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Tetanus toxoid immunization to reduce mortality from neonatal tetanus

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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

occur in a limited number of large countries with low coverage of facility births and tetanus toxoid immunization, such as India and Nigeria.

Neonatal tetanus is an acute disease presenting initially with loss of ability to suck, followed by generalized rigidity and painful muscle spasms as the disease progresses. The disease is caused by tetanus toxin produced by *Clostridium tetani*. The commonest port of entry for the tetanus spores is the unhealed umbilical cord. Most (90%) cases of neonatal tetanus develop symptoms during the first 3–14 days of life with the majority presenting at 6–8 days.[1] Mortality tends to be very high: in the absence of medical treatment, case fatality approaches 100%; with hospital care 10–60% of NT cases die, depending on the availability of intensive care facilities.[1] Clearly, prevention measures for tetanus are more effective than case management even if full intensive care were available, and certainly much more cost-effective.[3]

Even before tetanus vaccine was available, neonatal tetanus became increasingly rare in most of Europe and North America through hygienic childbirth practices and cord care.[4,5] The advent of the vaccine resulted in further reduction in high-income countries, and also opened opportunities for progress in low-income settings. The vaccine is an inactivated toxin (toxoid) that was first produced in 1924.[6] It became commercially available in 1938 and was successfully used extensively during the Second World War. In the late 1940s, it was combined with diphtheria and pertussis vaccines to produce the DTP triple vaccine used in many childhood immunization programmes. A trial in Papua New Guinea published in 1961 was the first demonstration that use of two or more doses of tetanus toxoid during pregnancy could prevent neonatal tetanus.[7] In the mid-1970s, tetanus toxoid vaccination of pregnant women was included in the WHO's Expanded Program on Immunization.[4]

Concentrations of tetanus anti-toxin exceeding 0.1–0.15 IU/ml, measured by standard (indirect) enzyme linked immunosorbent assay, are considered protective. These are achieved 24 weeks after the second dose of tetanus toxoid in 90% of adults. Although immunity wanes over time, more than three-quarters of women will maintain 'protective levels' for 3 years. A third dose given 6–12 months after the first two doses increases both the level of neutralizing IgG antibody and duration of immunity for at least an additional 5 years. Additional doses given at least 1 year apart further prolong duration of protection; after the fifth dose, protective antibody levels last for at least 20 years.[8]

Tetanus antitoxin is actively transported by the placenta from an immunized mother to her fetus, providing passive protection against tetanus during the neonatal period and the following month or two of life. Maternal and neonatal tetanus antibody concentrations at the time of delivery are usually similar.[8] However, placental antibody transfer may be reduced in the presence of maternal malaria and HIV infections.[9–11]

While tetanus immunization is now a standard practice, the evidence base to support the mortality effect estimate for use in the LiST tool is limited, mainly because the vaccine was accepted for practice before the era of randomized controlled trials. The Cochrane review ('Vaccines for women to prevent neonatal tetanus') includes two trials, one from Columbia in 1966 and the second from Bangladesh in 1980.[12]

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.[13] 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).

