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Tetanus immunisation in geriatric patients with accidental wounds: How much is needed?

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Summary

Objective: In the industrialised world, the elderly carry the highest risk for tetanus. This prospective serological study was performed to evaluate the reliability of tetanus immunisation histories and the antibody response to tetanus vaccinations in the elderly.

Methods: 40 individuals >65 years with a bleeding trauma were included in the study. Their tetanus vaccination histories were investigated, and accordingly a single booster (group A, n = 7), or a three dose basic immunisation against tetanus (group B, n = 33) was provided. In addition, tetanus antitoxin levels were determined.

Results: Age varied between 67 and 95 years. Inconsistencies regarding the vaccination history were found between patients and their physicians in 30% (12/40), between patient statements and vaccination documents in 57.1% (8/14) and between physicians' records and vaccination documents in 35.7% (5/14). Antitoxin titres >0.15 IU/ml were considered protective, giving a seroprevalence of 92.5%. Sensitivities and negative predictive values for tetanus immunity were 30.6% and 10.7% based on patient histories and 2.8% and 7.9% based on physicians' records. In group A, after the single booster immunisation the median titre rose from 1.2 to 14.2 IU/ml, in group B from 0.9 to 5.3 IU/ml after the first, and to 9.6 IU/ml after the third tetanus toxoid dose ($p < 0.001$ using Friedman's test).

Conclusions: In Switzerland, elderly patients with a tetanus prone wound provide an unreliable vaccination history but their seroprotection against tetanus is high. A single booster for secondary immunisation is therefore sufficient. It is not necessary to take the largely unreliable vaccination history into account.

Key words: Tetanus immunisation; wound; antitoxin titre; tetanus toxoid booster

Introduction

In industrialised countries tetanus has become a rare disease and cause of death, mainly due to the implementation of broad immunisation programmes. In the US the yearly morbidity for tetanus fell from 3.7 to 0.15 per million population between 1947 and 1997 and the case fatality decreased from 91% to 11% [1–4]. In Switzerland the incidence of tetanus decreased from 4.3 to 1.1 per million population between 1979 and 1996, while the case fatality did not change [5]. Thus, tetanus remains a rare, but feared disease, which results in prolonged hospitalisations or even death.

The epidemiology of tetanus in Switzerland between 1980 and 1989 has been investigated by Zuber et al. [6]. A total of 91 cases was recorded and a decrease in morbidity from 1.93 to 0.88 per million population was found, while 28 deaths occurred in an estimated 135 tetanus cases. Women contracted tetanus twice as often as men. The peak of morbidity was found in the age group of 75 to 79 years. The case fatality increased with increasing age. More than half of the related wounds were minor and no patient had had sufficient prior immunisation. In a large seroprevalence study in a US population, insufficient immunity against tetanus was found in 72.2% of people >70 years [7].

In Switzerland immunoprevalence to tetanus

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has not been previously investigated. However, Bula *et al*. [8] recorded the vaccination history of 145 Swiss geriatric rehabilitation patients in 1996. In only 12.4% was the vaccination history positive, with the >80-year-olds having the lowest rate. No attempt was made to verify the reliability of the information given by the patient or his relatives.

According to the international consensus, adopted by the Swiss Federal Office for Public Health, three doses of tetanus toxoid spaced within 4 to 6 weeks and 6 to 12 months, respectively, are recommended for basic immunity against tetanus. Thereafter, in the case of a contaminated wound a single booster vaccination should be given after >5 years, otherwise routinely every 10 years [9]. In the US, the Advisory Committee on Immunization Practices (ACIP) in addition suggests an actualisation of tetanus immunity status at the age of 50 years by the primary care provider [4].

