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Burden of Brucellosis in the Middle East: A Systematic Review

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Short running head: Burden of brucellosis in the Middle East

Burden of Brucellosis in the Middle East:

A Systematic Review

SUMMARY

A systematic review of studies providing frequency estimates of brucellosis in humans and ruminants and risk factors for Brucella spp. seropositivity in humans in the Middle East was conducted to collate current knowledge of brucellosis in this region. Eight databases were searched for peer-reviewed original Arabic, English, French and Persian journal articles; the search was conducted on June 2014. Two reviewers evaluated articles for inclusion based on pre-defined criteria. Of 451 research articles, only 87 articles passed the screening process and provided bacteriological and serological evidence for brucellosis in all Middle Eastern countries. Brucella melitensis and B. abortus have been identified in most countries in the Middle East, supporting the notion of widespread presence of Brucella spp. especially B. melitensis across the region. Of the 87 articles, 49 were used to provide evidence of the presence of Brucella spp. but only 11 provided new knowledge on the frequency of brucellosis in humans and ruminants or on human risk factors for seropositivity and were deemed of sufficient quality. Small ruminant populations in the region show seroprevalence values that are among the highest worldwide. Human cases are likely to arise from subpopulations occupationally exposed to ruminants or from the consumption of unpasteurized dairy products. The Middle East is in need of well-designed observational studies that could generate reliable frequency estimates needed to assess the burden of disease and to inform disease control policies.

Keywords: brucellosis, burden, systematic review, Middle East

INTRODUCTION

Brucellosis is a zoonotic disease which affects a wide range of animals including domestic livestock. It is caused by members of the genus *Brucella*; among the ten known species of *Brucella*; *B. melitensis*, *B. abortus*, *B. suis*, *B. cani*s and *B. ceti* have been isolated in human cases in addition to their specific animal hosts [1, 2, 3, 4]. Although accurate estimates of human incidence are lacking, largely because of under-reporting and misdiagnosis [5], brucellosis is considered one of the most common bacterial zoonoses worldwide [6].

In endemic areas, brucellosis is responsible for significant economic losses to livestock production due to abortions, reduced milk yield and infertility in addition to the public health burden [7]. The disease is transmitted to humans via consumption of un-heat treated milk and dairy products from infected animals and through direct contact with afterbirths and aborted materials. As a result, individuals with occupational livestock contact in endemic areas, including farmers, abattoir workers, shepherds and veterinarians are at high risk [8]. The symptoms of human infection are non-specific, but the majority of patients with the acute form, present with fever, malaise, anorexia, headache, arthralgia, and backache. Persistent and recurrent fever is the most common clinical symptom in sub-acute cases. A small proportion of cases may develop complications including arthritis, endocarditis, spondylitis, sacroiliitis, osteomyelitis and meningoencephalitis [9, 10].

Infected livestock are the source of the vast majority of human cases; therefore, prevention of human brucellosis is dependent on the control of the disease in livestock. This has been achieved with varying degrees of success using a combination of vaccination, test and removal of positive animals and quarantine / animal movement controls [11]. Cattle brucellosis caused primarily by *B. abortus* has been successfully eradicated from several countries including Japan, Canada, some European countries, Australia and New Zealand [12]. However, the control of *B. melitensis* in small ruminants is more challenging than that of *B. abortus*, potentially as a result of its higher infectivity as well as the characteristics of the livestock systems where it is endemic including increased mobility of small ruminant populations compared to large ruminants [12, 13]. Different control strategies have been recommended by the Food and Agriculture Organisation

(FAO) depending on the flock-/herd-level seroprevalence, therefore reliable disease frequency estimates are of great importance to inform and monitor the control programme. In low-prevalence areas (<2%) test and slaughter of positive animals accompanied by sanitary measures is recommended. In settings where prevalence ranges between 2% and 10% FAO advocates vaccination of young animals, non-compulsory vaccination of adult animals and test-and slaughter of infected animals. In regions where prevalence is higher than 10%, mass vaccination of all livestock is proposed as the optimal control strategy until a significant prevalence reduction is achieved and the strategy can be revised [12]. The appropriate strategy also depends on the socioeconomic context, the applied surveillance system, the policy set by the competent authorities as well as the baseline level of infection. Ultimately, decisions on whether to prioritize brucellosis control over other diseases should ideally be informed by estimates of the human health burden expressed as Disability Adjusted Life Years (DALYs) and measures of monetary impact i.e. economic losses due to human illness and decreased livestock productivity [14]. The assumed high burden of the disease, particularly in low-income countries, is not matched by the attention it receives from health systems worldwide and as a result brucellosis has been included in the WHO's list of Neglected Zoonotic Diseases [6] Brucellosis is a major public health problem in the Middle East, Mediterranean region, and parts of Asia, Africa and Latin America [15]. In this paper we focus on the Middle East, a region where brucellosis is assumed to be among the zoonoses with highest burden [16]. The region includes 15 countries; Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, United Arab Emirates, Yemen, and Israel [17] (**Fig. 1a).** Most of these countries have many similarities regarding livestock management systems, environmental conditions and culture [16]. Brucellosis is receiving increasing attention in the Middle East; some countries such as Egypt and Oman are implementing mass vaccination programs for small and large ruminants whereas others e.g. Iran, Iraq and Israel are adopting mass vaccination of small ruminants **Fig. 1b**. The aim of this study was to systemically identify, evaluate and summarize relevant published data on the presence and frequency of ruminant and human brucellosis in the Middle Eastern countries as well as on the strength of association between potential risk factors and *Brucella*. spp. seropositivity in humans.

