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Risk Factors for Leptospirosis Infection in Humans and Implications for Public Health Intervention in Indonesia and the Asia-Pacific Region

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Abstract

Prevention and control of leptospirosis require an understanding of risk factors. This review identifies risk factors associated with leptospirosis infection from countries in the Asia-Pacific region, and compares and contrasts these data with those available from Indonesia. MEDLINE, PubMed, and Scopus databases were used to search for relevant articles. Indonesian gray literature was searched for leptospirosis risk factor studies in Indonesia. A total of 34 articles were included in this review. The contrast between peer-reviewed publications and Indonesian gray literature revealed that the variety of risk factors associated with leptospirosis infection is region or area specific. The presence of skin wounds, the existence of rodents, especially rats, and activities related to contact with contaminated surface water are factors frequently reported to have significant association with leptospirosis infection in human in Indonesia and in other Asia-Pacific countries.

Keywords

leptospirosis, risk factors, prevention, Indonesia, Asia-Pacific region

Introduction

Leptospirosis is a globally important bacterial zoonotic disease caused by a variety of leptospiral serotypes. It occurs worldwide especially in the tropical and subtropical areas with heavy rainfall. Clinically, leptospirosis is an illness characterized by fever, headache, and myalgia. Other manifestations that might be present are jaundice, acute renal failure, bleeding, including pulmonary hemorrhage syndrome, meningitis, myocarditis, and uveitis.[1]

Leptospirosis incubation period is usually 5 to 14 days. Diagnosis of leptospirosis requires confirmation from laboratory tests. Several laboratory methods to diagnose leptospirosis are available, for example, microscopic agglutination test (MAT), indirect hemagglutination assay, enzyme-linked immunosorbent assay, polymerase chain reaction, and culture.[2-4]

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Data on the worldwide incidence and prevalence of human leptospirosis are limited.[5] Incidence of leptospirosis is in the range of 0.1 to 1 per 100 000 per year in temperate climates, 10 to 100 per 100 000 per year in the tropics, and more than 100 per 100 000 during outbreaks.[4] The World Health Organization's regions with the highest median incidence of leptospirosis are in Africa (95.5/100 000) and the Western Pacific (66.4/100 000). The median incidence for America and Southeast Asia regions is 12.5/100 000 and 4.8/100 000, respectively.[6] Victoriano et al[7] classified the annual incidence of leptospirosis for countries in the Asia-Pacific region into 3 groups: low (<1 per 100 000), moderate (1-10 per 100 000), and high (>10 per 100 000). The mortality among severe leptospirosis cases is in the range of 5% to 40%.[3] Leptospirosis generally imposes public health, economic, and societal costs that affect both the individual and communities. Such impact may include illness and health care costs, the lowering of worker productivity and output, and lost productivity due to illness and death of livestock.[1,3,8]

The occurrence of leptospirosis is closely related to the chain of infection, and the link in the leptospirosis infection chain is associated with many factors. These factors or conditions that increase the chance of being infected or developing the disease are considered to be risk factors of infection or disease in humans.[9] Risk factors for leptospirosis can be classified into 3 main groups: animal factors, environmental factors, and human factors.[3,10] Understanding the risk factors, within and between these groups, is important in the selection of approaches, to disrupt the chain of infection and prevent the spread of leptospirosis.

Indonesia is one of many countries in the Asia-Pacific region with a moderate annual incidence of leptospirosis.[7] The first case of leptospirosis in Indonesia was documented in 1918 by Schuffner in the east coast of Sumatra island.[11] In 1922, Vervoort confirmed human leptospirosis among plantation workers on the east coast of Sumatra.[12] Since then, most of the main islands of Indonesia such as Java, Bali, Kalimantan, and Sulawesi have identified and reported cases of leptospirosis. The number of human leptospirosis cases reported annually to the Ministry of Health from 2007 to 2011 was 664, 426, 335, 409, and 857, respectively; however, not all provinces routinely report leptospirosis cases annually. Annual case fatalities for the years 2007 to 2011 were 8.28%, 5.16%, 6.87%, 10.51%, and 9.57%, respectively.[13,14] The actual number of leptospirosis cases in Indonesia is possibly higher than that reported. The underreporting is often because of the infection being clinically unapparent, too mild for definitive diagnosis, misdiagnosed as dengue fever or other endemic diseases, and because of the lack of laboratory centers' ability to perform confirmatory tests. There is a paucity of available data about the risk and incidence of leptospirosis in Indonesia in comparison with other communicable diseases, such as dengue hemorrhagic fever or malaria. Peer-reviewed publications on leptospirosis research conducted in Indonesia have predominantly focused on clinical and laboratory factors rather than public health determinants. Studies focusing on risk factors for human leptospirosis in Indonesia are mainly available as reports in gray literature. Consequently, data sourced from gray literature is an important resource for public health planning for prevention or control of leptospirosis in Indonesia.

To the best of our knowledge, no systematic review is available comparing and contrasting risk factors for human leptospirosis reported in Indonesian gray literature and studies from other Asia-Pacific countries. This study will check and synthesize data from gray literature and peer-reviewed sources to find similarities and differences associated with leptospirosis risk factors in the Asia-Pacific region. Additionally, this review will consider regional implications for implementing public health prevention and control programs.

