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Identification and distribution of pathogens coinfecting with *Brucella* spp., *Coxiella burnetii* and Rift Valley fever virus in humans, livestock and wildlife

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Summary

Zoonotic diseases, such as brucellosis, Q fever and Rift Valley fever (RVF) caused by *Brucella* spp., *Coxiella burnetii* and RVF virus, respectively, can have devastating effects on human, livestock, and wildlife health and cause economic hardship due to morbidity and mortality in livestock. Coinfection with multiple pathogens can lead to more severe disease outcomes and altered transmission dynamics. These three pathogens can alter host immune responses likely leading to increased morbidity, mortality and pathogen transmission during coinfection. Developing countries, such as those commonly afflicted by outbreaks of brucellosis, Q fever and RVF, have high disease burden and thus common coinfections. A literature survey provided information on case reports and studies investigating coinfections involving the three focal diseases. Fifty five studies were collected demonstrating coinfections of *Brucella* spp., *C. burnetii* or RVFV with 50 different pathogens, of which 64% were zoonotic. While the literature search criteria involved 'coinfection', only 24/55 studies showed coinfections with direct pathogen detection methods (microbiology, PCR and antigen test), while the rest only reported detection of antibodies against multiple pathogens, which only indicate a history of co-exposure, not concurrent infection. These studies lack the ability to test whether coinfection leads to changes in morbidity, mortality or transmission dynamics. We describe considerations and methods for identifying ongoing coinfections to address this critical blind spot in disease risk management.

KEYWORDS
Brucellosis, co-exposure, diagnostics, especially dangerous pathogens, Q fever, Rift Valley fever, serology, zoonotic disease

1 | INTRODUCTION

Brucella spp., Rift Valley fever virus (RVFV) and *Coxiella burnetii* cause debilitating illnesses in humans and are associated with substantial socio-economic losses in livestock. The diseases they cause (brucellosis, Rift Valley fever [RVF] and Q fever) are important zoonoses and often spillover to humans from livestock and wild animals (Dean et al., 2013; Fayiz Abakar et al., 2014; Rostal et al., 2017). Rift Valley fever and Q fever have been categorized as neglected tropical diseases, which are recognized as being

understudied and disproportionately affecting developing areas. Additionally, brucellosis (also called undulant fever, Malta fever and Mediterranean fever) has recently been identified as a neglected zoonotic disease by the World Health Organization (Franc et al., 2018).

Understanding the ecology surrounding transmission and severity of these infectious diseases is key to limiting disease risk and mitigating adverse health outcomes. One aspect of these diseases, especially in developing areas, concerns hosts coinfected with other pathogens, which themselves may be other important zoonotic diseases or those that are often neglected and impact millions of people per year (e.g. onchocerciasis, leishmaniasis, Dengue fever and Chagas disease). Coinfection biology and ecology are neglected concepts in infectious disease research, but are especially relevant in places where coinfections are common. Each disease poses a significant challenge on its own, but coinfections with other pathogens can alter host immune responses, influence morbidity and mortality and impact transmission, which can all make disease outcomes and outbreaks worse (Abbott & Crotty, 2020; Ezenwa & Jolles, 2011; Griffiths et al., 2011; Kenney et al., 2015). Despite this, little is known about coinfecting pathogens in humans, livestock and wildlife involving these three neglected zoonotic diseases.

The goal of this review is to identify the diversity of pathogens that have been found to coinfect hosts with the three focal pathogens, *Brucella* spp., *C, burnetii* and RVFV. All three pathogens are (re) emerging zoonotic pathogens and cause febrile illness in humans. In livestock, they cause febrile illness and abortions, leading to food and health insecurities where they are prevalent. Thus, we chose to use them as focal pathogens in this review of coinfection literature. We aim to understand the macroecology of these coinfections and to identify areas in need of research in locations where disease risk is greatest. These three pathogens are considered especially dangerous pathogens (EDPs), because they cause severe disease and have limited therapeutics and vaccine availability. We first provide a brief background on each of the diseases. Comprehensive reviews of each disease have been published recently (Ducrotoy et al., 2017; Fawzy & Helmy, 2019; Rahaman et al., 2019); therefore, a thorough review of each is not within the scope of this article. We then provide details regarding how coinfections can impact host health, including immunological responses and disease severity and put this information in the context of the three focal pathogens. From a literature survey, we draw inferences regarding specific information on coinfecting pathogens. We also document coinfection distribution to identify areas where coinfections occur, where studies have been conducted, and where studies are lacking. We highlight a disconnect in the literature between using the term coinfection and researchers performing serology studies, which only indicate co-exposure. Finally, we end by providing risk identification strategies in a One Health context to inform data-driven mitigation efforts. We urge the shift from co-exposure to coinfection studies, in which diagnostic tests and strategies to screen hosts for multiple pathogens will require careful consideration.