METHODS

Systematic Review Protocol

A systematic review was conducted using a predefined protocol based on Cochrane [18] and PRISMA [19] guidelines. The protocol includes four main steps; i) literature search to identify potential articles of relevance, ii) screening for relevance, iii) quality assessment and iv) data extraction. **Figure 2** summarizes the steps of the protocol with the number of papers that fulfilled the necessary criteria at each step.

Search Strategy and identification

Eight electronic data bases; BioMed Central Journals, CAB Direct (CABI), Cochrane Library - Cochrane Database of Systematic Reviews (Wiley), ScienceDirect, ERIC plus Text (ProQuest), IBSS (CSA), PubMed, and Web of Science (ISI) Zetoc, were searched using the following terms:

1) Brucellosis OR Malta fever OR *Brucella* OR "*Brucella melitensis"* OR *"Brucella abortus".*

   AND

2) Middle East OR (Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, United Arab Emirates, Yemen, Israel).

   AND

3) Prevalence OR Incidence OR Burden OR Risk AND Factors.

The search was conducted on June 2014 for papers published since the original search. No time limits were set.

Screening Process

All references were imported to EndNote (Thomson Reuters) and duplicated articles were excluded. The retrieved abstracts were screened by the primary author for entry into the next stage (quality assessment) based on the following inclusion criteria:

1. The reported research is original and studies a human or animal population in one or more of the Middle Eastern countries.

   AND

2. The article is published in a peer reviewed section of a journal.

AND

3. The article is written in Arabic, English, French or Persian languages.

AND

4. The research provides:

   a. Estimates of the frequency ((sero)-prevalence and/or incidence) of *Brucella* spp. infection in domestic ruminants and/or humans.

   AND

   b. Estimates of the strength of association between *Brucella* spp. infection in domestic ruminants and/or humans.

For articles that met the primary inclusion criteria or articles where the relevance could not be determined by reading the abstract alone; full texts were retrieved and the article was subjected to a quality assessment and data extraction.

Quality assessment and Data extraction

Two reviewers independently assessed the quality of the articles based on a set of criteria adapted from Cochrane guidelines [18], and Downs & Black guidelines for cross-sectional studies [20]. Reviewers were firstly asked to specify the type of study, whether it was descriptive or analytical (i.e. involving an element of comparison across groups). Studies that were limited to the description of the characteristics of a series of cases (case reports) were excluded. Reviewers were asked a series of questions to summarise the objectives, study design, study population, sampling strategy, diagnostic test/s performed, statistical methods used and main outcomes of the study. These general questions were followed by a series of questions specific for each study type and to which reviewers could answer "yes", "no" or "unclear".

Selected studies were appraised by the two reviewers against the following five criteria and rated as "high quality" studies when all five criteria were met:

1. The type of study design was clear from the information provided;

2. Sampling strategy was clearly described and the study population was considered fairly representative of the target population;
3. The study was not deemed to have high potential for selection bias;
4. Diagnostic tests used were those recommended by the World Organisation for animal Health (OIE) in the study species [7]; given that no time limit was set in the search process, OIE and WHO recommendations at the time when the study was conducted were considered.
5. The vaccination status of the study population was stated.

When provided, estimates of the frequency of infection (incidence or prevalence) and of the strength of association (relative risks or odds ratios) where extracted.

Each reviewer extracted data independently using a data extraction form prepared by the primary author. Disagreements between reviewers were discussed in detail between them and resolved by consensus. The quality assessment checklist and data extraction forms are available upon request from the primary author.

Data management

Studies considered to be of "high quality" were grouped according to whether they investigated the frequency of brucellosis or risk factors for infection. Because of the heterogeneity within each group of studies in terms of study design, geographical areas, human or ruminant subpopulations under study and sample sizes, no statistical tests for heterogeneity or quantitative meta-analysis were performed; instead data were extracted, summarized and organized in a qualitative manner.

Studies that passed the initial screening but did not fulfil the quality assessment criteria and were therefore deemed not to be of sufficient quality to generate unbiased estimates of frequency of disease or strength of association for human seropositivity were used to summarize available evidence of the presence of Brucella spp. in different host populations in the Middle East, where appropriate.

RESULTS

Searching

The initial search revealed 681 research articles, after removing duplicates 451 research articles remained, among these 23, 405, 3 and 20 were written in Arabic, English, French and Persian languages, respectively. Abstract screening was then performed and articles were excluded when they reported studies that were not carried out in one or more of the Middle Eastern countries (95 articles excluded), if they were not original research articles (114 articles excluded), if they were published in non-peer-reviewed journals (65 articles excluded) and if they did not provide estimates of brucellosis frequency in humans or domestic ruminants or potential risk factors for human seropositivity (90 articles excluded). A total of 87 articles (5 Arabic, 77 English, 5 Persian) met the primary eligibility criteria.

