Epidemiology of Brucellosis in Saudi Arabia

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ABSTRACT

الأهداف: تقديم ملخص شامل للإصابة بداء البروسيلات وانتشارها وعوامل الخطر المرتبطة بها وتأثيرها على السكان السعوديين.

المنهجية: أجريت مراجعة منهجية باستخدام قاعدة بيانات PubMed. كتبت المقالات المشمولة في المراجعة باللغة الإنجليزية وتحققت في علم الأوبئة أو مسببات المرض أو التوزيع أو التأثير أو عبء داء البروسيلات في السكان السعوديين. تم الانتهاء من المقالات المراد إدراجها بعد إجماع متبادل بين الباحثين.

النتائج: اشتملت الدراسة على سبعة عشر (n=17) دراسة أجريت في مناطق جغرافية متنوعة في المملكة العربية السعودية. من بينها، أفادت 3 دراسات عن انتشار داء البروسيلات بين النساء الحوامل ونتائج الحمل؛ 3 دراسات ركزت على العوامل المرتبطة بالأعراض وعلامات داء البروسيلات بين الأطفال؛ أبرزت دراستان انتشار داء البروسيلات بين العمال؛ ذكرت 9 دراسات انتشار/حدوث وعوامل الخطر المرتبطة لداء البروسيلات. تختلف الإصابة بالبروسيلات وانتشارها على نطاق واسع بين المناطق. الاتصال بالحيوانات المصابة واستهلاك الحليب غير المعالج ومنتجات الألبان باعتبارها أهم عوامل الخطر المرتبطة بمرض البروسيلات. كانت معدلات الإجهاض ووفيات الجنين داخل الرحم أعلى بكثير بين النساء الحوامل المصابات بداء البروسيلات مقارنة مع النساء الحوامل دون داء البروسيلات.

الخلاصة: يشكل داء البروسيلات تأثيرًا كبيرًا على الإنسان وله معدل انتشار أعلى في البلدان النامية مقارنة بالدول المتقدمة. كشفت نتائجنا أن داء البروسيلات هو عامل خطر للنتائج التناسلية السلبية.

Objectives: To provide a comprehensive summary of brucellosis incidence, prevalence, risk associated factors, and impact on the Saudi population.

Methods: A systematic review was conducted using the PubMed database. The articles included in the review were written in English and investigated the epidemiology, etiology, distribution, impact, or burden of brucellosis in the Saudi population. Articles to be included were finalized after a mutual consensus of 2 researchers.

Results: Seventeen (n=17) studies were included which were conducted in diverse geographical areas of Saudi Arabia. Of them, 3 studies reported the prevalence of brucellosis among pregnant women and pregnancy outcomes; 3 studies focused on risk associated factors and symptoms and signs of brucellosis among children; 2 studies highlighted the prevalence of brucellosis among workers; 9 studies reported the prevalence/incidence and risk associated factors of brucellosis. Brucellosis incidence and prevalence vary widely among regions. Contact with infected animals and consumption of raw milk and milk products were identified as the main risk associated factors of brucellosis. Abortion and intrauterine fetal deaths rates were significantly higher among pregnant women with brucellosis compared with pregnant women without brucellosis.

Conclusion: Brucellosis poses a considerable impact on human and has a higher prevalence in developing countries as compared to developed countries. Our results revealed that brucellosis is a risk factor for adverse reproductive outcomes.

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Brucellosis is one of the common bacterial zoonotic infections worldwide, and it poses a major threat to human and animal health.[1] *Brucella spp*. is responsible for causing brucellosis. Due to its contagious nature and impact on human health, it is considered as a biological agent.[2] In Sub-Saharan Africa, brucellosis infects over 500,000 humans annually.[3] However, lack of reporting and misdiagnosis with other diseases is responsible for its inaccurate incidence.[3] Moreover, the socio-demographic profile of the population and the strength of the country's brucellosis eradication program leads to diversity in brucellosis incidence.

