Vaccines for women to prevent neonatal tetanus (Review)

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[Intervention Review]

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ABSTRACT

Background

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by Clostridium tetani. It occurs in newborn infants born to mothers who do not have sufficient circulating antibodies to protect the infant passively, by transplacental transfer. Prevention may be possible by the vaccination of pregnant or non-pregnant women, or both, with tetanus toxoid, and the provision of clean delivery services. Tetanus toxoid consists of a formaldehyde-treated toxin which stimulates the production of antitoxin.

Objectives

To assess the effectiveness of tetanus toxoid, administered to women of childbearing age or pregnant women, to prevent cases of, and deaths from, neonatal tetanus.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (July 2007), *The Cochrane Library* (2007, Issue 2), MEDLINE (1966 to June 2007), EMBASE (1974 to June 2007). We also used the results from handsearching and consultations with manufacturers and authors.

Selection criteria

Randomised or quasi-randomised trials evaluating the effects of tetanus toxoid in pregnant women or women of childbearing age on numbers of neonatal tetanus cases and deaths.

Data collection and analysis

Three review authors independently assessed trials for inclusion and trial quality, and extracted data.

Main results

Two trials (10,560 infants) were included. One study (1919 infants) assessed the effectiveness of tetanus toxoid in preventing neonatal tetanus deaths. After a single dose, the relative risk (RR) was 0.57 (95% confidence interval (CI) 0.26 to 1.24), and the vaccine effectiveness was 43%. With a two or three dose course, the RR was 0.02 (95% CI 0.00 to 0.30); vaccine effectiveness was 98%. No effect was detected on causes of death other than tetanus. The RR of cases of neonatal tetanus after at least one dose of tetanus toxoid was 0.20 (95% CI 0.10 to 0.40); vaccine effectiveness was 80%. Another study, involving 8641 children, assessed the effectiveness of tetanus-diptheria toxoid in preventing neonatal mortality after one or two doses. The RR was 0.68 (95% CI 0.56 to 0.82); vaccine effectiveness was 32%. In preventing deaths at 4 to 14 days, the RR was 0.38 (95% CI 0.27 to 0.55), and vaccine effectiveness 62% (95% CI 45% to 73%).

Authors' conclusions

Available evidence supports the implementation of immunisation practices on women of childbearing age or pregnant women in communities with similar, or higher, levels of risk of neonatal tetanus, to the two study sites. More information is needed on possible interference of vaccination by malaria chemoprophylaxis on the roles of malnutrition and vitamin A deficiency, and on the quality of tetanus toxoid production and storage.

PLAIN LANGUAGE SUMMARY

Vaccines for women to prevent neonatal tetanus

Vaccinating childbearing women against tetanus rather than influenza or cholera appears to decrease incidence of tetanus in newborn babies but possible adverse effects not assessed.

Neonatal tetanus is an infection causing rigidity, muscle spasm and often death in newborn babies. It is quite common in income-poor countries and comes from insufficient protection being passed from mother to baby in utero together with infection getting into the baby through the umbilical cord stump. The review of two studies (10,560 infants) assessing vaccinating women of childbearing age showed fewer cases of neonatal tetanus when two or three doses were used, but no potential adverse effects were assessed. Administrative and operational aspects also need to be of good quality for vaccination programmes to be effective.

BACKGROUND

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by Clostridium tetani. Tetanus is characterised by generalised rigidity and convulsive spasms of skeletal muscles. The muscle stiffness usually involves the jaw and neck and then becomes generalised.

Neonatal tetanus is a form of generalised tetanus that occurs in newborn infants born to mothers who do not have sufficient circulating antibodies to protect the infant passively by transplacental transfer. It usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with an unsterile instrument. Neonatal tetanus is still a major cause of childhood mortality in developing countries. In 1997 an estimated 277,376 neonatal deaths were attributed to tetanus, corresponding to a global mortality rate of 2.1 per 1000 live births (WHO 1998). At present, neonatal tetanus is the second leading cause of death from vaccine-preventable diseases among children worldwide (WHO 1999). In 1996, China, which comprises nearly 20% of the world population, began routine neonatal tetanus case reporting to the World Health Organization (WHO). In 1997, 25% of all reported cases globally came from China, with 60% of cases coming from China, India and Pakistan combined.

In 1997, only 77 out of 166 developing countries (representing 81% of the total developing country population) reported cases of neonatal tetanus to WHO. The number of reported cases of neonatal tetanus globally decreased from 31,849 in 1988 to 9948 in 1995, but increased again to 15,716 in 1997. This increase

largely reflects an increased number of countries providing neonatal tetanus case data to WHO and improved case detection, particularly in the Western Pacific Region. The number of countries reporting data to WHO was 156 in 1988, 169 in 1995 and 181 in 1997 (WHO 1999). Because of this low notification rate, WHO produces estimates of annual neonatal tetanus morbidity and mortality. The estimated global number of neonatal tetanus cases appears to have decreased from 510,000 in 1990 to 355,000 in 1997. The estimated global number of neonatal tetanus deaths showed a 39% decline from 1990 to 1997. The estimated neonatal tetanus mortality rate decreased in 27 out of 32 countries, showing an overall decrease of 42%. The greatest decreases were observed in Brazil (100%), Vietnam (93%), Egypt (86%), China (81%) and Indonesia (70%). An increase or no change was noted in five countries (Cameroon, Democratic Republic of Congo, Mali, Senegal and Somalia) (WHO 1999).

