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Risk Factors and Outbreak Management of Brucellosis in Asia: A Meta-Analysis

Čimbenici rizika i upravljanje epidemijom bruceloze u Aziji: meta-analiza

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Summary

Objectives: Brucellosis affecting both humans and animals has been present in Asia for many generations. It continues to be a major public health concern, particularly where livestock is a major source of food and income. The study aims to analyse the risk factors of brucellosis and compare the outbreak management among Asian countries.

Methods: A systematic search was performed from PubMed, Scopus and Web of Science search engines using the PRISMA checklist 2009. PICO tool was applied for keyword search. A total of 14 articles were included in qualitative synthesis and four articles were included in a meta-analysis. The included studies originated from high endemic countries and low endemic countries.

Results: Most cases had a direct contact with the infected animal through occupational exposure. The overall odds ratio for consumption of raw animal products was 9.51 (3.24,27.92), P<0.05. For the history of contact with an infected animal, the overall odds ratio was 5.74 (1.89,17.39), P<0.05. The livestock related workers also had a significant overall odds ratio, 4.45 (1.15,17.19), P<0.05.

Conclusion: The common risk factors for human brucellosis outbreak are consumption of infected animal products, history of contact with animals and livestock related workers. As the outbreak of human brucellosis and animal brucellosis is interrelated, an integrated approach to outbreak management is crucial.

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Sažetak

Cilj: Bruceloza je prisutna u Aziji već mnogo generacija te se pojavljuje u ljudi i životinja. I dalje predstavlja veliki javnozdravstveni problem, posebno tamo gdje je stoka glavni izvor hrane i prihoda. Rad ima za cilj analizirati čimbenike rizika za razvoj bruceloze i usporediti načine upravljanja epidemijom u azijskim zemljama.

Metode: Sustavno su pretražene baze PubMed, Scopus i Web of Science koristeći PRISMA smjernice 2009. Ključne riječi su pretraživane po modelu PICO. Ukupno je 14 radova uključeno u kvalitativnu analizu, a četiri u meta-analizu. Analizirana istraživanja obuhvaćala su zemlje visokog i zemlje niskog endemiciteta.

Rezultati: Većina slučajeva bilježi izravan kontakt sa zaraženom životinjom kroz profesionalnu izloženost. Ukupni omjer izgleda za konzumaciju sirovih životinjskih proizvoda bio je 9.51 (3.24, 27.92), P<0.05. Ukupni omjer izgleda za prethodni kontakt sa zaraženom životinjom iznosio je 5.74 (1.89, 17.39), P<0.05. Radnici koji se bave stočarstvom također su imali značajan ukupni omjer izgleda u iznosu od 4.45 (1.15, 17.19), P<0.05.

Zaključak: Najčešći čimbenici rizika za razvoj bruceloze kod ljudi su konzumacija zaraženih životinjskih proizvoda, te prethodni kontakt sa životinjama i stočarima. Budući da su bruceloza u ljudi i bruceloza u životinja međusobno povezane, integrirani pristup u upravljanju epidemijom je od ključne važnosti.

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Introduction

Brucellosis has been present in Asia for many generations affecting both human and animals and is responsible for massive economic losses. It continues to be a major public health concern worldwide and is recognized as one of the most common zoonotic diseases, particularly where livestock is a major source of food and income.

There are several different *Brucella* species; four of which are pathogenic to humans. These species are normally found in domesticated animals; *B. melitensis*, affecting primarily goats, sheep and camels; *B. abortus*, affecting primarily cattle, other Bovidae and Cervidae; *B. suis*, affecting primarily swine; and *B. canis* affecting dogs.[1,2] These four species are the predominant cause of both human and animal brucellosis, especially in regions of endemicity.[3] Transmission of brucellosis from infected animals to human has been reported through direct contact with infected animals, placenta or aborted foetus as well as through the consumption of unpasteurized dairy products.[4]

Brucellosis affects all age groups. It usually presents as an acute febrile illness and may persist as relapse, chronic localized infection or delayed convalescence.[5] Most brucellosis cases are likely to occur among people who engage in breeding, grazing and slaughtering of the animals, thus a predominance among males is related to occupational exposure.[6,7] The acute and chronic symptoms of the disease in humans can result in a significant loss of workdays and a decline in the socioeconomic status of infected persons and their families from the associated loss of income. Thus, brucellosis can have a major economic implication due to time lost by patients from normal daily activities as well as losses in animal production.[4]

Human brucellosis is often neglected. In some Middle Eastern countries, more than 100 cases per 100,000 population may be seen.[2] Many cases were diagnosed late, causing the disease to spread as an outbreak in the population. As human interaction with the livestock and animals is inevitable, human brucellosis infection should not be a forgotten disease. Comprehensive procedures of controlling the source of infection among the livestock and the implementation of a comprehensive health education program should significantly reduce the incidence rate of brucellosis in humans and animals.[7]

The burden of the disease to society includes significant human healthcare costs for diagnosis and treatment and non-healthcare costs such as public education efforts to reduce disease transmission. There are numerous risk factors contributing to the outbreaks that were described qualitatively and quantitatively in previous literature. However, to the author's knowledge, there are no systematic reviews that focus on the risk factors during outbreak management and the control measures. There are a number of articles focussing on bovine brucellosis, but not on human brucellosis. Therefore, this review focused on the risk factors of human brucellosis and the outbreak management in Asian countries for future references.

