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Risk factors and preventive role of vaccination in adult tetanus fatality: a systematic review of reported cases (1990-2024) and meta-analysis

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ABSTRACT

Objectives: This study identifies key risk factors for fatality among adult tetanus patients, assesses the impact of vaccination status and antibody levels on disease severity and outcomes in tetanus cases. Despite widespread vaccination, fatality rates remain high due to diagnostic and management challenges.

Design/Methods: A meta-analysis of 182 tetanus cases from 36 countries, published since 1990, was conducted. The analysis focused on risk factors such as autonomic dysfunction, opisthotonus, incubation time, diabetes mellitus, cardiovascular diseases, and dermatological conditions.

Results: Key risk factors for fatality included autonomic dysfunction, opisthotonus, shorter incubation periods, diabetes mellitus, cardiovascular diseases, and ulcers and dermatological conditions. Interestingly, fatalities occurred in patients with antibody levels above the proposed protective threshold, showing that serological evidence of immunity is not absolute. Importantly, patients with a complete vaccination history experienced less severe disease, and no fatalities were observed among those who had received a full course of childhood vaccinations.

Conclusions: The findings highlight the importance of maintaining up-to-date vaccination schedules to reduce the severity of disease and improve outcomes in tetanus cases. The results suggest that while immunity may not always prevent infection, prior vaccination significantly mitigates disease severity. Given that immunity may not be entirely protective and up-to-date vaccinations seem to improve the outcomes, prompt diagnosis and effective booster vaccinations are crucial to further reduce mortality in tetanus patients.

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Introduction

Tetanus, a severe bacterial infection caused by the bacterium *Clostridium tetani*, poses an important threat to human health. The bacterium enters the body particularly through the skin contaminated with soil, saliva, or faeces [1]. The symptoms of tetanus typically appear within a few days to several weeks after infection. Once inside the body, *C. tetani* produces a neurotoxin called tetanospasmin which affects the nervous system, causing muscle spasms and rigidity. The symptoms, disease severity and the fatality differs depending on the type of tetanus diagnosed: generalized, localized, neonatal, and cephalic [2]. According to the Global Burden of Disease report, there were more than 30,000 tetanus deaths and over 73,000 tetanus cases globally in 2019 [3]. The fatality rates of tetanus can reach up to 80% in low to middle income countries [4]. Even though tetanus is almost eliminated in developed countries with the help of established vaccination schedules there are still reported tetanus cases.

There is no diagnostic laboratory test for tetanus. Antibody levels are primarily used to assess vaccine efficacy, with the pro-

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tective threshold often cited as 0.16 IU/mL based on enzyme-linked immunosorbent assay (ELISA) and 0.01 IU/mL in in vivo neutralisation assays [5–7]. This threshold originated from animal experiment research conducted in 1937 [8] and revised in 1986 [9]. The neutralization assay is considered the "gold standard," but the lack of standardized protocols complicates comparisons across studies. Over the past three decades, advancements in ELISA technology—such as innovations in assay design, improved reagents, and automation—have significantly enhanced its diagnostic performance, as highlighted in the World Health Organization's (WHO) updated book [6]. However, ELISA remains susceptible to inaccuracies, including false positives from cross-reactivity and variability in assay conditions. Moreover, the WHO notes that the protective antibody threshold is not definitive, as cases of tetanus have been documented even in individuals with presumed protective levels. This underscores the importance of understanding the dynamics of tetanus over the past decades. In this study, we aim to provide a snapshot of global adult tetanus cases over the last 30 years, including patients with antibody levels at or above the proposed protective threshold to investigate the associated risks of higher mortality.

Methods

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) they involved adult patients (>18 years old) who were diagnosed with tetanus; (2) they were published by January 1, 1991, or later; (3) they were published in English, Turkish, or French; (4) they were case reports or case series that provided detailed information about each individual patient, including clinical presentation, underlying conditions, management, and outcomes; (5) they included both inpatient and outpatient cases of tetanus; and [6] they provided sufficient patient-level data for detailed analysis. Studies were excluded if they met any of the following criteria: (1) they were reviews, randomized controlled trials, or did not present individual patient data; (2) they reported duplicate patient data; (3) they involved mixed populations where tetanus data could not be separated from other conditions; (4) they were non-human studies.