Quality assessment

During the quality assessment 76 articles were excluded for not fulfilling all five quality criteria listed in the quality assessment and data extraction part of the methods. Eighteen of studies were excluded because they were descriptive case-series, 43 studies were excluded due to unclear study design or non-representative sampling therefore deemed to have high potential for selection bias. In five studies, the diagnostic tests used were not those recommended by WHO/OIE in the study species. Furthermore, in 10 studies the authors did not mention clearly whether the sampled animals were vaccinated or not, which may lead to inaccurate seroprevalence estimates. Of these 76 articles, 49 were retained and used to provide evidence of the presence of Brucella spp. in different ruminant hosts in Middle Eastern countries (Table 1). The range of the years of publication was 1974–2014 with a median of 2005. At least one B. melitensis biovar (1, 2, 3) was identified in each country and at least one B. abortus biovar (1, 2, 3, 9) was identified in nine of the 15 countries supporting the widespread presence of Brucella spp. especially B. melitensis across the region. Moreover, B. suis biovar 1 was isolation from cattle in Egypt [25]. Only 11 articles were considered of sufficient quality and were used to provide frequency estimates in humans and ruminants or information on risk factors for brucellosis in

humans. Table 2 describes the features of the eleven included studies. The number of papers that passed the quality assessment step by country is presented in Figure 3.

Frequency of brucellosis in humans

The frequency of brucellosis in humans was investigated in many of the Middle Eastern countries but only one study [6] fully met the quality criteria. The study described a population-based surveillance for patients with acute febrile illness in Egypt and estimated an annual incidence of brucellosis at 64 and 70/100 000 population in 2002 and 2003, respectively.

Seroprevalence of brucellosis in ruminants

A considerable number of studies assessed the frequency of brucellosis in different ruminant sub-populations in the Middle East. Four studies met the inclusion criteria; three in Egypt and one in Jordan. **Table 3** summarises the findings of those studies. Sheep, goat, cattle and buffaloes were the studied species, and in all cases frequency of infection was estimated as seroprevalence.

In Jordan, seroprevalence in Awassi sheep in the Northern part of the country was estimated at 2.2% (95% CI: 0.5 - 3.5) and 45% (95% CI: 32- 58) at individual animal and flock levels, respectively, in 2000/2001 [29]. In Egypt, prevalence estimates for different livestock species are available for Kafr el-Sheikh Governorate (the largest governorate of the Nile Delta region) and for the Upper Egypt region. In Upper Egypt, true seroprevalence was estimated to be 1.16 (95%CI: 1.05-1.27) in sheep, 0.44 (95%CI: 0.34-0.54) in goats, 0.79 (95%CI: 0.71-0.87) in cows and 0.13 (95%CI: 0.08-0.18) in buffaloes. These estimates were obtained from a study using secondary data for the period 2005-2008 in 7 governorates of Upper Egypt [51]. In Kafr el-Sheikh Governorate, a study conducted in 2008 [52] estimated true prevalence to be 12.2% (95%CI: 8.4-16.0) in individual sheep, 11.3% (95%CI: 7.8 - 14.8) in individual goats, 41.3% (95%CI: 26.1-56.7) in “village flocks”, 12.2% (95%CI: 7.0 - 13.3) in milk tanks from cows and 11.3% (95%CI: 7.8 - 14.8) in milk tanks from buffaloes. A small study conducted in one single village in another governorate of the Nile Delta (Menufiya) estimated that 11% (95% CI: 3.06-18.4) of unvaccinated individual cows and buffaloes had

detectable antibodies in milk and that 15.5% (95% CI: 6.61% to 24.7%) of households keeping cows or buffaloes had at least one positive animal [53].

Risk factors associated with human brucellosis in the Middle East

The review identified six studies that measured the strength of association between potential risk factors and human brucellosis in the Middle East. All of them were case-control studies and were conducted in in Iran, Saudi Arabia, Yemen, Jordan and Egypt (2 studies). Details of these studies are summarized in Table 4 and the studied risk factors are summarized below.

Consumption of dairy products

Generally, the consumption of unpasteurized dairy products was a statistically significant risk factor for seropositivity in the Middle East. The study in Saudi Arabia revealed that consumption of unpasteurised milk (OR: 3.8, 95% CI 2.2-6.4) and buttermilk (dairy product locally known as laban) (OR: 3.0, 95% CI 1.2-7.6) were significant risk factors for infection. The consumption of unpasteurised dairy products was also a risk factor for infection in Yemen and Iran, with Iran sheep-derived products posing the greatest risk in the study conducted in this country. In Jordan, the consumption of raw feta cheese (OR: 2.8, 95% CI: 1.4–5.6) was positively associated with brucellosis, whilst the consumption of cows' milk (OR: 0.4, 95% CI: 0.2–0.8) and the consumption of boiled feta cheese (OR: 0.4, 95% CI: 0.2-0.8) decreased the risk of brucellosis [50]. In Egypt eating ice cream from street venders (OR: 2.4, 95% CI: 1.2 – 4.6) was a risk factor for the disease.

