

Incremental cost-effectiveness of supplementary immunization activities to prevent neonatal tetanus in Pakistan

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Objective This study aimed to estimate the incremental cost-effectiveness of supplementary immunization activities to prevent neonatal tetanus in the Loralai district of Pakistan. The supplemental immunization activities were carried out in two phases during 2001–03.

Methods A state-transition model was used to estimate the effect of routine vaccination with tetanus toxoid as well as vaccination with tetanus toxoid during supplementary immunization activities. The model follows each woman in the target population from birth until the end of her childbearing years, using age-specific fertility data and vaccination history to determine the number of births at risk for neonatal tetanus. Recently published data on the incidence of neonatal tetanus from Loralai was used to determine the number of cases occurring with and without supplementary immunization activities. Data on the costs of the activities were collected from the UNICEF office in Balochistan and from the Provincial Health Department.

Findings Using base-case assumptions we estimated that the supplementary immunization activities would prevent 280 cases of neonatal tetanus and 224 deaths from neonatal tetanus between 2001 and 2034. Implementation of the supplementary activities was relatively inexpensive. The cost per tetanus toxoid dose delivered was US\$ 0.40. In the base-case analysis the cost per death averted was US\$ 117.00 (95% confidence interval (CI) = US\$ 78–205) and the cost per disability-adjusted life year (DALY) averted was US\$ 3.61 (95% CI = US\$ 2.43–6.39).

Conclusion Compared with similar analyses of other interventions, the cost per DALY averted is a favourable cost–effectiveness ratio. However, if routine diphtheria–tetanus–pertussis vaccination coverage in the Loralai district had been higher (at a coverage rate of about 80%) the cost-effectiveness of the intervention would have been even more favourable, at US\$ 2.65 per DALY averted.

Keywords Tetanus/prevention and control; Infant, Newborn; Tetanus toxoid/administration and dosage/economics; Immunization, Secondary/economics; Disability evaluation; Costs and cost analysis; Cost-benefit analysis; Pakistan (*source: MeSH, NLM*).

Mots clés Tétanos/prévention et contrôle; Nouveau-né; Anatoxine tétanique/administration et posologie/économie; Rappel vaccination/économie; Évaluation incapacité; Coût et analyse coût; Analyse coût-bénéfice; Pakistan (*source: MeSH, INSERM*).

Palabras clave Tétanos/prevenición y control; Recién nacido; Toxoide tetánico/administración y dosificación/economía; Inmunización secundaria/economía; Evaluación de la incapacidad; Costos y análisis de costo; Análisis de costo-beneficio; Pakistán (*fuentes: DeCS, BIREME*).

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يمكن الاطلاع على الملخص بالعربية في صفحة 650.

Introduction

Neonatal tetanus remains one of the major causes of neonatal death in a number of developing countries (1, 2). The disease is primarily caused by a lack of hygiene during delivery, and it usually occurs when the umbilical cord is contaminated while it is being cut with a non-sterile instrument, or dressed.

Symptoms, in the form of spasms, begin 3–14 days after birth. Without specific treatment more than 95% of infants with neonatal tetanus die, and even with treatment 10–90% die, depending on the intensity of supportive care (3). Community-based studies in developing countries have reported case–fatality ratios ranging from 25–100% (4). Evidence suggests that a

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significant proportion of infants surviving neonatal tetanus suffer from brain damage, which manifests as neurological abnormalities and developmental impairments (5–10).

Neonatal tetanus can be prevented by immunizing pregnant women and women of childbearing age with tetanus toxoid. Following the administration of sufficient doses to the mother, antibodies pass to the fetus across the placenta and provide protection against neonatal tetanus. The newborn is protected at birth if the mother was vaccinated during or before the pregnancy. To protect women of childbearing age for at least five years, an initial dose should be given at the first contact with immunization services, a second dose at least 4 weeks after the first dose, and a third dose at least 6 months after the second dose. This basic course of vaccinations will provide protection for 90–95% of women (11).

In 1989 the World Health Assembly called for the elimination of neonatal tetanus (12). UNICEF, WHO and the United Nations Population Fund have set the year 2005 as the target date for worldwide elimination of the disease (1). As of mid-2004, the focus of global efforts is on 51 countries that have not yet eliminated the disease and on six countries that seem to have eliminated the disease. (Global elimination of neonatal tetanus is defined as the reduction of cases to fewer than 1 per 1000 live births in every district in every country.)

The recommended strategy for eliminating neonatal tetanus is the “high-risk approach” (2). This approach focuses on providing three properly spaced doses of tetanus toxoid vaccine for all women of childbearing age in districts, or in areas within districts, where women have no access or only limited access to routine tetanus toxoid vaccination services; where there is limited or no antenatal care; and where births occur without assistance from skilled personnel. These three doses are provided through supplemental immunization activities, i.e. the tetanus toxoid vaccine is given through a campaign-style approach that is organized specifically to increase coverage of tetanus toxoid vaccination among the targeted groups and areas. Following the implementation of supplementary immunization activities, the elimination of neonatal tetanus should be maintained by routinely vaccinating pregnant women through fixed services, outreach strategies or other methods, as well as by improving antenatal and birth services.

In this study, the incremental cost-effectiveness of carrying out supplementary immunization activities in 11 Union Councils in the district of Loralai, Pakistan, are examined. High quality data on the incidence of neonatal tetanus is available from this district (13). This type of surveillance data is rarely collected in the developing world, which is one of the reasons why neonatal tetanus is often referred to as the “silent killer” (14).