In our study, we prioritized transparency in medical records to ensure accurate extraction of individual patient data. While the maximum number of cases obtained from any single source was six, our primary criterion for inclusion was the level of detail provided, rather than the size of the dataset.

Grouping of studies for synthesis

Studies were grouped for synthesis based on several factors. Demographic characteristics such as age, gender, and occupation were considered. Further stratification was done by country of origin, classifying studies based on whether they were conducted in high-income or low- to middle-income countries (LMICs), as per the OECD classification [10].

Disease characteristics were grouped based on the source of infection, incubation period, and anatomical location of entry. Clinical types of tetanus and clinical manifestations were also considered.

Comorbidities, including diabetes mellitus, hypertension, and other health conditions, were recorded, with exact definitions provided in Supplementary File 1. Patients described as "otherwise healthy" were presumed to have no relevant comorbidities. Clinical outcomes were analyzed based on mortality, Intensive Care Unit (ICU) admission, ICU stay duration, and the need for mechanical ventilation.

Search strategy

The literature search included PubMed, Cochrane Library, Scopus, Web of Science, and Ovid MEDLINE databases. The search was conducted on August 15, 2024, using the keywords "*C. tetani* infection," "tetanus," "case," and "adult" (Supplementary File 2). Language (English, Turkish, French) and year (January 1, 1991 and August 15, 2024) restrictions were applied.

The selection process involved two stages. First, duplicates and retrievals were removed using EndNote 20.0. Next, three independent reviewers (S.K., D.G., K.D.K.) screened the remaining articles against the inclusion criteria. No automation tools were used.

The protocol of this study was registered with PROSPERO (CRD42024612155), and the study followed PRISMA 2020 guidelines, with the corresponding file provided in Supplementary File 3.

Data collection

Data extraction was performed independently by three reviewers (S.K., D.G., K.D.K.), each completing a pre-prepared Excel sheet structured by the predefined grouping system. Following extraction, the data from all reviewers were merged for further analysis. Discrepancies were resolved through discussion to ensure consistency and accuracy in the dataset. No automation tools were used during the data collection process. Disagreements regarding study inclusion were resolved by discussion and consensus among the reviewers.

Variables and outcomes

Key outcomes of interest included mortality, ICU admission, and mechanical ventilation needs. Vaccination status was also recorded, with inclusion based on patient reports or medical records, and antibody levels if available.

Receiver Operating Characteristic analysis was performed to evaluate the predictive value of continuous variables, including age, incubation duration, and ICU stay duration, for mortality. Optimal cutoff values for each variable were determined using the Youden index to maximize sensitivity and specificity. These thresholds were then used to dichotomize the variables, assigning a value of "1" for observations above the threshold and "0" for those below.

Missing value patterns are provided in Supplementary File 4, and sensitivity analyses are detailed in Supplementary File 5. For comorbidities, if a study described patients as "otherwise healthy," it was assumed they had no other diseases; otherwise, data were used as reported. Missing or unclear data were addressed by contacting study authors for clarification whenever possible. For vaccination status, if not explicitly reported, patients were classified as having an unknown status. Unresolved discrepancies were treated as missing data. All data were handled meticulously to minimize bias and ensure the integrity of the analysis.

In this review, we conducted a risk of bias assessment for each included case report using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports [11]. The evaluation focused on key elements relevant to our research objectives. Specifically, we appraised the completeness and clarity of patient demographics, including age, gender, and relevant background characteristics; clinical presentation, capturing initial symptoms, disease onset, and diagnostic findings; and comorbidities that may influence disease progression or outcomes, such as diabetes mellitus or hypertension. Additionally, we assessed mortality outcomes and tracked the disease progress, including requirements for ICU admission and mechanical ventilation support, to evaluate disease severity and management needs.

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While the complete JBI checklist includes additional criteria, such as reporting of interventions and follow-up care, these aspects were excluded from our assessment as they were outside the scope of our primary focus on demographic, clinical, and disease course data. Two reviewers independently applied the checklist to each case report, and discrepancies were resolved through discussion to reach a consensus. No automation tools were utilized in the risk of bias evaluation process.

