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Tetanus seroprotection in people living with HIV: Risk factors for seronegativity, evaluation of medical history and a rapid dipstick test

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ABSTRACT

Objectives: Tetanus is a vaccine-preventable disease. Booster immunization is required in order to induce long-lived tetanus-toxoid (TT) specific antibody response. We investigated the prevalence and risk factors of TT seronegativity in a cohort of people living with HIV (PWH) in Belgium along with the respective performance of vaccine history and a rapid dipstick test (Tetanus Quick Stick ® or TQS) compared to ELISA testing.

Methods: PWH were prospectively enrolled and answered a questionnaire. ELISA was performed on serum or plasma using a commercial kit. A TT antibody level $\geq$ 0.15 IU / mL was considered protective. The TQS test was performed on a limited number of subjects.

Results: Three-hundred forty-four subjects were included. The prevalence of tetanus seroprotection was 84,9%. Median age was 46.7 and 68% were born outside Belgium. Antiretroviral therapy coverage was almost universal (98.5%). After multivariable analysis, two risk factors were independently associated with TT seronegativity: an education level equivalent or below than secondary school and being born outside Europe. Vaccine history was shown to be unreliable (sensitivity: 43.8%; specificity: 76.5%; positive predictive value: 91.4% and negative predictive value :19.3%). The correlation between vaccine history and tetanus seroprotection was low (kappa coefficient = 0.09). The TQS performances were good (sensitivity 86.4%, specificity 96.0%, positive predictive value 99.3%, negative predictive value 52.17%). The correlation between TQS and tetanus seroprotection was substantial (kappa coefficient = 0.61).

Conclusions: In this cohort of PWH with a high proportion of migrants, socio-demographic and educational factors were associated with TT seronegativity while HIV-related factors were not, indicating that vaccine information should be tailored to cultural and educational background. As vaccine history is not reliable, TQS could represent an efficient tool for screening of TT-seronegativity.

1. Introduction

Tetanus is a severe infectious disease caused by *Clostridium tetani*, a Gram-positive sporogenous and strict anaerobic bacillus. This bacterium is found worldwide, mainly in warm, moist soils where it can persist for many years as spores. In contact with a wound, spores release active bacilli, which in turn release various toxins including tetanospasmin, a potent neurotoxin [1,2]. In more than 80% of cases, tetanus infection becomes generalized with a mortality rate ranging between 25 and 70% [2]. Since the advent of vaccination programs and post-exposure prophylaxis, the incidence of tetanus in industrialized countries has declined considerably. In the European Union, in the last decade, between 49 and 167 cases per year have been reported, with a downward trend [3]. Anti-tetanus vaccination is critical in the prevention of the disease as, indeed, there is no natural immunity or herd immunity against this disease [1,2].

Vaccines containing tetanus toxoid (TT) can be safely administered to people with HIV (PWH) regardless of their CD4 + count. A limited number of studies have shown a lower response to anti-

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tetanus vaccination in PWH as compared to HIV-uninfected subjects [4,5]. Guidelines recommend to administer TT-containing vaccine regardless of CD4 cell count, ART use and viral load [6].

Studies in developing countries suggest that PWH may be at higher risk for complications and mortality during tetanus infection [7]. It is therefore critical to identify patients who do not have adequate protection.

In Belgium, 36% of PWH are migrants from outside Europe, mainly from Sub-Saharan Africa (29%) [8]. Low seroprotection rates against tetanus are found among migrants in various studies in Europe [9–11].

Numerous studies have shown that vaccination history does not predict the protection against tetanus [12–14]. In recent years, it has been shown that a rapid tetanus antibody test (Tetanus Quick Stick test or TQS) can help identify patients without evidence of recent tetanus toxoid vaccination requiring tetanus boosting. This test is performed by immunochromatography with a blood sample from the finger. It has been validated in the general population, mostly in patients attending emergency departments, but there is no study validating its use in PWH subjects [12,13,15,16].

The objectives of this study are to: 1) Estimate the prevalence of tetanus seroprotection in a cohort of PWH living in Belgium, 2) Identify the risk factors associated with non-protection against tetanus, 3) Assess the performance of medical history compared to ELISA testing and 4) Validate the TQS test, a rapid dipstick test in PWH.

2. Methods

2.1. Subjects & data collection

Patients were recruited prospectively at the outpatient clinic of the AIDS Reference Center of Saint-Pierre University Hospital (Brussels, Belgium) between 04/01/2018 and 15/02/2019. The study protocol was previously approved by the Ethics committee of Saint-Pierre University Hospital (BE076201734347) and each patient signed an informed consent form before inclusion.

