Reviews/Analyses

Performance and potency of tetanus toxoid: implications for eliminating neonatal tetanus

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Neonatal tetanus (NT) is a major cause of mortality in developing countries, with over 400000 deaths estimated to occur annually. WHO has adopted the goal of eliminating NT worldwide, and a major strategy for its prevention is the administration of at least two properly spaced doses of tetanus toxoid (TT) to women of childbearing age in high-risk areas to protect passively their newborns at birth. In certain countries the locally produced TT vaccine has been shown to be subpotent, while other countries have reported NT among infants born to vaccinated women.

An extensive review of production and quality control procedures was carried out between 1993 and 1995 in 8 of 22 TT-producing countries that also report NT cases, with a more superficial assessment being carried out in the remaining 14 countries. Only 4 of the 22 countries have a functioning national control authority to monitor TT production and vaccine quality. A total of 80 TT lots from 21 manufacturers in 14 of the 22 NT-reporting countries were tested for potency. Of these, 15 lots from eight manufacturers in seven countries had potency values below WHO requirements. TT potency can also be compromised by improper vaccine handling. To eliminate neonatal tetanus worldwide requires assurance that all doses of TT meet WHO production and quality requirements and that the field effectiveness of TT is monitored through systematic NT case investigations and assessment of coverage.

Introduction

In 1989 the World Health Assembly adopted a resolution calling for the global elimination of neonatal tetanus (NT) as a public health problem by 1995.[a] In this respect, one of the key strategies identified by WHO is the achievement and maintenance, among women of childbearing age in high-risk areas, of high coverage levels for at least two doses of tetanus toxoid (TT).[b] Studies have demonstrated that two doses of properly spaced TT protect the offspring of female recipients against NT (*1–3*). To be maximally effective, the first two doses of TT (TT1 and TT2) should be given at intervals of at least 4 weeks, with the ideal interval between TT2 and birth being at least 4 weeks (*4*, *5*).[c] In addition, the interval between TT1 and TT2 and that between TT2 and the delivery of the child are critical to ensuring good immunogenicity (*6*). The proportion of women whose titres reach a protective level becomes greater with increasing intervals between TT1 and TT2 and between TT2 and birth. WHO estimates that in 1994,

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[a] Resolution 42.32. *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board*, vol. III, third edit. (1985–92). Geneva, World Health Organization, 1993.

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[b] *Revised plan of action for neonatal tetanus elimination.* Unpublished document WHO/EPI/GEN/94.4, 1994 (available upon request from Global Programme for Vaccines and Immunization, World Health Organization, 1211 Geneva 27, Switzerland).

[c] **Galazka A.** *Immunization of pregnant women against tetanus.* Unpublished WHO document EPI/GEN/83/5, 1983 (available upon request from Global Programme for Vaccines and Immunization, World Health Organization, 1211 Geneva 27, Switzerland).

a total of 46% of pregnant women had received two doses of TT (*7*).[d]

To eliminate NT globally, not only must TT coverage levels be raised but the vaccine must be safe and potent. There have been reports of NT occurring in infants born to women who had received at least two doses of TT (*8*, *9*), causing some workers to question its potency (*8*, *10*). However, as with any vaccine, some seroconversion failures are to be expected, even when it is administered at the appropriate intervals. Thus, case reports of NT among infants born to vaccinated women do not necessarily imply that TT is not effective. Nevertheless, monitoring case reports of NT and the vaccination status of the mothers concerned is important since this provides information about the field performance of TT. Therefore, reports of NT cases in infants born to vaccinated women (i.e. potential TT failures) must be evaluated to determine whether the observed number of failures is greater than expected and whether the doses were properly spaced. If either of these is found to be the case, further evaluation of TT production and effectiveness would be warranted.