Supplementary immunization activities in Loralai

Loralai is one of 26 districts in the province of Balochistan, the least developed province in Pakistan (15). Rural settlements are small in this district: the area has a population of 300 000, and the primary sources of income are agriculture and livestock farming. Communication infrastructure is poor as are the roads and transport services.

According to the national immunization schedule of Pakistan, children should receive the diphtheria–tetanus–pertussis (DTP) vaccine at 6, 10 and 14 weeks of age, and pregnant women should receive one dose of tetanus toxoid at the first contact with the health system and a second dose 4 weeks later (16). However, access to health services, including vaccination

with tetanus toxoid, is limited in Loralai. In a survey of immunization coverage in 1998, it was reported that only 4% of pregnant women had received at least two doses of tetanus toxoid (17). Vaccination coverage of the third dose of DTP for infants was estimated at only 6% in the survey, although the routine reporting system recorded 21% for the same period (I. Ahmad, personal communication on behalf of EPI Federal Cell, Pakistan, March 2004). The survey found that that 85% of infants were delivered at home, suggesting a high risk of neonatal tetanus (17). A community-based cross-sectional study in 1997 estimated that the mortality rate for neonatal tetanus was 23 deaths per 1000 live births (95% confidence interval (CI) = 16–30), accounting for 38% of all neonatal deaths (13).

The supplementary immunization activities analysed in this study took place in two phases during 2001–03 and covered 11 out of a total of 17 Union Councils in Loralai. Phase 1 of the activities covered the Union Councils of Tor Thana, Lahore, China Alazai and Mekhter. The second phase covered the Union Councils of Kach Amiqzai, Loralai Town, Nasirabad, Sadar Duki, Sadar Bori, Oryagai and Poonga. The three rounds of phase 1 took place in July 2001, September 2001 and September–October 2002. The three rounds of phase 2 took place in August 2002, October–November 2002 and August 2003. All women aged between 15 and 45 years were targeted with the aim of giving them three doses of tetanus toxoid. A total of 33 054 women were targeted (9000 women during phase 1 and 24 054 during phase 2); coverage rates are summarized in Table 1. Coverage with the third dose was 49% during the first phase and 54% during the second phase (Table 2).

Since the target coverage rate for supplementary immunization activities for neonatal tetanus is normally at least 80% for the third dose of tetanus toxoid (1), the achievements of the supplementary activities were relatively poor. Among the reasons contributing to the low performance and the high refusal rates seen in Table 1, are the fact that only a limited number of health workers was available to deliver the vaccines; conflicting activities occupied the district health team during the first phase of the project; and there was resistance to vaccination as a result of rumours that it would cause infertility (there were also loudspeaker announcements made by unknown people warning against having tetanus toxoid injections).

Methods

Our goal was to assess the incremental costs and effects of the supplementary immunization activities, as measured by neonatal tetanus cases, deaths and disability-adjusted life years (DALYs) averted, and to compare these with a situation in which only routine DTP and tetanus toxoid vaccination were offered in Loralai (which represents the usual scenario for the area). The cost data were collected from the viewpoint of the public health sector.

A state-transition model was developed to calculate the impact of DTP vaccination and tetanus toxoid vaccination on the number of cases of neonatal tetanus and deaths from the disease. Because vaccination began in Pakistan in 1980, the model tracks the current immunization status (number of doses ever received together with the duration of immunity) of women of childbearing age from 1980 to 2050. This model can be used to evaluate the impact of routine immunization given alone and in conjunction with supplementary activities. By looking at the difference between these two scenarios, the incremental effects

Table 1. Vaccination coverage during supplementary immunization activities for tetanus toxoid vaccination in Loralai district, Pakistan, 2001–03

	No. of women targeted	No. of women vaccinated	No. of refusals	Coverage rate (%) ^a	Refusal rate (%)
Phase 1					
1st round	9 000	5 222	669	58	7
2nd round	9 000	5 970	668	66	7
3rd round	9 000	6 158	417	68	5
Phase 2					
1st round	24 054	14 118	2 053	59	9
2nd round	24 054	15 736	404	65	2
3rd round	24 054	18 673	665	78	3

Source: UNICEF, Balochistan, unpublished data.

^a The coverage rate is the percentage of women who received a tetanus toxoid dose during the round.

Table 2. Data used for the base-case scenario and uncertainty analysis

Data	Value	Distribution used in uncertainty analysis ^a	Range used in uncertainty analysis	Source
Neonatal tetanus mortality rate/1000 live births	23	Weibull	16–30	(13)
Case–fatality ratio (%)	80	Triangular	0.75–0.95	(3) (13)
Neonatal tetanus incidence ratio	0.02875			Derived from mortality rate and case–fatality ratio
Life expectancy at birth (years)	61.5	NA	NA	(25)
Vaccine efficacy (%)	90	Triangular	0.85–0.95	(11)
Discount rate	0.03	NA	NA	Assumed
Phase 1 vaccination coverage				
<i>% of targeted women receiving:</i>				
only one dose tetanus toxoid	26	NA	NA	UNICEF, Balochistan ^b
two doses tetanus toxoid	10	NA	NA	
three doses tetanus toxoid	49	NA	NA	
0 doses tetanus toxoid	15	NA	NA	
Phase 2 vaccination coverage				
<i>% of targeted women receiving:</i>				
only one dose tetanus toxoid	19	NA	NA	— ^b
two doses tetanus toxoid	10	NA	NA	— ^b
three doses tetanus toxoid	54	NA	NA	— ^b
0 doses tetanus toxoid	17	NA	NA	— ^b

^a NA = not applicable.

