REVIEW ARTICLE

Association of Brucellosis with Abortion Prevalence in Humans and Animals in Africa: A Review

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Abstract

Brucellosis is a worldwide zoonotic disease suspected to be the cause of abortions which remain largely undiagnosed in both humans and animals. A review of literature was performed to elucidate the contribution of brucellosis to abortions in humans, livestock and wildlife in Africa. A total number of 18 published articles associated brucellosis to abortions observed in humans and livestock in some parts of Africa. The contribution of brucellosis to abortions in humans was less reported in the literature compared to livestock; and no report was done in wildlife in Africa. The association of brucellosis to abortions in Africa was mostly based on bacteriologic, serologic or molecular techniques and *Brucella abortus biovar* 3 seemed more associated to abortions in cattle. The isolation and molecular characterization of *Brucella* species could advance the assessment of the contribution of brucellosis to abortions in Africa, focusing much in humans. The epidemiologic approach based on case-control comparisons could elucidate more about the contribution of brucellosis to abortions in Africa. The economic impact evaluation of abortions due to brucellosis could justify implementation of eradication programs of this disease in Africa, such as occupational and food hygiene in humans; with a vaccination and culling in animals. *(Afr J Reprod Health 2018; 22[3]: 120-136).*

Keywords: Spontaneous abortions, Brucellosis, mammals, Africa

Résumé

La brucellose est une maladie zoonotique mondiale soupçonnée d'être à l'origine d'avortements qui restent largement non diagnostiqués chez l'homme et chez l'animal. Une revue de la documentation a été réalisée pour élucider la contribution de la brucellose aux avortements chez l'homme, le bétail et la faune en Afrique. Au total, 18 articles publiés ont associé la brucellose aux avortements observés chez l'homme et le bétail dans certaines régions d'Afrique. La contribution de la brucellose aux avortements chez l'homme était moins rapportée dans la documentation par rapport au bétail; et aucun rapport n'a été fait sur la faune sauvage en Afrique. L'association de la brucellose aux avortements en Afrique était principalement basée sur des techniques bactériologiques, sérologiques ou moléculaires et Brucella abortus biovar 3 semblait davantage associés aux avortements chez les bovins. L'isolement et la caractérisation moléculaire des espèces de Brucella pourraient faire progresser l'évaluation de la contribution de la brucellose aux avortements en Afrique, en se concentrant beaucoup sur l'homme. L'approche épidémiologique basée sur des comparaisons cas-témoins pourrait élucider davantage la contribution de la brucellose aux avortements en Afrique. L'évaluation de l'impact économique des avortements dus à la brucellose pourrait justifier la mise en œuvre des programmes d'éradication de cette maladie en Afrique, tels que l'hygiène professionnelle et alimentaire chez l'homme; avec la vaccination et l'élimination chez les animaux. *(Afr J Reprod Health 2018; 22[3]: 120-136).*

Mots-clés: Avortements spontanés, brucellose, mammifères, Afrique

Introduction

Brucellosis is a zoonosis of both veterinary and public health significance with an economic impact on livestock production in most developing countries[1]. This disease, which has a worldwide distribution, is caused by Gram-negative bacteria of the genus *Brucella*. Currently, there are 11 recognized *Brucella* species[2], and six of them, are known to be pathogenic for both animals and to humans, namely: *B. abortus, B. canis, B. inopinata, B. melitensis, B. pinnipedialis, and B. suis*[3]. The sources of infection for animals include aborted materials, vaginal discharges, milk and semen from *Brucella* infected animals. Domestic animals (Cattle, sheep, goats and pigs) are the main reservoirs of *Brucella*. The transmission of brucellosis to humans occurs through occupational or environmental contact with infected animals or their products (cheese, raw milk and unpasteurized milk) including a travel-association to the disease[4]. Person-to-person transmission is extremely rare.

