NIH Public Access
Author Manuscript
J Zoo Wildl Med. Author manuscript; available in PMC 2012 August 1.

Published in final edited form as:
J Zoo Wildl Med. 2009 March ; 40(1): 95–102.

RETROSPECTIVE ANALYSIS OF WOUND CHARACTERISTICS AND TETANUS DEVELOPMENT IN CAPTIVE MACAQUES

Danielle A. Springer, V.M.D., Dipl. A.C.L.A.M, **Kathrine Phillippi-Falkenstein, M.P.H.**, and **Gary Smith, M.A., M.A., D. Phil.**
From the National Heart Lung and Blood Institute, National Institutes of Health, 9000 Rockville Pike, Building 14E, Rm 107A, Bethesda, Maryland 20892, USA (Springer); the Tulane National Primate Research Center, 18703 Three Rivers Road, Covington, Louisiana 70433, USA (Phillippi-Falkenstein); the Section of Epidemiology and Public Health, School of Veterinary Medicine, University of Pennsylvania, New Bolton Center, 382 West Street Road, Kennett Square, Pennsylvania 19348, USA (Smith)

Abstract

Traumatic wounds and access to outdoor enclosures containing soil contribute to development of tetanus in non-human primates. A retrospective matched case-control study was conducted at a primate center to evaluate these factors by analysis of medical records of animals sustaining traumatic injuries during a three year study period: 31 macaques with traumatic injuries and a clinical diagnosis of tetanus were selected as cases and 62 macaques with traumatic injuries and no diagnosis of tetanus were selected as controls. For an animal with injuries to the digits, the odds of developing tetanus were 9.6 times those of a similar animal without injuries to the digits (OR = 9.55, 95% CI = 1.56 – 58.59); with injuries to the tail, the odds of developing tetanus were 8.0 times those of a similar animal without injuries to the tail (OR = 7.95, 95% CI = 0.82 – 77.04); and with injuries in more than one location, the odds of developing tetanus were 8.5 times those for a similar animal with injuries in just one location (OR = 8.45, 95% CI = 1.01 – 70.46). A non-human primate with injuries to the leg was less likely to develop tetanus than a similar non-human primate without injuries to the leg (OR = 0.19, 95% CI = 0.03 – 1.2). Results indicated that wound location is associated with development of tetanus infection in rhesus macaques. Identification of high risk trauma cases will allow better allocation of wound management and tetanus prophylaxis in institutions, especially those housing non-human primates outdoors.

Keywords

Matched case-control study; macaque; non-human primate; tetanus; wound

INTRODUCTION

Tetanus is a severe neurologic disease caused by the potent neurotoxin of *Clostridium tetani*, a gram positive anaerobic spore forming bacillus. The spore originates in the intestines and feces of animals and humans, remains viable for years in soil and thus is extremely widespread.[33] The disease is typically caused by direct inoculation of spores into an acute penetrating skin wound.[12,25] Devitalized or infected tissue within the wound provide an anaerobic environment optimal for spore germination and subsequent toxin elaboration by vegetative organisms.[9,33]

Corresponding author: Danielle A. Springer, National Institutes of Health, 9000 Rockville Pike, Building 14E, Rm 107A, 14 Service Road West, Bethesda, Maryland 20892, USA, ds628k@nih.gov, (301) 594-6171(w), (571)241-6753(c).

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

The two major exotoxins produced by *C. tetani* are tetanolysin, a hemolytic toxin involved in local tissue invasion, and tetanospasmin, the neurotoxin responsible for the clinical manifestations of tetanus. Upon production and release within the wound, tetanospasmin is disseminated to the nervous system, binds to peripheral nerve gangliosides, and travels to presynaptic terminals of spinal cord inhibitory interneurons and inhibits the release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).[4,12,29] The resultant loss of alpha motor neuron inhibition results in sustained excitation, manifested clinically as a generalized increase in muscle tone, rigidity and spastic muscle contractions. The first typical clinical sign is trismus,[2,4,12,36] followed by neck stiffness, facial rigidity (risus sardonicus), and laryngospasm. As the disease progresses, generalized stiffness and intense muscle spasms are observed which are exacerbated by light, touch, and noise. Serious sequelae develop including; vertebral fractures, pneumonia, pulmonary embolus, nosocomial infections, cardiovascular instability, and renal failure. Mortality rates are reported between 18.2% – 59.4% in humans despite aggressive intensive care management practices. [4,25,29,36] The most common cause of death in patients not receiving mechanical ventilation is respiratory compromise due to laryngospasm or respiratory muscle paralysis.[33] In mechanically ventilated patients, dysarrthymia and cardiac arrest secondary to instability or disinhibition of the autonomic nervous system is the most frequent fatal complication.[33]

