Are current UK tetanus prophylaxis procedures for wound management optimal?

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Accepted 26 December 2008

ABSTRACT

Tetanus is a potentially fatal disease that occurs after contamination of a wound with *Clostridium tetani* spores. The introduction of comprehensive infant vaccination programmes in the 1960s dramatically reduced the incidence of tetanus in the UK. To achieve comprehensive protection against tetanus, the World Health Organization guidelines recommend the administration of the five-dose childhood immunisation regimen and an additional sixth dose, after approximately 10 years, to ensure long-lasting immunity. To supplement these measures, tetanus prophylaxis with human tetanus immunoglobulin is considered essential for incompletely immunised individuals presenting with dirty wounds. However, identifying those individuals who are not fully immunised has, until recently, been problematical. The use of a new rapid, point-of-care immunoassay to assess tetanus immune status may facilitate the optimal management of patients with wounds.

The use of comprehensive infant vaccination programmes has dramatically reduced the incidence of tetanus in westernised countries. The World Health Organization (WHO) management guidelines recommend a six-dose tetanus vaccination course to ensure long-term immunity to the disease. There is a concern that changes in the UK Department of Health tetanus guidelines and the lower seroprotection rates in certain demographic populations may compromise the management of patients entering the emergency department with high-tetanus-risk wounds. This review discusses the potential implications of suboptimal tetanus seroprotection rates in patients presenting with wounds. It goes on to consider ways of accurately assessing tetanus seroprotection status in the emergency department to ensure that individual patients receive the most appropriate tetanus prophylaxis.

LITERATURE SEARCH

The literature was searched in November 2008 through PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez) for articles published in English since 2000 using the search terms *tetanus*, *wound* and *prophylaxis*. A total of 110 articles were identified. Articles describing vaccination programmes in general terms or neonatal tetanus were excluded. Articles subjectively deemed relevant were retrieved, and the reference lists were reviewed for additional articles of interest. WHO sites were searched for current data on the incidence of tetanus. Emergency medicine conference proceedings were also reviewed for data of interest.

TETANUS INCIDENCE

Tetanus is a potentially fatal disease that occurs after contamination of a wound with *Clostridium tetani* spores, which are ubiquitous in the environment. Spores are able to grow in the anaerobic wound environment, releasing a highly potent neurotoxin that causes tetanus symptoms of muscle spasm and rigidity.[1] The muscle rigidity initially involves the jaw (hence "lockjaw") and neck (episthotonus) but can progress to become more generalised, at which point the patient requires respiratory support and intensive care and is at a significant mortality risk. However, presentation is varied and can present as localised tetanus, where the rigidity is only in one muscle group close to the site of injury or in cephalic form presenting as cranial nerve palsies after head wounds. The introduction of comprehensive infant vaccination programmes in the 1960s dramatically reduced the incidence of tetanus in the UK.[2] Surveillance has estimated the current annual incidence at about 0.2 cases per million, which is comparable with that in other westernised countries.[3–5] Some groups are at greater risk of developing tetanus, particularly older individuals with an incomplete vaccination history,[1 6] with the UK incidence being highest in those > 64 years (approximately 0.66 cases per million).[7] In recent years, sporadic tetanus outbreaks have also occurred in intravenous drug users.[7 9]

TETANUS VACCINATION

Immunity to tetanus requires effective immunisation, as the small amount of toxin able to cause disease symptoms is not sufficient to trigger an immune response.[8] In the UK, all parents are offered primary tetanus immunisation for their infant children, comprising doses at 2, 3 and 4 months and two boosters administered before starting and before finishing school.[1] Tetanus vaccines are produced by formaldehyde inactivation of tetanus toxin to produce the toxoid.[6] Tetanus toxoid is administered in a variety of forms: the diphtheria–pertussis–tetanus and diphtheria–tetanus vaccines are currently used in children; tetanus toxoid alone and the tetanus-diphtheria vaccine, containing a reduced amount of diphtheria toxoid, are used in adults; and the alternative tetanus-diphtheria-pertussis formulation can be used in adolescents and adults.[1 8 10] In addition, if a patient presents with a dirty wound that could be infected with *C tetani*, treatment can be given in the form of antibiotics and human tetanus immunoglobulin (HTIG), to ensure instant protection, and/or a toxoid booster dose.[1 10 11] However, it is difficult to identify tetanus-prone wounds.[12]

The primary tetanus vaccinations trigger small and transient antibody responses, but the fourth

dose and boosters, given approximately 5 and 10 years later, aim to ensure long-lasting protection.[8] Individuals who have received a complete five-dose vaccination course should have immunity to tetanus that persists for about 20 years.[15] After this time, additional booster doses are given to travellers going to regions where medical attention is not available.[1] This implies that using the UK regimen, those >35 years may experience reducing immunity.