Occupational exposure

Among exposures not associated with the foodborne route, assisting with animal parturition was a significant risk factor for infection (OR: 3.6, CI 2.1 – 6.1). Farmers (OR: 2.5, 95% CI: 1.4-4.5), shepherds (OR: 7.8, 95% CI: 1.0-61) and microbiologists (OR: 24.5, 95% CI: 2.9-204) were the groups at highest occupational risk of acquiring brucellosis in Yemen, [46]. The study in Tanta Fever Hospital in Egypt (2003) identified contact with sheep (OR: 6.2, 95% CI: 1.9 – 20.4), high-risk occupation (OR: 4.4, 95% CI: 1.3-14.5) and history of

having an aborted animal (OR: 3.5, 95% CI: 1.3 – 9.1) as significant risk factors for human brucellosis [48]. Similarly, the study in Alexandria Fever Hospital in Egypt identified direct contact with goats (OR: 3.2, 95%CI: 1.2 – 8.7) and occupations dealing with animals (OR: 2.4, 95% CI: 1.2 – 4.9) as significant risk factors [49]. The case-control study from Jordan revealed that milking small ruminants was a risk factor for infection (OR: 3.5, 95%CI: 1.5–8.4). Finally, the study in Iran also showed that the existence of another case of brucellosis in the home (OR: 7.55, 95% CI: 3.9- 14.6) was a major risk factor for infection.

Discussion

Brucellosis is considered endemic in most Middle Eastern countries where it is assumed to impose a considerable burden as a result of human disease and impaired livestock productivity [31, 32]. Our work aimed to systematically review available data regarding Brucella spp. presence and frequency estimates in humans and ruminants and associations between potential risk factors and human seropositive status in the Middle East. Although the primary search revealed 451 studies, after assessing their relevance, only 87 articles met the primary inclusion criteria and 49 of these provided evidence relevant for this review. Using strict quality criteria, only 11studies were deemed of sufficient quality to provide reliable seroprevalence estimates that could eventually be used to quantify the burden of brucellosis in the region or data to inform disease prevention programmes prioritizing populations based on specific risk factors.

Most studies were excluded due to incomplete or unclear description of the design, or a design that was unlikely to generate unbiased estimates, including prevalence studies carried out using non-probabilistic sampling, studies comparing seroprevalence in purposively selected subpopulations without consideration of potential biases and studies where clustering of individual animals within herds was ignored. Most of the articles deemed of sufficient quality were produced in the last 15 years (9 of 11) and the other two articles were produced in the 1990s; moreover, 7 of 11 articles were collaborative work between European or US and Middle Eastern researchers. This reflects the relatively modest and recent development of epidemiological research in the region and the importance of international collaboration.

Another critical issue with some studies was the use of diagnostic tests that are not recommended by the WHO/OIE for the host species being studied making the reliability of the obtained estimates questionable. Uncertainty with regard to the sensitivity and specificity of diagnostic tests being used hinders adjustment of observed apparent seroprevalence to obtain true seroprevalence estimates. Moreover, ignoring clustering of animals within the herd/flock during sampling will result in inaccurate estimates, given the use of imperfect diagnostics; herd specificity can be very low when several animals are tested in the same cluster and only one seropositive result is required for the herd to be classified as positive. Diagnostic specificity may also be low due to cross-reactive bacteria or vaccination with smooth Brucella strains.

Lack of consideration of the vaccination status of the sampled animals was another reason why some studies were excluded, because vaccination of livestock against *Brucella* spp. is practiced in some Middle Eastern countries and most of the serological tests used are not able to differentiate between vaccinated and infected animals which can lead to biased estimates. For example two studies estimated the seroprevalence of brucellosis in sheep in Jordan; the first one was conducted in the Northern governorates and reported a seroprevalence of 2.2% (95 %CI: 0.5 - 3.5) and 56% (95% CI: 44.0-69.0) at individual animal level and herd level respectively. The other one reported a seroprevalence at 37.6% and 47% (95% CI: 29, 52) at individual animal and herd levels respectively, the vaccination status of the sampled flocks was not mentioned in the second study. As mentioned previously, they may also have an issue of low herd specificity in these studies.

Although a considerable number of studies did not pass the inclusion criteria in this review, they still were used to provide evidence for the presence of *Brucella* spp or *Brucella* seropositivity in different hosts in the Middle East. These studies provided evidence for *Brucella* seropositivity in all the countries of the region and all host species with a few exceptions: lack of evidence of infection in large of small ruminants in Bahrain (where there is serological evidence of infection in humans) and lack of evidence of infection in large ruminants in Lebanon and Palestine (where there is evidence of infection in small ruminants and humans). Such finding is of great importance in adapting collaborative work for the control of brucellosis in the Middle East. Data extracted from these studies show that *B. meletinsis biovars* 3, 1 and *B. abortus* bivars 1, 2, 3 and 9 were the most frequently isolated *Brucella* spp. in the majority of the Middle East countries.

Despite the scarcity of sound prevalence or incidence estimates, the review found serological evidence of Brucella spp. in humans in all countries (Table 1). Isolation of B. abortus from humans only in Israel could be the result of transmission from cattle to humans before it has been eliminated from the country after adapting vaccination programme.