Despite its global distribution, data on the prevalence of brucellosis among humans and animals in Africa is limited. In Africa, the intensive interactions between humans and animals in the ecosystems favor cross-infections in mixed husbandry systems or at the livestock-wildlife interface[5]. Brucellosis remains endemic in most areas of the world[6], even if, some of the developed countries have eradicated it from their domestic animal populations. In some parts of Africa, the disease is underreported due to insufficient awareness, inadequate diagnostic protocols, including lack of laboratory reagents[7]. In addition, limitations in the implementation of blood testing, milk pasteurization, food hygiene measures, slaughter and heifer vaccination programs, are some of factors which negatively affect the surveillance networks of brucellosis in Africa. However, brucellosis infections in humans can be avoided by applying occupational and food hygiene together with the implementation of bio-security measures in laboratories, while the prevention in animals could be based on good herd management and hygiene strengthened with a careful vaccination program[4].

Brucellosis poses diagnostic and confirmation challenges in humans, domestic and wild animals[8]. In humans, brucellosis resembles other febrile diseases such as malaria, and is often misdiagnosed or underreported[9]. Even where good laboratory facilities exist, the disease is still misdiagnosed because of the low diseases suspicion levels among the medical practitioners. In some cases, infections due to brucellosis are not necessarily recognized based on clinical evidences because the disease has no pathognomonic signs, and therefore confirmation must be based only on laboratory tests. In livestock industry, the economic impact of brucellosis is mainly attributed to abortions which mostly occur during the last third of pregnancy. In African countries, abortions are followed in some cases by temporary or definitive infertilities also with a decrease or a total absence of milk production[10]. Unfortunately, in *Brucella* infections, the causes of abortions often remain undiagnosed even after a complete necropsy, histopathologic and microbiological examinations[11]. Furthermore, there are some limitations on how to make a differential diagnosis with other infectious diseases, making it difficult to assess the real contribution of brucellosis to the observed abortions in humans and in animals. Several studies in Africa have shown an association between seropositivity and abortions[11–13]; but in many cases these relationships have been established based on statistical association between prevalence and the history of abortions in herds, not as counter-factual events, which could make an ambiguous interpretation about the role played by brucellosis in the causation of abortions. Furthermore, the presence of organisms does not necessarily indicate a causal association between *Brucella* and abortions in risk groups, because of several other factors that could bring about abortions. Therefore, the aim of this review was to assess the contribution of brucellosis to abortions observed in humans, domestic and wildlife in Africa, considering the above catalogued shortcomings. For this purpose, the objectives of the review study were: to identify different causes of abortions in humans and animals; to evaluate the impact of abortions in humans and animals and to assess the contribution of brucellosis to abortions observed in humans and animals in Africa.

Methods

This literature review was done to demonstrate from published information the contribution of brucellosis to abortions in livestock, humans and wildlife in Africa. Articles in English and French published between 1997 and 2015 were retrieved using large-scale search engines including the Google, Google Scholar, Pubmed, Gopubmed, Freefullpdf and African journals Online. The inclusion criterion was any article in which the authors attributed the responsibility of *Brucella* infections to abortion occurrence in humans, domestic animals and wildlife in Africa. Articles reporting prevalence of brucellosis in Africa without any association of abortions in humans, domestic and wild animals were excluded. The key words for the search were: [brucellosis, abortion, livestock, Africa]; [brucellosis, abortion, humans, Africa]; [brucellosis, abortion, wildlife, Africa]; [Contribution, brucellosis, abortion, Africa]. For the balanced information, it was necessary to review the *Brucella* and non- *Brucella* causes of abortions in humans and animals, as well as their economic impact evaluation without limit only to Africa continent. In this review, the focus was based only on the causes of spontaneous abortions in humans and animals (not induced abortions).

Results

Different causes of abortions in humans and animals

The general causes of spontaneous abortions are due to infectious and non-infectious causes. There are several causes of spontaneous abortions and some of such common causes in humans and animals are discussed below.