TETANUS VACCINATION GUIDELINES

To achieve comprehensive protection against tetanus, the WHO guidelines recommend administration of the five-dose childhood immunisation regimen and an additional sixth dose, after approximately 10 years, to ensure long-lasting immunity. To supplement these measures, tetanus prophylaxis with HTIG is considered essential for incompletely immunised individuals presenting with dirty wounds.[10] This conflicts with the current UK Department of Health guidelines, which consider five vaccine doses to be sufficient to provide long-term immunity, as long as HTIG is given as prophylaxis for high-risk wounds[1 12] and extra toxoid doses are administered when travelling to areas with limited medical resources. It has been noted that the change in UK policy, in the absence of long-term immunity data, may primarily be an attempt to reduce the likelihood of adverse reactions with additional benefits in terms of time and healthcare resource implications,[13] but there is, as yet, no evidence regarding change in incidence of tetanus.

However, some data indicate that restricting immunisation to five tetanus toxoid doses may compromise immune status: Simonsen *et al*[13] showed that serum tetanus antitoxin titres gradually subside after immunisation. As a result, 28% of individuals, who had undergone full primary vaccination, had low antitoxin titres 25–30 years later.[13] This decline in antitoxin titres may lead to older people having insufficient protection.[16] Such findings have led the Australia and New Zealand health authorities to not only recommend the full six-dose immunisation schedule but also offer additional boosters later in life.[14]

The changes in UK wound management guidelines may not have been adopted by some emergency departments. Savage *et al*[17] assessed the tetanus prevention practises in staff across 67 English emergency departments. The survey estimated that tetanus guidelines were consistently followed by 29% of emergency department staff, with most staff erring of the side of caution when assessing tetanus risk status. In addition, 46% of staff who responded stated that they would give a sixth booster toxoid dose if the previous administration had occurred >10 years before. These findings indicate that many clinicians are managing wounds in line with the WHO guidelines rather than the most recent UK recommendations. Because the UK policy change was not based on a failure of previous practise, it has been suggested that this more rigorous management approach may be appropriate.[17] High non-compliance with guidance in Italy has been reported, with only 1.5% of physicians following guidance.[18]

DETERMINING TETANUS PROTECTION STATUS

Because tetanus usually results from *C tetani* growth and toxin production in a wound, hospital emergency departments are most likely to see patients at risk of the disease. Data from the USA have estimated that approximately 5.8% of emergency hospital visits involve the treatment of open wounds and management of potential infection complications.[11] In the UK, it has been estimated that about 11% of emergency department visits are for the treatment of lacerations.[19] Effective immunity against *C tetani* relies on the presence of sufficiently high antibody levels being present at the wound site. A number of studies have assessed adult tetanus seroprotection rates (antitoxin levels of > 0.1 or >0.15 IU/ml) in countries with comprehensive vaccination programmes: protective antitoxin levels were seen in 72% to 90% of patients in the USA,[20 21] 80% in England and Wales[22] and 64% in Belgium.[23] Of note was the observation that the degree of protection was lower in older people (31% to 60% in individuals > 60 years[20 24] in the USA, UK and Belgium), in women (64% to 86% in the US studies[20 21]) and in immigrants (52% to 75% in the US studies[20 21] and 45% to 52% in the Belgian study[23]).

Given the variability in tetanus seroprotection rates, the emergency medicine clinician needs to identify which patients presenting with wounds require either a booster toxoid dose or prophylactic HTIG. Traditionally, this is done by questioning patients as to their immune status, a practise that is highly imprecise. Fishbein *et al*[25] showed that only 57% of patients were able to correctly recall their tetanus vaccination status. When considered in terms of seroprotection data, incorrect recall of immunisation status led to 57% of wound patients who needed additional prophylaxis not receiving it.[21] Laboratory tests assessing serum antitoxoid levels have relied on an ELISA. However, this method is too technically demanding and time-consuming to be of much use to the emergency medicine clinician.[26] Given the uncertainties faced when treating a high-tetanus-risk wound, a rapid and accurate means of assessing seroprotection status would be beneficial. The facility to determine a patient's tetanus immune status at the point-of-care would have two major advantages: firstly, it would minimise the risk of acute tetanus by ensuring that unprotected individuals receive prophylactic HTIG. Secondly, it would reduce the likelihood of overtreatment in those identified as seroprotected.