Statistical analysis

Statistical analyses were conducted using Stata 16.0 software (StataCorp, College Station, TX, USA) and IBM SPSS 28.0 software (IBM Corp, Armonk, NY, USA). Synthesis methods involved grouping studies based on predefined criteria, such as patient demographics, clinical features, and disease characteristics, to identify trends and patterns within the dataset. This qualitative synthesis allowed for comparisons across cases from different settings, including high-income and low- to middle-income countries, and consideration of potential influencing factors.

After data entry and curation, we performed descriptive and analytic statistics. Descriptive statistics were expressed as frequency (proportion) for categorical variables and mean ± standard deviation or median (interquartile range) for continuous variables. Univariate analyses were conducted using the chi-square test, independent samples t-test, Mann-Whitney U test.

Univariate and multivariable Cox regression analyses were used for the assessment of significant factors associated with death. Only statistically significant factors ($p < 0.05$) in univariate analyses were included in the logistic regression. The enter method was applied, with inclusion and removal criteria set at $p \leq 0.05$ and $p > 0.10$, respectively. The classification cutoff was set at 0.05. Odds ratios and 95% confidence intervals were reported to evaluate the strength of associations.

Results

Our literature search yielded a total of 3093 articles. After exclusions, a total of 154 case reports/series containing the individual patient data of 182 eligible adult tetanus patients were included (Figure 1).

In assessing the risk of bias across the included studies, publication bias was observed, with tetanus case reports more frequently published from high-income countries than LMICs. Reporting bias was identified, as over 75% of studies lacked complete data on patient demographics, vaccination history, and clinical outcomes. Demographic details were fully described in 15% of cases, while 85% provided partial descriptions, with missing information commonly related to vaccination status and social factors, such as smoking, alcohol use, and intravenous drug use. Clinical presentations were adequately detailed in 47% of reports, partially described in 44%, and insufficiently reported in 9%, with the most frequently missing

