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REVIEW ARTICLE

Effectiveness of Antibiotic Prophylaxis for Leptospirosis among Adults: A Systematic Review

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Abstract

Leptospirosis is one of the most widespread re-emerging zoonoses in the world. Malaysia is known to be an endemic country for human leptospirosis, with a case fatality rate of 2.11%, and an average annual incidence rate of 7.80 cases per 100,000 individuals. This systematic review is conducted to determine the effectiveness of antibiotic prophylaxis for leptospirosis among the adult populations who are highly at risk of getting infected. A systematic search was performed for the relevant titles, abstracts and keywords on PubMed, Scopus, Cochrane and Google Scholar from inception to November 2017 based on the PICO strategy; which returned 126 studies. Screening of abstracts had shortlisted 19 studies and data extraction was conducted for 8 studies which had been accepted after review of the full text. For the evaluation of antibiotics prophylaxis effectiveness against leptospirosis, only trials and cohort studies with risk ratio (RR) were selected. The articles were analyzed from the viewpoint of the dosage, adverse effects, study settings and effectiveness of the antibiotic prophylaxis. Using fixed effects model, pooled RR showed protective association between antibiotic prophylaxis use against the incidence of leptospirosis (RR = 0.31; 95% CI: 0.20, 0.48). Antibiotic prophylaxis for leptospirosis had been shown to be effective in preventing the incidence of the disease among high-risk populations and carries minimal adverse effects. It is recommended that the practice of antibiotic prophylaxis for leptospirosis is included in the standard protocol for leptospirosis prevention among people at high-risk, including disaster response teams and patrons of eco-sports tourism activities; with the drug of choice being doxycycline, either as a single 200 mg dose or weekly dose of 200 mg for the duration of exposure, based on the setting, duration of event and resources available.

Keywords: Adult; prophylaxis; antibiotic prophylaxis; flood; leptospirosis.

Introduction

Leptospirosis, an infection caused by a spirochete of genus Leptospira, is considered as one of the most widespread zoonoses in the world. Although it has a global distribution, higher incidence is observed in the tropics and subtropics and less so in temperate regions, with incidence ranging from 10 to 100 cases per 100,000 individuals (Guerra, 2013). Leptospirosis is considered a re-emerging tropical disease or re-emerging zoonosis due to human encroachment into wildlife habitat which resulted in increased contact between humans and animals. The principal reservoirs for the pathogen may include at least 150 mammalian species including rodents, dogs, cattle, and swine; although rodents are most commonly discussed when typical leptospirosis outbreaks occur. Climate change, human agricultural activities, human industrial activities, urbanization and its associated environmental factors can affect the degree of transmission of leptospirosis and modulate its risk.

Based on a meta-analysis conducted in 2015, it was estimated that there were 1.03 million cases (95% CI: 434,000 – 1,750,000) of leptospirosis annually, while 58,900 deaths (95% CI: 23,800, 95,900) were estimated as a result of leptospirosis globally (Costa et al., 2015). Almost half of the cases (48%; 95% CI: 40, 61%) and more than two fifths of deaths (42%; 95% CI: 34, 53%) were estimated to occur in adult males with the age of 20 – 49 years (Costa et al., 2015). The highest estimates of disease morbidity and mortality were observed in South Asia, Southeast Asia, Tropical Latin America, Central America, Oceania, East Sub-Saharan Africa, and Caribbean and Andean regions (Costa et al., 2015). Malaysia is known to be an endemic country for human leptospirosis (Benacer et al., 2016). The number of cases has risen dramatically since the Ministry of Health Malaysia had outlined leptospirosis as a notifiable disease in 2010, with reported cases increasing by 30 folds from 263 cases in 2004 to 7806 cases 10 years later in 2014 (Wahab, 2015). Between January 2004 and December 2014, there were cumulatively 24,970 leptospirosis cases recorded, in which 528 were fatal cases (Wahab, 2015). This gives an overall case fatality rate of 2.11%. The annual incidence rate in Malaysia ranged from 1.03 to 25.94 cases per 100,000 individuals over the 11-year period with an average annual incidence of 7.80 cases per 100,000 individuals (Wahab, 2015).

