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2022-11-17

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CABI One Health

https://doi.org/10.1079/cabionehealth.2022.0008

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Bwatota et al.
CABI One Health (2022)
https://doi.org/10.1079/cabionehealth.2022.0008

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SYSTEMATIC REVIEW

OPEN ACCESS

Epidemiology of Q-fever in domestic ruminants and humans in Africa. A systematic review

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Abstract

Q-fever is a zoonotic infectious disease caused by the gram-negative, intracellular, spore-forming bacterium *Coxiella burnetii*. Infected ruminants (cattle, sheep, and goats) are the reservoirs of the pathogen and thus an important source of infection in humans. This systematic review aims to consolidate the knowledge and awareness of Q-fever in Africa and identify future research opportunities and possible interventions in low-resource settings. We review information on Q-fever epidemiology and the diagnostic challenges in humans and domestic ruminants in Africa from the last 23 years. Six databases including university repositories were searched for relevant articles. A total of 84 studies and 4 theses met the selection criteria and were thus included in the review. They include serological and molecular studies of Q-fever in humans or domestic ruminants in 24/54 African countries. The mean seroprevalence estimates were 16% (95%CI 11–23%) in humans; 14% (95%CI 10–20%) in cattle; 13% (95%CI 9–18%) in sheep; and 21% (95%CI 15–29%) in goats. The mean prevalence for molecular detection of the pathogen were 3% (95%CI 0–16%) in humans; 9% (95%CI 4–19%) in cattle; 16% (95%CI 5–41%) in sheep; and 23% (95%CI 20–80%) in goats. The number of studies that identified risk factors for exposure among domestic ruminants was: sex (n = 6), age (n = 17), contact with other animals (n = 5), lack of quarantine of newly purchased animals (n = 1), extensive grazing system (n = 4), herd size (2), history of abortion (n = 5), absence of vaccination (n = 2), and high temperature (n = 1). The number of studies that reported protective factors was: sanitation (n = 2), burying and/ or burning the aborted foetus (n = 2), and young (age) (n = 2). The studies that identified risk factors for human disease infection included: close contact to animals (n = 7), age (n = 3), and gender (n = 5), while those identifying protective factors included: living in non-irrigated areas (n = 1), awareness/knowledge about zoonosis (n = 1), rodent control (n = 1), sanitation/disinfection of equipment after and before use (n = 1), occasional grazing (n = 1), and do nothing to aborted materials (n = 1). Diagnostic challenges such as poverty, lack of a well-equipped laboratory with biosafety level 3 specific for Q-fever testing, unspecific and self-limiting clinical signs/symptoms, lack of gold standard test, and variation in test specificity and sensitivity were identified. The disease is likely to be widespread in Africa and of public importance and underreported thus 'One Health' approaches to future studies are recommended. Further studies should focus on concurrent studies of human and livestock populations.

One Health Impact Statement

This review applies to One Health stakeholders including, the public, players in the livestock value chain, animal/ human/ environmental health workers, policy makers, and other implementers. This review summarizes the available information regarding Q-fever (*Coxiella burnetii*) in animals and humans in Africa, providing new information on the magnitude of the disease, and risk factors for infection. This information highlights the need for collaboration among One Health stakeholders and multisectoral cooperation towards achieving the One Health goals. The sharing of knowledge generated through research from academic, non-academic, and local/ indigenous knowledge will allow a new foundation for disease control that is applicable and beneficial to all stakeholders under the One Health umbrella rather than academic scientists alone.

Keywords: Q-fever, Coxiellosis, *Coxiella burnetii*, epidemiology, ruminants, humans, Africa

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Received: 17 August 2022. Accepted: 13 October 2022. Published: 17 November 2022.

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Introduction

BACKGROUND INFORMATION

Q-fever is a zoonotic disease caused by the unique gram-negative, obligate intracellular, and spore-forming bacteria, *C. burnetii* (Miceli et al., 2010; Tesfaye et al., 2020). The organism and the disease it causes are distributed worldwide, except in New Zealand and Antarctica (Tagesu, 2019; WHO-FAO-OIE, 2004). It has been reported in a wide range of host species including wild animals, zoological collections, domestic ruminants, camels, rabbits, rodents, tortoises, lice, ticks, and humans (Amanzougaghene et al., 2017; Eldin et al., 2017; Tagesu, 2019; Theonest et al., 2020). *C. burnetii* exists in two morphological forms namely the large and small-cell variants (LCV and SCV). The LCV is the reproductive form while the SCV is the spore-like form which is non-reproductive, metabolically dormant, and persists for a long time in the environment (Coleman et al., 2004). Its ability to withstand environmental stresses means that once *C. burnetii* is deposited in the environment it can be exposed to a diverse range of hosts (Coleman et al., 2004; Eldin et al., 2017). Furthermore, animal trade, the porous nature of country borders, and the illegal hunting of wild herbivores for game meat contribute to the spread within livestock (Loibooki et al., 2002; Wardrop et al., 2016). The lack of knowledge regarding the epidemiology of the disease among pastoral communities, veterinarians, and medical/public health experts as well as the fragmentation and lack of coordination of medical, public health, and veterinary systems further contribute to the global spread of *C. burnetii* in both humans and animals (Eldin et al., 2017; Koka et al., 2018; Rahaman et al., 2019; URT, 2020; Vanderburg et al., 2014).

Livestock production in both rural and urban areas in Africa has contributed significantly to providing sources of protein, food security, employment, and income. In addition, livestock is an important component of many traditional, cultural, and religious practices such as naming ceremonies, marriage dowry, tribal rituals, and spiritual ceremonies (Abdullah et al., 2019; Hussien et al., 2017; Rahal et al., 2018). However, various challenges have resulted in livestock keepers not achieving the anticipated yields from their livestock. For instance, several challenges, including lack of grazing land, low animal feed quality and lack of supplies, lack of veterinary and health support, and poor levels of animal husbandry have been identified as contributing to poor animal health and increased susceptibility to infectious diseases such as Q-fever (NORD, 2021; Omitola & Taylor-Robinson, 2020; Pandit et al., 2016). The World Health Organization (WHO) has linked Q-fever to other neglected zoonotic diseases which are characterized as affecting poor and marginalized populations in low-resource settings, have direct and indirect modes of transmission, and spread especially in communities where people are in close contact with livestock and wildlife (Cook, 2014; Gummow, 2003; Kazwala, 2016).

Domestic ruminants (cattle, sheep, and goats) are documented as the primary reservoir of the organism (Anastácio et al., 2016; Martins-Bessa et al., 2020; Tagesu, 2019). Susceptible animals acquire infections through inhalation of the organism in fine-particle aerosols, by ingestion through grazing contaminated pastures, or by tick bites (Benaissa et al., 2017; Everman James, 2019; Guo et al., 2019). In livestock, infection with *C. burnetii* is often asymptomatic but can lead to abortion (Ameur et al., 2018; Derdour et al., 2017; Emery et al., 2014). Though it may also affect other organs such as liver, spleen, and lungs (Ndeereh et al., 2017). The infected animals shed the pathogen into the environment via the aborted and birth materials, vaginal discharges, urine, feces/manure, milk, and semen (Anastácio et al., 2016; CFSPH, 2017b; Tagesu, 2019).

The proximity of humans to domestic ruminants contributes significantly to the spread of the disease through direct contact with infective material or inhalation of aerosolised particles from infected animals (CFSPH, 2017a; Ndeereh et al., 2016). People working closely with livestock such as slaughterhouse workers or animal health experts or farmers/herds(wo)men handling birthing materials are particularly at high risk (Cook, 2014; Lacheheb & Raoult, 2009). Furthermore, Q-fever has been identified as a co-infection with diseases such as malaria, tuberculosis, and HIV in humans in tropical and subtropical Africa (Dhaka et al., 2020; Khaled et al., 2016). Upon inhalation of aerosols or ingestion of the pathogen, humans develop acute, self-limiting and non-specific symptoms such as high fever, severe headache, vomiting, pneumonia, fatigue, and chills or chronic symptoms such as endocarditis, hepatitis, osteomyelitis, endovascular infections, and sometimes spontaneous abortions in pregnant women (NORD, 2021).

Q-fever in humans is treatable with antibiotics characterized by high cell membrane permeability such as macrolides, quinolones, and tetracycline (Flores-Ramirez et al., 2014) after laboratory confirmation of the disease. However, a big challenge remains to identify cases through active surveillance and there is a need for highly sensitive and specific diagnostics that are affordable in low-middle-income countries (LMICs). For example, a narrative review reported challenges such as poor timing and storage of samples prior to testing, poor quality surveillance data, and high costs in terms of testing, compounded the more widely recognized problems of test accuracy (Semret et al., 2018). Also, a study in Kenya found that patients with Q-fever were likely to leave the hospital without specific treatment for Q-fever due to misdiagnosis (Njeru et al., 2016). Therefore, the lack of diagnostic tools to differentiate Q-fever (and other zoonoses) contributes to misdiagnosis and mistreatment of febrile illnesses in LMICs as malaria and typhoid in humans (Dhaka et al., 2020). Serological tools such as enzyme-linked immunosorbent assay (ELISA), and immunofluorescence assay (IFA) have replaced the conventional isolation of the bacterium due to the hazards and costs associated with handling the organism in biosafety level (BSL)-3 laboratories and the difficulty of purifying *C. burnetii*. However, antibody based tools only provide information on exposure and suffer from relatively poor specificity and sensitivity and inconsistencies (Chen et al., 2014). Increasingly molecular tools that can directly identify the organism and thus infection are also now becoming more widely used. Polymerase chain reaction (PCR) linked to sequencing/genotyping are fast, specific, relatively easy to deploy in low resource settings and can confirm the pathogen from multiple sample types such as vaginal swabs, feces, semen, blood, plasma etc. However, molecular tools are more expensive and require better trained staff and equipment than is often available in low resource settings (Frangoulidis et al., 2012).