Based on our inclusion criteria, only one study provides good quality estimates of the frequency of brucellosis in humans. It is based on a population-based surveillance implemented in Fayoum Governorate in Egypt in 2002 and 2003. Most studies concerning human infection consisted of case-series describing cases retrospectively using data from hospital records without a control group – therefore precluding the investigation of risk factors for infection. Other studies have investigated the prevalence among high risk subpopulations such as nomadic people or among patients who suffered manifestations compatible with infection such as women with miscarriage. Such studies were excluded when selection of individuals was not done probabilistically, although the estimates provided by these studies could be of use and in fact, have been included in a recently published review on human brucellosis, commissioned by the WHO [54]; the reason for their inclusion was to fill gaps in some countries to offer frequency estimates to be used in the calculation of Disability-Adjusted Life Years (DALY) for human brucellosis.

Studies estimating the frequency of brucellosis in humans in the Middle East often rely on the use of records of public hospitals and primary health centres. Such records depend largely on the clinical presentation of the disease rather than laboratory confirmation. Furthermore, a considerable number of cases do not seek medical care or may be referred to private health centres rather than official ones. As a result, such records would result in estimates that are unreliable. There is a need for population-based surveillance combining clinical presentations and laboratory confirmation [6].

Although the seroprevalence of brucellosis in ruminants has been intensively investigated across the Middle East, the current review identified only four studies of sufficient quality reporting seroprevalence in four ruminant sub-populations; sheep, goats, cattle and buffalos in two countries; Egypt and Jordan [29, 51, 52, 53].

The reported seroprevalence varied widely from country to country and even between regions within the same country. In Egypt, for example, the true seroprevalence at individual animal level in sheep was estimated as 1.16 (95%CI: 1.05-1.27) in seven of Upper Egypt governorates, whereas it was estimated as 12.2% (95%CI: 8.4 - 16.0) in one governorate of the Nile Delta. The results of Upper Egypt study [51] are similar to the results of the Jordanian study which reported a true seroprevalence of 2.2% (95%CI: 0.5- 3.5) at individual animal level [29]. Available estimates suggest that brucellosis is endemic at high levels not just among small ruminants but also in bovine subpopulations in Egypt and reported seroprevalence in Egyptian cattle and buffalo herds varied between governorates.

This variation in the estimates could result from the heterogeneity of studied populations in terms of husbandry practices and livestock densities as well as different environmental conditions. At flock or village levels the relatively high reported true seroprevalence values in Egypt at 41.3% (95% CI: 26.1–56.7) and in Jordan at 45% (95% CI: 32- 58) were explained by the authors as possibly the cause of free uncontrolled movement of sheep flocks between villages, which facilitates contact between infected and susceptible animals [29], which also has implications for the likely success of control programs. This finding is of high importance and supports the notion that brucellosis is widespread, at least in some Middle Eastern countries, with flock-level seroprevalence estimates which are among the highest when compared with endemic situations reported in other parts of the world. Moreover, animal movement between different countries in the region and the intense animal movement between the Horn of Africa and the Middle East for trading represent a challenge for the control and require more collaboration at the international level.

Risk factors for human infection with *Brucella* spp. can be grouped into two main categories; direct contact with animals and in particular with abortion or parturition material and consumption of contaminated milk and dairy products from infected animals. These high risk practices, coupled with lack of sufficient knowledge of the disease and absence of effective prevention strategies result in maintenance of the disease in the region.

In addition, knowledge of farmers and herders regarding the disease and its control is a key factor influencing the spread of the infection. The similarities in the culture and livestock management practices in the Middle

Eastern countries mean it may be possible to extrapolate findings with regard to risk factors identified in one country to other countries. In Saudi Arabia and Yemen, consumption of raw milk and other dairy products had a greater effect as a risk factor for human infection compared to direct contact with animals [45, 46]. Conversely, studies from Iran and Egypt identified direct contact with infected animals to be more strongly associated with infection [47, 48, 49]. The reason for these differences in the identified risk factors can be attributed to the nature of the populations under study (e.g. urban vs. rural). Although the number of studies that fulfil the quality criteria of this review is small, data presented in these studies indicate that ruminant brucellosis is endemic at high levels in both small and large ruminants in some countries in the Middle East, such as Egypt and Jordan. The lack of good quality estimates demonstrates the need for more comprehensive and well- designed epidemiological studies to bridge the current gap in brucellosis research in the Middle East; this can be achieved through regional and international collaboration. At the regional level, competent authorities should develop sustainable surveillance systems, apply strict monitoring programmes on livestock movement and provide training programmes for both; veterinarians and provincial doctors in the region. At the international level, technical and financial support should be directed to endemic areas in the world such as the Middle East.

CONCLUSIONS

Brucellosis is considered a major public health burden on human populations in the Middle East and available evidence, although limited, supports this belief. Cases are likely to arise from subpopulations directly exposed to ruminants or from the consumption of unpasteurized dairy products from infected ruminants, with some ruminant subpopulations in the region showing among the highest seroprevalence levels when compared to other endemic regions. Serological and microbiological evidence supports the widespread presence of *Brucella* spp. across the region. However, there is a lack of reliable estimates of the frequency of disease both in humans and livestock which precludes the formulation of multi-sectorial control policies. There is a need for well-designed observational studies that could generate reliable frequency estimates needed to assess the burden of disease and to inform disease control policies.