Methods

Medline, PubMed, and Scopus databases were used to search for peer-reviewed articles on leptospirosis risk factors. Criteria used for selecting the articles were (1) articles in English published before January 2012, (2) study on leptospirosis in humans, (3) the study objective was to

assess risk factors for leptospirosis infection or disease in humans, (4) strength of association was measured and presented, and (5) the study site was in the Asia-Pacific region. The Asia-Pacific region included countries in Asia and the countries of Pacific Rim. Terms 'leptospirosis, risk factor' were entered for searching and they were separated by the Boolean "AND." A total of 826 articles were identified on leptospirosis risk factors of which 737 articles were related to humans. After removing repeated articles, abstracts from 363 articles were reviewed and assessed in relation to the extent they provided information on risk factors for leptospirosis infection or disease in humans. Ninety-six articles fulfilling criterion 3 were selected. The full text of 96 selected articles was searched and evaluated for the strength of association values presentation (odds ratio, risk ratio, or prevalence ratio. The total number of articles that measured and presented the strength of association was 36. Seventeen articles with study sites not in the Asia-Pacific region were excluded. The final selected peer-reviewed articles fulfilling all the inclusion criteria were 19 articles. Relevant studies found in the reference list of the chosen articles and not found in the selected articles were also searched. Although no articles on Indonesian studies of human leptospirosis risk factors were found in the databases searched, these data were sourced from Indonesian gray literature studies published prior to January 2012. These Indonesian studies were obtained by searching local university library Web sites and local government health office Web sites. Searching articles or gray literature for leptospirosis risk factors studies that were specific to Demak district, Central Java Province, was conducted by visiting local health offices and related institutions. Fourteen studies that examined risk factors of leptospirosis infection or disease in humans were included as these studies assessed and reported the strength of association. This resulted in a total of 34 peer-reviewed and other publications being included in this review. The flowchart of the selection process of article is shown in Figure 1.

Reported risk factors for leptospirosis infection in humans were summarized. Similarities and differences of reported human leptospirosis risk factors in Indonesia and in other Asia-Pacific countries is identified and presented.

Results

This section reports the differences and similarities found in the selected peer-reviewed journal articles and the gray literature from Indonesia.

Characteristics of Selected Studies

Table 1 presents characteristics of the 34 selected studies. Case–control (21; 61.8%) and cross-sectional (13; 38.2%) designs were the main designs used in the studies. The majority of Indonesian leptospirosis risk factor studies (13; 92.9%) were conducted by Indonesian university researchers. In contrast, government agencies of the other Asia-Pacific countries were leading contributors for the majority of studies that investigated leptospirosis risk factors (14; 70.0%). Many of the leptospirosis risk factor studies in Indonesia lacked diagnostic confirmation for cases cited (9; 64.3%), as only rapid test results and clinical characteristics of respondents were relied on to support the diagnosis. By contrast, leptospirosis risk factor studies from other Asia-Pacific countries used MAT (13; 65.0%) and enzyme-linked immunosorbent assay (7; 35.5%) for diagnostic confirmation of leptospirosis disease or infection (data are not presented in the table).

Environmental Risk Factors for Leptospirosis Infection

Indonesian studies frequently (13; 92.9%) point to flooding, stagnant water surrounding the house, poor sewer condition, and poor sanitation of the house and surroundings as potential environmental risk or modifiable determinants for leptospirosis infection. This contrast to the risk

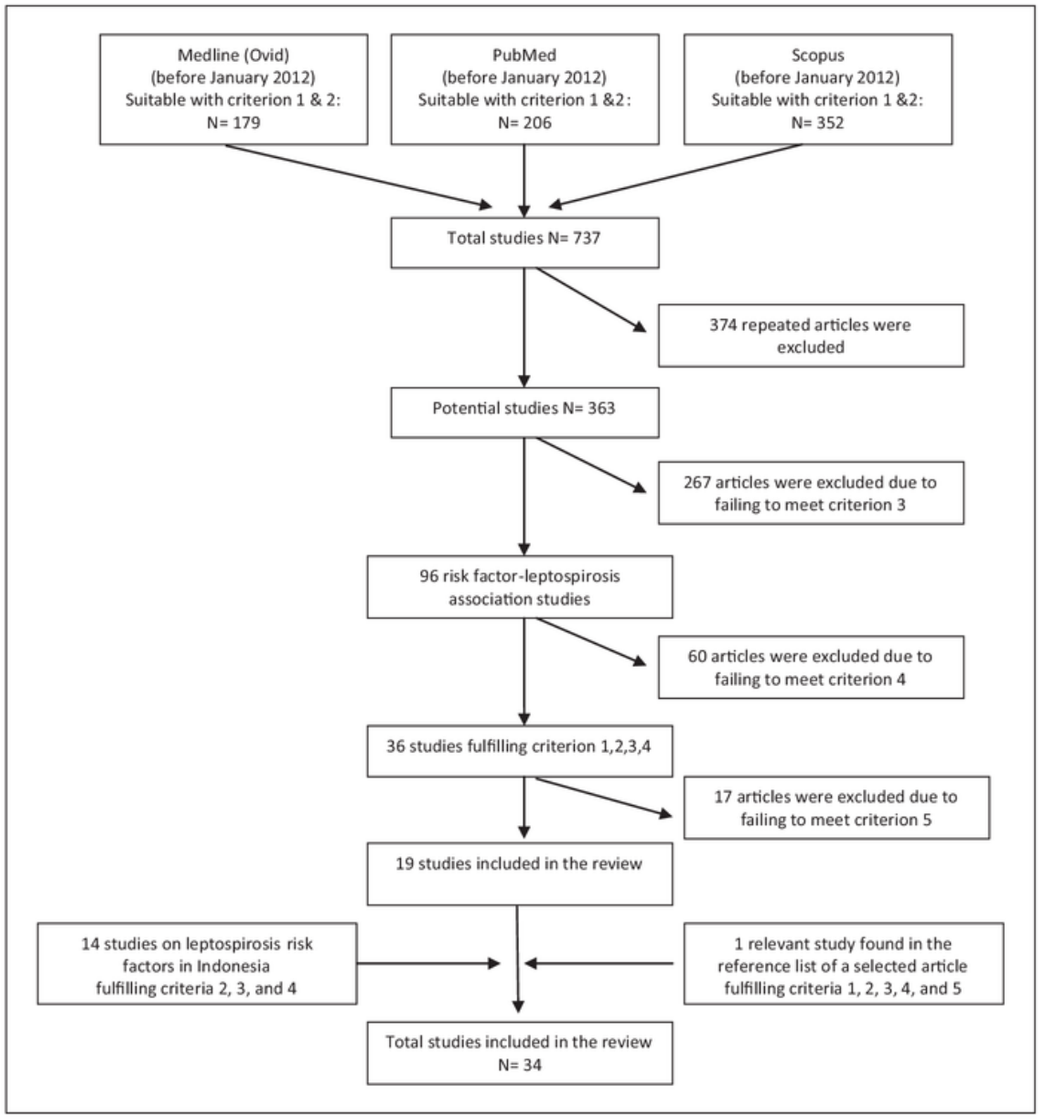

Figure 1. Flowchart of selection of articles.
Inclusion criteria: (1) Peer-reviewed article in English, (2) study on leptospirosis related to human, (3) the study objective was to asses risk factors for leptospirosis infection in humans, (4) strength of association was measured and presented, and (5) the study site was in the Asia-Pacific region.