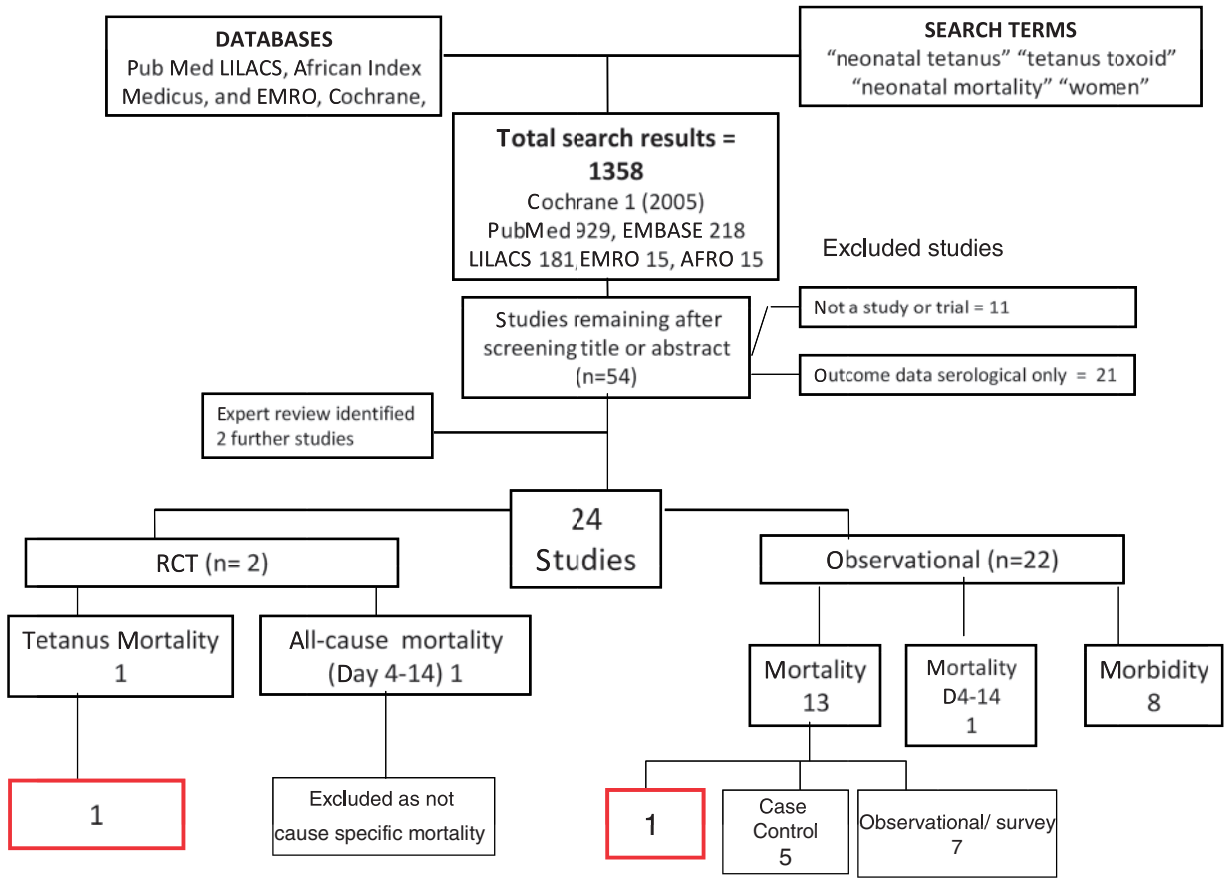

Figure 1 Synthesis of study identification in the review of the effect of tetanus toxoid immunization on mortality from neonatal tetanus.

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.

Abstraction, analyses and summary measures

All studies meeting the inclusion/exclusion criteria were abstracted onto a standardized abstraction form for each outcome of interest.[13] Each study was assessed and graded according to the CHERG adaptation of the GRADE technique.[14] 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[15] 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