An epidemiological study conducted in Uganda also highlighted that the prevalence and incidence of brucellosis are not clearly understood.[4] Though the disease is prevalent all over the globe, the major regions for the public health concern are the Mediterranean region, the Middle East, Africa, and Latin America.[3,5]

Human brucellosis is life-threatening and its clinical presentation includes non-specific symptoms such as intermittent fever, weight loss, depression, hepatomegaly, splenomegaly joint pain.[6] Also, brucellosis leads to financial burden due to loss of normal daily activities[7] and there is a loss of animal production as well.[8] An animal disease evaluation in Kenya listed brucellosis as one of the top 10 factors that affect the lives of the poor.[9]

Transmission of brucellosis in humans is either by direct or indirect contact with infected animals or with the consumption of contaminated foods.[10] Unpasteurized dairy products from infected animals are considered as a source of public infection in developing countries as limited infrastructure for disease control was available.[11] For meat packaging industry workers, contaminated carcasses are the major source of infection.[11] According to veterinarians, contamination while supporting births in infected livestock and unintentional vaccine exposure are also responsible for obtaining brucellosis.[12]

Also, the transmission is being remarkably affected by the contact with infected products of aborted animals,[12] in addition clinical laboratories and abattoirs have reported airborne transmission of bacteria to humans.[13] Due to the traditional practice of consuming raw milk primarily from sheep and camel in Saudi Arabia, the main causative factors are unpasteurized raw milk consumption and contact with the infected animals.[14-16]

One of the most frequently reported diseases in Saudi Arabia is human brucellosis, especially in Riyadh city.[13-15,17-20] Numerous studies have been conducted on brucellosis in different regions of Saudi Arabia.[13-15,20-23] However, the threat of brucellosis to humans has expanded as no systematic review has been conducted to assess the epidemiology of brucellosis in Saudi Arabia. To evaluate the extent of the disease and to identify the current knowledge on brucellosis in the Saudi population, this review aims to provide a comprehensive overview of brucellosis incidence, prevalence, risk associated factors, and its effects. To avoid future brucellosis epidemics, this review also identifies areas where research is sorely required.

Methods. Relevant papers published until March 2016 were searched online using PubMed. The following keywords were used in the search approach: "brucellosis," "*Brucella*," "epidemiology," "prevalence," "incidence," "risk," "impact," and "Saudi Arabia". All the relevant articles, except interventional studies and case reports/series which focused on brucellosis's epidemiology, etiology, distribution, impact or burden on Saudi people and were written in English were included in the review.

After conducting the online search, 51 articles were identified. The post-abstract screening were classified into 2 segments: i) relevant articles (which focused on human brucellosis infection); and ii) irrelevant articles (which were related to non-human brucellosis or which were out of scope of the current review, such as articles on brucellosis genetic behavior, the laboratory diagnostic tests associated with the screening of human brucellosis, as well as the experimental studies on animal models). The articles were further analyzed by screening their full text versions. This involved 2 reviewers who assessed each article and confirmed if they were relevant or irrelevant for the study. In case of classification related discrepancies, discussion was conducted for resolution.

Furthermore, the relevant articles were classified as following frequency studies: a) Prevalence studies which included definite study population: setting and outcome. For example, to identify study population as seropositive for brucellosis. b) Incidence studies which indicated the time period of observation: included study population size, setting, and outcome. For example, the number of new brucellosis cases per population at risk per time period.

Articles to be included in the study were finalized after the mutual consensus of 2 reviewers. Newcastle

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Ottawa scale for case-control and cohort study was used to assess the quality as well as the risk of bias of the included studies.

Results. After the mutual consensus of the researchers, 17 articles met the inclusion criteria with publication dates ranging between 1984 and 2011 (**Figure 1**). According to Newcastle Ottawa scale, most of the studies included scored from medium to lower bias. The studies included were conducted in a variety of geographical areas in Saudi Arabia. Of the 17 articles, 3 studies reported the prevalence of brucellosis among pregnant women and pregnancy outcomes. Likewise, 3 studies reported the risk associated factors and symptoms and signs of brucellosis among children. Moreover, 2 studies reported the prevalence of brucellosis among workers, while 9 studies reported the prevalence/incidence and risk associated factors of brucellosis (**Table 1**).