Field epidemiological studies in Bangladesh and in selected areas of Pakistan have demonstrated that the effectiveness[e] of two doses of TT in preventing NT was <50% (*11*, *12*). In Bangladesh, subsequent inspection of production facilities revealed multiple deficiencies in TT production, and locally produced TT was determined to be subpotent by two WHO reference laboratories (*11*). In Pakistan, UNICEF-supplied TT collected from the field in 1992 in selected areas and nationally produced TT (used for the army but not in the national Expanded Programme on Immunization (EPI)) were tested for potency. The potency of the UNICEF-supplied TT collected from the field several years after the observations on TT field effectiveness was borderline, although the potency of the vaccine at release had been adequate, and the potency of the nationally produced TT was subpotent.[f]

In this article we review two aspects of monitoring the performance of TT: published reports of NT cases from a review of the literature that included information on the vaccination status of the mothers of infants who developed NT; and currently available information on the quality of TT manufactured in countries where NT cases still occur.

Sources of data

Data on vaccination coverage, reported disease incidence, and NT estimated deaths were obtained from the EPI Information System, Global Programme for Vaccines and Immunizations, WHO, Geneva.[d] Information on TT production procedures, quality, and potency were obtained through the Task Force on Situation Analysis (TFSA) of the Children's Vaccine Initiative. The TFSA has identified as high priority for production assessments, vaccine-producing countries that also report NT cases. Manufacturers in 10 of these countries (Bangladesh, Brazil, Egypt, India, Indonesia, Islamic Republic of Iran, Mexico, Pakistan, Philippines, and South Africa) have received formal on-site assessments of vaccine supply sources by teams of experts fielded by the TFSA.[g] In addition, several of these countries have been identified by WHO/EPI as being high priority for accelerated activities for NT elimination since they accounted for over 80% of the estimated global NT deaths in 1994. The 12 EPI priority countries are as follows: Angola, Bangladesh, China, Ethiopia, Ghana, India, Indonesia, Nigeria, Pakistan, Somalia, Sudan, and Zaire.

In the course of TFSA site visits to TT manufacturers, production and control processes are analysed. Also evaluated is the extent of overseeing provided by national control authorities, if any, on TT manufacturing, compliance with good manufacturing practice, the proportion of TT lots that fail quality control and potency testing, the capacity and ability of the manufacturer to meet production targets, production costs per dose, technical aspects of vaccine production (e.g., sterility and purity) and compliance with WHO norms. If possible, samples of TT are randomly selected from representative production lots for potency testing of the tetanus component at WHO Collaborating Laboratories. Potency testing involves an assessment of protection against a lethal challenge of tetanus toxin in mice or

[d] *Expanded Programme on Immunization information system.* Unpublished document WHO/EPI/CEIS/95.2, 1995 (available upon request from Global Programme for Vaccines and Immunization, World Health Organization, World Health Organization, 1211 Geneva 27, Switzerland).

[e] Vaccine efficacy refers to the ability of a vaccine to protect against disease under ideal circumstances. Vaccine effectiveness refers to the ability of a vaccine to protect against disease under field conditions. Thus, in this article effectiveness and not efficacy is generally discussed.

[f] Unpublished WHO document EPI/TECHCOM/WP/93.33, 1993 (available upon request from Global Programme for Vaccines and Immunization, World Health Organization, 1211 Geneva 27, Switzerland).

[g] Reports of these assessments are available from Global Programme for Vaccines and Immunization, Vaccine Supply and Quality Unit, World Health Organization, 1211 Geneva 27, Switzerland.

guinea-pigs, standardized against the International Standard for Tetanus Toxoid (*13*). A potency value of at least 40 International Units (IU) per human dose is specified by WHO requirements (or ≥60 IU per human dose if the potency of the tetanus component is measured in the presence of the pertussis component in mice), and lots possessing this minimum potency level are classified as having passed (*13*). During other TFSA site visits at which complete assessments are not carried out, vaccine production and control procedures are inventoried. A detailed summary of the evaluations completed to date by the TFSA has been prepared (*14*), and in this article we report on the results of potency testing of TT produced in countries that also report NT cases.

Results

Performance failures

Case reports of NT in infants of women "adequately" immunized with TT. Two doses of TT given at the appropriate interval should result in protection against NT in at least 90% of recipients (*5*).[h] Protection is defined as a tetanus antitoxin level ≥0.01 IU/ml in *in-vivo* neutralization tests or a level ≥0.1 IU/ml in *in-vitro* tests (*15, 16*). However, NT cases have been reported in infants born to vaccinated mothers (*8–10, 17–20*). For example, in Nigeria, 17 (33%) of 52 mothers of infants with NT had a history of immunization with TT (*8*), and 12 of these 17 mothers were said to have received adequate doses of TT — defined as two doses given during pregnancy, with the last dose being given 2 weeks before delivery; however, a 2-week interval between TT2 and birth may not be optimal. In addition, information about the interval between TT1 and TT2 was not provided, precluding determination of whether the doses were properly spaced. Thus, a statement about TT performance cannot be made with any confidence.

