

RESEARCH ARTICLE

Risk factors for human leptospirosis following flooding: A meta-analysis of observational studies

Cho Naing^{1,2☯*}, Simon A. Reid^{3☯}, Saint Nway Aye^{1‡}, Norah Htet Htet^{1‡}, Stephen Ambu¹

1 International Medical University, Kuala Lumpur, Malaysia, **2** Division of Tropical Health and Medicine, James Cook University, Townsville, Queensland, Australia, **3** School of Public Health, University of Queensland, Brisbane, Queensland, Australia

☯ These authors contributed equally to this work.

‡ These authors also contributed equally to this work.

* cho3699@gmail.com



Abstract

Leptospirosis is probably the most widespread zoonotic disease in the world especially in tropical countries. There has been an increase in individual studies, which assessed the frequency of leptospirosis in flood conditions. Some studies showed contact with floods was significantly associated with the occurrence of leptospirosis while other studies reported differently. The objective of this meta-analysis was to synthesize the evidence on the risk factors which are associated with human leptospirosis following flooding. We set up the inclusion criteria and searched for the original studies, addressing leptospirosis in human with related to flood in health-related electronic databases including PubMed, Embase, Ovid Medline, google scholar and Scopus sources. We used the terms 'leptospirosis', 'flood', 'risk factor' and terms from the categories were connected with "OR" within each category and by "AND" between categories. The initial search yielded 557 citations. After the title and abstract screening, 49 full-text papers were reviewed and a final of 18 observational studies met the pre-specified inclusion criteria. Overall, the pooled estimates of 14 studies showed that the contact with flooding was a significant factor for the occurrence of leptospirosis (pooled OR: 2.19, 95%CI: 1.48–3.24, I^2 :86%). On stratification, the strength of association was greater in the case-control studies (pooled OR: 4.01, 95%CI: 1.26–12.72, I^2 :82%) than other designs (pooled OR:1.77,95%CI:1.18–2.65, I^2 :87%). Three factors such as 'being male'(pooled OR:2.06, 95%CI:1.29–2.83), the exposure to livestock animals (pooled OR: 1.95, 95%CI:1.26–2.64), the lacerated wound (pooled OR:4.35, 95%CI:3.07–5.64) were the risk factors significantly associated with the incidence of leptospirosis following flooding in the absence of within-study heterogeneity (I^2 : 0%). We acknowledge study limitations such as publication bias and type 2 statistical errors. We recommended flood control and other environmental modifications that are expected to reduce the risk of leptospiral infection, and a multi-sectoral effort to this aspect would have long-term benefits.

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Introduction

Leptospirosis is probably the most widespread zoonotic disease in the world [1] caused by corkscrew-shaped pathogenic bacteria *Leptospira interrogans* of the genus leptospira [2]. Human infection occurs through direct contact with the urine of animal reservoirs or through contact with contaminated soil or water [3]. The global burden of disease study estimated that approximately 2.9 million (1-25-4-54 million) Disability Adjusted Life Years were lost to leptospirosis. This is more than 70% of the global burden of cholera in that year. On stratification, males were approximately 80% and young adults aged 20–49 years were 52% of the total burden [4]. Although a widespread zoonotic in the world, it is particularly common in the tropics [1]. Clinical manifestations range from a mild form of illness including fever, chills and headache to life-threatening conditions (e.g., Weil disease), characterized by jaundice, renal impairment and hemorrhage [5]. The microagglutination titre (MAT) remains the definitive serological investigation technique in both humans and animals [6].

Leptospirosis as a human disease is the result of complex interactions between humans, animal reservoirs/carriers, and the environment where the bacteria can survive [7,8]. There remain significant gaps in our understanding of its transmission dynamics and of the trigger factors for disease outbreaks, including natural disasters. Flooding is the most common natural disaster both in developed and developing countries and is expected to occur with increasing frequency [9]. Flooding refers to the overflow of areas that are not normally submerged with water or a stream that has broken its normal confines or has accumulated due to lack of drainage [10].

There has been an increased in number of individual studies which assessed the risk of leptospirosis in flood conditions. Some studies showed contact with floods was significantly associated with the occurrence of leptospirosis [11–13], while other studies reported differently [14,15]. In addition to the increased risk of leptospirosis after exposed exposure to flooding, socio-demographic (being male gender) and other predictors like sighting of rats were commonly reported in the individual studies. These individual studies varied in study population, study design, confirmation/ diagnostic methods of leptospirosis, among others. It is of an immense value to conduct a meta-analysis review, addressing the occurrence of human leptospirosis following flooding and identification of the associated risk factors. Taken together, the review questions were: what are the associated factors among human leptospirosis following flooding? If associated, what is the strength of association?