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CONFLICT OF INTEREST

None.

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Table 1. Microbiological and serological evidence of the presence of *Brucella* spp. in the Middle East identified in a systematic review of peer-reviewed journal articles published in English or Arabic (search conducted on June 2012 and repeated on June 2014). 510 511 512

Country	Species (reference)	Microbiological evidence		Serological evidence
		B. abortus (biovar)	***B. melitensis*** (biovar)	
Bahrain	Humans [21]		3	yes
	Large ruminants			no
	Small ruminant			no
Egypt	Humans[16, 22]		3	yes
	Large ruminants [16,22]	1	3	yes
	Small ruminants [16, 22, 23]		1,3	yes
Iran	Humans [24]		Unknown	yes
	Large ruminants [24]	2,3, 9	2,3	yes
	Small ruminant [24]			yes
Iraq	Humans [16]		3	yes
	Large ruminants [25]	2,3,9	1,3	yes
	Small ruminant [7]			yes
Israel	Humans [16]	3		yes
	Large ruminants [16]	1, 3		yes
	Small ruminant			
Jordan	Humans [25]		1, 3	yes
	Large ruminants [27, 28]		3	yes
	Small ruminant [30, 31]	9	1,3	yes
Kuwait	Humans [32]	9	1	yes
	Large ruminants [16]		1	yes
	Small ruminant [16]		1	yes
Lebanon	Humans [34]		1	yes
	Large ruminants			no
	Small ruminant [16]		1	yes
Oman	Humans [35]		3	yes
	Large ruminants[16]	9		yes
	Small ruminant[16]		3	yes
Palestine	Humans		3	yes
	Large ruminants[36]			no
	Small ruminant [36]		3	yes
Qatar	Humans[37]			yes
	Large ruminants [38]		1	yes
	Small ruminant [16]		1	yes
Saudi Arabia	Humans [39]		1,2	yes
	Large ruminants [40]		1,2,3	yes
	Small ruminant [16]		2	yes
Syria	Humans [16]		3	yes
	Large ruminants [41]	9		yes
	Small ruminants			
UAE	Humans [42]		2	yes
	Large ruminants [16]	9	1	yes
	Small ruminant [43]		3	yes
Yemen	Humans [44]		3	yes
	Large ruminants [44]			yes
	Small ruminant [44]		3	yes

Table 2. Summary of studies on brucellosis the Middle East deemed as relevant and of sufficient quality to be included in this systematic review describing the country, year, type of study, diagnostic tests used and the main outcomes obtained.

Reference	Country	Year	Species	Type	Tests	Main outcome
5	Egypt	2002, 2003	human	Population-based surveillance	STA	Annual Incidence
45	Saudi Arabia	1988	human	Case- control	STA, Coombs	Risk factors, OR
46	Yemen	1991-1993	human	Case- control	STA	Risk factors, OR
47	Iran	2005	human	Case- control	STA	Risk factors, OR
48	Egypt	2003	human	Case- control	RBPT, TAT	Risk factors, OR
49	Egypt	2007	human	Case- control	STA	Risk factors, OR
50	Jordan	2013	human	Case- control		Risk factors, OR
29	Jordan	200-2001	sheep	Cross-sectional	RBPT, ELISA	TP
51	Egypt	2008	Cattle, buffalo, sheep, goat	Cross-sectional	RBPT, CFT, iELISA	TP
52	Egypt	2005- 2008	Cattle, buffalo, sheep, goat	Cross-sectional	RBPT, CFT	TP
53	Egypt	2009-2010	Cattle, buffalo	Cross-sectional	iELISA	TP

OR: Odds Ratio; TP: true seroprevalence; STA: Standard Tube Agglutination, RBT: Rose Bengal Test, CFT: Complement Fixation Test, ELISA: Enzyme Linked Immnuno-Sorbent Assay, iELISA: indirect ELISA

Table 3. Summary of studies investigating the seroprevalence of brucellosis in different ruminant sub-populations in the Middle East deemed as relevant and of sufficient quality to be included in this systematic review.

Reference	Species	Country	Level of study	True seroprevalence %(95% CI)	
				Individual level	Herd/Flock level
29	sheep	Jordan	Governorates	2.2 (95% CI: 0.5 – 3.5)	56 (95% CI: 44 - 69)
51	Cattle, buffalo, sheep, goat	Egypt	Governorate	Cattle: 0.79 (95% CI: 0.71-0.87) Buffalo: 0.13 (95% CI: 0.08-0.18) Sheep: 1.16 (95% CI: 1.05-1.27) Goats: 0.44 (95% CI: 0.34-0.54)	0.2 (95% CI: 0.16 – 0.23)
52	Cattle, buffalo, sheep, goat	Egypt	Governorates	Cattle: 12.2 (95% CI: 7.0 - 13.3) Buffalo: 12.0 (95% CI: 7.1 - 13.0) Sheep: 12.2 (95% CI: 8.4 - 16.0) Goats: 11.3 (95% CI: 7.8 - 14.8)	Cattle: 15.1 (95% CI: 4.0 – 26.2) Buffalo: 15.1 (95% CI: 4.0 – 26.2) Sheep: 41.3 (95% CI: 26.1 – 56.7) Goats: 32.2 (95% CI:17.8 – 46.7)
53	Cattle and buffalo	Egypt	Village	11.0 (95% CI: 3.06 – 18.4)	15.5 (95% CI: 1.44 – 27.9)

Table 4. Risk factors for human brucellosis: summery of case-control studies included in this systematic review.

