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# Assessment of tetanus immunity status by tetanus quick stick and anamnesis: a prospective double blind study

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*Key words: Tetanus, Tetanus Quick Stick, Prophylaxis, Emergency medicine*
*Parole chiave: Tetano, Tetanus Quick Stick, Profilassi, Medicina di emergenza*

**Abstract**

***Background:*** *In patients with wounds admitted to Emergency Departments (ED) acquiring tetanus vaccination history by interview is very unreliable. Protected patients may receive unnecessary prophylaxis and unprotected nothing. Aim of the study was to evaluate tetanus immunity status comparing the traditional anamnestic method with the Tetanus Quick Stick (TQS), a rapid immunochromatographic test.*
***Methods:*** *A double-blind prospective study was carried out in the ED of the 1,000 bed teaching hospital Umberto I in Rome. Adult patients (≥18) with wounds attending at the ED were randomly included. Tetanus immunity status was evaluated by healthcare workers (HCWs) comparing the TQS test with the anamnesis. TQS test was performed by a trained HCW and afterwards the anamnesis about tetanus immunity status was collected by another HCW unaware of the TQS result. Also cost analysis was carried out.*
***Results:*** *Overall 400 patients (242 males and 158 females) were included, mean age was 46.7 ± 20.2 years (median 44 range 18 – 109), 304 (76.0%) were italians and 96 foreigners (24.0%). Overall, 209 (52.2%) resulted TQS +, and protective immunity level was associated to lower mean age (40.1 ± 16.8 vs 53.8 ± 21,1; p<0,01). Using the anamnestic method 336 (84.0%) patients resulted "unprotected", 52 (13.0%) "partially unprotected" and 12 (3.0%) "completely protected". TQS test results showed that 154 (45.8%) out of 336 "unprotected" and 45 (86.5%) out of 52 "partially unprotected" actually had a protective antibody level. Finally two (16.7%) out of 12 "completely protected" group presented a non protective antibody level. Following only the anamnestic method 201 (50.0%) patients would have received some inappropriate treatment. Adopting TQS test in all patients would also be cost-effective saving € 1.95/patient. As tetanus immunity is inversely related to age, for <51 years old patients unnecessary treatment would have been avoided in 57.1% of patients, with a mean reduction per patient of € 7.50/patient with the TQS vs. € 12.69/patient without.*
***Conclusion:*** *The study showed that tetanus protective immunity prevalence among adult patients attending our ED is about 50% and is mainly influenced by class age. TQS use allowed to reduce drastically inappropriate tetanus vaccine and immunoglobulins booster treatment. Also TQS use reduced costs.*

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## Introduction

Tetanus is a life-threatening disease caused by the bacterium *Clostridium tetani* which usually enters the body through an acute wound, and it has been described as the "inexcusable disease" because of its serious and completely preventable nature (1).

Despite the wide availability of an excellent vaccine, tetanus cases continue to occur in Italy and notifications have been reported to be higher with respect to the rest of Europe. Although different case definitions are used in the various countries, during 2008-2012 period, Italy has been reporting the highest number of cases in the European Union with 280 (43.4%) tetanus notifications out of 645 (2, 3).

In Italy, as all industrialised countries, most cases occur among non-immunised patients after an acute wound (4, 5) and approximately 30-40% of them are fatal (5, 6).

Tetanus prophylaxis is the cornerstone of disease prevention, and when patients present in emergency department (ED) for wounds and injuries, according to the Italian legislation the decision whether or not to give prophylaxis currently depends on evaluation of the patient's immunity based on the vaccination history (7). Given the variability in tetanus immunity rates, the emergency physician needs to identify which patients require either a vaccine booster or immunoglobulin dose. Normally the immune status is identified by anamnesis, a practice that is highly imprecise (5, 8, 9, 10, 11), because many patients attending at the ED do not remember whether they were vaccinated or when they received the last prophylaxis booster.

ED physicians face a double task, as underestimation puts the patient at risk of contracting tetanus but over-immunisation increases costs and risks of secondary effects unnecessarily (5, 12, 13).

Therefore a rapid and accurate system to assess patient's immunity status would be beneficial.