factors reported in other Asia-Pacific country studies; 7 out of 20 studies investigated these environment factors as studied potential risk factors for leptospirosis (Table 2). Eleven out of 14 studies in Indonesia showed that stagnant water, flooding, poor sewer condition, and poor house sanitation were the environmental factors that had a significant association with leptospirosis infection.[15-24] In Indonesia, none of the selected studies reported significant association between flooding and leptospirosis infection in the multivariate analysis. However, 2 out of 9 Indonesian studies that investigated the association between the existence of stagnant water surrounding residential properties and human leptospirosis infection reported a significant association in the multivariate analysis.[15,19]

Table 1. Characteristics of the Studies.

Studies	Study Design	Characteristics			Total Number of Samples
		Institution	Study Sites	Population for Comparison Group	
Indonesia[a]					
Handayani and Ristiyanto, 2008[16]	CS	Indonesia-Gov	Indonesia	General population	101
Priyanto, 2008[17]	CC	Indonesia-Univ	Indonesia	Hospital patients	123
Putri, 2009[18]	CC	Indonesia-Univ	Indonesia	Neighborhood of the cases	120
Ikawati, 2010[29]	CC	Indonesia-Univ	Indonesia	Neighborhood of the cases	88
Anies et al, 2009[15]	CC	Indonesia-Univ	Indonesia	Hospital patients	120
Wiharyadi, 2004[19]	CC	Indonesia-Univ	Indonesia	Hospital patients	86
Sarwani, 2005[20]	CC	Indonesia-Univ	Indonesia	Hospital patients	126
Suratman, 2008[21]	CC	Indonesia-Univ	Indonesia	Neighborhood of the cases	114
Murtiningsih, 2005[44]	CC	Indonesia-Univ	Indonesia	Neighborhood of the cases	106
Okatini et al, 2007[22]	CC	Indonesia-Univ	Indonesia	Hospital patients	190
Hasanah, 2007[24]	CS	Indonesia-Univ	Indonesia	General population	50
Prasetyo, 2006[23]	CC	Indonesia-Univ	Indonesia	Hospital patients	154
Hernowo, 2002[39]	CC	Indonesia-Univ	Indonesia	General population	180
Suprapto, 1997[48]	CC	Indonesia-Univ	Indonesia	Neighborhood of the cases	70
Other countries[b]					
Sulong et al, 2011[40]	CS	Malaysia-Univ	Malaysia	Town service workers	296
Stern et al, 2010[42]	CC	USA-Gov	USA	Adventure race participants	192
Sugunan et al, 2009[43]	CC	India-Gov	India	Neighborhood of the cases	156
Bhardwaj et al, 2008[27]	CC	India-Univ	India	People visiting the hospital	315
Kawaguchi et al, 2008[45]	CS	Japan-Univ	Lao-PDR	General population	406
Thai et al, 2006[28]	CS	Netherlands-Univ	Vietnam	Schoolchildren	961
Vijayachari et al, 2004[32]	CS	India-Gov	India	Schoolchildren	341
Johnson et al, 2004[33]	CS	Peru-Gov and USA-Univ	Peru	General population	195
Leal-Castellanos et al, 2003[30]	CS	Mexico-Gov	Mexico	General population	1169
Sehgal et al, 2003[34]	CS	India-Gov	India	Hospital patients	3682
Sejvar et al, 2003[31]	CC	USA-Gov	Malaysia	Echo-challenge athletes	189
Phraisuwan et al, 2002[41]	CS	Thailand-Gov	Thailand	Pond cleaning participants	104
Morgan et al, 2002[46]	CC	USA-Gov	USA	Triathlon participants	834
Tangkanakul et al, 2001[26]	CC	Thailand-Gov	Thailand	Neighborhood of the cases	201
Ashford et al, 2000[35]	CS	USA-Gov and Nicaragua-Gov	Nicaragua	El Sauce town community	566
Tangkanakul et al, 2000[25]	CC	Thailand-Gov	Thailand	Neighborhood of the cases	177
Campagnolo et al, 2000[47]	CS	USA-Gov	USA	People exposed to UMC swine herd	163
Murhekar et al, 1998[36]	CC	India-Gov	India	General population	1014
Sasaki et al, 1993[38]	CC	USA-Gov	Hawaii	Hospital patients	110
Childs et al, 1992[37]	CS	USA-Univ	USA	People visiting the clinic	200

Abbreviations: CS, cross-sectional study; CC, case–control study; Gov, government; Univ, university.
[a]Gray literature.
[b]International peer-reviewed literature.

Animal Factors for Leptospirosis Infection to Humans

Twenty-five of the 34 studies from both Indonesia and other Asia-Pacific countries point out that presence of rats and domestic animal are important risk factors in the potential transmission of human leptospirosis. Eight out of 13 Indonesian studies and about a quarter of studies from other Asia-Pacific countries have reported a significant association between the existence of rats in close proximity to human habitation and the occurrence of human leptospirosis infection or disease (Table 2). Surprisingly, none of the 11 Indonesian studies showed a significant association between the existence of domestic animals/livestock close to residential premises and leptospirosis infection. On the contrary, several leptospirosis risk factor studies from other Asia-Pacific

Table 2. Environmental and Vector-Related Risk Factors Associated With Leptospirosis Infection.

