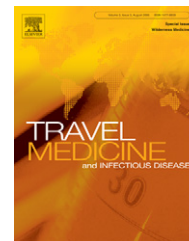




Available at www.sciencedirect.com



journal homepage: www.elsevierhealth.com/journals/tmid



Diphtheria boosters for adults: Balancing risks

Claire Cameron*, Joanne White, Deirdre Power, Natasha Crowcroft

Immunisation Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

Received 13 February 2006; accepted 20 February 2006

Available online 23 May 2006

KEYWORDS

Tetanus;
Vaccine reactions;
Adult vaccination

Summary

Combined tetanus–diphtheria vaccines are now the only means of protecting adults from tetanus or diphtheria. When advising on the benefits and risk of vaccinating for one disease, clinicians now have to consider the other vaccine component, and questions have arisen about where the balance of risk lies for different patients.

Five doses of diphtheria–toxoid containing vaccine are probably sufficient protection for individuals who remain in low-incidence countries such as those in most of Western Europe. Adults who remain in the UK are extremely unlikely to be exposed to diphtheria and this needs to be taken into account when assessing the balance of risk where individuals have received fewer than five doses of diphtheria toxoid but five or more doses of tetanus toxoid. In contrast to diphtheria, if someone has received fewer than five doses of tetanus toxoid but is up to date for diphtheria toxoid, the balance of lifelong risk is probably in favour of giving tetanus toxoid irrespective of the individual's diphtheria status.

For travellers to diphtheria endemic countries boosters are recommended if more than 10 years has elapsed since the last dose. For individuals who have already received five or more doses of tetanus vaccine in the past, receiving further boosters of tetanus in combination with diphtheria toxoid is unlikely to cause any significant reactions. The only absolute contraindication to such boosters is a previously documented anaphylactic reaction to either diphtheria or tetanus toxoid. Individuals who have a history of such a reaction should be well advised regarding probable risk of infection, symptoms of the disease and the need to seek early treatment.

© 2006 Elsevier Ltd. All rights reserved.

Background

Diphtheria was a highly endemic disease with a significant health burden in the pre-vaccine era. Diphtheria toxoid vaccine became incorporated into routine immunisation

programmes in Western Europe in the 1940s and 1950s and childhood immunisation programmes were introduced in Europe in the 1950s and 1960s. Mass vaccination controlled the disease and aside from rare outbreaks or sporadic imported cases diphtheria was contained. In the UK, high levels of infant vaccine uptake¹ have ensured that diphtheria has not been a significant public health problem for decades.

*Corresponding author. Tel.: +20 8327 6150; fax: +20 8200 7868.
E-mail address: Claire.Cameron@hpa.org.uk (C. Cameron).

Despite effective control of the disease through vaccination in many countries, circulation of toxigenic strains of *Cornebacterium diphtheriae* has persisted in much of the world. In industrialised countries with high vaccine coverage such as the UK, circulation of *C. diphtheriae* has virtually ceased and nearly all cases are associated with cutaneous infections and travel to endemic countries.²

The Russian Federation saw a resurgence of diphtheria in the 1990s and although studies have identified more than one reason for the epidemic,^{3–5} arguably the most overwhelming factor was the accumulation of large numbers of susceptible individuals among both adults and children. Resurgence of diphtheria in Russia marked the largest diphtheria epidemic in an industrialised country in three decades.⁶ The Russian experience illustrated the opportunistic nature of diphtheria and how rapidly a well-controlled disease could re-emerge. Reports of importations of the disease to other neighbouring countries highlighted the very real potential of further outbreaks in Western Europe and raised global concerns about efficacy of diphtheria control programmes, levels of susceptibility of adults to the disease and immunogenicity of the diphtheria toxoid vaccine. However, despite documented high levels of susceptibility⁷ in older individuals within Western Europe, diphtheria has not re-emerged supporting the effectiveness of the programme.

Recent changes to UK diphtheria vaccination recommendations

In May 1994, in an effort to improve adult immunity and in line with recommendations from the World Health Organisation, The Department of Health advised that single low-dose diphtheria vaccine for adults and adolescents (d) be replaced by the combined tetanus/low-dose diphtheria (Td).⁸ The combined vaccine was introduced for routine use as the school leaving booster and recommended for those aged 13–18 years. It was also recommended for use in hospital A&E departments and clinics for people needing tetanus toxoid after suffering a tetanus-prone wound.