Leptospirosis tends to occur in four major settings (Smith et al., 2013). The first setting revolves around people with occupations that involve contact with infected animals or environments contaminated by infected animals, such as agricultural work, livestock industry, and working in abattoir. The second setting is related to crowded urban environments where sanitation may be subpar and rodents are present in abundance. The third setting, which has only become significant over recent decades, is recreational exposures, including water sports activities and eco-sport tourism. The fourth setting, which is also becoming more apparent in the last two decades or so, involves settings with common natural disasters namely monsoon downpour and flooding. Although there is widespread use of prophylaxis in the form of antibiotics to prevent leptospirosis for travel into endemic countries, there are few guidelines on such practices in other settings, such as prophylaxis for first responders in flood disasters or patrons of water-related recreational activities. This systematic review is conducted to determine the effectiveness of antibiotic prophylaxis for leptospirosis among the adult population who are highly at risk of getting infected. In doing so, this review will peruse the literatures and identify the type and dose of antibiotic prophylaxis used for leptospirosis, identify the adverse effects of antibiotic prophylaxis for leptospirosis, identify the high-risk settings related to leptospirosis infection, and determine the association between antibiotic prophylaxis use and leptospirosis. The findings from this review may be of interest to the relevant authorities to revamp the guidelines on people entering leptospirosis-related settings which may include the recommendation for antibiotic prophylaxis.

Materials and Methods

Search Protocol

A systematic search was performed on PubMed, Scopus, Cochrane and Google Scholar from inception to November 2017. Search strategy follows the PICO strategy and the search was done scrutinizing titles, abstracts and keywords. The terms used for P (Population or Problem) were leptospirosis AND flood* OR "water recreation*" OR "natural disaster*". The terms used for I (Intervention) were prophylaxis OR chemoprophylaxis OR doxycycline OR "antibiotic prophylaxis". There was no term search for C (Comparison). Lastly, the terms used for O (Outcome) were "risk ratio" OR "relative risk" OR effectiveness OR incidence. The final result consists of all PICO terms searches; i.e. P AND I AND O. There were no restrictions placed on location, year of study publication or language. Unpublished literatures were not searched.

Study Selection

Studies that have been chosen for the first screening process were each randomly allocated to two reviewers. The two reviewers decide on the appropriateness of a study based on the title, abstract and keywords of the said study. Both reviewers must reach a consensus in order for the study to be accepted into the next phase of screening. A third reviewer will be involved in the screening process should the initial two reviewers fail to agree with one another and the decision for accepting the study will be made by a consensus from the three reviewers. However, no study had required a third reviewer. The next phase of the article selection involved retrieval of the full articles for further scrutinization. Two reviewers, who were different from the initial reviewers, were allocated for each study. Data extraction was conducted for the studies which had been accepted after review of the full article. Studies were included if 1) the study was an original article (not a review or commentary); and 2) the study had included the assessment of prophylactic antibiotics use (of any type) against leptospirosis. The exclusion criteria were 1) the absence of full article in English; and 2) populations other than adult. There was no restriction imposed on minimum sample size. The selection flow was summarized in Figure 1.