Definition of abortion

Spontaneous abortion, or miscarriage, is defined as a pregnancy that ends spontaneously before the fetus has reached a viable gestational time (20th week of gestation)[14]. Abortion can be defined also as an expulsion of a dead or living fetus of recognizable size at any stage of gestation. Abortion is also defined as a loss of a fetus which occurs from the moment in which the pregnancy diagnosis is usually performed to the point at which the fetus is considered capable of sustaining life outside the uterus[15]. Abortion may be either spontaneous (occurring from natural causes) or induced (artificially or therapeutically). Abortion is most of the time the result of a disturbance in the functioning of the placenta and, it may occur at any stage of pregnancy[16]. In case of brucellosis, the presence in uterus of erythritol (a 4-carbon sugar alcohol) is associated with abortions occurrence because it constitutes the placental tropism for the development of *Brucella* specifically in ruminants[17]. This carbon sugar is not found in human uterus or fetus, a reason which makes it more difficult to understand the contribution of *Brucella* infections to abortions in pregnant women. The pathogenic mechanism for induction of abortion by bacterial and viral infections is not the same depending of the characteristics of each infectious disease which may induce this syndrome[18]. Protozoan parasites are common causes of extensive abortion in livestock and some species, including *Toxoplasma gondii*, *Neospora* and *Sarcocystis,* have a two-host life cycle[19]. In addition, the pathogenesis of fungal abortions is possibly based on the penetration of fungi and their toxins in the uterus and the fetus by hematogenous route[20]. In case of brucellosis, the pathogenesis of abortion is very unclear although, some studies have demonstrated the interactions between brucellosis and the animal trophoblast, which is not the case for the human trophoblast[21].

Causes of abortions in humans

Genetic causes

Abnormal chromosomes (translocations) in either partner can cause miscarriage[22]. Chromosomal aberrations in parents are a major pre-disposing factor and causative of abortion if carried over to the embryo[23]. Generally in Africa, it is rare to diagnose and get service in such cases[24] due to the difficulties in finding trained medical geneticists, genetic counselors and medical scientists. Other causes of abortions may include genetic factors because of lethal gene combinations[25].

Endocrinologic causes

In humans, an important cause of early and late abortions is due to an insufficient progesterone (disorders of the luteoplacental progesterone) secretion[26].

Immunologic causes

Some studies reported the maternal immunologic aberrations to be the cause of repeated abortions[27,28], and the larger numbers of unexplained abortions may have immunological reasons.

Nutritional deficiency and toxic agents

Abortions may also be due to some deficiencies of vitamins, minerals and energy in the body of pregnant females. In terms of maternal health, clinical deficiency (vitamin B12, E) may be a cause of infertility or recurrent spontaneous abortion[29,30]. Furthermore, poor iodine tenancy in pregnant woman body has been found in West Africa to be associated to reproductive failure including miscarriage[31]. A long exposure to toxic agents such as pesticides may also cause abortions or early embryonic human deaths[32].

Environmental and occupational factors

On rare occasions, an individual may abort after developing a very high fever due to an infection. Spontaneous abortions can be due to environmental factors: for example, the tobacco exposure in some occasions can cause spontaneous abortions[32–34]. Occupations; even the income of people (poverty, lifestyle) can in some cases expose them to risk of abortions[32,35].

Causes of abortions in domestic animals

Genetic causes

In animals, abortions due to genetic abnormalities occur as an individual case problem rather than as a herd problem. Studies reported abortions and neonatal losses in cattle linked to chromosomal aneuploidy[11,23].

Endocrinologic causes

An experimental study reported significant alterations caused by *T. brucei* in the hypothalamus, adenohypophysis, uterus, placenta and fetal liver with infertility in goats[36]. In South Africa, a study reported cases of abortions in Angora goats due to an abnormally low level of adrenal function, coupled with some qualitative changes in adrenal steroid biosynthesis[37].

Immunologic causes

It has been proved with clinical evidence that using some vaccines in pregnant animals can cause abortions. A study reported an outbreak of abortions following the use of intramuscular infectious bovine virus vaccine in a dairy herd in Canada[38]. Abortions which may occur after administration of *Leptospira* vaccines have also been discussed[39]. In case of brucellosis, although the available vaccines RB51 and S19 are effective in controlling brucellosis, studies reported their numerous drawbacks, such as potential to cause abortion in pregnant animals[8,40,41]. For *Brucella* immunization, cattle are vaccinated mostly as heifer calves at 4–12 months of age whereas adult cattle may be vaccinated only in selected high-risk situations.

Nutritional deficiency and toxic agents

Mineral deficiencies were reported in 4% of abortions in goats in California[42]. However, a study conducted in South Africa could not associate the observed abortions in Angora goats to nutritional deficiencies[43]. Abortions may occur, especially in late gestation if animals are exposed to sufficiently high levels of nitrates in forage (55 % or greater). Experimentally, studies have proved abortions caused by mycotoxins such as zearalenone[44,45] and ergot alkaloids[46].