The objective was to synthesize the evidence on the risk factors which are associated with human leptospirosis following flooding. A better understanding of leptospirosis pertinent to flood exposure and its risk factors will enable the health policy planners to formulate more effective disease prevention and control strategies.

Materials and methods

The current study adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [16] (S1 Table).

Search strategy

One investigator searched for the original studies, addressing leptospirosis in human with related to flood in health-related electronic database of PubMed, Embase (Ovid), Ovid Medline, Scopus sources, Google Scholar, the Latin American and Caribbean Health Sciences Literature (LILACS) and African Journals online (AJOL). Following the guidelines for the electronic search strategies [17], we searched the relevant studies using the following terms: 'leptospirosis', 'flood', 'risk factor'. Terms from the categories were connected with "OR"

within each category and by “AND” between categories. The PubMed search string used is provided in [S2 Table](#). The search strategy was slightly adjusted according to the requirements of different databases. The search was limited to studies published in English until December 2018. The reference lists of the selected studies and relevant reviews were manually searched for any additional papers that were not captured by the electronic search.

Selection criteria

Using the PICO format (population, participants or problem, intervention or exposure of interest, comparison and outcome) [18], the inclusion criteria of primary studies are shown in [Table 1](#).

A laboratory-confirmed leptospirosis was as defined in the primary studies. These included the demonstration of a four-fold MAT rise between paired serum samples [5], a MAT reciprocal titre greater than 800 in one or more serum samples, or leptospires identified in blood or urine cultures by dark-field microscopy [19]. If more than one study presented data from the same participants, the most comprehensive study was included.

Studies were excluded, if they did not meet the inclusion criteria. Therefore, studies that included leptospirosis without revealing exposure to flooding were excluded. Also, reviews, case studies, editorials and conference abstracts were excluded.

Data extraction

Two investigators individually screened the titles and abstracts, and then selected full-text articles, according to the inclusion criteria. The two investigators independently extracted information from each included study using a pre-tested data extraction form prepared for this meta-analysis. Information collected were first author, year of publication, year of study conducted, country, patient characteristics (e.g. age, gender), study characteristics (e.g. study design, sample size), flood description, risk factors (e.g. being male, sighting of rats) and the clinical characteristics (clinical form of leptospirosis, confirmation method). For any missing data, we planned to request from the corresponding author. However, this was not necessary. Disagreements between the two investigators were reached by consensus.

Methodological quality assessment

The methodological quality of primary studies was assessed using the Newcastle-Ottawa Scale (NOS) [20]. This instrument uses a star system to evaluate methodological quality in relation to control of confounding variables, adequate sample size, minimised selection bias and clear

Table 1. Inclusion criteria.

Key point	Description
Participants	Individuals infected residing in endemic countries and had exposed to flooding, regardless of age and gender.
Exposure of interest	Studies which had explicitly revealed flooding as an exposure factor.
Comparison	1) Those individuals infected with leptospirosis following flooding and those who did not. 2) Those with associated predictors among human leptospirosis following flooding and those who did not.
Outcomes	1) Frequency of human leptospirosis following flooding. 2) Following flooding, frequency of human leptospirosis with associated risk factors. The strength of association was measured as odds ratio (OR) and its 95% confidence interval (CI). To be eligible, study must have reported data on at least one outcome.
Study design	Human observational studies investigating potential predictors for leptospirosis following flooding.

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definitions of exposures. Each article is given a score in number of stars from three perspectives: a) selection of the study groups (maximum: 4 stars), b) comparability of the study groups (maximum: 2 stars), and c) ascertainment of the outcome (maximum: 3 stars). Hence, a study could be achieved a maximum of nine scores. We used these scores only to facilitate the interpretation of the meta-analysis results, but not used as a criterion for inclusion or exclusion of articles. During these processes, any discrepancy between the two investigators was reached by consensus.