^b Unpublished data.

of the supplementary activities are estimated. The data input used for the base-case analysis and the assumptions made in the uncertainty analysis are summarized in Table 2.

Vaccination and immunity

The length of time during which a woman will have sufficient levels of antibodies to provide protection when giving birth varies depending on how many tetanus toxoid doses she has received during her lifetime (11). After receiving a second dose of tetanus toxoid, a woman is immune for 3 years from the date of vaccination; the third dose confers immunity for 5 years; the fourth for 10 years; and the fifth dose for 20 years. Additionally,

we assumed that if a woman was fully immunized with three doses of DTP as a child, it was the equivalent of having received two doses of tetanus toxoid (11).

To determine how many cases and deaths might occur, we assumed that if the birth is “at risk” (meaning that the mother does not have sufficient levels of antibodies to protect the fetus against neonatal tetanus) then the incidence rate among those newborns who are susceptible is constant as is the case–fatality ratio. Thus:

$$\text{Cases} = \text{Susceptible newborns} \times \text{Incidence among susceptible newborns}$$

$$\text{Deaths} = \text{No. of cases} \times \text{Case–fatality ratio}$$

To determine how many newborns are susceptible at birth, the number of pregnant women who are susceptible must be known; since this in turn depends on the lifetime number of doses a woman has received, and the time since the last dose, we developed a state-transition model to track the immunity of women of childbearing age. We tracked the number of women in each category by time (t), age, number of tetanus toxoid doses ever received (N_t) and current duration of immunity (D_t). At the beginning of the childbearing years we assumed that all women were not immune ($N_t=0$ and $D_t=0$). However, some had had the equivalent of two doses of tetanus toxoid through routine childhood DTP vaccination, thus $N_t=2$ and $D_t=0$. Although the model could also account for additional protection from DTP boosters given during childhood, there is no evidence of coverage with such an intervention in Loralai. Similarly, there is no indication that women in Loralai have been receiving tetanus toxoid vaccinations when bringing their infant children in for routine immunizations.

If a woman becomes pregnant (according to age-specific fertility rates), then based on estimates of coverage of routine tetanus toxoid vaccinations and vaccine efficacy, she may become immune (Fig. 1) for a given number of years depending on how many doses she has received. If a woman is currently immune through immunizations given at any point during or prior to the current pregnancy, then the infant is not at risk; otherwise, we assume the infant is at risk. Finally, during each year, we track the loss of immunity caused by the time elapsed since the last immunization. Women can move from a non-susceptible state to a susceptible state if sufficient time passes between vaccinations. Women who die (from any cause) are no longer considered to be either susceptible or non-susceptible.

Population and vaccination coverage data

Estimates of the female population of Pakistan stratified by five-year age groups for the years 1980–2050 were obtained from the United Nations Population Division (18, 19). Data were extrapolated from these estimates and smoothed to obtain the population for each year of age. To obtain the age-specific probability for each single year between 1980 and 2050 that a woman may be pregnant we used a similar process for data on age-specific fertility rates that had also been stratified by five-year age groups and five-year intervals (20, 21) and estimates of the total number of births by five-year age groups (22). We assumed that the national data on age distribution and fertility rates were representative for the 11 Union Councils in Loralai.

Infant vaccination with DTP started in Pakistan in 1978, and the vaccination of pregnant women with tetanus toxoid began in 1985. We used coverage rates for routine vaccination with three doses of DTP, one dose of tetanus toxoid and two doses of tetanus toxoid for Loralai from 1996 to 2003, and adjusted national rates from 1980 to 1995 based on the observed relationship between coverage in Loralai and the WHO–UNICEF estimates of national immunization coverage (16). (Coverage rates in Loralai were taken from personal communication from Irtaza Ahmad, on behalf of EPI Federal Cell, Pakistan, March 2004. Coverage with three doses of DTP varied markedly over this period, from a low of 21% to a high of 47%. Coverage with two or more doses of tetanus toxoid ranged from 2% to 6% prior to the supplementary activities to a high of 16% in 2002.)

DALYs

DALYs were estimated using data from the 1996 Global Burden of Disease study (23). We included age weighting, and

carried out the analysis using a 3% discount rate for future life years. The disability weight for the acute phase of tetanus in children aged 0–4 years is reported as 0.640 per episode (23), with a duration of 2 months for survivors and 3 days for those who die. We reviewed six studies showing that some children who survived neonatal tetanus (11–50%) have brain damage manifesting as microcephaly, mild neurological abnormalities, developmental impairment and behavioural problems (5–10). In some of the studies, mental retardation was the most frequent form of disability, while in others motor deficits were more common. We assumed that 15% of neonatal tetanus survivors developed lifelong motor deficits and that 15% had lifelong mental retardation. We used the disability weights for motor deficits (0.388) and mental retardation (0.469) from meningococcaemia without meningitis (23).

Costs of the supplementary immunization activities

The incremental costs of the intervention are the economic costs of the supplementary immunization activities, which were collected from UNICEF and the district health office in Balochistan. Three external partners were involved in the financing: UNICEF provided vaccines, syringes and per diems; logistics were funded by the Government of Japan; and the Save the Children Fund paid for social mobilization, which consisted of provincial, district and community orientation meetings followed by more specific interpersonal and mass orientation. The most important financial contribution made by the Government of Pakistan was the health workers' time. This item is considered to be an opportunity cost, since it is not a direct, financial cost included in the supplementary activities budget. However, the health-care staff could have spent their time on other activities and it is therefore important to include their salaries as costs.