Environmental factors

Some abortions in animals may be a result of an increase in environmental temperature[47], but, evidences are not sufficient to support heat stress as a common cause of abortions.

Abortions caused by infectious diseases in humans and animals

There are a larger number of infectious agents causing abortions in humans and animals and some of them are zoonotic (Table1). In fact, *Brucella spp.*, are among the important bacterial agents associated with abortion during mid-to late gestation including *Chlamydia spp., Salmonella spp., Campylobacter spp., Listeria monocytogenes* and *Coxiella burnetii*[8,48,49]. In case of *Toxoplasma gondii*, it used to be misidentified while it is the most probably significant cause of repeated abortion in humans, cattle and dogs[50–52]. The evidences are lacking to consider *Neospora caninum* as a cause of abortions in humans; however, it is one the causative agents of abortions in cattle and dogs[53].

Causes of abortions in wildlife

Toxoplasma gondii infections are suspected to be mostly associated to abortions cases in wildlife[54,55]. The *Coxiella burnetii* and *Chlamydiales* species have been associated with abortions in wild ruminants[54–57]. Some infectious diseases are reported in wildlife such a Rift valley fever (RVF) in Kenya[58], Food and Mouth Disease (FMD) in Zimbabwe[59], tuberculosis in African buffalo in South Africa[60], but little is documented about their association with abortion in wild species in Africa. Serological evidence of brucellosis and abortion were reported in wildlife in USA[61] where *B. abortus* was isolated for the first time from an aborted female bison[62]. In addition, *Brucella abortus* biovar 1 was isolated from a bison (*Bison bison*) fetus collected in Yellowstone park[70]. In Africa, different studies are reporting on prevalence of brucellosis in wildlife[61,71–73], but little is known about the association of abortions occurrence with infectious diseases including brucellosis in wild species.

Detection of the causes of abortions

The role of infectious agents could be less important if the presence of organisms does not necessarily indicate a causal association with abortion, although the reports indicate 20-30% of their implication in abortions cases diagnosed in laboratories[74]. The detection of the causes of abortions in the population may be done by serological assay, immunological, bacteriological and molecular techniques, based on clinical evidences. The seroepidemiological approaches can establish a high degree of association between infections and the abortion level in the farm[75]. However, it is difficult to establish that *Brucella* is a cause of abortion based on serological results only. Furthermore, the gold standard for the diagnosis of brucellosis is isolation and identification of the causative bacterium in a biological containment level three[76]. In humans, the history of the patient, the physical examinations, a pelvic ultrasound, the laboratory orientation may be the foundation for a detection of causes of abortions[77].

Management of abortions

In humans, abortions may require expectant management for up to two weeks, and medical therapy which can usually give successful results[78]. In animals, vaccination contributes a lot to protection against infectious diseases of public health importance[79]. Neosporosis, one of the economically most important causes of abortion in cattle, has prompted researchers to invest in the development of measures to prevent infection of cattle by vaccination[80]. However, there are

Table 1: Infectious agents which can cause abortions in humans and animals

Host	Bacteria	Virus	Fungi	Protozoans	References
Humans only	***Staphylococcus aureus, Ureaplasma urealyticum*** ***Mycoplasma hominis*** ***Treponema pallidum***	***human immunodeficiency Virus*** ***Dengue virus*** ***Influenza virus*** *Herpes simplex virus*		***Plasmodium***	18,63,64
Humans and Animals	*Brucella* *Leptospira Salmonella* *Listeria*			*Toxoplasma gondii* *Chlamydia* *Mycoplasma*	48,51,62,65,66
Animals (domestic and wildlife)	*Campylobacter (vibrio)* *Arcanobactericium (Actinomyces)* *Escherichia coli* *Streptococcus Zooepidemicus* *Rhodococcus equi* *Leptospiras interrogans*	*Phlebovirus* *Aphthovirus* *Bovine herpes virus-1* *Equine herpes virus-1* *Bovine viral diarrhea* *Border disease* *Mycoviruses* *Bluetongue* *Parvovirus* *Suid herpisvirus 1* *Equine viral arteritis*	*Aspergillus* *Mucor* *Candida*	*Neospora caninum* *Trichomona fetus* *Coxiella (Q fever)* *Coccidia* *Babesia* *Trypanosomum equiperdum*	12,44,48–50,52,54,58,67–69

vaccines which may cause abortions in pregnant animals. In case of abortions due to infectious diseases such as brucellosis, a good disposal of aborted materials and culling are required to avoid the human contaminations and the dissemination of infectious agents in the herd.