Data analysis

For comparison of dichotomous data, we assumed that relative risk (RR) from cohort studies approximate OR from case-control studies [18]. As the incidence of human leptospirosis following flooding is not very high, a more conservative estimate of OR was used for the pooled analysis. If studies did not report RR or OR, we derived it from the raw data provided. Due to the availability of data, certain risk factors (e.g. gender difference, sighting of rats, behaviour related factor such as walking barefoot) that included in the primary studies were identified for this meta-analysis. To be included in pooled analysis, there must be at least three individual studies referring to a given risk factor. For the meta-analysis of flood-associated leptospirosis, we used inverse variance weighting, after transforming the estimates of each study into log OR and its standard error. For the meta-analysis of risk factors identification, we only included adjusted ORs from multivariate designs to minimise confounding in pooling of the effects. The heterogeneity within studies was assessed with the I^2 test. A value of $I^2 > 50\%$ indicated substantial heterogeneity [18]. In the presence of substantial heterogeneity within studies, we used random-effect model for pooling of the effect sizes. To investigate the reasons for heterogeneity, subgroup analysis was done with study design and diagnostic methods of human leptospirosis (MAT or not). We assessed the publication bias by visualizing funnel plot asymmetry [21]. Data analyses were done by RevMan 5.3 (The Cochrane collaboration, Copenhagen), R, version 3.5.1 (The R Foundation) and *metan* package in STATA 15 (College Station, TX: StataCorp LLC).

Results

A four-phase flow chart of the study selection process is illustrated in (Fig 1). The initial search yielded 557 citations. After the title and abstract screening, 49 full-text papers were reviewed and a final of eighteen studies met the pre-specified inclusion criteria [11,12, 14,15,19, 22–34]. Table 2 provides characteristics of these included studies. A summary of the thirty-one studies [5,7,13,35–62] are provided in S3 Table.

Of total eighteen studies, seven studies (39%) were case-control designs [12, 15, 22, 24, 25, 27, 31] and the remaining eleven studies (61%) were cohort or cross-sectional designs [11, 14, 19, 23, 26, 28–30, 32–34]. Of these, ten studies (55.6%) made confirmation of leptospirosis with the use of MAT (Table 2).

Five studies (28%) included in this meta-analysis were conducted in Brazil [19, 23,24,14,32], while two studies (11%) each were in Jamaica [15,25] or Thailand [31, 34]. The remaining nine single studies were conducted in Argentina [12], India [27], Guyana [29], Lao [28], Mexico [11], Nicaragua [22], Sri Lanka [30], Taiwan [33] and the USA [26] (Fig 2). The studies included were published between 1995 and 2018. All these included studies revealed exposure to flood/flooding, albeit with variation in the descriptions. For instance, “home flooded”, “flooding in the household”, “flooding on one’s own property”, “flooding in the study district” or “inside flooded areas” [14,30,34]. Only one study indicated specifically about duration of stay in flood as “exposure to flood more or less than 3 hours per day” [31].