Generally, people and animals in LMICs have a high risk for the disease/infection, yet there is inadequate screening, especially in domestic ruminants which are reported to be the primary source of infections in humans (Maina et al., 2014). Several studies have reported the endemicity and underreporting of the disease in Africa, especially in rural areas where pastoralists are living in close proximity to their animals (Abdullah et al., 2019; Elelu et al., 2019; Salifu et al., 2019). In addition to human infections, the disease results in direct economic losses for livestock keepers due to increased abortion rates and loss of milk production on infected farms (Canevari et al., 2018). Infections in animals are linked to a lack of knowledge, awareness, and diagnosis of the disease among veterinarians and public health experts as well as farmers (Alonso et al., 2015; Ndeereh et al., 2016; Porter et al., 2011).

Therefore, the paper aimed to review the literature on Q-fever epidemiology and the diagnostic challenges in humans and domestic ruminants in Africa since 2000.

Materials and methods

SEARCH STRATEGY

A thorough and comprehensive search of the literature was carried out to identify studies associated with human, domestic ruminant

Q-fever in Africa. To retrieve all related information, a Boolean operator ("OR" and "AND") with a combination of keywords was set and Scopus, PubMed, HINARI, African Journals Online (AJOL) Google Scholar (reached via Research4Life using NM-AIST library account), databases, university repositories, and conference books of abstracts were used to retrieve published papers, peer-reviewed articles, theses, case reports, posters, and conference presentations. In addition, article references were cross-checked and saved as the source of studies included in this systematic review. Five databases were searched for relevant articles using the search string *("Q-fever" OR "C. burnetii" OR "q-fever" OR "Coxiella") AND ("epidemiology")* AND *("small ruminants" OR "ruminants" OR "humans" OR "human" OR "children" OR "cattle" OR "sheep" OR "goats") AND ("Africa" OR "African" OR "Algeria" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Congo" OR "Cote d'Ivoire" OR "Ivory Coast" OR "Zaire" OR "Djibouti" OR "Egypt" OR "Equatorial Guinea" OR "Ethiopia" OR "Eritrea" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Libya" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Morocco" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Reunion" OR "Rwanda" OR "Sahara" OR "Sao tome" OR "Senegal" OR "Somalia" OR "South Africa" OR "Sudan" OR "Swaziland" OR "Togo" OR "Tanzania" OR "Tunisia" OR "Tunis" OR "Uganda" OR "Zambia" OR "Zimbabwe"*) with a publication limitation January 2000–April 2022.

The Mendeley (Mendeley.com) software was used to manage citations. Duplicate entries were identified by considering the author, the year of publication, the title of the article, and the volume, issue, and page numbers of the source. The following criteria were used to screen abstracts, full original research articles, and case studies on Q-fever epidemiology and diagnostic challenges in domestic ruminants (cattle, sheep, and goats) and humans in Africa: (1) published in the English language between January 2000 and April 2022; (2) sero/prevalence data included and (3) some information relating to diagnostic tests provided. In general, non-peer-reviewed or reviewed articles were excluded. A validity assessment was done after applying the forementioned screening steps, and the full text of each selected article was retrieved for detailed analysis.

Disease sero/prevalence data whether individual or herd were directly obtained from the respective studies. Other information gathered were species (animal/humans), sample size, sample collected, risk/protective factors, diagnostic test used, study design, and paper type (study or publication). Data were collected, entered in a Microsoft Excel spreadsheet, and saved as CSV (Comma delimited) (*.csv) and all statistical analyses were performed using R version 4.2.0 (2022-04-22 ucrt) and Platform: x86_64-w64-mingw32/x64 (64-bit).

Meta-analysis was done using only cross-sectional studies with the *metafor* R package (Viechtbauer, 2010). The sero/prevalence of the respective species was estimated and presented in forest plots subdivided by country and author/reference using *forest.meta* function. The African map was filtered from the world map using *data* function of *spData* R package (Nowosad, 2021) and then joined with our dataset to specifically align the number of studies for sero/prevalence with the respective country. Other R packages used in the analysis were *tidyverse* (Wickham et al., 2019), *janitor* (Sam et al., 2021), *sp* (Bivand et al., 2013), *sf* (Pebesma, 2018), *spDataLarge* (Nowosad, 2021), *leaflet* (Wickham et al., 2022), *tmap* (Tennekes, 2018), *RColorBrewer* (Neuwirth, 2011), *ggplot2* (Hadley, 2016), *meta* (Balduzzi et al., 2019), and *dmetar* (Harrer & Ebert, 2018).

Results

We identified 84 studies and 4 publications (theses) that were included in this review after thorough screening as shown in the PRISMA chart Figure 1.

The results of 88 retrieved articles were summarized in Supplementary Tables 1–3 indicating the distribution, species affected, sero/prevalence, and diagnostic tests used.

Q-FEVER IN DOMESTICATED RUMINANTS AND HUMANS

Out of 88 studies and publications screened, the majority n = 78 were cross-sectional studies, 5 prospective cohort studies, 3 case-studies, and 2 retrospective cohort studies. In addition, 63 studies reported on domestic ruminant species, 10 studies on both (domestic ruminants and humans), and 15 studies reported on humans only. Furthermore, among all reviewed studies and publications 63 studied the epidemiology of antibodies against *Coxiella burnetii* at the individual animal/human level while 3 reported at the herd/flock level (Supplementary Table 1). On the other hand, 19 (17 cross-sectional and 2 case-studies) papers reported on the detection of *C. burnetii* DNA in humans and domestic ruminants at the individual level (n = 18) and herd level (n = 1) (Supplementary Table 2) which suggests active infection. Although several diagnostic tests were deployed for Q-fever diagnosis, 67 papers reported using an antibody ELISA/iELISA (Supplementary Table 1).

EPIDEMIOLOGY SERO/PREVALENCE OF Q-FEVER IN DOMESTIC RUMINANTS IN AFRICA

The majority of studies were conducted in northern (n = 25), western (n = 16), and eastern (n = 18) African subregions with fewer studies in southern (n = 5), and central (n = 4) Africa.

There were large differences in the number of molecular (n = 12) and seroprevalence (n = 58) studies performed among domestic ruminants in Africa Figure 2A and B.

The forest plots further demonstrate the mean prevalence estimate by species and country (Figures 3–6).

In North Africa, the overall seroprevalence of Q-fever in domestic ruminants ranged from 0% to 37% with reports from Algeria (n = 2), Egypt (n = 7), and Sudan (n = 2). On the other hand, the prevalence for molecular detection of *Coxiella burnetii* DNA ranged between 2% and 91% in Algeria (n = 3), Egypt (n = 2), Tunisia (n = 1). Most of these studies were conducted in farms/flocks with a high prevalence of abortion where veterinarians were ill-informed about the disease. For instance, a study by Dechicha et al. (2010) reported Q-fever in a dairy farm where abortion was prevalent, and veterinarians considered brucellosis before the laboratory confirmation.

In West Africa, studies were conducted in Nigeria (n = 8), Mali (n = 1), The Gambia (n = 2), Côte d'Ivoire (n = 1), Ghana (n = 2), Guinea (n = 1), and Togo (n = 1). Disease seroprevalence across these countries ranged between 2.3% and 55.3% and prevalence for molecular detection of *C. burnetii* DNA ranged between 3% and 47.2% in domestic ruminant species.

Few studies were conducted in central/middle Africa (4) including Chad (n = 2), and Cameroon (n = 2) with the disease seroprevalence in domestic ruminants ranging from 4.0% to 31.3%. In addition, studies conducted in southern African countries included Namibia (n = 1) and South Africa (n = 5) with a seroprevalence of 4.3–38.0% in domestic ruminants whereas, in eastern African countries including Tanzania (n = 1), Kenya (n = 10), Ethiopia (n = 4), and Zambia (n = 2) the overall seroprevalence ranged between 0.0% and 89.7% and molecular detection of *C. burnetii* DNA ranged between 2.1% and 7.8% in domestic ruminants. In addition, one molecular prospective study conducted in Tanzania from abortive samples (vaginal swabs) reported a prevalence of 22.5%, 24.5%, and 27.3% in cattle, goats, and sheep respectively.