Tetanus has been reported in rhesus macaques (*Macaca mulatta)*,[10,18,19,30] squirrel monkeys (*Saimiri sciureus*),[20] and olive baboons (*Papio cynocephalus Anubis)*.[14] Non-human primates exhibit several characteristic early signs of tetanus intoxication, including torpor, reluctance to interact with others, bipedal locomotion characterized by adduction of pectoral limbs, hopping and falling, piloerection, and difficulty with food prehension characterized by meticulous chewing, grasping of food but inability to place in mouth, or trying to eat in a crouched position due to inability to grasp food.[18,20–22,24,32] Later, they develop the typical signs of trismus, rigidity, and opisthotonos observed in humans. If treatment is attempted, it typically involves basic nursing care and standard measures such as tetanus antitoxin, tetanus toxoid, high dose penicillin, muscle relaxors and tranquilizers. Non-human primates experience a high mortality rate ranging from 77–100%,[10,18–20,24,30] with the most frequent cause of death attributed to respiratory compromise.[21,22,24,30]

Non-human primates housed in outdoor groups are at most risk of tetanus infection due to close contact with contaminated soil and an increased risk of fight wounds. Rhesus macaques coexist in groups stratified by a dominance hierarchy of low to high ranked individuals and matrilines. Aggression and wounding will occur during the challenge or defense of members' social rankings within the hierarchy and during sexual competition in the breeding season.[38] Fight wounds incurred during the breeding season have been identified as a major risk factor for tetanus infection in rhesus macaques.[18] Social instability and fighting in both wild and captive macaques increases the risk of wounding and potentially tetanus infection, especially when housed on soil.

Although fight wounds have been reported as the most frequent cause of tetanus in non-human primates, no studies have examined wound character, severity, and location and tetanus development in non-human primates. The purpose of this study is to examine wound associated factors with the development of tetanus in outdoor housed non-human primates at the Tulane National Primate Research Center (TNPRC). As non-human primates that sustain injuries during aggressive encounters in outdoor group housing environments are susceptible to the development of tetanus, more information relating to the location, character, and severity of the wounds of these affected animals would provide useful insight for improving tetanus prophylaxis and wound management measures for injured non-human primates.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

During a three year period, between January 2002 –January 2005, 31 cases of outdoor non-human primates with trauma were clinically diagnosed with tetanus. Clinical records were analyzed to determine risk factors associated in the development of tetanus in wounded non-human primates by conducting a retrospective matched case-control study design.

MATERIALS AND METHODS

Criteria for selection of cases

A three year (01/01/2002–01/01/2005) retrospective case-control study was conducted using the computerized medical record system at Tulane National Primate Research Center (TNPRC) which is an AAALAC-accredited primate center located in southern Louisiana. The center's population consists of approximately 5,000 old world primates including rhesus macaques, pig-tailed macaques (*Macaca nemestrina)*, cynomolgus macaques (*Macaca fasiscularis)*, baboons (*Papio* species), white-collared mangabeys (*Cercocebus torquatus)*, vervet monkeys (*Chlorocebus aethiops)*, and Patas monkeys (*Erythrocebus patas*). Rhesus macaques represent the majority of the population and are predominantly housed in social groups in outdoor corral enclosures that range from 1/8 to 1 acre with earthen and grass substrates. Monkeys are fed commercially available primate biscuits twice daily, fresh water is available *ad libitum* via lixits, and fruits, vegetables, and other forage materials are provided several times a week. Outdoor enclosures include shelters and windbreaks to protect animals from the elements.

All wounded non-human primates with a clinical diagnosis of tetanus at presentation or within 14 days during the study period were selected as cases. Animals with a clinical diagnosis of postpartum tetanus, or tetanus without evidence of wounding were excluded from the study as the purpose of this study was determination of the nature of the wounds following a traumatic injury on the development of tetanus.

Each case was matched for age, gender, species, and date of injury with two controls defined as animals admitted to the center's infirmary for a traumatic injury but without a subsequent clinical diagnosis of tetanus. For each case, the next two animals of the same species, sex, closest age match and date of injury were selected as controls. A total of 31 case and 62 control animals were selected.