A new single-step immunoassay has recently been described that can determine tetanus seroprotection status within 10 minutes using one drop of blood. The ProTetanus diagnostic kit (Prospect Diagnostics, Dronfield, Derbyshire, UK) has been evaluated in a number of emergency departments in France, Belgium and Korea (as the Tetanos Quick Stick). Comparison of the test with the gold standard ELISA demonstrated about 80% sensitivity and 100% specificity at identifying tetanus seroprotection status in emergency departments in two French studies (77% specificity and 98% sensitivity in the work of Colombet *et al*[4] and 87% sensitivity and 100% specificity in the work of Ardelean-Jaby *et al*[27]) and one Korean study (80% sensitivity and 99% specificity[28]). One study described a slightly lower specificity (87%) value for the test when using a threshold antitoxoid level of 0.15 IU/ml. However, this is higher than the threshold recommended by the WHO, and reanalysis of the data using the recommended 0.1 IU/ml results in sensitivity and specificity values (85% and 94%, respectively) in line with those found by other studies.[23] When considered in terms of identifying the most appropriate treatment for patients with wounds, the Tetanos Quick Stick was estimated as having 98% predictive accuracy for identifying patients with seroprotection and 92% accuracy at identifying those with low antitoxoid levels.[26] In contrast, assessment of vaccination history has 82% predicative accuracy when identifying seroprotection and 46% accuracy when identifying low antitoxoid levels.[25] A study in Belgium suggested that use of the test in the emergency department would reduce the number of booster injections by 40% and the number of HTIG administrations by 80%.[29] A cost-effectiveness analysis estimated that the Tetanos Quick Stick would prevent unnecessary intervention in 57% of patients, thereby reducing the total treatment cost per patient from €11.34 to €10.58.[30] Updated

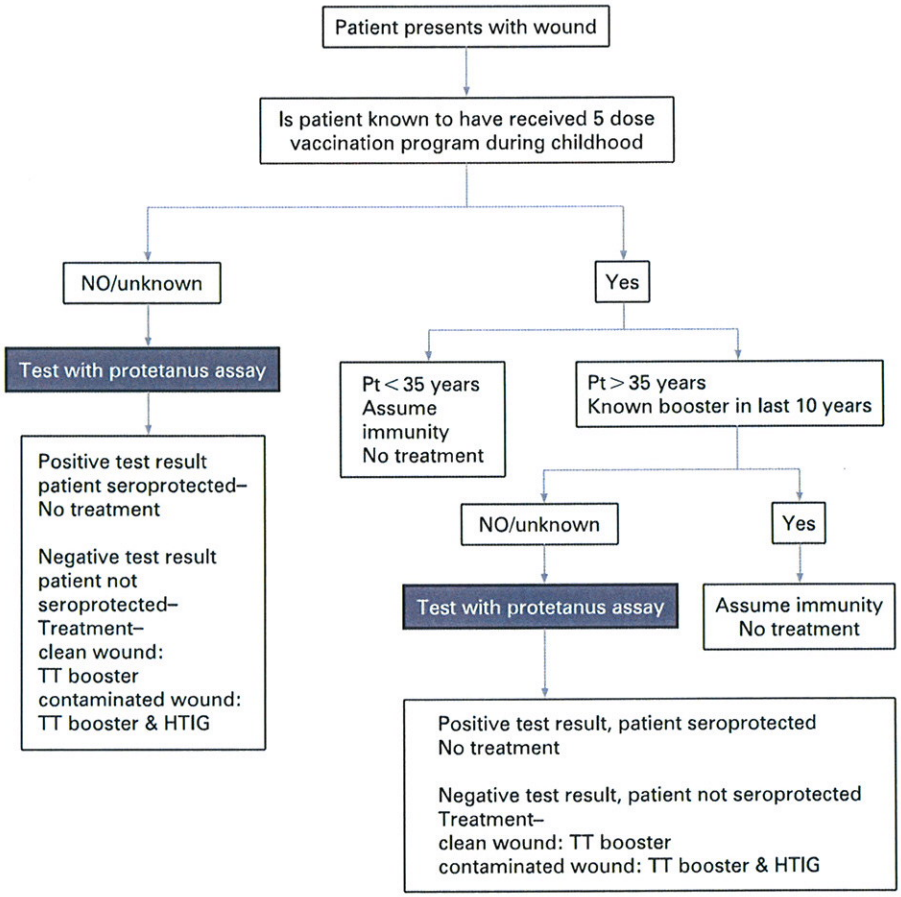

Figure 1 Proposed medification to tetanus prophylaxis using immunoassay.

