

Diagnosis of Tetanus Immunization Status: Multicenter Assessment of a Rapid Biological Test

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Diagnosis of tetanus immunization status by medical interview of patients with wounds is poor. Many protected patients receive unnecessary vaccine or immunoglobulin, and unprotected patients may receive nothing. The aim of this study is to evaluate the feasibility and accuracy of the Tetanos Quick Stick (TQS) rapid finger prick stick test in the emergency department for determining immunization status. We designed a prospective multicenter study for blinded comparison of TQS with an enzyme-linked immunosorbent assay (ELISA). Adults referred for open wounds in 37 French hospital emergency departments had the TQS after receiving standard care (emergency-TQS). TQS was also performed in the hospital laboratory on total blood (blood/lab-TQS) and serum (serum/lab-TQS). ELISA was performed with the same blood sample at a central laboratory. We assessed concordance between emergency-TQS and blood/lab-TQS by the kappa test and the diagnostic accuracy (likelihood ratios) of medical interview, emergency-TQS, and lab-TQS. ELISA was positive in 94.6% of the 988 patients included. Concordance between blood/emergency-TQS and blood/lab-TQS results was moderate ($\kappa = 0.6$), with a high proportion of inconclusive blood/emergency-TQS tests (9.8%). Likelihood ratios for immunization were 3.0 (95% confidence interval [CI], 1.8 to 5.1), 36.6 (95% CI, 5.3 to 255.3), 89.1 (95% CI, 5.6 to 1,405.0), and 92.7 (95% CI, 5.9 to 1,462.0) for medical interview, blood/emergency-TQS, blood/lab-TQS, and serum/lab-TQS, respectively. The sensitivity of the blood/emergency-TQS was 76.7%, and the specificity was 98% by reference to the ELISA. TQS use in the emergency room could make tetanus prevention more accurate if its technical feasibility were improved, and our assessment will be supplemented by a cost effectiveness study.

Tetanus is now rare in France and other industrialized countries, thanks to large, systematic immunization campaigns. However, specific mortality due to tetanus has remained around 0.4/million inhabitants since 1994 (1). Several groups within the population remain at risk of insufficient immunization coverage (9). The at-risk categories are the elderly, women, and immigrants, as reported in France (6), as well as in the United States (12). Moreover, the abolition of obligatory national military service in France and the increase of immigration are likely to decrease vaccination coverage over the next decades.

In 2000, almost 1,320,000 patients were referred to the 550 French hospital emergency departments for wounds, accounting for 12% of the 11 million referrals (7). According to guidelines issued in 1992 by the French Ministry of Health, measures to prevent tetanus in these patients (essentially, appropriate wound cleaning and the injection of immunoglobulin and/or vaccine) should depend on wound characteristics and the patient's immunization status (10). However, this algorithm is expected to change because it is difficult to apply for two

reasons. First, the severity of the wound does not accurately predict the risk of tetanus; for example, a small cut while gardening (contact with soil) may entail a greater risk than a larger wound made with a clean kitchen knife. Second, enzyme-linked immunosorbent assay (ELISA) is currently the only methodology available for evaluation of serum tetanus antitoxin levels.

The objective of this study was to evaluate the feasibility and the accuracy of a rapid blood test, Tetanos Quick Stick (TQS), used in emergency departments for the diagnosis of tetanus immunization status. The ELISA test was considered as the criterion standard. The feasibility of the test must be evaluated prior to its cost-effectiveness. A secondary objective was to compare the performance of the TQS to the performance of a reported structured clinical history for the diagnosis of vaccination status.

MATERIALS AND METHODS

Theoretical model of the problem. The World Health Organization acknowledges the ELISA test as the criterion standard, with a threshold of 0.1 IU/ml, to diagnose tetanus immunization status. This threshold is 10 times higher than the serum antitoxin level considered to be protective (8). As ELISA is not readily available in emergency departments, immunization status in this context is generally assessed from the immunization history reported by the patient, which is known to be inaccurate (13). This results in both the over- and underprescription of vaccine and tetanus immunoglobulin (mainly of human origin). The risk of communicable disease due to the injection of human blood products is small but

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should nonetheless encourage a responsible attitude to prescription, with diagnostic tests used to determine vaccine status accurately in the emergency department itself. We aim to evaluate the potential value of being able to perform laboratory tests in the emergency room that provide information about a patient's immune status. The characteristics of a test that could be incorporated into this setting should be a short turnaround time and a high availability (rural settings, nights, or weekends), technical simplicity, and ease of interpretation. However, appropriate training of doctors and nurses would be required, with supervision by a laboratory biologist. Reliability depends on tests being carried out with the same rigor applied in the laboratory, particularly in regard to quality criteria for each step.