Procedures

Medical records were analyzed and data obtained regarding signalment, history, and outcome. Species, sex, age, date of injury and outcome were recorded. Based on histories provided by the attending clinician at time of presentation the following variables regarding wounds were assessed; location, severity, character, necrosis and infection. Locations of the wounds were recorded: face, neck, pinna, hip, thigh, leg, arm, cubitus, trunk, distal appendage (either hand or foot), tail, and other. The total number of wound locations per animal was then calculated. Animals sustaining wounds at one location or at more than one location were noted. Wound severity was documented as minor wound (1), moderate wound (2), or severe wound (3). Minor wounds included those wounds described as minor by the attending clinician or wounds described as superficial, abrasions, or small healing cuts and scratches. Moderate wounds included fresh, clean subcutaneous lacerations, moderate conspecific induced trauma (crushing trauma characterized by tissue swelling and contusions with subsequent deep tissue damage), and punctures described as small or minor. Severe wounds were those described as old, contaminated, or extensive subcutaneous lacerations, deep, full thickness lacerations, muscle transections, puncture wounds, bone exposure, and severe conspecific induced trauma. Wound character was recorded in six classifications; not specified (0), superficial wounds, scratches, and abrasions (1), full

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

thickness subcutaneous lacerations and flap wounds (2), full thickness deep lacerations with muscle transaction, or bone exposure, including puncture and bite wounds (3), female trauma (4), and hematoma (5). Lastly, whether or not a wound was necrotic or infected was also noted.

Statistical analyses

Data were analyzed by use of Stata Statistical Software [Stata Corporation, College Station, Texas, USA].34 This study was a matched case-control so conditional logistic regression was the appropriate model. A preliminary univariate screen of all exposures was performed to select those that would be included in the final multivariate analysis. In the univariate analysis, odds ratios calculated using standard conditional logistic regression methods were used to measure the association between each independent categorical variable and the outcome of interest (tetanus). The significance of univariate associations was determined by use of the likelihood ratio chi-square statistic. All exposures associated with tetanus in the univariate analysis at a value of $p < 0.25$ were chosen for inclusion in the multivariate logistic regression analysis. A value of $p < 0.25$ was chosen to avoid too rigorous initial selection among variables.16 Thereafter, the components of the multivariate model were determined by a combination of purposeful backwards model-selection and an automated step-wise backwards model selection process. The order in which the contribution of an independent variable was evaluated in the purposeful selection procedure was based on an examination of the Wald statistic for that variable; variables with a Wald statistic that was greater than the absolute value of 2 were considered in order of magnitude. After selection and removal of the variable, the new model was compared with the old model by the use of the likelihood ratio χ^2 test. Following the recommendation by Hosmer and Lemeshow16, a variable was permanently excluded from the model if $p > 0.15$ for the likelihood ratio χ^2 test unless its removal caused >50% alteration in the magnitude of the odds ratios for the remaining variable.

Clinically plausible interaction terms were defined and included in the main effects model. Individual interaction terms were examined in a step-wise manner and deleted or retained using criteria already stated.

A single overall goodness of fit statistic for matched case control studies is difficult to compute16. Therefore, the scheme proposed by Hosmer and Lemeshow16 was followed in which we examined the sensitivity of the fit of the final conditional logistic regression model to individual case-control pairs. Two diagnostic statistics were involved: these were the change in the Pearson chi-squared test statistic after deletion of each covariate pattern ($\Delta\chi^2$, used to identify covariate patterns that were poorly fit) and the Prebigon influence statistic ($\Delta\beta$, used to identify covariate patterns that had a large influence on the estimated parameters of the model). Both statistics were calculated using the methods recommended by Hosmer and Lemeshow16 for conditional logistic regression models with 1 to M matching (where M = 2). Particular strata within covariate patterns were examined more thoroughly if the corresponding value $\Delta\chi^2$ was > 4 or if $\Delta\beta$ was > 1. The data for animals in these strata were evaluated for any indication that might be any clinical justification for removing these strata from the analysis.16

RESULTS

The study population consisted of 31 case animals: 22 female and eight male rhesus macaques (*Macaca mulatta*) and one female pig-tailed macaque (*Macaca nemistrina).* The female rhesus macaques ranged in age from one to 16 years and the male rhesus macaques ranged in age from one to six years. The single female pigtailed macaque case was 11 years of age. All cases of tetanus occurred in the rhesus and pigtailed macaque breeding colonies

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

housed in outdoor enclosures. Most cases occurred in October (peak) through December (rhesus breeding season) and were predominately in five to seven year old females. The 62 macaques comprising the control population were subsequently matched for age, sex, date of injury and species with the aforementioned study animals.