In India, a study of 30 cases of NT showed that 17% of the children's mothers were partially, and 13% completely immunized (*9*); however, no information was provided on the vaccination intervals. An investigation of an NT case series in Madras, India, found that 20% of 61 NT cases in 1987–88 and 32% of 19 NT cases in 1989 were born to mothers who had received at least two prior doses of TT (*17*). Information on the timing of these doses was provided for only 6 of the 18 cases; of these six mothers, only two appeared to have an adequate interval between doses, while a further two had received all three doses during the ninth month of pregnancy. In another report from India, 2% of 100 NT cases in infants studied were born to mothers who had received adequate doses of TT, although neither the timing nor the intervals between doses were reported (*18*). Finally, a study of 385 NT cases in Delhi, India, found that 6% were born to mothers reported to be fully immunized (*19*). Thus, although potentially an important source of information for monitoring TT effectiveness, the data provided in case reports are often insufficient to permit a reliable evaluation of the field performance of TT, since the vaccination intervals are often not specified.

Retrospective investigations using medical records are often unable to ascertain the immunization history of the mothers of infants who develop NT. For example, in a retrospective review of over 400 hospitalized NT infants in Nigeria, the investigators were able to obtain information from the hospital records on the immunization status of only 8 mothers (*20*). In Uganda, 228 hospitalized NT infants were retrospectively investigated but the immunization status was ascertained for only a few cases because of lack of information (*21*).

Effectiveness of TT in the field setting

Field estimates of TT vaccine effectiveness can also be biased if the interval between doses is not verified. For example, a case–control study of risk factors for 26 NT cases showed that the protection conferred by TT vaccine against NT was less than optimal, with a vaccine effectiveness of only 70% (95% confidence interval (CI) = 52–100%) (*22*). Information was not available on 13 of the 26 NT cases; of the remaining 13 cases, 10 were incompletely vaccinated, i.e. they had received <2 doses. Moreover, the intervals were not stated for the three NT cases born to women who had received ≥2 doses. Had even one of the three vaccinated women received improperly spaced doses, TT vaccination would have been protective against NT with an estimated vaccine effectiveness of 82%, and 92% if two of the cases had been misclassified.

In a previous review, reports of TT failures were also noted (*16*); these were attributed to inaccurate immunization histories or improperly spaced doses. Some reports of TT failures were attributed to poor maternal immune response, inadequate placental transfer, or excessive toxin exposure; the potential role of these factors is discussed elsewhere (*23*). Thus, because information about the timing of doses may not be available, reports of NT in infants born to vaccinated women, or TT failures, although po-

[h] See footnote *c*, p. 619.

tentially very useful, are often difficult to evaluate; caution should be exercised in interpreting them.

TT failures have therefore not been well documented by data from case investigations; in-the-field effectiveness studies of TT provide a better basis for evaluation. We could identify no recent field evaluations other than those conducted in Bangladesh (*11*) and Pakistan (*12*). In 1990, a population-based survey involving 60 clusters was undertaken in Punjab Province, Pakistan (*12*). Of the nearly 24000 live births during the year preceding the survey, 229 were considered to be NT cases. The mothers of 15 of these infants had histories of appropriate TT immunization as defined above, while two additional mothers met all criteria except that the intervals between TT1 and TT2 were less than 1 month (26 days and 27 days). Only 5 of the 15 mothers had card documentation of vaccination status. Relative to mothers who reported that they had never received a TT dose (NT incidence = 11.2 per 1000) the incidence of NT among live births involving mothers who fully met criteria for appropriate immunization by history (NT incidence = 5.9 per 1000) or with card documentation (8.5 per 1000) suggested a vaccine effectiveness of <50% by either history or card. A subsequent case–control study also confirmed inadequate protection from the UNICEF-supplied TT in use at that time. Tetanus toxoid coverage was approximately 11%.

