02–0.2) (Figure 2).

A third study, identified in the Cochrane review was a RCT assessing all-cause neonatal mortality from day 4–14 as a proxy for neonatal tetanus mortality. The trial was originally designed to test a cholera vaccine and tetanus toxoid was given to participants in the control group. The estimated relative risk of neonatal mortality (4–14 days) was 0.33 (95% CI 0.21–0.50). This figure is likely to substantially underestimate the effect on neonatal tetanus mortality, as a number of the deaths during this period would have been due to other causes (e.g. sepsis and complications of prematurity) not susceptible to prevention through tetanus toxoid immunization.

Four papers reporting the effect of tetanus toxoid immunization on the occurrence of neonatal tetanus were also abstracted (Supplementary Table 1). Three case–control studies whose design controlled for confounding reported a protective effect of two doses of tetanus toxoid in the current pregnancy [odds ratio (OR) = 0.05 (0.005–0.4); OR = 0.1 (0.03–0.4); OR = 0.2 (0.03–0.7). A study of hospital neonatal tetanus admission rates pre- and post-mass immunization campaign reported a reduction in neonatal tetanus admissions, RR = 0.35 (95% CI 0.29–0.42).

The CHERG Rules for Evidence Review were applied. The effect seen was large and broadly consistent across different types of study. There were 71 neonatal tetanus deaths in the two highest quality studies with an overall evidence grade of moderate, hence more than the minimum of 50 events were required by the CHERG rules (Box 1). The evidence grade allocated is moderate, upgraded from low because although the input data are limited, the effect size is very large and is consistent across the various data identified.

**Discussion**

Mortality from neonatal tetanus remains an important, yet preventable, cause of neonatal mortality.
Our systematic review identified three studies of moderate-quality providing supporting evidence of a large effect of tetanus toxoid immunization on neonatal tetanus mortality, when at least two doses are given at least 4 weeks apart with the last dose given during the current pregnancy. Applying CHERG Rules for Evidence Reviews for LiST, our new meta-analysis includes two trials with cause-specific mortality and gives an estimate that two or more properly timed doses of tetanus toxoid immunization given to pregnant women or women of childbearing age will reduce neonatal tetanus mortality by 94% (95% CI 80–98%).

The main limitation of this review and the resulting effect estimate is the dearth of high-quality trials. Our estimate is based on two studies including 2146 women and 71 neonatal tetanus deaths. However, there is consistency with one other moderate-quality study with deaths by day 14 and with the 19 other, lower quality observational studies reviewed. There is moderate-quality evidence to suggest that this strategy can reduce the risk of neonatal tetanus mortality by >90%.

Tetanus toxoid immunization of pregnant women is currently recommended by WHO and is included in the immunization policy of most Member States. Widespread programmatic use of tetanus toxoid has removed the equipoise required to carry out randomized studies and has also convincingly reduced the global burden of deaths from neonatal tetanus by ~90% in the past 25 years (Figure 3). There are strong grounds for recommending immunization of pregnant women or women of childbearing age with tetanus toxoid to prevent neonatal tetanus. Immunization, in combination with clean, hygienic delivery practices remains of central importance if global elimination goals are to be met finally.

Progress towards elimination of neonatal tetanus that is being made with a number of low-income countries have been validated as reaching Elimination Status. Ninety countries had not eliminated maternal and neonatal tetanus in 1990. That figure has now been reduced to 44 countries. However, there remains an unfinished agenda especially in a few large countries with low coverage of facility births and low tetanus toxoid immunization. In addition, as tetanus spores are ubiquitous and eradication is not an option, ongoing attention to maintaining high levels of tetanus toxoid immunization is required, as well as strengthening and integrating national surveillance systems.

**Conclusion**

This review provides clear evidence of the high impact of two doses of tetanus toxoid immunization given at least 4 weeks apart on neonatal tetanus. Given the low additional cost of the immunization at around 60 cents...
per dose, including full operational costs, and the feasibility of reaching high coverage even in weak health care systems, the recurrent failure to reach global elimination goals is hard to justify. With recent investments in the campaign for Maternal and Neonatal Tetanus Elimination, there appears to be more substantial progress (Figure 4). The next few years will be critical to finally meeting Elimination goals.
Supplementary data
Supplementary data are available at IJE online.

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KEY MESSAGES
- A very large effect of tetanus toxoid immunization on reducing neonatal mortality from neonatal tetanus is observed based on a moderate level of evidence.
- Tetanus toxoid immunization coverage is increasing with progress being made towards maternal and neonatal tetanus elimination.
- High levels of immunization and strengthening and integrating surveillance systems are required to maintain progress and meet elimination targets.

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