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Review Article

Review of Undulant Fever in Jordan

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Abstract

Brucellosis is one of the zoonotic diseases that cause devastating losses to the livestock industry, the main source of the disease is ingesting contaminated food and unpasteurized dairy products or occupational exposure, and it's highly prevalent in the northern part of the kingdom among small ruminants' herds due to low vaccination coverage and poor surveillance system. Vaccinating livestock and food safety are the best methods-of controlling the disease in Jordan.

Keywords: Undulant Fever; Jordan; Brucellosis; Small Ruminants

Introduction

Undulant fever or human brucellosis is an endemic zoonotic disease mainly transmitted to humans from livestock animals such as cattle, sheep, and goats, whether through direct contact with contaminated body fluids such as blood, placenta, fetus or uterine secretions or through consumption of contaminated raw animal products such as unpasteurized milk and soft cheese [1], as it is prioritized in the zoonotic diseases list, with high prevalence among men and livestock [2].

The causative agent of Undulant fever is a gram-negative bacterium of the genus Brucella, which are facultative intracellular pathogens that multiply in monocyte-macrophage cells [3] and is caused by several species of Brucellae including *Brucella abortus*, biovars 1-6, 9; *Brucella melitensis*, biovars 1-3; *Brucella suis*, biovars 1,3 and 4 and *Brucella canis* [1]. The incubation period of the subclinical phase is from 2 to 4 weeks, which is often difficult to determine, with an insidious or abrupt onset. In the simplest case, the onset is influenza-like with fever reaching 38 to 40°C, the limb and back pains with sweating and fatigue. Furthermore, hepatomegaly and lymphadenopathy with local lesions such as epididymo-orchitis and spondylodiscitis may occur. The acute phase may progress to a chronic condition which may develop a syndrome resembling the "chronic fatigue syndrome" [3,4]. Many patients will recover spontaneously, within 3 to 12 months, others may suffer a series of exacerbations such as an undulant fever [5].

Unfortunately, if the disease is not treated, the symptoms may continue for 2 to 4 weeks, as well as the mortality associated with complicated cases [5]. For instance, the most effective regimen is Doxycycline (six weeks) plus Streptomycin (two or three weeks) [6].

Unlike human brucellosis, it has received different names and clinical manifestations in domestic animals, as it typically affects the reproductive tract causing abortion, due to that the diseases is called contagious abortion, infectious abortion, and epizootic abortion. Bang, which is another name for bovine brucellosis, is caused by *Brucella abortus*, whereas *Brucella melitensis* rarely causes abortion but the infected cattle may become a carrier and excrete it in milk. The susceptibility of the disease among heifers is more than in bulls, as well as it increases during pregnancy, but its self-limiting infection within calves [7]. The incubation period varies

and is influenced by gestation, exposure dose, age, and vaccination. The major clinical sign in pregnant females is abortion, which usually occurs from the 5th to the 8th month of gestation, the infection spreads rapidly and causes abortions in unvaccinated cattle [8]. The occurrence of abortion is related to some factors, such as the stage of pregnancy, the number of infecting organisms, and the animal resistance, it is often followed by placental retention and metritis, which may cause permanent or transient infertility. Unless abortion occur, premature stillborn or weak calves may be born. In addition to that, it may cause mild interstitial inflammatory reactions in the mammary gland, which is associated with elimination of bacteria in the milk [7]. In human, abortion is not a feature of brucellosis in pregnant women. Noticeably, it is transmitted by ingestion of contaminated food or water, licking other animals' infected genitals or through artificial insemination. The Infection of the bull's reproductive tract may lead to orchitis, epididymitis, ampullitis and seminal vesiculitis [8].

Sheep and goats are commonly raised in Jordan due to lack of water, the etiological agent of zoonotic caprine and ovine brucellosis is *Brucella melitensis*, as well as it infects the dromedary or Arabian camel (*Camelus dromedaries*). The clinical signs are same as the Bangs disease, as it occurs through ingestion of microorganism, and it causes abortion at approximately the fourth month of pregnancy and arthritis and orchitis may occur for males [9].