Clostridium tetani cannot be eradicated because it is ubiquitous in the environment and prevention of infection remains the mainstay of control. Current strategies toward neonatal tetanus elimination rely on a number of approaches. These include:

- achievement of high coverage levels with two or more doses of tetanus toxoid among women of child-bearing age and, in particular, among pregnant women;
- ensuring that doses of tetanus toxoid meet production and quality requirements;
- development of culturally appropriate programmes for promoting vaccination of girls and women and clean-cord and post-surgical care in neonates;
- development of operational approaches to reach and vaccinate, on a priority basis, women with a history of a previous child with neonatal tetanus and implementation of effective surveillance systems and promotion of strong political will.

The World Health Organization, in 1989, and the World Summit for Children, in 1990, adopted the goal of neonatal tetanus elimination. This target was more precisely defined, in 1993, as the occurrence of less than one case per thousand live births. The primary strategy for achieving this goal was based on vaccination of pregnant women with at least two doses of tetanus toxoid, and the provision of clean delivery services to all pregnant women. An additional strategy was supplemental vaccination in targeted 'high-risk' areas, having been increasingly implemented during the 1990s. Since 1990, substantial progress has been achieved towards neonatal tetanus elimination and in 1997 around 1.2 million cases were estimated to have been prevented through vaccination and clean delivery services (WHO 1999). The current goal is to achieve maternal and neonatal tetanus elimination in each health district of all countries worldwide by 2005.

However, a number of problems still appear to impede achievement of this goal (Dietz 1996; WHO 1998). These include the lack of sensitive surveillance of the disease and of immunisation coverage, lack of knowledge of field effectiveness of tetanus toxoid, lack of knowledge of optimal vaccination schedules for high long-lasting immunity levels, difficulties of control over tetanus toxoid production procedures and on the quality and potency of the toxoid and scarce knowledge of optimal topical antimicrobial practices.

Tetanus toxoid has been regarded as safe and useful since Descombey first reported its production in 1924 (Descombey 1924). Tetanus toxoid consists of a formaldehyde-treated toxin, which after a primary series of properly spaced doses stimulates the production of antitoxin which protects against tetanus toxin. Local adverse events (erythema, induration, pain at the injection site) are common but usually self limited. Occasionally exaggerated local reactions are also reported (extensive painful swelling) most often in adults. Severe systemic reactions such as generalised urticaria, anaphylaxis or neurological complication are rare.

The WHO strategy of administering two properly spaced doses of tetanus toxoid to 80% of women childbearing age is mainly based on a follow-up study which provides most of the information currently used to implement vaccination campaigns (Koenig 1998). According to this study, two doses of tetanus toxoid provided significant protection against neonatal tetanus for infants born to women vaccinated up to 13 years before and a single dose offered some protection for at least five years. Apart from this observational study, current knowledge on vaccine efficacy is only inferred from antitoxin levels and the availability of both field and experimental evidence on the effect of the tetanus toxoid appears to be insufficient. In order to try to help fill this gap, there is an urgent need for a systematic review of all available evidence on the subject.

OBJECTIVES

1. To identify, retrieve and assess all studies evaluating the effects of tetanus toxoid vaccination administered to women of childbearing age, or pregnant women, on neonatal tetanus.

2. To assess the effectiveness of vaccination administered to women of childbearing age, or pregnant women, in preventing cases of neonatal tetanus.

3. To assess the effectiveness of vaccines in avoiding deaths from neonatal tetanus.

4. To estimate the frequency of adverse effects associated with tetanus toxoid vaccination in pregnancy or in women of childbearing age.

The following hypotheses will be tested comparing groups intended for tetanus toxoid vaccination versus control/placebo groups.

1. There is no difference in the number of cases of neonatal tetanus.

2. There is no difference in the number of deaths.

3. There is no difference in the number and severity of adverse effects (both systemic and localised).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised studies comparing tetanus toxoid in humans with placebo, control vaccines or no intervention or comparing types, doses or schedules of tetanus toxoid vaccine.

Types of participants

Pregnant women or women of childbearing age irrespective of immune status.

Types of interventions

Tetanus toxoid administered by any route, irrespective of dosage and schedules.

Types of outcome measures

Clinical

Numbers of neonatal tetanus cases and deaths from neonatal tetanus occurring in vaccine and placebo groups.

Adverse effects

Number and seriousness of adverse effects (classified as local and systemic). Systemic adverse effects include cases of fever and more generalised and serious signs. Local adverse effects include induration, soreness and redness at the site of inoculation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (July 2007).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 36 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched *The Cochrane Library* (2007, Issue 2), MEDLINE (1966 to June 2007), EMBASE (1974 to June 2007), using the search strategy in Appendix 1.

We used the results of the handsearch of the journal Vaccine (Jefferson 1996; Jefferson 1998). In order to locate unpublished trials we wrote to the tetanus toxoid manufacturers listed at the WHO website. We read the bibliography of retrieved articles in order to identify further trials. We did not apply any language restrictions.

Data collection and analysis

Inclusion procedure

Two review authors read all trials retrieved in the search and applied the inclusion criteria. They judged the studies separately and controversies were arbitrated by the co-ordinator of the Cochrane Vaccine Field.

Trial quality assessment

Trials fulfilling the review inclusion criteria were assessed for quality and results analysed.

Assessment of methodological quality

We assessed the methodological quality of randomised, cluster randomised, and quasi-randomised trials using the following definitions adapted from the Cochrane Reviewers' Handbook (Alderson 2004).

Randomisation

We assessed randomisation using the following criteria:
A = individual participants allocated to vaccine or control group;
B = groups of participants allocated to vaccine or control group.

Generation of the allocation sequence

We assigned a quality score for each trial using the following criteria:
A = adequate, e.g., table of random numbers or computer-generated random numbers;
B = inadequate, e.g., alternation, date of birth, day of the week, or case record number;
C = not described.