Prevalence/incidence, risk associated factors, signs, and symptoms of brucellosis. Aloufi et al[21] described the trend of human brucellosis disease in Saudi Arabia between 2004 and 2012 in 37,477 reported cases during this period. The study reported a significant decrease in the incidence risk from 22.9 in 2004 to 12.5 in 2012. Fallatah et al[22] conducted a study on 159 brucellosis patients and >1:160 *Brucella* titer patients. Fever was observed in 126 (79.2%) patients; joint pain in 112 (70.4%); and bone pain in 77 (48.4%) patients. In addition, abdominal pain in 18 patients (11.3%), vomiting in 9 (5.7%), anorexia in 6 (3.8%); splenomegaly in 6 (3.8%), hepatomegaly and lymphadenopathy in 2 (1.3%) patients were also observed. In 1984, Talukder et al[23] reported an estimated prevalence of brucellosis at the Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia of 1733 patients, of this 153 (8.8%) cases were positive. Another study conducted in 1997 by Elbeltagy[24] in Tabuk province, Saudi Arabia of 137 cases estimated brucellosis prevalence as 34 in 100,000 people with the mean (SD) age of 33.8 (13.9) years and male:female ratio of 1.8:1. There were 63.5% cases residing in rural areas, 58.4% retained livestock at home, 27% worked on farms and with livestock and 88.3% reported ingestion of raw milk in past. *Brucella melitensis* was the most common infecting agent followed by *Brucella abortus,* and *Brucella suis*. Cases of splenomegaly in 25.5% and hepatomegaly in 22.6% were reported.[24] Likewise, Malik[10] assessed 104 Saudi patients and reported the most common symptoms as fever in 100%, sweating in 96.2%, headache in 76.9%, joint pain in 76.9%, and backache in 73.1% cases. Fever (96.2%), splenomegaly (42.3%), hepatomegaly (46.2%), spine tenderness (30.8%), arthritis (26.9%) and lymphadenopathy (19.2%) were the some of the physical findings.

Symptoms including mild anemia, leukopenia, and relative lymphocytosis commonly observed among the study participants. A significant factor in disease transmission was ingestion of raw milk (84.6%), followed by occupational contact with animals in 73%, and raw liver consumption in 63.3%.[10]

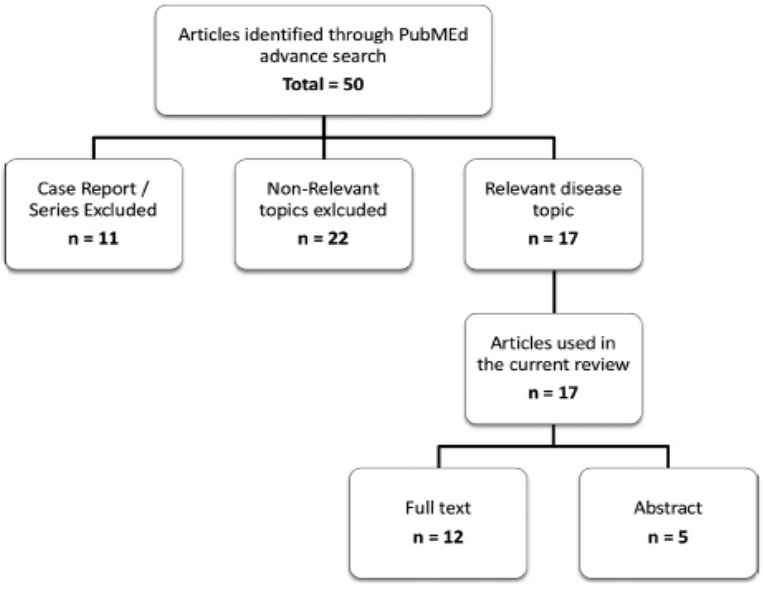

Figure 1 - Flow chart of the literature review search.

Table 1 - The summary of studies involved in the systematic review.