There were 33 studies that reported seroprevalence in cattle. The mean seroprevalence for cattle in Africa was 14% (95% CI 10–20%) (Figure 3). There was at least one seroprevalence study of Q-fever

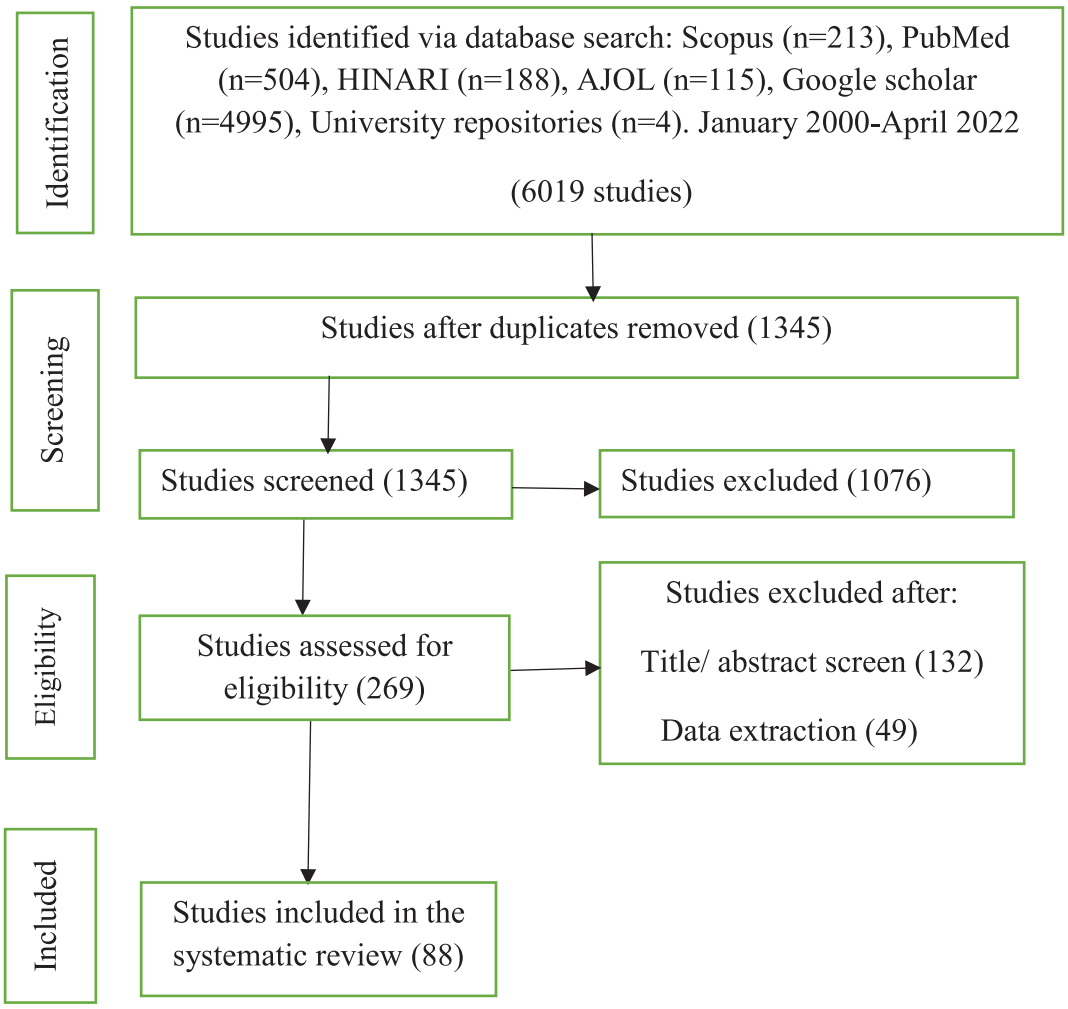


Figure 1. PRISMA chart showing the systematic selection for inclusions and exclusions of articles on Q-fever epidemiology and diagnostic challenges since 2000 in Africa.

in cattle in each subregion and many were conducted in western and eastern subregions. There were Five studies that reported the detection of *C. burnetii* DNA in cattle. The detection was done in vaginal swabs (n = 2) and blood (n = 1) in the eastern region. In northern zone, the detection was done in blood (n = 1), placenta tissue (n = 1), and milk (n = 1). The overall mean prevalence for cattle was 9% (95%CI 4–19%) Figure 7a.

There were 24 studies that reported the seroprevalence of antibodies to *C. burnetii* in goats. The mean seroprevalence for goats was 21% (95% CI 15–20%) (Figure 5). The highest seroprevalence estimates were in Ethiopia followed by Kenya. There were 5 studies that reported the detection of *C. burnetii* DNA in goats. Two studies were conducted in the northern region and reported the pathogen in blood, sera, and raw milk, and the remaining three reported the pathogen in the blood (n = 1) and vaginal swabs (n = 2). The overall mean prevalence for goats was 23% (95%CI 20–80%) Figure 7c.

There were 23 studies that reported the seroprevalence of antibodies to *C. burnetii* in sheep. The mean seroprevalence for sheep was 13% (95% CI 9–18%) (Figure 6) with the highest estimates in west African countries, Mali, and Ghana. There were 8 studies that reported the detection of *C. burnetii* DNA in sheep. Four studies from the northern region reported *C. burnetii* in vaginal swabs, blood, raw milk, and sera. Of the other four, two originated from the eastern which reported *C. burnetii* in vaginal swabs and two from the western reported the pathogen in milk and vaginal swabs. The overall reported prevalence for sheep was 16% (95%CI 5–41%) Figure 7d.

EPIDEMIOLOGY OF Q-FEVER IN HUMANS IN AFRICA

Studies of Q-fever in humans were also conducted in all sub-regions (northern, western, eastern, central, and southern) and included both serology and molecular (Figure 2C and D). Many studies (16) were conducted in eastern Africa (Tanzania, Kenya, Ethiopia) with an overall anti-*C. burnetii* antibodies seroprevalence ranging between 1.9% and 37.1%, and molecular *C. burnetii* DNA detection prevalence of 0.0–2.2%. Most of these studies were done in Kenya (10) compared to other countries: Tanzania (4) Ethiopia (1) and South Sudan (1).

Most of Kenyan human studies (n = 8) reported anti-*C. burnetii* antibodies seroprevalence ranging between 2.2% and 37.10% and others (n = 2) reported *C. burnetii* DNA detection prevalence of 2.2% and 11.10%. Interestingly, antibodies against this pathogen were detected in tourists who participated in a trip to the Masai Mara reserve in Kenya and entered a traditional hut made up of cattle hides, straw, and covered with mud and/or manure (Potasman et al., 2000). In North Africa, only Algeria (1) Egypt (2) and Sudan (1) reported the disease with seroprevalences between 16.0% and 24.2%. A case-study in Tunisia (1) reported a MST5 strain of *C. burnetii* from a patient suffering from severe endocarditis (Delaloye et al., 2018). Only one molecular study was conducted in Egypt and reported a prevalence of 57.1% among farm workers (Khalifa et al., 2010).

Other reports were in west Africa such as The Gambia (n = 2), Ghana (n = 2), and Mali (n = 3). Among seven studies in this

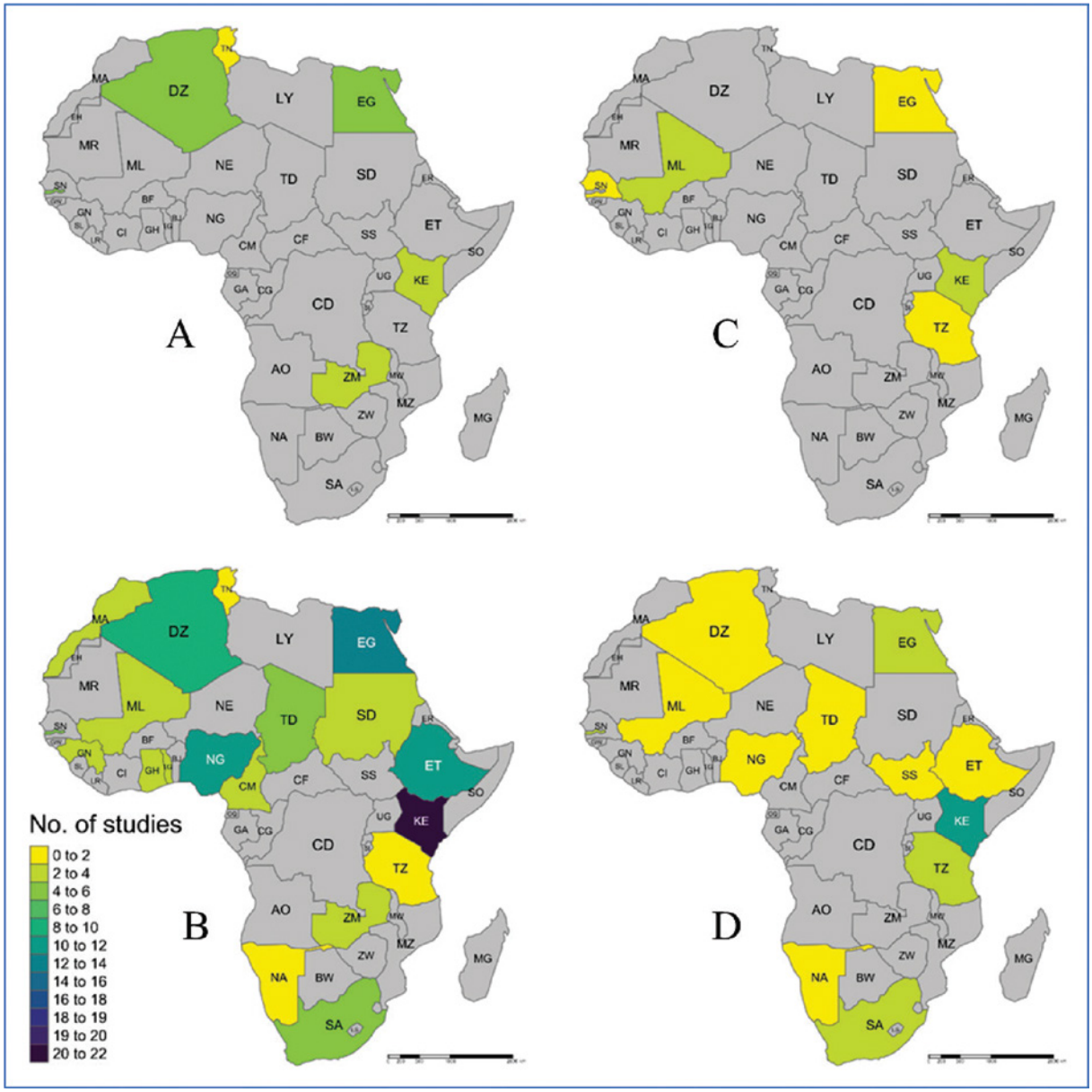


Figure 2. Maps of Africa demonstrating the number of studies in respective countries where seroprevalence and molecular studies were performed. Molecular and seroprevalence studies in animals (cattle, sheep, and goats) are respectively shown in A & B. Molecular and seroprevalence studies in humans are respectively shown in C & D.