The impact of abortions in humans and animals

The economic impact of abortions

The economic impact of abortions in animals can be evaluated based on direct costs (value of fetuses lost) and indirect costs: establishing the diagnosis, re-breeding cows that aborted, possible loss of milk yield, and replacement costs if cows that aborted are culled[74]. Abortions in domestic animals are of great concern to farmers because the fetus that would form replacement stock is lost and a prolonged period of uterine disease and infertility or sterility may follow leading to unproductive females being maintained for long periods[81]. Some loss estimates around US $110.00 for abortions caused by *Neospora caninum* in a pregnant dairy cow in USA[82]. Abortions extend calving interval and increase culling and the economic evaluation from each pregnancy loss was estimated at approximately $2,333 in Korea[83]. In Burkina Faso, a study reported an impact of the spontaneous abortion in women of US $56 (27 668 CFA) and underlined the high expenses with short-term economic repercussions on households' poverty[84]. In sub-Saharan Africa, very few articles focused exclusively on the cost of treating abortion complications in humans, but authors agreed that it consumes a disproportionate amount of hospital resources[85]. In fact, the number of fetus including the milk losses due to abortions in animals are easy to quantify whereas in humans the fetus including the emotion stress associated to abortions are difficult to measure.

Economic impact of abortions due to brucellosis

Higher productivity losses are associated with higher prevalence of brucellosis. *Brucella* seropositive animals have higher rates of abortion, stillbirth, infertility and calf mortality, as well as reduced growth and longer calving intervals. Often, infected females will abort only once, although they may remain infected their entire life. Studies on the economic production losses of bovine brucellosis are reasonably consistent across a range of production systems in Africa and Asia[13].

Table 2: Papers reviewed per region and species on the contribution of brucellosis to abortions in Africa

Region	Countries	Humans	Dom. Animals	Humans & dom. animals	Wildlife	Total	References
North Africa	Morocco, Egypt, Tunisia	1	3	0	0	4	[94–97]
West Africa	Nigeria, Niger	0	3	0	0	3	[12,98,99]
Central Africa	Cameroon, Chad	0	1	0	0	1	[86]
East Africa	Tanzania, Kenya, Rwanda, Ethiopia	1	3	2	0	6	[100–105]
Southern Africa	Zimbabwe, Zambia, South Africa	1	3	0	0	4	[106–109]

In African regions where the infection rate is 30% for bovine brucellosis in breeding females (20% of the herd), the result in economic losses approximate to 5.8% of gross income per animal reared[86]. In Mongolia, after estimating the proportion of abortions among brucellosis seropositive animals, a mass vaccination program was implemented with a cost of $8.3 million[87,88]. If the costs of the vaccination were shared between the livestock and public health sectors, the intervention may be cost-saving and cost-effective. In Ethiopia, the economic impact of abortions due to brucellosis in camels was estimated to 21% of the total cost[89] while in Sudan it was representing 8.2% of the total losses due to bovine brucellosis[90].

The public health impact of abortions

Aborting animals shed large quantities of infectious agents and pose considerable risk to humans in contact. In some cases, consumers may also be at risk; for example, *Coxiella burnetti*, responsible for Q-fever, can be excreted in the milk of aborting goats for up to 52 days[91]. The disposal of aborted fetuses might be well managed to avoid humans and animal exposure to the pathogen. The human assistance rendered during parturition in abortive cattle, sheep or goat has been associated in some cases to brucellosis infections in humans[92]. Some case of abortive animals could result in infection of entire households when animals are kept in close proximity to living accommodation, or when they are brought inside of houses, especially in severe weather[4].

The social impact of abortions

Abortion is a tragic loss and can be associated with significant psychological problems for women, their partners and families in general. For women who get an experience of spontaneous abortion, it is a stressful event as well as they are not sure to conceive and arrive at term successfully with the next pregnancies. About 1% of couples will experience recurrent spontaneous abortion[93]. In animals, abortions can lead to nutrition insecurity because of the decrease of milk production and loss of calves. In addition, infectious diseases which lead to abortions can unable livestock producers to meet their social obligations such as the man's position, influence and the respect in the community as well as the payment of children school fees, medication, clothes[110,111].