Methods

Search Strategy

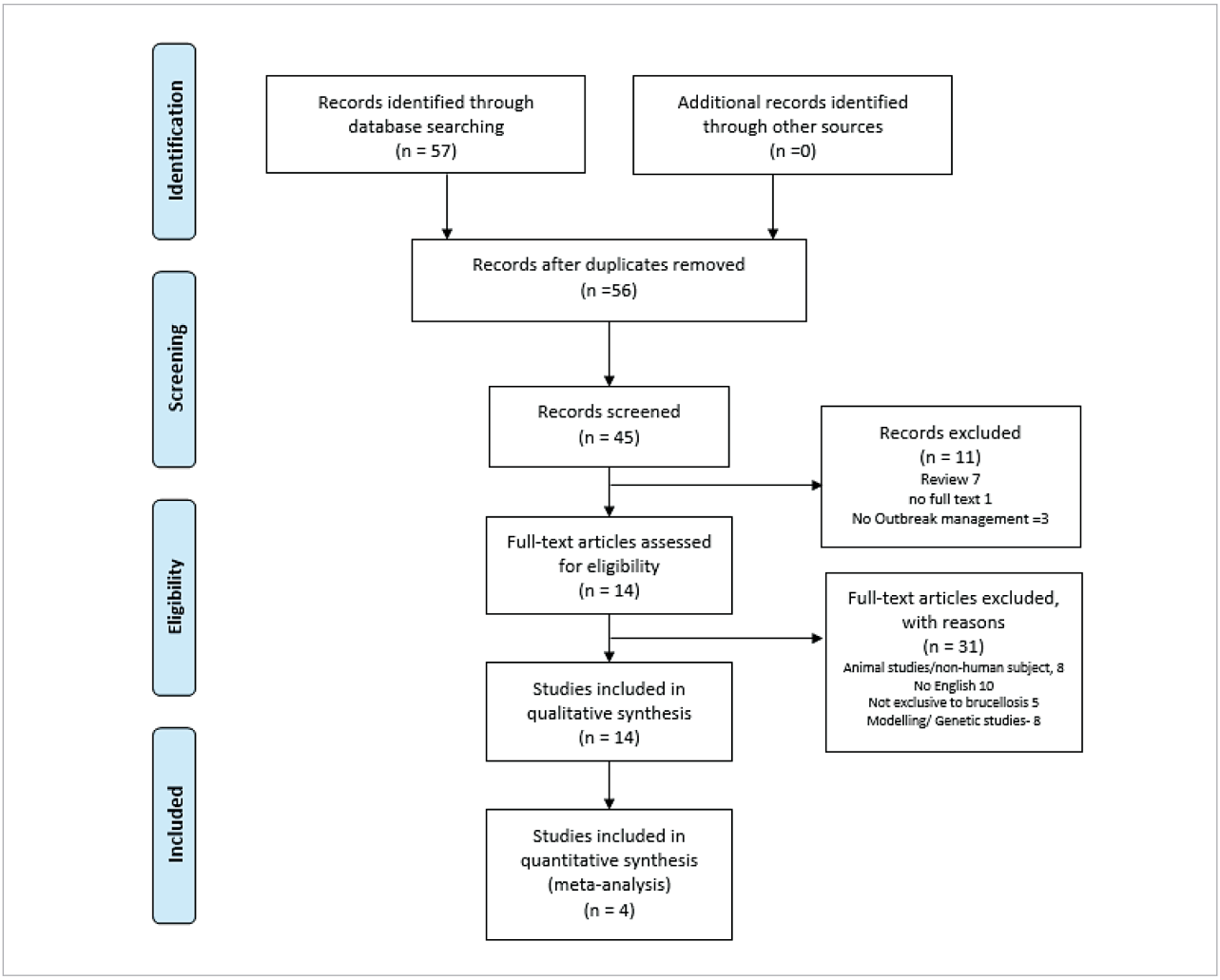
A comprehensive search of literature from PubMed, Scopus and Web of Science (WOS) was performed to search for relevant studies. PRISMA checklist was used for the workflow of publications` search. Text keywords and controlled vocabulary of the Medical Subject Headings were used in the searched studies that were based on PICO framework where; the problem was defined as brucellosis, comparison between Asian countries; and outcomes as outbreak management, risk factor, control or prevention. The text keywords that were used included "brucella" OR "brucellosis" AND "outbreak" AND "control" OR "prevention" OR "risk factor" AND "Asia".

Study Selection

Titles of each article were read by all authors and an agreement was obtained to exclude articles that did not match the PICO statement. If there was any doubt, the abstract was retrieved and read to justify the decision. The abstracts of the articles were distributed among the authors for assessment of inclusion and exclusion criteria. Then, full articles that have been selected were retrieved and distributed to the authors. Two independent authors were responsible for examination and extraction of the data for each article. At a point of disagreement, the third author was consulted.

Studies included in the review had to meet the following criteria: a study on risk factors of human brucellosis and outbreak management report. Articles that were not exclusive to brucellosis, study subjects not human, no full text, not in English, systematic review and meta-analysis were excluded. The internet-based search: PubMed identified 49 articles, Scopus 1 article, WOS 7 articles. By screening and reviewing for title and abstract, 45 potentially relevant articles were identified and retrieved for more detailed evaluations. Out of these 45 articles, 14 articles fulfilled all the inclusion and exclusion criteria while the remaining 31 articles were excluded with a certain reason. There were seven articles rejected because they were review articles, one article had no full text available, three article were not discussing outbreak management, eight articles were discussing non-human subjects, ten articles were not available in English, five articles were not exclusive to brucellosis and eight articles were modelling and genetic studies, all of which were excluded. After completing all steps of identification, screening and assessment of eligibility, there were 14 articles that were included in the qualitative synthesis and four articles proceed to the meta-analysis study. The detailed PRISMA flow diagram is illustrated in Figure 1.