Data from non-Punjab regions of Pakistan provided contrasting information. Surveys of live births from April 1987 to May 1991 documented only three NT deaths among 1519 live births (NT incidence, 1.97 per 1000) to mothers with card documentation of appropriate TT vaccination with UNICEF-procured TT, while 324 deaths occurred among 27368 live births (NT incidence, 11.8 per 1000) to mothers who had never received a dose of TT. This corresponds to an in-the-field estimated effectiveness of 83.3%. Furthermore, the risk of NT death among infants whose mothers reported receipt of only one dose of TT one or more months before delivery (NT incidence; 2.4 per 1000) was substantially less than that among unimmunized mothers ($P = 0.04$, Fisher's single-tailed test), with an estimated efficacy (80%) similar to that of those appropriately immunized; 409 of these 414 women (including the mothers of the cases) received their single dose of TT less than 20 months before delivery. These findings are consistent with earlier observations that deaths among 4–14-day-old infants were reduced equally by either one or two doses of TT within the first 20 months following vaccination (*25*). It should be noted that the NT incidence among infants of mothers who had card documentation of appropriate immunization was significantly higher in Punjab than elsewhere in Pakistan (8.5 per 1000 versus 1.95 per 1000, resp.; $P = 0.042$, Fisher's two-tail test), but that the incidences for the infants of unimmunized mothers were similar (NT incidence, 11.2 per 1000 versus 11.8 per 1000, resp.; $P = 0.60$).

Finally, NT cases have been reported in infants born with satisfactory levels of laboratory-confirmed tetanus antitoxin (*26*).

Global TT production and quality control

At least 63 manufacturers in 42 countries produce TT (Table 1) (*14*). Neonatal tetanus cases are reported in 22 of these countries (with 33 TT production facilities) (Table 2), and these 22 countries accounted for 74% of all NT cases reported to WHO in 1994, and for 59% of NT deaths estimated in 1994 (WHO, EPI Information System, 1994), as well as accounting for 88 million births each year, i.e. 71% of the 124 million births estimated to occur each year in developing countries (*27*). In 1994, an estimated 219.4 million doses of TT were produced in these 22 countries. Five TT-producing countries (China, India, Pakistan, Bangladesh, and Indonesia) also had the greatest numbers of estimated NT deaths in 1994. These five countries (with 53% of the total number of births in developing countries each year) have a TT production capacity in excess of 150 million doses.

Although 42 countries produce TT, only the nine manufacturers (in Australia, Canada, France, Germany, Hungary, India, Italy, Yugoslavia (Serbia and Montenegro), and Switzerland) that supply the vaccine to UNICEF are formally permitted to state that their products meet WHO requirements and are acceptable for purchase by U.N. agencies (*14*). This does not necessarily imply that TT produced elsewhere is of poor quality; for example, the USA and the United Kingdom have independent, competent national control authorities and review processes, and tetanus toxoid produced there is of acceptable quality.

Only four of the 22 countries that both produce TT and report NT cases (Brazil, India, Indonesia, and Mexico) possess fully functioning national control authorities, leaving the women and children in the remaining countries with no guarantee of quality for the locally produced vaccines they receive. In the five countries with the highest estimated number of NT deaths, and which also produce TT, only two have functioning national control authorities; in reality, the situation in these countries may be even worse. Tests carried out on 80 TT lots produced by 21 manufacturers in 14 of the 22 countries found

Table 1: **Countries reporting production of tetanus toxoid, by WHO region**[a]

Africa	Americas	Eastern Mediterranean	South-East Asia	Western Pacific	Europe
South Africa	Argentina	Egypt	Bangladesh	Australia	Austria
	Brazil	Islamic Republic of Iran	Democratic People's Republic of Korea	China	Bulgaria
	Canada	Jordan	India	Japan	Croatia
	Chile		Indonesia	Philippines	Czech Republic
	Colombia		Myanmar	Republic of Korea	Denmark
	Cuba		Thailand	Viet Nam	Finland
	Ecuador				France
	Mexico				Germany
	Uruguay				Hungary
	USA				Israel
	Venezuela				Italy
					Netherlands
					Poland
					Romania
					Russian Federation
					Switzerland
					Turkey
					United Kingdom
					Yugoslavia (Serbia and Montenegro)

[a] See ref. *14*. Jordan recently notified WHO that it no longer produces vaccines; Pakistan has produced TT in the past, but it is now blending and filling imported TT bulk.