Impacts

- Zoonoses caused by *Brucella* spp., *Coxiella burnetii* and Rift Valley Fever virus can have devastating effects on human and livestock health. The impact caused by coinfections with these three neglected pathogens remains mostly unknown.

- A literature survey identified the diversity of coinfecting pathogens. Interestingly, we found that more than half of the coinfecting pathogens are zoonotic, yet few studies were done in wildlife. This leaves a blind spot in understanding the broader ecology of coinfections and drivers of disease spillover.

- Many coinfection studies used serological methods that show co-exposure rather than coinfection. We describe considerations for identifying ongoing coinfections in host individuals to address whether coinfections involving these pathogens affect host morbidity, mortality and transmission.

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2 | BRUCELLOSIS, Q FEVER AND RIFT VALLEY FEVER

Brucella spp. and *C. burnetii* have worldwide distributions, while RVFV outbreaks have been mainly limited to countries within Africa (Godfroid, 2017; Kenawy et al., 2018; Porter et al., 2011). RVFV is found in almost every African country including the island nations of Comoros, Mayotte and Madagascar representing many environments and climates (Kenawy et al., 2018; Linthicum et al., 2016). As recently as 2000, there were major outbreaks of RVFV in Saudi Arabia and Yemen, raising concerns it could spread and become endemic in Europe, Asia and North America (Rolin et al., 2013; Turell et al., 2010). All three of these EDPs are a global threat and have the ability to negatively impact livestock and human health across large regions. Research addressing the epidemiology, mechanisms and consequences of infections involving these pathogens is imperative for public health preparedness.

In humans, brucellosis presents with a wide range of symptoms including intermittent fever, arthralgia, myalgia, fatigue and, in some cases, neurological disorders (Table 1). Q fever is also a febrile illness, but in about 40% of the cases, patients develop pneumonia and hepatitis. A portion of the severe cases (30%–52%) lead to chronic fatigue syndrome that can persist for many years (Maurin & Raoult, 1999; Morroy et al., 2016) (Table 1). Many human RVF cases are asymptomatic; however, about 8% of them result in a severe disease manifesting as haemorrhagic fever, hepatitis, endocarditis and/or encephalitis with a high (up to 50%) mortality rate (Njenga et al., 2009) (Table 1). Thus, these diseases have the potential to severally impact human health in addition to affect the livelihoods of people living in endemic areas, making them serious threats to health security on multiple fronts.

