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A Review on Small Ruminants Brucellosis

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Abstract- Brucellosis is an important zoonotic disease that causes huge economic losses to the livestock owners and is of great public health concern worldwide. It is a chronic infectious disease of livestock, rodents, marine animals and human beings. Brucellosis affects both public and animal health as well as production, and is widespread in many regions of the world. The disease is caused by non-motile, facultative intracellular Cocco-bacilli of genus Brucella. The two specific isolates of Brucella, Brucella melitensis and Brucella ovis, cause brucellosis in small ruminants. Brucella ovis causes the disease in sheep while B. melitensis is the etiologic agent of brucellosis in man, sheep and goats. Direct contact with infected animal secretions, inhalation of the organism, ingestion of contaminated food, and poor hygienic practices favor the transmission of brucellosis between animals and humans. Brucellosis affects the reproductive tract of animals which is manifested by late term abortions, retention of placenta in the case of female animals, epididymitis and orchitis in males. The disease is also characterized by infertility and reduced milk production. The diagnosis of brucellosis focuses onculture, serological tests and molecular investigations. Because of the high relapse rate associated with the disease, the use of a multidrug therapy is recommended. Brucellosis can be prevented by implementing appropriate animal-disease-control measures; avoiding the consumption of undercooked meat and unpasteurized dairy products; and using appropriate barrier precautions to exclude exposure to aerosols in humans.

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I. Introduction

Small ruminants, which account for more than half of the domesticated ruminants in the world, are an important component of the farming systems in most developing countries (Gebremedhin et al., 2015). Recent studies in different regions of the world indicate that the global population of small ruminants increased from 1.35 billion to 1.94 billion (Tedeschi et al., 2011).

Small ruminants are an integral part of livestock keeping in developing countries, especiallyin Sub-Saharan Africa that are mainly keep for immediate cash sources, milk, meat, wool, manure, and saving or risk distribution. Small ruminants also have various social and cultural functions that vary among different cultures, socio-economies, agro-ecologies, and locations in tropical and subtropical Africa (Gobena, 2016). Sheep and goats have many advantages over large ruminants for most smallholder farmers, including among others: fewer feed costs, quicker turnover, easy management and appropriate size at slaughter (Zahra *et al.,* 2014). They also have greater tolerance to less favorable conditions, as they suffer far less in mortality during periods of drought than large ruminants. Also, breeders prefer sheep and goats as the risk of losing large ruminants is too high (Zahra *et al.,* 2014).

Ethiopia is one of the African countries with the largest small ruminant population in the continent (Abebe 2013). A recent estimate indicates that there are about 27.35 million sheep and 28.16 million goats in the country (CSA, 2014). Almost all of the small ruminant populations comprise of local breeds. The CSA data further indicates that of those who own small ruminants, about 64% and 58% own less than five heads of sheep and goats, respectively (Gebremedhin et al., 2015).

Despite the importance of small ruminants in the livelihoods of producers, the current productivity of goats and sheep in developing countries remains low, mainly due to under-feeding, poor management system and diseases (Gizaw 2010). Brucellosis is one of the infectious diseases considered as most constraints for sheep and goats productivity (Tewodros and Dawit, 2015). Brucellosis is an economically important and widespread zoonosis in the world caused by bacteria of the genus Brucella, which tend to infect specific animal species (Awah-Ndukum et al., 2018).

Brucellosis occurs worldwide in domestic animals such as cattle, sheep, goats, camels and pigs and creates a high economic problem for both the intensive and extensive livestock production system in the tropics and a threat to public health. It shows that brucellosis causes high economic losses in the livestock industry. Economic losses stem from breeding efficiency, loss of offspring, reduced meat and milk production as well as an impediment to free animal movements and export of animals and their products (Tewodros and Dawit, 2015).

Brucellosis is a zoonotic infectious disease affecting a wide range of species of animals and humans with an estimated half a million human cases reported annually (Kelkay et al., 2017). Cattle, goats, pigs, sheep, horses, and dogs play a significant role in the transmission of this disease to man. It is also defined as a contagious systemic bacterial disease primarily of ruminants, characterized by inflammation of the genital organs and fetal membranes, abortion, sterility, and formation of localized lesions in the

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lymphatic system and joints (Awah-Ndukum et al., 2018). Additionally, the disease also poses a major constraint to international trading of animal and animal products (Seleem et al., 2010). As the problemoften goes undetected, identification of infected herd and animals is of prime importance for the control of the disease. Having large livestock resource at hand coupled with an intermingling of livestock species may cause uninfected animals to easily get exposed to the disease from multiple sources such as abortion discharges and direct contact with infected animals. Mixed farming especially raising goats and sheep along with cattle was also reported by many researchers to be a risk factor for Brucella transmission between different animal species (Padilla et al., 2010, Godfroid et al., 2013).

Therefore, this review is undertaken with the objectives of compiling currently available information worldwide about brucellosis in small ruminants and humans, and creating awareness regarding the disease to animal producers, product users, researchers, and investigators.

II. Origin and Classification

a) *Brucella and Brucellosis*

Brucellosis is an infectious disease caused by the genus Brucella. It is a disease of worldwide importance and affects some animal species (Tegegn et al., 2016). *Brucellais smallcocci*, Cocco-bacilli or short rods, they are 0.5-0.7 by 0.6-1.5 pm in size, non-sporulating and non-encapsulated and nonacid-fast bacteria which stain gram-negative. Brucellosis is an important zoonotic disease of worldwide importance and affects some animal species. The causal organism is first isolated by Bruce in1870 from the liver of a patient died of undulant fever (Malta fever) (Hirsh et al., 2004, Khan and Zahoor, 2018). The old classification of the genus included six species, namely, *Brucella (B) abortus* (cattle), *B. melitensis* (sheep and goats), *B. suis* (pigs), *B. ovis* (sheep), *B. canis* (dogs) and *B. neotomae* (El Abdin et al., 2014). Latter a marine species has been noted as *B. maris* (Sohn et al., 2003).There are two other species that affect marine mammals, and they are *B. ceti* and *B. pinnipedialis* (Foster et al., 2007).

Complete genome sequences of *B. abortus, B. melitensis, B. suis, B. canis*, and *B. ovis* are available while many other strains are being sequenced. They are considered to be very similar in size and genetic makeup (Sriranganathan et al., 2009). *B. melitensis* is predominantly found in goats and is the most widely distributed of all the Brucella species. It is also the most pathogenic and virulent species for humans and affects almost all domestic animals and many wild animals (Benkirane, 2006). *B. abortus* is mainly found in cattle and buffaloes, *B. suis* in pigs, *B. ovis* in sheep and *B. canis* in dogs (Seleem et al., 2010).

The different species cannot be distinguished from each other morphologically. For microscopic demonstration in or outside of tissues, selective staining methods are applied which can show the tiny bacteria (Stamper Hansen's staining). For culturing Brucella require complex media. They grow best if special peptones, like tryptose and trypticase-soya-peptone, are added to the medium at a neutral PH and 3-10% CO2 atmosphere with an incubation temperature of 37°C is required. Delicate translucent colonies of 2-3 mm in diameter grow on blood or glucose-agar. Brucella ovis (*B. ovis*) always grows in the M-(mucoid) form, Brucella abortus (*B. abortus*) and *B. melitensis* grow at the beginning in the S-(smooth) form later dissociate into the R-(rough) and the M-form (Radostits et al., 2007).

III. Brucellosis in Small Ruminants

Brucella melitensis is the most important cause of brucellosis which primarily affects sheep and goats and also very pathogenic for human beings. The disease is also caused by *B. ovis* which severely affects sheep. Although the disease has preferred hosts, the bacteria can cross-infect other domestic animals. Hence, sporadic infections in small ruminants can also be caused by *B. abortus* or *B. suis*, but such cases are rare (OIE, 2012a; Kelkay et al., 2017).