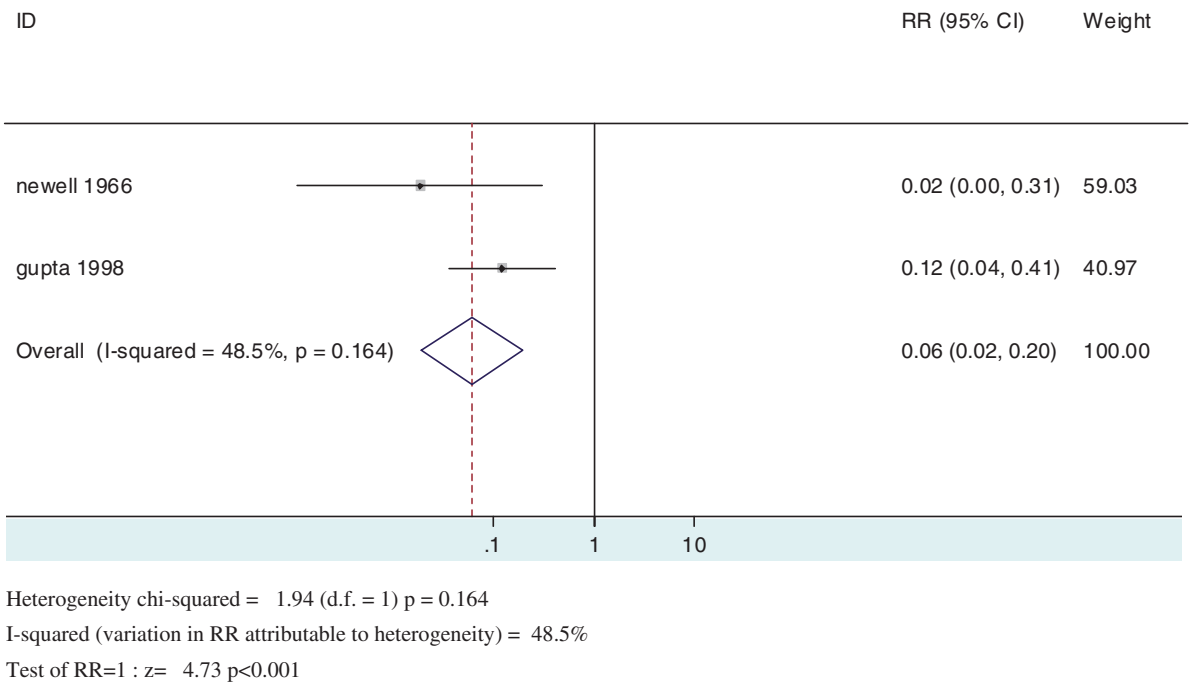

Figure 2 Meta-analysis of the effect of tetanus toxoid on neonatal tetanus mortality

studies were excluded at this stage: 10 observational studies[7, 16–24] and 5 case–control studies,[25–29] 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[30] and 1 study which had used sub-potent vaccine[31] (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.[32–33] 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).[34] 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[35–37] 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).[38]

The CHERG Rules for Evidence Review were applied.[13] 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.

Table 1 Quality assessment of trials of the evidence for tetanus toxoid immunization to prevent neonatal tetanus mortality

	Quality assessment					Summary of findings				
				Directness		Intervention group		Control group		
No. of studies(ref)	Design	Limitations	Consistency	Generalizability to population of interest	Generalizability to intervention of interest	No. of events	No. of live births	No. of events	No. of live births	RR (95% CI)
Mortality (neonatal tetanus deaths): moderate/low outcome-specific quality										
2[32,33]	RCT/cohort		Consistent and both studies showing benefit	Both low-income countries, one high NT prevalence	Yes	3	1103	49	1043	0.06 (0.02–0.2)[a]
Mortality (D4–14 all-cause): moderate outcome-specific quality										
1[34]	RCT		NA	Low-income setting	Yes	41	4255	110	4386	0.38 (0.27–0.55)[b]
Incidence of neonatal tetanus: low outcome-specific quality										
1[38]	Before and after		NA	Low-income setting	Low	74		212		0.35 (0.29,0.42)[b]
3[35–37]	Case–control adjusted for confounding		Yes	Low-income settings	Low					AOR 0.05– 0.2[b]

[a]MH pooled RR.
[b]Directly calculated from study results.

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.[39] 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).[5] 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.[40] That figure has now been reduced to 44 countries.[41] 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