Figure 1. PRISMA flow diagram
Slika 1. Dijagram toka PRISMA



Data Synthesis and Quality Assessment

The data from 14 selected studies were extracted and the information recorded including study details, method and outcome were done by two independent authors for each article selected. At the disagreement point, the third author was consulted. The Newcastle-Ottawa Quality Assessment was used to assess the quality of the evidence. For studies that met at least five out of nine criteria, they were considered to be high quality and proceed to meta-analysis.

The authors used Review Manager 5.2 to perform all analyses. The effect measurement for dichotomous outcomes were estimated using the odds ratio as the summary statistics. The inconsistency in study results was assessed using statistical heterogeneity by reviewing forest plots that displayed the study-specific estimates of outcome measures along with the 95% CIs where poor overlap of results indicated the presence of statistical heterogeneity. A result greater than 50% indicated heterogeneity. The authors used random effect model when heterogeneity was detected. Subgroup analysis was not done due to the limited number of studies. A funnel plot was used to check for the existence of publication bias.

Results

In total, we included 14 studies for comparing the outbreak management of brucellosis in humans and analysed the risk factors from various Asian countries ranging from 1996 to 2018. The studies consisted of three cohort design studies, three case control studies, five cross sectional studies and three case studies originating from high endemic countries namely Mongolia, Lebanon, Saudi Arabia, Qatar, Turkey and Israel as well as low endemic countries such as Korea, China and Thailand. All studies, except one study by Chen et al.[8], had described the risk factors of human brucellosis whereas three studies by Nemenqani et al.,[9] Ning

et al.[7] and Garcell et al.[10] did not stress on outbreak management. Overall, the study population included children and adults with sample population ranging from the smallest of three to the largest sample size of 838.956.

Out of the 14 studies, 11 reported risk factors of consuming raw milk, dairy product such as cheese or eating meat as a risk factor. Direct contact with infected animals was found as a risk factor for brucellosis outbreak in 6 out of 14 studies. Most cases recorded a direct contact with infected animal through occupational exposure such as participating in calf deliveries and contact with cow's blood and placenta or contact with aborted goats. Two studies demonstrated improper use of personal protective equipment while conducting risky job as a risk factor for brucellosis outbreak. A case of brucellosis in a laboratory technician involved infection through inhalation of Brucella species bacteria while handling specimens of brucellosis patients. Positive family history of brucellosis was a risk factor for brucellosis outbreak in one study. High humidity, low temperature and low sunlight were other risk factors found in a study in China. Characteristics of each study, prevalence of cases according to occupation, risk factors for brucellosis outbreak and control measures for each study are summarized in Table 1.

Table 1. Summary of study characteristics, risk factors for brucellosis outbreak and control measures
Tablica 1. Pregled obilježja istraživanja, čimbenika rizika za epidemiju bruceloze i kontrolnih mjera

Reference	Country	Study design	Sample size	Occupational exposure among cases- % (n/total cases)	Risk factors	Control measures
Al-Shaar et al.[12]	Lebanon	Case control	150	Animal related work – 0% (0/50)	Consumption of raw cheese	Animal vaccination Enhance food safety standard, increase monitoring in food industry, health education
Aypak et al.[20]	Anatolia, Turkey	Cross sectional	501	Livestock related work – 77.2%(34/44)	Consumption of raw milk and dairy product, family history of brucellosis, raising livestock	Controlling the disease in animals Investigate seroprevalence of human brucellosis during brucellosis outbreak in livestock Improve education regarding risk factors for brucellosis transmission
Chen et al.[8]	China	Retro-spective cohort	50002	N/A	Not applicable	One health approach which need close coordination from health and agriculture sectors. The Quarantine-Slaughter-Immunization strategy Determine high risk area using spatial- temporal analysis Awareness campaigns Recommend decentralizing of basic disease prevention and control units to the town or even village level
Ekpanyas-kul et al.[11]	Thailand	Cross sectional	86	Livestock related work – 51.2% (20/39)	Contact with laboured or aborted goats, consumption of raw goat milk and meat	Raise awareness and knowledge among physicians and public health officers, health education, surveillance system of brucellosis, community investigation teams to identify the cause, the risk factors and work to identify other asymptomatic cases
Gottesman et al.[17]	Israel	Case report	88	N/A	Consumption of unpasteurized milk and dairy product	Vaccination with anti-Brucella vaccine in animals, modern medical facilities provided, enable prompt treatment after early diagnosis.
Megged et al.[13]	Israel	Cross sectional	105	N/A	Consumption of cheese	Control of unpasteurized dairy products, health education program, improve regional cooperation