Eight additional animals were diagnosed with clinical tetanus during the study period, but because no traumatic injuries or wounds were noted in the clinical records of these animals they were excluded from the study. Four of these animals were adult female postpartum pigtailed macaques.

The results of the univariate analysis are provided (Table 1). Nine variables satisfied the criteria for inclusion in the initial multivariate model. Seven of them described whether or not there were injuries to the face, pinna, leg, elbow, digits, hand or foot, and tail (face1, pinna1, leg1, elbow1, digits1, handfoot1, tail1). One described whether there were injuries in one - or in more than one - of the defined locations (locnum1), and one was an index of the severity of the injuries (sever3) (Table 1). Four of these nine variables survived the subsequent selection process (digits1, tail1, leg1 and locnum1) (Table 2). None of the tested interaction terms were retained in the final model. Examination of the diagnostic statistics revealed four strata with extreme values, however re-examination of the original data for each of the patients in these strata showed no obvious reason to exclude them from the analysis so the results presented here include data from these patients.

For a macaque with injuries to the digits, the odds of developing tetanus were 9.6 times those for a similar animal without injuries to the digits. For a macaque with injuries to the tail, the odds of developing tetanus were 8 times those for an animal without injuries to the tail. Finally, for a macaque with injuries in more than one location, the odds of developing tetanus were 8.4 times those for a similar animal with injuries in just one location. A macaque with injuries to the leg was less likely to develop tetanus than a similar animal without injuries to the leg (OR = 0.2).

DISCUSSION

In the analysis of these cases of tetanus in non-human primates with traumatic injuries, factors involving wound location were associated with the development of tetanus while factors of wound severity, character, and whether or not the wound was infected or necrotic were not associated.

The majority of cases observed in this study occurred in the outdoor rhesus macaque breeding field cages and corrals during the breeding season and reflects that fighting during the mating season and housing environments containing soil may contribute to the susceptibility of macaques to tetanus. Tetanus cases in rhesus macaques have been most frequently reported during the breeding season, coinciding with the time of most severe wounding due to competitive mating behaviors.[18,20,30] In fact, fight wounds occurring during the mating season have been identified as the most important contributing factor for tetanus infection in free living rhesus macaques on the island of Cayo Santiago,[18] a large population for which tetanus was the most frequent cause of mortality.[18,19,24,30] In addition, most cases of tetanus have been reported in free ranging monkeys and group housed monkeys living in outdoor enclosures containing dirt floors.[10,14,18–20,30] Rhesus macaques are semi-terrestrial, having frequent contact with the soil.[23] They pick at their wounds and the wounds of others, and even rub dirt in wounds to stop hemorrhage.[10,23] The opportunity for aggressive encounters and subsequent soil contamination of wounds create a significant risk of tetanus for outdoor housed non-human primates.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Macaques with injuries to the digits and tail were more likely to develop tetanus than animals with wounds to other locations (OR=9.5, digits; OR=8, tail), while wounds located on the legs appeared less risky (OR=0.2). These results are in agreement with findings in human tetanus studies in that injury locations at most risk of soil contamination, such as the lower limb or extremity, are the most frequently reported location associated with the development of tetanus infection.[12,25,29,39] In one study, wounds to lower limb accounted for 86.5% of cases compared to 5.4% of the cases which had upper limb wounds.[33] Other studies show similar findings; 54.5% and 42.7% of cases having lower limb wounds versus 22.7% and 19.3% with upper limb wounds.[25,39] Unfortunately, these studies did not report the region of the lower limb that was wounded. The higher incidence of wounds in tetanus patients to the lower limbs compared to other locations has been attributed to the closer proximity of these wounds to the soil, increasing the likelihood of wound contamination with the causative organism.[25] Nonhuman primates would be more prone to tetanus contamination of the tail and digits, just as humans are more prone to tetanus contamination in the lower extremities.