Table 2: **TT-producing countries reporting cases of NT, ranked by the estimated number of NT deaths in 1994, and the number of reported NT cases by year, 1992–94**

		Reported number of NT cases in:		
	Estimated NT deaths in 1994	1992	1993	1994
China	84 000	NR[a]	NR	NR
India	83 000	4 010	4 438	2 226
Pakistan	49 000	1 737	1 685	1 677
Bangladesh	26 000	588	720	834
Indonesia	26 000	807	638	NR
Islamic Republic of Iran	5 900	18	12	17
Myanmar	4 900	111	105	NR
South Africa	4 700	13	16	7
Egypt	4 600	1 830	1 277	998
Philippines	4 000	347	343	NR
Viet Nam	3 600	187	333	NR
Turkey	1 300	29	46	NR
Thailand	1 000	120	67	62
Brazil	80	229	218	76
Mexico	60	137	97	63
Democratic People's Republic of Korea	40	3	0	NR
Colombia	25	100	71	25
Argentina	10	13	6	9
Ecuador	10	71	81	13
Venezuela	10	29	27	13
Jordan	5	6	6	5
Chile	1	3	1	1
Subtotal	298 241 (59)[b]	10 388 (64)	10 187 (67)	6 026 (74)
Global total	509 000	16 316	15 258	8 157

[a] NR = Report not received.
[b] Figures in parentheses are the % of the global total.

suboptimal potency, i.e. batch failure, in 15 lots (19%) from eight (38%) manufacturers in seven (50%) countries, including India (Table 3). The low potency results from Indian vaccine produced by some (but not all) manufacturers are linked to the potency testing requirements in India, which differ from those of WHO; although all Indian vaccines meet Indian Pharmacopoeia requirements, this does not necessarily imply compliance with WHO levels.

Table 3: **Potency testing results for tetanus toxoid (TT) in 14 countries, July 1995**

Country	Year	No. of lots	Results of TT potency testing: Passed[a]	Failed
Bangladesh	1993	10	10	—
	1994	5	5	—
Brazil	1992	3	3	—
China (manufacturer):				
A	1995	1	—	1
B	1995	2	—	2
C	1995	1	1	—
D	1995	2	2	—
E	1995	1	1	—
Colombia	1992	3	2	1
Democratic People's Republic of Korea (DTP)[b]	1994	2	2	—
India (manufacturer):				
A	1992	2	2	—
	1993	3	3	—
B	1993	5	2	3
C	1993	3	3	—
D	1995	2	2	—
Indonesia	1994	3	3	—
Islamic Republic of Iran (DT)[b]	1994	3	1	2
Mexico	1992	3	3	—
Pakistan[c]				
Manufactured, from seed	1991	1	—	1
Imported bulk	1994	2	1	1
	1995	2	2	
Philippines				
DTP[b]	1993	2	—	2
TT	1995	5	4	1
South Africa (DTP)[b]	1993	3	3	—
	1994	3	3	—
Venezuela	1992	3	3	—
Viet Nam	1993	5	4	1
Total	—	80	65 (71)[d]	15 (19)

[a] Passed implies potency test results ≥40 IU per human dose.
[b] The tetanus component was tested.
[c] Production of TT from seed has ceased in Pakistan; the national manufacturer is currently blending and filling imported bulk vaccine.
[d] Figures in parentheses are percentages.

Discussion

Field studies suggest that cases of NT are being born to women who have received at least two doses of TT. Investigations conducted by the TFSA have confirmed that TT produced in several countries is subpotent. Case reports of NT are, however, difficult to interpret since the interval between doses and timing of vaccination is not often clear. Country reports, which represent a crucial source of information about TT performance, are therefore not being used to their full potential to monitor TT performance.