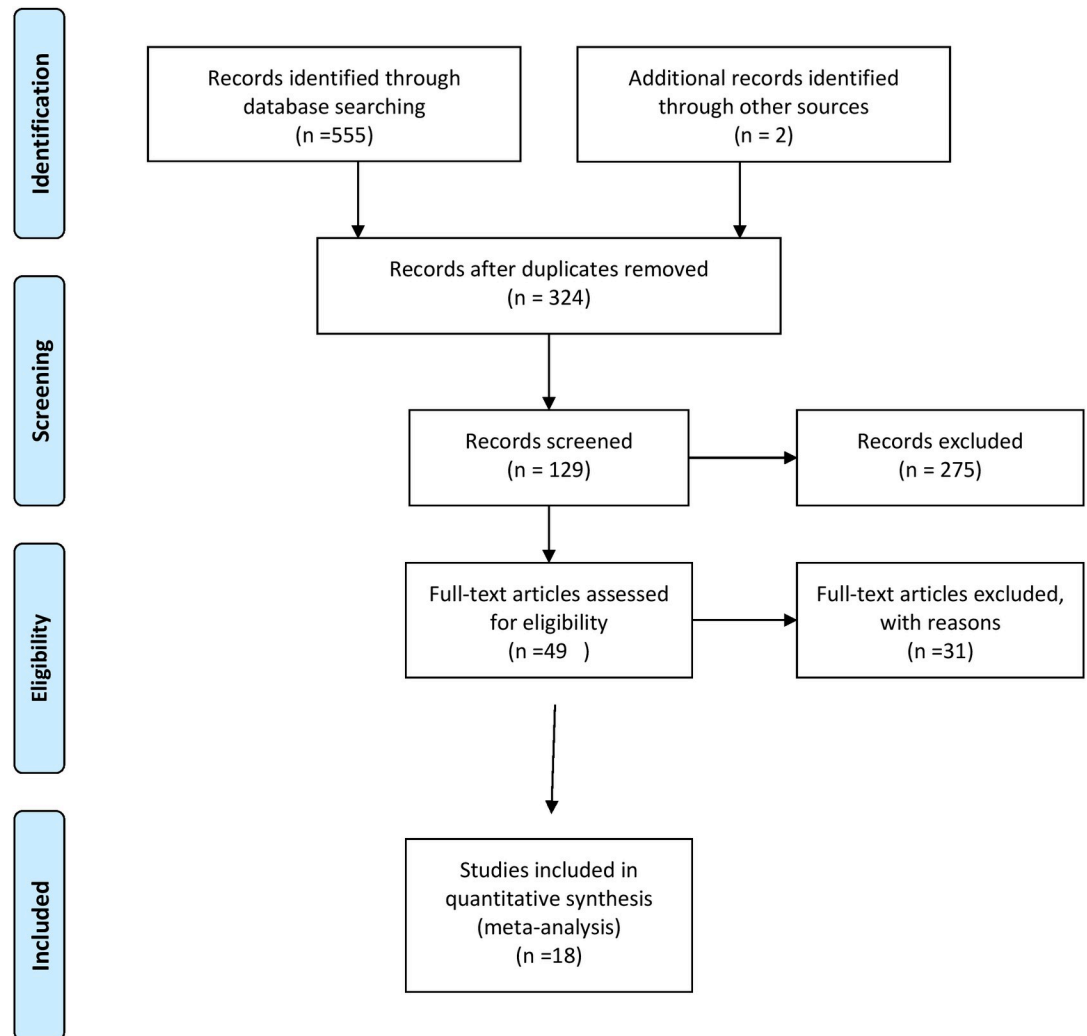


Fig 1. PRISMA flow diagram showing the study selection process.

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Relationship with flooding

Of eighteen studies included, fifteen [11, 12, 14, 15, 19, 23–25, 27–29, 30–32, 34] studies assessed the relationship between flooding and leptospirosis. Overall, the pooled estimates of fourteen studies showed that the contact with flooding was a significant factor for the occurrence of (increased) leptospirosis (pooled OR: 2.19, 95%CI: 1.48–3.24, I^2 :86%). On stratification, the strength of association was greater in the case-control studies (pooled OR: 4.01, 95%CI: 1.26–12.72, I^2 :82%) than other designs (pooled OR: 1.77, 95%CI: 1.18–2.65, I^2 :87%). However, the confidence limit became wider in the pooled estimates of case control studies (Fig 3). This implied that the study design had only a minor impact on the effect estimation. When we retained studies that confirmed leptospirosis with MAT, there was only a negligible change in effect estimates (pooled OR: 2.18, 95%CI: 1.47–3.22, I^2 :86%) (S1 Fig); this implied that the diagnostic methods in these studies had only a very little impact on the effect estimation.

Table 2. Characteristics of studies included in the meta-analysis.