Waste management of used syringes is an activity that still needs to be improved in Loralai and in Pakistan as a whole. Following the supplementary activities, the used syringes were either burned on the ground or in an enclosure. The cost of this activity is negligible and is not included in the analysis.

Treatment costs averted

Prevention of neonatal tetanus will result in future savings on treatment costs, since fewer newborns with neonatal tetanus will need treatment in government health facilities. The cost-effectiveness results presented in this paper represent an upper range (i.e., they are underestimates of the true cost-effectiveness) because treatment costs averted are not included due to difficulties in collecting the relevant resource utilization data.

Uncertainty analysis

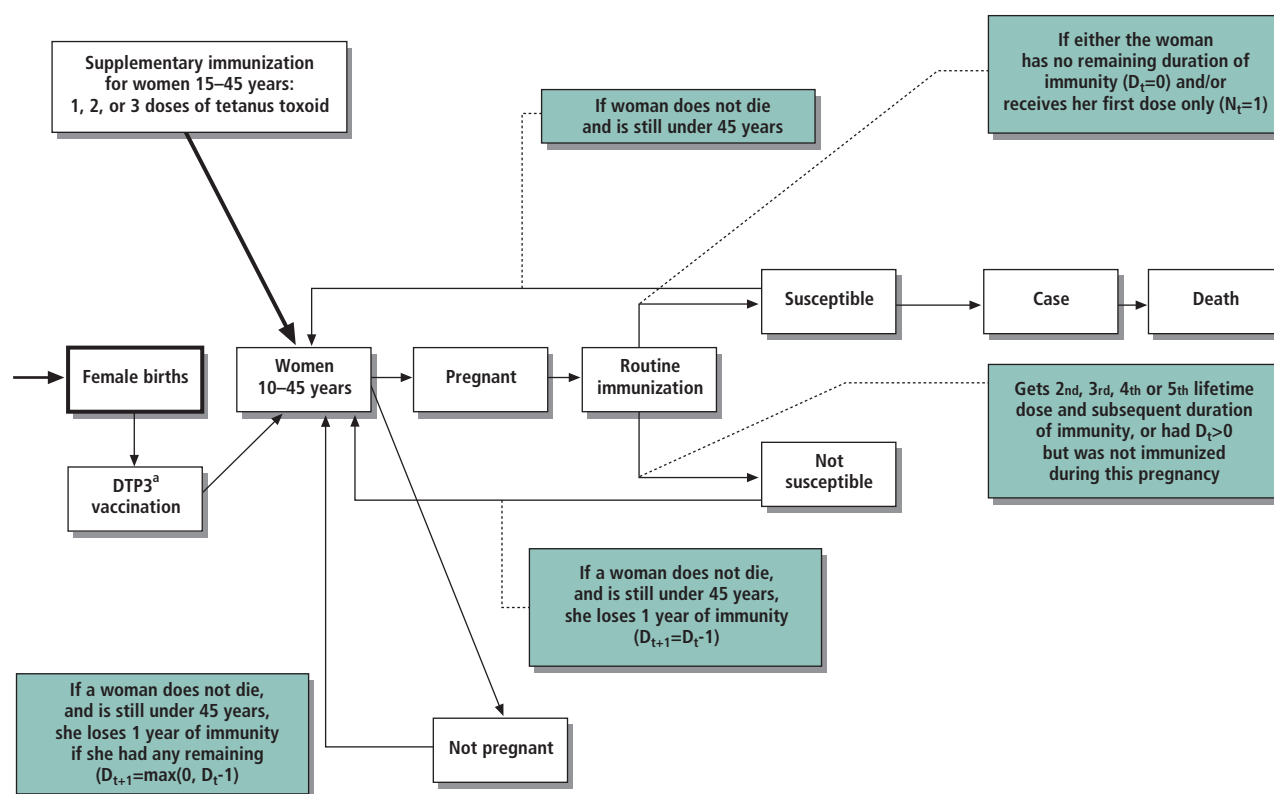
Based on assumed ranges and distributions of the uncertainty variables used in the model, a probabilistic uncertainty analysis was done via a Monte-Carlo simulation (1000 simulations) using the Crystal Ball software programme (Decisioneering, Inc., Denver, Colorado). This process gave prediction intervals around the mean cost-effectiveness ratios. The assumed ranges and distributions are summarized in Table 2.

Findings

Costs of supplementary immunization activities

The costs of the supplementary immunization activities in US\$ are illustrated in Table 3. The total costs (phases 1 and 2) amounted to US\$ 26 108. UNICEF procured the tetanus toxoid

Fig. 1. Relationship between pregnancy, immunization and protection against neonatal tetanus



^aDTP3 = three doses of diphtheria–tetanus–pertussis.

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vaccine at a cost of US\$ 0.04 per dose, including freight charges; the vaccine accounted for 11% of total costs. Syringes were considerably more expensive than the vaccine (accounting for 23% of total costs), whereas per diems amounted to 16% of total costs and salaries to 14%. Hence, the Government of Pakistan (through salary costs) funded approximately 14% of the total. Since 65 877 doses of vaccine were delivered during the supplementary activities, the cost per dose amounted to only US\$ 0.40. The cost per woman vaccinated with three doses was US\$ 1.19.