subregion, three molecular studies reported a prevalence between 0.5% and 5.1% while other studies reported a seroprevalence between 3.8% and 61.3%. There were only four human-related studies from southern Africa, one from Namibia with a seroprevalence of 26.1% and three from South Africa one having seroprevalence of 27% while the other two having 33% and 38.3%. Studies in Chad (1) and Sao Tome (1) in the central subregion had respective seroprevalences of 1% and 6.7%.

There were 26 studies that studied the seroprevalence of antibodies to *C. burnetii* in humans. The mean seroprevalence for humans was 16% (95% CI 11–23%) (Figure 4) with the highest estimates in Nigeria and the lowest in Guinea.

There were six studies that reported the detection of *C. burnetii* DNA in humans. The *C. burnetii* was detected in different samples including blood (n = 4 with a percentage between 0% and 5%), and the rest in sera with 2% and 57% prevalence Figure 7b.

RISK AND PROTECTIVE FACTORS FOR *COXIELLA BURNETII* INFECTION IN DOMESTIC RUMINANTS

The number of studies reporting different risk factors among domestic ruminants across the continent were as follow; animal intrinsic factors for example age (n = 17), species (n = 7), sex (Females) (n = 6), breeds (n = 2); managemental factors like abortion (n = 5), animal contact (n = 3), animal origin (n = 2), extensive grazing (n = 4), herd-herd contact (n = 2), lambing (n = 1), new animals (n = 1), no vaccination (n = 2), nuisance animals (n = 2), parity (n = 2), semi-intensive (n = 1) herd-size (n = 1), and geographical/environmental factors such as location (n = 2). On the other hand, the number of studies reporting different protective factors were: age (n = 2), sanitation (n = 2), and precipitation (n = 1). Further pieces of information regarding the increased odds (risks) and decreased odds (protective factors) in cattle, and small ruminants (sheep and goats) are summarized in Supplementary Tables 4 and 5 respectively.

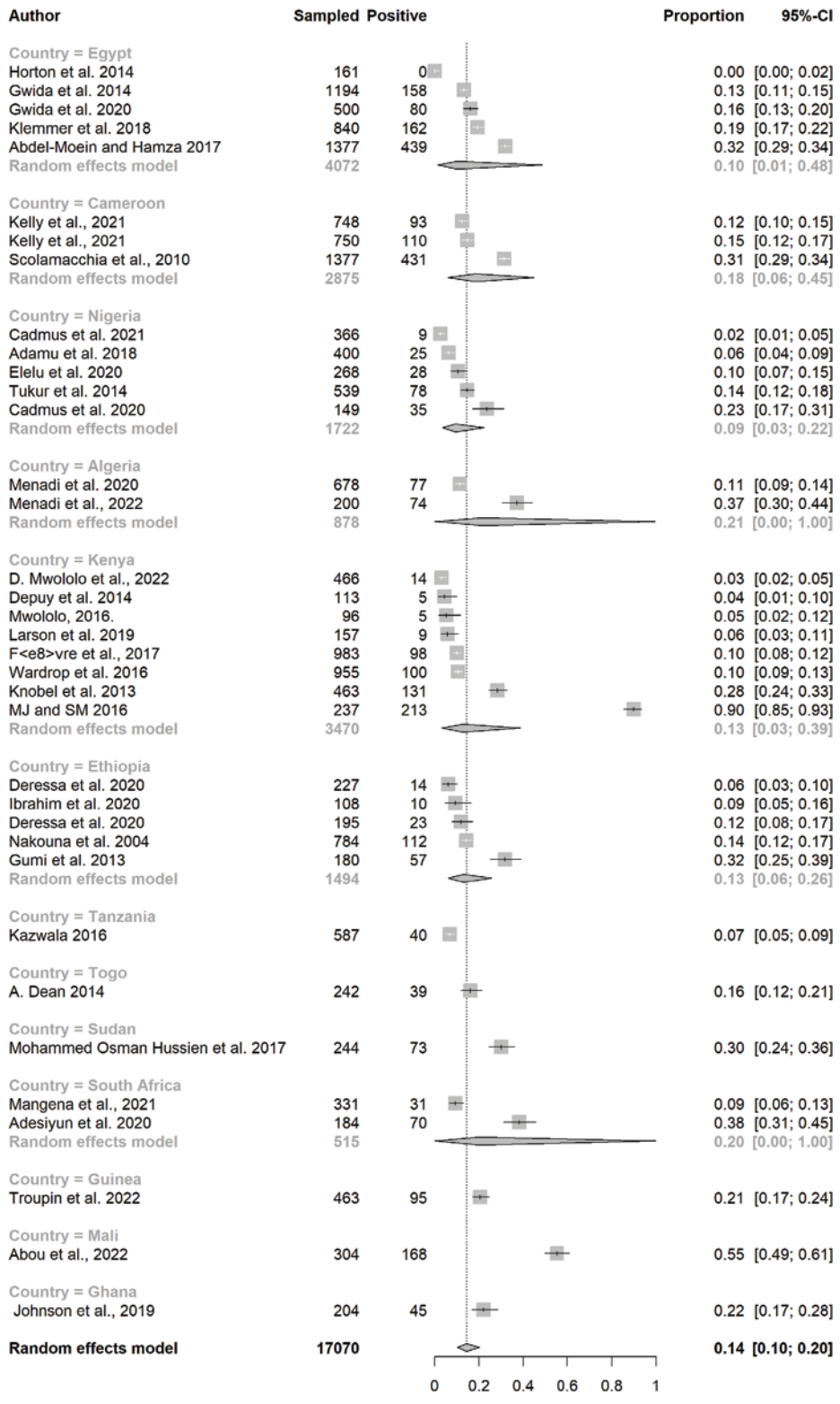


Figure 3. Cross-sectional meta-analysis studies by country, author, total population, positives, proportions, and 95%CI and species (cattle). Forest Plot represents seroprevalence (Antibodies) studies.

RISK AND PROTECTIVE FACTORS FOR *COXIELLA BURNETII* INFECTION IN HUMANS

The most common disease risk factors in humans were reported in different studies. For instance, occupation (n = 8), followed by animal contact was highly reported (n = 7), then sex (n = 5), and age (n = 3). The other risk factors such as living in rural areas, the onset of the rain season, and disease clinical signs/ lesions (e.g., hepatomegaly, splenomegaly, anemia, leukopenia, jaundice) were reported in one study each. On the other hand, high education (n = 2), preventive measures like rodent control (n = 1), animal quarantine (n = 1), and sanitation (n = 1) were reported as protective factors (Supplementary Table 6).