analyses estimate a cost saving per patient of approximately €5.[31] This has been equated to a cost saving, to a French emergency department, of €4096 over 3 months.[32] The use of the Tetanos Quick Stick has been incorporated into the French Ministry of Health recommendations for wound management.[26]

As, in the UK, emergency departments use HTIG less frequently but tetanus toxoid is more expensive (€11.08), the estimated cost savings based on the model of Stubbe *et al*[30] would be about €0.74 per patient. Extrapolating to a UK emergency department seeing 50 000 patients per annum, with 11% of cases being lacerations, annual savings of €4070 could be expected. However, significantly greater benefit is seen when restricting Tetanus Quick Stick use to patients <61 years,[30] where unnecessary treatment is avoided in 77% of patients and the cost per patient is reduced from €11.34 to €8.31. Selective use of the assay in this group of patients (assuming that approximately 18% of patients are >61 years) would result in an annual cost saving of approximately €13 304 for a UK emergency department. This costing model assumes that the older age group would automatically receive a toxoid booster as the tetanus seroprotection rates are inherently low.

THE INCREASING NEED FOR KNOWLEDGE OF TETANUS SEROPROTECTION STATUS

In the UK, it is assumed that all individuals born after the 1960s have undergone a full tetanus vaccination programme and, having received at least five tetanus toxoid doses, have lifelong immunity. However, recent studies indicate that this may not be the case and suggest that wound management guidelines incorporate assessment of tetanus antitoxin status for individual patients.[33]

A number of studies indicate that tetanus seroprotection rates may be lower in immigrant populations, as comprehensive immunisation programmes are not available in some areas.[20 21] WHO initiatives mean that the global incidence of tetanus has fallen dramatically in recent decades, with the number of cases reported annually having fallen as worldwide immunisation has increased to approximately 85%.[34] Despite the overall high global level of immunisation, the coverage rate in certain countries in Africa, Asia and South America is notably lower, and immigrants from such regions may have inadequate seroprotection.[34] In addition, certain westernised countries have an unexpectedly high tetanus incidence given their reported vaccination coverage—for example, on the basis of WHO data,[32] the incidence of tetanus in Poland is 0.6 cases per million despite 99% immunisation coverage. Although the overall tetanus immunisation rate in Turkey has been estimated at 90%,[34] some studies suggest that some regional levels may be substantially lower.[35] Limitations in the vaccination status in certain immigrant populations have led to the occurrence of acute tetanus in the UK in recent years.[36]

A lower incidence of seroprotection has also been noted in older individuals.[21 23 30] A general decline in immune function means that older people do not develop antibodies as quickly and that

the magnitude and persistence of the antitoxoid response are blunted.[18] As a result, careful assessment of tetanus seroprotection status is warranted in older patients to ensure that inappropriate treatment does not put them at risk of developing acute tetanus.[57 59] An additional application of the point-of-care assay could involve regularly monitoring individuals, as part of a personalised healthcare system, to ensure that tetanus protection status is effectively maintained throughout life.

Some studies have shown that patients attending an emergency department with a wound may receive unnecessary booster or HTIG doses.[21 30] The consequences of such over-immunisation are usually considered in terms of the cost implications and the risk of adverse effects.[30] The adverse effects associated with administration of tetanus booster doses usually comprise local hyperergic reactions[40] and neuritis and neuropathies, the incidence of which may be underestimated.[41] A recent report suggests that administration of tetanus toxoid to individuals who are already seroprotected may also result in a transient, attenuated booster response that compromises efficacy and may lead to the development of tolerance.[42] Should this prove to be the case, access to a rapid and effective assay for tetanus antitoxoid status will also be important in preventing overimmunisation.

CONCLUSIONS

Various studies show that questioning patients with wounds as to their tetanus immunisation status is ineffective at identifying those in need of either an antitoxoid booster or HTIG administration. This problem is probably being exacerbated by low levels of seroprotection in certain immigrant populations and may be further compromised in future older populations by the current UK tetanus management guidelines. The new point-of-care tetanus antitoxoid assay (ProTetanus) is a promising methodology that may help to clarify the seroprotection status of the individual patient. The adoption of such a test should help ensure that patients who need tetanus protection receive it and that boosters or HTIG are not given unnecessarily and should also prove to be clinically and economically beneficial. Trials of its use are required to determine its role in routine wound management guidelines. Further research is required to determine the relative amendments of UK and WHO guidelines by establishing knowledge of decreasing immunity with time after various regimes.