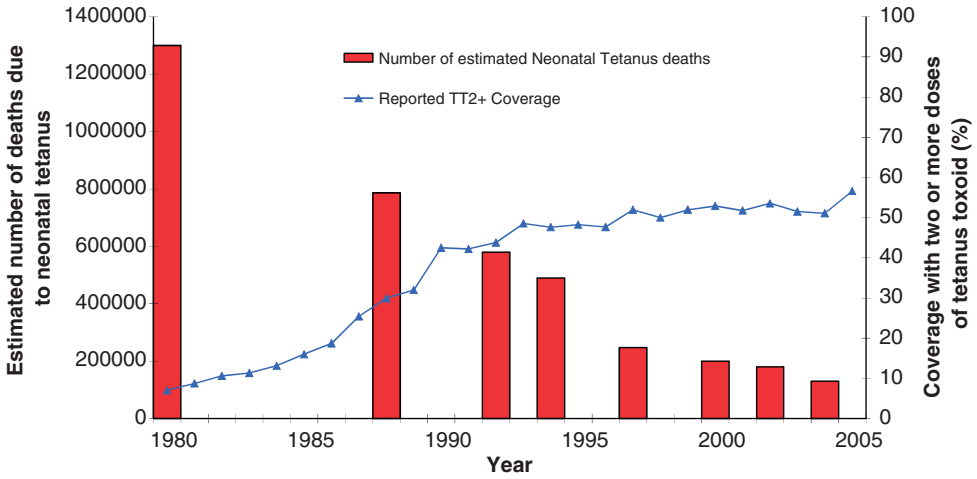

Figure 3 Global and national progress towards maternal and neonatal tetanus elimination. *Source*: Updated from Roper *et al.*[1] Data for 2005 based on WHO[2]

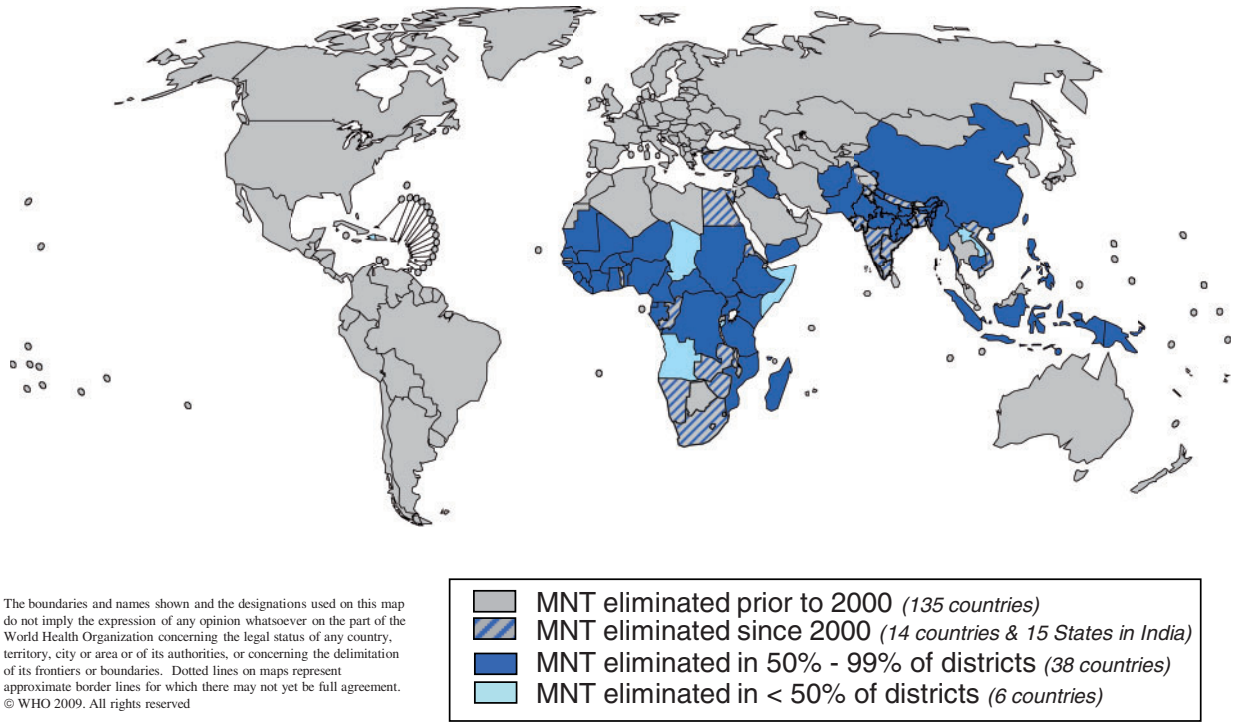

Figure 4 Global and national progress towards maternal and neonatal tetanus elimination. *Source*: Map courtesy of WHO – reproduced with permission, http://www.who.int/immunization_monitoring/diseases/MNTE_initiative/en/index4.html

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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Conflict of interest: None declared.

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.

References

[1] Roper MH, Vandelaer JH, Gasse FL. Maternal and neonatal tetanus. *Lancet* 2007;**370:**1947–59.