No	Author	Year of publication	Ref. no.	Year of study	Country of study	Study design	Age (mean ± SD in yr)	Males	Method of diagnosis ¹	Description of flood exposure	Incidence rate or cases vs controls	Quality grading
1	Trevejo	1998	22	1995	Nicaragua	CC	14.9	54.9%	MAT	following heavy flooding	51/2269	6
2	Ko	1999	19	1996	Brazil	CS	35.9 ± 15.2	79.3%	MAT	exposure to contaminated water	126/326	7
3	Barcellos	2001	23	1995	Brazil	CS ²	NA	NA	NA	inside flood areas	35/83241	4
4	Sarkar	2002	24	2000	Brazil	CC	36.0 ± 14.2	89%	IgM (ELISA) + MAT	contact with flood water	101/157	8
5	Karande	2003	25	2000	Jamaica	CC	children	60.3%	IgM (ELISA)	h/o flood water contact	18/53	6
6	Leal-castellanos	2003	11	2000	Mexico	CS	≥15	22.6%	MAT	foot skin cuts or abrasion during flooding	441/1950	5
7	Dias	2006	14	2002	Brazil	CO	≥15 (74.6%)	41.7%	MAT	flooding in the household	172/1390	5
8	Gaynor	2007	26	2004	USA	CS	NA	NA	IgM EIA.	within 30 days of contact with flood water	1/48	5
9	Bharadwaj	2008	27	2006	India	CC	29.06 ± 11.09	NA	IgM (ELISA)	contact of injured part with flood water	129 vs 253	7
10	Kawaguchi	2008	28	2006	Lao	CS	≥15	58.7%	MAT	flooding on one's own property	97/406	6
11	Vanasco	2008	12	2000	Argentina	CC	32±16.2	87%	MAT	contact with contaminated surface water & flood	182/812	6
12	Keenan	2010	15	2006	Jamaica	CC	37.8	79.1%	IgG ELISA/ DST	home flooded	43 vs 89 ³	7
13	Dechet	2012	29	2005	Guyana	CO	NA	NA	MAT +RDT	extensive flooding	105/ 236	7
14	Agampodi	2014	30	2011	Sri Lanka	Prospective CO	40± 12	63.5%	qPCR	Following heavy rains and floods	96 ⁴	7
15	Chusri	2014	31	2013	Thailand	CC	≤60 (85.8%)	55.5%	IFAT/ MCAT	exposure to flood water	22/663	7
16	Felzemburg	2014	32	2003	Brazil	CO	≥15(88%)	60.7%	MAT	contact with flood water	35/1585	6
17	Lin	2015	33	2009–2010	Taiwan	longitudinal	58.42 ± 12.73	33%	IgM/IgG	after flooding	2/288	6
18	Suwanpakdee	2015	34	2011	Thailand	CS	NA	NA	MAT/ MCAT/ ELISA/ IFA/PCR/ Culture	flooding	2129 in 2010; 3320 in 2011; 2213 in 2012	6

¹: Method used to diagnose leptospirosis

²: spatial analysis

³: only numerator cases with no denominator population

⁴: probable case

CC: case-control design; CS: cross-sectional design; CO: Cohort design; DST: Dip-S-Ticks; IFAT: indirect immunofluorescent antibody test; Incidence: Incidence of leptospirosis (%);MAT:microscopic agglutination test; MCAT:microcapsule agglutination test; md: median and range; yr: year; wk: week

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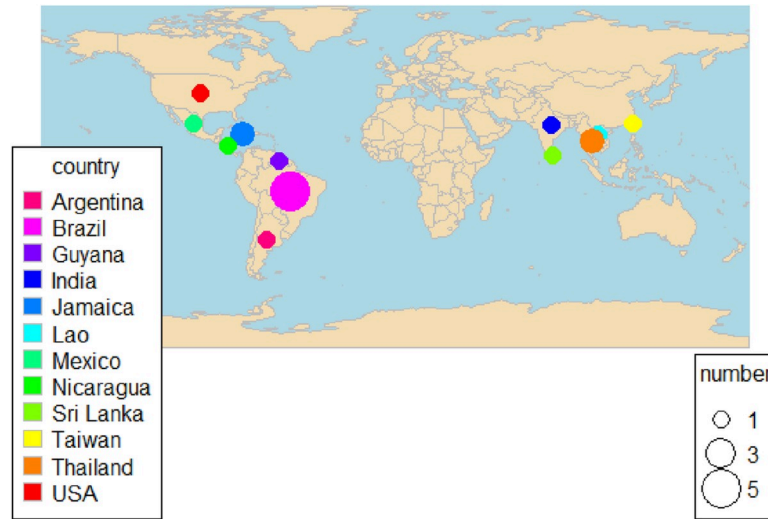


Fig 2. Distribution of the included studies.

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Identification of risk factors

The pooled estimates of five studies [11,22,24,27,28] showed that the sighting of rats was tended to be a significant risk factor for leptospirosis following flooding (pooled OR: 1.33, 95% CI:0.96–1.71, I^2 :0%). Also, the pooled estimates of three studies [11,27,31] showed that the lacerated wound was significantly associated with the occurrence of leptospirosis following flooding (pooled OR:4.35, 95%CI:3.07–5.64, I^2 :0%). Further, the pooled estimates of four studies [19,28,31,32] showed that being male was significantly associated with the occurrence of