The variables of wound character, severity, and whether the wound was infected or contaminated did not meet the criteria for inclusion in the final multivariate model (Table 2). In the human literature, wounds are often classified as tetanus prone to guide clinicians in instituting the appropriate level of tetanus prophylaxis to wound patients in accordance with the recommendations of The Advisory Committee on Immunization Practices(ACIP) published by the CDC.[7] Wounds identified as tetanus prone include those contaminated with dirt, feces, soil, punctures, avulsions, crushing wounds, frostbite, and burns.[7,35] A similarly defined tetanus-prone wound was not observed in the non-human primates, as only the category of wound location was associated with tetanus development. It is likely that the majority of wounds sustained had some level of contamination with soil or feces due to the animals' housing environment in the outdoor corrals. Instead, the location was more highly linked to tetanus than the character of the wound, suggesting a higher risk of contamination for extremity wounds as previously discussed.

In agreement with the current study, wound severity has not been uniformly associated with the development of tetanus in the human literature. A significant proportion of tetanus patients have wounds classified as minor.[6,25,26,29] These patients are less likely to seek medical attention, as well as receive appropriate tetanus prophylaxis[2,35] at medical institutions in comparison to patients with severe wounds, contributing to an overall reduction in tetanus infection in those with tetanus-prone wounds versus non-tetanus prone wounds.[6] The ACIP guidelines consider both vaccination history, and wound type when initiating tetanus prophylaxis in a wound patient[7], conferring protection to all patients yet allowing the degree of prophylaxis to match patient risk. Likewise, institutions housing non-human primates should also develop tetanus prophylaxis guidelines for wound patients. Defining the wound patients at greatest risk would allow the most appropriate allocation of prophylactic treatments and reduce unnecessary adverse reactions. In instituting tetanus prophylaxis guidelines in nonhuman primates, population demographics should be considered in conjunction with wound location, relevant, and applicable information obtained from the human literature, and sound clinical judgment.

Vaccination with tetanus toxoid is the most effective means to prevent tetanus infection in non-human primates. Tetanus, which accounted for 19.5% of the total mortality in the colony of free ranging rhesus macaques at Cayo Santiago from 1977–1984 was eliminated after implementing a two dose series tetanus toxoid vaccination program.[18,19] No tetanus cases were recorded in this immunized population from 1985–2003, and tetanus antibody titres were shown protective 18 years after the booster immunization.[19] Vaccination programs of an intramuscularly administered 0.5 ml primary tetanus toxoid inoculation followed a year later with a single booster has been reported as protective in macaques.[18,19] Success has been reported in baboons after a primary inoculation, booster at 1 month, followed by boosters every five years.[14] Until the recent past, many primate research institutions, including TNPRC, withheld instituting a prophylactic vaccination program due to concerns that an immunized population of nonhuman primates would be unsuitable candidates for infectious disease research studies. For example, tetanus antigen has been used as a T-cell dependent immunogen for both *in vivo* and *in vitro* tests to assess the changes in the humoral and cellular immune responses associated with simian immunodeficiency virus (SIV) infection in rhesus macaques, the principal model for human immunodeficiency virus (HIV).[1,5,8,15,17,28,31,37] In humans, tetanus antigen is used as a recall antigen where responses to delayed hypersensitivity testing (DTH) and *in vitro* cell proliferation assays predicts time to progression to AIDS, survival time and progressive HIV illness.[1,8,11,31] The prognostic utility of tetanus antigen in these tests is based on a higher level of prior exposure to it in the human population than other available recall antigens.[5,11] Although non-human primate SIV studies often used tetanus as a neo-antigen to evaluate the immune response after a primary immunization,[28,37] pre-exposure to the tetanus antigen does not necessarily negate its utility in monitoring immunologic parameters in SIV-+ macaques. Considering the availability of other recall antigens, neo-antigens, mitogens, alloantigens and the continued development of other available immunological assays[1,3,5,8,11,13,15,17,27,28,31,32,37], withholding the prophylactic vaccination of nonhuman primates is not warranted. TNPRC began vaccinating its animals in 2005. The authors recommend that all institutions housing non-human primates consider implementing a tetanus vaccination program, and to check the vaccination status of any newly acquired non-human primates.