Data Extraction

A standardized collection form was used to extract data such as publication year, study design (randomized controlled trial, non-randomized control trial, cohort, case-control or cross-sectional), sample size, population derivation, setting (flood, water-related recreational activities, agriculture setting, urban area etc), country, and risk estimates or the data used to calculate risk estimates. For the evaluation of antibiotics dose, side effects of antibiotic prophylaxis, and the population at risk/study settings, all study designs were included. However, for the evaluation of antibiotic prophylaxis effectiveness against leptospirosis, only studies where risk estimation in the form of risk ratio (RR) was possible were selected. Hence, for assessment of prophylaxis effectiveness, only randomized controlled trials, non-randomized controlled trials and cohort studies were considered. All types of antibiotics for prophylaxis and all doses were included for this purpose, although only studies that reported pre-exposure prophylaxis were accepted. The outcome was determined as confirmed cases of leptospirosis, as proven by laboratory confirmation. The accepted laboratory confirmation tests that form the basis of the outcome (confirmed case of leptospirosis) included in the quantitative analysis of risk estimation were Microscopic Agglutination Test (MAT), Microcapsule Agglutination Test (MCAT), and Enzyme Immunoassay (ELISA).

Statistical Analysis

Fixed effects model was used to calculate pooled RR and 95% confidence intervals to determine the effectiveness of antibiotic prophylaxis against leptospirosis. Heterogeneity was

tested by chi squared testing with $p < 0.05$ denoting level of significance (i.e. heterogeneous). The quantification of the degree of heterogeneity was done using the I^2 statistic, which represents the percentage of the total variability across studies. I^2 values of less than 25% is considered as homogenous, while values up to 50%, up to 75% and more than 75% corresponded to low, moderate, and high degrees of heterogeneity respectively. All analyses were performed with Review Manager (ReviewManager(RevMan), 2014).

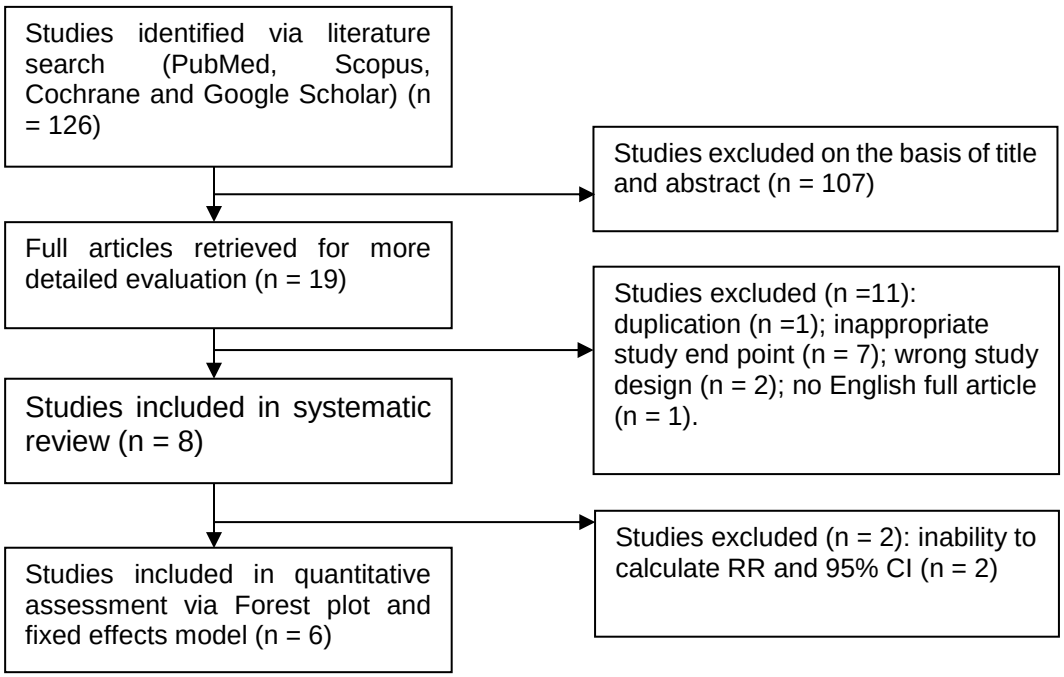

Figure 1. Study selection flow sheet.