The contribution of brucellosis to abortions observed in humans and animals in Africa

Some studies in this review (5/18) reported data on the abortion associated with brucellosis in Africa[96,100]. These estimates of abortions reported in this review are high (0.17-16.2%) compared to the normal abortion rate, which is ranged between 2-5% in cattle[86]. Domenech *et al.*[112] demonstrated, using a formula, the existence of correlation between the manifestation of brucellosis symptoms and the increases of abortion cases in African cattle. Some authors have also reported the association between brucellosis and abortions observed in Africa based on the calculated odds ratio[101,103].

Table 3: Data extracted from literature on the contribution of brucellosis to abortions observed in Africa

Studies/ species	Study design	Sample size	Samples type	Diagnostic methods	Prevalence	Ethical issues	Abortion rate	(OR)	References
Humans	Case-control	324 women	Blood	SAT	26.8%	Yes	NR	2.3	101
	Cross-sectional	129 women	Blood	SAT	38.8%	Yes	NR	NR	97
	Prospective	125 women	Blood, swabs	NR	4%	NR	NR	NR	106
Humans and domestic animals	Cross-sectional	60 women, 27 cattle	Blood	RBPT	25%	Yes	NR	NR	104
	Cross-sectional	483 cattle, 120 humans	Blood	RBPT, ELISA	0 – 28.95%	Yes	NR	NR	105
Domestic animals	Cross-sectional	20 herds (214 cattle)	blood, swabs, milk	RBPT, culture, RT-PCR	31.3%	Yes	NR	NR	95
	Cross-sectional	23 sheep	Blood		4.34%	NR	7%	NR	96
	Cross-sectional	5192 cattle (681 herds)	Blood, hygromas fluids)	ELISA, MLVA-VNTR	Herd:11.2- 17.2% Individ: 1.3%	Yes	No	3.0	12
	Cross-sectional	24 cattle	Blood	RBPT	15.4 - 85%	NR	0.17- 11.8	NR	86
	Cross-sectional	700 cattle	Blood, milk	RBPT, culture, ELISA, PCR	6.7 – 9%	Yes	NR	NR	107
	Cross-sectional	200 cattle, 50 goats, 35 sheep	Blood, milk, aborted materials	RBPT, ELISA, MRT, culture, PCR, MLVA-VNTR	48%	Yes	NR	NR	102
	Cross-sectional	283 cattle, 756camels, 757 goats	Blood,	RBPT, CFT	Cattle : 10.6% camel : 2.2% goats : 1.9%	Yes	Camels: 23.4% cattle: 13.8% goats 12.4%	cattle: 4.7 goats: 6 9 camel: 1	103

Cross-sectional	886 cattle	Blood	RBPT, ELISA	23.9%	NR	Herd: 50% Individ: 16.2%	3.4	108
Cross-sectional	239 cattle	Blood	RBPT, SAT, CFT	3.8		NR	NR	109
Cross-sectional	28 sheep	Milk, blood, vaginal swab	RBPT, SAT, MRT, culture	14.3%	NR	NR	NR	98
Cross-sectional	22 sheep	Milk	RBPT, SAT, MRT, Culture	14.5%	NR	NR	NR	99
Cross-sectional	260 cattle	Blood	ELISA	16.8%	NR	6.5%	0.7 1.1	100
Cross-sectional	10 cattle, 5 buffalo, 9 goats,1 sheep	Blood	RT-PCR	-cattle: 100%; -buffaloes: 50%; -goats:33.3%; -ewe:100%	NR	NR	NR	94

CFT: Complement fixation test**; ELISA:** Enzyme-linked immunosorbent assay**; MRT:** Milk ring test**; MLVA-VNTR:** Multiple-locus variable number tandem repeat analysis**; RT-PCR:** reverse transcription-polymerase chain reaction**; RBT:** Rose Bengal plate test**; SAT:** Serum agglutination test**; NR:** not reported