While there is no doubt that adequate immunisation prevents tetanus in younger age groups, little is known about the efficacy and feasibility of these immunisation recommendations in the elderly. In addition, vaccination history does not reliably predict immune status against tetanus [10]. According to current recommendations, in the presence of a tetanus prone wound with no proof of prior immunisation, the complete three dose immunisation is required. This practice is supported by findings that point to a weaker and shorter-lived immune response with increasing age [11, 12]. Also, hyperimmunisation as a result of repeated booster vaccinations does not seem to imply a risk for relevant side effects in the elderly [13].

However, some authors have reported a sufficiently strong immune response to tetanus toxoid in the elderly [14] even with a lower dose [15]. Others have reported that in advanced age, adequate immunity could already be observed after single or double booster vaccinations [16, 17].

Due to the rarity of tetanus in our population, a case-control study to investigate how many vaccinations are needed for secondary immunisation in the elderly is not feasible.

Thus, we conducted a prospective serological study to investigate the reliability of the vaccination history and the tetanus antitoxin titres in the elderly after one to three booster doses with tetanus toxoid according to official recommendations [9].

Patients and methods

Between 12/1998 and 12/1999, the immunisation history of all elderly patients (n = 48), presenting in a geriatric clinic in Basel (Felix Platter Spital) with a tetanus prone wound was examined. Their current hospital files, their vaccination documents and their family physicians were consulted for tetanus immunisation status. Patients aged <65 years (n = 2), in the terminal stage of a consuming disease (n = 2), with documented immunisation within the previous 5 years (n = 1) or those refusing vaccination (n = 3) were excluded. Patients >64 years of age, with a tetanus prone wound and a negative vaccination history, were included (n = 40) after giving informed consent (obtained either personally or from their legal representative). Their ages ranged from 67 to 95 years with a median of 81 years, 57% were men.

The selection of patients is summarised in figure 1. Patients with documented immunisation against tetanus >5 years ago were included in group A (n = 7). Blood samples for tetanus antitoxin titres were obtained prior to and 4 weeks after the booster vaccination. This group consisted of one woman and six men. Their ages ranged between 79 and 95 years (median 87). Patients with no documented prior tetanus immunisation were included in group B (n = 33) for basic immunisation (3 doses of tetanus toxoid at time 0, 1 and 6 months). Prior to each vaccination and 4 weeks after the last vaccination blood samples for antitoxin titre analysis were taken. The age in this group ranged from 67 to 95 years (median 81), women-to-men-ratio was 22:11 and nationalities included people from Switzerland (n = 30), France, Germany and USA (each n = 1).

DiTeAnatoxal Berna® was used for vaccination in all patients. A single dose (0.5 ml) contains antigen. diphtheric. purificat. et adsorbat. with a potency of ≥2 IE (estimated value ≥4 IE) and antigen. tetanic. purificat. et adsorbat. with a potency of ≥20 IE (≥40 IE). Additives: max. 0.05 mg Thiomersal (Conversans), 2 mg Aluminiumphosphat (Adsorbens), 4.5 mg Natriumchlorid, Aqua ad iniectabilia. The vaccine was applied by the intramuscular route into the deltoid muscle.

All blood samples were centrifuged, filtered and stored at –30 °C. After collecting all samples, tetanus antitoxin titres were determined at the Berna Biotech AG as previously described [18] using a slightly modified enzyme linked immunosorbent assay (ELISA). The EU values from the tested sera were subsequently converted and expressed as International Units (IU) per ml by interpolation using the reference values. Quality in the analysis of antitoxin titres was controlled using the standard measures of the laboratory.

After concluding the experimental part of the study, the archive of the surgical emergency room of the central hospital (Kantonsspital Basel) was searched for evidence of documented tetanus vaccination in the study patients in the previous ten years. The intention was to detect vaccinations that were documented neither in the vaccination papers nor in the primary care provider's records.

The database consisted of routinely repeated titre measurements and double-checked data processing and data entry. Raw data as well as the log-transformation of titre values revealed a broad variance in standard deviations of individual measurements. Therefore, the Friedman-two-way analysis of variance was applied to test the significance of the trend of median titre development after immunisation. Further, patients' age was not normally distributed; hence medians instead of mean values were used. In agreement with two large serological surveys in the US, a titre >0.15 IU/ml was regarded as protective [7, 19].