The species *B. melitensis* is the causal organism of brucellosis in small ruminants and undulating or "Malta fever" in humans. Brucella melitensis primarily affect the reproductive tract of sheep and goats, and it is characterized by abortion, retained fetal membrane and to a lesser extent, impaired fertility. Although *B. melitensis* infects mainly sheep and goats and its zoonotic importance, plays a significant role in the national economy and the public health of many developing countries. Before *B. melitensis* was recognized as the same symptoms in regions hindering the Mediterranean was known as tibris andulans (Radostits et al., 2007).

The disease caused by the infection of sheep with *B. ovis* is characterized by infertility in rams due to epididymitis. Abortion and neonatal mortality are also caused by the infection (Radostits et al., 2007).

IV. Epidemiology

a) *Occurrence and Geographical Distribution*

Brucellosis is of major economic importance in most countries of the world, and it affects approximately 50% of the livestock population worldwide and continues to increase in distribution (OIE, 2012a). Small ruminant brucellosis has been shown to occur worldwide. It is mostly present in Mediterranean countries, the Middle East, Asia, India, China, Mexico and parts of Latin America (OIE, 2009) (Table 1-3). *Brucella ovis* has been reported in parts of Eastern Europe, Africa (Table 4), Western State of the

United States of America (USA), New Zealand and Australia, it does not occur in the United Kingdom (UK) (Foster et al., 2017) (Table 1-3).

Brucella melitensis and *B. ovis* create an economic problem for the intensive and extensive animal production systems of the tropics. While the disease has been eradicated in most industrial countries, especially in Europe, through intensive schemes of control and eradication, its occurrence is increasing in developing countries in an even aggravating epizootological situation. This depends on the policy of many developing countries of importing exotic high production breeds without having the required veterinary infrastructure and the appropriate level of development of the socioeconomic situation of the animal holder. Furthermore, the increasing international animal trade with increasing movements of animals and the trend towards intensification of animal production favor the spread and transmission of the infection (Radostits et al., 2007).

Table 1: The Distribution of *Brucella Melitensis* and *Brucella Ovis* in Asian Countries

Continent / Country / Region	Distribution		Reference
	Brucella Melitensis	*Brucella Ovis*	
Asia			
Armenia	Present	Not Reported	Oie, 2009
Azerbaijan	,,	,,	Oie, 2009
China	Restricted Distribution	,,	Oie, 2009
Georgia (Republic Of)	Last Reported In 1991	,,	Oie Handistatus, 2005
Iran	Present	,,	Oie, 2009
Iraq	,,	,,	Oie, 2009
Israel	,,	,,	Oie, 2009
Jordan	,,	,,	,,
Kuwait	,,	,,	,
Kyrgyzstan	Restricted Distribution	Restricted Distribution	,,
Lebanon	Present	Not Reported	,,
Malaysia	,,	,,	,,
Mongolia	,,	,,	,,
Oman	,,	,,	,,
Pakistan	Restricted Distribution	,,	,,
Qatar	Present	,,	,,
Saudi Arabia	,,	Present	,,
Syria	,,	Not Reported	,,
Tajikistan	,,	,,	,,
Thailand	,,	,,	,,
Turkey	,,	,,	,,
Uzbekistan	,,	Not Reported	Oie Handistatus, 2005
Yemen	,,	,,	,,

Table 2: Brucellosis Infected Countries in North, Central and South America Continents

Continent / Country / Region	Distribution		Reference
	Brucella Melitensis	*Brucella Ovis*	
North and Central America			
Canada	Not Reported	Absent	Oie, 2009
Mexico	Present	Not Reported	Oie, 2009
Usa	Not Reported	Restricted Distribution	,,
United States Virgin Islands	Present	Not Reported	Ahlet Al., 1993
South America			
Argentina	Present	Restricted Distribution	Oie, 2009
Chile	Not Reported	Restricted Distribution	,,
Sao Paulo	Present	Not Reported	Gouvêaet Al., 1989
Peru	Restricted Distribution	,,	Oie, 2009
Uruguay	Not Reported	Present	,,

Table 3: Distribution of *Brucella Melitensis* and *Brucella Ovis* in Europe and Oceania

Continent / Country / Region	Distribution		Reference
	Brucella Melitensis	*Brucella Ovis*	
Europe			
Albania	Present		Oie, 2009
Andorra	,,	Not Reported	Oie Handistatus, 2005
Bulgaria	,,	Present	Oie, 2009
Croatia	,,	,,	,,
Cyprus	,,	Not Reported	,,
Gibraltar	,,	,,	Yantzis, 1984
Greece	,,	,,	Oie, 2009
Hungary	Not Reported	Present	,,
Italy	Restricted Distribution	Not Reported	,,
Macedonia	,,	,,	Oie, 2009
Malta	,,	,,	Abela, 1999, Oie, 2009
Moldova	,,	,,	Oie Handistatus, 2005
Portugal	,,	,,	Oie, 2009
Romania	Not Reported	Present	,,
Russian	,,	,,	,,
Serbia	,,	Not Reported	,,
Slovenia	Not Reported	Present	,,
Spain	Present	Restricted Distribution	,,
Yugoslavia	,,	Not Reported	Oie Handistatus, 2005
Oceania			
Australia	Not Reported	Present	Oie, 2009
New Caledonia	,,	,,	,,
New Zealand	,,	,,	,,

Adopted from: CABI (2017b) for B. Melitensis and CABI (2017a) for B. Ovis.

Table 4: Distribution of *Brucella Melitensis* and *Brucella Ovis* in Africa

Country	*Brucella Melitensis*	*Brucella Ovis*
Egypt	+	ND
Ethiopia	+	ND
Kenya	+	ND
Sudan	+	ND
Somalia	+	ND
Eritrea	+	+
Libya	+	ND
Lesotho	ND	+
Algeria	+	+
Tunisia	++	ND
Namibia	+	+
Niger	+	+
Nigeria	+	ND
Cotd' Ivor	ND	+
Zimbabwe	+	+
Botswana	ND	+
South Africa	+	+

Source: (FAO, 2010; OIE, 2012b)

(++: High prevalence, +: Sporadic low prevalence, ND: No Data)

b) *Occurrence in Ethiopia*

The states of brucellosis of the small ruminant in Ethiopia are not well known or are not more than mere report. This may be due to the lack of attention given to small ruminant production sector. The absence of research activity in animal diseases, poor veterinary development, lack of awareness of the economic and zoonotic impact of the disease have contributed to the less amount of information observed. Though limited, sero-surveillances carried out so far indicate that brucellosis may be one of the important diseases in goat rising communities. A sero-surveillance study carried out in small ruminants in different regions clearly demonstrated that the disease exists in Ethiopia. According to the currentsero-surveillance findings of the disease in the country, low infection rate was recorded at Bahir Dar Town of Amhara Regional State (Ferede et al., 2011) and the highest was reported at Tellalak District of Afar Regional State (Tadeg et al., 2015) (Table 5).The existence of the disease was also confirmed and reported in Southern Nations Nationalities and Peoples Regional state (SNNPRS) of Ethiopia, according to the annual report of Soda Regional Veterinary Laboratory in the year 2005 (Table 5).