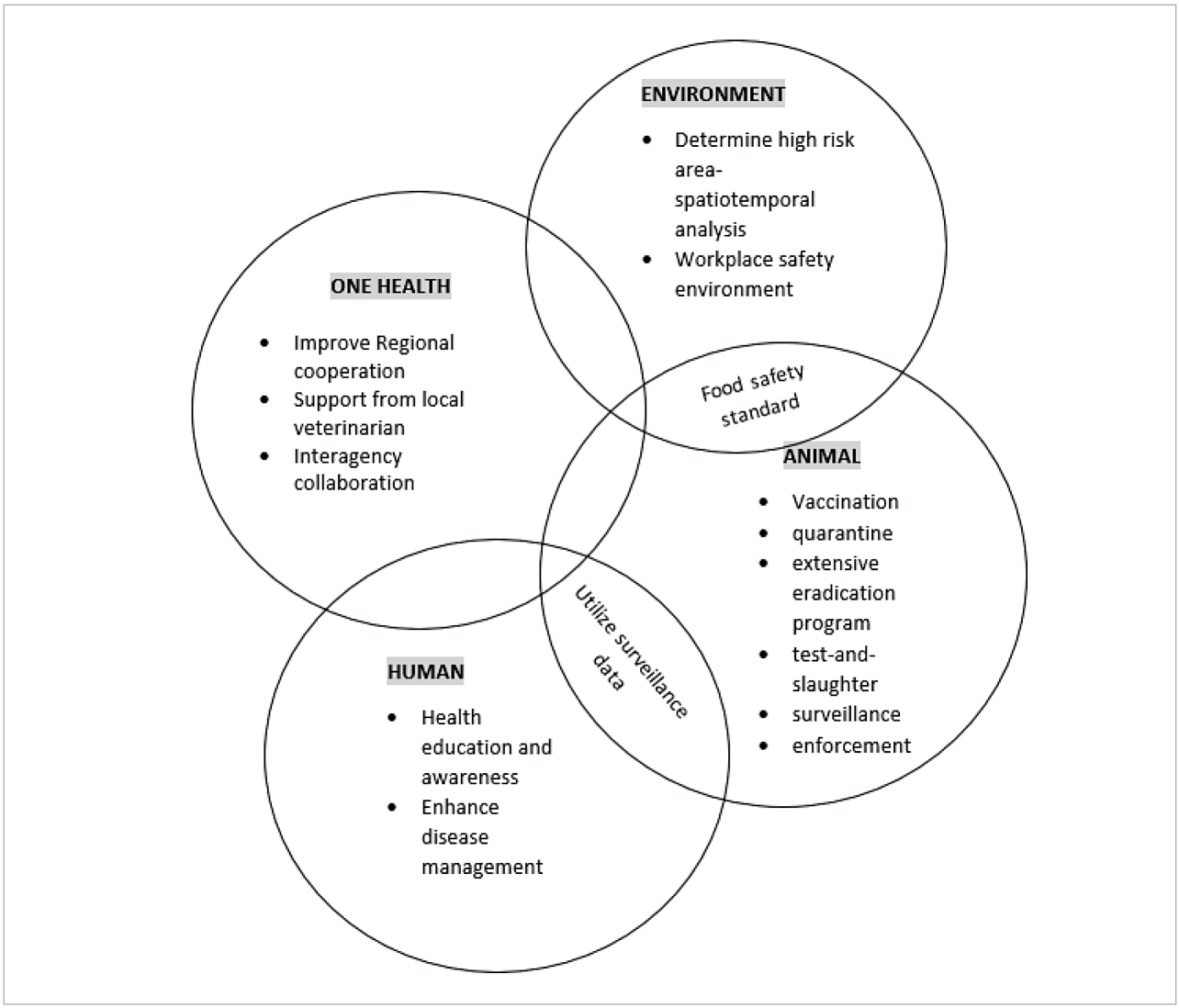
Mishal et al.[15]	Israel	Cross sectional	158	Livestock related work – 93.8% (15/16)	Consume unpasteurized milk, work in the cow-shed, participation in calf deliveries and had contact with cow's blood and placenta	Eradicating disease among herds
Ning et al.[7]	Mongolia	Cross sectional	838956	N/A	Risky behaviours Exposure history to infected livestock and their products No personal protective equipment (PPE) during conducting risky operations.	Utilize the surveillance data – to see the relation between animal and human infection Controlling the source of infection among the livestock; Vaccination of animals Massive campaign for eradication of infectious livestock Comprehensive health education program Recommend- quarantine of imported livestock
Park et al.[18]	Korea	retrospective cohort	620	Farmer: 49.7% (297/620)	Male Farmers Rural inhabitant	Extensive eradication program for brucellosis outbreak control (test-and-slaughter)
Garcell et al.[10]	Qatar	case-control	26	Farm owner: 53.8%(14/26)	Consumption of raw camel milk	Address human and animal infection Ongoing surveillance Education of medical staff-early diagnosis and treatment Health education- population
Tan el al.[14]	China	Retrospec-tive Cohort	69	Raising domestic goats: 14.5% (10/69)	Direct contact with the goats, or with aborted foetuses	Effective collaboration among different agencies Health education to the residents and non-epidemic area Screening animal commercial Enforcing the supervision of animal quarantine regulations Support from local veterinarian
Tantisiri-wat et al.[21]	Thailand	case report	3	Laboratory technician : 1 person	Own or live near a goat farm Consume goat milk Inhalation of brucellosis pathogen in laboratory	Workplace safety enforcement Health education for community live near the goat farm
Yoo et al.[19]	South Korea	case report	5	Farmer: 3 person Livestock dealer: 1 person Government worker – 1 person	Eating raw calf foetus (traditional practice to reduce alcohol intoxi-cation)	Continuous surveillance of bovine brucellosis Eliminate the source Public awareness of public health risks of human brucellosis
Zhan et al.[16]	China	Case control	11	Pharmaceutical factory worker : 5.0% (14/282)	Occupational exposure; direct contact with infected materials Repeated use of PPE High humidity, low temperature and no sunlight	Continuous surveillance of bovine brucellosis Health education to handlers Control of infected calf before distribution