Impact and cost-effectiveness of the supplementary activities

For the base case, the model predicts that a total of 280 cases and 224 neonatal deaths are prevented by the supplementary activities (Table 4). These deaths are prevented over 33 years (the duration of the childbearing years of the youngest women vaccinated), as illustrated in Fig. 2. Most deaths are averted in the years immediately following the supplementary activities. In subsequent years the effect begins to disappear due to waning immunity and young, unimmunized women entering childbearing age. While the number of deaths per year caused by neonatal tetanus should decline by the year 2034 (mostly due to declining fertility), by that time the impact of the supplementary activities will have disappeared, and approximately 75 deaths will occur per year.

The cost per death averted is US\$ 117.00, and the cost per discounted DALY averted is US\$ 3.61 (Table 4). These figures are among the lowest values reported in comparable cost-effectiveness analyses. Goodman et al. found that implementing

preventive interventions against malaria in a very low-income African country cost in the range of US\$ 4–85 per discounted DALY averted (24).

Uncertainty analysis

The probabilistic uncertainty analysis reveals that the cost-effectiveness ratios are located within fairly wide prediction intervals (Table 4). Fig. 3 illustrates the frequency of costs per discounted DALY averted, showing a 95% prediction interval for the median cost-effectiveness ratio of US\$ 3.61 (95% CI = US\$ 2.43–6.39).

Among the assumptions being used in the uncertainty analysis, the cost per discounted DALY averted is most sensitive to the incidence rate among susceptible newborns. Clearly, the model must also be sensitive to the conservative assumptions of the duration of immunity. However, in a situation with low routine coverage, the effect of underestimating the duration of immunity is to correspondingly overestimate the cost-effectiveness ratio.

Conclusion

Despite the low coverage rates achieved during both phases of the supplementary immunization activities, the intervention was highly cost-effective. There are three overriding reasons for the favourable cost-effectiveness ratio. First, a large percentage of the women of childbearing age in Loralai had not been immunized against tetanus before. Second, the district has a high incidence of neonatal tetanus. And last, the intervention does not involve high capital costs or operational costs.

Table 3. Cost of the supplementary immunization activities in US\$^a

Activity or item	Unit of measure	Quantity	Unit costs	Total costs	% of total
Training				3 719	14
Of district trainers	NS ^b	NS	NS	225	NS
Orientation for 25 health workers	NS	NS	NS	177	NS
Of field staff, phase 1	NS	NS	NS	2 056	NS
Of field staff, phase 2	NS	NS	NS	1 261	NS
Social mobilization				432	2
Vaccine supplies				8 867	NS
Vaccines	Dose	73 197	0.040	2 947	11
Syringes	Each	69 344	0.087	6 005	23
Safety boxes	Each	693	0.78	541	2
Per diems				4 040	16
For field staff	Person-days	2 184	1.7	3 771	NS
For supervisors, phase 1	Person-days	48	2.6	124	NS
For supervisors, phase 2	Person-days	42	3.5	145	NS
Salaries				3 682	14
For female health workers	Person-days	1 092	0.9	1 006	NS
For female health supervisors	Person-days	437	1.7	754	NS
For health workers administering vaccines	Person-days	655	2.3	1 508	NS
For district supervisors	Person-days	90	4.6	414	NS
Rental of vehicles	Days	177	20.7	3 667	14
Fuel	Days	18	8.6	155	1
Ice for the cold chain	NS	NS	NS	173	1
Miscellaneous	NS	NS	NS	121	0.5
Monitoring and evaluation	NS	NS	NS	627	2
Total				26 108	100

^a 1 Pakistani rupee = US\$ 0.017.

^b NS = data not shown.

Table 4. Incremental cost-effectiveness estimates: base-case analysis and uncertainty analysis, 2001–34, in US\$^a

Activity	Costs (US\$)	Neonatal tetanus cases	Neonatal tetanus deaths	Discounted DALYs ^b	Costs per case averted	Costs per death averted	Costs per discounted DALY averted
Routine immunization	Unknown	2 846	2 277	73 551	NA	NA	NA
Routine plus supplementary immunization activities	Unknown	2 566	2 053	66 316	NA	NA	NA
Incremental values							
Base case	26 108	280	224	7 236	93	117	3.61
Median	NA	269	225	7 210	96	116	3.61
95% prediction interval		150–405	126–331	4 070–10 667	64–170	78–205	2.43–6.39

^a 1 Pakistani rupee = US\$ 0.017.

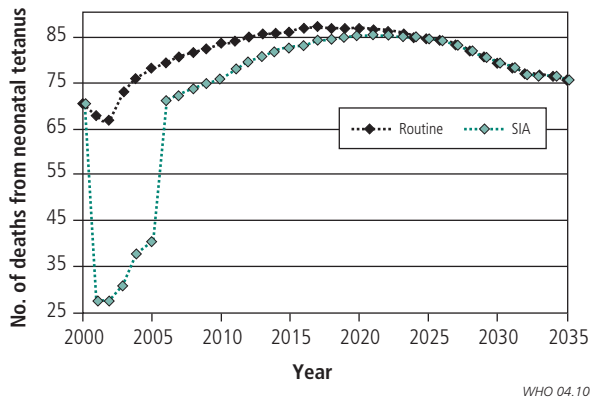
^b DALYs = disability-adjusted life years.