Each patient who agreed to participate in this study responded to a questionnaire about socio-demographics characteristics and vaccine history. Data were collected using the REDCap electronic data capture tool [17] and were encoded by the investigator during an interview with the patient. The last vaccination dates were checked in the patient's vaccination cards, in the patient's medical file of the Saint-Pierre University Hospital or by contacting the general practitioner of the patient directly.

2.2. Vaccine history

Patients were interviewed about their perceived status of TT immunization. Patients were considered as up-to-date if they reported having benefited from a complete vaccine schedule in childhood and having received a TT booster dose <10 years before.

2.3. Anti-tetanus antibody ELISA

Serum or plasma samples from patients included in the study were retrieved from routine samples of up to 3 months old. After blood collection, serum was separated from blood within 4 h of collection. It was then stored at −20° C until the assay was performed. Anti-tetanus antibody (ATA) concentration was determined using a commercial ELISA assay (Vacczyme anti-Tetanus Toxoid IgG, The Binding Site, Antwerp, Belgium) in accordance with the manufacturer's recommendations. According to these, a serum concentration $\geq$ 0.15 IU / mL is considered protective. This threshold differs from that recommended by WHO that is 0.1 IU/mL. ELISA tests were performed on serum samples or plasma samples. A correlation test of ATA levels was performed on 6 plasma and serum samples and showed a significant correlation ($R = 0.93$, $p < 0.05$).

2.4. Tetanus quick stick (TQS)

The TQS test (Gamma, Beaufays, Belgium) is a immunochromatographic rapid test which detect ATA with a semi-quantitative method. It was performed by 3 different people following the manufacturer's recommendations. TQS was performed systematically starting from 1/07/2018.

2.5. Statistical analysis

This study evaluated the association between tetanus seroprotection and potential predictors of non-protection. For univariate hypothesis testing, the Fisher's exact test was used. For multivariable hypothesis tests, a logistic regression was performed. For each predictor of the multivariable analysis, the odds ratios with 95% confidence intervals was calculated. To compare continuous variables, the Mann Whitney test was used. For all analyses, a p-value < 0.05 was considered significant. Statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC, USA), GraphPad (GraphPad Software, version 5.03, San Diego California, USA) and XLSTAT software.

3. Results

3.1. Characteristics of the population

Three-hundred forty-four patients agreed to answer the questionnaire and had a recent serum or plasma sample available for testing. The characteristics of the patients included are shown on Table 1.

3.2. Tetanus seroprotection: Prevalence and risk factors

ELISA tests were performed on serum samples in 270 patients (78,5%) and on plasma samples in 74 patients (21,5%), respectively. Considering a protective level at 0.15 IU/mL, the prevalence of tetanus protection was 84.9%. Using the protection threshold recommended by WHO (0.1 IU / mL) [3], seroprotection rate was 90.1%. The median ATA level was 0.7 IU / mL. Risk factors for non-protection are depicted in Table 2. After univariate analysis, three variables were associated with tetanus seronegativity: sex, place of birth and education level. After multivariable analysis, two independent predictors of non-protection against tetanus were identified: being born outside of Europe and having an education level lower than or equivalent to secondary school. There was no association between seroprotection and current HIV viral load, current CD4 + or nadir CD4 + count, or being on antiretroviral therapy. However, the number of individuals who were not receiving ART was low (n = 5) precluding any definitive conclusion on this aspect.

3.3. Evaluation of vaccine history as a predictor of TT seroprotection

About the perception of their status of TT immunization, among the 341 patients who answered, 139 (40.8%) were considered as up-to-date, 92 (27%) did not meet these criteria and 110 (32.3%) did not know their status. Patients who did not know their immunization status were considered unprotected. Comparative results of vaccine history and ATA assessed by ELISA for each patient are presented in Supplementary Table 1. Among patients considered as up-to-date, 127/139 (91.4%) had detectable levels of ATA (>0.15 IU/mL) while among those who considered themselves as

Table 1
Characteristics of the study population (n = 344).

Characteristics	N (%)
Median age (years) (range)	46.7 [19.2-87.1]
Sex ratio M :F	232/344 (67.4)
Birthplace	
Belgium	110/344 (32.0)
Sub-Saharan Africa	129/344 (37.5)
North Africa	15/344 (4.4)
Asia	8/344 (2.3)
South America	24/344 (7.0)
North America	4/344 (1,2)
Europe (except Be)	54/344 (15.7)
Date of arrival in Belgium for non-Europeans	
> 5 years	151/180 (83.9)
< 5 years	29/180 (16.1)
Follow-up by general practitioner	
Yes	254/344 (73.8)
No	90/344 (26.2)
Level of education	
No	15/344 (4.4)
Primary school	39/344 (11.3)
Secondary school	129/344 (37.5)
University	161/344 (46.8)
Covered by health insurance	
Yes	313/344 (91.0)
No	31/344 (9.0)
HIV Transmission mode	
Vertical	10/344 (2.9)
MSM	159/344 (46.4)
Heterosexual	109/344 (31.8)
Transfusion / Nosocomial	11/344 (3.2)
IVDU	8/344 (2.3)
Unknown	46/344 (13.4)
Time since HIV diagnosis	
Median (range)	10.9 years [0.0-35.2 years]
Current CD4 + T lymphocyte count	
< 350/mm^3	21/344 (6.1)
> 350/mm^3	323/344 (93.9)
Median current CD4 + count (range)	704 /mm^3 [66-2584/mm3]
CD4+ nadir count	
< 200/mm^3	113/344 (32.8)
> 200/mm^3	231/344 (67.2)
On antiretroviral therapy	
Yes	339/344 (98.5)
No	5/344 (1.5)