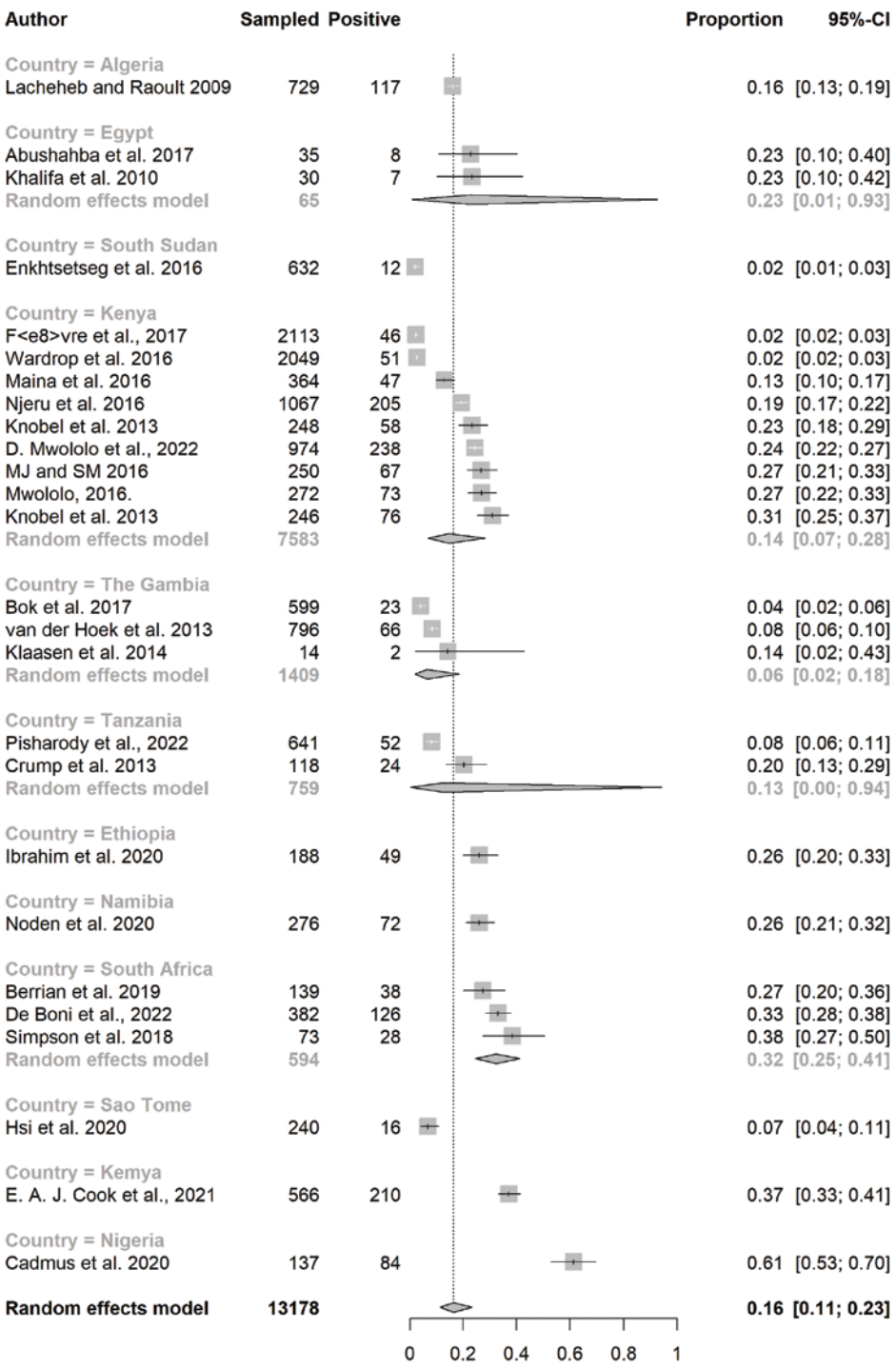


Figure 4. Cross-sectional meta-analysis studies by country, author, total population, positives, proportions, and 95%CI and species (humans). Forest Plot represents seroprevalence (Antibodies) studies

DISEASE DIAGNOSIS

Almost 80% of the studies conducted in five African sub-regions both in humans and animals (domestic ruminants) were focused on detecting antibodies against *C. burnetii* in serum by using ELISA and IFA compared to molecular diagnostic tests to detect the *C. burnetii* DNA and antigens (Figure 8A–D). This signifies that most studies intended to determine disease exposure through serology in the respective subregion compared with few molecular studies investigating active infections. Furthermore, Figure 8A–D shows the diagnostic tests done in respective studies and countries in humans, sheep, cattle, and goats.

Discussion

Twenty-four out of the 54 countries in Africa reported Q-fever within the 23 years from 2000 to 2022, and we reviewed a total of 88 studies in five subregions of Africa (Northern, Southern, Eastern, Western, and Central) to assess the magnitude of Q-fever in domestic ruminants and humans and the risk factors associated with

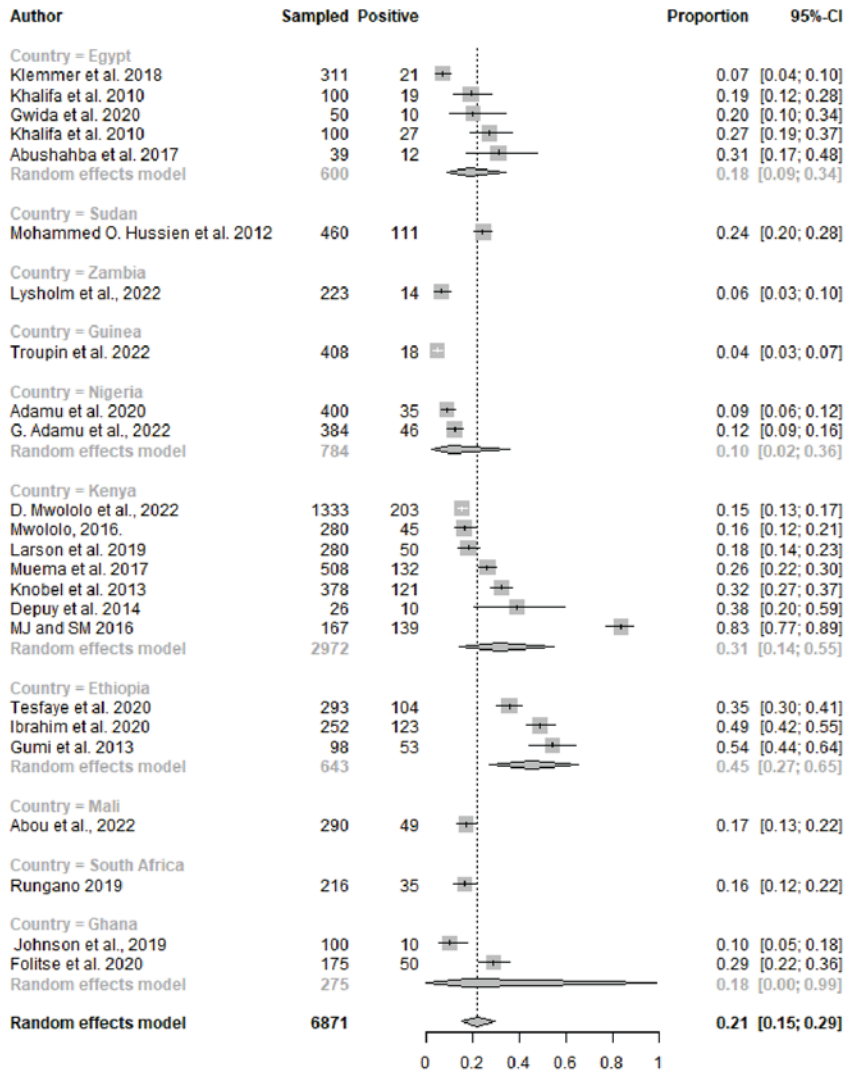


Figure 5. Cross-sectional meta-analysis studies by country, author, total population, positives, proportions, and 95%CI and species (goats). Forest Plot represents seroprevalence (Antibodies) studies.

Coxiella burnetii infection and transmission. The data presented in this review show that the prevalence of Q-fever in domestic ruminants differs among African subregions as also reported by other authors (Van den Brom et al., 2015; Vanderburg et al., 2014). The differences could be associated with various factors. Firstly, the difference in study design, whether sampling is for serosurveillance or active infection and sample size. For example, results both in serology and molecular studies have shown where small numbers were used, the disease prevalence was high compared to other places where large numbers were used. The majority of the studies were cross-sectional seroprevalence studies whereas farms with a small number of sampled animals may be those reporting abortions and thus have a high prevalence of Q-fever (Selim et al., 2018). Secondly, there was a distinct difference in the animal species kept at different locations. For instance, in eastern Africa, cattle are kept in large numbers compared to other subregions and the disease prevalence reported was higher in cattle. Likewise, the reports on small ruminants are mostly from northern Africa (Abushahba et al., 2017). Thirdly, differences in climatic conditions between locations could favor pathogen survival such as semi-arid and arid environments where the shedding of the pathogen into the environment can easily spread by wind/dust (Alonso et al., 2019; de Souza et al., 2018; Rahman et al., 2016). Finally, different diagnostic kits were used with inherent sensitivity and specificity variations.

The majority of studies focused on Q fever in cattle (n = 38). Many of these were seroprevalence studies (n = 33). The mean seroprevalence in cattle was 14% (95%CI 10–20%). This is similar to studies that reported a seroprevalence range of 1–44.9% in Europe (Boroduske et al., 2017; Pexara et al., 2018). Our findings also coincide with a previous systematic review in Africa that reported the seroprevalence in cattle to be higher than 13% (Vanderburg et al., 2014). The highest seroprevalence was found in the eastern region. This might be due to the high number of cattle kept in the region (Herrero et al., 2014) as well as many reports of reproductive disorders in cattle which need more research to ascertain the cause (Campbell et al., 2021; Getahun et al., 2021).