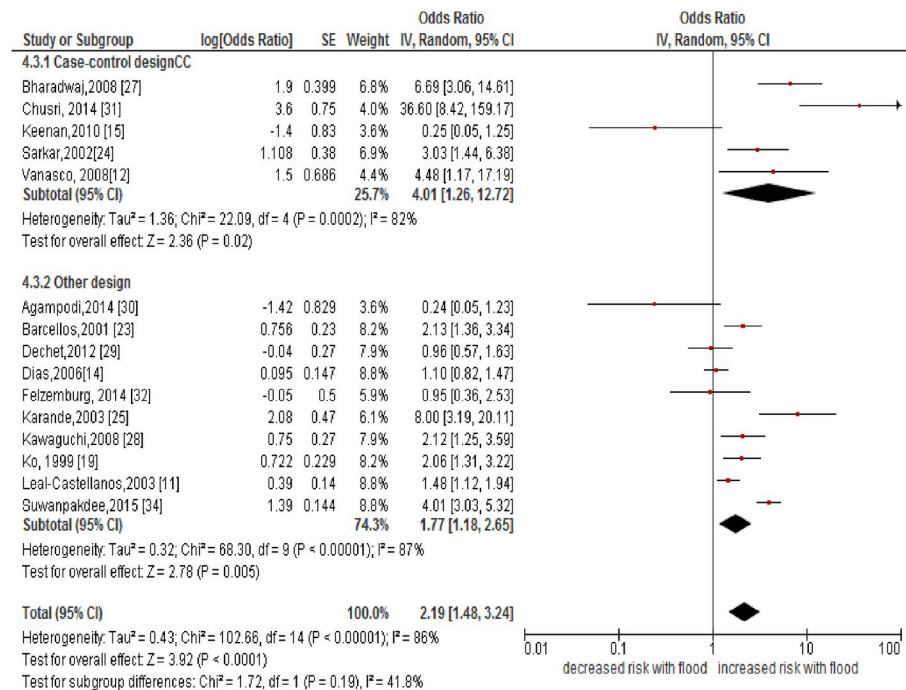


Fig 3. Forest plot showing an association between flooding and human leptospirosis.

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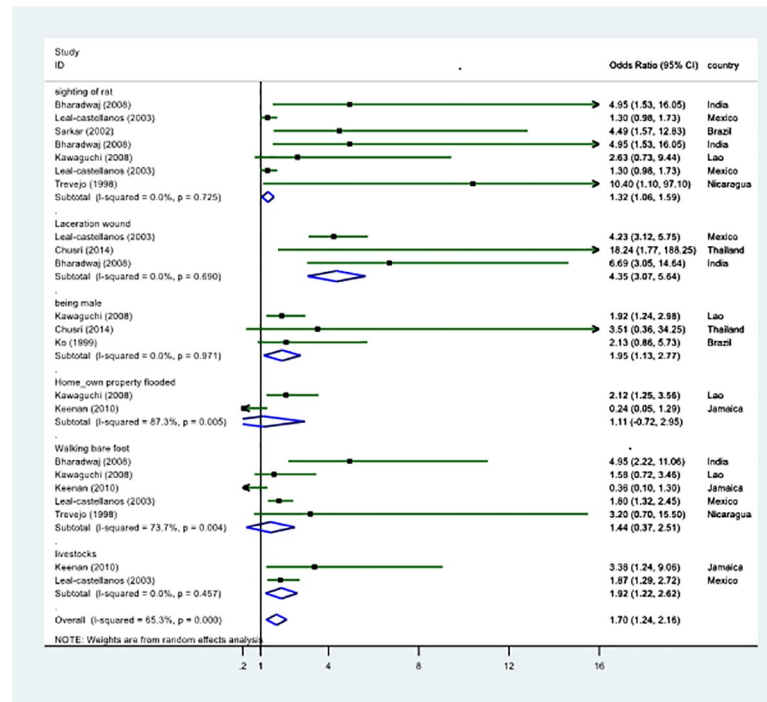


Fig 4. Associated risk factors for human leptospirosis following flooding.

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leptospirosis following flooding (pooled OR:2.06, 95%CI:1.29–2.83, I^2 :0%). Moreover, the pooled estimates of three studies [11,15,27] showed that exposure to livestock animals was associated with increased risk of leptospirosis cases (pooled OR: 1.95, 95%CI:1.26–2.64, I^2 :0%). Notably, three factors showed the increased associations with the risk of leptospirosis following flood in the absence of within-study heterogeneity (I^2 : 0%). A behaviour related factor such as ‘walking barefoot’ was reported in four studies [11,15,22,28], and the pooled estimate showed that it was not a risk for flood-related leptospirosis (pooled OR: 1.44, 95%CI:0.37–2.51, I^2 :74%) (Fig 4). There was evidence of publication bias in the current analysis (S2 Fig).