not up-to-date, 163/202 (80.7%) had detectable levels of ATA (>0.15 IU/mL). Overall, vaccine history had a sensitivity of 43.8%, a specificity of 76.5%, a positive predictive value of 91.4% and a negative predictive value of 19.3%. The correlation between vaccine history and tetanus seroprotection assessed by ELISA was low (kappa coefficient = 0.09) (Table 3).

3.4. Evaluation of Tetanus Quick Stick

A rapid tetanus antibody detection test was performed in 187 patients. Comparative results of TQS and ATA assessed by ELISA for each patient are presented in Supplementary Table 2. The prevalence of tetanus protection according to TQS was 75.4% (n = 141/187). As compared to ELISA, TQS had a sensitivity of 86.4%, a specificity of 96.0%, a PPV of 99.3% and a NPV of 52.2%. Patients with a positive TQS had a median ATA level of 0.96 IU/mL whereas those with a negative TQS had a median ATA level of 0.14 IU/mL ($p < 0.001$). The correlation between TQS and tetanus levels obtained using ELISA was substantial (kappa coefficient = 0.61). Comparison of the performance of vaccine history and TQS are depicted in Table 3.

4. Discussion

In this cohort of PWH living in Belgium, a tetanus seroprotection rate of 84.88% considering a protective threshold at 0.15 IU / mL was found. Using the protection threshold recommended by WHO (0.1 IU / mL) [3], seroprotection rate was 90.1%. Seroprevalence studies in Belgium in the general population found protective levels of ATA in 64.2 to 97.0%, using the threshold of 0.1 IU / mL [12,18,19]. Few studies of TT seroprotection have been performed in PWH [9,20]. In a study conducted in France among sub-Saharan African PWH migrants on ART, 70.7% of subjects had a protective rate of ATA [20] while a study in Austria of 700 PWH patients showed a seroprotection rate of 51.0% [9].

We identified two independent predictors of non-protection against tetanus: being born outside of Europe and having a level of education lower than or equivalent to secondary school. Previous studies, performed in Europe and North-America have already reported lower rate of TT seroprotection in migrants [9–11,21]. Lower rate of seroprotection against vaccine-preventable disease among migrants is multifactorial and includes factors like lower immunization coverage in countries of origin, long journeys among different countries economic crises in host countries and lack of access to medical care precluding the administration of consecutive doses of vaccines [10]. Moreover, newcomers face barriers to immunization such as cultural factors, knowledge barriers, lack of vaccine awareness, inadequate access to health care, and vaccine hesitancy [22].

We found that an education level lower than or equivalent to secondary education is an independent risk factor for TT seronegativity. The link between education level and immunization uptake has already been reported. Lower maternal education level has been shown to be linked to lower probability of children immunization uptake [23]. A lower education level has been correlated with poorer health literacy which has been shown to impact vaccine-related behaviors [24,25].

This finding highlights the need for adequate tools adapted to the patient education level in order to enhance vaccine uptake. Low-literacy education tools have been shown to increase pneumococcal vaccine uptake in the general population in the US [26]. Similar experience was reported among Pakistan in pregnant women [27].

We found that vaccine history is not predictive in PWH. These data are consistent with other studies in the general population, mainly performed in emergency departments [12–14]. A significant proportion of the subjects (9.5%) who considered themselves up-to-date with TT vaccination were actually not protected. Considering the high mortality of tetanus, it is thus inappropriate to rely on vaccine history. In addition, a large proportion (80.7%) of patients who considered themselves as not up-to-date or did not know their status were in fact protected against tetanus.

Unlike vaccine history, TQS test was shown to be a quick and reliable test in our population. These results are in line with the validity studies carried out in the general population which show a sensitivity between 55% and 93%, a specificity between 87.2% and 100%, a positive predictive value between 92.1% and 99.6% and a negative predictive value between 42.9% and 83% [12–16].