In terms of outbreak management, many countries implemented one health approach for prevention and control, as health of the people was closely connected to health of animals and the environment. The management can be divided into three categories which were management in humans, management in animals and environmental management. Raising awareness regarding brucellosis among healthcare workers, community and workers who are at risk is one of the prevention and control measures. The community and workers at risk were trained regarding proper ways to pasteurize milk and handle meat. Ekpanyaskul et

al.[11] and Garcell et al.[10] reported raising awareness and knowledge among physicians in hospitals and public health officers as one of the important aspects in brucellosis outbreak management in order for the disease to be diagnosed and treated early. Figure 2 illustrates the integrated one health approach between humans, animals and the environment based on the management mentioned in the included studies.

Consumption of animal products, consumption of raw milk or dairy products or infected meat, were major risk factors for outbreak as highlighted by most of the included studies. Hence, the enhancement of food safety on animal products by legislation, monitoring programme on food safety were one of the measures as mentioned by Al-Shaar et al.[12] Inter-agency collaboration and cooperation between health and veterinary

Figure 2. Integrated approach to brucellosis outbreak using "one health" concept
Slika 2. Integrirani pristup epidemiji bruceloze primjenom koncepta "jednog zdravlja"



departments during an outbreak of brucellosis in animals and humans is an important aspect of outbreak management.[13,14] Eradicating disease among animals,[15] through quarantine of imported animals,[14,16] and vaccination of anti-brucella vaccine in animals were other measures mentioned by some authors[17,7]. This was in addition to the test and slaughter program as reported by Park et al.[18]

Brucellosis surveillance among humans during an outbreak in animals as well as strengthening the surveillance system has been documented by few studies in managing outbreak of brucellosis.[8,11,19,20] Workplace safety was another aspect in outbreak management among workers. These included avoiding direct contact with animals in high risk procedure by engineering control of building and work process.[21]

Meta-analysis

The overall odds ratio for consumption of raw animal products was 9.51 (3.24,27.92). Overall Z-test value was statistically significant. However, there was substantial heterogeneity across the included studies with I^2 value of 79%. Details of the result are presented in Figure 3. For the history of contact with infected animals, the overall odds ratio was 5.74 (1.89,17.39) with a p-value of less than 0.05. However, the studies were substantially heterogenous. The forest plot of the odds ratio is detailed in Figure 4. Livestock related workers also had a significant overall odds ratio 4.45 (1.15,17.19). The funnel plots for all three outcomes were not concentrating on the real effect line and were asymmetrical, which may be suggestive of publication bias (Fig. 5, 6, 7 and 8).

Figure 3. Forest plot of overall odds ratio for history of consumption of raw animal products

Slika 3. Grafički prikaz (forest plot) ukupnog omjera izgleda za prethodnu konzumaciju sirovih proizvoda životinjskog podrijetla

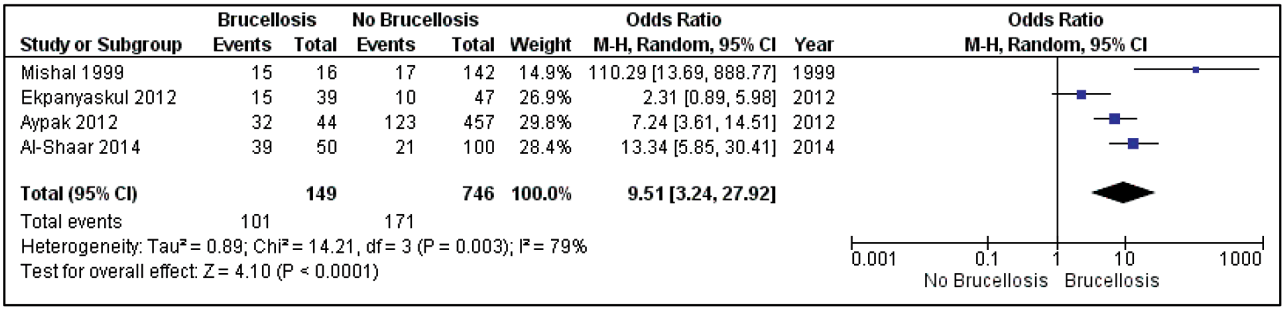


Figure 4. Forest plot of overall odds ratio for history of contact with infected animals

Slika 4. Grafički prikaz (forest plot) ukupnog omjera izgleda za prethodni kontakt sa zaraženom životinjom