Recently the Tetanus Quick Stik (TQS), a new immunochromatography-based test that can determine tetanus seroprotection status within 10 minutes using one drop of blood, has been introduced in Italy. The TQS has been evaluated in several ED worldwide and comparison with the gold standard ELISA showed >80% sensitivity and >97% specificity at identifying tetanus protective immunity status (5, 8, 9, 11, 14, 15, 16, 17, 18, 19).

Therefore we carried out a prospective double blind study in order to estimate the prevalence of tetanus protective immunity, evaluate the contribution of the TQS in the choice of tetanus prophylaxis and perform a cost analysis among adult patients attending at the ED of a teaching hospital in Rome.

## Methods

The study was carried out in the ED of the 1,000 bed teaching hospital Umberto I in Rome. We included 400 patients randomly selected from those attending for wounds treatment. Exclusion criteria were age <18 years, pregnancy, inability to provide a history (i.e. psychiatric disease, dementia or confusion, patient in traumatic shock). Consent was obtained from all participants and the study was approved by the Hospital Ethical Committee (Protocol n° 40/13).

The TQS test was performed by a trained nurse and afterwards the anamnesis about tetanus immunity status was collected by another healthcare worker (HCW) unaware of the TQS result. The evaluation by anamnestic method of the tetanus immunity status was made (unaware of the TQS result), according to the official algorithm defined by the Italian Ministry of Health (6) as follows: a patient was considered "protected" if had undergone a complete vaccination program

(three doses of tetanus antitoxin) and last booster had been administered within the previous 5 years; a patient with a complete vaccination program (three doses of tetanus antitoxin) and last booster administered > 5 years < 10 years previously would be considered "partially unprotected" and needing 1 vaccine booster; a patient with an "unknown vaccination history or not vaccinated" or "last booster >10 years previously" would be considered "unprotected" and needing administration of both immunoglobulins and vaccine.

All subjects were interviewed by means of a questionnaire containing information on demographic characteristics (age, sex, nationality), wound presentation, tetanus immunization and the TQS test result was recorded.

The TQS test requires one drop of blood that can be taken by finger prick, and detects anti-tetanus toxoid (anti TT) antibody using immunochromatography. There are no contraindications to this test. The tests were performed on whole blood and were interpreted after 10 minutes in accordance with the manufacture's recommendation. Each test panel has two distinct wells, indicated by "C" for control and "T" for test. Appearance of a pink to purple line in the control area indicates validity of the test process, whereas a line in the test area indicates the presence of tetanus immunoglobulin. The detection threshold asserted by the company is 0.2 IU/mL on whole blood (Figure 1). A training course was organized for the HCWs before starting the study. All tests were carefully preserved.

The cost of the tetanus prophylaxis based on the vaccination history was compared with the cost of prophylaxis based on the TQS result. The unit prices of tetanus-specific immunoglobulins (€ 14,20; Igantet, Grifols Italia or Tetanus Gamma, Kedrion), and TQS (€ 7.50; Erga Omnes, Italy) used were those charged for in hospital; as tetanus vaccines were not administered in the hospital, we estimated the medium price charged to a patient (€ 8,00).

Data were collected and analysed using an Epi-Info software (version 2011, Centers for Disease Control, Atlanta, GA). The chi-square test was used to examine differences between groups. Statistical significance was defined as a P value of less than 0.05.