The study protocol, including patient information and the consent forms, were presented to and accepted by the Ethical Committee of the University Hospitals of Basel.

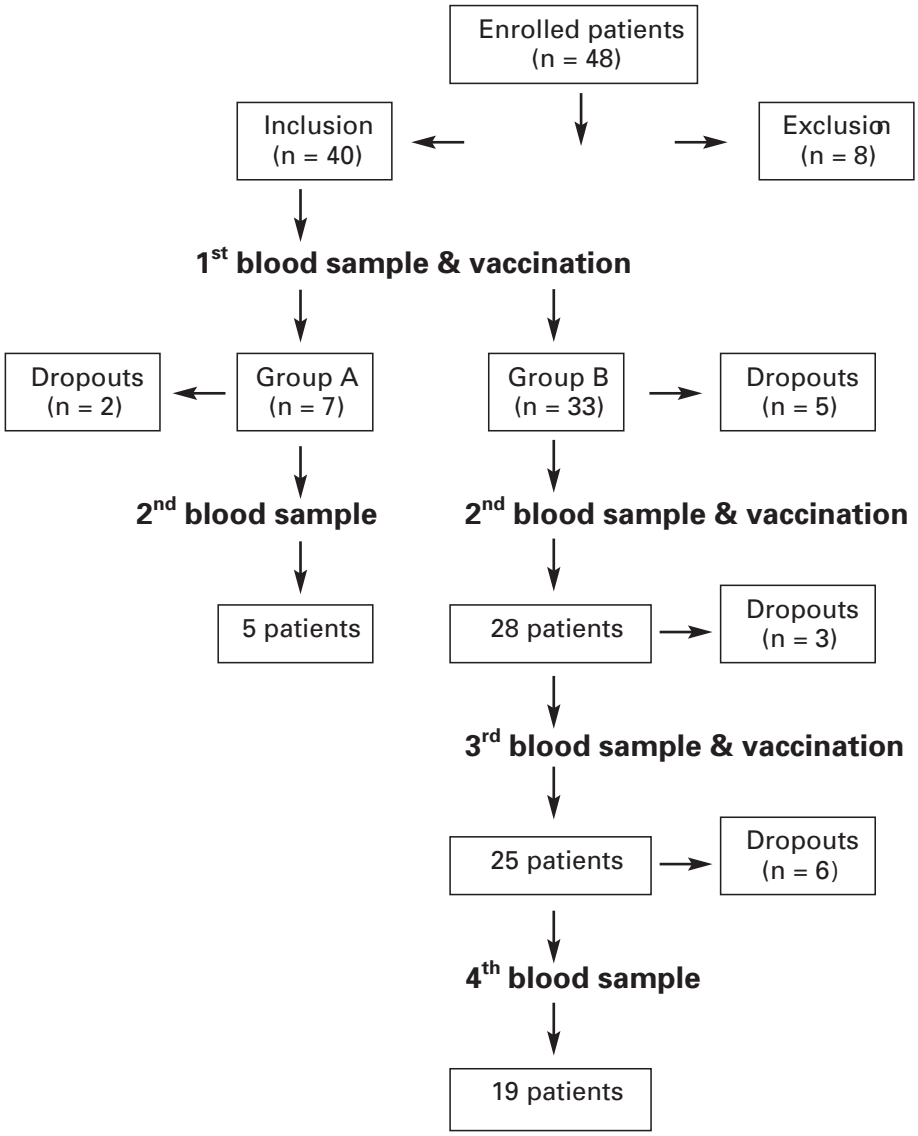


Figure 1

Patient selection in group A that is "single booster group" and group B that is "full immunisation group".