Studies	Environmental and Vector-Related Factors					
	Flooding in the Past 14 Days	Stagnant Water in the Surrounding House	Poor Sewer Condition	Poor House Sanitation	Existence of Rats	Existence/Owned Domestic Animals
Indonesia[a]						
Handayani and Ristiyanto, 2008[16]	o	~	o	X	X	^
Priyanto, 2008[17]	o	X	XX	XX	XX	^
Putri, 2009[18]	^	^	o	X	X	^
Ikawati, 2010[29]	^	^	^	^	^	o
Anies et al., 2009[15]	o	XX	^	o	^	^
Wiharyadi, 2004[19]	X	XX	^	X	X	^
Sarwani, 2005[20]	o	X	X	XX	XX	^
Suratman, 2008[21]	X	o	XX	^	XX	^
Murtiningsih, 2003[44]	o	o	o	o	XX	^
Okatini et al, 2007[22]	o	o	X	X	^	o
Hasanah, 2007[24]	~	o	o	X	^	^
Prasetyo, 2006[23]	X	X	X	X	XX	^
Hernowo, 2002[39]	X	o	o	o	o	^
Suprapto, 1997[48]	o	^	^	^	^	o
Other countries[b]						
Sulong et al, 2011[40]	^	o	o	^	XX	^
Stern et al, 2010[42] #	o	o	o	o	o	o
Sugunan et al, 2009[43]	o	o	o	o	^	XX
Bhardwaj et al, 2008[27]	o	o	o	o	XX	o
Kawaguchi et al, 2008[45]	XX	o	o	o	^	^
Thai et al, 2006[28] *	o	o	o	o	o	^
Vijayachari et al, 2004[32] *	—	—	—	—	—	X
Johnson et al, 2004[33]	o	o	o	X	^	^
Leal-Castellanos et al, 2003[30]	X	X	o	o	^	XX
Sehgal et al, 2003[34]	o	X	o	X	X	X
Sejvar et al, 2003[31] #	o	o	o	o	o	o
Phraisuwan et al, 2002[41]	o	o	o	o	o	o
Morgan et al., 2002[46] #	o	o	o	o	o	o
Tangkanakul et al, 2001[26]	o	o	o	^	^	^
Ashford et al, 2000[35]	o	o	o	o	^	^
Tangkanakul et al, 2000[25]	o	o	o	o	o	X
Campagnolo et al, 2000[47]	o	o	o	o	o	o
Murhekar et al, 1998[36]	o	^	o	o	^	^
Sasaki et al, 1993[38]	o	o	o	o	^	^
Childs et al, 1992[37]	o	o	o	o	^	X
Number of studies with significant association/number of studies examined the association	6/10	7/12	5/9	10/15	11/25	6/25

X = significant ($P < .05$) in the bivariate analysis; XX = significant ($P < .05$) in the multivariate analysis; * = study among children; # = study among adventure race participants; o = factor was not examined; ^ = factor was examined, no significant association; ~ = factor was examined, no information regarding association test; — = no information provided.
[a]Gray literature.
[b]International peer-reviewed literature

countries showed that the presence of domestic animals was significantly associated with human leptospirosis infection.

Human Factors for Leptospirosis Infection

The human behavior–related risk factors included in Indonesian leptospirosis studies (Table 3) were contact with stagnant water (4; 28.6%); contact with river or flood water, muddy areas (4; 28.6%); swimming in a river (2; 14.3%); taking a bath in a river (6; 42.9%); washing in a river

Table 3. Human-Related Risk Factors: Behavior-Related Factors Associated With Leptospirosis Infection.

	Behavior-Related Factors										
Studies	Contact With Stagnant Water	Contact With Flood Water/ River/Muddy Area	Swimming in the Stream/ River/Flood	Taking a Bath in the River/Pond / Flood Water	Washing in or Using the River/ Pond/Flood Water	Contact With Rat's Body/ Urine/Tissues	Contact With Domestic Animal' Body, Urine	Not Wearing Personal Protection	Walking Barefoot	Wearing Shorts in the Watery Place	Using Stream as Source of Drinking Water
Indonesia[a]											
Handayani and Ristiyanto, 2008[16]	o	o	^	^	^	o	o	o	o	o	o
Priyanto, 2008[17]	o	o	o	X	X	o	o	o	XX	o	o
Putri, 2009[18]	o	o	o	o	o	o	o	o	o	o	^
Ikawati, 2010[29]	^	^	o	o	o	^	o	o	o	o	o
Anies et al., 2009[15]	X	^	o	X	X	^	^	^	o	o	o
Wiharyadi, 2004[19]	X	X	o	o	o	o	o	o	o	o	o
Sarwani, 2005[20]	o	o	o	^	^	o	o	^	^	o	o
Suratman, 2008[21]	o	o	o	^	^	XX	o	^	o	o	^
Murtiningsih, 2003[44]	o	o	^	X	X	o	o	o	o	o	o
Okatini et al., 2007[22]	o	o	o	o	o	o	o	o	o	o	o
Hasanah, 2007[24]	o	o	o	o	o	o	o	o	o	o	o
Prasetyo, 2006[23]	X	X	o	o	o	o	o	o	o	o	o
Hernowo, 2002[39]	o	o	o	o	o	^	^	XX	o	o	o
Suprapto, 1997[48]	o	o	o	o	o	o	o	o	o	o	o
Other countries[b]											
Sulong et al, 2011[40]	o	o	o	o	o	^	^	XX	o	o	o
Stern et al, 2010[42] #	o	o	^	o	o	o	o	o	o	^	o
Sugunan et al, 2009[43]	^	o	^	o	^	^	^	o	XX	o	XX
Bhardwaj et al, 2008[27]	o	XX[c]	X	X	X	^	^	o	XX	o	^
Kawaguchi et al, 2008[45]	o	^	^	o	o	o	o	o	X	o	^
Thai et al, 2006[28] *	o	XX	X	o	X	o	o	o	^	o	^
Vijayachari et al, 2004[32] *	—	X[d]	—	X	—	—	—	—	—	—	—
Johnson et al, 2004[33]	o	o	o	X	o	o	o	XX	o	o	^
Leal-Castellanos et al, 2003[30]	X	o	X	o	o	o	XX[e]	XX[e]	X	o	o
Sehgal et al, 2003[34]	o	o	o	X	X	o	X	o	o	o	o
Sejvar et al, 2003[31] #	o	o	XX	o	o	o	o	o	o	o	o
Phraisuwan et al, 2002[41]	o	o	o	o	o	o	o	o	o	XX	o