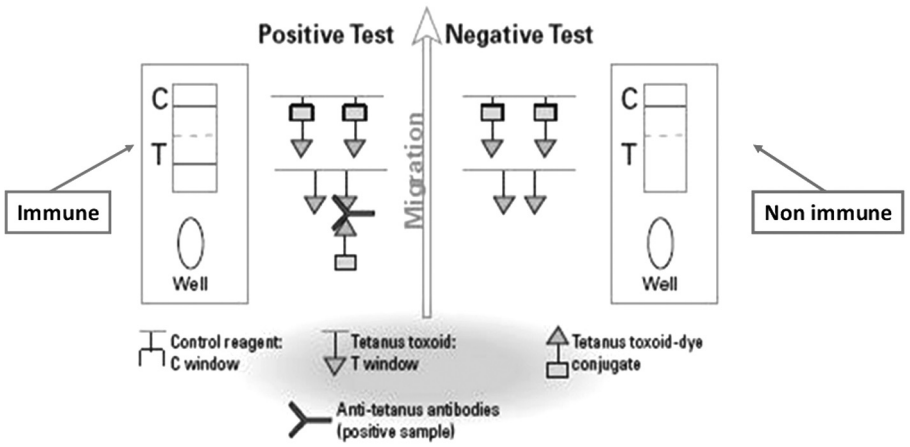


Figure 1 - Tetanus Quick Stick (TQS); principle and operating mode TQS + (patient is immune): a prink coloured band appears at the test (T) and control (C) windows TQS - (patient is not immune): test (T) window remains blank: A prink coloured band appears only at control (C) window

Univariate relationship was tested using relative risk and its 95% confidence interval ($CI_{95}$).

## Results

Overall 400 patients (242 males and 158 females) admitted to the ED for wound treatment were included in the study. The mean age of patients was 46.7 ± 20.2 years (median 44 range 18 – 109), and when considering the nationality 304 (76.0%) were Italians and 96 foreigners (24.0%). Among the latter patients came from Europe (38.6%), Asia (22.9%), America (20.8%), Africa (16.7%) and Oceania (1.1%).

Overall, according to the TQS test, patients with a protective immunity against tetanus resulted 209 (52.2%). Mean age was significantly lower in the population with a protective immunity level (40.1 ± 16.8 vs 53.8 ± 21,1; p<0,01). Immunity decreased with increasing age as shown in Figure 2. Although not significant the immunity rate was higher among men (53.7% vs. 48.7%) and italians (52.1% vs. 50.5%).

According to the anamnestic method on tetanus immunization history 336 (84.0%) patients resulted "unprotected", 52 (13.0%) partially unprotected and only 12 (3.0%) completely protected (Table 1).

When we compared anamnestic vaccination history vs. TQS test result, analysis showed that in the first two groups classified as "unprotected" 154 (45.8%) patients out of 336 had a protective antibody level. Among the third group needing only tetanus vaccination 45 (86.5%) out of 52 had a sufficient immunity level. Finally two (16.7%) patients out of 12 in the "protected" group presented a non protective antibody level (Table 1). Results showed that following only the anamnestic method 201 (50.0%) patients would have received some inappropriate treatment.

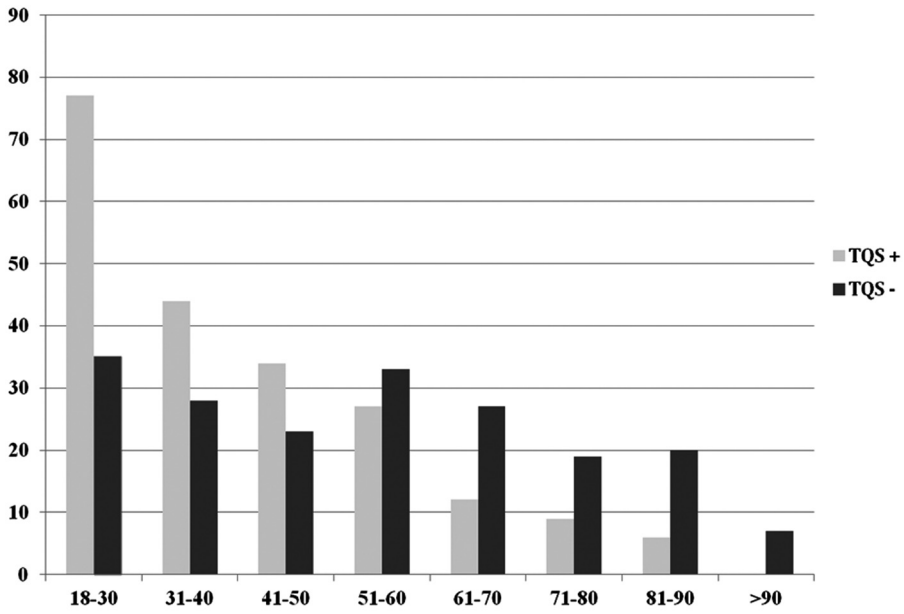


Figure 2 – Trend of tetanus immunity according to age classes

Table 1 - Determination of tetanus immunity by amnesis vs. Tetanus Quick Stick test