Among patients with a negative TQS, 47.8% were actually protected against tetanus according to the ELISA assay. However, among these patients, the median tetanus antibody level was lower than those who had a positive TQS (0.27 IU/mL vs 0.96 IU/mL respectively). A booster dose may therefore also be beneficial in these patients in order to increase long-term immunity.

The TQS was shown to have good specificity (96%) and positive predictive value (99%) compared to the ELISA assay, drastically limiting the number of false positives. The only false positive identified had an antibody level of 0.12 IU / mL and thus exceeded the protection threshold of 0.1 IU / mL recommended by WHO.

Historical studies performed in the early or pre-ART era found lower antibody response following TT immunization in PWH as

Table 2
Risk Factors for Tetanus seronegativity among 344 subjects living with HIV.

Characteristics	ATA< 0.15 UI/mL n/total (%)	OR (IC 95)	p-value (Fisher test)	AOR (IC 95)	p-value
Age					
- <50 years old	26/203 (12.8)	0.65	0.17		
- > 50 years old	26/141 (18.4)	[0.34- 1.23]			
Sex					
- Male	25/232 (10.8)	0.38	**0.002**	1.67	0.14
- Female	27/112 (24.1)	(0.12-0.73)		(0.84-3.29)	
Recent pregnancy (<5 years)					
- < 5 years	1/15 (6.7)	0.20	0.11		
No recent pregnancy	26/97 (26.80)	[0.004- 1.42]			
Birthplace					
- Europe	13/164 (7.9)	3.20	**0.0004**	3.02	**0.007**
- Outside Europe	39/180 (21.7)	(1.59-6.82)		(1.35-6.76)	
Arrival date in Belgium for non-Europeans					
- < 5 years					
- > 5 years	5/29 (17.2)34/151 (22.5)	1.39(0.47-5.02)	0.63		
Level of education					
- No university	37/183 (20.2)	0.41	**0.006**	2.35	**0.02**
- University	15/161 (9.3)	(0.20-0.80)		(1.14-4.85)	
Health Insurance Coverage					
- Yes	45/313 (14.4)	0.58	0.29		
- No	7/31 (22.6)	[0.22-1.68]			
General practitioner					
- Yes	37/254 (14.6)	1.17	0.61		
- No	15/90 (16.7)	(0.56-2.33)			
Time since HIV diagnosis					
- < 5 years	5/68 (7.4)	1.50	0.59		
- > 5 years	10/94 (10.6)	(0.44-5.87)			
Current CD4 + count					
- > 350/mm^3	48/323 (14.9)	1.35	0.54		
- < 350/mm^3	4/21 (19.0)	(0.32-4.38)			
Recent viral load					
- < 50 copies/mL	51/321(15.9)	0.24	0.22		
- > 50 copies/mL	1/23 (4.3)	[0.01- 1.56]			
CD4+ count nadir					
- < 200/mm^3	22/113 (19.5)	1.62	0.15		
- > 200/mm^3	30/231 (13.0)	[0.84-3.08]			
Current antiretroviral therapy					
- Yes	52/339 (15.3)	∞	1.		
- No	0/5 (0.0)	[0.16-∞]			

Table 3
Comparison between vaccine history and Tetanus Quick Stick for tetanus seroprotection.

	Vaccine history	TQS
Concordance (kappa coefficient)	0.1	0.6
Sensitivity (%)	43.8	86.4
Specificity (%)	76.5	96
Positive predictive value (%)	91.4	99.3
Negative predictive value (%)	19.3	52.2

compared to HIV-negative individuals [4,5,28]. In our study, where ART uptake was almost universal and 93% of the subject had CD4 + count > 350/mm^3, no factor related to HIV-infection nor ART was found to predict TT seronegativity. The low number of individuals not on ART at the time of sampling limits the interpretation of this finding. Only socio-demographic and education-related factors were found to be associated with TT status suggesting that our findings could also apply to HIV-uninfected individuals with similar migration and education background.

Our study has some limitations. First, the proportion of migrants born outside Europe was higher as compared to the proportion of PWH living in Belgium (68% vs 36%), indicating that our study population was not representative of PWH living in Belgium. Secondly, we used as a reference method an ELISA specific for ATA. The ELISA was not specifically validated in PWH. However, our findings were comparable to other studies performed in PWH in Europe that also used commercial assay to detect ATA [9,20].

5. Conclusion

In this population of PWH living in Belgium, two factors were associated with a higher risk of TT seronegativity: being born outside of Europe and having an education level below university. These findings highlight the need to provide adequate information tailored to educational and cultural background in order to improve TT vaccine uptake. As previously reported in the general population, vaccine history is unreliable to predict TT seroprotection. Although the performances of rapid diagnostic test such as TQS are better than medical history, their cost-effectiveness remains to be demonstrated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.02.062.

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