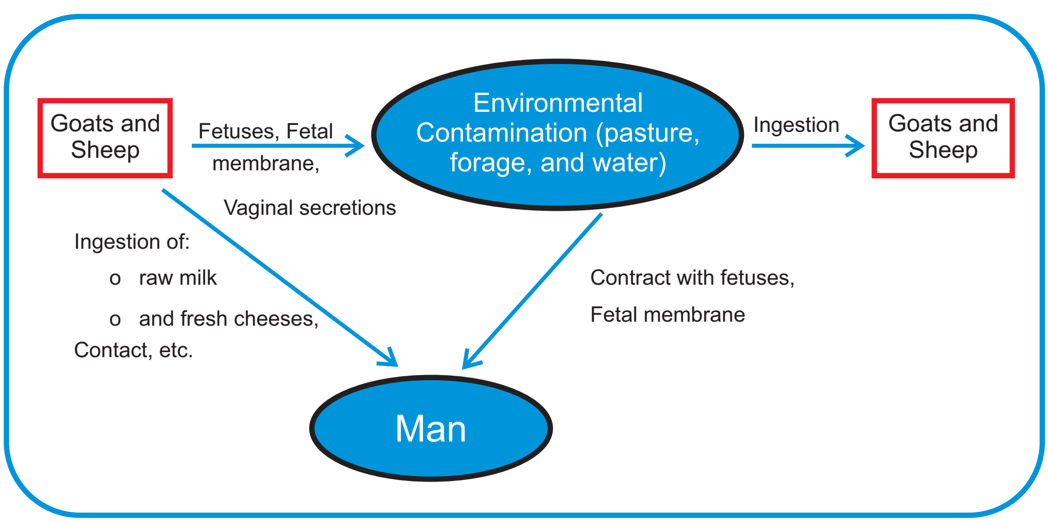
Table 5: The Epidemiology of Small Ruminant Brucellosis in Ethiopia

Sr. No.	Study Area	Region	Prevalence	Source
1	Tellalak District	Afar	13.7%	Tadeg et al., 2015
2	Chifra and Ewa Districts	Afar	12.35%	Tegegn et al., 2016
3	Yabello districts of Borena Zone,	Oromia	8.1%	Wubishet et al., 2018
4	Liban District of Guji Zone	Oromia	6.2%	Wubishet et al., 2017
5	Southern Zone of Tigray	Tigray	3.5%	Teklue et al., 2013
6	Selected Export Abattoirs	Addis Ababa	2.7%	Nigatu et al., 2014
7	Werer Agricultural Research Center	Afar	2.25%	Bezabih and Bulto, 2015
8	Selected Pastoral and Agro-pastoral Lowlands of Ethiopia	Somali and Oromia	1.9%	Sintayehu et al., 2015
9	Southern and Central Ethiopia	SNNP and Oromia	1.9 %	Asmare et al., 2012
10	Tselemti Districts	Tigray	1.79%	Kelkay et al., 2017
	South Wollo	Amhara	1.5%	Yesuf et al., 2011
11	Three Selected districts of Jijiga Zone	Somali	1.37%	Mohammed et al., 2017
12	In and Around Kombolcha	Amhara	0.7%	Tewodros and Dawit, 2015
13	In and Around Bahir Dar	Amhara	0.4 %	Ferede et al., 2011

c) *Modes of Transmission*

The primary route of infection is through ingestion of contaminated feed and water, inhalation during overcrowding, contact through intact skin and conjunctiva, lambs may be infected while in the uterus or by suckling infected milk of their mother. Venereal transmissions by the infected ram to susceptible ewes appear to be rare. Transmission may occur by artificial insemination (Radostits et al., 2007). Transmission between animals occurs readily after massive exposure to aborted materials, contaminated placenta and postpartum discharge in an infected female. In sheep, the degree of infection of milk and in uterine exudates is much lesser than goats. Studies indicate that 70-90% cause of Brucella infection occurs via the skin and mucus membrane by direct contact (Franc et al., 2018) (See the mode of transmissions in figure 1).

Transmission to man is as a result of contact with infected animal carcasses, aborted fetus, placenta, consumption of unpasteurized milk and cheese. It is common to observe human cases that are in contact with goats in an area where active brucellosis outbreak occurs. Raw vegetable and water contaminated with the extra of infected animals can also serve as a source of infection. Brucella organisms can remain viable in milk, water, and damp soil for up to four months (Radostits et al., 2007).



Sources: WHO (2006)

Fig. 1: Small Ruminant Brucellosis (*B. Melitensis*) Mode of Transmission

d) Communicability of the Disease between Humans

Brucellosis is not usually transmit from person to person. Rarely, bacteria have been transmitting by bone marrow transplantation, blood transfusion or sexual intercourse (Wikipedia, 2018). Rare congenital infections have also been documented. In some cases, the infant appeared to be infected through the placenta and in others by the ingestion of breast milk. Brucellosis was reported in an obstetrician infected infants respiratory tract at birth (Saxena et al., 2018).

V. Zoonotic aspects of Brucellosis

It is considered by the Food and Agriculture Organization (FAO), the World Health Organization (WHO) and the Office International des Epizooties (O1E) as one of the widest spread zoonosis in the world. Reported incidence in endemic disease areas varies widely, from< 0.01 to > 200 per 100,000 populations (Franco et al., 2007).

The bacterium *B. melitensis* is the most invasive and pathogenic for humans among the three classical species (*B. abortus*, *B. melitensis* and *B. suis*) of the genus Brucella. Brucellosis remains a most serious zoonosis in areas of the world where *B. melitensis* is enzootic in goats and sheep, and the resulting disease in human is severe and long lasting (Radostits et at, 2007). Human brucellosis is widely distributed all over the world, with regions of high endemicity such as Mediterranean, Middle East, Latin America and parts of Asia (Khan et al., 2018).

Brucellosis due to B. melitensis is a zoonotic disease causing a debilitating illness in human. Symptoms of acute brucellosis caused by *B. melitensis* are flu-like and highly nonspecific. Chronic brucellosis is an insidious/dangerous disease with vague/unclear symptoms that might be confused with other disease affecting various organ systems (Kelkay et al., 2017).

The risk for infection is high in cultures that cohabit with their animals or when weak, infected newborn animals are brought in to the house for warmth and intensive care. Flaw milk and cheese products from infected goats and sheep provide a risk for human and were the mechanism for the occurrence of Malta fever that initiated the definition of the disease (Radostits et al., 2007).

VI. Risk Factors

The factors influencing the epidemiology of brucellosis infection in any geographical location can be classified into factors associated with the transmission of the disease between herds and factors influencing the maintenance and spread of infection within the herd (WHO, 2006). Factors associated with brucellosis include host factors (age, sex, and breed), agent and extrinsic factors (environmental factors) including management and ecology (Guven et al., 2013, Hotez et al., 2012).

It is widely accepted that susceptibility increases with sexual development and pregnancy (Guven et al., 2013). Kids and lambs may become infected before or soon after birth, and tend to become free from infection before reaching breeding age, occasionally infection persist much longer (WHO, 2006). Brucella melitensis infection causes disease only in adult (sexually mature) females and males. Young animals may be infected but do not show any clinical sign and generally show only a weak and transient serological response (Radostits et al., 2007).

In B. melitensis infection males of sheep and goat are less susceptible than females. *Brucella ovis* has a great affinity for the reproductive tract of the male than the female. Breeding ewes with infected rams seldom cause the disease in ewe and incidence of abortion is low (WHO, 2006).

Animals of an exotic breed and their hybrid are found to be at higher risk. This may associate with better producers and intensively managed (Rossetti et al., 2017). Most breeds of goats are fully susceptible to *B. melitensis*. There is great variation in the susceptibility of different breeds of sheep, where Malta sheep are very resistant whereas fat-tailed sheep are very susceptible (WHO, 2006).

Brucella is intracellular bacteria, hence has protection from the innate host defense and from therapeutics, moreover in quiescent state does not cause formation of humeral antibodies (Guven et al., 2013).

Humidity and PH of the environment influence the survival of B. melitensis. The organism is sensitive to direct sunlight, disinfectant, and pasteurization (WHO, 2006).

Brucella survives for up to 4 months in milk, urine, water and damp soil under proper environmental condition (WHO, 2006). Disinfectants like caustic soda, formalin 2%, and Lysol 1% destroy Brucella (Radostits et al., 2007).

The husbandry systems as well as environmental conditions greatly influence the spread of infection. Thus lambing in the dark, crowded enclosures is more favorable to spread than lambing in the open air in a dry environment. The spread of infection between flocks generally follows the movement or gathering of infected animals. The main risk for introducing the disease into a previously non-infected area is by the purchase of infected animals. In several countries, there is a strong correlation between the prevalence of brucellosis in small ruminants and the practice of transhumance (Khan et al., 2018).