| Vaccination history | TQS + patients | TQS - patients | Total |
|---|---|---|---|
| Unknown vaccination or without vaccination | 75 (44.9%) | 92 (55.1%) | 167 |
| Last booster >10 years previously | 79 46.7%) | 90 (53.6%) | 169 |
| Last booster >5 years <10 years previously | 45 (86.5%) | 7 (13.5%) | 52 |
| Last booster <5 years previously | 10 (83.3%) | 2 (16.7%) | 12 |
| Total | 209 (52.2%) | 191 (47.8%) | 400 |

We also investigated the effect of TQS use on the cost of the prophylactic treatment as reported in Table 2. Adopting TQS test in all patients was cost-effective saving € 1.95/patient. Cost-benefit analysis revealed that application of TQS only in patients considered "unprotected" according to the anamnestic method and therefore needing both immunoglobulins and vaccination would have avoided unnecessary treatment in 45.8% of patients, leading to a reduction in the mean cost per patient (€ 7.50/patient with the TQS vs. € 10.17/patient without). As tetanus immunity is inversely related to age, the same analysis was performed in selected groups. For <61 years old unnecessary treatment would have been avoided in 52.7% of patients, with a mean reduction per patient of € 7.50/patient with the TQS vs. € 11.70/patient without; in <51 years old unnecessary treatment would have been avoided in 57.1% of patients, with a mean reduction per patient of € 7.50/patient with the TQS vs. € 12.69/patient without.

## Discussion

This study revealed that prevalence of tetanus protective immunity by TQS test among adult patients attending our teaching hospital in Rome was about 50%. As reported by others the single most important factor associated to immunity rate was increasing class age (3, 20). There are several reasons for this observation as lack of systematic vaccination before 1962, increased life expectancy without administration of the recommended tetanus booster and deficient immune response to vaccine associated with immunosenescence. Moreover, the abolition of obligatory national military service in Italy, and the increase of immigration may decrease vaccination coverage over the next decades.

The survey confirmed previous findings that patient's recall of their immune status for tetanus is often unreliable (21). Given the variability in seroprotection rates, the emergency medicine clinician needs to identify which patients presenting with

Table 2 - Cost analysis of Tetanus Quick Stick test vs. anamnestic method

| Vaccination history | | Inappropriate IG administration | Inappropriate vaccine administration | Total |
|---|---|---|---|---|
| | N° patients | Cost (€) | Cost (€) | Cost (€) |
| Unknown vaccination or without vaccination | 75 | € 1.065,00 | € 600,00 | € 1.665,00 |
| Last booster >10 years previously | 79 | € 1.121,80 | € 632,00 | € 1.753,80 |
| Last booster >5 years <10 years previously | 45 | - | € 360,00 | € 360,00 |
| Last booster <5 years previously | - | - | - | - |
| Total | 199 | € 2.186,80 | € 1.592,00 | € 3.778,80 |

wounds require either a booster vaccine or immunoglobulins. Traditionally this is done by anamnesis, which is a highly imprecise practice. We found impressive that, although 50% of the sample showed protective tetanus immunity, only 3% had referred at the anamnesis a protective vaccination status. In particular among the "unprotected" ("unknown vaccination history or not vaccinated" or "last booster >10 years previously"), requiring administration of immunoglobulins and vaccine, half the patients would have received an inappropriate treatment.

Excessive administration of immunoglobulins and anatoxins increases the risk of adverse effects. Clinical features associated with over-immunisation induced by anatoxin range from local reaction at the injection site to serum disease (13). Immunoglobulins are biologically active blood byproducts, and their use may be associated with possible transmission of pathogen agents (5, 12).

Also among the small group of patients referring to be "protected" with "last booster <5 years" about 16.7% resulted TQS negative.

Given the anamnestic uncertainties faced by ED HCWs when treating a wound, it would be very important to acquire a more precise diagnostic system. First, it would minimise the risk of acute tetanus by ensuring that unprotected individuals receive prophylactic immunoglobulins. Second, it would reduce the likelihood of overtreatment in those identified by anamnesis as not seroprotected (22).