Conversely, the cost-effectiveness estimates presented in this paper represent an understatement of the potential cost-effectiveness of supplementary immunization campaigns: if either prior routine coverage with three doses of DTP or tetanus toxoid had been higher, or if routine tetanus toxoid immunization continued at a higher rate after the supplementary activities, the campaign would have been more cost-effective. If routine three-dose DTP immunization coverage had been 80% from 1980 onwards, the cost per DALY averted would have been US\$ 2.65. Improvements in delivering routine coverage of two doses of

tetanus toxoid after the campaign will have a greater impact than they would have had without the campaign, as these doses may be the fourth and fifth doses for many women, thus extending their immunity throughout their childbearing years. These results illustrate the importance of increasing routine immunization coverage as part of efforts to eliminate neonatal tetanus.

While the supplementary immunization activities can be considered to be a cost-effective intervention, we predict that there will be more than 2500 cases of neonatal tetanus and 2053 deaths from the disease between 2001 and 2034. This

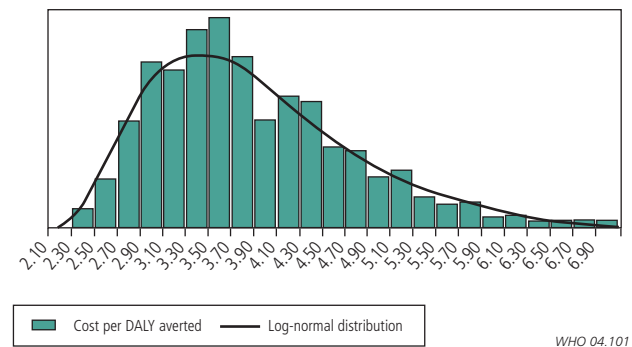
Fig. 2. Predicted deaths from neonatal tetanus in Loralai district, Pakistan, with and without supplementary immunization activities for tetanus toxoid vaccination



highlights the urgent need for additional interventions in the Loralai district.

The basic model presented in this paper for estimating the proportion of births at risk can also be used to evaluate other interventions, such as the optimal timing between campaigns, two-dose or four-dose campaigns, and school-based immunization services, keeping in mind some small caveats. This model is a compartmental state-transition model done using discrete blocks of time; numerous refinements in accounting for the duration of protection by dose could be introduced. (Spreadsheets of the model are available from the authors.) Models are only approximations of reality, but in this case the model provides an important tool for analysis. Surveillance for neonatal tetanus in Loralai is not comprehensive. In 1997, eight cases of neonatal tetanus were reported through the surveillance system, but an

Fig. 3. Frequency of costs (US\$) per discounted disability-adjusted life year (DALY) averted calculated using uncertainty analysis, shown with fitted log-normal distribution



additional 36 cases were identified through a community-based survey of less than 10% of the women who had given birth during the preceding 18 months (13), indicating that possibly as few as 2% of all cases are reported. Only one case of neonatal tetanus was reported in Loralai in 2003 (unpublished data from the Polio Eradication Initiative, Provincial Surveillance Cell, Quetta, Balochistan, 2003). This could reflect a decline from the eight cases reported in 1997, but since neonatal tetanus surveillance is based only in hospitals and most neonatal tetanus cases do not reach the hospital, it is difficult to draw conclusions from the surveillance data. Recent efforts to expand the surveillance system for acute flaccid paralysis to measles and tetanus will hopefully lead to improved surveillance in the future. In the interim, models such as this one can be used both to evaluate interventions and to help calibrate expanding surveillance systems. ■

Conflicts of interest: none declared.

Résumé

Prévention du tétanos néonatal au Pakistan : augmentation de rentabilité des activités de vaccination supplémentaires

Objectif La présente étude avait pour but d'estimer l'augmentation de rentabilité des activités de vaccination supplémentaires en vue de prévenir le tétanos néonatal menées dans le district de Loralai au Pakistan. Ces activités ont été menées en deux temps de 2001 à 2003.

Méthodes Un modèle de transition a été utilisé pour estimer les conséquences de la vaccination systématique par l'anatoxine tétanique et celles de la vaccination par l'anatoxine tétanique au cours des activités de vaccination supplémentaires. Le modèle suit chaque femme de la population cible de la naissance jusqu'à la fin de sa période de procréation en utilisant les données de fécondité par âge et les antécédents de vaccination pour déterminer le nombre de naissances exposées au risque de tétanos néonatal. Les données récemment publiées sur l'incidence du tétanos néonatal dans le district de Loralai ont été utilisées pour déterminer le nombre de cas survenus avec ou sans activités de vaccination supplémentaires. Les données concernant le coût des activités ont été recueillies auprès du bureau de l'UNICEF au Baloutchistan et du service provincial de santé.

Résultats En nous appuyant sur les chiffres de l'hypothèse de base, nous avons estimé que les activités de vaccination supplémentaires conduiraient à prévenir 280 cas de tétanos néonatal et 224 décès par tétanos néonatal entre 2001 et 2034. La mise en œuvre des activités supplémentaires est relativement peu coûteuse. Le coût par dose d'anatoxine tétanique administrée était de US \$0,40. L'analyse d'après l'hypothèse de base a montré que le coût par décès évité était de US \$117,00 (intervalle de confiance à 95 % (IC) = US \$78-205) et que le coût par année de vie perdue ajustée sur l'incapacité (DALY) évitée était de US \$3,61 (IC 95 % = US \$2,43-6,39).

