Comment on: Efficacy of antibiotic prophylaxis for the prevention of Lyme disease: an updated systematic review and meta-analysis

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Sir,

The recent article by Warshafsky et al.¹ may encourage the use of single-dose doxycycline for tick-bite prophylaxis, which in my opinion and in the light of other evidence, is likely to be ineffective. The recommendation for single-dose prophylaxis was first made by Nadelman et al.² in 2001 as a result of a randomized controlled trial in 482 patients and was included in the Infectious Diseases Society of America’s (IDSA’s) guidelines for the treatment of Lyme disease.³ Three of the authors of the Nadelman et al.² article were also authors of the IDSA guidelines. In their original article, Nadelman et al.² showed that their single-dose regimen was 87% effective in blocking both the erythema migrans (EM) and the appearance of anti-Borrelia antibodies expected with borreliosis, but they did not show that it blocked actual infection in the antibiotic recipients. This is analogous to observations made in the 1950s that low-dose penicillin blocked cutaneous lesions of syphilis in rabbits but not the infection.⁴ The study by Nadelman et al.² did not comment on complaints of fever and flu-like illness and limited its follow-up to 6 weeks instead of the 1–2 years used in other studies and no normal control group was used to compare the incidence of fever and flu-like illness with that of the treated/placebo groups.

However, investigators at the CDC in Fort Collins, Colorado, showed that 80% of newly infected mice treated with a comparable single oral dose of doxycycline developed persistent borreliosis,⁵ which was found by grinding up tissues and using culture and PCR for bacterial detection. The sera from these mice were discarded without testing for anti-Borrelia antibodies so we do not know if they remained seronegative despite proven infection.

Not surprisingly when the same criteria are used in the recent meta-analysis⁶ a similar result is obtained, i.e. a single oral dose blocks both EM and antibodies. By promoting this potentially flawed recommendation, the authors and the IDSA may actually promote persistent borreliosis that will be seronegative, and therefore difficult to diagnose.

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Efficacy of antibiotic prophylaxis for the prevention of Lyme disease: an updated systematic review and meta-analysis—authors’ response

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Sir,

We thank Professor Volkman for his letter.¹ We disagree with his comments, and we would like to take the opportunity to
elaborate on the use of antibiotic therapy for chemoprophylaxis of spirochaetal infections.\textsuperscript{2–11}

As discussed in detail in our recent report, antibiotic therapy has clearly been shown to be effective in curing Lyme disease in both humans and animals when given during the incubation period of the infection.\textsuperscript{12} When administered at this time, the antibiotics are, by definition, being used after the actual infection has occurred. It is expected that relatively few spirochaetes are present at this time, which provides the opportunity to eradicate them with a much shorter course of treatment than would be necessary at later stages of infection. This concept has been experimentally validated in rabbits infected with \textit{Treponema pallidum}.\textsuperscript{13–15}

In addition, evidence indicates that the pharmacodynamics and the pharmacokinetics of the specific antibiotic administered affect the efficacy of chemoprophylaxis for \textit{Borrelia burgdorferi} infection following a tick bite.\textsuperscript{16} A single parenteral dose of a long-acting doxycycline preparation after a tick bite was 100\% effective in eliminating \textit{B. burgdorferi} from mice in two different studies,\textsuperscript{17,18} whereas a single oral dose was 43\% effective in the original study addressing this question.\textsuperscript{17} Although the 43\% efficacy rate is less than the 87\% efficacy rate observed in the human trial of single-dose doxycycline,\textsuperscript{19} a single dose of doxycycline given orally to mice was nevertheless significantly more effective than the water control employed ($P=0.02$),\textsuperscript{17} thus providing a proof of concept.

Perhaps the most important reason that a single oral dose of doxycycline was found to be less effective in mice than in humans is that the pharmacokinetics of oral doxycycline in the mouse species studied differs substantively from that found in humans. According to a published analysis, the area under the curve of unbound doxycycline ($\text{AUC}_{0–1}$) was 2.25 times higher in humans after a single 200 mg dose of doxycycline than that provided by the dose of doxycycline used in the mouse study.\textsuperscript{16}

Another potentially important factor is that five ticks were placed on each mouse,\textsuperscript{17} which probably delivered a several-fold higher inoculum of spirochaetes compared with the bite of just a single tick that the humans experienced. In a second mouse study,\textsuperscript{18} the efficacy of a single oral dose of doxycycline decreased to 20\%, but 10 ticks were fed on each mouse; five infected with \textit{B. burgdorferi} and five infected with \textit{Anaplasma phagocytophilum}. The authors of the study hypothesized that the reduction in efficacy of oral doxycycline was due to the biological effects of the tick saliva that was inoculated by the larger number of ticks simultaneously feeding on the mice.\textsuperscript{18} Tick saliva \textit{per se} enhances both viral and bacterial transmission in vivo.\textsuperscript{19,20} The authors also raised the question of whether the simultaneous delivery of both \textit{B. burgdorferi} and \textit{A. phagocytophilum} might have affected the metabolism of the oral doxycycline preparation that was used. To gain more information pertinent to humans, additional mouse studies should be conducted to identify more precisely the AUC value of unbound doxycycline (relative to the MIC of doxycycline for the borrelial strain studied ($\text{AUC}_{0–1}/\text{MIC}$)) associated with curing a \textit{B. burgdorferi} infection in its incubation period after the bite of a single infected tick.

Professor Volkman’s concerns about seronegative late Lyme disease are based at least in part on a 1988 study that he co-authored.\textsuperscript{21} The T-lymphocyte proliferation assay that served as the basis for that diagnosis in his study,\textsuperscript{21} however, is now recognized to be non-specific for Lyme disease.\textsuperscript{10,11,22,23} Experimental and clinical studies to date have not demonstrated that failures of antibiotic prophylaxis for spirochaetal infections lead to a modified presentation of the disease or seronegative persistent infection.\textsuperscript{2,6,10,13,15} In the experimental study on syphilis that Professor Volkman cited,\textsuperscript{13} rabbits that received penicillin for incubating infection were ‘either cured or subsequently developed clinically recognizable lesions’. Single subcutaneous doses of penicillin only prolonged the ‘incubation period of experimental syphilis…up to a limit of 30–40 days’. After lesions developed, all of the animals become seropositive. Furthermore, single-dose \textit{β}-lactam therapy for the treatment of incubating syphilis has been widely and successfully prescribed for thousands of patients with gonorrhoea.\textsuperscript{7}

Finally, the 2006 Infectious Diseases Society of America (IDSA) Lyme disease treatment guidelines did endorse single-dose doxycycline for prevention of Lyme disease, but only for selected patients if certain conditions were met.\textsuperscript{24} Professor Volkman is correct that 3 of the 14 members of the IDSA guideline panel co-authored the pivotal clinical trial on single-dose doxycycline,\textsuperscript{2} but failed to mention that on 22 April 2010 a separate panel of eight individuals, none of whom was a co-investigator on the doxycycline trial or served on the prior guidelines panel, unanimously endorsed this recommendation.\textsuperscript{25}

Transparency declarations
None to declare.

References