The findings in Pakistan and the unconfirmed reports of NT cases in vaccinated women in other countries emphasize the need to standardize investigation of NT cases.[i] Standard guidelines must be used to evaluate such reports.[j] National authorities can expect the occurrence of more NT cases among infants born to vaccinated women, since (even with highly effective but imperfect vaccine) as TT coverage increases a greater proportion of NT cases will occur among infants born to fully vaccinated women (*28*). For example, at a vaccine effectiveness of 80%, managers would expect to see 6% of NT cases born to vaccinated women if coverage with TT2 were 25%, and 17% if coverage were 50% (Table 4). In addition, since the effectiveness of two properly spaced doses of TT in unvaccinated women should be greater than 90%, ≤10% of vaccinated women may be at risk for primary vaccine failure, i.e. are nonresponders. Since not all TT doses are properly spaced (i.e. the intervals are too short) nor are all newborns born during the period of protection from the last valid TT dose, additional NT cases will be born to vaccinated women. Furthermore, vaccinated mothers of infants with NT may self-select for notification through their health care utilization behaviour or may live closer to health facilities and be more likely to use services and thus be detected; this would produce a bias towards detection of NT cases born to vaccinated rather than unvaccinated women. Since vaccine effectiveness depends on both the proportion of cases born to vaccinated (PCV) and to unvaccinated women, and because PCV would be artificially inflated, such trends would underestimate TT vaccine efficacy. Thus, managers may face increasing numbers of reports of NT cases involving infants born to vaccinated women, due not to TT failure but to improved detection of NT cases. A case of NT involving an infant born to a "vaccinated" mother cannot necessarily be regarded as a TT failure until comprehensive investigation of the prior vaccination history permits such a conclusion to be reached.

Reports of NT cases must be investigated to confirm the clinical diagnosis; confirm both the number and dates of TT doses received, ideally from a vaccination card or from health facility records; and assure that unimmunized mothers are immunized, in view of the substantially higher risk of additional NT cases among infants born to mothers with a prior history of an infant with NT (*29*). Only an NT case that meets the standard WHO case definition,[k] who was born to a woman with at least two properly-spaced doses of TT should be considered a TT failure. Thus, the TT status of mothers of NT cases must

Table 4: **Expected proportion of NT cases among infants born to mothers vaccinated with two or more doses of properly spaced TT, by vaccine effectiveness (VE) level**

	% of cases at VE level of:[a]	
Coverage (%)	80%	90%
20	5	2
25	6	3
30	8	4
35	10	5
40	12	6
45	14	8
50	17	9
55	20	11
60	23	13
65	27	16
70	32	19
75	38	23
80	44	29
90	64	47
100	100	100

[a] $$\frac{PCV = PPV - (PPV \times VE)}{1 - (PPV \times VE)}$$

where PCV = proportion of NT cases born to vaccinated women; PPV = proportion of the population vaccinated (coverage with ≥TT2); and VE = vaccine effectiveness. Zero doses are compared to at least 2 TT doses. See ref. *24, 28, 34.*

[i] *Guidelines for investigating suspected cases of neonatal tetanus.* Unpublished document WHO/EPI/TRAM/93.3, 1993 (available upon request from Global Programme for Vaccines and Immunization, World Health Organization, 1211 Geneva 27, Switzerland).

[j] *Detection of tetanus toxoid vaccine failure and response in the field.* Unpublished WHO document EPI/TECHCOM/WP/93.34, 1993 (available upon request from Global Programme for Vaccines and Immunization, World Health Organization, 1211 Geneva 27, Switzerland).

[k] An infant with normal suck-and-cry during the first 2 days of life, who develops the inability to suck between days 3 and 28 of life and who develops either stiffness, convulsions or both.

also be appropriately classified. For example, in Kenya the TT status of NT cases was classified as follows: protected with documentation; protected without documentation; unprotected; uncertain; and unknown (*30*). Caution must be exercised in determining the TT vaccination status of women without card documentation, although some workers have suggested that maternal history of the number of doses received correlates well with antibody levels (*31*); also, similar efficacy estimates were obtained when either histories or card documentation were used to assess effectiveness in the Pakistan study cited above.