Brucella suis is the only species that causes systemic infection leading to reproductive problems in the swine, which is an uncommon domestic animal to be raised in Jordan. The main clinical manifestations of swine brucellosis is abortion, but also there is another clinical manifestation such birth of weak piglets, infertility, orchitis, epididymitis, or no signs, but death is rare [7]. Although dogs occasionally become infected with *Brucella abortus*, *B suis*, or *B melitensis*, but they are the only definitive host for *Brucella canis*, where abortion during the last trimester of pregnancy without premonitory signs, stillbirths, and conception failures are the primary signs [10].

Obviously, brucellosis accounts for huge economic losses in livestock industries due to loss of offspring, increased calving interval, decreased fertility and culling of the infected animals [11]. This review will represent the zoonotic aspects of brucellosis in Jordan among high risk people and domestic livestock.

Material and Methods

The current review will seek to establish the extent of brucellosis in Jordan during the period 1988 to 2016, and the health risk and impact of this public health burden among the local livestock and high-risk citizens.

Several databases were searched to collect relevant published literature, these are included in Pubmed; Spriger; Researchgate; EMBase and Wiley online Library. Database searches started with the identification of appropriate keywords. The following keywords were identified from literature in Jordan: Brucellosis, Undulant Fever, Livestock, Bangs Disease, Children Brucellosis, Endemic brucellosis, Epizootic/Zoonotic Brucellosis, Ovine/Caprine brucellosis, Canine Brucellosis, Ministry of Health, Ministry of Agriculture.

Results

The screened studies and reports were arranged into two categories, brucellosis among high-risk people and domestic animals.

O High risk people

M. Abu Shahada and M. Abuhalawa [12] conducted in case control study that the main source of human brucellosis in Jordan is contaminated animal and milk products, by involving cases who had been treated for brucellosis. They examined 17 related risk factors, which are contact with various livestock (sheep; goat; cattle; manure; slaughtered animals and helping in animal delivery and milking and living near houses), livestock milk and milk products consumption, drinking-water treatment and disease awareness. The univariate analysis of the endemic isolate of *Brucella melitensis* in Jordan revealed that milking sheep and goats and consumption of raw feta cheese made from sheep and goat milk increased the OR (odds ratio) by 3.5 and 2.8 units respectively, as small ruminant milk is mostly purchased from farmers and consumed directly without pasteurization as most of them are nomads who lacks milk heat-treatment facilities. While the consumption of cows' milk and boiled feta were protective factors by decreasing the odds by 0.4 as the available cow's milk is pasteurized products. In another study between April to October 1992, M. AbuShahada [2] assessed the seroprevalence of brucellosis in northern Jordan high-risk occupations namely sheep farmers, meat handlers, veterinarians, cattle farmers, and milk handlers. Their sera were evaluated using the

Rose Bengal plate agglutination test (RBPT) and enzyme-linked Immunosorbent assay (ELISA-IgG) tests. The effects of occupation, age, years at work, sex, and location on the seroprevalence of brucellosis among individuals were also determined. The ELISA results confirmed a significantly higher overall brucellosis seroprevalence of (8.2%) among high-risk people in northern Jordan compared to the seroprevalence of (0.5%) in the control group. Seroprevalence among sheep farmers and meat handlers were significantly higher than other occupations (Table 1). Veterinarians working as clinicians in Jordan had a prevalence of (24.5%), none of them working in other veterinary areas were seropositive. As for the work years, the seroprevalence among people working in high-risk occupations for > 22 years is (15%) compared to < 22 years (6.8%). Besides that, the Seroprevalence among veterinarians in northern Jordan (20.7%) did not differ significantly from veterinarians in central Jordan (17.4%). Seroprevalence was present only among veterinarians working in clinics with working age between (34-43 years). Overall, the seroprevalence increased with age and years at work, but sex or locality didn't have influence on the results.