Results

Group A

Tetanus antitoxin titres before and after a single booster vaccination in patients with documented previous immunisation >5 years are shown in figure 2 (n = 7). In two patients, the second blood sample was unobtainable due to death and denied consent, respectively. One patient had a pre-existing unprotective titre, despite documented previous vaccination. Her last booster was documented in 1993. After booster vaccination she seroconverted. The remaining six patients had protective pre-existing titres. The median antitoxin titres rose from 1.5 IU/ml to 18.9 IU/ml. No side effects of vaccinations were reported.

Group B

Of the 33 patients enrolled in this group, 14 dropped out in the course of the study due to death (n = 8), denied consent (n = 2) or absence of the second dose of tetanus toxoid (n = 4). In one patient, the blood sample for the pre-existing antitoxin titre was lost. Only two of the remaining 32 patients had an unprotective pre-existing antitoxin titre (≤0.15 IU/ml). One of them seroconverted after the first vaccination, the other did not. Interestingly, the latter was later diagnosed with a consuming disease leading to death within a few weeks.

Combined seroprevalence of both groups was 92.5%, with males having a higher median antitoxin titre (1.8 IU/ml) than females (0.8 IU/ml).

Following tetanus immunisations, a broad variation in the level of the immune response was observed. In 66.7% of the patients, a median titre increase of 7.4 IU/ml (0.2–47.4) was observed after the first toxoid dose. In one patient, the titre remained stable. In 12% of the patients a median decrease of 1.1 IU/ml (0.1–2.5) was observed. In the remaining 18% of the patients, either the first or the second titre could not be obtained.

After the second toxoid dose, 24% of the patients dropped out. Only six patients (18%)

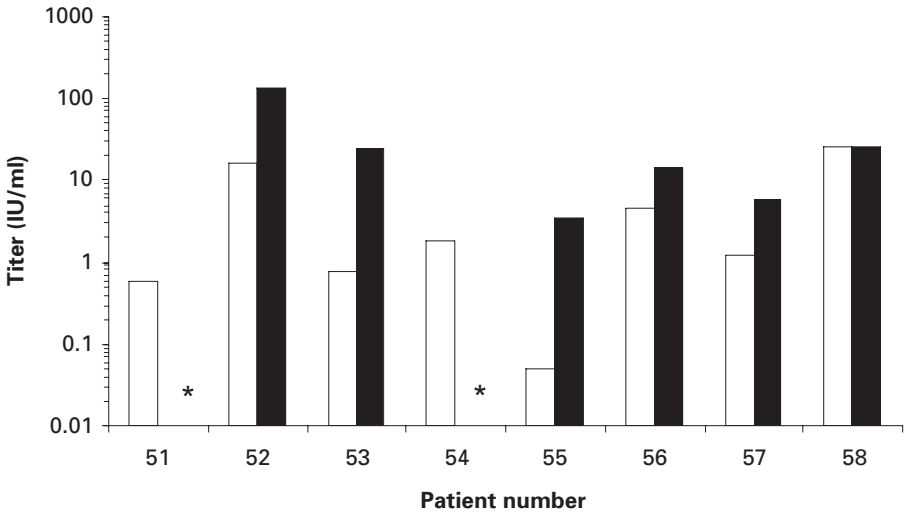


Figure 2

Tetanus antibody titres in group A before (white) and after (black) a single booster vaccination (half-logarithmic scale). * denotes «no data available».