Conclusion Des analyses comparables menées sur d'autres interventions montrent que le rapport coût/efficacité par DALY évitée est favorable. Cependant, si la couverture par la vaccination systématique antidiphthérique antitétanique-anticoquelucheuse dans le district de Loralai avait été plus étendue (voisine de 80 %), le rapport coût/efficacité de l'intervention aurait encore été plus favorable, soit US \$2,65 par DALY évitée.

Resumen

Costoeficacia marginal de las actividades suplementarias de inmunización para prevenir el tétanos neonatal en el Pakistán

Objetivo Estimar la costoeficacia marginal de las actividades suplementarias de inmunización emprendidas para prevenir el tétanos neonatal en el distrito de Loralai en el Pakistán. Dichas actividades se llevaron a cabo en dos etapas durante 2001–2003.

Métodos Se usó un modelo de transición de estados para calcular los efectos de la vacunación sistemática con anatoxina tetánica, así como de la vacunación con anatoxina tetánica durante las actividades suplementarias de inmunización. El modelo hace un seguimiento de todas las mujeres de la población destinataria desde el nacimiento hasta el final de su periodo de fecundidad, usando los datos de fecundidad específicos para la edad y los antecedentes de vacunación para determinar el número de nacimientos con riesgo de tétanos neonatal. Para determinar el número de casos con y sin actividades suplementarias de inmunización se emplearon datos de publicación reciente sobre la incidencia de tétanos neonatal en Loralai. Los datos sobre los costos de las actividades se obtuvieron de la oficina del UNICEF en Balochistán y del Departamento Provincial de Salud.

Resultados A partir de las hipótesis asumidas sobre la tendencia de base, calculamos que las actividades suplementarias de inmunización prevendrían 280 casos de tétanos neonatal y 224 defunciones por tétanos neonatal entre 2001 y 2034. La ejecución de las actividades suplementarias fue relativamente barata. El costo por dosis de anatoxina tetánica suministrada fue de US\$ 0,40. Según el análisis de la tendencia de base, el costo por defunción evitada es de US\$ 117,00 (intervalo de confianza (IC) del 95% = US\$ 78–205), y el costo por año de vida ajustado en función de la discapacidad (AVAD) evitado, de US\$ 3,61 (IC95% = US\$ 2,43–6,39).

Conclusión Comparado con análisis similares de otras intervenciones, el costo por AVAD evitado muestra una relación costo-eficacia favorable. Sin embargo, si la cobertura de la vacunación sistemática contra difteria–tétanos–tos ferina en el distrito de Loralai hubiera sido mayor (tasa de cobertura en torno al 80%), la costoeficacia de la intervención habría sido aún más favorable: US\$ 2,65 por AVAD evitado.

ملخص

المردود الإضافي لأنشطة التمنيع التكميلي في الوقاية من كزاز الوليد في باكستان

التكميلي يمكن أن تقي من ٢٨٠ حالة من كزاز الوليد ومن ٢٢٤ وفاة بسبب كزاز الوليد، وذلك طيلة الفترة من عام ٢٠٠١ إلى عام ٢٠٣٤. كما تبين أن تكلفة تنفيذ الأنشطة التكميلية كانت معتدلة نسبياً. وبلغت تكلفة جرعة ذيفان الكزاز المعطاة ٠,٤٠ دولار أمريكي. وتبين من تحليل الحالات القاعدية أن تكلفة الوفاة التي أمكن اتقاؤها بلغت ١١٧ دولاراً (عند فاصلة ثقة ٩٠٪، إذ تراوحت من ٧٨ دولاراً إلى ٢٠٥ دولاراً)، وبلغت تكلفة كل سنة من سنوات العجز التي أمكن اتقاؤها من سنوات العمر المصححة باحتساب مدد العجز ٣,٦١ دولاراً (عند فاصلة ثقة ٩٥٪، إذ تراوحت من ٢,٤٣ دولار إلى ٦,٣٩ دولار).
الخصيلة: بمقارنة نتائج هذه الدراسة مع نتائج تحليل مماثلة لمداخلات أخرى، يتبين أن مردود نسبة تكلفة كل سنة من سنوات العجز التي أمكن اتقاؤها من سنوات العمر المصححة باحتساب مدد العجز عال. ولكن لو ازدادت التغطية بالتلقيح الروتيني للقاح الثلاثي للدفتريا والكزاز والشاهوق في منطقة لورالاي (إلى حوالي ٨٠٪) لكانت مردودية المداخلة أعلى، إذ يمكن أن تصل التكلفة إلى ٢,٦٥ دولار لكل سنة من سنوات العجز التي يمكن اتقاؤها من سنوات العمر المصححة باحتساب مدد العجز.

الغرض: استهدفت هذه الدراسة تقدير المردود الإضافي لأنشطة التمنيع التكميلي التي تستهدف وقاية الولدان من الكزاز في منطقة لورالاي في باكستان. وكانت أنشطة التمنيع التكميلي قد نفذت على مرحلتين في الفترة من عام ٢٠٠١ إلى عام ٢٠٠٣.

