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Skin Wounds as a Risk Factor for Leptospirosis in Semarang City: a Meta-analysis Study

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Abstract

Background:. A wound is one of entry points of leptospires into the human body. Previous leptospirosis risk factor studies in Semarang city, before 2012, had included skin wounds as an examined factor. However, results of these studies varied. This study is focused to answer whether skin wounds is related to the occurrence of leptospirosis in Semarang city, and the size of the risk to get leptospirosis when skin wounds exist.
Method: Systematic review and meta-analysis of previous leptospirosis risk factor studies in Semarang city were performed. Steps taken in the study were collecting previous articles on leptospirosis risk factors in Semarang published in national and international journal or grey literatures, all the selected articles were reviewed for their quality based on the Newcastle-Ottawa Scale. Next step was statistical analysis using Comprehensive Meta-analysis (CMA) program.
Results: Seven previous studies were included in the analysis, all of them were using case-control design. Calculation of Pooled Odds Ratio was based on random effect model. Heterogeneity of the effect-size of all included studies was shown by Cochran's Q test, p: 0.031 and I^2= 56.68%. Pooled Odds Ratio of all studies included in the analysis was 8.46 with 95% CI: 3.85-18.59 ($p< 0.001$).
Conclusion: People with skin wounds have risk of getting leptospirosis 8.46 times than those without skin wounds. Health practitioners who live in Semarang and find patients with high fever and history of skin wounds should think of leptospirosis infection in their differential diagnosis

Keywords: leptospirosis, skin wound, risk factor, Semarang, Indonesia.

1. INTRODUCTION

Semarang city is one of endemic areas in Central Java province. The number of leptospirosis cases in Semarang city is fluctuating every year. The number of leptospirosis cases and case fatality rate (CFR) in 2010, 2011, 2012, and 2013 were 71 (CFR:8%), 70 (CFR: 36%), 81(CFR:17%), and 71 (CFR: 17%) respectively.[1]

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Leptospirosis prevention and control activities have been implemented in Semarang city. One of the activities to control leptospirosis in Semarang city is to conduct leptospirosis risk factors study. Leptospirosis risk factor studies in human in Semarang have been performed by many related institutions. [2-7] Observational study using survey method and cross sectional or case control approaches are the design and method of study usually used for leptospirosis risk factor studies in Semarang city.

One of factors related to the transmission of leptospirosis is skin wound. Skin wound is one of entry points for leptospirosis agent (leptospires)

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into the human body.[8, 9] Many leptospirosis studies in Semarang city had included skin wound as a factor that had to be examined.[2, 3, 5-7, 10]

Results of these studies varied; some studies reported that skin wound was a risk factor of leptospirosis and other studies reported that skin wound was not a risk factor of leptospirosis. Additionally, there was a variety of the size of the risk for leptospirosis occurrence for individual with skin wound compared to those with no skin wound. Different results from previous studies regarding association between skin wound and leptospirosis infection may cause different interpretation regarding the role of skin wound in the transmission of leptospirosis. This will influence the decision makers in deciding the strategy or policy to control leptospirosis. This study is aimed to answer the question whether skin wound is associated with leptospirosis occurrence in Semarang city and the risk of getting leptospirosis infection when skin wound exists.

METHODS

This study was an explanatory study using systematic review and meta-analysis procedure to synthesize and analyze the data. The procedures to synthesize and analyze the data were summarized into six steps: 1) determination of criteria for previous studies to be included in the study, 2) strategy to find previous studies, 3) selection of previous studies to be included in the review, 4) finding fultext articles or reports of the selected studies, 5) critical review/ quality assessment of the selected studies, 6)`data extraction and statistical analysis.

Criteria for previous studies to be included in the study were 1) studies were reported before 2014, 2) the study site was in Semarang city, 3) the study design was an observational study (cross-sectional, case control, or cohort design), 4) association analysis between skin wound and leptospirosis infection or disease was performed, 5) the strength of association and 95% confidence interval values were measured and presented. Searching for articles containing leptospirosis study in Semarang and published in international journals were performed through MEDLINE, Scopus, and PubMed data bases. Terms 'leptospirosis, risk factor, Indonesia' were entered for searching the articles and the Boolean "AND" was entered to separate them. Searching for articles published in Indonesian peer-reviewed journals and in Indonesian grey literatures was performed through 'Google searching machine', then went to the journal's web address showed in the Google. Terms entered were 'leptospirosis, risk factor, Indonesia', and articles with the study site in Semarang city were selected. Reports of leptospirosis risk factors study in Semarang city that were not published in the journals were also searched in the related institutions and related seminar or scientific meeting proceedings. Relevant articles stated in the reference list of each selected article were searched and of included in the study if they fulfilled the inclusion criteria.