The findings of this study identified location of wound in non-human primates as associated with increased risk of tetanus infection. Awareness of these factors should ultimately contribute to clinical decisions regarding wound management and tetanus prophylactic measures, especially at institutions in which resources must be carefully allocated. Non-human primates at high risk, i.e. those housed outdoors with multiple wounds or wounds on the tail or digits, should receive aggressive prophylactic measures including tetanus toxoid, tetanus antitoxin, and, potentially, even human tetanus immunoglobulin. Bearing in mind the susceptibility of non-human primates to tetanus as well as the potential that all wounds may be contaminated with tetanus, it is strongly encouraged that all institutions with nonhuman primates, especially those housing monkeys outdoors, implement an institution-wide program of tetanus vaccination.

Acknowledgments

This research was funded by a National Center for Research Resources (NCRR) base grant (5P51-RR00164) and additional NCRR grants (U24-RR18111, U42-RR016026). We thank Dr. Rudolf Bohm for supporting this study, and Dr. Erin Ribka and Dr. Marion Ratterree for clinical support.

LITERATURE CITED

1. Ananworanich J, Nuesch R, Teeratakulpisarn S, Srasuebkul P, Chuenyam T, Siangphoe U, Ungsedhaphand C, Phanuphak P, Ruxrungtham K. Letters to the editor. In vivo cell-mediated immunity in subjects with undetectable viral load on protease inhibitor-based versus non-protease inhibitor-based highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2003; 32:570–573. [PubMed: 12679711]
2. Aydin K, Caylan R, Caylan R, Bektas D, Koksal I. Otolaryngologic aspects of tetanus. Eur Arch Otorhinolaryngol. 2003; 260:52–56. [PubMed: 12520358]
3. Bernstein LJ, Ochs HD, Wedgwood RJ, Rubinstein A. Defective humoral immunity in pediatric acquired immune deficiency syndrome. J Pediatr. 1985; 107:352–257. [PubMed: 4032129]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

4. Bhatia R, Prabhakar S, Grover VK. Tetanus. Neurol India. 2002; 50:398–407. [PubMed: 12577086]
5. Borleffs JCC, Schuurman H-J, Vrehen HM, Van Schaik M, Bast EJEG. In vitro and in vivo measurement of cell-mediated immunity in patients with HIV-1 infection. Scand J Immunol. 1993; 37:634–636. [PubMed: 8100361]
6. Bowen V, Johnson J, Boyle J, Snelling CFT. Can J Surg. 1988; 31:7–9. [PubMed: 3337978]
7. Centers for Disease Control and Prevention. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. MMWR Recommendations and Reports. 2006; 55:1–33.
8. Colebunders RL, Lebughe I, Nzila N, Kalunga D, Francis H, Ryder R, Piot P. Cutaneous delayed-type hypersensitivity in patients with human immunodeficiency virus infection in Zaire. J Acquir Immune Defic Syndr. 1989; 2:576–578. [PubMed: 2585248]
9. Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. Br J Anaesth. 2001; 87:477–87. [PubMed: 11517134]
10. DiGiacomo RF, Missakian EA. Tetanus in a free-ranging colony of Macaca mulatta: a clinical and epizootiologic study. Lab Anim Sci. 1972; 22:378–383. [PubMed: 4338701]
11. Dolan MJ, Clerici M, Blatt SP, Hendrix CW, Melcher GP, Boswell RN, Freeman TM, Ward W, Hensley R, Shearer GM. In vitro T cell function, delayed-type hypersensitivity skin testing, and CD4+ T cell subset phenotyping independently predict survival time in patients infected with human immunodeficiency virus. J Infect Dis. 1995; 172:79–87. [PubMed: 7797948]
12. Farrar JJ, Yen LM, Cook T, Fairweather N, Binh N, Parry J, Parry CM. Neurological aspects of tropical disease: tetanus. J Neurol Neurosurg Psychiatry. 2000; 69:292–301. [PubMed: 10945801]
13. Ghaffari G, Passalacqua DJ, Bender BS, Briggs DJ, Goodenow MM, Sleasman JW. Human lymphocyte proliferation responses following primary immunization with rabies vaccine as neoantigen. Clin Diagn Lab Immunol. 2001; 8:880–883. [PubMed: 11527796]
14. Goodwin WJ, Haines RJ, Bernal JC. Tetanus in baboons of a corral breeding colony. Lab Anim Sci. 1987; 37:231–232. [PubMed: 3599896]
15. Gordin FM, Hartigan PM, Klimas NG, Zolla-Pazner SB, Simberkoff MS, Hamilton JD. Delayed-type hypersensitivity skin tests are an independent predictor of human immunodeficiency virus disease progression. J Infect Dis. 1994; 169:893–897. [PubMed: 7907646]
16. Hosmer, DW.; Lemeshow, S. Applied Logistic Regression. 2. John Wiley & Sons Inc.; New York, New York: 2000.
17. Kelleher AD, Roggensack M, Jaramillo AB, Smith DE, Walker A, Gow I, McMurchie M, Harris J, Patou G, Cooper DA. Safety and immunogenicity of a candidate therapeutic vaccine, p24 virus-like particle, combined with zidovudine, in asymptomatic subjects. AIDS. 1998; 12:175–182. [PubMed: 9468366]
18. Kessler MJ, Berard JD, Rawlins RG. Effect of tetanus toxoid inoculation on mortality in the Cayo Santiago macaque population. Am J Primatol. 1988; 15:93–101.
19. Kessler MJ, Berard JD, Rawlins RG, Bercovitch FB, Gerald MS, Laudenslager ML, Gonzalez-Martinez J. Tetanus antibody titers and duration of immunity to clinical tetanus infections in free-ranging rhesus monkeys (Macaca mulatta). Am J Primatol. 2006; 68:725–731. [PubMed: 16786523]
20. Kessler MJ, Brown RJ. Clinical description of tetanus in squirrel monkeys (Saimiri sciureus). Lab An Sci. 1979; 29:240–242.
21. Kessler MJ, Martinez HS. Treatment of tetanus in the rhesus monkey (Macaca mulatta). J Zoo Anim Med. 1979; 10:119–122.
22. Kessler MJ, Rawlins RG. Tetanus. Comparative Pathology Bulletin. 1983; 15:3.
23. Kessler MJ, Rawlins RG. Absence of naturally acquired tetanus antitoxin in the free-ranging Cayo Santiago rhesus monkeys (Macaca mulatta). J Med Primatol. 1984; 13:353–357. [PubMed: 6520863]
24. Kessler, MJ.; Rawlins, RG.; London, WT. AAZV Annual Proceedings. New Orleans, Louisiana: 1982. Tetanus in monkeys: symptomatology, epizootiology, treatment and prophylaxis; p. 37-39.
25. Lau LG, Kong KO, Chew PH. A ten-year retrospective study of tetanus at a general hospital in Malaysia. Singapore Med J. 2001; 42:346–350. [PubMed: 11764050]