These recommendations were further enforced in 2003 when Department of Health supplies of single adsorbed diphtheria vaccine became exhausted as a result of licensure issues between the manufacturer and the marketing authorisation.⁹ Since that time, only the combined tetanus and low-dose diphtheria vaccine has been available for adults.

Current UK Department of Health guidelines on immunisation recommend a minimum of 5 doses of diphtheria and tetanus toxoid-containing vaccine are given to all individuals at appropriate intervals, regardless of age at which immunisation commences.¹⁰ Decennial booster doses are only recommended routinely for two groups: individuals who may be exposed to diphtheria in the course of their work (mainly laboratory staff) and for travellers to particular destinations, depending on the nature of their travel.

The lack of single diphtheria vaccine has raised a number of questions which we attempt to address in this paper. Firstly, is the five-dose schedule, developed for tetanus, sufficient for life-long protection against diphtheria in the UK? Secondly, a number of travellers are recommended

either to have diphtheria toxoid whilst being up to date for tetanus, or vice versa. Without single tetanus or diphtheria vaccines some people, particularly travellers to diphtheria endemic countries, may require extra doses of either tetanus or diphtheria toxoid to be fully protected; could this be harmful? Finally, what policy should be adopted for those individuals who require diphtheria vaccine but who have a history of severe allergic reaction to tetanus toxoid?

Methods

A literature review was performed using computerised databases Medline (1996–2004) and Pubmed to add to a collection of research papers already collated over many years by the Immunisation Department of the Health Protection Agency. The evidence was analysed with reference to the following questions:

1. Is the five-dose schedule sufficient for life-long protection against diphtheria in the UK?
2. The option to offer single tetanus or diphtheria has been removed. The possibility therefore exists that some people may receive unnecessary extra doses of either tetanus or diphtheria. Could this be harmful?
3. In the absence of single antigen diphtheria what policy should be adopted for those individuals who require diphtheria vaccine with known history of severe allergic reaction to tetanus toxoid?

Results

1. Is the five-dose schedule sufficient for life-long protection against diphtheria in the UK?

During 1985–2004, there were 39 laboratory-confirmed cases of diphtheria infection and 1 death in England and Wales due to toxigenic *C. diphtheriae*. In addition there were 50 laboratory-confirmed infections due to *C. ulcerans*.¹¹ Tetanus notifications were higher during the same period with 213 reported cases of the disease and 45 deaths.^{12,13}

The potential for spread of diphtheria is directly related to proportion of the population that are susceptible to the disease. It is considered that if 70–75% of the population have protective antibody levels herd immunity will prevent spread of the disease.¹⁴ In the UK, successful immunisation programmes in infancy and schools have led to there being few susceptible children and young adults. Since 1992, at least 94% of children in England and Wales have completed a primary course of three doses by 2 years of age. Coverage of four doses by 5 years of age is about 86%.¹⁵ The proportion of susceptible persons however increases with age for two reasons: older cohorts are less likely to have received five doses of vaccine, and immunity wanes with time. The need to secure immunity in adulthood has been discussed by several authors.^{7,16–18}

A UK survey carried out on residual sera confirmed a significant trend of decreasing immunity with increasing age.¹⁹ It suggested a progressive decline in protection from 70% in those aged 25–29 years to 29% in those aged 60. In addition other sero-prevalence studies indicate

50% of UK adults over 30 years are susceptible to diphtheria.²⁰ Many of these adults will not have received primary immunisation as children and in addition grew up when circulation of natural infection was declining, so opportunities for acquiring natural immunity from exposure were reduced. As the five-dose schedule only commenced in 1994, the possibility exists that there may be a significant cohort of the adult population in the UK who may not have optimal immunity. Despite this large gap in immunity of adults, diphtheria remains extremely rare in the UK and as previously discussed current high level of childhood vaccination and a reduction in circulation of toxigenic strains, make a resurgence of diphtheria in the UK unlikely at this time.²¹

Consideration however should be given to risk of transmission through travel to, and emigration from, endemic countries, which alters the balance of risk.^{21,22}

In 1997, diphtheria was confirmed in an un-immunised UK woman aged 72 years who developed a sore throat during a cruise round the Baltic Sea. Isolates taken from the woman subsequently linked it to a strain circulating in Eastern Europe at that time.²³ In addition; a recent paper has highlighted the incidence of imported cutaneous diphtheria in the UK and stressed the need for continued high diphtheria vaccination coverage.²

Unlike diphtheria, control of tetanus does not rely on herd immunity and the object of immunisation is to provide individual protection. In common with diphtheria serological studies have found a progressive decline in protection against tetanus with age. Studies again concluded that although 80% of those aged between 4 and 35–39 years had protective tetanus antitoxin levels, there was a progressive decline in protection from 70% in the 40–49 year age groups to 53% in those aged 60 and over.¹⁹

For the majority of individuals living in the UK, five age appropriate doses of diphtheria/tetanus vaccine, given at recommended intervals, are likely to be satisfactory for long-term protection against tetanus. As recommended by the Department of Health un-immunised children and adults coming to the UK or individuals with unknown or incomplete immune status should be reviewed at the first available opportunity and Department of Health guidelines followed in full.