Discussion

The current study containing eighteen observational studies from twelve endemic countries provides evidence on the effect of flooding and the associated risk factors for the occurrence of leptospirosis following flooding. The major observations of the current analysis are as follows;

1. A significant association between flooding and an increased risk of human leptospirosis was observed. This was more pronounced in the pooled analysis of case- control studies.
2. Following flooding, three factors such as being male, the lacerated wounds and exposure to livestock animals were significantly associated with the occurrence of leptospirosis, while sighting of rats was tended to be an increased risk.

Leptospirosis cases result from a combination of negative social and environmental conditions [23]. Earlier reviews addressed the occurrence of leptospirosis in various conditions [63, 64], while the current analysis focus solely on the flood related leptospirosis. This is because leptospiral infection would be more favourable in flooding as pathogenic *Leptospira* can survive freely in water and flooding prevents animal urine from being absorbed into the soil or

evaporation. Hence, flooding would likely to be one of the main drivers for transmission by providing an optimal environment for survivability of leptospires [26]. Moreover, flooding may be possible in both rural settings and urban slums in many tropical countries. Evidence-based identification of risk factors is amenable to focused interventions in the peri-domiciliary environment. Environmental control of transmission may help to greatly reduce the incidence of leptospirosis [24].

Similar to the earlier reviews [63, 64], the present meta-analysis observed an increased risk of flood-related leptospirosis. A substantial within-study heterogeneity of the association might be partly due to differences in the definition of exposure to flooding or in the measurement of leptospirosis. Widespread flooding may offer potential risk of leptospirosis or lead to conditions favourable for outbreak leptospirosis when compared with non-flooded areas. This is because: (i) temporarily formed water accumulation is an ideal environment for proliferation of the leptospires contained in the urine [14]; (ii) there might be contaminated drinking water which is a possible transmission routes [4]; and (iii) there might be disruption of routine health facilities, allowing a poor/delayed health services. Natural disasters (flood in this case) cause sudden changes in the environment and also in human and animal behaviour. However, widespread transmission is limited at normal times due to a subtle balance between the determining factors, sudden changes in the environment and human behaviour create a situation conducive for the rapid transmission of leptospirosis resulting in outbreaks [65].

Peridomiciliary sighting of rats is feature of rat infestations and it was also a significant reservoir for leptospirosis [34]. Along this line, an empirical study had shown that *L. interrogans* (36% of positive samples) and *L. borgpetersenii* (56% of positive samples) species were widely distributed amongst rodent populations. Although these two most abundant leptospira species displayed different habitat requirements, they were confirmed as reservoirs for human leptospirosis [55]. During the flood or outbreak, specific rodent control programs could not be feasible to implement. A lack of proper rodent control during flood time had compounded to further transmission of infections.

Likewise, an earlier review [64], the present analysis documented the exposure to livestock as a significant risk for the occurrence of flood-related leptospirosis. Of note is that the associations documented in this review is merely a temporal relationship, but not a causation and the true source of infection could have been the rodents around animal farms rather than the animal themselves. Although live stocks livestock around residence was not reservoirs by themselves, rats were attracted to chicken feed and waste. A study had reported that 48% (519/1079) households in a slum community had practice of raising chickens [34]. Another epidemiologic study has reported a marginally increased risk (OR 1.15, 95%CI: 1.05–1.26) of seropositivity of leptospirosis and piggeries within 250 m and above house [7].

The increased risk of 'being male' might be due to the nature of their daily activities or occupational exposures likely to have more contact with leptospires [19,28] than the females. Laceration wound was defined as a wound caused by tearing of the skin deeper than the epidermis and through the soft tissue [31]. An association of a presence of laceration wound and leptospirosis was reported in the current analysis and this might be explained that cuts or abrasions in the skin or mucous membranes could facilitate entry of leptospira spirochetes through the mechanisms of counter-clockwise rotation of the periplasmic flagella [66]. This would be more favourable in flooding as pathogenic leptospira can live freely in water. This implied that leptospira multiplied in the walking paths where water remained in the flooded areas [27]. The ability to adhere to host tissue via adhesion proteins is also thought to be a necessary component of leptospire pathogenicity [67].