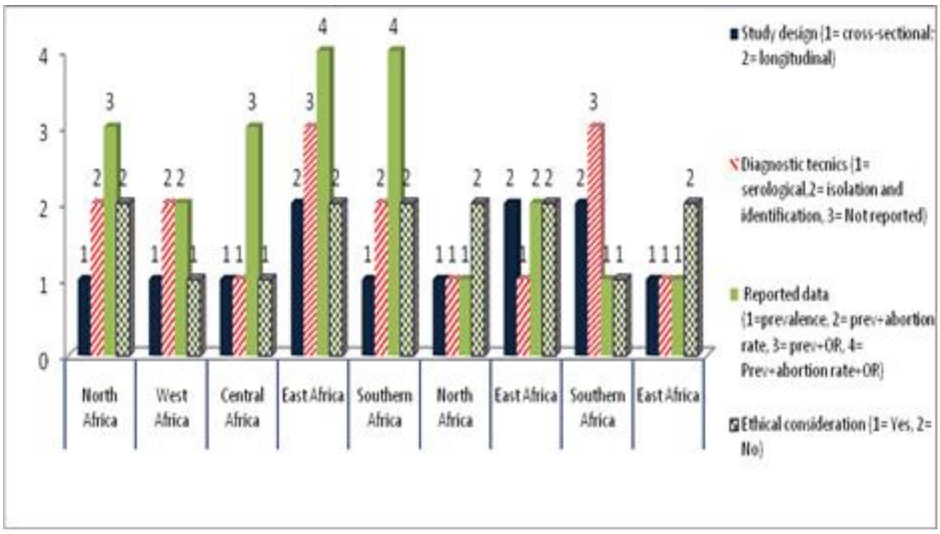

Figure1: The study design, diagnostic methods, reported data, ethical considerations per species and regions to assess the contribution of brucellosis to abortions in Africa

However, some abortions recorded in Africa may be due to co-infections between brucellosis and others infectious diseases[95,100]. Differential diagnosis of brucellosis with others abortive infections prevalent in the study area could reveal the true association between the observed abortions and the prevalence of each disease.

Discussion

Brucellosis is one of the major zoonotic diseases on the African continent and has an economic impact on livestock productivity (abortions, decrease of milk production). The syndrome of abortion affects the household's income and constitutes a risk factor for the dissemination of *Brucella* in humans and animals. A review of online literature has been done with an objective of assessing the contribution of brucellosis to abortions in humans, domestic animals and wildlife in Africa. The association may exist between brucellosis and abortions in animals which manifest clinical symptoms for this disease in Africa[12], and a correlation exists between the manifestation of brucellosis symptoms and the increases of abortion cases in African cattle[86]. Some events at farm or risk group level such as exposure to aborted materials, unpasteurized milk consumption, artificial insemination, could be recorded during follow up for completing the differential diagnosis with other prevalent infectious diseases related to abortions. The high prevalence of brucellosis in cattle reported in Africa is most of time associated with abortions[13]; around one fifth of cows may abort where seroprevalence is higher than 30%.

Actually, studies on the seroepidemiology of brucellosis in Africa are reported with an improvement in the sample size calculation and sampling methods, the diagnostic methods, the ethical considerations[98,101,113]. However, in this review the sample size and type varied from studies, species and regions in Africa (Tables 2 and 3). This could be because brucellosis is a herd level disease: an occurrence of abortion in risk groups is enough to start investigation. Otherwise, the large sample size and appropriate sampling method is very important to determine the association between brucellosis and observed abortions. Methods used for the diagnosis of brucellosis in the reviewed papers include: RBPT, ELISA, MRT, SAT, culture, identification and molecular characterization of *Brucella* species (Figure1). The serologic methods are the most used in Africa to determine the role played by brucellosis in abortions even if these tests are known to be less specific, and the results can be biased with false positive because of some cross-reactions with other bacteria. However, the contribution of brucellosis to abortions is less highlighted by molecular techniques[114,115], although this disease is considered to be one of the major causes of abortions in cattle in Africa[109,116]. In this review, *Brucella abortus* seemed to be the specie most associated with abortions in Africa[12,99,102,109]. Generally, the cost of molecular techniques could be a challenge to African countries. However, this technique could be a good way to detect the presence of infectious agents in aborted materials and to assess the real contribution of brucellosis in abortions recorded in humans and animals on the continent. Molecular epidemiology could contribute as a tool for identification and characterization of *Brucella* species from aborted animals, determining their origin and possible spillover to other species (especially wildlife). Studies could extend their exploration to the presence of *Brucella* in the human aborted materials or breast milk after abortions, this will complete data on seroprevalence studies and questionnaire surveys in Africa.