Study	Sample size	Study setting	Year of data collection	Prevalence/ incidence	Other findings
Prevalence/incidence, risk associated factors, signs, and symptoms of brucellosis					
Talukder et al,[23] 1984	1733 patient	Hospital	1984	8.8%	The result of 1733 patients sera tested revealed that 153 (8.8%) were positive.
Cooper,[27] 1991	300 individuals 150 cases with brucellosis 150 controls	Hospital	1988	_	Notable increase in brucellosis with increasing age and a higher incidence amongst women than men in some age groups. There was a seasonal variation in the occurrence of brucellosis.
Sadat et al,[28] 1991	173 patients with a backache and a history of ingestion of raw milk	Hospital	1990	12.1%	Twenty-one patients are suffering from *Brucella spondylitis*. Out of 21 patients, 14 (67%) presented with acute signs and symptoms of *B. spondylitis*.
Cooper,[26] 1992	300 individuals 150 cases with brucellosis 150 controls	Hospital	1988		There was a statistically significant effect of direct contact after allowing for indirect contact (OR= 1.77, p<0.05). When food types were examined, a significant effect was noted for buttermilk (OR=3.06, p<0.05) and a significant and greater effect were noted for milk (OR=3.82, p<0.00l).
Albula,[25] 1995	4794 subjects	Household	_	2.3%	Direct contact with infected animals and consumption of raw milk and milk products were identified as the main risk associated factors
Malik,[10] 1997	104 cases of brucellosis	Hospital	1986-1989	_	Raw milk ingestion was an important factor in disease transmission (84.6%), followed by close animal contact (73%) and raw liver consumption (63.3%).
Elbeltagy,[24] 2001	137 cases of brucellosis	Hospital	1997	34/100 000	There were 63.5% of cases residue in a rural area, approximately 58% kept animals at home, 27% worked with animals or farms. Moreover, a history of raw milk ingestion was reported 88.3% of the study participants. The most common infecting agents were *Brucella melitensis, Brucella abortus,* and *Brucella suis*.
Fallatah et al,[22] 2005	159 cases of brucellosis		1995-2001	_	One hundred and 59 patients had a diagnostic label of brucellosis and a *brucella* titer of >1:160. They recorded abdominal pain in 18 patients (11.3%) vomiting in 9 (5.7%) and anorexia in 6 (3.8%); splenomegaly in 6 (3.8%), hepatomegaly and lymphadenopathy in 2 (1.3%) patients.
Aloufi et al,[21] 2016	37,477 cases	Saudi National Registry	2004-2012	22.9-12.5	The IRs significantly decreased from 22.9 in 2004 [95% confidence interval (CI) = 22.3, 23.5] to 12.5 in 2012 (95% CI= 12.1, 13). Young, male Saudi citizens living in highly endemic areas were at greatest risk of acquiring brucellosis.
The incidence of brucellosis among pregnant women and pregnancy outcomes					
Sharif et al,[31] 1990	537 pregnant women	Hospital	_	_	Of the 513 women who were tested, 18 (3.5%) have a positive titer. Of 24 patients in whom the test was carried out because of symptoms suggestive of brucellosis, all were positive.
Khan et al,[30] 2001	92 pregnant women with acute brucellosis	Hospital	1983-1995	1.3/1000	Overall, 43% of pregnant women with acute brucellosis had spontaneous abortions during the first or second trimester, and 2% had intrauterine fetal deaths in the third trimester.
Elshamy et al,[29] 2008	Groups: 55 pregnant women positive for *Brucella* antibodies 395 matched pregnant controls	Hospital and Clinic	2005-2007	_	A statistically significant difference was found in abortion and intrauterine fetal death rates. No statistically significant difference was found in the preterm labor rates between the pregnant women with positive brucellosis antibodies and control groups.
Risk associated factors, signs, and symptoms of brucellosis among children					
Al-Eissa et al,[19] 1990	102 children with brucellosis	Hospital	1990	_	The most source of infection was the consumption of raw milk (80%) patients. The common symptoms were fever, arthralgia, malaise, weight loss, arthritis, hepatosplenomegaly, and lymphadenopathy.
Benjamin et al,[33] 1992	157 children with brucellosis	Hospital	1991	_	Approximately 22% gave a history of animal contact or ingesting raw milk, milk products, or raw liver. Three-quarters of the patients had an acute or subacute presentation with diverse symptomatology
AlShaalan et al,[34] 2002	115 with brucellosis	Hospital	1984-1995	_	Consumption of unpasteurized milk mainly camel was the primary source of infection. The clinical picture was dominated by arthritis 70%.
Prevalence of brucellosis among workers					
AlSekait,[32] 1993	1200 abattoir workers	Abattoir	1991	4.0%	Brucellosis was common among butchers, veterinarians (8.9%), and veterinary assistants (5.4%), and administrative personnel (1.1%).
Elsheikh et al,[35] 2011	2 Groups: 540 healthy people 900 patients	Farms and abattoir Hospital	2009-2010	(2.2%) (7.3%)	The results of ELISA revealed that all healthy people samples were negative for IgM antibodies, while 12 were positive for IgG antibodies. Thirty of the feverish patient's samples were positive for IgM antibodies, while 66 were positive for IgG antibodies.

CI - confidence interval, OR -odds ration, IR - Interquartile range

A house-to-house survey was conducted to assess the nationwide prevalence of brucellosis and randomly collected 4900 subjects. The study reported serological evidence of exposure to *Brucella* antigen in 19.2% of southern region population and active disease in 2.3% population. Major risk factors associated were direct contact with infected animals and consumption of raw milk and milk products.[25] Similarly, Cooper[26] reported consumption of unpasteurized dairy products as the main risk factor associated with brucellosis. When considering products from particular animal, intake of milk and Zaban (buttermilk) had higher risks than cheese or uncooked liver.