Allocation concealment

We assigned a quality score for each trial using the following criteria:
A = adequate, e.g., numbered or coded identical containers administered sequentially, on site computer system that can only be accessed after entering the characteristics of an enrolled participant, or serially numbered, opaque, sealed envelopes;
B = possibly adequate, e.g., sealed envelopes that are not sequentially numbered or opaque;
C = inadequate, e.g., open table of random numbers;
D = not described.

Blinding

We assessed blinding using the following criteria:
A = adequate blinding, e.g., both participants and assessor are blind;
B = single blind, i.e., only participants or assessor are blind;
C = no blinding.

Data collection

We extracted, checked and recorded the following data using an agreed form:

- characteristics of participants;
- number of participants;
- age and ethnic group.

Statistical analysis

We carried out statistical analysis using the Review Manager software (RevMan 2003). We used random-effects meta-analysis for combining data from the two trials. The relative risks of events (cases of neonatal tetanus and deaths), the number needed to treat and the vaccine effectiveness, defined as 1 - RR, comparing vaccination and control groups were calculated from the individual trials and introduced into the analysis. Although not specified in the protocol a subgroup analysis was performed on the only trial presenting data separately by doses. Interaction between estimates was assessed by means of the method of calculating a ratio of relative risks and its 95% confidence interval (Altman 2003).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
We included two trials involving 95,704 immunised individuals (including women of childbearing age, pregnant women and children aged one to 14 years) and 10,560 infants born to them.
Our search strategies identified 1738 potentially relevant studies. Following analysis of the titles and of the available abstracts, 34 studies were retrieved and considered for inclusion. Only two studies met the inclusion criteria; these had been published as full paper articles. The 32 excluded studies were rejected because: they had a study design different from that described in the protocol (28 studies) or dealt with treatments different from those considered for this review (four studies).

Types of studies

One trial used individual randomisation (Newell 1966) while the other did not report details of randomisation methods and was included as a quasi-randomised trial (Black 1980).

Types of interventions

One study assessed the effects of aluminium phosphate adsorbed tetanus toxoid (10LF) against polyvalent influenza vaccine (Newell 1966) and the other study assessed the effects of adsorbed tetanus-diphtheria toxoid against cholera toxoid (Black 1980).

Types of participants

The trial that compared tetanus-diphtheria toxoid with cholera toxoid (Black 1980) included a total of 92,928 healthy women aged at least 15 years, and children aged one to 14 years, who were

immunised with one or two doses of the vaccine preparations. Follow up was performed on 8641 infants born from these group of women and began nine months after immunisation, to ensure that women pregnant at the time of vaccination had been excluded from the analysis.

In the trial with influenza vaccine as control (Newell 1966), 2776 women aged between 13 and 45 years were enrolled. They were randomised to receive three doses of one vaccine preparation. Of these, 1158 declined to receive any immunisation and their infants were not included in the analysis (n = 601). Also, 136 infants born to the immunised groups were not included in the analysis because they were born before mothers could receive the first dose of the vaccine. Overall 1182 infants were included in the analysis.

A total of 9823 births were considered from the two studies combined.

Types of outcome measures

One trial used cases of neonatal tetanus, deaths from neonatal tetanus, and non-tetanus deaths as outcome measures (Newell 1966). The other study presented results in terms of neonatal mortality and mortality on days four to 14 from birth (Black 1980).

Follow-up periods covered the first months of life while the two studies were carried out for five (Newell 1966) and two years respectively.

Date and location of the trials

Newell 1966 was carried out between 1961 and 1966 in the 'Corregimiento of Gachene' 45 km south-east of Cali, department of Cauca, Columbia. Black 1980 took place between July 1974 and March 1977 in the Matlab area of Bangladesh. Both were sponsored by the Government but for Newell 1966 the employed toxoid was provided by Lederle Laboratoires. Both were published in WHO Bulletins.

See tables 'Characteristics of included studies' and 'Characteristics of excluded studies' for further details of individual studies.

Risk of bias in included studies

Allocation concealment was described and considered to be adequate in one study (Newell 1966) and the other study did not report details on the allocation concealment procedures (Black 1980). The generation of random allocation sequence was adequate in one study (Newell 1966); the remaining study did not give enough details on how the allocation sequence was generated. Both trials reported a double-blind design. In one of the two studies there were no losses to follow up (Black 1980) while the other one analysed the data "per-protocol" and the information given in the report did not allow us to re-analyse the results on the 'intention-to-treat' basis.

Effects of interventions

Two trials involving a total of 10,560 infants were included.

Tetanus toxoid versus influenza vaccine

Neonatal tetanus deaths

One study (Newell 1966) assessed the effectiveness of tetanus toxoid in preventing neonatal tetanus deaths after one-dose and two- or three-dose vaccination courses. Altogether, 494 births after a single-dose vaccination were considered, the relative risk (RR) of death was 0.57 (95% confidence interval (CI) 0.26 to 1.24) and the vaccine effectiveness was 43% (95% CI -24% to 74%).

Six hundred and eighty-eight births were assessed after a two- or three-dose course, the RR of death was 0.02 (95% CI 0.00 to 0.30) and the vaccine effectiveness was 98% (95% CI 70% to 100%).

Comparing the estimates for the two courses of vaccination, the ratio of relative risks (RRR) was 30.86 (Z = 2.319; P = 0.01).

Considering the total of 1182 births independently from the number of received doses, the RR was 0.12 (95% CI 0.00 to 7.88), with an efficacy of 88% (95% CI -688% to 100%).

Death from non-neonatal tetanus causes

The same study (Newell 1966) did not detect any effects on causes of death other than tetanus after one dose (RR 2.14, 95% CI 0.97 to 4.76); and after two or three doses (RR 0.75, 95% CI 0.38 to 1.47). The RR considering the total population was 1.24 (95% CI 0.44 to 3.47).