Funding: This work was supported by an unconditional grant from Prospect Diagnostics.

Competing interests: None.

REFERENCES

1. **Department of Health,** Scottish Executive, Health Department, Welsh Assembly Government, DHSSPS (Northern Ireland). Tetanus. In: Salisbury DM, Ramsay ME, Noakes K, eds. *Immunisation against infectious diseases—"the green book"*. London: TSO, 2006:367–84.
2. **Galbraith NS,** Forbes P, Tillett H. National surveillance of tetanus in England and Wales 1930-79. *J Infect* 1981;**3**:181–91.
3. **Centres for Disease Control and Prevention**. Summary of notifiable diseases—United States, 2005. *MMWR Morb Mortal Wkly Rep* 2007;**54**:14.
4. **Colombet I,** Saguez C, Sanson-Le Pors MJ, *et al*. Diagnosis of tetanus immunization status: multicenter assessment of a rapid biological test. *Clin Diagn Lab Immunol* 2005;**12**:1057–62.
5. **Pedalino B,** Cotter B, Ciofi degli AM, *et al*. Epidemiology of tetanus in Italy in years 1971-2000. *Euro Surveill* 2002;**7**:103–10.
6. **PHLS**. Diphtheria, tetanus and poliomyelitis in England and Wales: 1999 and 2000. *CDR* weekly **11**(34):7–9. (23 August 2001).
7. **Rushdy AA,** White JM, Ramsay ME, *et al*. Tetanus in England and Wales, 1984–2000. *Epidemiol Infect* 2003;**130**:71–7.
8. **Galazka AM.** *The immunologic basis for immunization: tetanus*. Geneva, Switzerland: World Health Organization, 1993.
9. **Health Protection Agency**. Tetanus in England and Wales: 2001 to 2004. *CDR Wkly* 2005. Report No: 15.
10. **WHO**. *Tetanus vaccine*. Geneva, Switzerland: World Health Organization, 2006. Report No: 81.
11. **Ball V,** Younggren BN. Emergency management of difficult wounds: part I. *Emerg Med Clin North Am* 2007;**25**:101–21.
12. **Rhee P,** Nunley MK, Demetriades D, *et al*. Tetanus and trauma: a review and recommendations. *J Trauma* 2005;**58**:1082–8.
13. **Simonsen O,** Bentzon MW, Kjeldsen K, *et al*. Evaluation of vaccination requirements to secure continuous antitoxin immunity to tetanus. *Vaccine* 1987;**5**:115–22.
14. **Bracebridge S,** Crowcroft N, White J. Tetanus immunisation policy in England and Wales—an overview of the literature. *Commun Dis Public Health* 2004;**7**:283–6.
15. **Simonsen O,** Badsberg JH, Kjeldsen K, *et al*. The fall-off in serum concentration of tetanus antitoxin after primary and booster vaccination. *Acta Pathol Microbiol Immunol Scand* 1986;**94**:77–82.
16. **Hainz U,** Jenewein B, Asch E, *et al*. Insufficient protection for healthy elderly adults by tetanus and TBE vaccines. *Vaccine* 2005;**23**:3232–5.
17. **Savage EJ,** Nash S, McGuinness A, *et al*. Audit of tetanus prevention knowledge and practices in accident and emergency departments in England. *Emerg Med J* 2007;**24**:417–21.
18. **Abbate R,** Di Giuseppe G, Marinelli P, *et al*. Appropriate tetanus prophylaxis practices in patients attending emergency departments in Italy. *Vaccine* 2008;**26**:3634–9.
19. **West Midlands Accident and Emergency Surveillance Centre**. Most common conditions. West Midlands Accident and Emergency Surveillance Centre 2007. http://pcpoh.bham.ac.uk/publichealth/aec/diagnosis.htm (accessed December 2007).
20. **McQuillan GM,** Kruszon-Moran D, Deforest A, *et al*. Serologic immunity to diphtheria and tetanus in the United States. *Ann Intern Med* 2002;**136**:660–6.
21. **Talan DA,** Abrahamian FM, Moran GJ, *et al*. Tetanus immunity and physician compliance with tetanus prophylaxis practices among emergency department patients presenting with wounds. *Ann Emerg Med* 2004;**43**:305–14.