Study design and setting. We carried out a prospective multicenter study to evaluate the feasibility and diagnostic accuracy of the Tetanos Quick Stick performed in the emergency departments of 30 French hospitals.

Eighty-two of the 550 emergency departments contacted by the French Emergency Sentinel Network agreed to participate. We selected participating centers from these 82 centers based on the following criteria: availability of a participating laboratory at or near the center and written consent of the emergency department and the laboratory for participation in the study. We selected centers so that the ratio of university to general hospitals was 1 to 3 and all types of emergency departments were represented (e.g., urban and rural).

Selection of participants. All patients over 18 years old referred to the emergency room for open wounds within 24 h of injury were prospectively included in the study after giving written informed consent and receiving appropriate treatment. Pregnant women, patients with severe injuries requiring immediate care or surgery, and patients with acute psychiatric problems requiring a special hospitalization procedure were excluded.

We wanted to recruit at least 30 centers, each including 30 patients. These numbers were considered sufficient to ensure an appropriate trade-off between representativeness of patients (largest number of patients per site) and operator multiplicity (which increases with the number of sites). Emergency physicians and biologists attended a national meeting, and they also were trained on site in the use of the TQS.

Diagnostic tests: TQS and ELISA. The Tetanos Quick Stick test was performed with blood obtained by finger prick by an attending physician or nurse from the emergency department (blood/emergency-TQS), and another blood sample was simultaneously sent to the hospital laboratory. The staffs of the emergency departments were trained in the use of the TQS.

The TQS method uses a combination of a solid phase coated with tetanus toxoid and tetanus toxoid-dye conjugate (colloidal gold). The operator takes a whole-blood sample from the patient's fingertip by means of a small pipette provided in the test kit. This sample is placed in the test sample well, to which diluent is added. The diluent flows through the absorbent pad, carrying the toxoid-dye conjugate along the chromatographic strip. A complex with antitetanus antibodies forms if such antibodies are present in the blood sample. These complexes react with the immobilized toxoid to form a pink line in the "T" (test) window. In the absence of anti-tetanus antibodies, no line appears in the test window. The excess gold conjugate binds to a control reagent immobilized in the "C" (control) window, forming a pink line, indicating that the test has been carried out correctly. The test should be read 20 min after diluent is added to the blood sample in the device.

Within 6 hours of the blood/emergency-TQS, the participating center laboratory carried out a second TQS test on a total blood sample (blood/lab-TQS) and a serum sample (serum/lab-TQS). The reference laboratory (Laboratory of Bacteriology and Virology, Lariboisière Hospital, Paris, France) performed ELISA (quantitative detection of immunoglobulin G after binding on a microplate coated with tetanus toxoid and calibration with the World Health Organization standard [Genzyme-Virotech GmbH, Rüsselsheim, Germany; distributed by In-Gen, Rungis, France]), according to the manufacturer's recommendations, for all included patients. ELISA, blood/lab-TQS, and serum/lab-TQS tests were performed blind to the results of the blood/emergency-TQS.

Data collection and processing. After inclusion, a structured clinical history was taken with (i) the main sociodemographic characteristics, (ii) a description of the wound and its risk for tetanus contamination (particularly contact with soil), and (iii) vaccination status for tetanus (items on the questionnaire are detailed in Table 1). Physicians were asked to perform the TQS test after appropriate care had been given and any prescription made, to ensure that they did not take the result of the test into account when deciding on their tetanus prevention strategy. They were encouraged to define the strategy used according to the algorithm recommended by the French Ministry of Health: (i) vaccine and immunoglobulin, in cases of no vaccination or doubts about vaccination history or severe wounds with incomplete or out-of-date (>10-year-old) vaccination; (ii) vaccine alone for minor wounds with incomplete or out-of-date (>10-year-old) vaccina-