VII. Pathogenesis

The initiation of Brucella infection depends on exposure dose, virulence of Brucella species and the natural resistance of the animal to the organism (Radostits et al., 2007, Sharifi et al., 2015). Resistance to

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infection is on the basis of host's ability to prevent the establishment of infection by the distraction of the invading organism. Invading Brucellais usually localized in the lymph nodes, draining the invasion site, resulting in hyperplasia of lymphoid and reticuloendothelial tissue and the infiltration of inflammatory cells. Survival of the first line of defense by the bacteria results in local infection and the escape of Brucella from the lymph nodes into the blood (Tadeg et al., 2015). During the bacteremic case, which may last 2-8 weeks, bones, joints, eyes, and brain can be infected, but the bacteria are most frequently isolated from super mammary lymph nodes, milk, iliac lymph nodes, spleen and uterus (Radostits et al., 2007).

There is preferential localization to the reproductive tract of the pregnant animals. Unknown factors in the gravid uterus collectively referred to as allantoic fluid factors, stimulate the growth of Brucella. Erythritol, a four-carbon alcohol, is considered to be one of these factors. Abortion is associated with the extensive replication of the brucellae within the chorioallantoic trophoblasts that form a vital component of the placenta. This massive intracellular replication ruptures the infected trophoblasts and allows the bacteria direct access to the fetus. The resulting loss of placental integrity and fetal infection lead to termination of the pregnancy or the premature birth of a weak and infected calf (Hotez et al., 2012). Localization in the placenta leads to the development of placentitis with subsequent abortion. After an abortion, the uterine infection persists for up to 5 months, and mammary gland may remain infected first years (Radostits et al., 2007, Saxenaet al., 2018).

There is initial bacteremia, often with a mild systemic reaction, and the organism can be isolated from the internal organs of animals slaughtered after experimental infection. However, systemic disease is not a feature of the natural disease, and clinical disease results from localization in this area results in sperm stasis and extravasations with a subsequent immunological reaction which is usually in the tail and unilateral, causing a spermatocele and therefore reduced fertility. Not all infected rams have palpable lesions in the epididymis and infection can also establish in the seminal vesicles. In either case, it is shed in the ejaculate. Testicular and epididymal lesions can be palpated at about nine weeks after infection but may occur earlier in some rams. A significant proportion of infected rams have no palpable lesions but still excrete the organism (Radostits et al., 2007).

This disease is well described by its original name undulant fever. The disease does not have precise symptoms besides general malaise, making it difficult to diagnose clinically. Brucellosis is characterized by acute fever, sweats, headaches, and flu-like symptoms in the humans (Franco et al., 2007). It is believed that brucellosis causes fewer spontaneous abortions than it does in animals because of the absence of erythritol in the human placenta and fetus. An additional reason for the lesser role of Brucella infection in human is the presence of anti-Brucella activity in human amniotic fluid (Hotez et al., 2012).

VIII. Clinical Findings

The primary clinical manifestations of brucellosis are related to the reproductive tract. The biggest problem of Brucella infection is the uncertain incubation period, which may vary between 15 days to month and years depending on the invasion site, infective dose, and others (FAO, 2010).The only symptom noted under natural infection is abortion. Infected goats show abortion and sometimes mastitis, with reduced milk production. Abortion usually occurs at 3-4 month of pregnancy. Goats that have aborted once are not likely to occur the second time, but sheep may abort a second time. Retention of the fetal membrane may or may not occur (FAO, 2010). Goats shade Brucella in milk for years, but sheep may shade during one or more lactation period. Execration in the vaginal fluid and urine may last for the 4-6 month (FAO, 2010). The first reactions in males are a marked deterioration in the quality of the semen together with the presence of leukocytes and Brucella. Acute edema and inflammation of the scrotum may follow, a systemic reaction, including fever, depression, and increased respiratory rate, accompanies the local reaction. Regression of the acute syndrome is followed latter a long latent period, by the development of palpable lesion in the epididymis and tunica of one or both testicles. The epididymis is enlarged and hard, more commonly at the tail, the scrotal tunics are thickened and hardened, and the testicles are usually atrophic. The groove between the testicle and epididymis may be obliterated. There is usually no clinical sign in the ewe, but in some flocks, infection causes abortion and the birth of week and stillborn lambs and kids, associated with microscopic placentitis (Radostits et al., 2007).

IX. Necropsy Findings

The abortus is characterized by thickening and edema, sometimes restricted to only a part of the placenta, firm, elevated yellow-white plaques in the intercotyledonary areas. The average degree of abnormality of the cotyledons, which is in the acute stages are much-enlarged, firm and yellow-white in color. When abortion occurs, the organism can be isolated from the placenta and the stomach and lungs of the lamb. Although placentitis is uncommon, it is occasionally seen in infected ewes (Radostits et al., 2007).

Some aborted fetuses appear normal others are autolysis or have variable amounts of subcutaneous edema and bloodstained fluid in the body cavities. In ruminant fetuses, the spleen and liver may enlarge, and the lungs may exhibit/show sign of pneumonia and fibrous pleuritis. Abortion caused by Brucella species are typically accompanied by placentitis. The cotyledons may be red, yellow, normal or necrotic. In small ruminants, the intercotyledonary region is typically leathery, with a wet appearance and focal thickening. There may be exudates on the surface. In adults, granulomatous to purulent lesions may found in the male and female reproductive tract, mammary gland, supra mammary lymph node, other lymphoid tissues, bones, joints and other tissues and organs. Mild to severe endometritis may be seen after an abortion, and males can have unilateral or bilateral epididymitis and/or orchitis (Saxenaet al., 2018). In rams infected with B. ovis, lesions are usually limited to epididymis and orchitis. Epididymal enlargement can be unilateral or bilateral, and the tail is affected more than the head or body. Fibrous atrophy can occur in the testis. The tunica vaginalis is often thickened and fibrous and can have extensive adhesions. In the acute stage, there is inflammatory edema in the loose scrotal fascia, exudates in the tunica vaginalis and early granulation tissue formation. In the chronic stage, the tunics of the testes become thickened and fibrous, and adhesions develop between them (Radostits et al., 2000,Saxenaet al., 2018).

Brucellosis is responsible for massive economic losses around the world especially in developing countries where accurate data are not available to truly assess the loss. Losses are usually due to culling of animals, abortion, infertility, reduced milk production, treatments costs of animals, vaccines, market losses, losses due to missed reproductive cycles, hospitalizations for human cases and administrative costs by governments in an attempt to control or eradicate the infection. In Latin America, annual economic losses were $600 million for ruminant brucellosis, and in the United States, the eradication program spent $3.5 billion between 1934 and 1997 and loss due to reduced milk production in 1952 amounting to about $400 million (Bamaiyiet al., 2014). In assessing the economic impact of brucellosis in case of a bioterrorist attack, it will have an economic impact of $477.7 million per 100,000 persons exposed. Many other losses due to loss of foetus, decreased milk yield, infertility, interference with farrowing management and sequential seasonal calving, joint infections, weakling calves, disease in man and others could not be accounted for financially but are likely to run into millions of dollars annually (Bamaiyiet al., 2014) (figure 2).