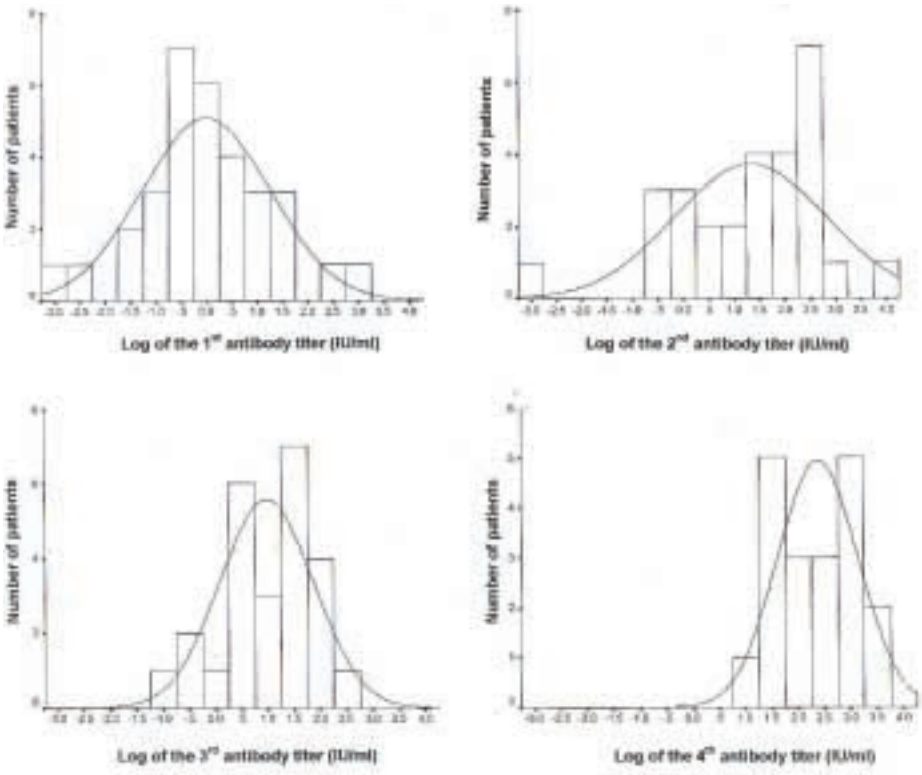


Figure 3

Individual antibody titers in group B with no documented prior immunization (n=32, half-logarithmic scale) before (upper panel left), after the first (upper panel right), after the second (lower panel left), and after the third (lower panel right) toxoid dose.

showed a slight median increase of 1 IU/ml (0.1–4.2). After the last toxoid dose, a total of 14 patients (42.4%) had dropped out. The remaining patients showed a median titre increase of 11.2 IU/ml (0.1–37.2).

Overall, all four titres could be determined in 19 patients. Of these, 18 showed an overall median titre increase of 11.9 IU/ml (1.7–39.1). The only patient with a falling titre after three vaccinations had by far the highest pre-existing antitoxin titre (15.8 IU/ml). The overall tendency to an increased titre after the first, a slight decrease after the second and a higher increase after the third toxoid dose is shown in figure 3. This trend was statistically significant according to the Friedman-Test ($p < 0.001$).

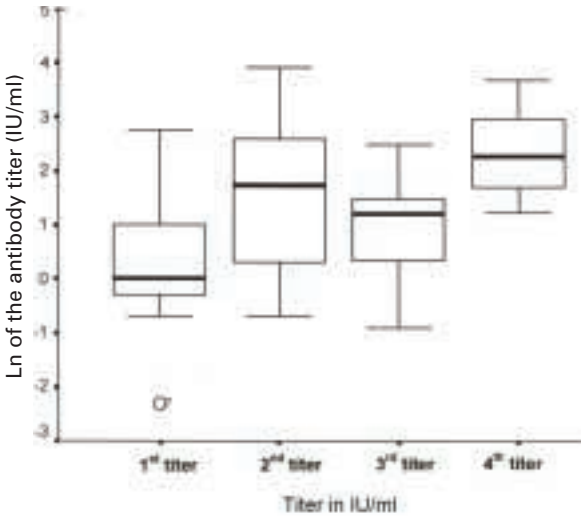
Vaccination history

The comparison of the patient's vaccination history and the physician's records with the pre-existing antitoxin titres is summarised in Table 1. Most patients who reported a negative vaccination history or whose medical records did not indicate previous vaccination, presented with a protective antitoxin titre. Immunisation histories based on patients' report and physicians' records thus indicated a high proportion of false vaccination histories. Concordance between records and pre-existing antitoxin titres was observed in only 35.9% of patient histories and in a mere10.3% of physicians' records.