There were fewer studies in small ruminants (goats n = 24; sheep n = 24). The mean seroprevalence in goats and sheep was 21% (95%CI 15–20%) and 13% (95%CI 9–18%), respectively. This is similar to a study in the Netherlands reported 21.4% in

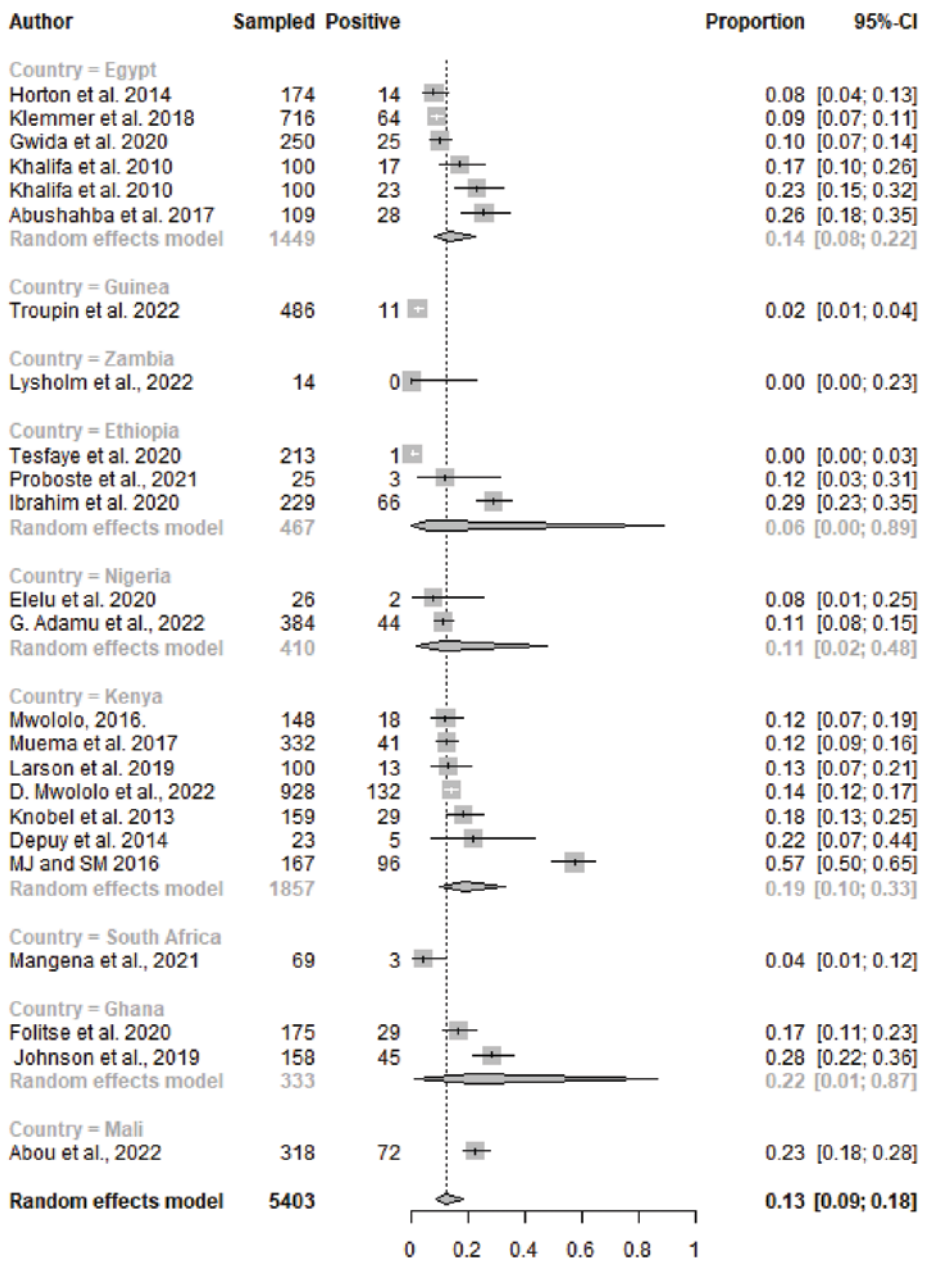


Figure 6. Cross-sectional meta-analysis studies by country, author, total population, positives, proportions, and 95%CI and species (sheep). Forest Plot represents seroprevalence (Antibodies) studies.

goats (Schimmer et al., 2014) but also a previous systematic review on the epidemiology of Q-fever in animals reported the mean prevalence range of 11–13% in small ruminants in Africa (Vanderburg et al., 2014). The knowledge regarding the pathogen infection among these species is scanty in Africa, therefore future research should focus on small ruminants as they are a known reservoir of the pathogen and the probable reservoir in the largest human Q-fever outbreak in the Netherlands (Jodełko et al., 2021; Roest et al., 2011).

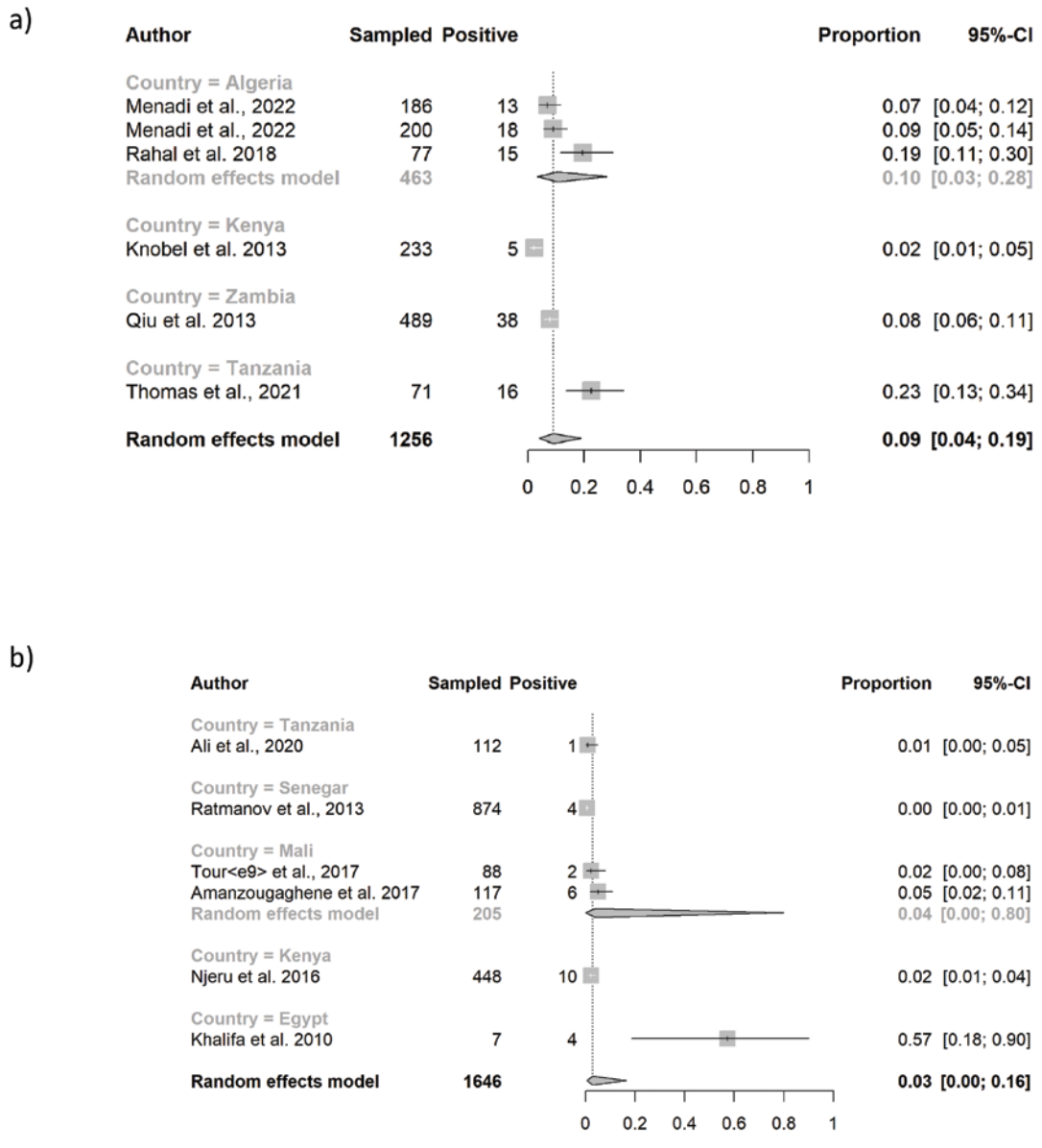
We noted that almost 70% of the serological studies for the detection of antibodies against *C. burnetii* in domestic ruminants were conducted concurrently in all species compared to few studies conducted in one species. Both studies conducted singly or simultaneously revealed the highest seroprevalence in goats despite different subregions where the animals originated. Additionally, antibody detection in mixed ruminants was higher (between 0% and 89.7%) compared to studies where single species were sampled (1.7–38%). This may suggest that animal intermingling increases the chance of disease spread and supports the need for testing the disease in more than one animal species including humans (Georgiev et al., 2013; McQuiston & Childs, 2002).

Thirty percent of the reviewed studies reported bacterial shedding in milk, vaginal swabs, serum, blood, and placental tissues. The majority of these studies were conducted in the northern subregion since 2010 with sheep being the leading animal studied followed by cattle and goats. This is consistent with reports from other scholars in Poland and Saudi Arabia who reported bacterial shedding in the placenta, vaginal swabs, milk, feces, urine, and blood samples from cattle and goats (Jodełko et al., 2021; Mohammed et al., 2014). Studies conducted elsewhere reported bacterial shedding via the reproductive route and were associated with abortion in

domestic ruminants (Clemente et al., 2009; Magouras et al., 2017; Rahman et al., 2016). Therefore, according to this review, *C. burnetii* detection in reproductive tissues, blood, serum, and milk by molecular methods in domestic ruminants is an important diagnostic since these animals may test negative under serology (Magouras et al., 2017). Most importantly our systematic review provides up-to-date information regarding *C. burnetii* shedding in domestic ruminants.