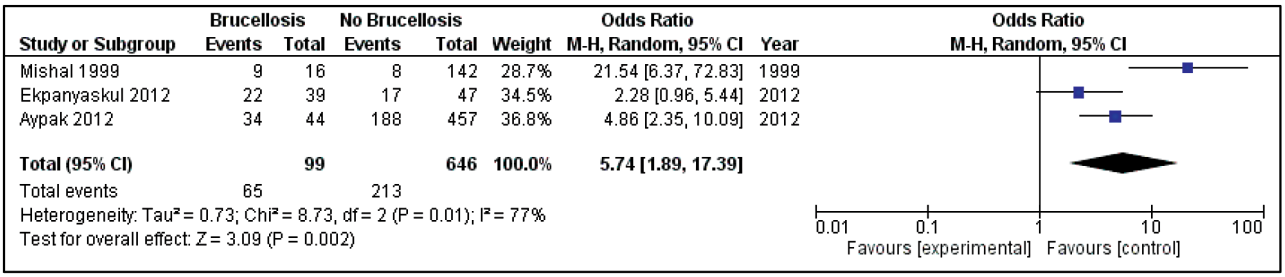
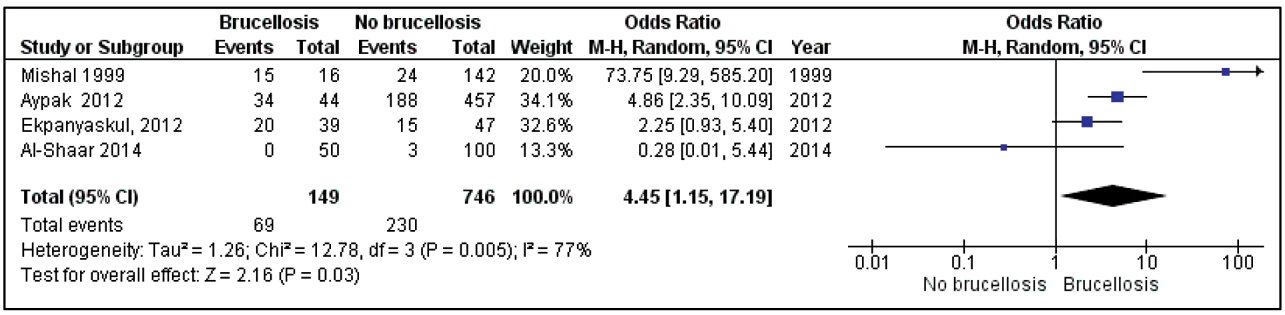


Figure 5. Forest plot of overall odds ratio for livestock workers

Slika 5. Grafički prikaz (forest plot) ukupnog omjera izgleda za radnike koji se bave stočarstvom



Discussion

The main objective of this review was to compare brucellosis outbreak management practices among Asian countries as well as to analyse the risk factors for brucellosis outbreak in humans. The coverage of the included articles ranged from the low endemicity countries such as Korea and Thailand; to high endemicity countries such as Mongolia and Lebanon. This signifies that the low endemicity countries also experienced human brucellosis outbreaks. However, brucellosis remains a neglected disease, especially in developing countries. This was due to the underreporting and lack of inter-sectoral coordination within the control.[22]

Figure 6. Funnel Plot of history of consumption of raw animal products

Slika 6. Grafički prikaz (funnel plot) prethodne konzumacije sirovih proizvoda životinjskog podrijetla