Comparing the estimates for the two courses of vaccination, the RRR was 2.86 (Z = 1.972; P = 0.02).

All causes of death

Considering deaths for all causes, no significant effect could be observed after one dose of vaccine - the RR was 1.08 (95% CI 0.75 to 1.79), whereas a significant effect was seen with two or three doses of tetanus toxoid (RR 0.31; 95% CI 0.17 to 0.55 , with an efficacy of 69%; 95% CI 45% to 83%). This positive association could not be found when the total study population was taken into account (RR 0.58; 95% CI 0.17 to 1.99).

Comparing the estimates for the two courses of vaccination, the RRR was 3.19 (Z = 2.944; P =0.00).

Tetanus cases

One thousand one hundred and eighty-two births were analysed in order to assess the effects of at least a single dose of tetanus toxoid on cases of neonatal tetanus. The RR was 0.20 (95% CI 0.10 to 0.40); vaccine effectiveness 80% (95% CI 60% to 90%).

Tetanus diphtheria toxoid versus cholera toxoid

Neonatal mortality

One study (Black 1980) considered the effectiveness of tetanus diphtheria toxoid in preventing neonatal mortality after one or two doses up to 32 months from vaccination. Eight thousand six hundred and forty-one births were assessed and the RR accounted for 0.68 (95% CI 0.56 to 0.82); vaccine effectiveness was 32% (95% CI 18% to 44%).

Four to 14 days neonatal mortality

The same study (Black 1980) considered the effectiveness on four to 14 days neonatal mortality. The RR was 0.38 (95% CI 0.27 to 0.55); vaccine effectiveness was 62% (95% CI 45% to 73%).

Adverse effects

No studies reporting adverse effects were found among the included studies. Among the excluded studies we identified two studies evaluating the safety of tetanus toxoid. One was carried out in order to evaluate of the safety of different types of vaccine's adjuvants (MacLennan 1965) and the second is a case-control study assessing the association between vaccination and congenital anomalies (Silveira 1995). Their characteristics are described in the additional Table 1.

Table 1. Studies evaluating safety outcomes

References	Study design	Study population	Intervention	Safety outcomes	Results
MacLennan 1965	2 studies are reported in this paper: a) 1 cluster-RCT evaluating reactogenicity and side-effects; b) 1 RCT assessing safety only, with a 24-weeks' follow up.	Both studies were performed in New Guinea on indigenous populations. a) Pregnant women belonging to the Abelam tribe (n = 179). b) Non-pregnant women from the Maprik area (n = 999).	a) Tetanus toxoid prepared by Parke Davis & co with different adjuvants and administered in different doses (Drakeol, 1 dose vs H - 24, 1 dose vs AlPO4, 2 doses vs none, 3 doses) or TT prepared by the Commonwealth Serum Laboratories without adjuvant, 3 doses. b) TT prepared by Parke Davis & co with Drakeol (A,	a) Swelling (severe or no tender). b) Abscess (A = 103 /327; B = 96/332; C = 2/340 at the 14th week after immunisation). c) Fever between 37.8-38.3 °C. d) Swelling.	Although oil-adjuvated preparations provide longer persistence of antitoxin and require to be administered only once, they caused frequently severe side-effects. The Al-adjuvated preparations, administered in 2 doses, appeared to be the best way at the time of the study to prevent the occurrence of NNT.

Table 1. Studies evaluating safety outcomes (*Continued*)

			one dose) vs H - 24 (B, one dose) vs AlPO4 (C, two doses).		
Silveira 1995	Case-control study.	Cases (n = 34,293): newborn with congenital malformation. The 10 most frequent in South America were considered. Controls (n = 34,777): non-malformed babies of the same sex, born in the same hospital immediately after the malformed ones. Data were obtained from examination of 1,282,403 neonates in 173 hospitals in 105 cities accross nine different countries in South America.	Immunisation of the mothers with TT during pregnancy.	Cleft lip, pes equinovarus, postaxial polydactyly, hip subluxation, haemangioma, periauricular tag, fistula auris, pigmented naevus, other skin defects, multiple malformed.	No association for each of the examined factors was found.

DISCUSSION

As a result of this systematic review only two experimental studies assessing the effectiveness of tetanus toxoid in preventing neonatal tetanus have been found. The size of the population included in the studies and the consistency of the results allow us to draw some firm conclusions.

The effectiveness of vaccination in preventing deaths from neonatal tetanus appears to be high when two or more doses are administered. The vaccination does not exert effects on causes of death other than tetanus. The two studies apparently show differences in the estimates of effect, but these differences are understandable when considering that the study showing lower effectiveness (Black 1980) was assessing a different intervention (vaccination with only one or two doses) and a less specific outcome (all causes neonatal deaths occurring four to 14 days from birth). In the interpretation of the results it must be also considered that one study (Newell 1966) had a third arm containing participants that refused vaccination and that data from this arm were not included in the analysis. Because of the limited number of eligible experimental studies included in this review we decided to carry out an extended search in order to retrieve all the available comparative studies on this topic. The same databases were explored in order to identify cohort, case-control studies and other non-randomised study designs. Seven further studies were identified (four surveys comparing the disease incidence before and after the introduction of the immunisation campaign, two case-control studies and a cohort study). The characteristics of these studies are summarised at the additional Table 2. Altogether 37,352 births were surveyed by the prospective studies and 552 subjects were included in the case-control studies. All the studies but one confirmed the existence of

a significant protective effect of an immunisation course of at least two doses of tetanus toxoid on the incidence of neonatal tetanus.