[2] WHO: ''The Global Burden of Disease 2004 Update''. Available at http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html (12 May 2009, date last accessed).

[3] Lawn JE, Wilczynska-Ketende K, Cousens SN. Estimating the causes of 4 million neonatal deaths in the year 2000. *Int J Epidemiol* 2006;**35:**706–18.

[4] Plotkin. In: Plotkin S, Orenstein W, Offit P (eds). *Vaccines*. 5th edn. Philadelphia: WB Saunders Company, 2008, pp. 805–40.

[5] WHO. Tetanus vaccine: WHO position paper. *Wkly Epidemiol Rec* 2006;**81:**198–208.

[6] Roper M, Immunological basis of immunisation: Module 3 tetanus. Update 2006. Available at http://www.who.int/vaccines-documents/DocsPDF07/869.pdf (15 November 2009, date last accessed).

[7] Schofield FD, Tucker VM, Westbrook GR. Neonatal tetanus in New Guinea. Effect of active immunization in pregnancy. *Br Med J* 1961;**2:**785–89.

[8] Ray B, Balmer P, Roper MH. Immunological basis for immunization - Module 3: Tetanus (Revision). http://www.who.int/immunization/documents/ISBN9789241595551/en/index.html (15 November 2009, date last accessed).

[9] Brair ME, Brabin BJ, Milligan P, Maxwell S, Hart CA. Reduced transfer of tetanus antibodies with placental malaria. *Lancet* 1994;**343:**208–9.

[10] de Moraes-Pinto MI, Almeida AC, Kenj G *et al*. Placental transfer and maternally acquired neonatal IgG immunity in human immunodeficiency virus infection. *J Infect Dis* 1996;**173:**1077–84.

[11] de Moraes-Pinto MI, Verhoeff F, Chimsuku L *et al*. Placental antibody transfer: influence of maternal HIV infection and placental malaria. *Arch Dis Child Fetal Neonatal Ed* 1998;**79:** F202–5.

[12] Demicheli V, Barale A, Rivetti A. Vaccines for women to prevent neonatal tetanus. *Cochrane Database Syst Rev* 2005; **4:**CD002959.

[13] Walker N, Fischer-Walker C, Bryce J, Bahl R, Cousens S writing for the CHERG Review Groups on Intervention Effects. Standards for CHERG reviews of intervention effects on child survival. *Int J Epidemiol* 2010; **39(Suppl 1)**: i21–31.

[14] Atkins D, Best D, Briss PA *et al*. Grading quality of evidence and strength of recommendations. *Br Med J* 2004; **328:**1490.

[15] *STATA/IC 10.1, in Statistical Program*. 2008, TX: STATA Corporation: College Station.

[16] Koenig MA, Roy NC, McElrath T, Shahidullah M, Wojtyniak B. Duration of protective immunity conferred by maternal tetanus toxoid immunization: further evidence from Matlab, Bangladesh. *Am J Public Health* 1998;**88:**903–7.

[17] Joshi PL, Bhattacharya M, Arya RC, Raj B, Walia D. Impact of universal immunization programme on the incidence of tetanus neonatorum. *Indian Pediatr* 1992;**29:**773–75.

[18] Rahman S. The effect of traditional birth attendants and tetanus toxoid in reduction of neo-natal mortality. *J Trop Pediatr* 1982;**28:**163–65.

[19] Stroh G, Kyu UA, Thaung U, Lwin UK. Measurement of mortality from neonatal tetanus in Burma. *Bull World Health Organ* 1987;**65:**309–16.

[20] Rahman M, Chen LC, Chakraborty J *et al*. Use of tetanus toxoid for the prevention of neonatal tetanus.

1. Reduction of neonatal mortality by immunization of non-pregnant and pregnant women in rural Bangladesh. *Bull World Health Organ* 1982;**60:**261–67.

[21] Yusuf B, Solter S, Bertsch D, Arnold RB. Impact of a tetanus toxoid immunization mass campaign on neonatal tetanus mortality in Aceh Province, Indonesia. *Southeast Asian J Trop Med Public Health* 1991;**22:**351–56.