The comparison of the vaccination history of the patients with the records of their primary care physicians is shown in Table 2. Again, a significant

Figure 4

Natural log of the antibody titre (IU/ml) before and after vaccination and revaccination in group B (n = 33, half-logarithmic scale).



portion was contradictory, relating predominantly to the combination of a positive history by the patient and a corresponding negative record from his physician. In the patient files of the emergency room of the central hospital, six cases were found (15%) where a study patient had received a tetanus booster during ambulatory wound care within the previous ten years. None of these patients declared this when asked about previous vaccinations. Five of these six patients could not produce their vaccination documents. One was able to present both his vaccination card and his military papers; in neither was the vaccination in the emergency room recorded. The corresponding pre-existing increase in this case was 2.7 IU/ml. A further patient had received a booster vaccination for three consecutive years (1995, 1996 and 1997). His corresponding pre-existing antitoxin increase was 1 IU/ml. In addition, another patient had been treated for wounds in 1993, 1994 and 1998 and had received a tetanus toxoid booster in 1993 and 1998. The corresponding pre-existing titre was 0.9 IU/ml. None of these vaccinations were registered by the patient or his primary health care provider.

Table 1

Clinical value of vaccination history: anamnesis versus titre (n = 39).

		titre (IU/ml)	
		negative (<0.15)	**positive (>0.15)**
Patient history	negative	3 (7.7%)	25 (64.1%)
	positive	0	11 (28.2%)
Physicians' record	negative	3 (7.7%)	35 (89.7%)
	positive	0	1 (2.6%)

Table 2

Clinical value of vaccination history: physicians' record versus patients' history (n=40)

		patient history	
		positive	**negative**
Physicians' record	positive	1 (2.5%)	1 (2.5%)
	negative	11 (27.5%)	27 (67.5%)

Discussion

The aim of this study was to determine the tetanus immune status and vaccination history in the Swiss elderly with a tetanus prone wound. A high seroprevalence for tetanus, a sufficient titre increase after the first booster dose and accordingly a high rate of excessive titres after further vaccine doses was found in this population. In addition, immunisation histories were unreliable.

One strength of our study is the heterogeneous study population in terms of age and health conditions, which reflects the geriatric population at risk, thus allowing extrapolation of the results to daily medical practice.

The limitations of the study are the relatively small size of the study population and the high drop-out rate. This latter was mainly due to the high median age of patients. Due to the small sample size, the influence of social or health characteristics on the vaccination history and the antitoxin titres could not be investigated.

The measured seroprevalence in our study was 92.5%. This value exceeds those of the elderly in other European countries, the US and Israel which are reported to vary between 28 and 53% [7, 12, 14–16, 19, 20]. This can partly be explained by the decreasing proportion of people who grew up before vaccination programmes were implemented. It is also consistent with the decreasing number of clinically confirmed cases of tetanus that were reported in Switzerland during the last 20 years from about 25 to 3 per year [5]. In our study, the median pre-existing titre level in males was more than twice as high as that in females. This corresponds to the reported higher prevalence for tetanus immunity in US males [7] and was interpreted as a result of reliable and repeated immunisations in military service.

We found a sufficient titre increase after a single tetanus booster. This has also been reported in studies from other countries [16, 17, 21]. However, it is in clear contrast to other reports describing an impaired immune response to tetanus vaccination in the elderly [11, 12, 22]. As we tested a selected geriatric hospital population with a bleeding trauma, it cannot be ruled out that these people had previously obtained more vaccinations than the elderly living at home. Therefore, it is conceivable that the excellent increase after a single

booster dose may only be valid for those elderly in a geriatric hospital and not for the general population of the elderly.