S. no	Age (yrs.)	Parity	Symptoms	Duration (months)	Co-existing problems	Imaging	Uterine size (weeks)	Pre- op diagnosis	Previous treatment	Route of surgery
1	54	3	HMB Delayed menopause	24	2 LSCS	MRI: adenomyosis ET-21 mm	16	AUB- A ↑ CA 125 (175)	D & C Mirena	Robotic
2	51	2	HMB- Severe Dysmenorrhoea	8	DVT 1 LSCS	MRI: adenomyosis ET-17.9 mm	14	AUB- A ↑ CA 125 (190)	D & C Mirena	Open
3	46	1	HMB Severe Dysmenorrhoea	24	Chronic pelvic pain	TVS: adenomyosis ET-11.6 mm	18	AUB- A ↑ CA 125 (105)	Medical D & C Mirena	Open
4	43	2	HMB Dysmenorrhoea	36	Anaemia	MRI: adenomyosis ET-8.6 mm	14	AUB- A ↑ CA 125 (416)	Medical	Robotic
5	43	2	Irregular BPV HMB PLA	2	Endometriosis (grade IV)	MRI: adenomyosis Right 4x3 cm endometrioma	10	AUB ↑ CA 125 (66)	-	Laparoscopic
6	43	0	HMB Dysmenorrhoea	96	Primary Infertility	MRI: adenomyosis	22	AUB- A ↑ CA 125 (256)	IVF Anti-tubercular treatment Myomectomy	Open
7	46	2	Polymenorrhagia HMB	3		TVS: multiple adenomyomas	10	AUB- A	Medical Treatment	Laparoscopic
8	48	1	HMB dysmenorrhoea	18	Endometriosis 1 LSCS	MRI: Adenomyosis, endometrioma	10	AUB- A	D&C	Laparoscopic
9	41	2	Dysmenorrhoea Pelvic pain	12	2 LSCS, bowel adhesions	TVS: Adenomyosis, TO mass 8 cm	8	Chronic pelvic pain	Dienogest	Open

10	49	2	HMB	48	-	TVS – Adeno-myosis +endome-trioma	16	AUB-A	-	Open
11	44	2	Polymenor-rhagia Chronic Pelvic pain	24	Endometrio-sis forming TO masses	MRI Uterus bulky ET 9.3 B/L endo-metrioma	8 weeks	AUB-A raised CA 125 (110)	Dienogest NSAIDS	Robotic
12	42	2	Continuous bleeding PV Chronic pain	5	-	MRI Uterus bulky ET 16 mm Adeno-myosis	8	AUB-A	NSAIDS Trenaxamic acid	Laparo-scopic
13	38	0	Dysmenor-rhea irregu-lar bleeding	24	Endome-trioma	MRI uterus Bulky + B/L Endome-trioma	8	AUB-A Endome-triosis	Dienogest, lap excision of en-dometrioma	Open
14	47	2	HMB Dys-menorrhea	48		MRI uterus 10 CM B/L Endome-trioma	10	AUB-A		Laparo-scopic

Table 1: *Main results.*

HMB: Heavy Menstrual Bleeding; LSCS: Lower Segment Caesarean Section; D&C: Dilatation and Curettage; NSAIDs: Non Steroidal Anti-Inflammatory Drugs; TVS: Transvaginal Sonography; MRI: Magnetic Resonance Imaging; IVF: Invitro Fertilization; B/L: Bilateral; ET: Endometrial Thickness; DVT: Deep Vein Thrombosis.

Between 1996 and 1998, Al Ani., *et al.* [13] conducted a study for human blood samples from healthy people who were reporting to local hospitals for routine health checks and from groups with high-risk individuals to brucellosis, such as veterinarians, sheep-herders and laboratory technicians. The cumulative percentage of brucella antibody titers, which were obtained were obtained using the micro titer agglutination test, was higher in the high-risk group than among the normal population (7% compared to 4.1%), the higher percentage of positive reactors among the high-risk group may indicate an increased risk factor among professional agricultural and veterinary personnel in Jordan. Moreover, they included a report for human cases of brucellosis, which was established by the Ministry of Health between 1988 and 1999, as it showed a fluctuating incidence, due to underreported human brucellosis in the private sector, lack of sensitivity in diagnosing and poor surveillance of the disease. *Figure 1* illustrates the Yearly Incidence of cases per 100,000 human population in Jordan.

PCR is a more sensitive diagnostic tool for brucellosis, in 2003 al Nimri [14] assessed the status of brucellosis for the Bedouin in the rural area by using peripheral-blood-based PCR assay in 120 cases and it was 72.7%. She also demonstrated the risk of the relapsed cases, which is common in such rural communities where they show up for treatment several weeks after having symptoms and discontinue treatment once the fever subsides. Also, they are at risk of contracting brucellosis due to lifestyle, environmental and social population.