Abstracts of articles of the previous studies were examined, then fultext of the selected articles were sought. Review or quality assessment of the selected studies was performed and *The Newcastle-Ottawa Scale* (NOS) was used to guide the review or assessment. Information from previous studies were recorded in a data extraction form. Pooled Odds-Ratio was calculated when two or more previous studies examined association between skin wounds and leptospirosis infection or disease. This combined estimates was obtained by calculating mean of the logarithmic values of ORs multiplied by their each weighted value. This weighted value was an inverse of a variance based on a fixed or a random effect model, and it depended also with the heterogeneity of effect size. Heterogeneity of the effect size was calculated using Cochran's Q and I^2 statistics; $p < 0.10$ or value of $I^2 > 50\%$ showed heterogenic. When there was a high heterogeneity ($I^2 > 75\%$), *pooled effect estimates* were calculated using *random effect* model based on DerSimonian and Laird method. Publication bias was detected using *Begg's adjusted rank correlation test* and *Egger's regression asymmetry test*. Value of $p > 0.05$ for both tests indicated that no significant publication bias. *Comprehensive Meta Analysis (CMA) program software, second version* was used for statistical data analysis.

3. RESULTS

No article regarding leptospirosis risk factor in Semarang city was found in the peer-reviewed international journals. Searching in the national journals and grey literatures found 27 articles. After reviewing abstract of those 27 selected articles, three of them were excluded due to not an observational analytical study, and 24 articles were included for the next step which was fultext review. Searching for fultext of 24 selected articles found 23 fultext articles, one fultext article could not be found. After reviewing all fultext of the selected articles, 16 articles were excluded. A total of 7 selected articles were included for data extraction and statistical

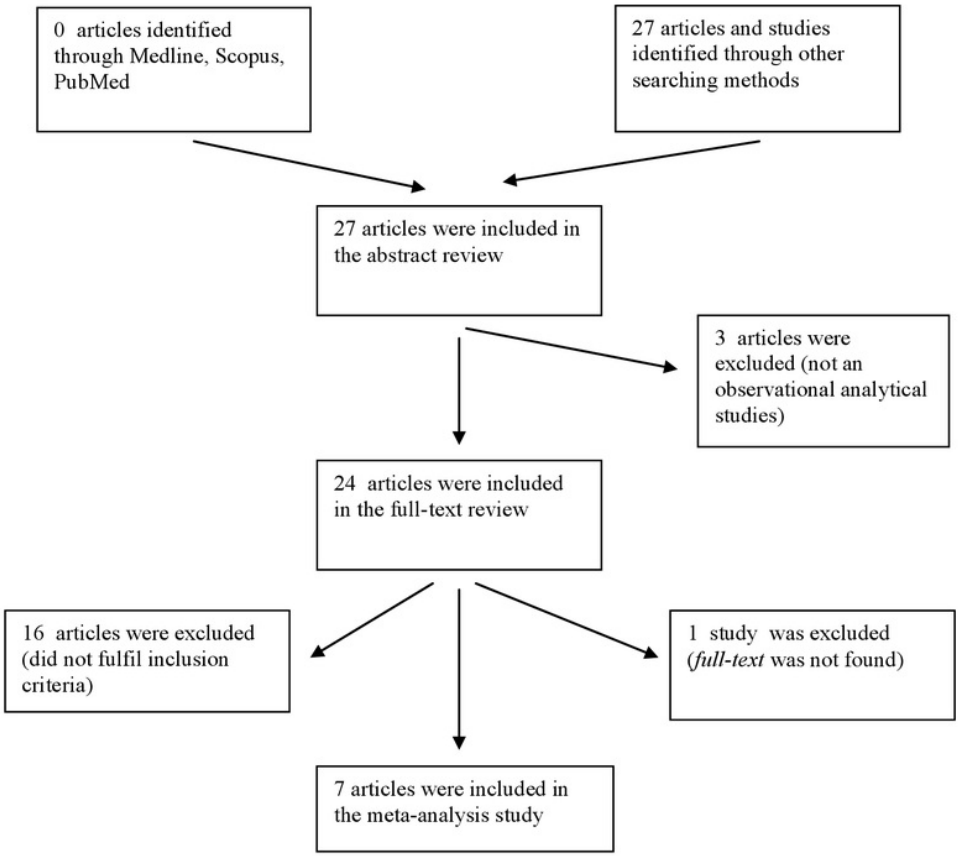

Figure 1. Flowchart of the articles selection

analysis. Flowchart for the articles selection was shown in figure 1.

Result of the quality assessment of the selected previous studies on leptospirosis risk factors in Semarang city using *The Newcastle-Ottawa Scale* (NOS) was shown in table 1. All studies included in the study were using case-control design. Maximum stars assigned for 'selection of study group' were four stars, for 'comparability of the groups' were two stars, and for 'ascertainment of exposure' were three.