Results

There were eight studies that met the inclusion criteria (Table 1). Full-text analyses were then conducted to cover all the studies which included four randomized controlled trials, one non-randomized trial, one retrospective cohort study, one case-control study, and one case series study. The studies assessed the prophylactic effect of antibiotics against leptospirosis infection with variations in route of administration, type, duration and dosage. Study populations differ between studies, but in general, all studies evaluated populations living in areas of high endemicity of leptospirosis or areas frequented by flood. Only one study evaluated populations involved in water sports or eco-sports tourism.

Dose

The sole retrospective cohort study included in this review found that out of the 189 contactable/traced athletes (who participated in the Eco-Challenge-Sabah 2000 multisport endurance race, held in Sabah, Malaysia between August and September 2000), 20 of them (11%) reported taking doxycycline for prophylaxis for either malaria or leptospirosis (James et al., 2003). 17 of these athletes reported taking a daily dose of 100 mg of oral doxycycline throughout the duration of the race; while the other three consumed the same daily dose but sporadically throughout the race. Symptoms of illness developed in 4 (20%) of the 20 athletes who reported taking doxycycline.

Table 1. Summary of included studies.

Author	Place	Design	Sample Size	Setting	Dose	Side effect(s)	Effectiveness (RR)
(Desai et al., 2016)	India	Case-control	Case: 100 Control: 300	Confirmed clinical cases and healthy neighbours	Doxycycline 200 mg / week	Not mentioned	-
(Chusri et al., 2014)	Thailand	Non-randomized trial	Trial: 600 Control: 41	Aged 18 years or above exposed to flood water	Doxycycline single dose 200 mg	Nausea, vomiting, skin rash	0.23 (95% CI: 0.09, 0.60)
(Illangasekera, Kularatne, Kumarasiri, Pussepitiya, & Premaratne, 2008)	Sri Lanka	Randomized controlled trial	Trial: 140 Control: 143	Farmers in an area of high leptospirosis endemicity	Oral Penicillin 500 mg BD for 1 month	Not mentioned	0.16 (95% CI: 0.01, 3.01)
(James et al., 2003)	Malaysia	Retrospective cohort study	Exposed: 20 Not exposed: 169	"Eco-Challenge" athletes (sports tourism)	Doxycycline, varying dose	Not mentioned	0.44 (95% CI: 0.18, 1.09)
(Sehgal, Sugunan, Murhekar, Sharma, & Vijayachari, 2000)	India	Randomized controlled trial	Trial: 386 Control: 396	Healthy adults in an area of high leptospirosis endemicity	Doxycycline 200 mg / week	Gastritis, erythema-tous rash	0.46 (95% CI: 0.23, 0.89)
(Gonsalez et al., 1998)	Brazil	Randomized controlled trial	Trial: 40 Placebo: 42	Residents living in an area with high risk of flooding	Doxycycline single dose 200 mg	Not mentioned	0.42 (95% CI: 0.09, 2.04)
(Gilks, Lambert, Broughton, & Baker, 1988)	United Kingdom	Case series	2	Laboratory technicians	Case 1: IM penicillin Case 2: Doxycycline 100 mg twice / week	Not mentioned	-
(Takafuji et al., 1984)	Panama	Randomized controlled trial	Trial: 469 Control: 471	US Army personnel involved in jungle training	Doxycycline 200 mg / week	Vomiting	0.05 (95% CI: 0.01, 0.37)

When the rate of leptospirosis infection in those who consumed doxycycline was compared with those not reporting doxycycline prophylaxis, doxycycline usage was deemed protective, although not significantly (RR = 0.4; 95% CI: 0.1, 1.1, p = 0.1).

Two of the RCTs and the solitary case-control study argued that the optimal dosage of doxycyline for the prophylaxis of leptospirosis was 200 mg per week for the duration of risk exposure (Desai et al., 2016; Sehgal et al., 2000; Takafuji et al., 1984). Another RCT proposed a counter-argument that an oral dose of penicillin of 500 mg twice daily for a month is another viable alternative for leptospirosis prophylaxis (Illangasekera et al., 2008). However the sole non-randomized trial involving 600 participants may have evidence that a single dose of 200mg doxycycline for prophylaxis was sufficient to prevent leptospirosis among flood victims compared to weekly dose (Chusri et al., 2014). Another RCT also showed similar conclusion (Gonsalez et al., 1998).