Table 2. Non-randomised studies

References	Design	Study Population	Treatment	Outcomes	Results
Baltazar 1994	Case-control study.	54 neonates admitted to hospital diagnosed with neonatal tetanus. 50 controls 1-4 months old admitted for causes other than neonatal tetanus. Manila.	Immunisation with tetanus toxoid, considered immunised if received at least 2 doses of tetanus toxoid during pregnancy, otherwise not.	Incidence of immunisation: cases (1/54), controls (12/49).	Protective effect against neonatal tetanus if at least 2 doses of tetanus toxoid.
Chai 2004	Case-control study. Surveillance data after TT mass immunisation campaign carried out 1995-96 in 320 out of 560 countries reaching about 23 million women aged 18-35 years, were also reported. Coverage with 2 doses of TT was estimate 10%. Surveillance data of 1996-2001 were analysed.	Cases: 60 children with NT (WHO case definition) reported by cards and hospital record in Bobai country (province of Guangxi, China) to the National Notifiable Disease Reporting System (NNDRS) from 1.1.97 to 30.4.98. Only children with accurate locating information were included. Controls: 60 infants born in the same village as the cases.	Mother of children were immunised with TT. No information about the number of administered doses is reported.	TT immunisation status of the mothers and other informations (maternal: age, education level, annual income < 1000 Yuan; infant: gender, order of birth, home delivery; parental knowledge and attitude regarding NT) were assessed by means of a detailed questionnaire given to parents of both cases and controls. TT immunisation history was based only of mother's recall because they were not provided with vaccinal records. Mothers of 7 cases and 17 controls received previously TT.	Receiving of 1 or more of TT was significant protective against NT. Maternal age, education, family income, birth order, parental knowledge, were also significantly associated with NT.
Gupta 1998	Survey.	1688 pregnant women. India.	Immunisation with tetanus toxoid, considered immunised if received 2 doses of tetanus toxoid at at least 4 weeks	Deaths from neonatal tetanus within 3 to 30 days of birth.	Immunisation during the antenatal period is highly protective against occurrence of neonatal tetanus.

Table 2. Non-randomised studies (*Continued*)

			apart or a booster dose. Partially immunised, if received 1 dose of tetanus toxoid either during the current pregnancy or in the past 3 years.		
Hlady 1992	Case-control study.	Infants with clinical diagnosed tetanus. 3 controls. Bangladesh.	Immunisation with tetanus toxoid, 2 doses 4 weeks apart, with second dose administered at least 30 days before delivery.	Incidence of immunisation: cases (33/112), controls (122/336).	Immunisation failed to provide the expected high level of protection.
Ysuf 1991	Follow-up survey.	Women aged 10-45 years. Indonesia.	Immunisation with tetanus toxoid, 1 or 2 doses.	Deaths from neonatal tetanus within 3 to 28 days of birth.	Immunisation caused an 85% reduction of neonatal tetanus.
Chongsuvivatwong 1993	Survey study.	Women aged 15-45 years. Thailand.	Immunisation with tetanus toxoid.	Cases of neonatal tetanus.	Immunisation caused a 8-10 times reduction of neonatal tetanus.
Rahman1982	Surveillance study.	Women from surveillance area. Bangladesh.	Immunised with tetanus toxoid at 6th, 7th, 8th month. Considered immunised if received 2 injections in 1974 or in the 1978-79 programme. Partially immunised, if received 1 injection in 1974 or 1978-79. Mixed immunised if received 1 or 2 doses in 1974 and again 1 or 2 doses in 1978-79.	Deaths attributed to neonatal tetanus within 4-14 days after birth.	Full immunisation reduced neonatal mortality rates by about one half and mortality rates on days 4-14 by about 70%.
Koenig 1998	Survey.	Children between 1-14 years and non-pregnant women at	Immunised with cholera toxoid (1 or 2 0.5 ml doses)	Deaths attributed to neonatal tetanus within 4-14	2 injections provided significant protection.

Table 2. Non-randomised studies (*Continued*)

		least 15 years. Bangladesh.	vs tetanus - diphtheria toxoid (1 or 2 0.5 ml doses).	days after birth.	Protection of 1 dose not significant.
Schofield 1961	Observational.	Pregnant women from 62 villages in New Guinea (Maprik, Wingei and Wosera areas). A retrospective "history-taking survey" on children born from 1945 to the time of the study was also performed in the Maprik area.	3 doses of fluid formalinised tetanus toxoid (Commonwealth Serum Laboratories, Melbourne). The first dose was administered as early as possible in pregnancy, the second 6 weeks later and the third between 6 weeks and 6 months after the second.	Cases of neonatal tetanus observed in children born from mothers who received different number of doses of TT during pregnancy. Not immunised: 8/86. Once immunised: 8/74. Twice immunised: 8/234. Three times immunised: 1/175. From the history-taking survey it results that during the examination period 184 deaths due to neonatal tetanus occurred out of 3017 live births.	3 doses of formalinised TT administered during pregnancy afforded substantial protection against neonatal tetanus. Immunisation with only 2 doses provided also a significant protection level. No reactions to the vaccine were noticed.

In conclusion, this review shows that vaccination with tetanus toxoid is effective in preventing neonatal tetanus cases and deaths specifically caused by neonatal tetanus. Even if the evidence is derived mainly from a single study this appears to be solid and consistent with the findings of all other comparative studies presently available.

Therefore, the reasons for the low performance presently achieved by the vaccination campaigns should be sought outside the field of vaccine efficacy and are probably related to organisational and quality issues. Our review did not find evidence on the main factors that can have negative influence on the impact of the immunisation practice and that may justify the present low level of performance of the campaign (Dietz 1996; WHO 1999). No studies were found assessing the interference of vaccination with malaria chemoprophylaxis, the potential negative effect of malnutrition and vitamin A deficiency, the impact of insufficient quality of tetanus toxoid production and storage. Future research should concentrate on evaluating these and other factors that may have a negative impact on the immunisation practice and look for possible interventions in order to improve the performance of the campaign.