(continued)

Table 3. (continued)

Studies	Behavior-Related Factors										
	Contact With Stagnant Water	Contact With Flood Water/ River/Muddy Area	Swimming in the Stream/ River/Flood	Taking a Bath in the River/Pond / Flood Water	Washing in or Using the River/ Pond/Flood Water	Contact With Rat's Body/ Urine/Tissues	Contact With Domestic Animal' Body, Urine	Not Wearing Personal Protection	Walking Barefoot	Wearing Shorts in the Watery Place	Using Stream as Source of Drinking Water
Morgan et al, 2002[46] #	o	o	^	o	o	o	o	o	o	o	o
Tangkanakul et al, 2001[26]	XX	o	o	o	o	o	o	o	o	o	o
Ashford et al, 2000[35]	o	^	^	X	X	o	o	o	^	o	XX
Tangkanakul et al, 2000[25]	XX	o	o	o	o	o	o	^	o	o	o
Campagnolo et al, 2000[47]	o	o	o	o	o	o	^	^	o	o	o
Murhekar et al, 1998[36]	X	o	o	X	o	o	^	o	^	o	^
Sasaki et al, 1993[38]	o	^	^	o	o	^	X	o	o	o	^
Childs et al, 1992[37]	o	o	o	o	o	XX	o	o	o	o	o
Number of studies with significant association/ number of studies examined the association	7/9	5/10	4/12	9/12	7/11	2/9	3/10	4/9	5/9	1/2	2/10

X = significant ($P < .05$) in the bivariate analysis; XX = significant ($P < .05$) in the multivariate analysis; * = study among children; # = study among adventure race participants; o = factor was not examined; ^ = factor was examined, no significant association; — = no information provided.

[a]Gray literature.

[b]International peer-reviewed literature.

[c]Contact of injured part with flood water.

[d]Contact with muddy floor in the house.

[e]Contact with animal excreta with no protection and with skin cut

(6; 42.9%); contact with animal urine, bodies, or tissues (4; 28.6%); not wearing personal protection equipment (4; 28.6%); walking barefoot (2; 14.3%); and using streams as a source of drinking water (2; 14.3%). Not all studies on behavior-related risk factors for leptospirosis in Indonesia showed significant association with leptospirosis infection in humans. Studies in other Asia-Pacific countries showed that contact with stagnant water (2; 40.0%) and contact with flood or river water (2; 33.3%) are significantly associated with leptospirosis infection in humans after accounting for the influences of other potential risk factors for human leptospirosis.[25-28] In contrast, studies in Indonesia did not show or only showed a weak association.[15,19,23,29] Only 2 of the 14 Indonesian studies examined association between leptospirosis infection in humans and swimming in the river, and both studies reported that no significant association was found (Table 3). However, 4 out of 10 studies in other countries[27,28,30,31] that examined association between swimming in river water and human leptospirosis infection showed significant associations.

Studies in other Asia-Pacific countries on the association between leptospirosis infection in humans and taking a bath in a river[27,32-36] or washing clothes in a river[27,28,34,35] showed similar results with corresponding studies in Indonesia. The Indonesian and other Asia-Pacific countries studies showed significant association in the bivariate analysis. Similarly, a significant association between direct contact with rat bodies, tissue, or urine and leptospirosis infection in humans was shown in the multivariate analysis by 1 out of 4 studies in Indonesia[21] and by 1 out of 5 studies in other countries.[37] None of 14 Indonesian studies showed significant association between contact with domestic animal and human leptospirosis infection. In contrast, 3 out of 8 studies in other Asia-Pacific countries showed significant association.[30,34,38]

Not wearing personal protective equipment was significantly associated with human leptospirosis infection. These findings were from studies that investigated specific study sites and activities, such as an outbreaks of leptospirosis after flooding,[39] among town service workers,[40] in a slum and flood-prone area,[33] in an endemic area, and in contact with animal excreta.[30] The protective benefit of wearing long trousers or long skirts, instead of shorts, in watery places has been shown in pond-cleaning activities in Thailand.[41] People who wore long trousers or long skirts reduced their risk of contracting leptospirosis infection (odds ratio = 0.217; 95% confidence interval = 0.067-0.701). However, this contrasts with findings from Stern et al[42] who found no association between wearing shorts and leptospirosis infection among adventure race participants in Florida.

Drinking contaminated water can be a risk for leptospirosis infection in human if the water is untreated. Two of 8 studies in other Asia-Pacific countries[35,43] showed that using streams as a source of drinking water (unboiled water) in the endemic areas was significantly related to leptospirosis infection in humans. Surprisingly, none of the 2 Indonesian studies that examined association between drinking or swallowing river water and leptospirosis infection in humans showed a significant association.

Table 4 details findings from studies that have reported an association between occupational factors and leptospires infection in humans. Risk factor studies for leptospirosis infection in Indonesia (12; 85.7%) and in other countries (10; 50.0%) included occupational related determinants as investigated variables. However, many of the studies combined multiple activities related to contact with suspected contaminated water or substances into one variable, such as outdoor labour,[36] work standing in water,[43] risk occupation,[15,20] manual labourers,[34] workplaces exposure to contamination, and activities in watery places.[19] Occupational factors associated significantly with leptospirosis infection included workers in contact with contaminated surface water or substances;[17,19,23,30,43] activities in the paddy field;[25,36,43,44] collecting wood in the forest;[35,45] clearing up garbage.[43] None of 14 the reviewed studies in Indonesia examined an association between work in forests and leptospirosis infection. However, 3 studies in other countries that examined association between working in forests and leptospirosis infection in humans had indicated a significant association. Indonesian studies (5; 50.0%) and other

Table 4. Human-Related Risk Factors: Occupation-Related Factors Associated With Leptospirosis Infection.