Reference	Country, study population	Risk factors (OR, 95% CI)
45	Saudi Arabia, 150 cases and 150 controls	Consumption of unpasteurised milk (OR: 3.82, 95% CI 2.26-6.46), consumption of buttermilk (laban) (OR: 3.1, 95% CI 1.2-7.6) and assisting with animal parturition (OR: 3.6, 95%CI 2.2 – 6.1)
46	Yemen, 235 cases and 234 controls	Drinking fresh milk (OR= 2.0, 95% CI: 1.3-4.3), drinking laban (OR= 2.7, 95% CI: 1.7- 4.2), occupation as farmers (OR= 2.5, 95% CI: 1.4-4.5), shepherd (OR =7.8, 95% CI: 1.0-61) and microbiologist (OR= 24.5, 95% CI: 2.9-204)
47	Iran, 150 cases and 150 matched controls	Existence of another case of brucellosis in the home (OR= 7.5, 95% CI: 3.9- 14.6) and consumption of unpasteurized dairy products (OR= 3.7, 95% CI: 1.6-8.3)
48	Egypt, 149 cases and 298 controls	Having sheep (OR= 6.2, 95% CI: 1.89 – 20.40), high-risk occupation (OR= 4.4, 95% CI: 1.4-14.5) and history of having an aborted animal (OR= 3.5, 95% CI: 1.3 – 9.1)
49	Egypt,72 cases and 144 age-matched controls	Direct contact with goats (OR=3.2, 95% CI: 1.2 – 8.7), occupations dealing with animals (OR= 2.4, 95% CI: 1.2 – 4.9) and eating ice cream from street venders (OR= 2.4, 95% CI: 1.2 – 4.6)
50	Jordan, 56 cases and 247 matched controls.	Milking small ruminants (OR= 3.5, 95%CI: 1.5–8.4), consumption of raw feta cheese (OR= 2.8, 95% CI: 1.4–5.6), consumption of cow's milk (OR= 0.4, 95% CI: 0.2–0.8) and the consumption of boiled feta cheese (OR= 0.4, 95% CI: 0.2-0.8)