In this review, studies reported abortions associated with brucellosis in Africa, focusing much on domestic animals[94,98,103] and less in humans (Tables 2 and 3). Although some authors reported the association between brucellosis and the observed abortions in humans in Africa[97,101,104,106], the pathogenesis of brucellosis in pregnant women still remains to be elucidated. However, the abortion process is well described in animals due to the role played by erythritol (sugar), which may confer the tropism for *Brucella* development in the uterus. Nevertheless, out of Africa, it has been suggested that brucellosis may cause higher rate of abortions, more frequently than do other bacterial infections in pregnant women[115]. Furthermore, in situations where brucellosis is suspected to be a cause of abortions in pregnant women, laboratory analyses are required to confirm the role played by others febrile diseases (such as malaria) or abortive infectious diseases (Rift valley fever, Toxoplasmosis) which are equally prevalent in Africa. The clinical symptoms observed in pregnant women could complete the differential diagnosis with the prevalent others abortive and febrile diseases. Furthermore, this gap can be rectified by applying for the confirmation of the brucellosis in humans based on isolation and molecular techniques.

Generally, no evidence of abortion due to this disease has been documented in wildlife; despite the findings from a single study that reported the impact of brucellosis on abortions in the wildlife-livestock interface[103]. In Africa, interactions are observed between domestic and wild animal species in pastoral farming systems where they may be exposed to aborted materials, when sharing the same pasture or common source of water. Furthermore, smallholder farmers might be affected by the abortions exposure due to brucellosis because of the cut and carry as feeding system[117].

Study Limitations

Eighteen papers were used to extract data because they reported on the role played by *Brucella* infections on abortions observed in animals and humans in Africa (Tables 2 and 3). However, the quality of this review could have been affected by the lack of assessment of bias in the studies, the non-inclusion of statistical management of data, also with the restriction of the study area only to Africa. Nevertheless, these limitations may be avoided by a systematic review (instead of a review) if published data on the contribution of brucellosis to abortions in humans and animals in Africa could have been found with a significant number of papers. Most of the studies reviewed were cross-sectional in design (Figure1). Despite of their time consuming, the loss of subjects (attrition) and the limitations of budgets for research, case control and longitudinal studies could reflect possibly good observations with clinical evidence during the assessment of the contribution of brucellosis to abortions in Africa.

Conclusion

Brucellosis is reported in Africa with high prevalence in humans and animals. However, there is limited published data about the contribution of this zoonotic disease to abortions in humans and animals. The literature reviewed stated little about the estimation of the abortion rate and the calculated odds ratio which are strong indications of association between brucellosis and abortions in humans and animals in Africa. More data are reported by eastern and southern parts of Africa on the assessments of the contribution of brucellosis to abortions, but generally in Africa, there is a lack of a rigorous sample size calculation, an inadequate study design planning, and ethical clearance considerations are also required. The identification of the causes of abortions in Africa, specifically the role played by brucellosis, is based on routine test (RBT) and immunological diagnosis (ELISA); but, the detection should be based on more definitive methods such as isolation and molecular characterization from blood, milk and aborted materials. Furthermore, little is reported about the association of brucellosis to abortions in humans (five papers out of 18). As the causes of abortions are multiple, the clinical observations in humans and animals could complete the differential diagnosis with the prevalent abortive diseases. In addition, the contribution of brucellosis to abortions in wildlife in Africa is not elucidated in the literature, and, the economic impact evaluation of abortions in the herds due to this disease remains to be completed. The epidemiologic approach based on collecting core data concerning both aborted and non-aborted individuals (humans and animals) could determine the contribution of brucellosis to abortions in populations and could help to monitor the prophylaxis in humans and the progress of vaccination programs in animals. Due to the strong interactions in the human-livestock-wildlife interface in Africa, the contribution of brucellosis to abortions calls for the interdisciplinary collaboration for its understanding and controlling.

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Contribution of Authors

The first and the fourth authors prepared the manuscript for publication. All the authors mentioned in the article reviewed the final version and they approved the manuscript.

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