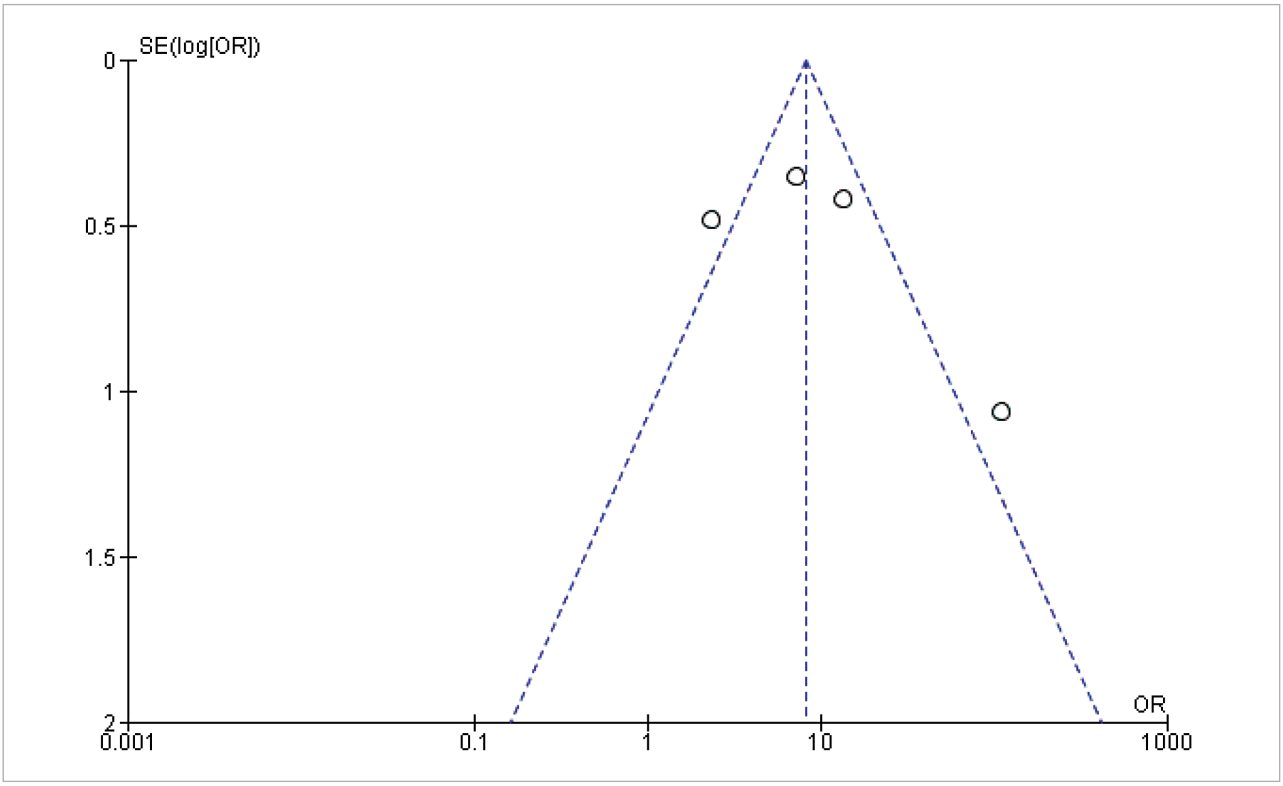


Figure 7. Funnel Plot of history of contact with infected animals

Slika 7. Grafički prikaz (funnel plot) prethodnog kontakta sa zaraženom životinjom

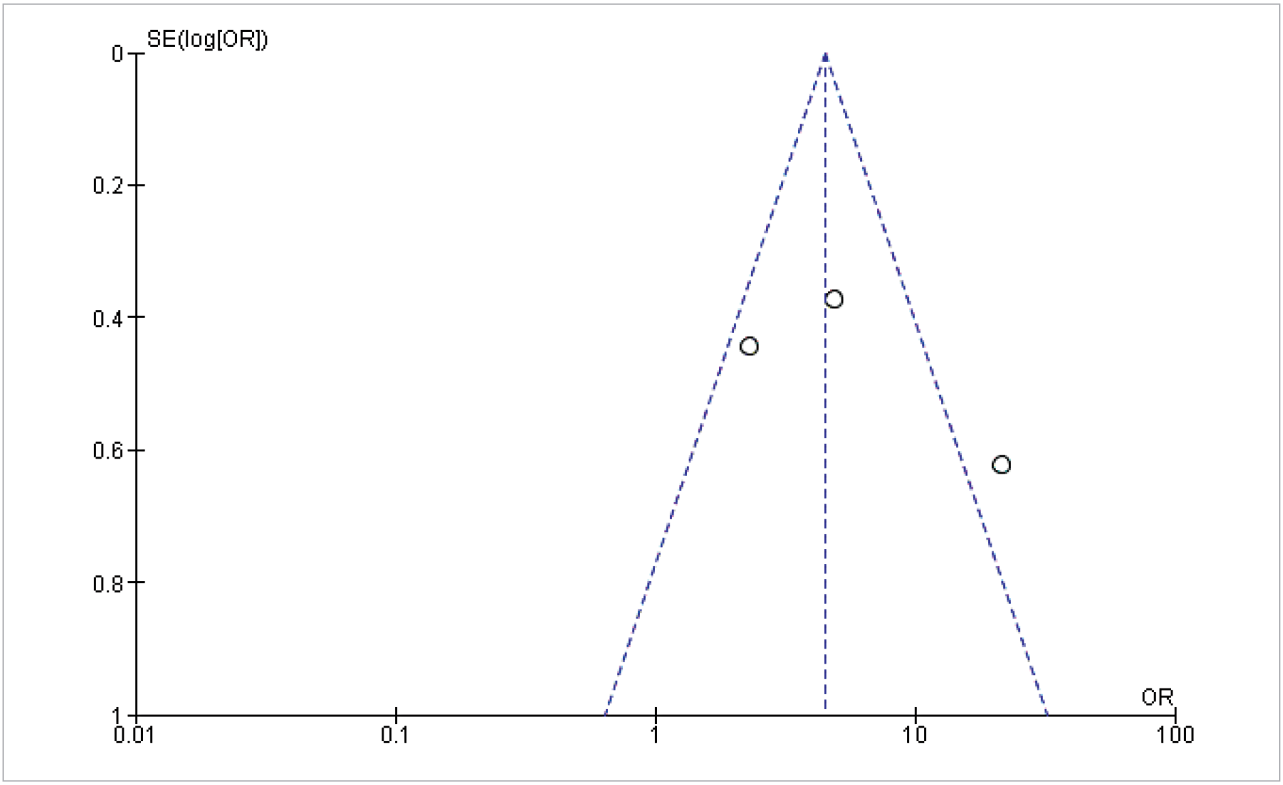
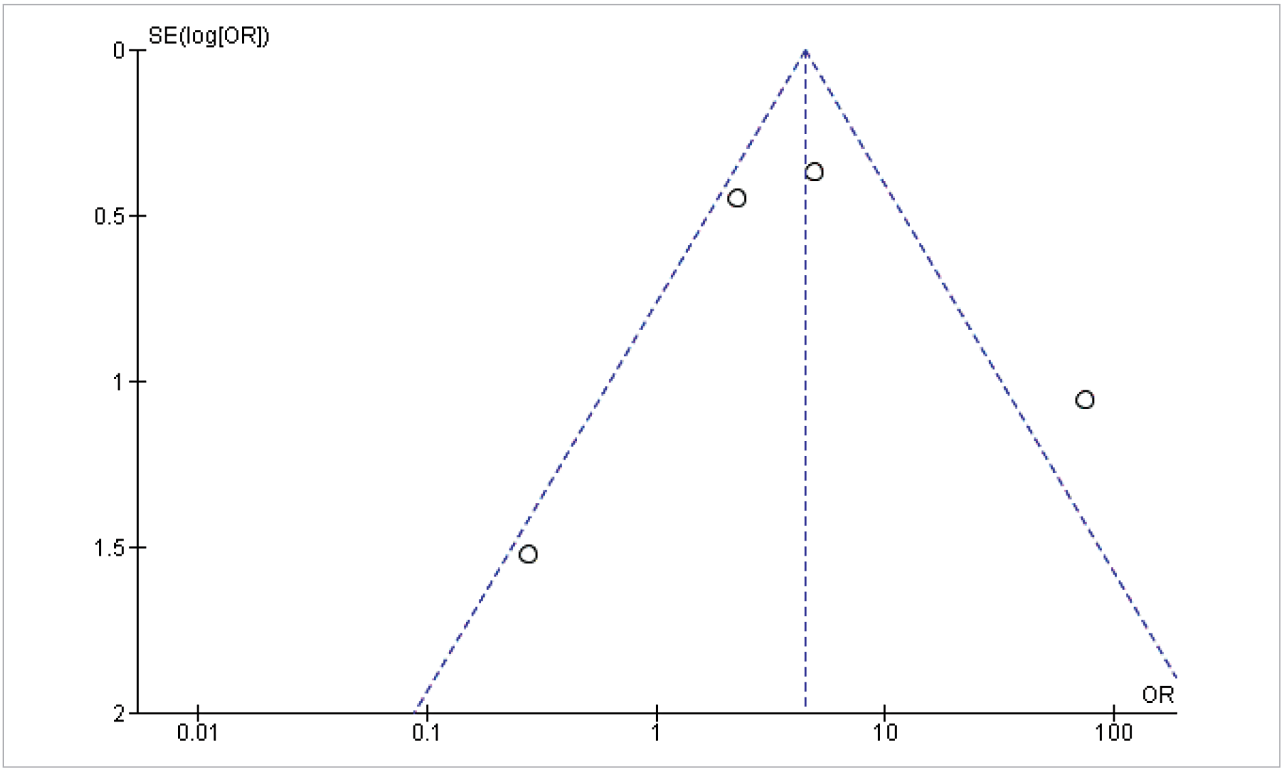