NIH-PA Author Manuscript

26. Luisto M. Unusual and iatrogenic sources of tetanus. Ann Chir Gynaecol. 1993; 82:25–29. [PubMed: 8323232]

27. Markert ML, Hicks CB, Bartlett JA, Harmon JL, Hale LP, Greenberg ML, Ferrari G, Ottinger J, Boeck A, Kloster AL, McLaughlin TM, Bleich KB, Ungerleider RM, Lyerly HK, Wilkinson WE, Rousseau FS, Heath-Chiozzi ME, Leonard JM, Haase AT, Shaw GM, Bucy RP, Douek DC, Koup RA, Haynes BF, Bolognesi DP, Weinhold KJ. Effect of highly active antiretroviral therapy and thymic transplantation on immunoreconstitution in HIV infection. AIDS Res Hum Retroviruses. 2000; 16:403–413. [PubMed: 10772526]

28. Mills, KHG.; Jones, WC.; Mahon, BP.; Katrak, K.; Taffs, F.; Stott, EJ.; Page, M. Cellular and humoral immune responses to poliovirus and tetanus following primary immunization of SIV-infected macaques. In: Racz, P.; Letvin, NL.; Gluckman, JC., editors. Animal Models of HIV and Other Retroviral Infections. Karger S. Inc.; Basel, Switzerland: 1993. p. 75-85.

29. Percy AS, Kukora JS. The continuing problem of tetanus. Surg Gynecol Obstet. 1985; 160:307–312. [PubMed: 3983794]

30. Rawlins RG, Kessler MJ. A five year study of tetanus in the Cayo Santiago rhesus monkey colony: behavioral description and epizootiology. Am J Primatol. 1982; 3:23–39.