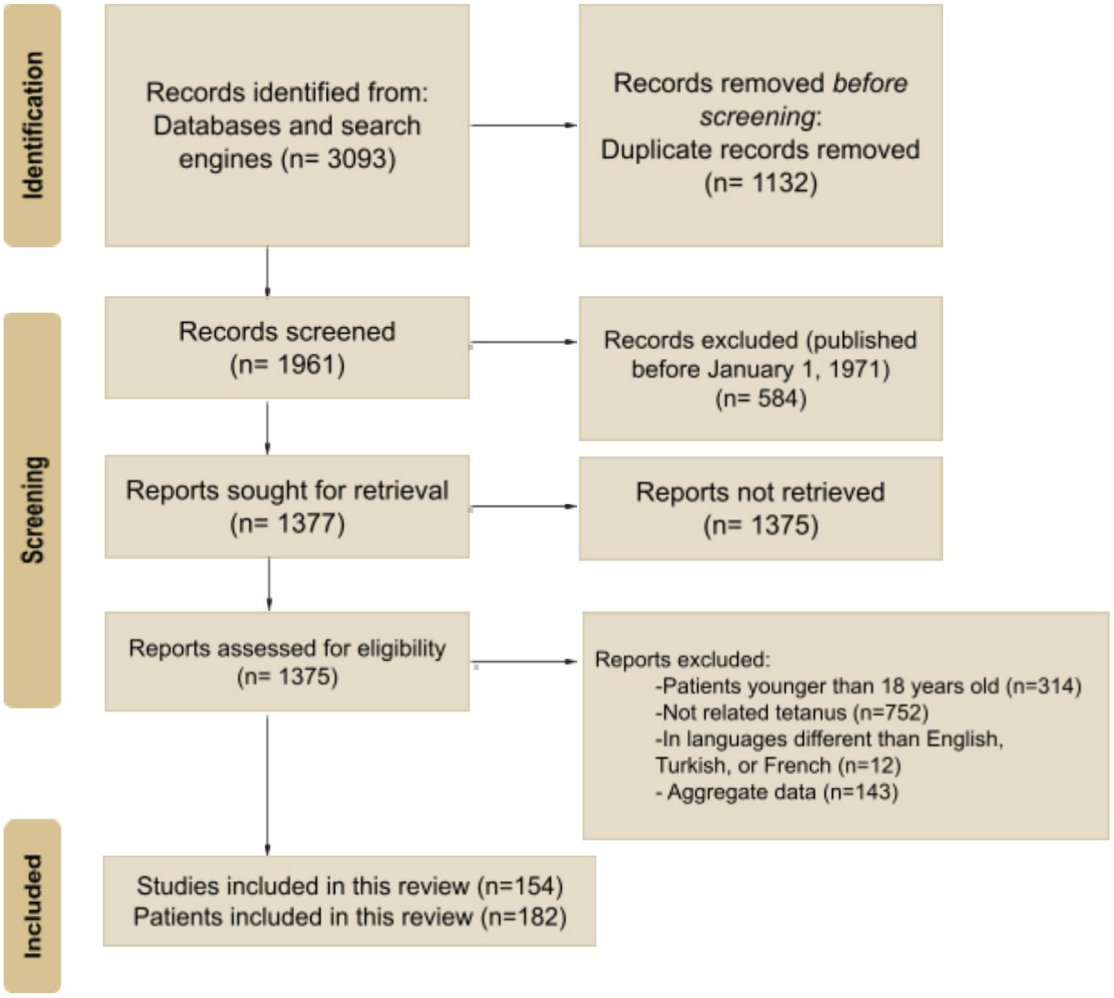


Figure 1. PRISMA Flow diagram illustrating the rigorous case report selection process employed within the study.

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Table 1
Descriptive characteristics of the study population, including demographic variables, clinical factors, and outcomes.

Variable	Observed Cases/Valid Cases	Frequency	Mean ± SD	Median (Q1-Q3)
Being female	69/182	37.90%		
Age (years)	182		55.4 ± 20.3	57.50 (39.5-74.0)
LMIC	33/182	18.10%		
Occupation				
Farmer	31/56	55.36%		
Construction worker	10/56	17.86%		
Housewife/Retired	6/56	10.71%		
Port of Entry				
Lower extremity	60/139	43.16%		
Head and face	26/139	18.70%		
Upper extremity	35/139	25.18%		
Type of tetanus				
Generalized	150/182	82.41%		
Cephalic	24/182	13.18%		
Localized	8/182	4.39%		
Clinical presentation				
Trismus	155/165	93.90%		
Stiff neck	84/113	74.30%		
Risus sardonicus	40/81	49.40%		
Rigid abdomen	46/80	57.50%		
Opisthotonus	78/107	72.90%		
Dysphagia	104/119	87.40%		
Autonomic dysfunction	92/138	66.70%		
Confusion	12/88	13.60%		
Mortality	49/182	21.40%		
Incubation period (days)	135	-	11.61 ± 16.6	8.0 (7.0-12.0)
Admission to ICU	123/182	82.00%		
Length of Stay at ICU (days)	109	-	27.36 ± 23.5	21.0 (14.0-34.5)
Mechanical ventilation	128/162	79.00%		
Comorbidities				
Immunsupression	14/64	21.90%		
Diabetes mellitus	17/72	23.60%		
Dermatologic problems	26/79	32.90%		
Hypertension	17/70	24.30%		
Cardiovascular diseases	10/61	16.40%		
Cancer	6/65	9.20%		
Recent surgery (<6 months)	21/75	28.00%		
Social factors				
IV drug use	9/32	28.10%		
Smoking	7/22	31.80%		
Alcoholism	5/19	26.30%		

Abbreviations: ICU: Intensive Care Unit; IV: Intravenous Drug.

data being abdominal rigidity and changes in mental status. Selection bias was noted, with many studies focusing on severe or atypical cases. Detection bias was minimal, as all cases were clinically diagnosed.

The mean age of the cases was 55.4 years (range, 18-93; SD: 20.36, $n = 182$), 113 patients (62.1%) were male, and 33 cases (18.1%) included in the study were reported from LMIC countries. The majority of cases have been reported from the USA, Japan, the United Kingdom, and Türkiye, collectively accounting for 44.4% of all reported cases.