X. Economic Impact of Brucellosis

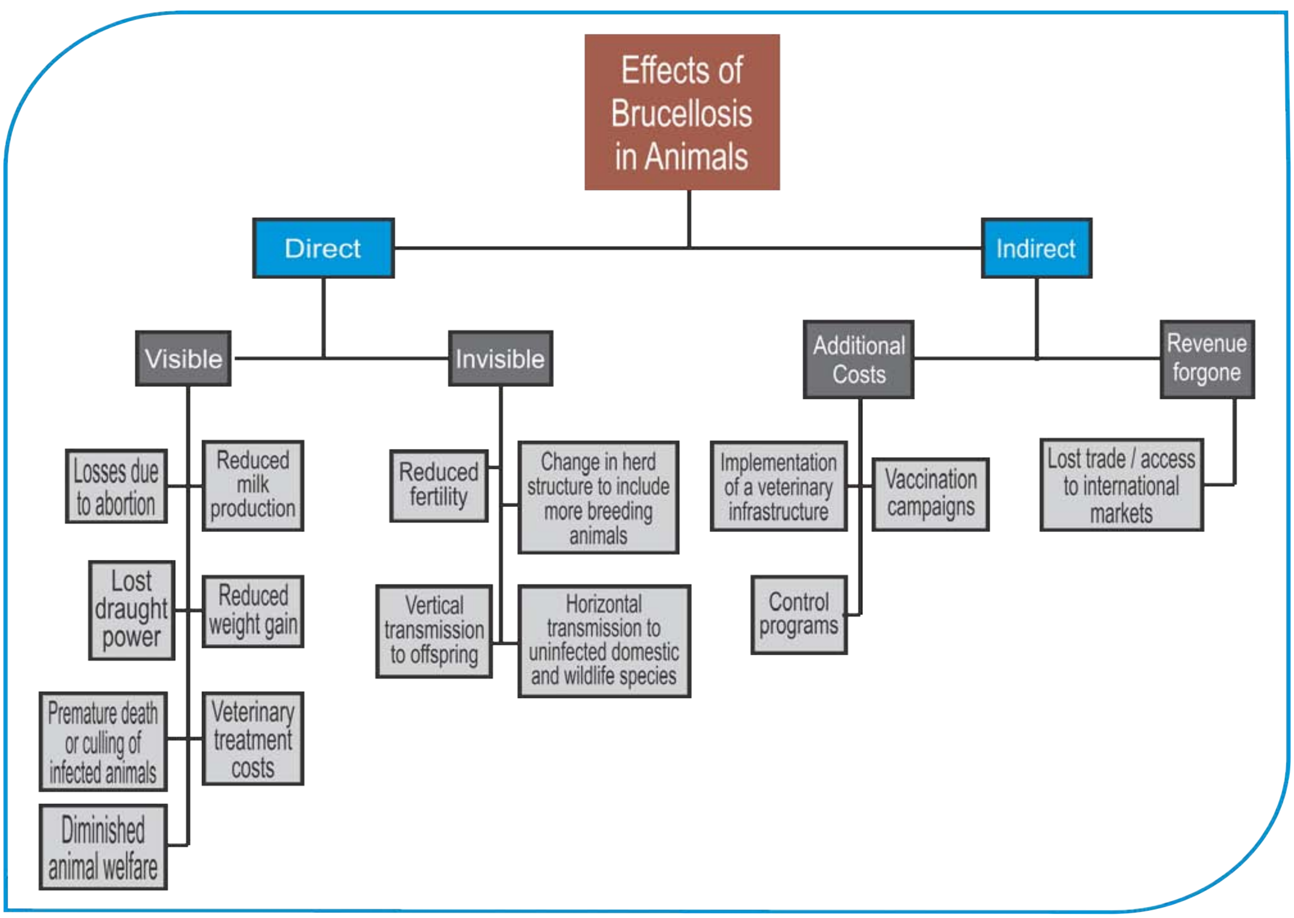

Fig. 2: Framework to Assess the Effect of Livestock Brucellosis in Regions where the Disease is Endemic (Franc et al., 2018)

XI. Diagnosis

Diagnosis and control of the disease in animals must be carried out on a herd basis. There may be a very long incubation period in some infected animals and individuals may remain serologically negative for a considerable period following infection. The identification of one or more infected animals is sufficient evidence that infection is present in the herd, and that other serologically negative animals may be incubating the disease and present a risk (Tewodros and Dawit, 2015).

Diagnostic tests fall into two categories: those that demonstrate the presence of the organisms and those that detect an immune response to its antigens (WHO, 2006). The isolation of Brucella is definitive proof that the animal is infected, but not all infected animals give a positive culture, and the methods and facilities that must be employed are not always readily available (Khan et al., 2018). The detection of an antibody or a hypersensitivity reaction provides only a provisional diagnosis, but in practice is the most feasible and economical means of diagnosis. False positive reactions to serological tests can occur through some factors, including vaccination, and this must be borne in mind when interpreting results. Similarly, dermal hypersensitivity only indicates previous exposure to the organism, not necessarily an active infection, and may also result from vaccination (WHO, 2006).

Laboratory diagnosis based on direct examination of clinical specimens using modified acid-fast stains, bacterial culture and serology (Arifet al., 2018). However, achievement of a reliable diagnosis of brucellosis is a tedious process since isolation is affected by some factors, such as high fastidious nature of Brucella, the presence of a lesser number of viable organisms in the sample and delay in the sample submission (leading to putrefaction). Also, a prolonged incubation period may lead to a failure in its isolation (Hanci et al., 2017).

Direct demonstration of the causal organism can be done microscopically with staining examination, fluorescence serologically, cultural on special nutrients, in animal experiments with guinea pigs. Primary bacteriological diagnosis can be made on smears from vaginal swabs, milk, placentas or aborted fetuses stained with stamps method. Confirmation on appropriate culture and selective media is recommended. Spleen and lymph nodes are most reliable from necropsy material. Polymerase chain reaction (PCR) is potentially a useful method on samples containing a low number of Brucella (Musallam et al., 2016).

Some of the most used diagnostic tests by indirect demonstration of the pathogen are Card test (C1) is the most suitable for detecting infected flocks and for a survey. It is simple and rapid and does not require laboratory facilities (Khan et al., 2018). Milk ring test (MR7) this procedure is valuable in screening dairy cows and has limitations in the diagnosis of caprine and ovine brucellosis. A serious disadvantage of the test is that its use is limited to milking animals. Allergic skin test (A81) is characteristic of brucellosis in man and some animals and appears through the delayed type of hypersensitivity to Brucella allergens in generalized infection, and the sensitivity may persist for several years (Musallam et al., 2016).

Individual Serologic Tests are Serum Agglutination Tube Test (SAT), Complement Fixation Test (CFT) this serologic test has a relatively high sensitivity and Specificity and is superior to the SATT. The CFT indicates active Brucella infection better than any other serologic test. It detects mostly IgG antibodies which are present in both acute and chronic stages of brucellosis (Musallam et al., 2016).

The use of the Rose Bengal Plate Test (RBPT) is easy to perform and considered as valuable screening test thoughless effective than CFT at detecting brucellosis in individual sheep and goats. The CFT is considered to be the most effective test for diagnosing brucellosis in small ruminants (WHO, 2006).

Most studies agree that the ELISA is as specific as the CFT, but it is more sensitive. Yet, for a reliable diagnosis of infected animals studies suggest using the ELISA in combination with other tests (Mohseni et al., 2017). Other studies consider the ELISA suitable for screening flocks of sheep and goats for brucellosis (Currò et al., 2012).

XII. Treatment

As a general rule, treatment of infected livestock is not attempted because of the high treatment failure rate, cost, and potential problems related to maintaining infected animals in the face of ongoing eradication programs (Yousefi-Nooraie et al., 2012).

Even though the complex nature of brucellosis makes it difficult to treat, long-term treatment with an antibiotic is thought to be beneficial. In most cases, antibiotics in combination are found to be more effective against the infection, however, the state of the disease still does not lose its importance (Falagas and Bliziotis, 206, Moon, 2014). Several conventional antibiotics including tetracycline, trimethoprim - sulfamethoxazole, amino-glycosides, rifampicin, quinolones, chloramphenicol, doxycycline, and streptomycin are commonly used in clinics (Saltoglu et al., 2002, Geyik et al., 2002). In several cases, the application of antibiotics in a specific order has given best results. Likewise, a case reported that treatment with doxycycline for six months, followed by streptomycin for three weeks was found very effective against brucellosis in human (Yousefi-Nooraie et al., 2012). Another study reported that the alkaloid columbamine in combination with jatrorrhizine was more effective against brucellosis caused by B. abortus compared to a combination of streptomycin and rifampicin (Azimi et al., 2018). The World Health Organization recommends that acute brucellosis cases be treated with oral doxycycline and rifampicin (600 mg for six weeks) (Ersoy et al., 2005). However, rifampicin monotherapy is in common practice for treating brucellosis in pregnant women, and combined therapy of sulphamethoxazole and trimethoprim is recommended for children (Karabayet al., 2004). In underdeveloped countries, treatment of cattle is not a common practice, however, the infected animals are isolated, culled or slaughtered to prevent the spreading of infection to other herd and at substantial veterinary costs. In China, a case of subdural empyema complicated by intracerebral abscess due to Brucella infection was effectively treated with antibiotic therapy (ceftriaxone, doxycycline, rifapentine) (Zhang et al., 2017). In line with this, several reports suggested the combination therapy of doxycycline and rifampicin for six weeks is enough to eradicate Brucella infection, as well as associated complications (Meng et al., 2018, Kaya et al., 2018). This combination of doxycycline and rifampicin has also been proven experimentally (Yang et al., 2018). As a result of continued efforts by the scientific community to develop an effective therapeutics, Caryopterismongolica Bunge (Lamiaceae) has been tested in combination with doxycycline (Tsevelmaa et al., 2018, Saxena et al., 2018). Even though several therapeutics are in practice which makes the disease manageable, an effective therapeutic is required for the complete treatment of brucellosis (Khan et al., 2018).