TABLE 1. Main characteristics of patients and description of wounds

Parameter	Value ^a
Characteristics and background of patients	
Sex (% men) (<i>n</i> = 985)	692 (70.3)
Mean age (SD) in yr (<i>n</i> = 968)	43.5 (19.0)
Homelessness (<i>n</i> = 968)	23 (2.4)
Clinical history taking was possible (<i>n</i> = 986)	952 (96.6)
Wound contaminated with soil (<i>n</i> = 985)	305 (31.0)
Patients consulting during the weekend or overnight (<i>n</i> = 979)	84 (8.5)
Tetanus vaccine status as reported by clinical history	
Reliable (in the physician's opinion) (<i>n</i> = 982)	869 (88.5)
Written evidence of primary vaccination (<i>n</i> = 981)	118 (12.0)
Reported vaccine status (<i>n</i> = 980)	
Complete and certain vaccination	588 (60.0)
Incomplete vaccination	97 (9.9)
Dubious or no vaccination	282 (28.8)
Unknown previous vaccination history	13 (1.3)
Prescription for tetanus prophylaxis (<i>n</i> = 969)	
No injection	569 (58.7)
TIG ^b , tetanus toxoid	145 (14.9)
Tetanus toxoid alone, first injection	69 (7.1)
Tetanus toxoid alone, booster	186 (19.2)

^a Figures are means (SD) or numbers (%), along with total numbers of patients for whom characteristics were available (*n*).

^b TIG, tetanus immunoglobulin.

tion or severe wounds with vaccination 5 to 10 years before; and (iii) neither vaccine nor immunoglobulin in cases of more recent vaccination (less than 5 years before for severe wounds and less than 10 years before for minor wounds) (10). The prescriptions made by each physician were recorded on the standardized form used to record the clinical history.

The feasibility of the TQS test was documented on two forms. The first concerned the procedure and result of the test (required for addition of the sample to the device, use of the pipette provided, time until reading, presence of a control line, and interpretation time) as performed at the emergency department and the laboratory. The form was filled out by the operator who performed the test for each included patient. The operator reported the TQS as positive if both the "C" and "T" lines were clearly apparent, as negative if the "C" line appeared but not the "T" line, and as inconclusive if the "C" line was not apparent or if the operator was unsure whether there was a line in either the "T" or the "C" window.

The second form (feasibility form) was filled in by each operator of the emergency department at the end of the study. Operators scored the feasibility of the test in an emergency context (with respect to time delays, simplicity, and interpretation) on a scale of 1 to 8 at the end of the study.

The results of the TQS tests were reported by the operators (a physician or nurse in the emergency department and a biologist or technician at the laboratory) on standardized forms, including details concerning the performance of the test.

Statistical analyses. The likelihood that the agreement between emergency department and laboratory TQS tests was not due to chance alone was assessed by means of the kappa test.

The accuracy of vaccination status diagnosis was assessed by determining the sensitivity, specificity, and positive likelihood ratio, with 95% confidence intervals (CI), for blood/emergency-TQS, blood/lab-TQS, and serum/lab-TQS and for status reported in the clinical history. We defined sensitivity as the proportion of subjects protected against tetanus according to the ELISA test with positive TQS results. We defined specificity as the proportion of unprotected subjects (on the basis of ELISA) with negative or inconclusive TQS tests. The positive likelihood ratio was calculated for any possible result *i* of the test (positive, inconclusive, or negative) as the proportion of patients with result *i* in protected patients divided by the proportion of result *i* in unprotected patients.

ELISA was considered to be the gold standard. We used a threshold of 0.1

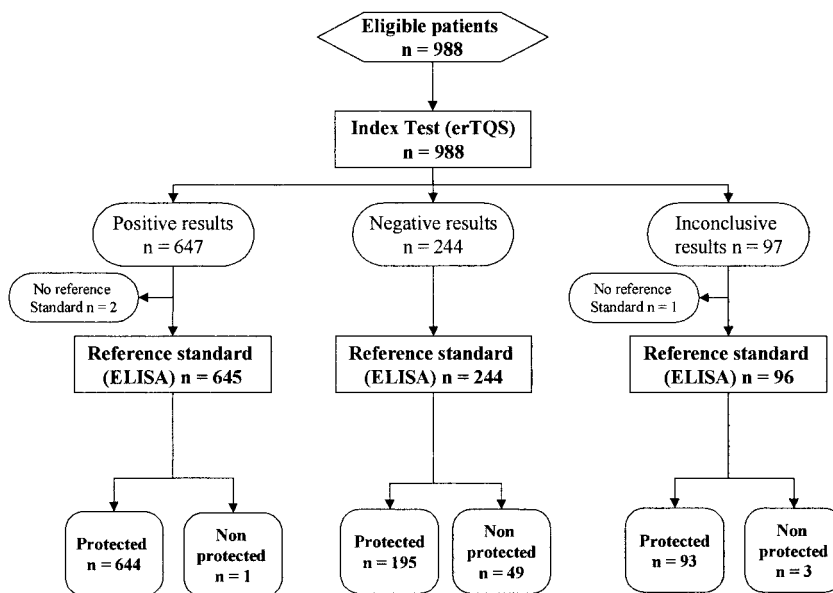


FIG. 1. Flowchart of the study.