Among the reported cases, 150 were generalized (82.4%), 24 were cephalic (13.1%), and eight were localized (4.3%). The autonomic dysfunction (OR: 3.5; CI:1.13-10.82; $p = 0.030$), ICU admission (OR: 21.2; CI:1.26-357.23; $p \leq 0.001$) and need for mechanical ventilation (OR: 25.2; CI:1.5-422.16; $p \leq 0.001$) were more common among generalized tetanus cases than the other types. Regardless of the tetanus type, the average incubation period was 11.61 days (IQR: 7-12; SD: 16.61; $n = 182$). Cases with incubation period over 9 days were associated with less need for ICU admissions (OR: 0.154; CI: 0.048-0.490; $p = 0.002$) and lower fatality (OR: 0.276; CI: 0.113-0.674; $p = 0.005$). Among the 182 cases included, 87 patients (47.8%) had no information about previous vaccination status, and 95 (52.2%) patients indicated their vaccination status, and 39 out of 95 (41.0%) were reported to be vaccinated at least once in their life. In patients receiving at least one dose of tetanus vaccine in their lifetime, longer incubation periods were observed ($p = 0.040$); the fatality rate did not change significantly ($p = 0.078$).

Of the 182 cases, 39 patients (21.4%) died during hospital stay. The fatality rate was not associated with being older than 68 years old (OR:0.9; CI:0.39-1.87; $p = 0.696$). The case fatality rate (CFR) in LMIC was 30.3% (10/33), whereas it was 19.4% (29/149) in high income countries (OR:1.8; CI:0.77- 4.19; $p = 0.174$).

In univariate analysis, higher CFR was found to be associated with generalized type tetanus (OR:10.5; CI:1.39-79.69; $p = 0.023$), developing stiff neck (OR:9.9; CI,1.28-77.42; $p = 0.028$), opisthotonos (OR:5.3; CI:1.16-24.22; $p = 0.031$), autonomic dysfunction (OR:3.5; CI:1.13-10.82; $p = 0.030$), incubation duration less than 9 days (OR:2.8; CI:1.33-5.71; $p = 0.005$), admission of the patient to ICU (OR:21.2; CI, 1.26-357.23; $p \leq 0.001$), ICU stay more than 21 days (OR:3.2; CI,1.59-6.64; $p \leq 0.001$), need for mechanical ventilation (OR:25.2; CI, 1.50-422.16; $p \leq 0.001$), diabetes mellitus (OR:3.8; CI,1.37-10.76; $p = 0.010$), cutaneous infections and ulcerative disorders (OR:2.7; CI, 1.13-6.65; $p = 0.026$), and cardiovascular disease (OR:4.1; CI:1.11-14.82; $p = 0.034$, Table 1). In multivariate analysis, cardiovascular disease (OR:112.3; CI, 1.41-106.81; $p = 0.023$) was associated with the increased case fatality (Table 2) whereas incubation longer than 9 days was associated with decreased CFR (OR: 0.3, CI, 0.09-0.74, $p = 0.012$) Table 3.

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Table 2
Case fatality rates according to variables.