31. Raymond, D. Stalking HIV Immune Dysregulation. The Body. 2002 [Accessed: 26 July 2006]. http://www.thebody.com/gmhc/issues/may02/in_vitro.html

32. Rubinstein A, Mizrachi Y, Bernstein L, Shliozberg J, Golodner M, Liu GQ, Ochs HD. Progressive specific immune attrition after primary, secondary and tertiary immunizations with bacteriophage phi X174 in asymptomatic HIV-1 infected patients. AIDS. 2000; 14:F55–62. [PubMed: 10770533]

33. Sheffield JS, Ramin SM. Tetanus in pregnancy. Am J Perinatol. 2004; 21:173–182. [PubMed: 15168315]

34. StataCorp. Stata Statistical Software. Release 7.0. Stata Corporation; Texas: 2001.

35. Talan DA, Abrahamian FM, Moran GJ, Mower WR, Alagappan K, Tiffany BR, Pollack CV, Steele MT, Dunbar LM, Gajani MD, Weyant RS, Ostroff SM. Tetanus immunity and physician compliance with tetanus prophylaxis practices among emergency department patients presenting with wounds. Ann Emerg Med. 2004; 43:305–314. [PubMed: 14985655]

36. Thwaites CL, Yen LM, Glover C, Tuan PQ, Nga NTN, Parry J, Loan HT, Bethell D, Day NPJ, White NJ, Soni N, Farrar JJ. Predicting the clinical outcome of tetanus: the tetanus severity score. Trop Med Int Health. 2006; 11:279–287. [PubMed: 16553907]

37. Villinger F, Rowe T, Parekh BS, Green TA, Mayne AE, Grimm B, McClure HM, Lackner AA, Dailey PJ, Ansari AA, Folks TM. Chronic immune stimulation accelerates SIV-induced disease progression. J Med Primatol. 2001; 30:254–259. [PubMed: 11990240]

38. Westergaard GC, Suomi SJ, Chavanne TJ, Houser L, Hurley A, Cleveland A, Snoy PJ, Higley JD. Physiological correlates of aggression and impulsivity in free-ranging female primates. Neuropsychopharmacology. 2003; 28:1045–1055. [PubMed: 12700686]

39. Yadav YR, Kala PC, Yadav S. Study of site and nature of injury as prognostic factors in tetanus. Trop Doct. 1990; 20:136–137. [PubMed: 2219431]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Results of a univariate conditional logistic regression analysis of risk factors for the development of tetanus following traumatic injury in non-human primates in a primate center.

Variable	Risk factor	Cases	Controls	OR	95% CIs	*p* value
Injury to:						
Face	No	14	38	1	NA	
	Yes	17	24	2.09	0.80, 5.45	0.13
Neck	No	28	59	1	NA	
	Yes	3	3	2.38	0.38, 14.97	0.36
Pinna	No	21	55	1	NA	
	Yes	10	7	4.00	1.22,12.07	0.02
Hip	No	27	56	1	NA	
	Yes	4	6	1.54	0.32, 7.45	0.60
Thigh	No	27	47	1	NA	
	Yes	4	15	0.52	0.17, 1.60	0.25
Leg	No	28	44	1	NA	
	Yes	3	18	0.22	0.05, 1.00	0.05
Cubitus	No	24	59	1	NA	
	Yes	7	3	6.31	1.29, 30.74	0.023
Trunk	No	26	53	1	NA	
	Yes	5	9	1.14	0.33,3.97	0.83
Digits	No	17	57	1	NA	
	Yes	14	5	11.84	2.66, 52.69	0.001
Hand/Foot	No	26	58	1	NA	
	Yes	5	4	2.5	0.67, 9.31	0.17
Tail	No	25	57	1	NA	
	Yes	6	5	4.00	0.77, 20.87	0.10
Arm	No	23	44	1	NA	
	Yes	8	18	0.87	0.35, 2.14	0.76
Multiple injury						
Locations	No	5	34	1	NA	
	Yes	26	28	20.82	2.71, 159.59	0.003

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Variable	Risk factor	Cases	Controls	OR	95% CIs	*p* value
Severity index						
> 3	No	9	36	1	NA	
	Yes	22	26	4.61	1.48, 14.34	0.008

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Results of multivariate conditional logistic regression analysis of risk factors for the development of tetanus following traumatic injury in non-human primates in a primate center

Risk factor	OR	95% CIs	P value
Injury to the digits	9.56	1.56, 58.59	0.015
Injury to the tail	7.95	0.82, 77.04	0.074
Injury to the leg	0.19	0.03, 1.21	0.079
Injuries in more than one location	8.45	1.01, 70.46	0.049