Adverse effects of antibiotic prophylaxis

The adverse effects of the antibiotic prophylactic regiment were rarely reported. The most common adverse effects reported were gastrointestinal symptoms and skin rashes. Out of the eight studies, only three mentioned about the adverse effects of antibiotic prophylaxis. There were 13 subjects who reported symptom of vomiting after taking doxycycline pills. Another subsequent study also reported the incidence of gastritis among subjects who had taken doxycycline (Sehgal et al., 2000). Additionally, the same study also reported one case of skin rash related to doxycycline. The latest study done in Thailand reported 12 subjects who received doxycycline had suffered from gastrointestinal symptoms and one subject had skin rash (Chusri et al., 2014).

Study Settings

In the eight studies included in this systematic review, four studies were conducted among those who were exposed to flood or area with monsoon season, three studies were done involving the high-risk occupations (army personnel, farmers and laboratory workers), and one study was done amongst population with water-related recreational activity. Among those exposed to flood, a study done in Thailand found that those exposed to flood for more than three hours per day were almost four times as likely to have leptospiral infection (OR = 3.70; 95% CI: 1.18, 11.11, p = 0.038) compared to those exposed less than three hours, and this risk was further increased in those with laceration wounds during flood (OR = 37.2, 95% CI: 8.43, 162.57, p < 0.001) (Chusri et al., 2014). Another study in Brazil revealed that 29% participants were tested positive for leptospirosis after exposure to flood water (Gonsalez et al., 1998).

Among the studies regarding high-risk occupations, Takafuji et al. (1984) demonstrated that the prevalence of leptospirosis among the US Army personnel involved in jungle training was 13% (Takafuji et al., 1984). This is in contrast to a study among farmers in Sri Lanka on effectiveness of oral penicillin as chemoprophylaxis against leptospirosis, whereby it was found that only 1% were positive for the disease (Illangasekera et al., 2008). Meanwhile, case studies among laboratory health workers have been published in which the workers turned out to have contracted leptospirosis due to the risk of handling the pathogen itself (Gilks et al., 1988). Among the studies for suspected or confirmed leptospirosis in the community, it was found that in the community in South Gujarat India, those who worked in waterlogged fields during the rainy season were associated with leptospirosis (OR = 4.6; 95% CI: 1.6, 17.9) (Desai et al., 2016). Further, other factors which contributed to the risk of infection were swimming/bathing in canals, open-air defecation practices, storage of cow dung in or surrounding house, residence in houses with walls made from cow dung, households with access of food to rodents, and injuries over hands/foot during the endemic season. Finally, from a study during the “Eco-Challenge” sports in Borneo, 12% of the contacted athletes were tested positive for leptospirosis (James et al., 2003).

Effectiveness of Antibiotic Prophylaxis against Incidence of Leptospirosis

Six studies satisfied the selection criteria for assessment of the effectiveness of leptospirosis antibiotic prophylaxis. There were four randomized controlled trials, one non-randomized controlled trial and one retrospective cohort study. All studies assessed the effectiveness of pre-exposure antibiotic prophylaxis; studies which had assessed the post-exposure prophylaxis for leptospirosis were excluded. Two studies used single dose of 200 mg doxycycline, three studies used multiple dosing of doxycycline with varying strengths, and only one study used antibiotic prophylaxis other than doxycycline (oral penicillin). A double-blinded, randomized and controlled clinical trial with a placebo was performed in South America, involving 40 and 42 subjects in the experimental and placebo groups respectively. It was found that for population with high risk of leptospirosis infection in a flood-prone area in Brazil, there was protective association of a single dose 200 mg doxycycline prophylaxis for confirmed cases of leptospirosis (RR = 2.3; 95% CI: 0.4, 11.5). However, the association was not statistically significant (Gonsalez et al., 1998). A more recent study published in 2014 had also evaluated the effectiveness of a single dose doxycycline prophylaxis against leptospirosis. In the said study, which was conducted in the city of Hat Yai, Thailand, 17 subjects (out of 600) who received a single dose of 200 mg doxycycline, and five (out of 41) who did not, were infected with Leptospira, resulting in a protective efficacy of 76.8% (95% CI: 34.3, 92.0%) (Chusri et al., 2014)