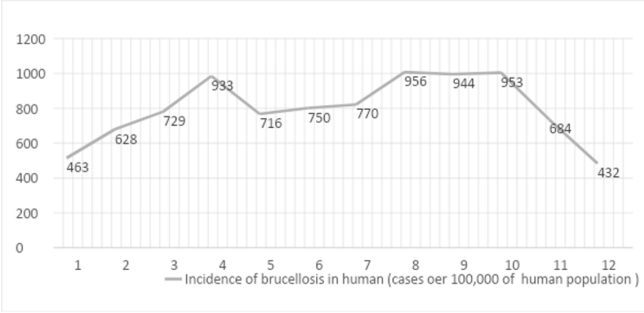

Figure 1: SEQ figure/*Arabic 1 incidence of brucellosis in human between the years 1988 and 1999.

The associated risk of miscarriage among pregnant Jordanian women and Brucellosis, was conducted by another study to Profes-

sor M. Abu Shahada., *et al*. [15].The study demonstrated that there was no significant difference between seroprevalence of *Brucella* among women with miscarriage and women with no history of miscarriage ($\chi 2 = 0.37$), the true seroprevalence among aborted women was 1.8% (95% CI: 0.6-3.0), while the true seroprevalence among women with no history of abortion was 1.0% (95% CI: 0.08-1.9).

Finally a study done by Almajali., *et al*. [16] identified that male gender (OR 2.5), age older than 10 years (OR 1.8), living in a village (OR 2.0), and assisting in raising small ruminants (OR 1.6) are risk factors for childhood *Brucella* seropositivity in Jordan.

o Domestic animals

The prevalence and risk factors of bovine brucellosis was demonstrated by Almajali., *et al.* [17] they detected the antibodies against Brucella by using Rose Bengal plate test and indirect ELISA from a serum of randomly selected cows. The true prevalence of antibodies against Brucella in individual cows and cattle herds was 6.5% and 23%, respectively. Larger herd and mixed farming increased the odds 1.3 and 2.0 units respectively. In contrast, use of disinfectants (OR = 1.9, β = -1.1) and the presence of adequate veterinary services (OR = 1.6, β = -0.8) were identified as protective factors. Almajali [18] also assessed the aspects related to camel brucellosis in a cross-sectional study during 2004 and 2006, camel sera was analyzed using Rose Bengal plate and complement fixation test, and the results revealed that incidence of Brucella-specific abortion was 1.9% significantly higher in the southern part of the country, caused by *Brucella melitensis* biotype 3 during the last 4 months of pregnancy, while the true prevalence of Brucella seropositive in camels was 12.1%. In addition to that, the results of logistic regression on both individual and herd levels revealed large herds (OR = 1.1) and contact with small ruminants (OR = 1.2) are risk factors for Brucella seropositivity. In contrast, using disinfectants was identified as a protective factor (OR = 0.8) only on the camel herd level.

The true seroprevalence and the associated risk factor of small ruminant brucellosis was estimated by Musalam and Abushehada [19]. Figure 2 illustrates the true seroprevalence and confidence interval for different livestock animals, mostly from the northern part, where the livestock density except for camel is higher. They also illustrated the associated factors to higher odds of seropositivity, which are : lending/borrowing rams (OR = 8.9, 43 95% CI: 3.0-26.1), feeding aborted material to dogs (OR = 8.0, 95% CI: 3.5-18.1) the presence of goats (OR = 6.9, 95% CI: 3.1-15.4), introducing new animals to the flock (OR = 5.8, 95% CI: 2.5-13.6), and a large flock size (OR = 2.2, 95% CI: 1.0-4.6). Conversely, separating newly introduced animals (OR = 0.16, 95% CI: 0.05-0.47), separating animals that had aborted (OR = 0.19, 95% CI: 0.08-0.46) and using disinfectants to clean pens (OR = 0.37, 95% CI: 0.16-0.83) were significantly associated with a lower odd of being seropositive. In addition to that, Musalam [20] had evaluated in another study the livestock owner's knowledge and attitudes and showed that only 19% were aware that the infection is spread through direct contact with fetal membranes and 13% via physical contact. Moreover, their practices increased the risk of transmitting brucellosis such as assisting in animal parturition 62%, disposing aborted fetuses without protective gloves (71.2%) or masks (65%), and not boiling milk before preparation of dairy products (60%).