Studies	Occupation-Related Factors						
	Work Related to Contact With Contaminated Surface Water or Substance	Activities in the Paddy Field	Activities In Agriculture Field Other Than Paddy Field	Catching Fish in the River/ Pond/Irrigation Waterway	Collect Wood/Work Activity in the Forest	Cleaning up Sewage	Clearing Garbage
Indonesia[a]							
Handayani and Ristiyanto, 2008[16]	o	^	o	^	o	o	o
Priyanto, 2008[17]	XX	o	o	o	o	o	o
Putri, 2009[18]	^	o	o	o	o	o	o
Ikawati, 2010[29]	o	o	o	o	o	o	o
Anies et al, 2009[15]	^	o	o	o	o	o	o
Wiharyadi, 2004[19]	XX	o	o	o	o	o	o
Sarwani, 2005[20]	^	o	o	o	o	o	o
Suratman, 2008[21]	X	o	o	o	o	o	o
Murtiningsih, 2003[44]	o	XX	o	^	o	o	o
Okatini et al, 2007[22]	^	o	o	o	o	o	o
Hasanah, 2007[24]	X	o	o	o	o	o	o
Prasetyo, 2006[23]	XX	o	o	o	o	o	o
Hernowo, 2002[39]	^	o	o	o	o	o	o
Suprapto, 1997[48]	o	o	o	o	o	o	o
Other countries[b]							
Sulong et al, 2011[40]	o	o	o	o	o	o	o
Stern et al, 2010[42] #	o	o	o	o	o	o	o
Sugunan et al, 2009[43]	XX	X	^	^	o	X	XX
Bhardwaj et al, 2008[27]	o	o	o	o	o	o	o
Kawaguchi et al, 2008[45]	o	^	^	^	XX	o	o
Thai et al, 2006[28] *	o	o	o	o	o	o	o
Vijayachari et al, 2004[32] *	—	—	X[c]	—	—	—	—
Johnson et al, 2004[33]	o	o	o	^	o	o	o
Leal-Castellanos et al, 2003[30]	XX	o	o	o	o	o	o
Sehgal et al, 2003[34]	X	o	o	o	o	o	o
Sejvar et al, 2003[31] #	o	o	o	o	o	o	o
Phraisuwan et al, 2002[41]	o	o	o	o	o	o	o
Morgan et al, 2002[46] #	o	o	o	o	o	o	o

(continued)

Table 4. (continued)

Studies	Occupation-Related Factors						
	Work Related to Contact With Contaminated Surface Water or Substance	Activities in the Paddy Field	Activities In Agriculture Field Other Than Paddy Field	Catching Fish in the River/ Pond/Irrigation Waterway	Collect Wood/Work Activity in the Forest	Cleaning up Sewage	Clearing Garbage
Tangkanakul et al, 2001[26]	o	o	o	o	o	o	o
Ashford et al, 2000[35]	^	o	X	o	XX	^	^
Tangkanakul et al, 2000[25]	o	XX	o	^	o	o	o
Campagnolo et al, 2000[47]	o	o	o	o	o	o	o
Murhekar et al, 1998[36]	X	X	X	X	X	o	o
Sasaki et al, 1993[38]	^	o	o	^	o	o	^
Childs et al, 1992[37]	o	o	o	o	o	o	o
Number of studies with significant association/number of studies examined the association	9/16	4/6	3/5	1/8	3/3	1/2	1/3

X = significant ($P < .05$) in the bivariate analysis; XX = significant ($P < .05$) in the multivariate analysis; * = study among children; # = study among adventure race participants; o = factor was not examined; ^ = factor was examined, no significant association; — = no information provided.

[a]Gray literature.

[b]International peer-reviewed literature.

[c]No information whether or not activity in the paddy field was included.

Asia-Pacific country studies (4; 66.7%) showed that an independent variable composed of several activities related to contact with contaminated water or substances was the most frequently identified occupational variable showing significant association with leptospirosis infection in humans.[17,19,21,23,24,30,34,36,43]

Recreation-related risk factors include all leisure activities, such as, sport or hobbies, which potentially expose participants to a contaminated source of infection (Table 5). Studies from Indonesia (1; 7.1%) and other Asia-Pacific countries (2; 10.0%) investigated leisure activities as a potential risk factor for human leptospirosis; 1 out of 1 Indonesian study and 1 out of 2 other country studies showed a significant association between leisure activities and leptospirosis infection in humans. Findings from all 2 studies in other Asia-Pacific countries that examined swallowing river water during sport competition in the endemic areas and leptospirosis infection in humans showed significant association.[31,42,46]

A greater number of studies in Indonesia (6; 42.9%) than in other Asia-Pacific countries (2; 10.0%) included personal hygiene as a studied potential risk factor for leptospirosis infection in humans. The association between personal hygiene and leptospirosis infection in humans was reported in 3 of the 6 Indonesian studies,[19,23,39] and in both of the studies in other Asia-Pacific countries.[40,47] Four out of 5 studies in Indonesia[19,21,23,25] and 6 out of 11 studies in other countries[27,30,38,41,43,48] reported a significant association between skin wounds and leptospirosis infection in humans.

Significant association between a person's educational attainment level and leptospirosis infection was only demonstrated in 3 out of 11 Indonesian studies.[19,22,23] In contrast, both of studies from the other Asia-Pacific countries reported no significant association. Similarly, 3 out of 5 studies in Indonesia[17,22,24] and 1 out of 2 studies from other Asia-Pacific countries[25] showed significant association between a lack of knowledge and leptospirosis infection in humans.