Humans are treated with antibiotics (doxicycline with rifamipicine). Relapses are, however, possible (Solis and Solera, 2012). In experimentally infected rams the combined administration of chlortetracycline (800mg intravenously) and streptomycin (Igram subcutaneously) injected daily for 21 days, eliminated infection. Streptomycin alone and streptomycin plus sulfadimidine were not satisfactory. Treatment is economically practicable only in valuable rams and must be instituted before irreparable damage to the epididymis has occurred. A dose of 1000 mg of long-acting tetracycline give every three days for the period of 6 weeks achieved a cure rate of 75% (Radostits et al., 2007).

XIII. Control and Prevention

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 obvious way to do this-elimination of the disease from animals is often beyond the financial and human resources of many developing countries. The technical and social difficulties involved in eradicating B. melitensis from small ruminants have even taxed the resources of some developed countries. In many situations, there is little alternative but to attempt to minimize the impact of the disease and to reduce the risk of infection by personal hygiene, adoption of safe working practices, protection of the environment and food hygiene. The lack of safe, effective, widely available vaccines approved for human use means that prophylaxis currently plays little part in the prevention of human disease (WHO, 2006).

Prevention and control of brucellosis can be adopted realistically through an understanding of local and regional variations in animal husbandry practices, social customs, infrastructures and epidemiological patterns of the disease (Dorneles et al., 2015). The common approaches used to control brucellosis includes quarantine of imported stoke and decide for or against immunization of the negative animals (Radostits et al., 2007).

Eradication by test and slaughter principles are based on the magnitude of disease prevalence and economic status at countries and handling hygienic disposal of aborted fetuses, fetal membrane and discharges with subsequent disinfection of contaminated area (WHO, 2006).

Control measures must include hygiene at lambing and the disposal of infected or reactor animals. Separate pens for lambing ewes, which can be cleaned and disinfected, early weaning of lambs from their dams, and their environment and vaccination, are recommended. In endemic areas, all placentas and dead fetuses should be buried as a routine practice. The need to test and cull, introduced and resident animals likely to be carriers is recommended, but difficult to be effective because of the inaccuracy of the tests. Because of the possibility that lambs may be infected at birth and carry the disease for life, it may be more economical to dispose off the entire flock (Radostits et al., 2007).

The experience from all over the world, that vaccination is in most situations the only practical method of control of brucellosis in sheep and goats. Immunization with effective vaccines helps to get the infection under control, limit its spread, prevent human infections and reduce economic losses (Musallam et al., 2016). Most workers agree that the smooth live organisms of *B. abortus* strain 19 and *B. melitensis* Rev 1have many advantages over inactivated vaccines. Their limitations, including interference with diagnostic tests, are well known. However, they provide good protection on a herd per flock basis by reducing clinical symptoms (exposure potential) and elevating to induce sexually mature animals. The reduced doses also reduce the physiologic and serologic effects. It is illogical to restrict the use of vaccines among mature animals where there are no controls on infected populations (Donev, 2010).

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XIV. Conclusions

Brucellosis is thought to be widespread zoonotic infectious disease that highly affects the health and economy of animals and humans in the world. The two species of Brucella, *B. ovis* and *B. melitensis*, are the main causative agents of infection to sheep and goats, respectively. The latter, is also the one in which, greatly contributes the infection to humans.

The disease is serious, therefore, proper veterinary legislation must be implemented and policies regarding animal health need to be encouraged. Current and modern awareness on brucellosis should be delivered to farmers, veterinary professionals, and health educators, especially for rural populations, which will help to prevail over the dispersal of Brucella infection worldwide. Effective and relatively safe vaccines should be available to provide long-term protection against brucellosis in both animals and humans.

In general, to combat the disease, there should be proper management practices such as rearing of brucellosis free animals, isolating and restricting movement of infected and/or suspected animals, following the guidelines of incineration or burial for proper disposal of animal discharges and wastes, formulating a schedule for cleansing and disinfection of animal houses, feeding and watering troughs, and understanding proper hygienic practices in all stages.

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References Références Referencias

1. Abebe, Y., Melaku, S. and Tegegne, A (2013). Assessment of sheep marketing system in Burie district, North Western Ethiopia. Wudpecker Journal of Agricultural Research 2 (3): 97-102.
2. Abela B. (1999). Epidemiology and control of brucellosis in ruminants from 1986 to 1996 in Malta. Revue Scientifiqueet Technique - Office International des épizooties, 18 (3): 648-659, 20 ref.
3. Ahl A. S, Bartlett P. C, Frerichs W. M (1993). Serological evidence for the presence of Brucella antibodies in sheep and goats on Saint Croix, U.S. Virgin Islands. Revue d'élevage et de Médecine Vétérinaire des Pays Tropicaux, 46 (½): 61-63, [Actes de la 2e Réunion Biennale de la Society for Tropical Veterinary Medicine, 2-6 février 1993, Saint FranÇois, Guadeloupe.], 14 Ref.
4. Arif, S., Heller, J., Hernandez-Jover, M., McGill, M.D., Thomson, C.P. (2018) Evaluation of three serological tests for diagnosis of bovine brucellosis in smallholder farms in Pakistan by estimating sensitivity and specificity using Bayesian latent class analysis. Prev. Vet. Med. 149, 21-28. [CrossRef] [PubMed].
5. Asmare K, Megersa B, Denbarga Y, Abebe G, Taye A, Bekele J, Bekele T, Gelaye E, Zewdu E, Agonafir A, Ayelet G, Skjerve E (2012) A study on seroprevalence of caprine brucellosis under three livestock production systems in southern and central Ethiopia. Trop Anim Health Prod. 45: 555-560, doi 10.1007/s11250-012-0258-2.
6. Awah-Ndukum J, Mouiche M. M. M, Bayang H. N, NguNgwa N, Assana E, Feussom K. J. M, Manchang T. K, Zoli P.A (2018). Seroprevalence and Associated Risk Factors of Brucellosis among Indigenous Cattle in the Adamawa and North Regions of Cameroon. Vet Med Int. 3468596.
7. Azimi, G., Hakakian, A., Ghanadian, M., Joumaa, A., Alamian, S. Bioassay - directed isolation of quaternary benzylisoquinolines from Berberisintegerrima with bactericidal activity against Brucella abortus. Res. Pharm. Sci. 2018, 13, 149-158. [PubMed].
8. Bamaiyi P. H., Hassan L., Khairani-bejo S., Zainal A.M. (2014). Updates on Brucellosis in Malaysia and South Asia. Malaysian Journal of Veterinary Research. (5): 71-82.
9. Bezabih M. K, Bulto W. C. (2015). Seroprevalence of small ruminant brucellosis in Werer Agricultural Research Center, Afar Region, North East Ethiopia. Acad. J. Microbiol. Res. 3 (2): 031-035.
10. CABI. (2017a, 11 09). Brucellosis (Brucella ovis). Retrieved 06 14, 2018, from https: //www.cabi.org/ isc/datasheet/90731.
11. CABI. (2017b, 11 09). Brucellosis (Brucella melitensis). Retrieved 06 14, 2018, from https: //www.cabi.org/isc/datasheet/90734.
12. Central Statistical Agency (CSA) (2014).Federal Democratic Republic of Ethiopia, Central Statistical Agency, Agricultural sample survey 2013/14 (2006 E.C). Vol II. Report on livestock and livestock characteristics (Private Peasant Holdings). Statistical Bull. PP. 573.
13. Currò, V., Marineo, S., Vicari, D., Galuppo, L., Galluzzo, P., Nifosì, D., Pugliese, M., Migliazzo, A., Torina, A., Caracappa, S. The isolation of Brucella spp. from sheep and goat farms in Sicily. Small Rumin. Res. 2012, 106, S2-S5.
14. Donev, D. (2010) Brucellosis control and eradication in the south eastern European countries: Current status and perspective strategies. Maced. J. Med. Sci. 3, 220. [CrossRef].