In another study which was conducted among athletes in an eco-challenge event, it was noted that varying doses of doxycycline offered protection against leptospirosis infection, although not significantly. The retrospective cohort study showed that doxycycline use was protective (RR = 0.4; 95% CI: 0.1, 1.1), and the preventive efficacy attributable to any doxycycline use was 55% (95% CI: 0.05%, 95%) (James et al., 2003). In 1982, a study which had a larger sample size, a double-blinded, placebo-controlled trial was conducted among military personnel involved in jungle training in a three-week period. The placebo group had a 4.2% rate of leptospiral infection compared to 0.2% in the experimental group (Takafuji et al., 1984). This represented a protective efficacy of 95% ($p < 0.001$). Another randomized controlled trial was done is a high-risk population in North Andaman, India, to assess the effectiveness of a weekly 200 mg of doxycycline as a prophylaxis against leptospirosis. It was shown that the relative risk of symptomatic leptospirosis developing in the subjects who received prophylaxis was 0.46 (95% CI: 0.23, 0.89) compared to those on placebo (Sehgal et al., 2000). The result proved that doxycycline prophylaxis had a statistically significant protective association against leptospirosis infection.

Only one randomized controlled trial evaluated the effectiveness of antibiotic prophylaxis other than doxycycline. Oral penicillin was given at 500 mg twice per day for one month, and studied among job-related leptospirosis risk among active farmers in Sri Lanka. Only farmers in the placebo group showed signs of leptospirosis infection while none of the 292 subjects in the experimental group got infected (Illangasekera et al., 2008).

Forest Plot for all six studies discussed and the measurement of the pooled risk ratio is illustrated in Fig. 2. In summary, using fixed-effects model, pre-exposure antibiotic prophylaxis (any type and any dose) had a protective association against incidence of leptospirosis (RR = 0.31; 95% CI: 0.20 – 0.48). Chi squared testing revealed no significant difference ($p = 0.33$) across the measured effect of all studies, which suggests homogeneity of the selected studies. Quantification of heterogeneity also suggest that the studies were homogenous ($I^2 = 13\%$).