22. **Maple PA,** Jones CS, Wall EC, *et al*. Immunity to diphtheria and tetanus in England and Wales. *Vaccine* 2000;**19**:167–73.
23. **Stubbe M,** Swinnen R, Crusiaux A, *et al*. Seroprotection against tetanus in patients attending an emergency department in Belgium and evaluation of a bedside immunotest. *Eur J Emerg Med* 2007;**14**:14–24.
24. **Korber A,** Graue N, Rietkotter J, *et al*. Insufficient tetanus vaccination status in patients with chronic leg ulcers. Results of a prospective investigation in 100 patients. *Dermatology* 2008;**217**:69–73.
25. **Fishbein DB,** Willis BC, Cassidy WM, *et al*. Determining indications for adult vaccination: patient self-assessment, medical record, or both? *Vaccine* 2006;**24**:803–18.
26. **Elkharrat D,** Espinoza P, De la Coussaye J, *et al*. Inclusion of a rapid test in the current Health Ministry Guidelines with the purpose of improving anti-tetanus prophylaxis prescribed to wounded patients presenting at French Emergency Departments. *Med Mal Infect* 2005;**35**:323–8.
27. **Ardelean-Jaby D,** Kaddari-Himeur F, Nkana-Tameze K, *et al*. Evaluation of a blood test TQS (Tetanos Quick Stick) used in emergency units. *Immunoanalyse Biol Specialisee* 2002;**17**:330–5.
28. **Yoon YS,** Kim EC, Lee WH, *et al*. Utility of Tetanos Quick Stick(R) test for selective tetanus prophylaxis. *J Korean Soc Emerg Med* 2004;**15**:95–101.
29. **Cavenaile JC,** Duchateau J. Use of Tetanos Quick Stick (TQS) in emergency departments [abstract]. Urgence 2005 Congress. September 2005, Paris, France.
30. **Stubbe M,** Mortelmans LJ, Desruelles D, *et al*. Improving tetanus prophylaxis in the emergency department: a prospective, double-blind cost-effectiveness study. *Emerg Med J* 2007;**24**:648–53.
31. **Cavenaile JC,** Herrero Garcia J. Interet clinique et economique du tetanos quick stick dans un sau [abstract]. Urgences 2007. May 2007, Paris, France.
32. **Brun C,** Gete E, Naibi A, *et al*. Double interest in the Tetanos Quick Stick in an emergency department [abstract]. *Urgence Pratique* 2004;**66**:47–8.
33. **Elkharrat D,** Boyer CA, Raskine L, *et al*. Impact of guidelines to alter antitetanus prophylaxis practices and reduce costs in the emergency department. *Am J Ther* 1999;**6**:203–9.
34. **WHO/IVB database.** Immunisation surveillance, assessment and monitoring Tetanus. 2007. http://www.who.int/immunization_monitoring/diseases/tetanus/en/index.html (accessed December 2007).
35. **Alp H,** Altinkaynak S, Arikan D, *et al*. Adolescent immunization rates and the effect of socio-demographic factors on immunization in a cosmopolitan city (ERZURUM) in the eastern Turkey. *Health Policy* 2006;**76**:179–85.
36. **Padmakumar B,** Date AR. Tetanus in an unvaccinated child in the United Kingdom: case report. *J Public Health (Oxf)* 2005;**27**:118–9.
37. **Two recent cases of severe tetanus**. *Euro Surveill* 2002;**7**:110–1.
38. **Kwan J,** Lim S, Allen SC. Lessons from a case of tetanus in an elderly woman. *Postgrad Med J* 1999;**75**:631–3.
39. **Beeching NJ,** Crowcroft NS. Tetanus in injecting drug users. *BMJ* 2005;**330**:208–9.
40. **Brabek E,** Kranke B, Stunzner D, *et al*. Epidemiologic data for tetanus prophylaxis. Assessment of the need for vaccination. *Wien Klin Wochenschr* 1999;**111**:851–4.
41. **Perriol MP,** Devos D, Hurtevent JF, *et al*. Flaccid tetraplegia following anti-tetanus vaccination. *Rev Neurol* 2004;**160**:942–4.
42. **Danilova E,** Shiryayev A, Kristoffersen EK, *et al*. Attenuated immune response to tetanus toxoid in young healthy men protected against tetanus. *Vaccine* 2005;**23**:4980–3.