In our review, we found that animal intrinsic factors such as age, sex, species, and breed were risk factors for *C. burnetii* seropositivity. Our findings were supported by the other original studies. For example, several studies reported that *C. burnetii* seropositivity among domestic ruminants increased with age (Ezatkhah & Alimolaei, 2015; Ruiz-fons et al., 2010). The association could be due to an increased time of disease exposure as the animal matures (Ruiz-fons et al., 2010). Females were the most susceptible to infection compared to male animals. This is consistent with previous reports indicating that there is a high concentration of bacteria in the placenta of infected females (Ezatkhah & Alimolaei, 2015) and because of the high affinity of *C. burnetii* for the placenta (Ezatkhah & Alimolaei, 2015; Sobotta et al., 2017) and mammary glands (Roest et al., 2020). Among animal species goats, followed by sheep, then cattle were serially at high risk similar to findings by (Eibach et al., 2012). This was contrary to another study which found a high risk in sheep than goats and cattle (Ruiz-fons et al., 2010). A similar study further suggested that the lowered risk among goats and cattle could be associated with management systems that reduce animal contact (Ruiz-fons et al., 2010).

History of abortion was positively associated with Q-fever seropositivity in all species. Many researchers have found an association between a history of abortion with Q-fever exposure in dairy cattle (Cabassi et al., 2006), goats and sheep (Asadi et al., 2014), and all species (Cantas et al., 2011; Parisi et al., 2006). Additionally, a review paper in Italy demonstrated evidence of an increased risk of abortion with disease exposure in cattle, and goats (Agerholm, 2013). Another risk factor frequently reported in the reviewed studies was animal contact. This was highly associated with grazing systems (extensive), large herd size, overcrowding, and animal gatherings (e.g., at the auction, dip



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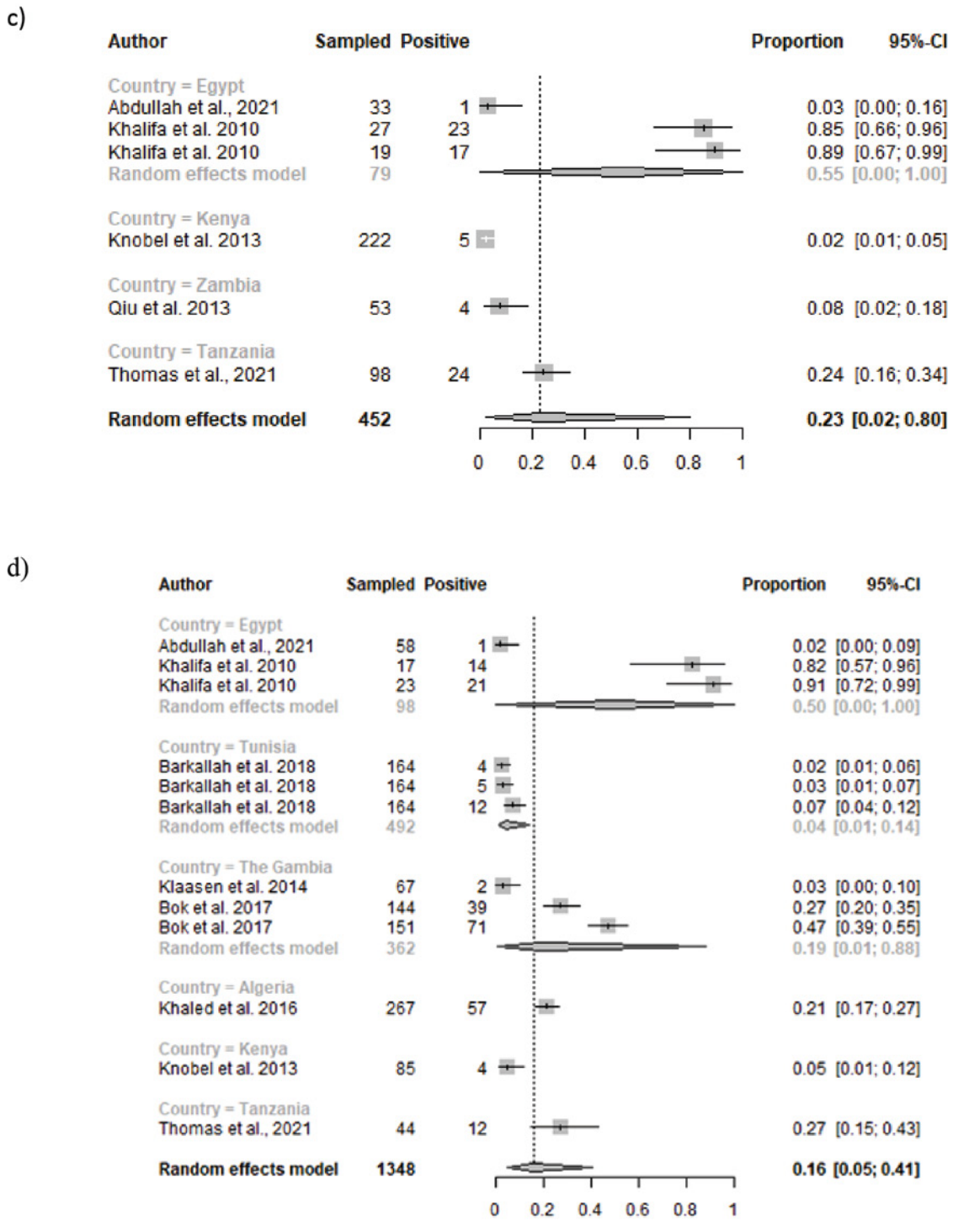

Figure 7. Cross-sectional meta-analysis studies by country, author, total population, positives, proportions, and 95%CI and species. Forest Plot represents antigen/DNA (prevalence) studies for (a) cattle, (b) humans, (c) goats and (d) sheep.

tanks, and during vaccination programs). Our findings agree with these other studies identifying risk factors such as increased herd size (Barlozzari et al., 2020), grazing (Carbonero et al., 2015), and overcrowding (Villari et al., 2018). We further found that purchasing new animals from different locations increased Q-fever exposure among domestic ruminants as it has been also reported by other authors (Boroduske et al., 2017; Nusinovici et al., 2015; Wolf et al., 2020).

Environmental factors including high temperature, open landcover, and high wind movement were risks to domestic ruminants in our review which were also found highly associated with *C. burnetii* seropositivity in Sweden (Nusinovici et al., 2015) as well as contaminations in birthing pens and other environments on the farm (Kersh et al., 2013). On the other hand; cleaning of the animal buildings, increased annual rainfall, and vaccination were less associated with disease among domestic ruminants (Nusinovici et al., 2015). Additionally, Nusinovici et al. (2015) recommended the use of vaccination (e.g., Coxevax®, Ceva Santé Animale) (EMA, 2015) as a disease management strategy since environmental factors are difficult to control.

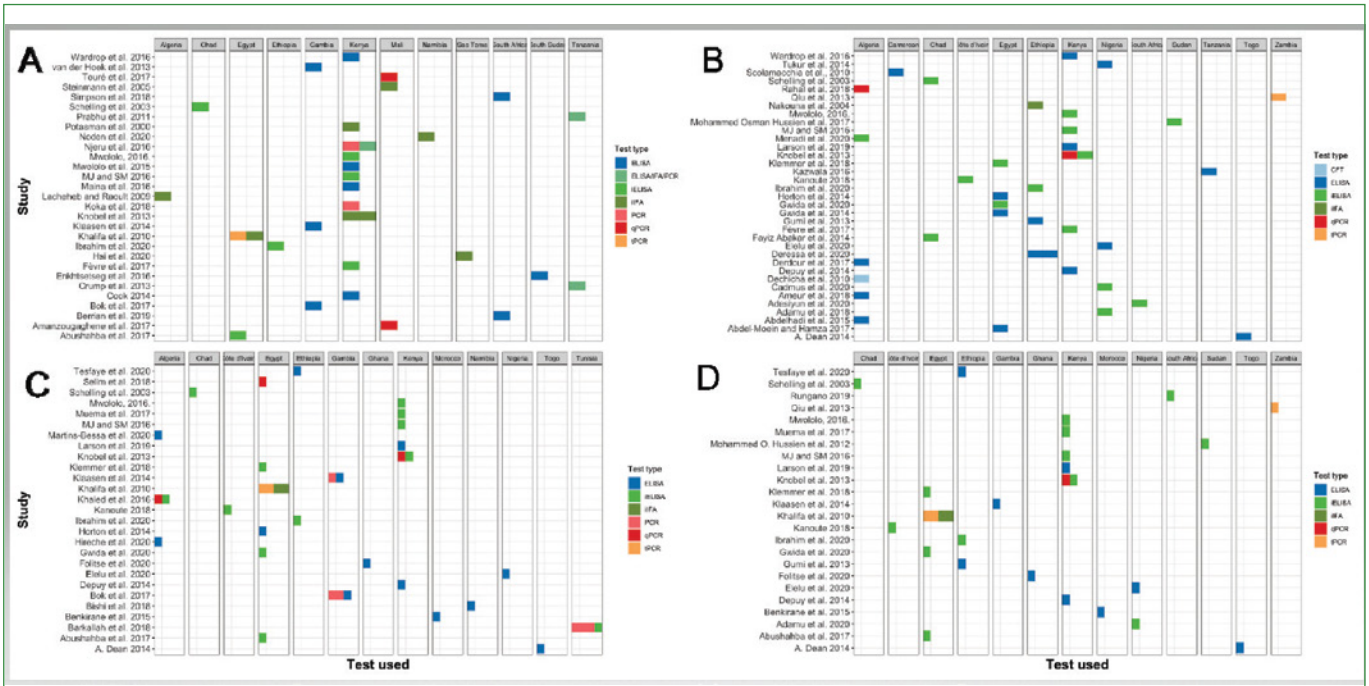

Figure 8. Serological and molecular tests used in studying Q-fever A = humans, B = cattle, C = sheep and D = goats.