In the case of diphtheria, individuals travelling to high endemic countries should be fully immunised according to the UK schedule and if necessary receive booster vaccination to secure individual protection and reduce the risk of importation on return.

2. The option to offer single tetanus or diphtheria has been removed. The possibility therefore exists that some people may receive unnecessary extra doses of either tetanus or diphtheria. Could this be harmful?

Local reactions including pain or tenderness at injection site, local swelling or erythema are common after vaccines containing toxoids.^{5,24,25} The frequency of these reactions is related to the number and spacing of prior doses received.^{26,27} Mild systemic reactions can also occur but are substantially less frequent with increasing doses.²⁵

Diphtheria toxin vaccines used to be associated with an unacceptable rate of reaction, with side effects of

vaccination in adults more pronounced than in children. With less reactogenic, lower-dose vaccines available today and decreased influence of naturally acquired immunity²⁸ there is little available evidence to suggest that excess doses of diphtheria would cause an individual any significant long-term harm.

A study in 1995 which followed up 192 schoolchildren who were given high-dose diphtheria instead of low dose concluded that although there was an increase in mild local reactions in this group compared to school children given the correct low-dose vaccine, no general reactions or serious effects were noted.^{29,30}

Tetanus-toxoid adverse reactions of many types have been reported since the use of immunisations became widespread and although not usually severe, increased local reactions are a well-documented side effect of excess doses of tetanus.³¹

Many individuals will have (and may still) received extra doses of tetanus in hospital A&E departments and GP surgeries and whilst it is recognised that these may cause local discomfort there is no evidence to suggest that long-term adverse effects will result. Indeed studies have concluded in the absence of single-dose diphtheria offering Td vaccine to children with a history of additional tetanus booster is an acceptable policy.³²

Wherever possible those who have received fewer than five doses of diphtheria toxoid but five or more doses of tetanus toxoid should be encouraged to complete the five recommended doses.

However, currently adults who remain in the UK are extremely unlikely to be exposed to diphtheria and for those individuals who have previously had a severe local reaction to tetanus the risk of diphtheria may be deemed too low to justify the greater risk of local reactions from unnecessary tetanus toxoid.

Of these few individuals who may be at risk of exposure through travel however, the benefit of protection from the disease versus the likelihood of repeat local reaction should be discussed with the individual and a course of action decided on in their best interests.

The issues for tetanus are different. Antibody levels, which may be linked to risk of adverse reactions, decline faster with age for diphtheria than tetanus, and in addition the risk of tetanus does not depend on the incidence of tetanus infection in the population. In contrast to diphtheria, if someone has received fewer than five doses of tetanus toxoid but is up to date for diphtheria toxoid, the balance of life-long risk is probably in favour of giving tetanus toxoid irrespective of the individual's travel plans or likelihood of local reaction.

3. In the absence of single antigen diphtheria, what policy should be adopted for those individuals who require diphtheria vaccine with known history of severe allergic reaction to tetanus toxoid?

Diphtheria is a rare disease in the UK, therefore the need for protection from the disease versus possible side effects of vaccination should be judged conservatively. For any patients with a history of severe allergic reaction to vaccination a thorough history should be taken to ensure vaccination was the true cause. Tetanus toxoid is one of the oldest and most efficacious of bacterial vaccines and early reports of severe reaction were

usually associated with Witte's peptone which is no longer used to prepare the vaccine.³³ Surveillance of adverse drug reactions within the developed world shows vaccine associated events are infrequently reported following Td.³⁴ Additionally, many misconceptions and false contraindications often surround vaccinations and often decisions not to vaccinate are based on the assumption that a previous reaction to vaccination will precipitate a more severe reaction with each subsequent dose.