The proportion of "toxoid failures" among a sequential sample of NT cases, e.g. the most recent 30 cases reported, should be updated as new cases are investigated. This information, along with TT coverage data, should then be used to assess periodically vaccine effectiveness using formulas for vaccine effectiveness (Table 4). The magnitude of further investigative efforts should be guided by these assessments, with indications of unsatisfactory effectiveness prompting more vigorous efforts. In addition, the WHO Steering Committee on Epidemiology and Field Research has been evaluating the use of tetanus serological methods to assist in evaluating potential toxoid failures (*32*).

Once a TT failure is detected, a review of the cold chain in the district should be conducted to determine whether the vaccine has been exposed to excessive cold or heat. Any women in the community who are found to be unvaccinated should be vaccinated. In addition, reviews of admission registries in health care facilities in the district (with emphasis on hospitals) can be used to identify other NT cases that may represent TT failures. Finally, national authorities should consult WHO and UNICEF as to the appropriateness of conducting TT potency testing, reviewing production facilities and carrying out any special studies, such as seroprevalence investigations, to identify the reasons for the magnitude of poor TT effectiveness.

The unexpected and unacceptable performance of TT in the Punjab, Pakistan, has not been satisfactorily explained. Exposure of Punjab neonates to greater concentrations of tetanus toxins does not seem likely, in view of the closely similar rates for unimmunized mothers in all regions. Babies of appropriately immunized mothers had a significantly higher risk of NT in Punjab than elsewhere; thus the toxoid used in Punjab appeared to be significantly less immunogenic. This may have arisen for the following reasons: the TT that was supplied to the area was intrinsically less potent; the TT was mishandled in the field; or differences in response of mothers because of host factors such as malaria. The first two of these factors provided the most likely explanations. Additional studies of in-the-field effectiveness of TT in preventing NT in the developing world are clearly needed.

In 1992, Member States at the Forty-fifth World Health Assembly resolved to use only vaccines that met WHO requirements in their immunization programmes and to include this requirement in their immunization plans[1] and requested that the Director-General obtain information on steps to assure vaccine quality, and specifically requested information on efforts to ensure that countries establish infrastructures for the quality assurance of tetanus toxoid and poliovirus vaccine. In addition, in 1980 the EPI Global Advisory Group recommended that WHO develop strategies for vaccine quality control (*33*). The findings in Bangladesh (*11*) and the data we have presented illustrate the urgency in reviewing production facilities in countries that both produce TT and report NT cases. However, it is important to note that evaluating production and ensuring that a vaccine is safe and effective involve more than just potency testing. Although it is reassuring that a vaccine has been shown to be potent, vaccines can vary in potency between lots and even within the same lot. Thus, a positive potency test result, i.e. potent vaccine, must be interpreted with some caution; however, a negative result, i.e., subpotent vaccine, demonstrates a production problem. By 1997 the WHO Global Programme for Vaccines and Immunization is planning to have completed follow-up evaluations of manufacturing and control processes in the 22 countries with reported NT cases and local production of TT. Priority has been given to those countries with demonstrated potency problems in their locally produced TT and which continue to report NT cases. All countries will be encouraged to develop some form of national control authority for vaccines, with all vaccine-producing countries receiving priority support for such development.

It is clear that the 1995 goal of NT elimination has not been achieved because vaccination coverage is unacceptably low, especially in high-risk areas, and thousands of cases continue to occur. Intensified immunization of women in these high-risk districts is urgently required. In addition, many countries with NT cases are using TT vaccine that is of unknown quality and of uncertain in-the-field effectiveness. Major efforts must be made to raise coverage and ensure that all TT is of good quality, that vaccines

[1] *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board*, vol. III, third edit. (1985–92). Geneva, World Health Organization, 1993.

are handled appropriately, and that suspected TT failures are properly investigated and classified appropriately either as true vaccine failure or occurring as a consequence of improper timing or interval of TT administration. Additional studies are needed to understand more fully the factors that may affect the immune response to TT. The monitoring of TT effectiveness is crucial and must be based on the following: accurate surveillance, including case investigation to ascertain vaccination history to minimize misclassification of vaccination status as well as selection bias in reporting NT cases; in-the-field performance estimates based on coverage and the proportion of toxoid failures among recent NT cases; and ongoing monitoring of TT potency and production. Unfortunately, current NT case reporting may not be adequate enough to conclude confidently that a problem does or does not exist. However, failure to act now to monitor TT effectiveness could compromise the activities and efforts of many countries that are actively involved in realizing the goal of global elimination of NT as a public health problem.