Inconsistencies between vaccination histories and immunoprevalence, as confirmed by our data, have been documented before [23]. Affirmative vaccination histories in the elderly were reliable in 50% and negative in 76% of those asked [10]. In our study, the negative predictive value of the vaccination histories was as low as 10.7%. This is the result of the high seroprevalence on the one hand and the incomplete documentation on the other hand. The low sensitivity of the patients' history in our study (30.6%) confirms previous findings about the low sensitivity and specificity of immunisation history memory, i.e. without vaccination documents [24]. In contrast, Shohat et al. [20] reported that a positive vaccination history was at least predictive for a sufficient titre rise after vaccination. According to Bula *et al.* [8], the functional status of the elderly had no influence on the reliability of the vaccination histories. Our study further revealed that the records of the family physicians, in regard to their patients' vaccination history, showed an even lower sensitivity for immunisation (2.8%) than the history given by the patient himself. This indicates inadequate patient-physician communication in respect to vaccinations, as well as insufficient record keeping by doctors. This observation has not been previously reported.

In conclusion, tetanus immunisation after trauma should be exclusively based on written immunisation documentation, as immunisation history in the elderly is unreliable. In elderly people without such documents, a single booster vaccination for secondary immunisation is adequate due to the high seroprevalence and the sufficient titre increase that we measured in our study. In general further investigation is needed in order to ascertain the seroprevalence and the rate of seroconversion after a single dose of tetanus toxoid in the community-based elderly population in Switzerland.