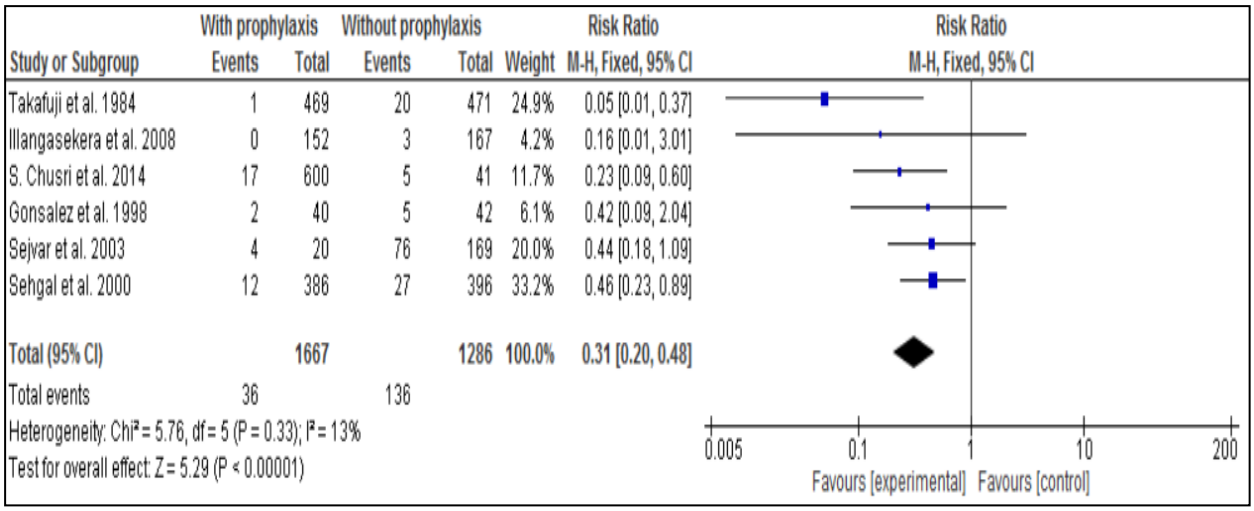

Figure 2. Effectiveness of pre-exposure antibiotic prophylaxis (any dose and any type) against incidence of leptospirosis

Discussion

In the retrospective cohort study, the number of subjects who took antibiotic prophylaxis in the form of 100 mg doxycycline per day as prophylaxis was a small proportion of the whole sample and was also unsupervised in their consumption; and their recollection could be susceptible to recall bias (James et al., 2003). Further, the single non-randomized trial reviewed suggested that a single dosage of 200mg doxycycline for prophylaxis might be effective for preventing leptospirosis rather than a weekly dose for duration of exposure (Chusri et al., 2014). Current guidelines for leptospirosis prophylaxis published by the Centre of Disease Control in United States also concluded optimal dosage of 200mg doxycycline per week for the duration of exposure.

A study reported that a person had developed an erythematous rash after the first dose of doxycycline 200 mg and had to be withdrawn from the trial (Sehgal et al., 2000). Later, two other individuals were reported to suffer from gastritis with severe stomach pain and vomiting, and thus they were also withdrawn from the trial. A few subjects in the control group who were given placebo, also reported mild adverse effects, mainly nausea. Allergic reactions were treated with antihistamines and gastritis with H2 receptor antagonists and antacids. However, none of the subjects needed hospitalisation owing to adverse reactions (Sehgal et al., 2000). In another study done in Southern Thailand, it was reported that 12 participants who received doxycycline developed gastrointestinal symptoms. Among these participants, ten developed nausea without vomiting. Two patients developed vomiting during the 2-hour observation period at the first assessment. However, none of these twelve patients developed leptospirosis or leptospiral infection. One participant developed a skin rash, mostly involving the anterior chest wall and neck which spontaneously resolved within a few days (Chusri et al., 2014). One study done among soldiers in Panama also reported that thirteen of the subjects had vomiting after given the doxycycline pills. There was also one subject who received placebo who had episode of vomiting. However, there were more subjects who received doxycycline and complained of vomiting than the subjects who received placebo ($p < 0.01$). Therefore, it was assumed that the vomiting was doxycycline-related. To summarize the occurrence of adverse effects of antibiotic prophylaxis (doxycycline) against leptospirosis, there were only a limited number of cases, and even those with adverse effects had mild symptoms and only received outpatient treatment. The benefits of prophylaxis use appear to outweigh the risk of adverse effects. There was no study which assessed the possible adverse effects of penicillin use as prophylaxis for leptospirosis.

Among the eight selected studies, all studies had related the association of leptospirosis with study settings. First, the most significant setting would be the occurrence of leptospirosis

due to contact with flood. The main route of transmission was due to flooding of homes during the summer rainy season when the rainwater catchment system was inadequate (Gonsalez et al., 1998). As the leptospira bacterium is commonly found in soil, the flood water sufficiently distributed the pathogen to the affected areas and increases the chance of getting the infection. Thus, as suggested by most of the selected studies, the occurrence of leptospirosis can be controlled through the use of prophylaxis among the population in areas with high risk of flooding. Second, the significant setting for leptospirosis infection was through the high-risk occupations that involve contact with possible contaminated environments or directly in contact with the pathogens such as the army, farmers and laboratory workers. Other occupation such as abattoir workers, front-liners in veterinary establishments, municipal workers and fire fighter/rescue responders also has high risk for getting leptospirosis. Last but not least, athletes that were involved with water-related activities showed increasing occurrence in contracting leptospirosis (James et al., 2003).