Discussion

Risk factors for leptospirosis infection or disease in humans, in all geographical areas are reliant on the characteristics of the environment, animals as maintenance or accidental hosts, and the nature of human activity. The Asia-Pacific region comprises both developed and developing countries with tropical and subtropical or temperate climates. Most human cases of leptospirosis infection or disease are found in developing countries in tropical zones, thus most risk factors for leptospirosis infection are found in this climate zone rather than in the subtropical developed countries.[5,7,8,49]

Most Indonesian community-based human leptospirosis risk factor studies only used rapid test procedures rather than a recognized test, such as MAT, for definitive case diagnosis. Reasons for this are there are a limited number of laboratories available to perform MAT and the inability to access these centers especially from rural areas. Consequently, most suspected leptospirosis cases, especially from rural areas, which test positive to rapid method assays are not further tested for diagnostic confirmation.

Some Indonesian studies have shown that several potential risk factors, such as flooding, contact with stagnant water or flood water, and taking a bath or washing in the river are associated with leptospirosis infection in humans only in the bivariate analysis. Although these are important modifiable determinants, it should nevertheless be recognized that other risk factors may also be contributory factors for an association with leptospirosis infection. Therefore, other more influential factors for leptospirosis infection should be considered, for example, the existence of infected animals in close proximity to households and the presence of skin wounds. These findings suggest that such risk factors for leptospirosis infection in humans should not be disregarded especially in endemic areas of Indonesia. These factors include the presence or owning of domestic animal, swimming in rivers, fishing in the streams or rivers, contact with

Table 5. Human-Related Risk Factors: Recreation-, Personal Hygiene–, Skin Wound–, and Sociodemographic-Related Factors Associated With Leptospirosis Infection.

	Recreation-, Personal Hygiene–, Skin Wound–, and Sociodemographic-Related Factors					
Studies	Swallowing Water (River)	Leisure/ Hobby Activities	Unhealthy Personal Hygiene	Existence of Wounds on the Limb(s)	Low Education Level	Lack of Knowledge or Education on Leptospirosis
Indonesia[a]						
Handayani and Ristiyanto, 2008[16]	o	o	o	o	^	o
Priyanto, 2008[17]	o	o	o	o	^	XX
Putri, 2009[18]	o	o	^	o	^	o
Ikawati, 2010[29]	o	o	o	o	^	^
Anies et al, 2009[15]	o	o	o	^	^	^
Wiharyadi, 2004[19]	o	o	XX	XX	X	o
Sarwani, 2005[20]	o	o	o	o	o	o
Suratman, 2008[21]	o	o	^	XX	^	o
Murtiningsih, 2003[44]	o	X	o	o	o	o
Okatini et al, 2007[22]	o	o	o	o	XX	XX
Hasanah, 2007[24]	o	o	o	o	~	X
Prasetyo, 2006[23]	o	o	X	XX	X	o
Hernowo, 2002[39]	o	o	XX	o	o	o
Suprapto, 1997[48]	o	o	^	X	^	o
Other countries[b]						
Sulong et al, 2011[40]	o	XX	XX	^	^	o
Stern et al, 2010[42] #	XX	o	o	^	o	o
Sugunan et al, 2009[43]	o	o	o	X	o	o
Bhardwaj et al, 2008[27]	o	o	o	XX[c]	o	o
Kawaguchi et al, 2008[45]	o	o	o	o	o	o
Thai et al, 2006[28] *	o	o	o	o	o	o
Vijayachari et al, 2004[32] *	—	—	—	—	—	—
Johnson et al, 2004[33]	o	o	o	o	^	o
Leal-Castellanos et al, 2003[30]	o	o	o	XX[d]	o	o
Sehgal et al, 2003[34]	o	o	o	o	o	o
Sejvar et al, 2003[31] #	X	o	o	^	o	o
Phraisuwan et al, 2002[41]	o	o	o	XX	o	o
Morgan et al, 2002[46] #	XX	o	o	^	o	o
Tangkanakul et al, 2001[26]	o	o	o	o	o	X
Ashford et al, 2000[35]	o	o	o	o	o	o
Tangkanakul et al, 2000[25]	o	o	o	X	o	o
Campagnolo et al, 2000[47]	o	o	X	^	o	^
Murhekar et al, 1998[36]	o	o	o	o	o	o
Sasaki et al, 1993[38]	o	^	o	X	o	o
Childs et al, 1992[37]	o	o	o	o	o	o
Number of studies with significant association/number of studies examined the association	3/3	2/3	5/8	10/16	3/13	4/7

X = significant ($P < .05$) in the bivariate analysis; XX = significant ($P < .05$) in the multivariate analysis; * = study among children; # = study among adventure race participants; o = factor was not examined; ^ = factor was examined, no significant association; ~ = factor was examined, no information regarding association test; — = no information provided.

[a]Gray literature.

[b]International peer-reviewed literature.

[c]Contact of injured part with flood water.

[d]Contact with animal excreta with no protection and with skin cut.

domestic animal tissues or urine, and using stream or river water as a source of drinking water. Although, proximity to domestic animals or contact with domestic animals or urine were reported not to be statistically associated with human leptospirosis in Indonesia, the potential for domestic animals as a source of infection should not be dismissed as evidence exists of leptospirosis infection in domestic animals in endemic areas of Indonesia.[50]

Although studies show that occupational contact with contaminated water or substances and activities in the paddy fields are related to leptospirosis infection in humans, other direct determinants, such as skin wounds or abrasions, are also likely to increase susceptibility to leptospirosis infection. Elucidating risk associated with other direct determinants, especially in endemic areas, is important for prevention and control program planning.

Studies, in Indonesia and Asia-Pacific countries, have shown that a lack of knowledge about leptospirosis is significantly related to human leptospirosis. Community education on mode of transmission and risk factors are important preventive measures.[51] Programs to improve community awareness about leptospirosis risk factors, in particular endemic areas or potentially infected areas, should promote avoidance of contact with potentially contaminated water or substance; if exposure is unavoidable because of work activities then personal protection should be encouraged.