	Total number of valid cases	Odds ratio (OR)	Confidence interval (%95)	*p value*
Demographics				
Being female	182	0.67	0.31 - 1.43	0.301
Age >68 yrs	182	0.86	0.39 - 1.87	0.696
LMIC	182	1.80	0.77 - 4.19	0.174
Clinical presentation				
Generalized type	182	10.52	1.39 - 79.69	0.023*
Trismus	165	2.43	0.30 - 19.91	0.407
Stiff Neck	113	9.94	1.28 - 77.42	0.028*
Dysphagia	119	1.18	0.24 - 5.74	0.836
Opisthotonos	107	5.30	1.16 - 24.22	0.031*
Risus sardonicus	81	1.27	0.36 - 4.55	0.713
Rigid abdomen	80	1.82	0.51 - 6.51	0.354
Autonomic dysfunction	138	3.50	1.13 - 10.82	0.030*
Confusion	88	0.60	0.07 - 5.16	0.642
Incubation time <9 days	135	2.75	1.33 - 5.71	0.005*
Prognosis				
Admission to ICU	150	21.20	1.26 - 357.2	<0.001*
≥21 days in ICU	109	3.25	1.59 - 6.64	<0.001*
Mechanical ventilation	162	25.19	1.50 - 422.1	<0.001*
Comorbidities				
Immunodeficiency	182	1.00	0.27 - 3.78	1.000
Diabetes mellitus	182	3.84	1.37 - 10.76	0.010*
Ulcers and dermatological conditions	182	2.74	1.13 - 6.65	0.026*
Hypertension	182	1.61	0.53 - 4.87	0.403
Cardiovascular diseases	182	4.06	1.11 - 14.82	0.034*
Cancer	182	0.73	0.08 - 6.41	0.773
recent surgery	182	1.17	0.40 - 3.41	0.778
Dental infections & operations	182	1.90	0.45 - 7.98	0.379
Social Life				
IV Drug use	182	3.15	0.81 - 12.37	0.099
Smoking	182	1.49	0.28 - 8.00	0.641
Alcoholism	182	2.52	0.41 - 15.66	0.321
Immune status				
Any vaccine	95	0.42	0.12 - 1.41	0.161
Full course childhood	92	0.15	0.02 - 11.94	0.007*
Booster	97	0.81	0.24 - 2.76	0.737
Last booster in < 10 years	20	0.71	0.05 - 9.50	1.000
Last booster in < 5years	20	2.33	0.16 - 34.89	0.509
Protective antibody level	16	0.71	0.51 - 1.00	1.000

Fatality rates according to different variables. In the second column, the number of valid cases after the missing data were excluded are shown. Odds ratios and the p values are calculated with Chi-square test of mortality for each variable.
Abbreviations: ICU, Intensive Care Unit; MV, Mechanical Ventilation.

Table 3
The predictors of fatality in adult tetanus cases, multivariate analyses.

	Odds ratio (OR)	Confidence interval (%95)	*p value*
Generalized type	5.39	0.61 - 47.62	0.129
Autonomic dysfunction	0.95	0.37 - 2.43	0.907
Diabetes mellitus	1.86	0.45 - 7.72	0.391
Ulcer and dermatological diseases	3.25	0.90 - 11.74	0.072
Cardiovascular diseases	12.27	1.41 - 106.81	0.023*
Incubation duration > 9 days	0.26	0.09 - 0.74	0.012*

Independent risk factors for increased mortality in patients with tetanus based on the binary logistic regression analysis.
Abbreviations: ICU, Intensive Care Unit.

Tetanus cases in vaccinated adults

Majority of the patients who have been vaccinated at least once in their lifetime (74.3%; 29 out of 39) were residing in high income countries, whereas ten of them (25.6%) were residing in LMIC. Related to booster doses, it was found that 25 patients out of 39 vaccinated patients (64.1%) had received at least one booster dose, 11 patients (28.8%) did not receive any boosters, and the booster status of three patients (7.0%) were not reported. Of the patients who reported having at least one booster dose, four individuals (20%) indicated receiving one within the last five years, while five of them (25%) reported receiving their last shot between 5 and 10 years ago. Besides, 11 patients (55%) stated that it had been more than 10 years since their last booster. Only six patients (23.0%) stated receiving a booster dose but were unable to report the timing. Having a booster was not found to be associated with less CFR (OR:0.811; CI:0.239 - 2.757; $p = 0.737$). The CFR was not found to be associated with receiving the last booster dose within the last five years or 10 years (OR:4.7; CI:0.15 - 151.4; $p = 0.444$).

Twenty-one out of 182 (11.5%) were reported to have had their full course of childhood vaccinations in their country of residence. None of the patients who completed childhood vaccinations died, whereas 16 patients out of 71 (22.5%) died who did not complete the recommended childhood vaccine series (OR:0.7; CI:0.68 - 0.87; $p = 0.017$). Three of those 16 people (18.7%) were vaccinated once