[22] Bjerregaard P, Steinglass R, Mutie DM, Kimani G, Mjomba M, Orinda V. Neonatal tetanus mortality in coastal Kenya: a community survey. *Int J Epidemiol* 1993;**22:**163–69.

[23] Arnold RB, Soewarso TI, Karyadi A. Mortality from neonatal tetanus in Indonesia: results of two surveys. *Bull World Health Organ* 1986;**64:**259–62.

[24] Kumar V, Kumar R, Mathur VN, Raina N, Bhasin M, Chakravarty A. Neonatal tetanus mortality in a rural community of Haryana. *Indian Pediatr* 1988;**25:**167–69.

[25] Baltazar JC, Sarol JN, Jr. Prenatal tetanus immunization and other practices associated with neonatal tetanus. *Southeast Asian J Trop Med Public Health* 1994;**25:**132–38.

[26] Eregie CO, Ofovwe G. Factors associated with neonatal tetanus mortality in northern Nigeria. *East African Med J,* 1995;**72:**507–9.

[27] Leroy O, Garenne M. Risk factors of neonatal tetanus in Senegal. *Int J Epidemiol* 1991;**20:**521–26.

[28] Roisin AJ, Prazuck T, Tall F, Sanou J, Cot M, Ballereau FV. Risk factor for neonatal tetanus in west Burkina Faso: a case control study. *Eur J Epidemiol* 1996;**12:**535–37.

[29] Parashar UD, Bennett JV, Boring JR, Hlady WG. Topical antimicrobials applied to the umbilical cord stump: a new intervention against neonatal tetanus. *Int J Epidemiol* 1998;**27:**904–8.

[30] Chongsuvivatwong V, Bujakorn L, Kanpoy V, Treetrong R. Control of neonatal tetanus in southern Thailand. *Int J Epidemiol* 1993;**22:**931–35.

[31] Hlady WG, Bennett JV, Samadi AR *et al*. Neonatal tetanus in rural Bangladesh: risk factors and toxoid efficacy. *Am J Public Health* 1992;**82:**1365–69.

[32] Newell KW, Dueñas Lehmann A, LeBlanc DR, Garces Osorio N. The use of toxoid for the prevention of tetanus neonatorum. Final report of a double-blind controlled field trial. *Bull World Health Organ* 1966;**35:** 863–71.

[33] Gupta SD, Keyl PM. Effectiveness of prenatal tetanus toxoid immunization against neonatal tetanus in a rural area in India. *Pediatr Infect Dis J* 1998;**17:**316–21.

[34] Black RE, Huber DH, Curlin GT. Reduction of neonatal tetanus by mass immunization of non-pregnant women: duration of protection provided by one or two doses of aluminium-adsorbed tetanus toxoid. *Bull World Health Organ* 1980;**58:**927–30.

[35] Tall F, Prazuck T, Roisin A *et al*. Risk factors for neonatal tetanus in western Burkina Faso. Case-control study. *Bull Soc Pathol Exot* 1991;**84(Pt 5):**558–61.

[36] Gitta SN, Wabwire-Mangen F, Kitimbo D, Pariyo G. Risk factors for neonatal tetanus–Busoga region, Uganda, 2002–2003. *MMWR Morb Mortal Wkly Rep* 2006; **55(Suppl 1):**25–30.

[37] Chai F, Prevots DR, Wang X, Birmingham M, Zhang R. Neonatal tetanus incidence in China, 1996-2001, and risk factors for neonatal tetanus, Guangxi Province, China. *Int J Epidemiol* 2004;**33:**551–57.

[38] el-Sherbini A. Study of tetanus neonatorum in Tanta Fever Hospital, 1988–1989. *J Trop Pediatr* 1991;**37:** 262–63.

[39] WHO. WHO Immunization, surveillance, assessment and monitoring. Available at http://www.who.int/immunization_monitoring/en/globalsummary/schedule select.cfm 2009.

[40] Wkly Epidemiol Rec. Expanded programme on immunization. The global elimination of neonatal tetanus: progress to date. 1993 Sep 17;**68**:277–82.

[41] WHO. Immunisation surveillance, assessment and monitoring. Available at http://www.who.int/immunization_monitoring/diseases/MNTE_initiative/en/index4.html (April 2009).