IU/ml of serum to define positive results in ELISA and serum/lab-TQS, which implied the use of a threshold of 0.2 IU/ml of blood in the blood/emergency-TQS and blood/lab-TQS tests.

We used McNemar’s tests (1 degree of freedom) to compare the sensitivities and specificities of blood/emergency-TQS and vaccine status reported in the clinical history.

Ethical aspects. The patient was required to give informed consent for inclusion. The therapeutic strategy was not modified by the result of the test, but the patient was provided with information and advice concerning his or her vaccination status based on the results of the various tests. The study was approved by the local ethics committee and was considered to correspond to research with direct individual benefit.

Two of the authors (G.C. and I.C.) were responsible for data input and statistical analysis.

RESULTS

Characteristics of study subjects. We recruited 37 emergency departments from 8 university hospitals and 29 general hospitals. We included 988 patients in June and July 2001: 27 centers included 30 subjects or more, and 4 centers included less than 15 patients. The main clinical characteristics of the patients and the prescriptions made are recorded in Table 1. All patients in this population underwent blood/emergency TQS tests, but ELISA was not performed for three of the patients (samples were not sent to the central laboratory). ELISA showed that 932 (94.6%) patients were protected against tetanus. A flowchart of the study is presented in Fig. 1.

Main results. The blood/emergency-TQS test was inconclusive in 97 (9.8%) patients, whereas the blood/lab-TQS test was inconclusive in only 38 patients (3.8%). We compared the conditions under which the test was performed in the emergency department and the laboratory (Table 2). The main differences were the grade of the operator (physician versus nurse at the emergency department or biologist versus technician at the laboratory), use of the disposable pipette provided with the test, and time between performance and reading. The mean scores (and standard deviations) awarded by operators in the satisfaction survey (scale of 1 to 8) were 5.7 (±1.7) for

ease of blood sampling from the fingertip, 4.9 (±1.8) for ease of use of the disposable pipette, 6.7 (±1.3) for the overall simplicity of the test, and 7.3 (±1.1) for the simplicity of the test in an emergency context.

Agreement between the results obtained was excellent for the blood/lab-TQS and serum/lab-TQS (0.912; 95% CI, 0.910 to 0.914) and moderate for blood/lab-TQS and blood/emergency-TQS (0.510; 95% CI, 0.508 to 0.511). Agreement did not depend on the qualification of the operator (0.513; 95% CI,

TABLE 2. Conditions of reading and interpretation of TQS in the emergency room and in the laboratory

Reading and interpretation of test	Blood/emergency-TQS [no. (%)] ^d	Blood/laboratory-TQS [no. (%)] ^d
Operator was a physician (in the emergency department) or a biologist (in the laboratory)	747 (76.5)	355 (36.2)
Use of the disposable pipette	800 (81.4)	636 (66.6)
Reading of test within the prescribed time (20 min) as reported by operator	842 (94)	938 (97.6)
Reading after more than 20 min ^d	111 (11.4)	0
Presence of the pink calibration strip ^b	955 (96.7)	977 (99.6)
Presence of the pink test strip ^b		
Yes	627 (64.0)	774 (79.0)
Unclear	94 (9.6)	46 (4.7)
No	257 (26.4)	160 (16.3)
Interpretation of test ^c		
Positive	647 (65.5)	779 (79.6)
Inconclusive	97 (9.8)	38 (3.9)
Negative	244 (24.7)	164 (16.8)

^a Calculated from the times reported by operators on TQS forms.

^b Although the TQS test was performed in emergency departments for all 988 included patients, data reported by the operator are missing for 7 patients for the pink calibration strip and for 9 patients for the pink test strip. In these cases, the test was interpreted as inconclusive.

^c Apparent incoherence of interpretation concerning the presence of the pink test strip (more positive tests than observed pink test strips) as reported by operators (in “intention to diagnose”).

^d Agreement between the tests was 0.510 (95% CI, 0.508 to 0.511).