Out of the six studies evaluated for effectiveness of antibiotic prophylaxis against leptospirosis, all had reported protective association, although only three were statistically significant. One of the studies which failed to show a significant association was a well-designed experimental study using double-blinded, randomized trial with placebo control. However, the study had a small sample size (40 in experimental group vs 42 in placebo group) and this was most likely the major reason for not getting a statistically significant result (Gonsalez et al., 1998). This is in contrast to another study, whereby the sample size was larger but the flawed study design may have caused the result to not be statistically significant (James et al., 2003). Subjects who participated in an eco-challenge sports tourism event in the Malaysian Borneo were recruited through phone call. History on symptoms and use of antibiotic prophylaxis were obtained, and it was difficult to ascertain the validity of their history due to recall bias. Although the cases were confirmed by laboratory investigation (microscopic agglutination test, MAT), for a retrospective cohort study in which most of the history taking was obtained via subject self-report, there is always the concern with bias that could have been eliminated by conducting a prospective study or a controlled trial.

Another study had also reported a protective association of antibiotic prophylaxis against leptospirosis but again the result was not statistically significant. This may be due to the fact that this was the only study using oral penicillin instead of doxycycline as the antibiotic for prophylaxis (Illangasekera et al., 2008). The same study also had the lowest incidence rate in its population at risk as compared to the other five studies of concern (1.8% incidence rate in control group vs. 4.2% incidence rate in control group of the next lowest study which was reported in 1982 (Takafuji et al., 1984)). The low incidence rate may represent the relatively lower risk of leptospirosis in the study setting, which had subsequently caused the experimental group to be free from leptospirosis for the study period and caused the result to become not statistically significant. In summary, antibiotic prophylaxis against leptospirosis, particularly doxycycline, irrespective of single or multiple doses regime, has been shown to be protective in preventing leptospirosis infection.

When the six studies were pooled, it was noted that there was significant protective association of antibiotic prophylaxis against the incidence of leptospirosis. The low heterogeneity of results suggests that the basis of antibiotic prophylaxis protective association against leptospirosis was generally reproducible across studies of differing settings. The association was also relatively strong whereby those who used antibiotic prophylaxis (any type and any dose) to protect against leptospirosis had only one third the risk of being infected compared to those without prophylaxis (RR = 0.31; 95% CI: 0.20, 0.48).

Conclusion

Antibiotic prophylaxis for leptospirosis had been shown to be effective in preventing the incidence of the disease among high-risk populations. It was also shown that the antibiotic prophylaxis carried minimal risk in the form of trivial adverse effects, which were manageable with outpatient treatment. It is recommended that the practice of antibiotic prophylaxis for leptospirosis is included in the standard protocol for leptospirosis prevention among people at

high-risk, and pre-exposure prophylaxis should always be considered. Guidelines for disaster response team, which usually include fire fighters, health care workers and other governmental or non-governmental personnel, should include provision for recommendation of antibiotic prophylaxis prior to entry to leptospirosis-related settings, especially flood areas. The use of pre-exposure antibiotic prophylaxis against leptospirosis among patrons of water sports or eco-sports tourism activities is also suggested. It is recommended to use oral doxycycline as the choice of prophylaxis, either as a single 200 mg dose or weekly dose of 200 mg for the duration of exposure, based on the setting, duration of event and resources available. Other types of antibiotics are not recommended as evidence from systematic review is still lacking.

Declaration of Interest

The authors declare no conflicting interests whatsoever. This study was self-funded and has received no financial support from any third-party organization.

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