AUTHORS' CONCLUSIONS

Implications for practice

From the two trials reviewed, the available evidence supports the implementation of immunisation with tetanus toxoid in communities with similar, or higher, levels of risk of neonatal tetanus.

Implications for research

More information is needed on factors that may have a negative

impact on the immunisation practice and on the effectiveness of interventions implemented in order to improve the performance of the campaign.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Black 1980

Methods	Volunteers received 1 of the 2 treatments on a double-blind basis, there was no information about the adopted manner of randomisation.
Participants	Children between 1 and 14 years of age and non-pregnant women at least 15 years old from Matlab, a community in rural Bangladesh. Altogether 92,928 participants were immunised and their 8641 infants followed up.
Interventions	1 or 2 doses of adult dose Al-adsorbed tetanus-diphtheria toxoid versus cholera toxoid. Both as 0.5 ml dose, intramuscular, double-blind.
Outcomes	Neonatal mortality on days 4-14 (as indicator for neonatal tetanus). Neonatal mortality. Both assessed on 2 following birth cohorts.
Notes	Carried out between July 1974 and March 1977. Governmental supported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Newell 1966

Methods	RCT (all registered were allotted a code number according to their ascertainment, which was previously randomly divided in 2 groups, A and B. Those who declined to participate were placed in a third group C, n = 1158).
Participants	Women between 13 and 45 years of age from Corregimiento of Guacene (Columbia) were immunised with TT or polyvalent influenza vaccine (n = 1618). Follow up carried out on 1182 infants.
Interventions	1 or 2 doses of 10 LF AlPO4 adsorbed tetanus toxoid vs polyvalent influenza vaccine, 1 ml intramuscularly, both preparations were not perfectly undistinguishable.
Outcomes	Incidence of neonatal tetanus cases or deaths. Non-tetanus death among the newborns in the 5 years following the immunisation.
Notes	Carried out between 1961 and 1965. Lederle Laboratories provided TT.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

RCT: randomised controlled trial
TT: tetanus toxoid
10 LF: aluminium phosphate absorbed tetanus toxoid
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Abuwa 1997	Not a trial.
Anh 1999	Not a trial. Serological measurement with means of the Toxin Binding Inhibition Test on pregnant women and children after 2 doses TT.
Axelsson 2002	Review on umbilical cord care and prevention of infections.
Aylward 1996	Surveillance study.
Baltazar 1994	Case-control study on efficacy of prenatal TT immunisation in preventing neonatal tetanus.
Berggren 1971	Retrospective survey.
Chai 2004	Case-control study.
Chongsuvivatwong 93	Incidence of neonatal tetanus mortality before and after mass immunisation in Thailand.
Dhillon 1975	Not a trial. Only serological outcomes.
Dietz 1996	Review.
Gupta 1998	Cohort study.
Hardegree 1970	Continuation of the study of MacLennan 65. 2 TT vaccine with different adjuvants were administered. Serological only.
Heredia 1968	Not a trial. Only serological assessment.
Hlady 1992	Case-control study.
Kielmann 1977	Not a trial. Administration of TT with 2 different adjuvants in women of childbearing age. Only serological outcomes.
Koenig 1998	Not a trial. 10-year follow up conducted on half of the area where Black 80 was carried out.
MacLennan 1965	No intervention: administration of vaccines containing same toxoids but different adjuvants in women of childbearing age. Efficacy outcomes are only serological.
Mulholland 1996	No intervention: trial with polyribosylribitol phosphate-tetanus vaccine.

(*Continued*)

Nohynek 1999	No intervention: participants were children receiving conjugate Hib and DTP vaccine, who were born from mother immunised with different doses of TT (0, 1, 2, 3 and more).
Perry 1998	Report on tetanus toxoid immunisation coverage.
Rahman 1982b	Consensus to vaccination.
Rahman 1982	Not a trial. Vaccination of pregnant women with 3 doses of TT. Immunisation program conducted in half of the Matlab area after Black 80.
Relyveld 1991	Only serological outcomes.
Schofield 1961	Not a trial.
Silveira 1995	Case control to assess relationship between exposition to TT in pregnancy and malformation in the newborns.
Stanfield 1973	Not a trial. Variation of seral antitoxin after administration of different TT preparation to pregnant women.
Suri 1964	Not a trial. Different TT preparation were administered and antitoxin in cord blood were measured.
Tall 1991	Case-control study.
Traverso 1991	Case-control study for assessing risk of developing neonatal tetanus, TT immunisation of the mothers was not evaluated as associated factor.
Yala 1980	Not a trial.
Yusuf 1991	Follow-up survey to determine incidence of neonatal tetanus before and after a vaccination campaign in Indonesia.

Hib: H. Influenza
TT: tetanus toxoid

DATA AND ANALYSES

Comparison 1. Tetanus toxoid versus influenza vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal tetanus deaths	1	1182	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.00, 7.88]
1.1 One dose	1	494	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.24]
1.2 Two or three doses	1	688	Risk Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.30]
2 Deaths from non-neonatal tetanus causes	1	1182	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.44, 3.47]
2.1 One dose	1	494	Risk Ratio (M-H, Random, 95% CI)	2.14 [0.97, 4.76]
2.2 Two or three doses	1	688	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.38, 1.47]
3 All causes of death	1	1182	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.17, 1.99]
3.1 One dose	1	494	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.65, 1.79]
3.2 Two or three doses	1	688	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.17, 0.55]
4 Neonatal tetanus cases	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Any dose	1	1182	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.10, 0.40]

Comparison 2. Tetanus diphtheria toxoid versus cholera toxoid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 4 to 14 days neonatal mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

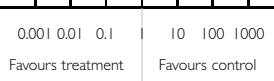
Analysis 1.1. Comparison 1 Tetanus toxoid versus influenza vaccine, Outcome 1 Neonatal tetanus deaths.