TABLE 3. Diagnostic accuracy of vaccination history and TQS test in the emergency department and in the laboratory, with ELISA as reference

Test	Protected ^a	Not protected ^a	Likelihood ratio (95% CI)
Structured clinical history			
Complete and certain vaccination	575	11	2.99 (1.77–5.09)
Incomplete vaccination	88	9	0.56 (0.30–1.05)
Dubious or no vaccination	250	31	0.46 (0.36–0.59)
Unknown vaccination history	11	2	0.31 (0.07–1.39)
Total	924	53	977
TQS in the emergency department ^b			
Positive	644	1	36.62 (5.25–255.3)
Inconclusive	93	3	1.76 (0.58–5.38)
Negative	195	49	0.22 (0.20–0.26)
Total	932	53	984
Total blood/lab-TQS at laboratory ^b			
Positive	779	0 ^c	89.08 (5.64–1405)
Inconclusive	36	0 ^c	4.12 (0.26–67.0)
Negative	112	52	0.12 (0.10–0.15)
Total	927	52	979
Serum/lab-TQS at laboratory ^b			
Positive	800	0 ^c	92.70 (5.87–1462)
Inconclusive	30	0 ^c	3.48 (0.219–57.0)
Negative	102	53	0.11 (0.09–0.13)
Total	932	53	985

^a Protected is defined as >0.1 IU/ml in ELISA; not protected is defined as ≤0.1 IU/ml in ELISA.

^b Serum/lab-TQS at laboratory is considered positive beyond a threshold of 0.1 IU/ml; total blood/lab-TQS in the laboratory and in emergency department are considered positive beyond a threshold of 0.2 IU/ml.

^c Likelihood ratios were calculated by taking the 0 value as 0.5.

0.512 to 0.515 for physicians and 0.526; 95% CI, 0.519 to 0.533 for nurses) or the time at which the test was performed (0.497; 95% CI, 0.479 to 0.515 for nights and weekends and 0.513; 95% CI, 0.512 to 0.515, for weekdays between 8 a.m. and 6 p.m.).

Results and likelihood ratios for TQS tests performed in the emergency department and in the laboratory are presented in Table 3, together with the vaccine status reported in the patient's clinical history. If we compared positive results with pooled inconclusive and negative results, diagnostic accuracy was higher for the blood/emergency-TQS (69% [95% CI, 66 to 72] and 98% [95% CI, 90 to 99], respectively, for sensitivity and specificity) than for clinical history (62% [95% CI, 59 to 65] and 79% [95% CI, 67 to 88]). This difference was highly significant ($P < 0.001$). The sensitivity and specificity of the blood/lab-TQS test were 84% (95% CI, 82 to 86) and 99% (95% CI, 92 to 100), respectively. The sensitivity and specificity of the serum/lab-TQS test were 86% (95% CI, 83 to 88) and 99% (95% CI, 92 to 100), respectively. The median (interquartile range) ELISA antibody titers for ELISA-positive and blood/emergency-TQS-negative and ELISA-positive and blood/emergency-TQS-positive patients were 0.7 (1.3) and 3.0 (3.3), respectively.

Prescriptions were recorded for 969 patients, three of whom could not have the ELISA test (Fig. 1): 914 (95%) were protected according to ELISA, and 52 were not. Immunoglobulin was unnecessarily given to 120 (13.1%) protected patients. If the blood/emergency-TQS had been used for decision making,

this prescription could have been avoided in 23 patients for whom positive results were obtained in this test. Eight unprotected patients (15%) received no treatment. If TQS had been used for decision making, this error would have been avoided in all these patients (all tested negative in blood/emergency-TQS).

DISCUSSION

We evaluated the TQS in a multicenter study, further validating the use of this test for the diagnosis of tetanus immunization status. This evaluation showed that vaccination status is more accurately assessed with the TQS (positive likelihood ratio, 36.6) than with a structured medical interview (positive likelihood ratio, 2.99). These results are consistent with the performance reported in a previous monocentric study, in which the sensitivity, specificity, and positive likelihood ratio of TQS were reported to be 82.6%, 97.3%, and 30.6, respectively (5), although our false-negative percentage was higher. More widespread use of this test would reduce inappropriate prescription of immunoglobulin in protected patients and would limit the proportion of unprotected patients receiving no preventive treatment.