Severe reactions to tetanus have been linked to high pre-existing antitoxin level usually as a result of over-immunisation.^{31,33} Other studies however have concluded the degree of reaction does not correlate with prior history of immunisation and that even individuals with a documented history of local and systemic reaction to tetanus showed no adverse reactions when re-vaccinated.³⁵ Reaction to primary tetanus vaccination is extremely rare. However evidence is accumulating that children who react to a dose of vaccine can go on to complete full primary course.³⁶ Thus, anaphylaxis following a tetanus or diphtheria-containing vaccine remains the only true contra-indication to subsequent boosters. Since the introduction of highly purified vaccines, confirmed anaphylaxis following tetanus-containing vaccine is extremely rare, 0.65–3 anaphylaxis events per million doses.³⁷ Thus in line with department of health guidelines there are very few individuals for whom tetanus vaccine is truly contraindicated.

Clearly for individuals with a history of severe allergic reaction the risks greatly exceed the benefit of revaccination for diphtheria protection. Such patients should be well advised regarding probable risk of infection, symptoms of the disease, and the need to seek early treatment if they are travelling to diphtheria endemic countries.

Conclusions

The debate about the use of combined vaccines can be summarised as a risk assessment which balances the risk of infection against the risk of a reaction to the vaccine. Although evidence from serological studies suggests that immunity in adults wanes with age, the very low incidence of disease in those who have received five doses indicates that the current UK schedule appears to provide sufficient protection against both diphtheria and tetanus. For diphtheria, this protection also depends upon continued high uptake of the vaccine to maintain the low incidence of infection in the population. The experience of other countries illustrates that global eradication of these diseases remains unlikely at present and those who may be exposed to diphtheria through travel to endemic countries, laboratory work or contact with travellers from endemic countries may not be sufficiently protected and should ensure that their immunity is maintained through boosters.

Vaccine associated events are infrequently reported following Td vaccination. In common with most immunisations the possibility exists that reactions will occur in some individuals who receive diphtheria/tetanus toxoids whether as part of a combined vaccine or indeed on its own. However

the risk must be put in context of added benefits of protection against disease.

It is also likely that some individuals may receive more than the current recommended five doses of either tetanus or diphtheria but again available evidence suggests systemic adverse events are very rare and minor local reactions should not represent an obstacle to vaccination. A history of anaphylaxis following diphtheria or tetanus vaccination remains the only contra-indication to further doses of the combined vaccine and is an indication for a full explanation of the likely risks to travellers and the measures they should take to protect themselves by other means.

References

1. Salisbury DM, Begg NT, editors. *Immunisation against infectious disease*. London: Her Majesty's Stationary Office; 1996.
2. De Benoist AC, White JM, Efstratiou A, et al. Imported cutaneous diphtheria, United Kingdom. *Emerg Infect Dis* 2004;10(3):511–3.
3. Dittmann S, Wharton M, Vitek C, et al. Successful control of epidemic diphtheria in the states of the Former Union of Soviet Socialist Republics: lessons learned. *J Infect Dis* 2000;181(Suppl 1):S10–22.
4. Vitek CR, Wharton M. Diphtheria in the former Soviet Union: re-emergence of pandemic disease. *Emerg Infect Dis* 1998;4(4):539–49.
5. Golaz A, Hardy IR, Strebel P, et al. Epidemic diphtheria in the newly independent states of the former Soviet Union: implications for diphtheria control in the United States. *J Infect Dis* 2000;181(Suppl 1):S237–43.
6. Begg N. Manual for the management and control of diphtheria in the European region of the WHO, ICP/EPI 038 (B) WHO Copenhagen. 1994. p. 1–16.
7. Levy-Bruhl D, Pebody R, Veldhuijzen I, Valenciano M, Osborne K. ESEN: a comparison of vaccination programmes. Part one: diphtheria. *Euro Surveill* 1998;3(10):93–6.
8. Department of Health. Chief Medical Officer Update. 2nd May 1994.
9. Department of Health. Replacement of single adsorbed diphtheria vaccine for adults by combined tetanus/low dose diphtheria for adults and adolescents. Update Letter to Immunisation Co-ordinators. 30th July 2003.
10. Department of Health. Immunisation against infectious disease. The 'Green book' chapters on diphtheria, hib, pertussis, polio and tetanus. Department of Health. 2004.
11. Health Protection Agency Diphtheria Notifications. Laboratory isolates of *Corynebacterium diphtheriae*, deaths and vaccine uptake rates. Accessible at http://www.hpa.org.uk/infections/topics_az/diphtheria/data_death_vaccine.htm
12. Rushdy AA, White JM, Ramsay ME, Crowcroft NS. Tetanus in England and Wales, 1984–2000. *Epidemiol Infect* 2003;130(1):71–7.
13. CDR. Tetanus in England and Wales 2001–2004. *Commun Dis Report* 2005;15:34.
14. Miller E, Rush M, Morgan-Capner P, Hutchinson D, Hindle L. Immunity to diphtheria in adults in England. *BMJ* 1994;308:598.
15. Department of Health Statistical bulletin. NHS immunisation statistics 2003–05. The Department of Health—Pubs and stats Statistics. Accessible at <http://www.dh.gov.uk/PublicationAndStatistics/Statistics/fs/en>
16. Mathias RG, Schechter MT. Booster immunisation for diphtheria and tetanus: no evidence of need in adults. *Lancet* 1985;1(8437):1089–91.
17. Mortimer J, Melville-Smith M, Sheffield F. Diphtheria vaccine for adults. *Lancet* 1986;2(8517):1182–3.