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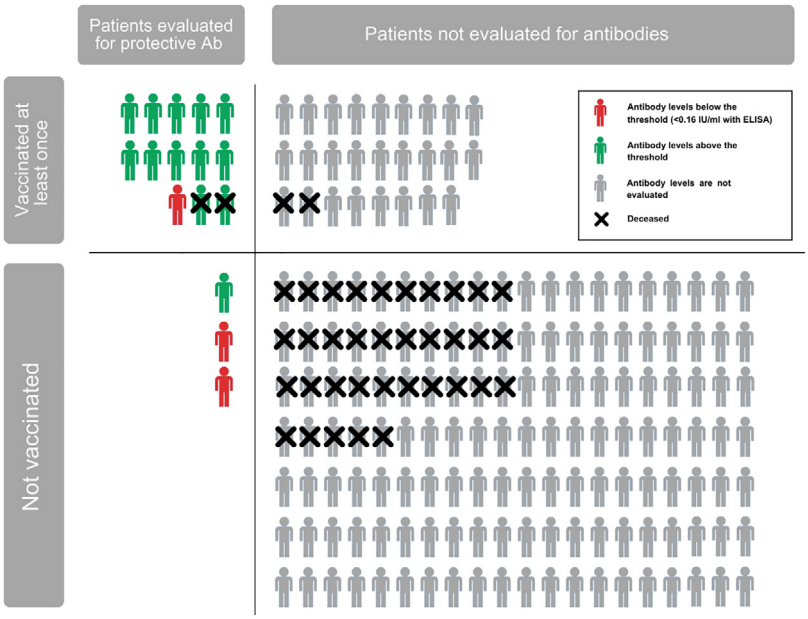


Figure 2. The figure illustrates tetanus cases from the study, with each person representing an individual. They're grouped and color-coded based on antibody levels. Red indicates levels below CDC's threshold [0.16 IU/mL by ELISA], green surpasses it, and grey denotes unassessed levels. Crossed individuals died during intervention.

in their lifetime but did not complete their childhood vaccination series and died during the hospital stay.

Patients evaluated for protective antibodies

Among all the patients, 16 individuals (8.79%) were reported to be tested for tetanus antibody level. The majority of these patients (14 individuals, 87.5%) were from high-income countries, and only one was from a LMIC, Georgia. Thirteen out of 16 (81.2%) exhibited antibody level above the specified protective threshold which was 0.16 IU/mL by standard ELISA [7]. Among the 13 individuals with protective antibody levels, two individuals died during their hospital stay; whereas, three patients lacking adequate antibodies survived (Figure 2).

It was revealed that eight of the 13 patients (61.5%) whose antibody levels were tested and detected above the protective threshold value, had received at least one dose of tetanus vaccine, four had unknown vaccination status and one had never had a tetanus vaccine in their life. Of the three individuals with antibody levels below the threshold level, one had previously received a tetanus vaccine, one had not, and the vaccination status of one was unknown. The fatality rate of patients with known vaccination status and/or antibody levels is summarized in Figure 2.

Discussion

We described the risk factors for the fatality among adult tetanus patients as generalized type, diabetes mellitus [12], autonomic dysfunction, shorter incubation time [13], experiencing opisthotonus [14], cutaneous infections and ulcerative disorders [15], and cardiovascular diseases [16]. Pre-existing cardiovascular diseases were detected as a contributor to increased mortality in tetanus patients, as it was previously described [16].

Particularly in the context of this global meta-analysis, we considered the fatality as the endpoint, which was more reliable than ICU admission. Consistent with the literature [17], there was no difference in fatality rates, ICU admission and mechanical ventilation between the patients who received the last booster vaccination five years ago and ten years ago. We couldn't detect the difference between 5 or 10 years of duration after the last booster, however our sample size was limited. Additionally, reliance on self-reported vaccination history introduces the risk of recall bias, further complicating the interpretation of booster vaccinations, the time since the last vaccination, and their correlation with immunity.

Our study indicates that individuals who received at least one tetanus vaccination during their lifetime exhibited longer incubation periods and a trend toward a less fatal disease course, though increased case fatality did not reach statistical significance. Notably, among those who had at least one vaccination, individuals who did not complete the full childhood vaccination series demonstrated less favorable outcomes. While booster doses are crucial for maintaining immunity, our results suggest that they may not fully compensate for the benefits conferred by the primary vaccination series. Therefore, ensuring full adherence to the childhood vaccination schedule is essential for mitigating disease severity, mortality, and complications.