الطريقة: استخدم نموذج تحول الحالات لتقدير تأثير التلقيح (التطعيم) الروتيني وأثناء أنشطة التمنيع التكميلي بدوفان الكزاز، وقد تابع النموذج المستخدم كل امرأة في المجموعة السكانية المستهدفة من يوم ميلادها إلى نهاية سنوات القدرة على الإنجاب لديها، مع استخدام معطيات الخصوبة الخاصة بكل فئة عمرية وسوابق التلقيح لتحديد عدد الولادات المعرضة لمخاطر الإصابة بزاز الوليد. واستخدمت المعطيات المنشورة حديثاً حول وقوع كزاز الوليد في منطقة لورالاي لتحديد عدد حالات الإصابة التي تحدث في ظل أنشطة التمنيع التكميلي أو في غيابها. وتم جمع معطيات حول تكاليف الأنشطة من مكتب منظمة الأمم المتحدة للطفولة (اليونيسف) في محافظة بالوشستان ومن الإدارة الصحية للمحافظة.

الموجودات: تبين من تطبيق افتراضات الحالات القاعدية أن أنشطة التمنيع

References

1. UNICEF, WHO, UNFPA. *Maternal and neonatal tetanus elimination by 2005. Strategies for achieving and maintaining elimination*. New York: UNICEF; 2000.
2. Vandelaer J, Birmingham M, Gasse F, Kurian M, Shaw C, Garnier S. Tetanus in developing countries: an update on the Maternal and Neonatal Tetanus Elimination Initiative. *Vaccine* 2003;21:3442-5.
3. Wassilak SGF, Roper MH, Murphy TV, Orenstein WA. Tetanus toxoid. In: Plotkin SA, Orenstein WA, editors. *Vaccines*. Philadelphia: Saunders; 2004. p. 745-81.
4. Galazka A, Birmingham M, Kurian M, Gasse F. Tetanus. In: Stein CE, Murray CJL, Lopez AD, editors. *The global epidemiology of infectious diseases*. Geneva: World Health Organization; In press 2004.
5. Anlar B, Yalaz K, Dizmen R. Long-term prognosis after neonatal tetanus. *Developmental Medicine and Child Neurology* 1989;31:76-80.
6. Barlow JL, Mung'Ala-Odera V, Gona J, Newton CR. Brain damage after neonatal tetanus in a rural Kenyan hospital. *Tropical Medicine and International Health*, 2001;6:305-8.
7. Khanna SS, Bharucha B, Bhatia AK, Dastur FD. Neonatal tetanus: psychomotor development in survivors. *Indian Pediatrics* 1985;22:125-30.
8. Okan M, Hacimustafaoglu M, Ildirim I, Donmez O, Eralp O, Ozer ET. Long-term neurologic and psychomotor sequelae after neonatal tetanus. *Journal of Child Neurology* 1997;12:270-2.
9. Teknetzi P, Manios S, Katsouyanopoulos V. Neonatal tetanus: long-term residual handicaps. *Archives of Disease in Childhood* 1983;58:68-9.
10. Tutuncuoglu S, Demir E, Koprubasi F, Selcuki D. The evaluation of late sequelae of tetanus infection. *Indian Journal of Pediatrics* 1994;61:263-7.

11. World Health Organization. The immunological basis for immunization services module 3: Tetanus. Geneva: World Health Organization; 1993. WHO document WHO/EPI/GEN/93.13.
12. World Health Assembly. *Expanded programme on immunization*. Geneva: World Health Organization; 1989 (Resolution WHA42.32).
13. Quddus A, Luby S, Rahbar M, Pervaiz Y. Neonatal tetanus: mortality rate and risk factors in Loralai District, Pakistan. *International Journal of Epidemiology* 2002;31:648-53.
14. UNICEF. *Maternal and neonatal tetanus*. Available from: http://www.unicef.org/immunization/facts_mnt.html
15. Hussain A. *Pakistan National Human Development Report 2003: poverty, growth and governance*. Karachi: Oxford University Press; 2003.
16. World Health Organization. *Vaccine-preventable diseases: monitoring system 2002 global summary*. Geneva: Vaccines and Biologicals, World Health Organization; 2002. WHO document WHO/V&B/02.20.
17. World Health Organization. *EPI coverage evaluation survey report*. Islamabad: World Health Organization; 2001.
18. United Nations. *World population prospects: the 2000 revision. Female population by age group, major area, region, and country, annually for 1950-2050 (in thousands), estimates 1950-2000*. New York: United Nations Population Division, 2001.
19. United Nations. *World population prospects: the 2000 revision. Female population by age group, major area, region, and country, annually for 1950-2050 (in thousands), medium variant, 2001-2050*. New York: United Nations Population Division; 2001
20. United Nations. *World population prospects: the 2000 revision. Age-specific fertility rates by major area, region, and country, 1995-2050 (in thousands), estimates 1995-2000*. New York: United Nations Population Division; 2001.
21. United Nations. *World population prospects: the 2000 revision. Age-specific fertility rates by major area, region, and country, 1995-2050 (in thousands), medium variant 2000-2050*. New York: United Nations Population Division; 2001 (POP/DB/WPP/Rev.2000/6/F2).
22. United Nations. *World population prospects: the 2000 revision. Births by major area, region, and country, 1950-2050 (in thousands), estimates 1950-2000*. New York: United Nations Population Division; 2001.
23. Murray CJL, Lopez L, editors, *The global burden of disease. Volume 1*. Cambridge, MA: Harvard University Press; 1996.
24. Goodman CA, Coleman PG, Mills AJ. The cost-effectiveness of antenatal malaria prevention in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene* 2001;64 Suppl 1:45-56.
25. World Health Organization. *The World Health Report: reducing risks, promoting healthy life*. Geneva: World Health Organization; 2002.