Review: Vaccines for women to prevent neonatal tetanus

Comparison: 1 Tetanus toxoid versus influenza vaccine

Outcome: 1 Neonatal tetanus deaths

Study or subgroup	Tetanus toxoid n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 One dose					
Newell 1966	9/224	19/270		55.1 %	0.57 [0.26, 1.24]
Subtotal (95% CI)	**224**	**270**		**55.1 %**	**0.57 [0.26, 1.24]**
Total events: 9 (Tetanus toxoid), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
2 Two or three doses					
Newell 1966	0/341	27/347		44.9 %	0.02 [0.00, 0.30]
Subtotal (95% CI)	**341**	**347**		**44.9 %**	**0.02 [0.00, 0.30]**
Total events: 0 (Tetanus toxoid), 27 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.80 (P = 0.00511)					
Total (95% CI)	**565**	**617**		**100.0 %**	**0.12 [0.00, 7.88]**
Total events: 9 (Tetanus toxoid), 46 (Control)					
Heterogeneity: Tau^2 = 8.03; Chi^2 = 8.34, df = 1 (P = 0.004); I^2 =88%					
Test for overall effect: Z = 0.99 (P = 0.32)					



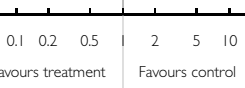
Analysis 1.2. Comparison 1 Tetanus toxoid versus influenza vaccine, Outcome 2 Deaths from non-neonatal tetanus causes.

Review: Vaccines for women to prevent neonatal tetanus

Comparison: 1 Tetanus toxoid versus influenza vaccine

Outcome: 2 Deaths from non-neonatal tetanus causes

Study or subgroup	Tetanus toxoid n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 One dose					
Newell 1966	16/224	9/270		47.9 %	2.14 [0.97, 4.76]
Subtotal (95% CI)	**224**	**270**		**47.9 %**	**2.14 [0.97, 4.76]**
Total events: 16 (Tetanus toxoid), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.87 (P = 0.061)					
2 Two or three doses					
Newell 1966	14/341	19/347		52.1 %	0.75 [0.38, 1.47]
Subtotal (95% CI)	**341**	**347**		**52.1 %**	**0.75 [0.38, 1.47]**
Total events: 14 (Tetanus toxoid), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.84 (P = 0.40)					
Total (95% CI)	**565**	**617**		**100.0 %**	**1.24 [0.44, 3.47]**
Total events: 30 (Tetanus toxoid), 28 (Control)					
Heterogeneity: Tau^2 = 0.41; Chi^2 = 3.89, df = 1 (P = 0.05); I^2 =74%					
Test for overall effect: Z = 0.41 (P = 0.68)					

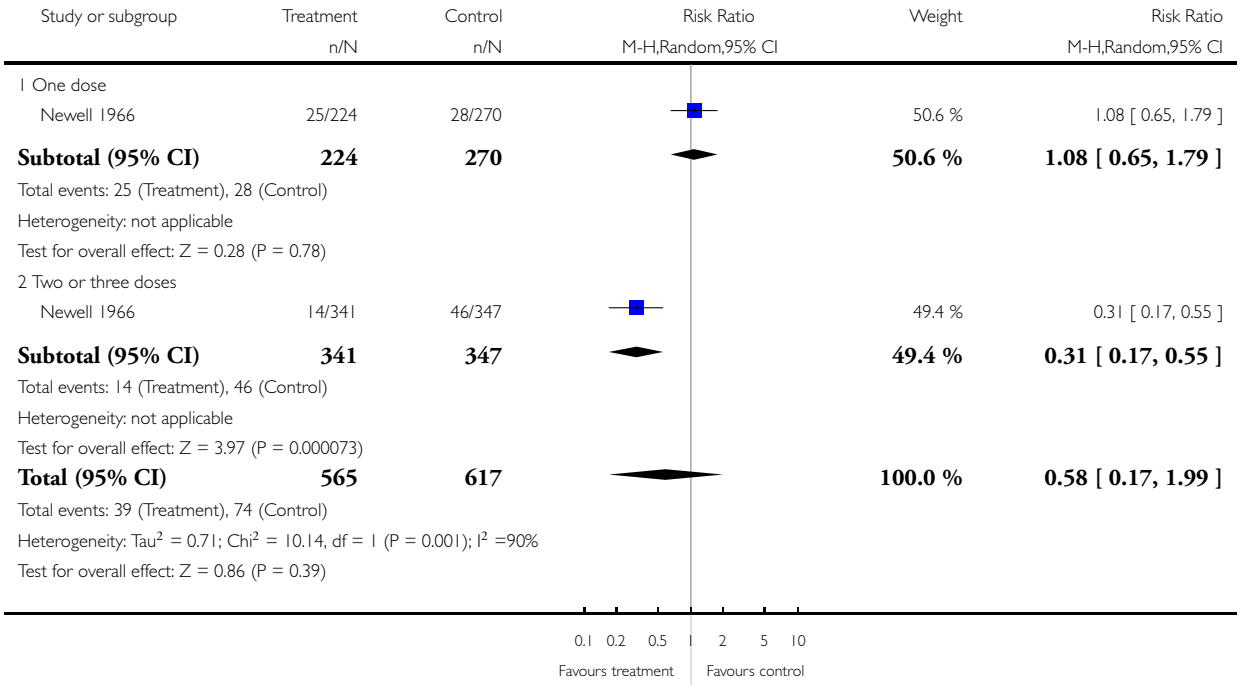


Analysis 1.3. Comparison 1 Tetanus toxoid versus influenza vaccine, Outcome 3 All causes of death.

