Lack of early antitoxin response to tetanus booster

J.D.H. Porter*, M.A. Perkin†, M.J. Corbel‡, C.P. Farrington*, J.T. Watkins‡ and N.T. Begge*

Tetanus immune globulin (TIG) continues to be recommended in persons with tetanus-prone wounds who have incomplete or unknown tetanus immunization status. The aim of this study was to determine whether, following a booster dose of tetanus toxoid in adults who had not been immunized in the previous 10 years, there was an antitoxin response to tetanus toxoid booster within 4 days. Thirty-one adults were investigated, baseline levels for tetanus antitoxin assayed using an ELISA technique, and an injection of adsorbed tetanus toxoid (0.5 ml) given. Blood samples for tetanus antitoxin levels were taken at daily intervals for the 4 days following immunization. Tetanus boosters following the primary course but before the present study did not significantly increase the levels of pre-study tetanus antitoxin and following the study booster there was no difference between the preboost levels and the levels on days 1 to 4. This finding indicates that the present recommendations for the use of TIG in tetanus-prone wounds are appropriate.

Keywords: Tetanus; booster; immunization; immune globulin; antitoxin

INTRODUCTION

The United Kingdom Department of Health's guidelines on immunization recommend the use of tetanus immune globulin (TIG) in persons with tetanus-prone wounds who have either never received a primary course of immunization or who have not received a booster within the previous 10 years. In the United States, TIG is recommended for the management of wounds in persons whose previous tetanus immunization status is unknown or uncertain, or who have received fewer than two previous doses of tetanus toxoid, or who have received only two previous tetanus toxoid doses and whose wound is more than 24 h old. This advice is based on the assumption that the antitoxin response to a booster dose of tetanus toxoid given at the time of injury is too slow to prevent the occurrence of clinical tetanus.

Studies which have investigated the response to booster immunizations have shown that antitoxin levels peak within 2 weeks, fall rapidly over 2 months and then fall more gradually over the following years. A constant log-linear decline in antitoxin level has been described. However, no study has reported on the early antitoxin response. If an adequate response to a booster could be demonstrated within 4 days, the minimum incubation period for tetanus, then tetanus immune globulin might not be necessary. The aim of this study was to determine whether, following a booster dose of tetanus toxoid in adults who had not been immunized in the previous 10 years, there was an antitoxin response within 4 days.

METHODS

Thirty-one adults who gave a clear history of a previous three-dose primary course of tetanus immunization (by intramuscular or deep subcutaneous injection) and of any booster injections, in whom >10 years had elapsed since the last dose of tetanus toxoid was administered, were enrolled in the study.

The following exclusions were made: a past history of tetanus; severe reaction to a previous dose of vaccine; pregnant or immunosuppressed; current acute illness; or recent immunization with other antigen(s).

A baseline venous blood sample was obtained from each participant and a single dose of adsorbed tetanus toxoid (0.5 ml) was given by deep subcutaneous or intramuscular injection. Postimmunization blood samples were taken at daily intervals for 4 days. Samples were assayed for tetanus antitoxin at the National Institute for Biological Standards and Control (NIBSC) by an enzyme-linked immunosorbent assay technique (ELISA). The relationship between log titres, age and interval since last immunization were investigated by means of linear regression analysis. Participants who had tetanus antitoxin levels of <0.01 IU ml\(^{-1}\) before the tetanus booster and who had levels of <0.01 IU ml\(^{-1}\) for the 4 days after the booster were non-responders and were classified as 'susceptible'. These participants were excluded from the regression analyses.
RESULTS

Twenty-three (74%) of the 31 patients were male and 8 (26%) female. The mean age of the participants was 55.2 years with a range of 23–86 years.

The primary tetanus course had been administered at a mean age of 24.9 years. Only 7 (23%) of the participants had received a booster and the mean age at which this had been given was 28.3 years. No participant had received more than one tetanus booster. The mean time interval between the last tetanus toxoid immunization and the present study was 27.1 years (minimum of 10 years and a maximum of 51 years).