15. Dorneles, E. M., Sriranganathan, N., Lage, A. P. (2015). Recent advances in Brucella abortus vaccines. Vet. Res. 46, 76. [Cross Ref] [Pub Med].
16. El abdin S. Z., Angara T. E., Elfadil A. A., El Sanousi E. M., Ibrahim A. M. (). Prevalence and Risk Factors of Ruminants Brucellosis in Jabel Aolia Locality, Sudan. Sudan Journal of Science and Technology 15 (2): 60-72.
17. Ersoy, Y., Sonmez, E., Tevfik, R. M., But, D. A. Comparison of three different combination therapies in the treatment of human brucellosis. Trop. Doct. 2005, 35, 210-212. [Cross Ref] [Pub Med].
18. Falagas, M. E., Bliziotis, I. A. Quinolones for treatment of human brucellosis: Critical review of the evidence from microbiological and clinical studies. Antimicrob. Agents Chemother. 2006, 50, 22-33. [Cross Ref] [Pub Med].
19. Ferede Y, Mengesha D, Mekonen G, Hilemelekot M. (2011). Study on the seroprevalence of small ruminant brucellosis in and around Bahir Dar, North West Ethiopia. Ethiop. Vet. J., 15 (2), 35-44.
20. Food and Agriculture Organization of the United Nations. (2010). Brucella melitensis in Eurasia and the Middle East. FAO Animal Production and Health Proceedings. No. 10 Rome.
21. Foster, J. T., Walker, M. F., Rannals, D. B., Hussain, H. M., Drees, P. K., Tiller, V. R., Hoffmaster, R. A., Al-Rawahi, A., Keim, P., Saqib, M (2017). African lineage Brucella melitensis isolates from Omani livestock. Front. Microbiol. 8, 2702. [Cross Ref] [Pub Med].
22. Franc, K. A, Krecek, R. C, Häsler, B. N, Arenas-Gamboa, A. M (2018). Brucellosis remains a neglected disease in the developing world: a call for interdisciplinary action. BMC Public Health 18: 125.
23. Franco, M. P., Mulder, M., Gilman, H. R., Smits, L. H (2007). Human brucellosis. Lancet Infect. Dis. 7, 775-786. [Cross Ref].
24. Franco, M. P., Mulder, M., Gilman, H. R., Smits, L. H. (2007) Human brucellosis. Lancet Infect. Dis. 7, 775-786. [Cross Ref].
25. Gebremedhin, B., Hoekstra, D., Tegegne, A., Shiferaw, K. and Bogale, A (2015). Factors determining household market participation in small ruminant production in the highlands of Ethiopia. LIVES Working Paper 2. Nairobi, Kenya: International Livestock Research Institute.
26. Geyik, M. F., Gur, A., Nas, K., Cevik, R., Sarac, J., Dikici, B., Ayaz, C. Musculoskeletal involvement of brucellosis in different age groups: A study of 195 cases. Swiss Med. Wkly. 2002, 132, 98-105. [Pub Med].
27. Gizaw S (2010 Sheep and goat production and marketing systems in Ethiopia: Characteristics and strategies for improvement (No. 23). ILRI (aka ILCA and ILRAD).
28. Gobena, M. M (2016). Review on Small Ruminant Production, Marketing and Constraints in Ethiopia. Advances in Life Science and Technology, V (48): 28-34.
29. Godfroid J, Al Dahouk S, Pappas G, Roth F, Matope G, Muma J, Marcotty T, Pfeiffer D, Skjerve E (2013). A "One Health" surveillance and control of brucellosis in developing countries: Moving away from improvisation. Comp. Immunol. Microbial. Infect. Dis. 36 (3): 241-248.
30. Gouvêa G, Roxo E, Lima MABS, Homerich D, 1989. Occurrence of brucellosis in goats from Sao Paulo State. Arquivos do Instituto Biológico (Sao Paulo), 56 (Supl.): 60.
31. Guven, T., Ugurlu, K., Ergonul, O., Celikbas, K. A., Gok, E. S., Comoglu, S., Baykam, N., Dokuzoguz, B. Neurobrucellosis: Clinical and diagnostic features. Clin. Infect. Dis. 2013, 56, 1407-1412. [Cross Ref] [Pub Med].
32. Hanci, H., Igan, H., Uyanik, M. H. Evaluation of a new and rapid serologic test for detecting brucellosis: Brucella Coombs gel test. Pak. J. Biol. Sci. 2017, 20, 108-112. [Cross Ref] [Pub Med].
33. Hirsh D. C, Maclachlan N. J, Walker R. L (2004) Veterinary Microbiology. Black well science USA 105-112.
34. Hotez, P. J., Savioli, L., Fenwick, A. Neglected tropical diseases of the Middle East and North Africa: Review of their prevalence, distribution, and opportunities for control. PLoSNegl. Trop. Dis. 2012, 6, e1475. [Cross Ref] [Pub Med].
35. Karabay, O., Sencan, I., Kayas, D., Sahin, I. Ofloxacin plus rifampicin versus doxycycline plus rifampicin in the treatment of brucellosis: A randomized clinical trial [ISRCTN11871179]. BMC Infect. Dis. 2004, 4, 18. [Cross Ref] [Pub Med].
36. Kaya, S., Elaldi, N., Deveci, O., Eskazan, E.A., Bekcibasi, M., Hosoglu, S. Cytopenia in adult brucellosis patients. Indian J. Med. Res. 2018, 147, 73-80. [Cross Ref] [PubMed].
37. Kelkay, M. Z., Gugsa, G., Hagos, Y., & Taddelle, H. (2017). Sero-prevalence and associated risk factors for Brucella sero-positivity among small ruminants in Tselemti districts, Northern Ethiopia. Journal of Veterinary Medicine and Animal Health, 9 (11), 320-326.
38. Khan M. Z, Zahoor M (2018). An Overview of Brucellosis in Cattle and Humans, and its Serological and Molecular Diagnosis in Control Strategies. Trop. Med. Infect. Dis. 3, 65.
39. Meng, F., Pan, X., Tong, W. Rifampicin versus streptomycin for brucellosis treatment in humans: A meta-analysis of randomized controlled trials. PLoS One 2018, 13, e0191993. [Cross Ref] [Pub Med].
40. Mohseni, K., Mirnejad, R., Piranfar, V., Mirkalantari, S. A comparative evaluation of ELISA, PCR, and