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References

1 Prevots R, Sutter RW, Strebel PM, Cochi SL, Hadler S. Tetanus surveillance – United States, 1989–1990. Morb Mortal Wkly Rep CDC Surveill Summ 1992;41:1–9.
2 Anonymous. Summary of notifiable diseases, United States 1994. Morb Mortal Wkly Rep 1994;43:1–80.
3 Izurieta HS, Sutter RW, Strebel PM, Bardenheier B, Prevots DR, Warthon M et al. Tetanus surveillance – United States, 1991–1994. Morb Mortal Wkly Rep CDC Surveill Summ 1997;46:15–25.
4 Bardenheier B, Prevots DR, Khetsuriani N, Wharton M. Tetanus surveillance – United States, 1995–1997. Morb Mortal Wkly Rep CDC Surveill Summ 1998;47:1–13.
5 Anonymous. Veska – medizinische Statistik, Gesamtstatistik 1978–1996. Diagnosen und Operationen. Vereinigung Schweizer Krankenhäuser, Aarau 1997.
6 Zuber PL, Schierz A, Aréstegui G, Steffen R. Tetanus in Switzerland 1980–1989. Eur J Epidemiol 1993;9:617–24.
7 Gergen PJ, McQuillan GM, Kiely M, Ezzati-Rice TM, Sutter RW, Virella G. A population-based serologic survey of immunity to tetanus in the United States. N Engl J Med 1995;332: 761–6.
8 Bula CJ, Closuit A, Meier-Padel S, Bart PA, Schluter L, Rossier P. Vaccination in elderly patients in rehabilitation: a missed opportunity? Schweiz Med Wochenschr 1996;126:2082–6.
9 Bundesamt für Gesundheit und Schweizerische Kommission für Impffragen. Impfplan für routinemässige Schutzimpfungen. Stand August 2001. Bulletin BAG 2001;37 (Suppl. VIII):1–7 .
10 Murphy SM, Hegarty DM, Feighery CS, Walsh JB, Williams Y, Coakley DP. Tetanus immunity in elderly people. Age Ageing 1995;24:99–102.
11 Burns EA, Lum LG, L'Hommedieu G, Goodwin JS. Specific humoral immunity in the elderly: in vivo and in vitro response to vaccination. J Gerontol 1993;48:B231–6.
12 Steger MM, Maczek C, Berger P, Grubeck-Loebenstein B. Immune reaction to tetanus in the elderly: what is the duration of vaccine protection? Wien Klin Wochenschr 1997;109:767–70.
13 Schroder JP, Kuhlmann WD. Avoidance of hyperergic reactions after booster tetanus toxoid vaccination [letter; comment]. Lancet 1992;340:379.
14 Simonsen O, Block AV, Klaerke A, Klaerke M, Kjeldsen K, Heron I. Immunity against tetanus and response to revaccination in surgical patients more than 50 years of age. Surg Gynecol Obstet 1987;164:329–34.
15 Bjorkholm B, Hagberg L, Sundbeck G, Granstrom M. Booster effect of low doses of tetanus toxoid in elderly vaccinees. Eur J Clin Microbiol Infect Dis 2000;19:195–9.
16 Ruben FL, Nagel J, Fireman P. Antitoxin responses in the elderly to tetanus-diphtheria (TD) immunization. Am J Epidemiol 1978;108:145–9.
17 Alagappan K, Rennie W, Kwiatkowski T, Falck J, Silverstone F, Silverman R. Seroprevalence of tetanus antibodies among adults older than 65 years. Ann Emerg Med 1996;28:18–21.
18 Richie E, Punjabi NH, Harjanto SJ, Wangsasaputral F, Sukandar M, Supriatman M et al. Safety and immunogenicity of combined diphtheria-tetanus-pertussis (whole cell and acellular)-Haemophilus influenzae-b conjugate vaccines administered to Indonesian children. Vaccine 1999;17:1384–93.
19 McQuillan GM, Kruszon-Moran D, Deforest A, Chu SY, Wharton M. Serologic immunity to diphtheria and tetanus in the United States. Ann Intern Med 2002;136:660–6 .
20 Shohat T, Marva E, Sivan Y, Lerman I, Mates A, Cohen A. Immunologic response to a single dose of tetanus toxoid in older people. J Am Geriatr Soc 2000;48:949–51.
21 Carson PJ, Nichol KL, O'Brien J, Hilo P, Janoff EN. Immune function and vaccine responses in healthy advanced elderly patients. Arch Intern Med 2000;160:2017–24.
22 Schatz D, Ellis T, Ottendorfer E, Jodoin E, Barrett D, Atkinson M. Aging and the immune response to tetanus toxoid: diminished frequency and level of cellular immune reactivity to antigenic stimulation. Clin Diagn Lab Immunol 1998;5:894–6.
23 Reid PM, Brown D, Coni N, Sama A, Waters M. Tetanus immunisation in the elderly population. J Accid Emerg Med 1996;13:184–5.
24 Heath TC, Smith W, Capon AG, Hanlon M, Mitchell P. Tetanus immunity in an older Australian population. Med J Aust 1996;164:593–6.

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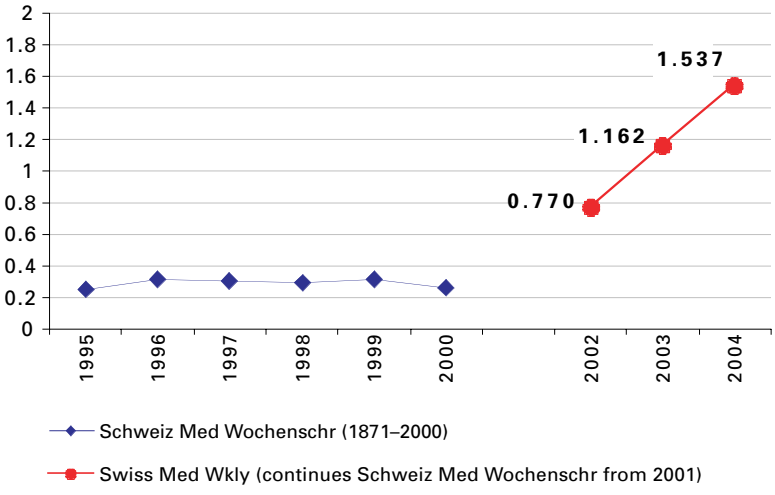

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