Implications for Prevention and Control

Preventive or control action in the public health field mostly deals with identification of sources of infection and controlling transmission of the disease.[52] The focus of leptospirosis prevention or control programs is to break the chain of infection by avoiding direct contact or minimizing the risk of indirect contact with sources of infection and by adopting control measures that show benefit in reducing leptospirosis transmission to humans.[3] Therefore, information on risk factors for leptospirosis disease or infection is a key requirement for successful leptospirosis prevention and control programs.

Leptospirosis prevention and control require community involvement; however, findings from these reviewed studies show that communities in endemic areas have limited knowledge about leptospirosis risk factors. This clearly indicates the need for a strategic approach to improve the risk communication messages. The dissemination of information regarding leptospirosis risk factors and associated preventive measures through educational activities is a priority. Furthermore, for program providers, there is a need to identify modifiable determinants of leptospirosis in the endemic area before developing leptospirosis prevention and control programs. In order to identify major modifiable determinants of leptospirosis, it is essential to analyze the results of leptospirosis risk factor studies. Information from these studies identifies area specific risk factors for leptospirosis infection and also reveals capability gaps and crucial-need areas.

Key findings from this review provide useful data in developing leptospirosis prevention and control programs and need to be considered in relation to other changes occurring in the region. The authors would like to highlight 6 considerations. First, data from these reviewed studies indicate that many Indonesian studies investigating leptospirosis risk factors did not definitively diagnose cases because of the limited availability and accessibility of laboratories able to perform confirmatory testing. To detect common source outbreaks and implement appropriate control measures, it is vital to provide local diagnostic testing laboratories that are accessible and affordable for communities. These testing facilities will benefit communities by enhancing leptospirosis research capabilities, and contribute toward leptospirosis prevention and control research. In 2012, Indonesia established a diagnostic zoonosis laboratory network to improve diagnostic capabilities and provide integrated and comprehensive surveillance system on zoonotic diseases including leptospirosis. However, the success of the roll-out and performance of this laboratory network system has not been evaluated.

Second, while some studies of potential risk factors for human leptospirosis infection in Indonesia reported no significant association or only significant association in the bivariate analysis, consideration needs to be given to the broader developing country literature in which these factors were found to be significant. Additionally, further inquiry for other more influential factors should be performed. One of the influential factors that should be taken into account when

conducting leptospirosis prevention and control program is skin wounds; a number of studies in Indonesia and in other Asia-Pacific countries have shown significant association of skin wound and leptospirosis infection.

Third, in Indonesia, tropical rainforest comprise 60% of the country's land area and a history of leptospirosis outbreak among plantation workers has been reported.[12] Rodents and wild animals are suspected sources of leptospirosis infection in tropical rainforests. With the advent of climate change, it is expected that the number of animal reservoirs with pathogenic leptospires living in or close to the forest may increase.[53] People living near forests or engaged in forest activities should be targeted for leptospirosis prevention programs.

Fourth, the number of leptospirosis cases related to recreational, leisure or hobby activities is increasing globally.[54] Gardening as a hobby is shown to be significantly related to leptospirosis infection in other countries.[40,55,56] Although, currently, no leptospirosis risk factor studies in Indonesia reported significant associations between gardening as a hobby and leptospirosis infection, leptospirosis prevention activities may in the future target individuals who are hobby gardener or who work as gardeners in leptospirosis endemic areas.

Fifth, some studies reported an association between personal hygiene and human leptospirosis infection. The nonuse of soap was mentioned as a potential risk factor. Using soap while taking a bath or washing hands/feet after doing activities related to contact with contaminated water or substance is hypothesized as one way to prevent leptospirosis infection. However, more detail studies are needed to provide definitive evidence regarding the association between personal hygiene and leptospirosis infection in human.

Finally, further investigation is needed for the influence of skin wounds in the association between human leptospirosis and the existence of rats, and between human leptospirosis and occupational contact with contaminated water or substances. This investigation is crucial for leptospirosis prevention and control programs as skin wounds are one of leptospires' potential entries into the human body, and it is a modifiable risk factor.

Study Limitations

Several limitations are identified in this study; these relate to limitations associated with the search process, limitations associated with the size of the studies, the lack of direct comparability between studies, and limitations associated with the study designs. Risk factors studies included in this study were limited to studies with accessible full-text articles in English and Indonesian. This excluded information regarding leptospirosis risk factors from countries with high endemicity of leptospirosis but with limited risk factor studies published in English or Indonesian. Some of the studies reported on were carried out in localized areas; hence the findings may have limited generalizability. The strength of associations of the studied potential risk factors, expressed as the odds ratio, are not presented since it cannot be directly compared because of difference in study designs, and the size of the effect of any leptospirosis risk factors also cannot be directly compared across studies. The authors acknowledge the inherent limitations of cross-sectional studies to investigate causal relationships. However, based on the assumption that leptospirosis risk factors are relatively stable at the time of exposure and the measurement/determination of leptospirosis infection, it is acceptable to treat cross-sectional data like data collected from case–control studies.

Conclusion

The contrast between the peer-reviewed and the Indonesian gray literature revealed that the variety of risk factors for leptospirosis infection in each region or an area is locally specific. Several factors are reported as having an association with leptospirosis infection in humans by the

majority of studies in Indonesia and other countries. Those factors include the presence of skin wounds, the existence of rodents especially rats, and occupational contact with contaminated surface water or substances. No studies in Indonesia showed significant association between exposure to domestic animals, swimming in a river, fishing in ponds or irrigation waterways, and leptospirosis infection in humans. The influence of skin wounds in the association between human leptospirosis and occupational contact with contaminated surface water or substances needs to be investigated further. Ultimately, the public health response should include detection, control, and prevention measures. For Indonesia, this would include but not be limited to (1) the development of a systematic approach for investigating cases in an effort to detect common source outbreaks and implementation of appropriate control measures to manage risk factors and prevent further cases; (2) the need to clearly identify contaminated sources or substances in areas where there is a potential high risk for infection, and inform people of such risk when they are involved in recreational or occupational activities; and (3) people living near endemic areas should routinely receive health education and prevention interventions.

Declaration of conflicting interest

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GENERAL COMMENTS

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