One of the crucial findings of our study is about the tetanus antibody level interpretation. In our study, 16 patients had been detected who tested for tetanus antibody. All serum samples were collected prior to the administration of tetanus antitoxin and immunoglobulin. Almost all of those patients were residing in a high income country, but one from Georgia. The expense of antibody testing makes it challenging to conduct in LMIC, potentially explaining the limited accessibility and utilization of this method in such regions.

The comparison of case fatality rates (CFRs) among patients with protective antibody levels and those below the threshold yielded unexpected results. Notably, two individuals with antibody levels above the specified threshold died due to tetanus, while all patients lacking protective antibody levels survived. This discrepancy highlights that detected antibody levels provide limited predictive value for clinical outcomes. Furthermore, the WHO acknowledges that cases can occur even in individuals with protective antibody levels, reinforcing the notion that the utility of serum samples for antibody detection in clinical settings may be unreliable, given their limited effectiveness in predicting outcomes in practice. It is essential to emphasize that a history of vaccination

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should not exclude patients from thorough tetanus evaluation, as antibody levels can fluctuate over time. Regular booster vaccinations are crucial for maintaining high antibody concentrations and enhancing protection against tetanus. Therefore, the relationship between vaccination status and antibody levels should be interpreted cautiously, as it does not definitively indicate immunity or clinical outcome. Our findings highlight the need for improved diagnostic methodologies and a more nuanced understanding of immunity in the context of tetanus.

The other interesting finding of this meta-analysis is that shorter incubation time (<10 days) was associated with a more severe disease in consensus with the literature [18–21]. Consequently, early attention and intervention for individuals at risk of tetanus is crucial, as those who develop symptoms earlier may face a worse prognosis. Therefore, prompt medical attention is a must to improve outcomes and minimize the severity of tetanus infection. In regions with inadequate tetanus prevention and management, the need for implementation of such protocols and diagnostic algorithms become crucial. Countries without existing policies should prioritize the establishment of comprehensive guidelines for tetanus prevention for those who are at risk.

This review acknowledges potential selection and reporting biases in case reports, which are often based on clinical interest, severity, or unusual presentations, limiting the generalizability of findings. Mild or typical cases of tetanus may be underreported, and the absence of data on key factors like tetanus severity, wound debridement rates, and pneumonia incidence could further impact the analysis. While our study focuses on comorbidities as prognostic indicators, we recognize that nutritional support, infection prevention, control, and access to mechanical ventilators are also crucial for improving prognosis. It is important to underline that the lack of consideration of these factors may introduce bias when comparing studies.

The lack of control groups, small and heterogeneous case numbers, and potential for selective reporting were considered key limitations in the synthesis. Additionally, the variability in clinical presentations across cases would contribute to the inconsistency of evidence, lowering confidence in the findings. Therefore, caution is needed when interpreting these results, and further research, preferably with larger and more systematic cohort studies, is warranted.

Conclusion

This study underscores the critical importance of maintaining up-to-date vaccination schedules to reduce the severity and improve outcomes in tetanus cases. While prior vaccination significantly mitigates disease severity, serological immunity does not always prevent infection or fatality, highlighting the limitations of relying solely on antibody levels for clinical decision-making. Autonomic dysfunction, shorter incubation periods, diabetes mellitus, cardiovascular diseases, and cutaneous infections were detected as risk factors for higher tetanus fatality. These findings emphasize the need for early suspicion of tetanus, prompt diagnosis, effective booster vaccinations, and cautious interpretation of antibody levels to ensure timely and effective treatment of tetanus patients.

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Ethical approval statement

This study utilized data from previously published cases and did not involve the collection of original data or patient interaction. As such, ethical approval was not required. All data were anonymized and obtained from publicly available sources in accordance with ethical guidelines for secondary data use. The authors confirm that the study adheres to ethical principles in research, including respect for privacy and confidentiality.

Author contributions

Concept: ÖE, SK; Data collection and analysis: SK, DG, KDK, ÖE; Manuscript writing: SK, DG, ÖE

Declaration of competing interest

The authors have no competing interests to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107781.

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