Résumé

Qualité et activité de l'anatoxine tétanique: répercussions sur l'élimination du tétanos néonatal

Le tétanos néonatal est une cause majeure de mortalité dans les pays en développement, où il provoque chaque année plus de 400 000 décès. L'OMS a adopté comme objectif l'élimination de cette maladie à l'échelle mondiale. La principale stratégie de prévention dans les régions à haut risque consiste à administrer aux femmes en âge de procréer au moins deux doses d'anatoxine tétanique convenablement espacées afin de protéger les nouveau-nés à la naissance par transfert d'anticorps. Des études ont toutefois montré que, dans certains pays, l'anatoxine tétanique de production locale possédait une activité inférieure à la normale, tandis que dans d'autres on observait des cas de tétanos néonatal chez des nouveau-nés dont la mère avait été vaccinée. Cependant, la plupart des rapports concernant ces derniers cas ne mentionnent pas le calendrier d'administration des doses d'anatoxine. Ces résultats, bien que très utiles, sont souvent difficiles à évaluer et doivent être interprétés avec prudence. Quoi qu'il en soit, des cas de tétanos néonatal chez des nouveau-nés dont la protection antitétanique avait été confirmée par des analyses de laboratoire ont été signalés. D'autre part, des études réalisées au Pakistan et au Bangladesh ont révélé que l'efficacité de l'anatoxine tétanique était inférieure à 50% chez les femmes vaccinées. Ces rapports ont incité l'OMS à évaluer les stocks d'anatoxine tétanique dans les pays où de tels cas sont rapportés. Certains cas de tétanos néonatal chez les enfants dont la mère a été vaccinée sont à prévoir, car aucun vaccin n'est efficace à 100%; il est toutefois indispensable d'observer un espacement convenable entre les doses administrées ainsi qu'un intervalle suffisant avant la naissance pour obtenir une efficacité protectrice. L'évaluation des cas de tétanos néonatal doit être normalisée pour tenir compte des antécédents vaccinaux de la mère. Un examen approfondi des procédés de production et de contrôle de qualité de l'anatoxine a été réalisé entre 1993 et 1995 dans huit des 22 pays producteurs où sont rapportés des cas de tétanos néonatal; une évaluation plus rapide a été faite dans les 14 autres pays. Bien que 42 pays produisent de l'anatoxine tétanique, seuls les neuf fabricants (de neuf pays) qui fournissent ce vaccin à l'UNICEF sont autorisés à déclarer que leurs produits satisfont aux normes de l'OMS et aux critères d'achat par les agences des Nations Unies. Il ressort d'un inventaire des fonctions de contrôle à l'échelon national dans les 22 pays qui produisent de l'anatoxine tétanique et où sont signalés des cas de tétanos néonatal, que seuls quatre d'entre eux (Brésil, Inde, Indonésie et Mexique) possèdent des autorités nationales de contrôle fonctionnant convenablement. Dans les cinq pays producteurs qui enregistrent le nombre le plus élevé de décès par tétanos néonatal, seuls deux possèdent des autorités nationales de contrôle fonctionnelles. Dans la réalité, la situation régnant dans ces pays pourrait être encore plus grave. Des essais d'activité ont été effectués sur 80 lots d'anatoxine tétanique provenant de 21 fabricants de 14 des 22 pays concernés. Une activité inférieure à la valeur optimale, indiquant un défaut de qualité, a été trouvée dans 15 lots (19%) provenant de huit fabricants (38%) de sept pays (50%). La contrôle de l'efficacité de l'anatoxine tétanique est fondamentale et doit reposer sur les points suivants: surveillance rigoureuse, avec investigation des cas pour vérifier les antécédents vaccinaux (afin d'éviter des erreurs sur l'état vaccinal et des biais de sélection dans la notification des cas de tétanos néonatal); des estimations, sur le terrain, de la qualité du vaccin, d'après la couverture vaccinale et la proportion d'échecs de la vaccination chez les cas récents de tétanos néonatal; la surveillance continue de l'activité de l'anatoxine tétanique et de ses procédés de fabrication.

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