Our study was subject to certain limitations. The reference test was not performed for three patients examined at one of the centers in the study. The other 27 patients from this center were retained in the final analysis, and their exclusion from analysis had no effect on the performance results for the blood/emergency-TQS. Four centers included less than 15 patients, and at one of these centers, the physician was less compliant with study procedures than staff elsewhere. This may account for the false-positive blood/emergency-TQS result obtained at that center.

Moderate agreement was observed between the blood/emergency-TQS and blood/lab-TQS results, probably due to the proportion of inconclusive tests, which was higher for TQS tests performed in the emergency department (9.8%) than for those performed in the laboratory (3.9%). Moreover, in a few cases, the emergency department operator reported the TQS test to be positive, despite being unsure or not seeing a pink strip in the test zone. Laboratory operators gave no such incoherent interpretations. This finding identifies several technical characteristics of the test, which may limit its feasibility in the emergency department: (i) the use of the disposable pipette may have resulted in false-negative results due to the presence of insufficient blood in the device; (ii) difficulties reading the control line were also reported by a few emergency department operators, representing 23 tests; (iii) compliance with the 20-minute interval until reading was less stringent in the emergency department than in the laboratory; and (iv) 76% of tests were performed by emergency department physicians, whereas routine tests in these departments (i.e., urinary or glucose tests) are performed by nurses well trained for these tasks. This suggests simple improvements that could be made to the test presentation: improvement of devices, such as the pipette or the lancet, and automation of reading. A quality assurance process should be defined for implementation of the TQS test in practice, taking into account all these difficulties. This should help to decrease the number of inconclusive test results and to improve diagnostic accuracy. Close collaboration

between clinicians and biologists is required for the selection of tests and for evaluation of test performance, for the training of staff and evaluation of their technical skills, for following results, and for setup and implementation of quality assurance procedures.

Almost 88.5% of the patients selected in this study reported a vaccination status that was considered by the physician to be reliable. This proportion may be lower in the real population in emergency departments. The selection criteria may also account for the high prevalence of people with protection against tetanus (as assessed by ELISA). Although this should not affect the performance of the test in terms of sensitivity, specificity, and likelihood ratios, it may result in underestimation of the impact of the blood/emergency-TQS test in preventing the inappropriate prescription of immunoglobulin.

The concordance between blood/emergency-TQS and blood/lab-TQS results was moderate, illustrating the feasibility and limitations of decentralized biological tests. The different thresholds used to interpret blood/emergency-TQS and ELISA tests may also partly account for the number of false negatives obtained with the TQS. However, the diagnostic accuracy of blood/emergency-TQS is much higher than that of the structured clinical history taken by the attending physician. Subject to a medicoeconomic study, we therefore recommend the use in France of a new strategy for evaluating serum tetanus anti-toxin levels in patients referred to emergency departments with open wounds, based on use of the Tetanos Quick Stick.

Two factors determine the risk of tetanus in patients with open wounds: immunization status and exposure risk, assessed on the basis of the wound description and the circumstances in which the wound occurred. Various strategies are therefore possible for improving the efficiency of tetanus prevention in emergency departments. The first involves investing resources in a fully implemented, regular 10-year booster program for all adults in the general population. This vaccination policy is currently recommended by the Centers for Disease Control and Prevention. The cost-effectiveness of this strategy has been analyzed in the United States (2) and criticized in the United Kingdom (4, 11). The second approach involves appropriate prevention in the case of a wound. This system is based on cleaning of the wound and on the diagnosis of immunization status. This diagnosis is often limited and can be improved by the use of rapid diagnostic tests in the emergency department. Such decentralized biological testing is of particular value if a large proportion of patients with wounds are seen during the weekend, in the evening, or during the night (8.6% in our study). Another diagnostic test has been compared with ELISA for use in emergency practice, but it was not retained for routine use because of its poor feasibility (3). Once a test is demonstrated to be valid in this setting, it is necessary to consider the impact of its use on medical prescriptions, its cost, and its acceptance by both physicians and biologists before it can be implemented in practice.

In summary, the high performance of the TQS test performed in the laboratory obtained in this multicenter study confirms the interest of this test over the usual clinical-history taking. Its use in emergency departments should not be considered without a quality assurance process and close collaboration between biologists and clinicians. We plan to complete our study with a cost-effectiveness study to compare the dif-

ferent strategies for tetanus prophylaxis treatment for wounds: test all, or test only those who are not protected. Since the French algorithm is not "appropriate" to identify tetanus-prone wounds, it will be necessary to change it.

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