Pooled Odds Ratio was calculated based on random effect model. Effect-size heterogeneity for all studies included in the analysis was shown by Cochran's Q test with p: 0.031, and I^2: 56.68%. Cochran's Q test < 0.1 or I^2> 50% indicated that all effect-size of all studies included in the analysis were heterogenic. Pooled Odds Ratio of all studies included in the analysis was 8.46, 95% CI: 3.85-18.59 (p < 0.001). A Group of people with skin wounds has a risk of having leptospirosis infection or disease 8.5 times compared to a group of people without skin wounds. Forest-plot of the pooled odds ratio analysis was shown in figure 2.

4. DISCUSSION

This study is considered the first meta-analysis study of leptospirosis risk factors in Semarang city. Results of this study strengthen the statement that the existence of skin wounds is a risk factor of leptospirosis infection in Semarang city. Individuals with skin wounds have a risk of being infected by leptospires 8.5 times more than individuals without skin wounds. Skin wounds should get serious attention because it can be an entry point for leptospires to infect the human body. Based on the result of this study, researchers and health programmers who want to conduct leptospirosis risk factors study or to conduct leptospirosis prevention or control should include

Table 1. Methodology quality of leptospirosis studies for meta-analysis

No	Studi/ tahun	Jenis Studi	NOS Selection of study group	NOS Comparability of the groups	NOS Ascertainment of Exposures
1	Maesaroh/ 2011 [11]	Case - control	**	*	*
2	Ryaningsih/ 2010[12]	Case - control	****	**	**
3	Anies/ 2009[7]	Case - control	****	**	**
4	Suratman/ 2008[6]	Case - control	***	**	**
5	Prasetyo/ 2006[5]	Case - control	***	**	**
6	Wiharyadi/ 2004[3]	Case - control	***	**	**
7	Suprapto/ 1997[2]	Case - control	****	**	**

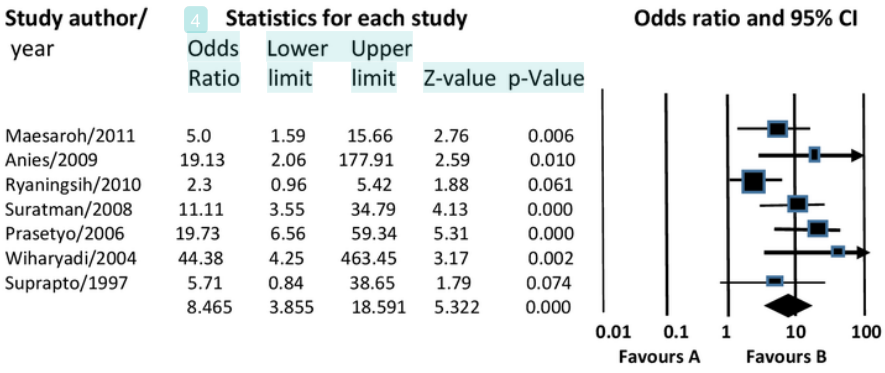

Figure 2. Forest-plot pooled odds ratio and previous studies odds ratios

skin wounds as one of examined variables. When conducting human cases or/and risk factors leptospirosis surveillance, the history of skin wounds a month before the first signs or symptoms of leptospirosis appear should be included in the list of questions.

Three things related to meta-analysis method, publication bias and determination of analysis model, and heterogeneity, will be discussed here. Publication bias is a term used to indicate systematical error in the selection of studies that are included in the analysis; only published studies that contains significant results that are included in the study. This situation produces an unrepresentative sample towards the true population.[13] In this study, publication bias might not exists due to no leptospirosis risk factor studies in Semarang were found in the international journals before 2012. In addition, articles used in this meta-analysis study were from national journals and grey literatures.

Analysis model selected in this meta-analysis study was a random-effect model. Assumption applied in the random-effect model here is that the true effect of studies included in the analysis is a result of sampling from one true-effects distribution. True-effect size for each study included in this meta-analysis varies between one and another. Summary of the effect-sizes variety of studies included in this meta-analysis (summary-effect) is a mean estimation of all relevant true-effects. The result will be different if the selected model is fixed-effect model. Assumption applied in the fixed-effect

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model is that the true-effect size of all studied included in this study is the same; summary-effect of all studies included in the meta-analysis an estimation of this true-effect size (common true-effect size).[14]

5. CONCLUSION

Skin wounds are proven to be the risk factor of leptospirosis infection in Semarang city. People with skin wounds have a risk of being infected by leptospires 8.5 times more than people without skin wounds. Researchers and health programmers who want to conduct leptospirosis risk factors study or to conduct leptospirosis prevention or control should include skin wounds as one of examined variables. It is recommended that health practitioners who live in Semarang or the endemic areas of leptospirosis and find patients with high fever and history of skin wounds for the last 3 weeks should think of leptospirosis infection in their differential diagnosis.

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