18. Settergren B, Broholm KA, Norrby SR, Christenson B. Diphtheria revaccination of adults. *Lancet* 1987;1(8532):557–8.
19. Maple C, Jones CS, Wall EC, et al. Immunity to diphtheria and tetanus in England and Wales. *Vaccine* 2000;19:167.
20. Edmunds WJ, Pebody RG, Aggerback H, et al. The sero-epidemiology of diphtheria in Western Europe ESEN Project. European Sero-Epidemiology Network. *Epidemiol Infect* 2000;126(2):331.
21. Begg N, Balraj V. Diphtheria: are we ready for it? *Arch Dis Child* 1995;73(6):568–72.
22. Simonsen O, Kjeldsen K, Vendborg HA, Heron I. Revaccination of adults against diphtheria : responses and reactions to different doses of diphtheria toxoid in 30–70-year-old persons with low serum antitoxin levels. *Acta Pathol Microbiol Immunol Scand [C]* 1986;94(5):213–8.
23. CDR. Diphtheria acquired during a cruise in the Baltic sea. *Commun Dis Report* 1997;7:219.
24. Gardner P. Issues related to the decennial tetanus–diphtheria toxoid booster recommendations in adults. *Infect Dis Clin North Am* 2001;15(1):143–53.
25. Centre for Disease Control. Diphtheria, tetanus, pertussis: recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991; 40(No.RR10): 1–28.
26. Trollfors B, Taranger J, Lagergard T, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. *N Engl J Med* 1995;333(16):1045–50.
27. Schmitt-Grohe S, Stehr K, Cherry JD, et al. Minor adverse events in a comparative efficacy trial in Germany in infants receiving either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP (DTP) or DT vaccine. The Pertussis Vaccine Study Group. *Dev Biol Stand* 1997;89:113–8.
28. Long SS, Deforest A, Smith DG, Lazaro C, Wassilak GF. Longitudinal study of adverse reactions following diphtheria–tetanus–pertussis vaccine in infancy. *Pediatrics* 1990;85(3): 294–302.
29. Smith G, Norman A, Banks J. Management of School leavers given a diphtheria and tetanus vaccine intended for children instead of the intended low dose preparation. *Commun Dis Report* 1997;7(5).
30. Sidebotham PD, Lenton SW. Incidence of adverse reactions after administration of high dose diphtheria with tetanus vaccine to school leavers: retrospective questionnaire study. *BMJ* 1996;313:533–4.
31. Wassilak SGF, Roper MH, Murphy TV, Orenstein WA. Tetanus toxoid. In: Plotkin SA, Orenstein WA, editors. *Vaccines*. 4th ed. Elsevier: Philadelphia; 2004 [Chapter 27].
32. Ramsay M, Joce R, Whalley J. Adverse events after school leavers received combined tetanus and low dose diphtheria vaccine. *Commun Dis Rev* 1997;7(5):65–7.
33. Collier LH, Polakoff S, Mortimer J. Reactions and antibody responses to reinforcing doses of adsorbed and plain tetanus vaccines. *Lancet* 1979:1364–8.
34. Lloyd JC, Haber P, Mootrey GT, Braun MM, Rhodes PH, Chen RT. Adverse event reporting rates following tetanus–diphtheria and tetanus toxoid vaccinations: data from the Vaccine Adverse Events Reporting System (VAERS), 1991–1997. *Vaccine* 2003;21:3746–50.
35. Jacobs RL, Lowe RS, Lanier BQ. Adverse reactions to tetanus toxoid. *JAMA* 1982;247(1):40–2.
36. Gold M, Goodwin H, Botham S, Burgess M, Nash M, Kempe A. Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. *Arch Dis Child* 2000;83:128–31.
37. Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; 112(4):815–20.