Review: Vaccines for women to prevent neonatal tetanus

Comparison: 1 Tetanus toxoid versus influenza vaccine

Outcome: 3 All causes of death

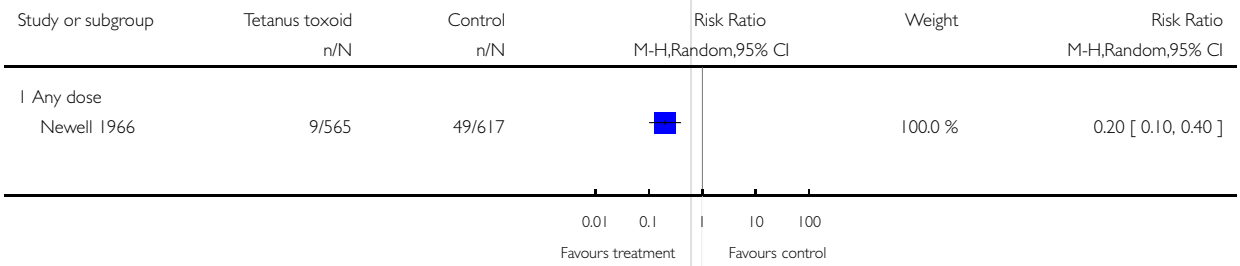


Analysis 1.4. Comparison 1 Tetanus toxoid versus influenza vaccine, Outcome 4 Neonatal tetanus cases.

Review: Vaccines for women to prevent neonatal tetanus

Comparison: 1 Tetanus toxoid versus influenza vaccine

Outcome: 4 Neonatal tetanus cases



Analysis 2.1. Comparison 2 Tetanus diphtheria toxoid versus cholera toxoid, Outcome 1 Neonatal mortality.

Review: Vaccines for women to prevent neonatal tetanus

Comparison: 2 Tetanus diphtheria toxoid versus cholera toxoid

Outcome: 1 Neonatal mortality

Study or subgroup	Td toxoid n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Black 1980	173/4255	262/4386		0.68 [0.56, 0.82]

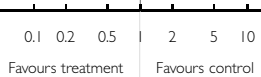
Analysis 2.2. Comparison 2 Tetanus diphtheria toxoid versus cholera toxoid, Outcome 2 4 to 14 days neonatal mortality.

Review: Vaccines for women to prevent neonatal tetanus

Comparison: 2 Tetanus diphtheria toxoid versus cholera toxoid

Outcome: 2 4 to 14 days neonatal mortality

Study or subgroup	Td toxoid n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Black 1980	41/4255	110/4386		0.38 [0.27, 0.55]



APPENDICES

Appendix 1. search strategy

#1 ("Tetanus Toxoid/adverse effects"[MeSH] OR "Tetanus Toxoid/contraindications"[MeSH] OR "Tetanus Toxoid/immunology"[MeSH] OR "Tetanus Toxoid/toxicity"[MeSH])
#2 ("Tetanus/epidemiology"[MeSH] OR "Tetanus/immunology"[MeSH] OR "Tetanus/mortality"[MeSH] OR "Tetanus/prevention and control"[MeSH])
#3 "neonatal tetanus"[Title/Abstract] OR ((tetanus[Title/Abstract]) AND (immunisation[Title/Abstract] OR vaccin*[Title/Abstract] OR inoculation[Title/Abstract] OR newborn[Title/Abstract] OR infant[Title/Abstract] OR pregnancy[Title/Abstract]))
#4 1 OR 2 OR 3
#5 "Pregnancy Complications, Infectious"[MeSH]
#6 "Maternal-Fetal exchange"[MeSH]
#7 "Umbilical Cord"[MeSH]
#8"Fetus"[MeSH]
#9 "Infant, Newborn"[MeSH]
#10 childbearing[Title/Abstract] OR pregnant[Title/Abstract] OR pregnancy[Title/Abstract]
#11 5# OR #6 OR #7 OR #8 OR #9 OR #10
#12 "Tetanus Toxoid"[MeSH] OR tetanus toxoid[Title/Abstract]
#13 #11 AND # 12
#14 #4 OR #13
#15 "Randomized Controlled Trials"[MeSH] OR "Controlled Clinical Trials"[MeSH] OR "Random Allocation"[MeSH] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Clinical Trials"[MeSH] OR "Placebos"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Prospective Studies"[MeSH] OR "Control Groups"[MeSH] OR "Patient Selection"[MeSH]
#16 controlled clinical trial*[Title/Abstract] OR randomised controlled trial*[Title/Abstract] OR randomized controlled trial*[Title/Abstract] OR clinical trial*[Title/Abstract] OR "clinical trial*" OR random* OR placebo* OR "double blind" OR "single blind" OR allocation[Text Word] OR "follow up"
#17 #15 OR #16
#18 #14 AND #17

WHAT'S NEW

Last assessed as up-to-date: 30 June 2007.

18 February 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 4, 2005

1 July 2007	New search has been performed	Seach updated. No new trials identified.
15 August 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Vittorio Demicheli produced the first draft and the final version of the protocol. Antonella Barale wrote the background section and commented on the draft protocol.

Vittorio Demicheli applied the inclusion criteria, checked the data extraction, structured the comparison and outcome tables, entered data into Review Manager, and drafted the report. Antonella Barale applied the inclusion criteria, extracted the data, and commented on the report. Alessandro Rivetti applied the inclusion criteria, extracted the data, and commented on the report.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- ASL 20 Alessandria, Italy.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Infant, Newborn; Randomized Controlled Trials as Topic; Tetanus [mortality; *prevention & control]; Tetanus Toxoid [*therapeutic use]

MeSH check words

Adult; Female; Humans; Pregnancy