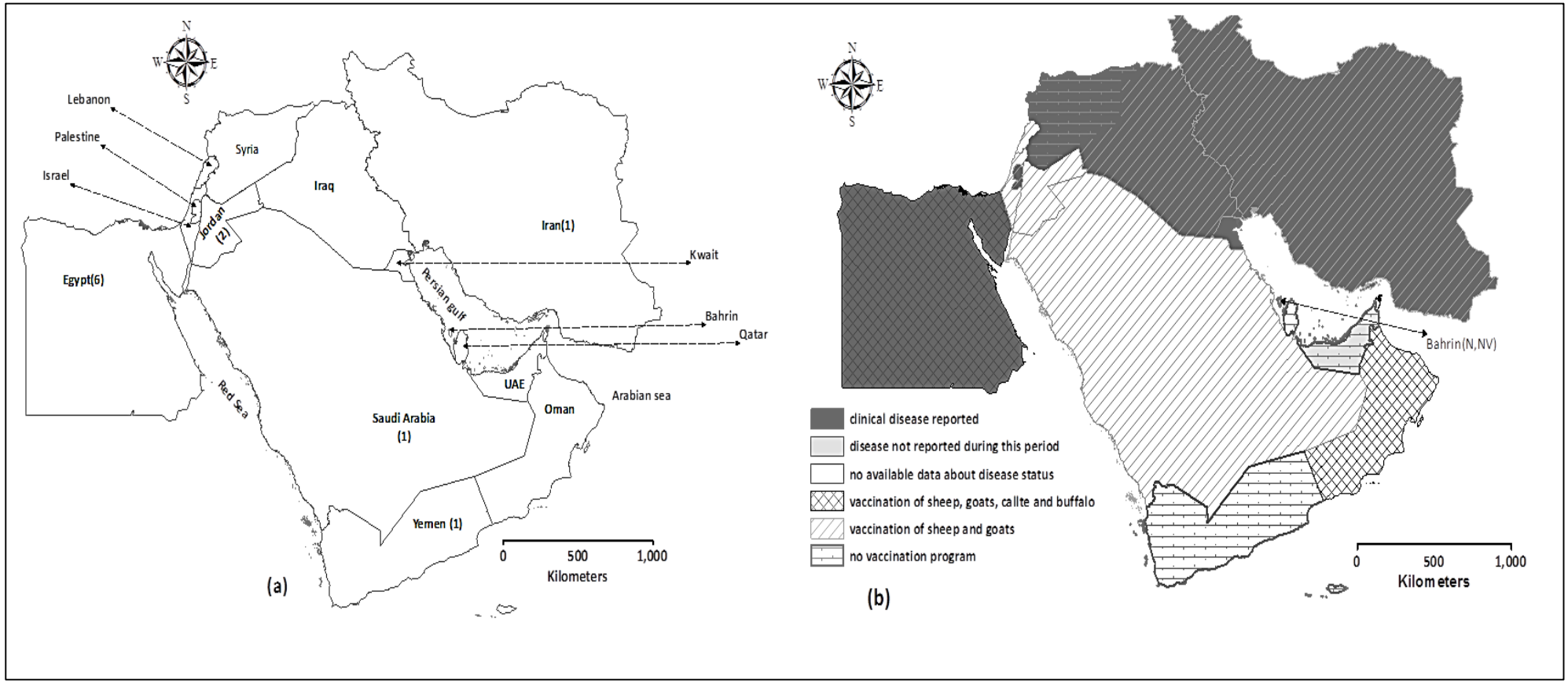

Fig. 1a Middle East countries with the number of studies per country deemed relevant and of suficient quality to be included in this review in brackets. b Ruminant brucellosis infection and vaccination status in the Middle East countries, data obtained from OIE, 2013. (N: disease not reported; NV: no vaccination program).

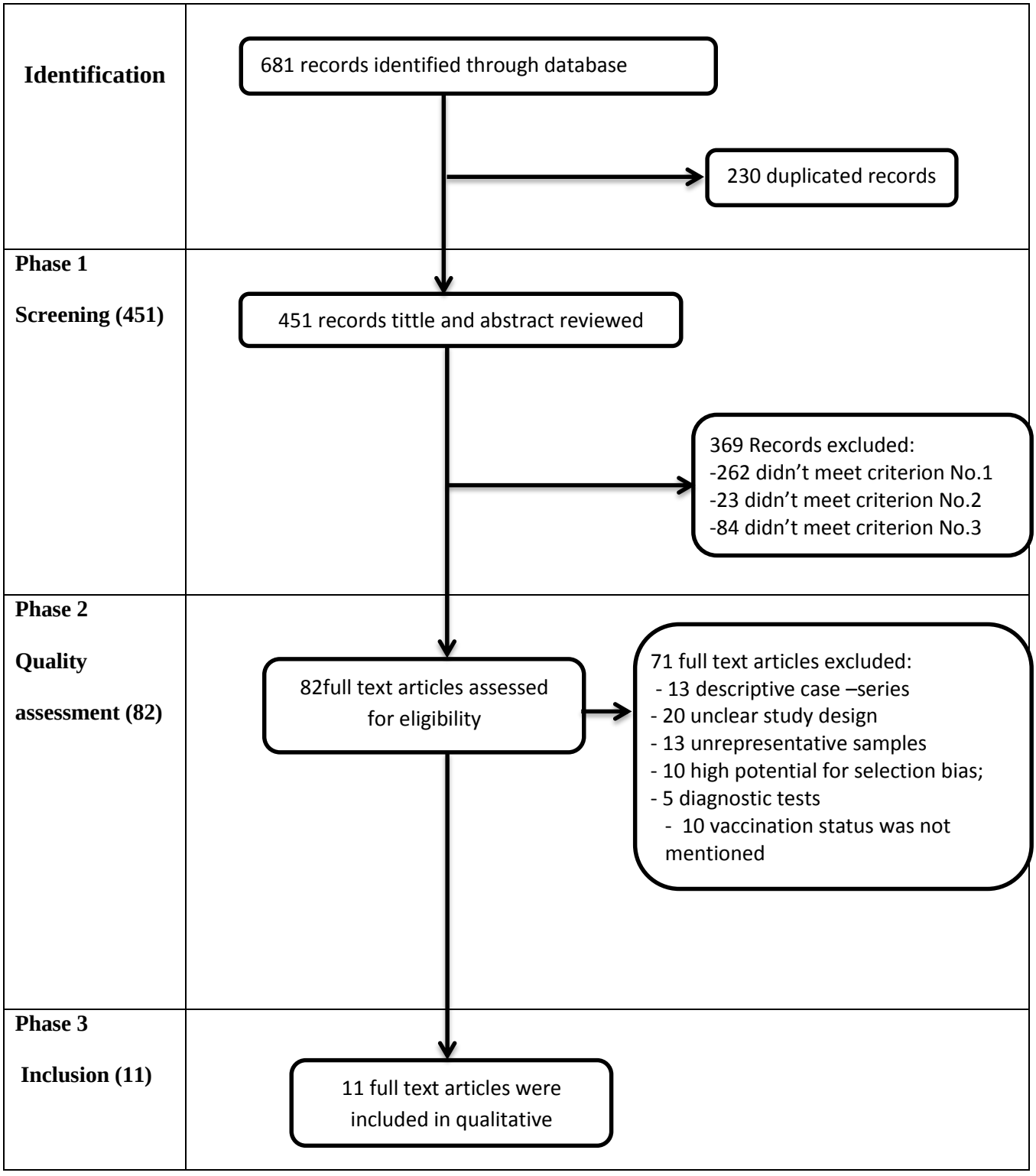

Figure 2 Flowchart (template provided by PRISMA) showing the numbers of peer-reviewed journal papers at each stage of the systematic review.