Cooper[27] reported brucellosis to be more common among Saudi residents than immigrants. The study also reported a substantial rise in brucellosis with increasing age. Females of some age groups were more affected as compared to males. Moreover, the study revealed an impact of season on brucellosis as its occurrence was more commonly observed in spring and summer seasons.[27] Sadat et al[28] prospectively screened patients (n=173) with backache complaint and history of raw milk ingestion and reported 21 patients infected with *Brucella spondylitis*. Among 21 patients, 14 had severe signs and symptoms of *B. spondylitis* and 6 patients were hospitalized. A positive titer of *B. melitensis* and *B. abortus* were present in most patients.[28]

The incidence of brucellosis among pregnant women and pregnancy outcomes. A prospective study on 450 pregnant women, conducted between August 2005 and December 2007, reported that incidence of brucellosis 12.2% among the study participant. Among them, the incidence of abortion was reported in 27.27% cases while the incidence of intrauterine fetal deaths was observed in 12.72% and preterm labor in 10.90% cases. Comparing women with a positive and negative titer, abortion and intrauterine fetal deaths rates had statistically significant difference while preterm labor rates had no significant difference.[29] Khan et al[30] reported that the incidence of pregnancy and brucellosis was 1.3 cases/1000 delivered obstetrical discharges between 1983 and 1995. The rate of incidence of abortion in the first and second trimesters was 43%, and the rate of intrauterine fetal deaths in the third trimester was 2%.[30] A study conducted by Sharif et al[31] showed that among 513 women who were tested routinely, positive titer was found in 3.5% (n=18) patients. Among 24 patients in whom the test was performed as symptoms indicative of brucellosis, 100% were positive. Abortion incidence among pregnant women with *Brucella titres* <1:160 was 7.7% and in >1:160 was 17.6% (p>0.05).[31]

Risk associated factors, signs and symptoms of brucellosis among children. AlShaalan et al[32] conducted a study on children to investigate signs and symptoms and the risk factors associated with brucellosis. Among the study participants, the intake of unpasteurized milk (camel) was the primary source of brucellosis. The majority (70%) of cases presented had arthritis, followed by 20% non-specific febrile illness without localizing signs and 10% febrile illness with rare presentations. Bacteremia was observed in 45% and in *B. melitensis* was observed in 96% cases. Benjamin et al[33] studied prospectively 157 brucellosis infected children at Abha, Saudi Arabia. History of animal contact or raw milk and milk products ingestion, or raw liver were found in approximately 92%. Acute or subacute presentation with diverse symptomatology was found in 75% of patients: fever in 100%, malaise in 91%, anorexia in 68%, cough in 20%, abdominal symptoms in 20%, and arthralgia in 25%. Some of the other common findings were hepatomegaly (31%), splenomegaly (55%), and lymphadenopathy (18%). Seven out of 16 (44%) patients were infected with *B. melitensis*.[33] Al-Eissa et al[19] also reported raw milk ingestion to be the main source of infection in 80% of the patients. Fever, arthralgia, malaise, weight loss, arthritis, hepatosplenomegaly, and lymphadenopathy were the main signs and symptoms presented. *B. melitensis* was isolated from 75% of the patients.

Prevalence of brucellosis among workers. AlSekait[34] documented an overall prevalence of brucellosis among abattoir workers to be 4%. Infection was prevalent among 8.9% butchers, 5.4% veterinarians and veterinary assistants and 1.1% administrative personnel. Elsheikh et al[35] followed up the latest situation in the Najran region in terms of the prevalence of brucellosis in humans and animals. The results revealed the prevalence of brucellosis infection in diseased humans as 7.3% and in animals as 15%.

Discussion. The current review is providing a comprehensive summary of brucellosis incidence, prevalence, risk associated factors, and impact on the Saudi population. One of the main factors that affected the quality of the identified studies in this review was the lack of clarity in describing the methods used, mainly on how they define the cases and the sampling technique. For some studies, we were not able to assess whether the study had been designed to control the bias.