Only five participants (16%) had baseline antitoxin levels <0.01 IU ml⁻¹. Their mean age was 49.8 years, range 33–70 years. Two were males who had received a tetanus booster in addition to a primary course; the remaining three were women who had received only a primary course. The remaining 26 participants had baseline antitoxin levels >0.1 IU ml⁻¹. A graph of baseline antitoxin log levels against age at the time of the study showed that levels decreased with the increasing age of the subject (regression slope = −0.02, s.e. = 0.006, 95% confidence interval (CI) −0.032, −0.008) (Figure 1). There was no significant correlation between the baseline level and the interval since the last tetanus immunization (regression slope = −0.009, s.e. = 0.008, 95% CI +0.007, −0.025).

![Figure 1](image1.png)  
**Figure 1** Relationship between baseline log of tetanus antitoxin level and age of participant (n = 26). Regression slope = −0.02; standard error = 0.006

Tetanus boosters following the primary course but before the present study did not significantly increase the levels of pre-study tetanus antitoxin (increase in log level = 0.041, s.e. = 0.271, 95% CI −0.501, 0.583). The upper limit of the confidence interval corresponds to a 1.8-fold increase in antibody titre.

Following the study booster there was no difference between the pre-boost levels and the levels on days 1 to 4 (Figure 2). Geometric mean levels for tetanus antibodies were 0.26 IU ml⁻¹ in the baseline samples, 0.25 on day 1, 0.27 on day 2, 0.30 on day 3 and 0.24 on day 4.

![Figure 2](image2.png)  
**Figure 2** Levels of tetanus antitoxin during 4 days following tetanus booster among 26 adult volunteers; 95% confidence interval = mean ± 2 standard errors

DISCUSSION

Tetanus is a continuing source of morbidity and mortality worldwide despite a highly effective immunizing agent. In 1981, it was estimated that there were 1 million tetanus-related deaths throughout the world. In the United Kingdom between 1983 and 1987, there were 44 notifications (two in children <15 years of age) and 12 deaths.

Immunity to tetanus is dependent on immunization. The proportion of the population immune therefore reflects the level of vaccine coverage and the rate at which antitoxin titres decline after immunization. There is evidence from the United Kingdom and elsewhere that the vaccine coverage for tetanus toxoid in adults is low.

This study demonstrates that, among people who have not received a tetanus primary course or booster in the previous 10 years, there was no significant serum antitoxin response to a tetanus booster during the 4 days after injection. This negative finding should however be interpreted with caution in view of the width of the confidence interval, the upper limit of which corresponds to a 1.8-fold increase in antibody level. Participants who had been given a previous booster dose of tetanus toxoid following their primary course responded no differently to those who had only received a primary course.

Despite previous immunization, five of the participants had baseline antitoxin levels <0.01 IU ml⁻¹, due either to primary vaccine failure or waning immunity. An antitoxin level of 0.01 IU ml⁻¹ of serum is widely employed as an indicator of immunity, but levels below this do not necessarily equate to susceptibility. In previously immunized persons in whom no antitoxin can be detected, immunity can be reinforced by a single dose of toxoid, for example, when tetanus toxoid is given in the event of an injury. However, there are two groups who may not respond to additional doses of tetanus toxoid: a percentage of people may not respond as a direct result of allelic variation in HLA class 2 genes in the population, and in the elderly immune responses may be impaired. Because a percentage of people may therefore never respond to tetanus toxoid, any tetanus-prone wound should be treated with TIG. A tetanus booster alone in these people may provide no protection.

The study findings of no significant serum antitoxin in response to a tetanus booster during the 4 days after injection and the presence of non- or poor responders in the population, suggest that the current United Kingdom Department of Health guidelines on the use of TIG are appropriate.
ACKNOWLEDGEMENTS

The authors are grateful to Angela Porter and Julie Sethna for collecting the blood specimens and Penny Forsyth and Justine Hollyer for assistance with the graphs.

REFERENCES

1 Department of Health. Immunisation against Infectious Disease. HMSO, London, 1990
3 Evans, D.G. Persistence of antitoxin in man following active immunization. Lancet 1943, ii, 316–317
4 Simonsen, O., Kjeldsen, K. and Heron, I. Immunity against tetanus and effect of vaccination 25 to 30 years after primary vaccination. Lancet 1984, ii, 1240–1242
19 Solomonova, K. and Vizev, S. Secondary response to boosting to purified aluminium hydroxide-adsorbed tetanus antitoxin in aging and in aged adults. Immunobiology 1981, 158, 312–319