Study limitations

There are some limitations in the present meta-analysis. Leptospirosis is considered to be widespread in many tropical countries. The limited number of studies to the limited countries made a limited geographic representativeness. Studies in non-English language were not included. This concern was supported by the presence of publication bias observed in the current analysis. Flooding results from the interaction of many factors including rainfall, surface run-off, sea level, catchment size and local topography [7]. Besides flooding as a factor, several other factors can affect the isolation of leptospira from water and soil, such as pH, temperature, characteristics of water and soil and the presence of animals that are considered as reservoirs of leptospira. The lack of significance in the remaining risk factors (e.g. barefooted walking) might partly be due to the relatively small number of studies with small sample sizes, which was an issue of Type II statistical error. Hence, the association between flooding and the occurrence of human leptospirosis observed in the present analysis could be interpreted in the light of these issues. Nevertheless, our analysis used the adjusted ORs controlling common factors for the strength of associations, and this made a confidence in our estimates.

Public health implications

Leptospiral infections cluster in the flooded areas was documented in the present analysis. Flooding is related to peri-domiciliary infrastructure deficiencies (inadequate rainwater drainage with silt and refuse, blockage of drainage system). Considering that leptospira can survive for weeks to months in fresh water, and are efficiently carried and disseminated by water [60] (e.g. flooding in this case). The identified risk factors are conditions that are potentially correctable not by individuals, but at the municipal and community level [24]. Hence, better control strategies and immediate response system involving multisectoral approaches including health and non-health sectors (e.g. land development, rural/urban settlement, animal husbandry, municipalities) would have a significant impact on the reduction of leptospirosis transmission amongst the targeted populations. For example, improving sanitation in slum communities and equitable access to improved sanitation [34] would reduce rat infestations and further exposure to an environment contaminated by the urine of rodent reservoirs.

Health education on proper garbage system in households and work stations would reduce source of food for rodents and further reduction in rodent infestations. Also, easily adopted measures as an example of protective wearing (e.g. avoidance of barefoot walking, protective clothing at work) should be promoted among high risk subjects [24]. This would prevent/reduce the occurrences of cuts/ abrasion in skin and subsequent entry of spirochetes. Local flooding is documented as an important role in the transmission of leptospirosis. Therefore, flood control and other environmental modifications are expected to reduce the risk of leptospiral infection [28] and a multi-sectoral effort to this aspect would have long term benefits.

As severe manifestations of leptospirosis are characterized by high mortality, point-of-care clinicians' index of clinical suspicion for leptospirosis in early stage is crucially important. This heightened awareness, and the availability of diagnostic testing will improve surveillance for sporadic cases of leptospirosis and help prevent, detect, and control future outbreaks [26].

Conclusions

Findings suggest that flooding was associated with the risk of occurrence of leptospirosis in endemic countries. Future public health interventions such as implementation of disease prevention measures including rodent control programs and health education should be valuable for preventing exposure to animal urine and subsequent leptospirosis. These findings may serve as evidence-based information for the national health planners for better formulation of

a package of emergency disease control strategy containing leptospirosis. To substantiate the findings, future well designed prospective studies complement to proper health care services during flooding are required.

Supporting information

S1 Table. PRISMA checklist.

(DOC)

S2 Table. The PubMed search string.

(DOC)

S3 Table. Excluded studies and reasons for exclusion.

(DOC)

S1 Fig. An association between flooding and the risk of human leptospirosis confirmed with MAT.

(TIF)

S2 Fig. Funnel plot showing publication bias.

(TIF)

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Author Contributions

Conceptualization: Simon A. Reid, Stephen Ambu.

Data curation: Cho Naing.

Formal analysis: Cho Naing, Saint Nway Aye, Norah Htet Htet.

Funding acquisition: Cho Naing, Simon A. Reid.

Investigation: Cho Naing, Saint Nway Aye, Norah Htet Htet.

Methodology: Cho Naing, Simon A. Reid, Saint Nway Aye, Norah Htet Htet, Stephen Ambu.

Project administration: Cho Naing, Simon A. Reid.

Resources: Simon A. Reid, Stephen Ambu.

Writing – original draft: Cho Naing.

Writing – review & editing: Cho Naing, Simon A. Reid, Norah Htet Htet, Stephen Ambu.

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