People were at high risk of contracting the disease based on their occupation like farmers, veterinary staff and/ or students, abattoir/ slaughterhouse workers, butchers/meat sellers, herders, and breeders (Benaissa et al., 2017; Bishi et al., 2018; Cook et al., 2021; Fayiz Abakar et al., 2014; Khalifa et al., 2010; Mwololo et al., 2015; Njeru et al., 2016; Rahal et al., 2018; Simpson et al., 2018).

Since animals (domestic ruminants) naturally harbor the pathogen, occupationally exposed individuals in contact with animals are likely to get infections. This has been observed in other studies whereby individuals in close contact with animals (domestic ruminants) (Groten et al., 2020; Lange et al., 2014; Massey et al., 2017; Mostafavi et al., 2019; Rooij et al., 2012) and those working at the hospital were at high risk (Groten et al., 2020). A review conducted in four European countries also revealed the disease infection among occupational groups e.g., farmers and veterinarians (Georgiev et al., 2013). In addition, increased risks of infection in pregnant women (Lacheheb & Raoult, 2009) were suggested by Georgiev et al (Georgiev et al., 2013).

Increased *C. burnetii* seropositivity among humans has been reported in all ages, although adults were at higher risk than children. Some scholars have reasoned that children could be susceptible because preschool-aged kids stay at home, sometimes playing with goats and sheep, and drinking raw milk (van der Hoek et al., 2013). On the other hand, high risk in adults has been linked with increased time of exposure from childhood (Roest et al., 2011) and increased exposure could result in chronic Q-fever (Kampschreur et al., 2012).

Risk factors like poverty, lack of awareness, and low education were related to the persistence of the disease (Amanzougaghene et al., 2017). It was further noted that a lack of knowledge about Q-fever prevails both in animal and/or public health experts (Salifu et al., 2019; Vanderburg et al., 2014; Zhang et al., 2016). Furthermore, a low level of education was ascertained by Mostafavi et al (Mostafavi et al., 2019) in a population found with high disease prevalence in Germany. Additionally, we learned that poverty and lack of education and/ or low knowledge about Q-fever especially in rural areas could result in inappropriate management of aborted fetuses as has been previously reported (Georgiev et al., 2013; Massey et al., 2017; Roest et al., 2020). This could accelerate environmental contamination and increase exposure to animals and pastoralists keeping large herds and also those who do not keep animals (El-Mahallawy et al., 2016; Lange et al., 2014; Mostafavi et al., 2019; Reedijk & Leuken, 2022; Smit et al., 2012). With that said, there's a need for a holistic "One Health" approach to sensitize the public about Q-fever and its importance as a zoonotic disease.

Q-fever is characterized by non-specific and diverse symptoms and/or clinical signs; some infections are self-limiting, and others develop into chronic infections in animals and humans (Deressa et al., 2020; Klemmer et al., 2018; Prabhu et al., 2011; Selim et al., 2018). A study in the Netherlands revealed that the disease could develop from acute to chronic if not treated inhumans (Kampschreur et al., 2012). Therefore, reliable diagnostic tools are needed to determine the antibodies and/or antigens revealing both current and previous infections. Also, modern molecular methods could contribute to disease detection (current infections) and active surveillance to understand disease epidemiology and improve control measures (El-Mahallawy et al., 2016; Kampschreur et al., 2012). It has been suggested that ELISA is the first and easy step in diagnosing Q-fever and if antibodies are not detected then PCR could be employed (Schack et al., 2014; Wolf et al., 2020). It has also been suggested that CFT is not as sensitive compared to ELISA and IFA (El-Mahallawy et al., 2016). Therefore, we concur with other scientists that the ELISA/IFA should be used for screening then followed by CFT and molecular diagnostics for confirmation.

In addition to the limited availability of diagnostic tests, we found some challenges including the lack/absence of a gold standard test for defining *C. burnetii* seropositivity i.e., available tests have variations in specificity, sensitivity, and protocols (El-Mahallawy et al., 2016). Such variations could result in challenges with diagnosing latent infections and may indicate a need for using more than one test to improve accuracy (Abiri et al., 2019). Moreover, lack of funds inhibits the use of confirmatory diagnostic tools like molecular tests to confirm the serological specificity (Bok et al., 2017; Noden et al., 2020; Raven et al., 2012; Steinmann et al., 2005).

The other challenges were a lack of laboratory equipment and specialized laboratories. It has been noted that isolation of

C. burnetii is a reliable diagnostic method but due to the hazardous nature of the pathogen it requires highly specialized laboratories (Biosafety level 3) which are few in developing countries (Klemmer et al., 2018; Selim et al., 2018) and as a diagnostic tool it is time-consuming as the pathogen takes a long time to grow.

Furthermore, a lack of interdisciplinary collaboration may lead to inadequate data for diseasesurveillance (Enkhtsetseg et al., 2016). Q-fever is unknown and underdiagnosed, especially in many African countries (Brah et al., 2015; Salifu et al., 2019). Hence it is not being prioritized and there is a lack of policies or strategies to curb the disease (URT, 2020). Therefore, we strongly recommend an interdisciplinary approach to fighting this disease.

STUDY LIMITATIONS

This study was limited to studies reporting Q-fever in domestic ruminants (cattle, sheep, goats) and humans and therefore excluded the contribution of wild ruminants to the epidemiology in Africa. We included only English-language publications conducted in Africa between January 2000 and April 2022 and therefore may have lost information from countries where publications were in other languages.

Conclusion and recommendations

We are confident that the disease is distributed throughout the entire continent and endemic in domestic ruminants and humans in areas where animals are kept. Animal contacts, movement of animals and animal products, and climate variability are risk factors to consider when managing the disease in animals and humans. Knowledge regarding the disease and its impacts on animals and humans is still limited and it is not prioritized among zoonotic diseases in most countries within Africa. Therefore, "One Health" oriented research and awareness, especially in areas with large numbers of animals and people at risk are recommended. Additionally, no country alone in the African continent could control a disease given the high cross-border and internal mobility of people and livestock; therefore, regional collaboration is needed for more effective Q-fever control. Animals shed the pathogen during birth or late abortion, and this leads to environmental contaminations and high exposure to other animals and humans; therefore, the separation of animals at birth and proper handling of the placenta and/or aborted foetus is recommended. We also recommend the inclusion of Q-fever in abortion differentials in domestic ruminants and febrile illness in humans. Q-fever has no specific symptoms and/or clinical signs, thus regular diagnosis with reliable diagnostic tools should be used both in animals and humans, and it is important to also consider biosafety during diagnosis to protect the personnel in the laboratory. Simultaneous testing is recommended i.e., serology and molecular to diagnose Q-fever, especially in natural reservoirs, and sampling from the environment to determine the environmental contamination. Diagnosis should be conducted with reliable diagnostic tools which require further studies to determine the most appropriate, efficient, and cost-effective methods.

CONFLICT OF INTERESTS

We declare that there is no conflict of interests.

ETHICS STATEMENT

Not applicable for this is a systematic review of the published original research works.

ACKNOWLEDGEMENTS

We give thanks to the Nelson Mandela African Institution of Science and Technology (NM-AIST) for the residential support during the entire course of this review study. We recognize the International Livestock Research Institute (ILRI) and NM-AIST Library for providing training and guidance on database and literature search strategies of this study. Special thanks to researchers from the International Livestock Research Institute, The Roslin Institute, and the SRUC for their support. However, our findings and conclusions contained in this work do not necessarily reflect the positions or policies of the Bill & Melinda Gates Foundation or the UK Government.

AUTHOR CONTRIBUTIONS

SFB, EAJC, BMB, and GMS worked on the conception and design of the work; SFB and LEH worked on the acquisition, analysis, or interpretation of data; EAJC, GMS, BMB, and NW have substantively revised it and all authors have approved the submitted version. All have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

FUNDING STATEMENT

This research was conducted as part of the CGIAR Research Program on Livestock. ILRI is supported by contributors to the CGIAR Trust Fund. CGIAR is a global research partnership for a food-secure future. Its science is carried out by 15 Research Centres in close collaboration with hundreds of partners across the globe (www.cgiar.org). This research was funded in part by the Bill & Melinda Gates Foundation and with UK aid from the UK Foreign, Commonwealth and Development Office (Grant Agreement OPP1127286) under the auspices of the Centre for Tropical Livestock Genetics and Health (CTLGH), established jointly by the University of Edinburgh, SRUC (Scotland's Rural College), and the International Livestock Research Institute (ILRI). This work was also supported by funding from the BBSRC (BBS/E/D/30002275). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DATA AVAILABILITY

All relevant data are presented within the manuscript and its supporting files i.e., supplementary materials.

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