Figure 8. Funnel Plot of livestock related workers

Slika 8. Grafički prikaz (funnel plot) radnika koji se bave stočarstvom



This review also found that there is still a lack of high-quality articles describing human brucellosis outbreak management and its risk factors. This was because most of the studies lacked clearly defined methods, sampling and analysis. The majority of studies focused on the description of the outbreak and the characteristics of the cases. In 2012, Dean et al.[4] also found that there was a lack of quality of evidence data globally (using 33 search engines) regarding the incidence of human brucellosis. Consequently, this contributes to the lack of discussion on this topic which could be one of the factors causing misdiagnosis, undernotification and underdiagnosis of this disease. Therefore, this review highlights gaps in the information that need to be further clarified/addressed in the future.

However, from most of the included articles, it was observed that the human brucellosis outbreak was highly correlated with the outbreak of animal brucellosis. This requires the attention of multiple agencies that are involved in the management and control of the disease between animals, humans and their environment. In Korea, an extensive eradication program to control outbreak among animals had reduced the outbreak in humans.[18] Apart from that, the exchange of information regarding outbreaks in livestock would increase awareness among health professionals, the community which is the main barrier described in most of the studies.

Our meta-analysis showed substantial heterogeneity of both outcomes measured. This could be due to the different study location, population and culture. It was noted that some risk factors of human brucellosis were culture-specific; for example, consumption of raw calf foetus as a traditional remedy in South Korea[19] and consumption of raw camel milk which is not routinely practised in other countries.[10] Besides that, the study also represented different endemic regions; for example, Lebanon as a high endemic region, Turkey with moderate, Israel as low and Thailand as non-endemic, based on the published brucellosis mapping in 2006.[23]

Livestock related workers were the highest risk occupation found in this review[7,8,10,11,13,15,16,18,20]. This was supported by the findings that workers in slaughterhouse have a high prevalence (58.7%) of seropositivity to brucellosis [24] particularly workers who were slaughtering animals and cleaning the slaughtered animal parts.[25] The positivity was significantly associated with hours of work which correlated with duration of contact with raw meat.[24] A previous study in Iran also highlighted that ranchers, farmers and housekeepers that possibly share living space with animals were occupations highly associated with brucellosis.[26] Hence appropriate preventive measures should be in place, for instance, improving knowledge about brucellosis for local communities and local public health officers,

education on proper sanitation measures, as well as using personal protective equipment when handling animals and their byproducts.[11] In view of the livestock farmers consuming unpasteurized milk or uncooked meat, education on the importance of heating the milk and cooking meat before eating also appeared as pertinent preventive measures for brucellosis transmission.

The limitation of this study was inadequate information from the studies to derive a good quality meta-analysis. This was due to the quality of the included studies. Secondly, this study did not include articles that were not in English. As English is not the first language in most Asian countries, certain outbreak management studies that were published in local languages were excluded. The brucellosis research agenda should focus on designing and implementing high-quality studies to improve the quality of evidence and highlight the importance of the disease.

Conclusion

Brucellosis is a potential public health concern even in low endemicity countries. Underdetection may lead to substantial disability and outbreak occurrence. The common risk factors for human brucellosis outbreak include consumption of infected animal products, history of contact with animals and livestock related workers. As outbreaks of human brucellosis and animal brucellosis are interrelated, an integrated approach between all relevant agencies in outbreak management is crucial.

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