In this study we compared the prophylaxis cost on the basis of vaccination history compared to that identified by the TQS. As expected (5, 11), overall TQS use enabled to decrease the mean cost per patient. However the cost saving was significantly increased for younger class age patients (<61 or <51 years age) up to about 60%, because protective immunity rate is higher.

We are aware of some limitations to our study, as it was carried out only in one center and we did not use also ELISA test as golden standard. However the sample size was among the largest in similar studies (9, 15, 16) and the population included represented almost the totality of patients admitted to the ED of a large hospital. Also several studies have demonstrated the high sensitivity and specificity of TQS test compared to ELISA.

## Conclusion

The study showed that the prevalence of tetanus protective immunity among adult patients attending our ED is about 50% and is mainly influenced by class age. The unreliability of the anamnestic method in identifying the tetanus immunity status was confirmed and TQS use allowed to reduce drastically inappropriate tetanus vaccine and immunoglobulins booster treatment. Also TQS use reduced costs.

**Competing Interests**
The authors declare that they have no competing interests.

**Riassunto**

***Valutazione della immunità antitetanica mediante tetanus quick stick ed anamnesi: studio prospettico in doppio cieco***

**Introduzione:** Nei Pronto Soccorso la valutazione dello stato di immunizzazione antitetanica dei pazienti con ferita mediante anamnesi è assai imprecisa. Pazienti realmente immuni potrebbero ricevere una profilassi non necessaria, mentre altri non protetti nulla. Finalità di questo studio era di valutare lo stato immunitario antitetanico confrontando il sistema anamnestico tradizionale con il Tetanus Quick Stick (TQS) un test immunocromatografico rapido.

**Metodi:** Uno studio prospettico in doppio cieco è stato condotto presso il Pronto Soccorso del Policlinico Umberto I di Roma. I pazienti adulti (≥18) con ferita

sono stati inclusi con metodo random. La valutazione dell'immunità antitetanica è stata effettuata dai sanitari confrontando il test TQS con l'anamnesi. Il test TQS è stato eseguito da una infermiera e successivamente è stata raccolta l'anamnesi da un altro sanitario non a conoscenza del risultato del TQS. Inoltre è stata svolta un'anali sui costi.

**Risultati:** 400 pazienti (242 maschi e 158 femmine) son stati inclusi, età media 46.7 ± 20.2 anni (mediana 44, range 18 – 109), 304 (76.0%) erano italiani e 96 stranieri (24.0%). In totale 209 pazienti (52.2%) sono risultati TQS +, ed un livello d'immunità protettiva era associata ad un'età media minore (40.1 ± 16.8 vs 53.8 ± 21,1; p<0,01). Usando il metodo anamnestico 336 (84.0%) pazienti risultavano "non protetti", 52 (13.0%) "parzialmente non protetti" e 12 (3.0%) "completamente protetti". I risultati mediante il test del TQS hanno evidenziato come 154 (45.8%) dei 336 "non protetti" e 45 (86.5%) dei 52 "parzialmente non protetti" effettivamente presentavano un livello anticorpale protettivo. Infine due (16.7%) dei 12 "completamente protetti" presentavano un livello anticorpale non protettivo. Seguendo solo il metodo anamnestico 201 (50.0%) pazienti avrebbero ricevuto un trattamento inappropriato. Inoltre utilizzando il TQS in tutti i pazienti avrebbe un costo beneficio di € 1.95/paziente. Poiché l'immunità antitetanica è inversamente associata all'età, per i soggetti con età <51 anni si sarebbe evitato un trattamento inappropriato nel 57.1% dei pazienti, con una riduzione media del costo per paziente di € 7.50/paziente con il TQS vs. € 12.69/paziente senza TQS.

**Conclusioni:** Lo studio ha evidenziato come la prevalenza dell'immunità antitetanica protettiva negli adulti che afferiscono al nostro Pronto Soccorso sia di circa il 50% ed è influenzato principalmente dall'età. L'uso del TQS ha consentito di ridurre drasticamente il trattamento inappropriato con vaccino ed immunoglobuline antitetaniche. Inoltre l'uso del TQS riduce i costi.

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