serum agglutination tests for diagnosis of Brucella using human serum. Iran J. Pathol. 2017, 12, 371-376. [Pub Med].
41. Moon, M. S. Tuberculosis of spine: Current views in diagnosis and management. Asian Spine J. 2014, 8, 97-111. [Cross Ref] [Pub Med].
42. Musallam, I. I., Abo-Shehada, N. M., Hegazy, M. Y., Holt, R. H., Guitian, J. F. Systematic review of brucellosis in the Middle East: Disease frequency in ruminants and humans and risk factors for human infection. Epidemiol. Infect. 2016, 144, 671-685. [Cross Ref] [Pub Med].
43. Neharika Saxena, Balbir Bagicha Singh and Hari Mohan Saxena. (2018). Brucellosis in Sheep and Goats and Its Serodiagnosis and Epidemiology. Int. J. Curr. Microbiol. App. Sci. 7(01): 1848-1877. doi: https: //doi.org/10.20546/ijcmas.2018.701.225.
44. Nigatu S, Deneke M, Kassa T (2014). Sero-Prevalence of Brucellosis in Sheep and Goat Destined for Slaughter in Selected Export Abattoirs, Ethiopia. African Journal of Basic & Applied Sciences 6 (3): 82-86.
45. Office International des Epizooties Terrestrial Manual (OIE) (2012a). Bovine brucellosis (Chapter 2.4.3). In: OIE Manual of diagnostic tests and vaccines for terrestrial animals. Paris: Off. Int. Epizoot. 616-650.
46. OIE (2009a). World Animal Health Information Database - Version: 1.4. World Animal Health Information Database. Paris, France: World Organization for Animal Health. http: //www.oie.int.
47. OIE (2012b). World Animal Health Information Database.Version 2. World Animal Health Information Database. Paris, France: World Organisation for Animal Health. http: //www.oie.int/wahis_2/public/wahid.php/Wahidhome /Home.
48. OIE Handistatus, (2005). World Animal Health Publication and Handistatus II (data set for 2004). Paris, France: Office International des Epizooties.
49. Padilla Poiester F, Nielsen K, Ernesto Samartino L, Ling Yu W (2010). Diagnosis of Brucellosis. Open Vet. Sci. J. 4: 46.
50. Radostits O. M, Gay C, Blood D. C, Hinchclift K. W (2007). Veterinary Medicine: a text book of the Disease of cattle, sheep, pigs, goats and horse. Harcourt publishers limited, London. PP. 882-885.
51. Rossetti, C. A., Arenas-Gamboa, A. M., Maurizio, E. Caprine brucellosis: A historically neglected disease with sigficant impact on public health. PLoSNegl. Trop. Dis. 2017, 11, e0005692. [Cross Ref] [Pub Med].
52. Saltoglu, N., Tasova, Y., Inal, S. A., Seki, T., Aksu, S. H. Efficacy of rifampicin plus doxycycline versus rifampicin plus quinolone in the treatment of brucellosis. Saudi Med. J. 2002, 23, 921-924. [Pub Med].
53. Saxena, H. M., Raj, S. A novel immunotherapy of Brucellosis in cows monitored non-invasively through a specfic biomarker. PLoSNegl. Trop. Dis. 2018, 12, e0006393. [Cross Ref] [Pub Med].
54. Seleem M. N, Boyle S. M, Sriranganathan N (2010). Brucellosis: A re-emerging zoonosis. Vet. Microbiol.140: 392-398.
55. Sharifi H, Mashayekhi K, Tavakoli MM (2015). Risk facts of small ruminant brucellosis: a cross-sectional study in Southeast Iran 2012. Human & Veterinary Medicine. International Journal of the Bioflux Society 7: 42-45.
56. Sintayehu G, Melesse B, Abayneh A. D, Sintayehu A, Melaku S (2015). Epidemiological survey of brucellosis in sheep and goats in selected pastoral and agro-pastoral lowlands of Ethiopia. Rev. Sci. Tech. Off. Int. Epiz., 2015, 34 (3).
57. Sohn, A. H., Probert, W. S., Glaser, C. A. (2003). Human neurobrucellosis with intra cerebral granuloma caused by a marine mammal Brucella spp. Emerging Infectious Diseases Journal, 9: 485-488.
58. Solis Garcia delPozo, J., Solera, J. Systematic review and meta-analysis of randomized clinical trials in the treatment of human brucellosis. PLoS ONE 2012, 7, e32090. [Cross Ref] [Pub Med].
59. Tadeg W. M, Gudeta F. R, Mekonen T. Y, Asfaw Y. T, Birru A. L, Reda A. A (2015). Seroprevalence of small ruminant brucellosis and its effect on reproduction at Tallalak district of Afar region, Ethiopia. J. Vet. Med. Anim. Health 7(4): 111-116.
60. Tedeschi, L. O., Nicholson, C. F. and Rich E. 2011. Using system dynamics modelling approach to develop management tools for animal production with emphasis on small ruminants. Small Ruminant Research 98: 102-110.
61. Tegegn A. H, Feleke A, Adugna W, Melaku S. K. (2016). Small Ruminant Brucellosis and Public Health Awareness in Two Districts of Afar Region, Ethiopia. J. Vet. Sci. Technol. 7 (335): 2.
62. Teklue T, Tolosa T, Tuli G, Beyene B, Hailu B (2013). Sero-prevalence and risk factors study of brucellosis in small ruminants in Southern Zone of Tigray Region, Northern Ethiopia. Trop. Anim. Health Prod. 45: 1809-1815.
63. Tewodros A. E, Dawit A. A (2015). Sero-Prevalence of Small Ruminant Brucellosis in and around Kombolcha, Amhara Regional State, North-Eastern Ethiopia. J. Vet. Sci. Med. Diagn. 4 (5).
64. Tsevelmaa, N., Narangerel, B., Odgerel, O., Dariimaa, D., Batkhuu, J. Anti-Brucella activity of Caryopterismongolica Bunge root extract against Brucella melitensis infection in mice. BMC Complement. Altern. Med. 2018, 18, 144.
65. Wikipedia. (2018, 05 24). Brucella. Retrieved 06 10, 2018, from https: //en.m.wikipedia.org/wiki/Brucella.

66. World Health Organization (WHO) (2006). Brucellosis in humans and animals. WHO Library Cataloguing-in-Publication Data.
67. Wubishet Z, Golo D, Chala F, Shubisa A, Huqa L Godana H, Ararsa D. Sero-Prevalence Of Brucellosis In Goats And Community Awareness In Liban District Of Guji Zone, Oromia Regional State, Southern Ethiopia. JOJ Pub Health. 2017, 2 (3): 555587. DOI: 10.19080/ JOJPH.2017.02.555587.
68. Wubishet Z, Sadik K, Abdala B, Mokonin B, Getachew T, Getachew K. Small Ruminant Brucellosis and Awareness of Pastoralists Community about Zoonotic Importance of the Disease in Yabello districts of Borena Zone Oromia Regional State, Southern Ethiopia.Curr Trends Biomedical Eng & Biosci. 2018, 12 (1): 555827. DOI: 10.19080/CTBEB.2018.12.555827.
69. Yang, H. X., Feng, J. J., Zhang, X. Q., Hao, E. R., Yao, X. S., Zhao, R., Piao, R. D., Cui, Y. B., Jiang, H. A case report of spontaneous abortion caused by Brucella melitensis biovar 3. Infect. Dis. Poverty 2018, 7, 31. [Cross Ref] [Pub Med].
70. Yantzis D, 1985. Brucella melitensis in Greece: current situation report. Brucella melitensis.CEC seminar, Brussels, November 1984, 43-46, [Current Topics in Veterinary Medicine and Animal Science volume 32], 12 Ref.
71. Yesuf M, Alemu S, Temesgen W, Mazengiac H, Negussie H (2010). Seroprevalence of Ovine Brucellosis in South Wollo, North Eastern Ethiopia. American-Eurasian J. Agric. & Environ. Sci., 9 (3): 288-291.
72. Yousefi-Nooraie, R., Mortaz-Hejri, S., Mehrani, M., Sadeghipour, P. Antibiotics for treating human brucellosis. Cochrane Database Syst. Rev. 2012, 10, Cd007179. [Cross Ref] [Pub Med].
73. Zahra, A., Mulema, A., Colverson, K., Odongo, D., and Rischkowsky, B. (2014). A review of Ethiopia small ruminant value chains from a gender perspective. Nairobi: ILRI and ICARDA. PP. 1-38.
74. Zhang, J., Chen, Z., Xie, L., Zhao, C., Zhao, H., Fu, C., Chen, G., Hao, Z., Wang, L., Li, W. Treatment of a subdural empyema complicated by intracerebral abscess due to Brucella infection. Braz. J. Med. Biol. Res. 2017, 50, e5712. [Cross Ref] [Pub Med].