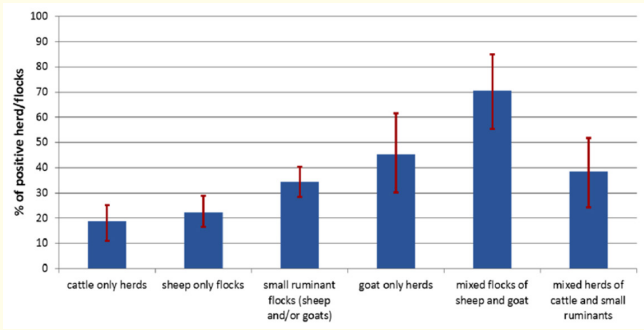

Figure 2

Hahabat., *et al.* [21] determined the seroprevalence and identified the risk factor of the neglected zoonotic infection, *Brucella canis,* in police, breeding and stray dogs and in at-risk humans in Jordan. Overall, 8.3% of the dog sera samples tested positive–for antibodies against *B. canis,* and 37.8% of stray dogs tested positive. Seroprevalence was higher in male dogs than in females. Furthermore, none of the tested human samples was positive to antibodies agains *B. canis.* There was a significant association between seropositivity and the type of dog, which was higher among stray dogs in Jordan.

Discussion

World Organization for Animal Health (WOAH) reported Brucellosis at Jordan in its top three zoonotic diseases, as its magnitude become more severe due to lack of appropriate control measures, low vaccination coverage especially among small ruminants (1.5%), no national eradication plan and deeply entrenched social misconceptions about it, which limit the economic growth and inhibit the access to international markets. The losses in livestock productivity compromise food security, as the premature birth and abortion lowers the milk production, and lead to shifts in the competency of the working generation, influencing gender inequality, and cause profound emotional suffering in farmers whose herds are affected [21]. 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. The burden of the disease to society includes significant human healthcare costs for diagnosis and treatment, and non-healthcare costs such as public education and transportation to medical care centers which take efforts to reduce disease transmission [21].

As the ultimate source of human brucellosis is direct or indirect exposure to infected animals or their products, prevention must be based on elimination of such contact. The most successful method for prevention and control of brucellosis in animals is vaccination [1], Brucella *melitensis* Rev. 1 vaccination has been internationally recognized as the key to successfully controlling the disease. In Jordan, the ministry of Agriculture provides veterinary service for free [24]. Additional prevention strategies to reduce the risk of infection are personal hygiene, adoption of safe working practices, protection of the environment and food hygiene (pasteurizing the raw milk).

Globally, Various frameworks aim to support capacity building for disease surveillance and response, including the World Health Organization's International Health Regulations (IHR), Animal Terrestrial Code and Pathway to Veterinary Services (PVS), the Global Health Security Agenda (GHSA) and the OIE. In Jordan, the MOH's Division of Zoonotic Diseases and veterinary public health actors at the MOA developed a cooperative relationship in reporting and responding to brucellosis [23]. There is no clear guidance for surveillance and outbreak response, as the surveillance is a key element for management of prevention and control programs [1], but they provide early case reports from ingesting dairy products. In the event of a suspect case or farm(s), the local veterinary services will quarantine the suspect farm(s) and collect samples, if the farm was three consecutive times negative, then it can be cleared. Furthermore, any animals testing positive must be culled, then those cases will be reported to the OIE [23].

Conclusion

The implementation of public policy focused on mitigating the socioeconomic effects of brucellosis in human and animal populations is desperately needed. When developing a plan mitigate the associated consequences, it is vital to consider both the abstract and quantifiable effects. This requires an interdisciplinary and collaborative, or One Health, approach that consists of public education, the development of an infrastructure for brucellosis surveillance and reporting in both veterinary and medical fields, and campaigns for control in livestock and wildlife species [21].

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