Varied incidence and prevalence of brucellosis exist between countries and in the country itself. Study bias might be the potential cause of these differences. However, they cannot be excluded or removed. A study

conducted in the Southern region of Saudi Arabia on 4900 subjects reported active disease in 2.3% and serological evidence of exposure to *Brucella* antigen in 19.2%.[25] However, a study in Riyadh on 1733 patients estimated the prevalence of brucellosis to be 8.8% (153 patients had positive brucellosis).[23] Time and region of the study might be the 2 differentiating factors. Seroprevalence rates in developing countries from the Middle East also vary from 8% in Jordan[36] and 5% in Lebanon to 12% in Kuwait.[37,38] Low and middle-income countries had a higher prevalence than in developed countries. However, specific sub-groups of these populations such as Turkish immigrants in Germany are targets of brucellosis.[20] In the United States, human brucellosis is uncommon. Prevalence is less than 0.5 cases per 100,000 persons and for the last 10 years, approximately 100 cases have been reported annually.[39] In China, prevalence of human brucellosis increased from 0.92 cases/100,000 people to 2.62 cases/100,000 people from 2004 to 2010.[40] National statistics from the Saudi Arabian Ministry of Health has reported that brucellosis prevalence in 1990 was the highest with 72 cases/100,000 persons annually and had been consistent since 1996 with 32 and 38 cases/100,000 persons per year.[41]

Moreover, our review revealed that brucellosis prevalence rate among pregnant women ranges from 0.13% (1.3 cases/1000 delivered obstetrical discharges) to 12.2%.[29-31] AlSekait[34] reported a 4% prevalence of brucellosis in abattoir workers, while, in the Najran region, the prevalence was 7.3% among farms and abattoir workers.[35] There has been an improvement in the identification of cases in 2011, which might be due to one or combination of the following: data accuracy, appropriate diagnosis (using better screening tools) or increased awareness of brucellosis among health care providers. Seroprevalence of brucellosis among abattoir workers was 37.6% in Algeria[42] and 4.1% in Brazil.[43] Direct contact with infected animals and raw milk and milk products intake were the main risk factors associated with brucellosis.[10,24-26] Likewise, the main source of infection in children was the consumption of unpasteurized milk[19,32,33] as reported from a prospective study conducted on 157 brucellosis children at Abha, Saudi Arabia. A majority (92%) demonstrated history of contact with animals and consumption of raw milk and milk products. In addition, many other countries reported similar factors.[44-46] However, many studies also reported other robust risk factors such as fresh cheese and unpasteurized milk products.[47-49]

Our review documented the most common presenting symptoms of brucellosis in Saudi patients to be fever, hepatomegaly, splenomegaly, tendered spine, arthritis, and lymphadenopathy. Mild anemia, leukopenia, and relative lymphocytosis were common as well.[10,22,24] *B. melitensis*, *B. abortus*,[28] and *B. suis* were the most common infecting agents.[24] Likewise, our review showed the most frequently encountered brucellosis symptoms among children as fever, arthralgia, malaise, weight loss, arthritis, hepatosplenomegaly, and lymphadenopathy and also the isolation of *B. melitensis* species from most patients.[19,32,33] It has been reported in the literature that almost every organ can be affected, and varied complications may occur.[50,51]

In comparison to other bacterial infections, brucellosis causes more abortion, preterm labor, and intrauterine fetal deaths as reported by Hartigan.[52] Pregnant women with brucellosis have more chances of abortion and intrauterine fetal deaths than pregnant women without brucellosis.[29] In pregnant women with brucellosis, spontaneous abortion incidence was 43% in first and second trimesters, and intrauterine fetal deaths rate was 2% in the third trimester;[30,53,54] however, the study by Seoud et al[55] contradicts and reports *Brucella* infection to play an insignificant role in abortion.

In order to decrease the incidence of brucellosis at the national level, substantial educational programs for healthcare workers, veterinary practitioners and cattle owners should be started in the high-risk areas covering the major risk factors associated with brucellosis as well as economic and zoonotic importance. Regular surveillance should be carried out to identify the status of this control and prevention programs.

This review limits our search for English-language papers. However, the majority of the studies conducted in the Arab world by research institutes and universities are in English. As we searched only PubMed, we might have missed some articles. In Saudi Arabia, of the major cross-sectional studies, few were observed for the prognosis, burden, and consequences of brucellosis on the society and healthcare services. Also, the findings of the included studies were not modified for test performance as they may show diversity as per the laboratory protocol and this information was not available.

In conclusion, the contribute to brucellosis disease incidence/prevalence varied within regions. Brucellosis has a huge impact on human and has higher prevalence in developed countries. Also, the results presented brucellosis as a risk factor for adverse reproductive outcomes. The studies conducted in Saudi Arabia identified contact with diseased animals and raw milk and milk products ingestion as the main risk factors associated with brucellosis. Identified risk factors associated with brucellosis are modifiable and

by focusing on public awareness programs, such issues can be eradicated. High-quality studies and healthcare services are required to explore the prognosis and burden of these diseases on the Saudi society and this should be emphasized for future study.

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