TABLE 1 Characteristics of brucellosis, Rift Valley fever (RVF) and Q fever

Disease	Pathogens responsible for disease	Vector	Human transmission	Animal transmission	Non-human hosts	Human symptoms	Animal signs	Mortality rate	Treatment
Brucellosis	B. melitensis, B. abortus, B. suis and B. canis (Adamu et al., 2018; Dutta et al., 2017)	None	Consumption of contaminated animal products, inhalation of infected aerosols, or by encountering infected animals through conjunctive or abrasions on the skin (Dutta et al., 2017)	Transmitted by direct contact with infected animals or through contact with contaminated animal products (CDC, 2019)	B. melitensis: Small ruminants (goats and sheep);B. abortus: Cattle;B. suis:domestic pigs (Leahy et al., 2020). Infections have also been identified in wildlife such as bison, elk, caribou, moose and wild hogs (CDC, 2019)	Undulant fever, night sweat, headache, joint, muscle, and back pain, fatigue, weight loss, hepatosplenomegaly and jaundice (Bektaş, 2014; Dutta et al., 2017)	Infertility, abortions and stillbirths (Seleem et al., 2010)	Human: Low, occurring in about 2% or less of all cases (CDC, 2019)	Antibiotics doxycycline and rifampin (CDC, 2019; Lai et al., 2009). Vaccine available for livestock
Rift Valley fever	Rift Valley fever virus	Mosquitoes, ticks and sandflies (Linthicum et al., 2016)	Humans can be infected by mosquitoes and contact with contaminated tissues or pasture (Kolawole et al., 2018)	Vector-borne, arthropods, mainly mosquitos, can act as mechanical vectors (Wright et al., 2019)	Goats, sheep, camels and cattle and wild African Buffalo (Beechler et al., 2015)	Fever, headache, backache, vertigo, anorexia and photophobia. In severe cases, liver damage can lead to jaundice and haemorrhagic disease. 2%–5% of cases develop ocular disease. Some may develop encephalitis and neurological disease (Wright et al., 2019)	Age dependent, young animals have higher mortality. Sever RVF can exhibit leukopoenia. Sheep and goats are highly susceptible with fever, listlessness, loss of appetite, disinclination to move, abdominal pain and bloody diarrhoea with post-mortem signs of liver necrosis and mild splenomegaly. Cattle are usually asymptomatic (Wright et al., 2019)	Livestock: Adult sheep—20%–30%, New born lambs—95%–100%, Cattle–0%–5%, Calves –10% (Wright et al., 2019). Humans: up to 4% (Paweska, 2015)	No FDA-approved treatment but can be treated with over-the-counter medications (CDC, 2020b). Most human cases do not require treatment (Wright et al., 2019). Vaccine for livestock
Q fever	Coxiella burnetii	Ticks	Inhalation of dust contaminated by infected animal fluids, ingestion of contaminated animal products	Vector-borne, can be transmitted by ticks, which are the main arthropod vectors (Khoo et al., 2016; Lai et al., 2009)	Small ruminants (goats and sheep), cattle and domestic cats (Porter et al., 2011). Found in many other mammals including Carnivora, Artiodactyla, Diprotodontia, Lagomorpha and Rodentia (González-Barrio & Ruiz-Fons, 2019)	Fever, chills, fatigue, headache, muscle aches, nausea, vomiting, or diarrhoea, chest pain, stomach pain, weight loss, non-productive cough and pneumonia. Immunocompromised people may develop chronic Q Fever with symptoms of hepatitis, endocarditis, or meningitis (CDC, 2020a; Porter et al., 2011)	Abortion, stillbirth, premature delivery and delivery of weak offspring for small ruminants. Cattle largely asymptomatic (Angelakis & Raoult, 2010; Porter et al., 2011)	Humans: 1%–2% in acute form (Porter et al., 2011)	Can recover without antibiotic treatment, but those who develop chronic Q Fever are treated with a combination of doxycycline and hydroxychloroquine (CDC, 2020a). Vaccine available for humans in Australia

Listed are the main pathogens responsible for the disease, transmission routes, non-human hosts, mortality rate and treatments available. We also list symptoms and signs for humans and animals respectively.

These pathogens are transmitted directly to new hosts or via arthropod vectors. *Brucella* spp. are transmitted directly, through aerosols, contaminated animal products or direct contact between both humans and animals or infected tissues (Dutta et al., 2017) (Table 1). *Coxiella burnetii* is also transmitted via multiple routes including inhalation of contaminated aerosols, and also through vectors such as ticks or direct contact, depending on the host species involved (Dean et al., 2013; Khoo et al., 2016; Lai et al., 2009; Rolain et al., 2005) (Table 1). RVFV can be transmitted through direct contact, contaminated aerosols or via mosquitoes; however, the transmission chain is primarily driven by mosquitos between wildlife and livestock and via contact with contaminated tissue between livestock and humans (Linthicum et al., 2016; Paweska, 2015) (Table 1). There are currently vaccines for *Brucella* spp. and RVFV for use in animals; however, there are no human vaccines (Table 1). There is a human vaccine against *C. burnetii*, but is only available for use in Australia.

3 | TRANSMISSION AT THE WILDLIFE–LIVESTOCK–HUMAN INTERFACE

Similar socio-economic conditions, animal husbandry practices and wildlife ecology all play roles in the distributions of these EDPs, leading to overlap in certain areas, especially in many African countries. All three pathogens can be transmitted from livestock to humans through direct contact with infected animal products (Table 1). *Brucella* spp. are also transmitted through indirect contact between livestock and wildlife (e.g. pasture contamination). On the contrary, *C. burnetii* and RVFV are typically transmitted through vectors between livestock and wildlife (Angelakis & Raoult, 2010; Wright et al., 2019) (Table 1). Transmission cycles of *C. burnetii* and RVFV between wildlife, livestock and humans can be facilitated by ticks and mosquitoes respectively (Table 1). Outbreaks of these EDPs are most common in areas where livestock live in close contact with wildlife capable of harbouring these pathogens and where livestock populations can maintain the EDPs themselves. The transmission between wildlife and livestock, and ultimately humans, suggests that local wildlife species play a significant role in whether humans and livestock are coinfected with other zoonotic pathogens.

In most industrialized countries, *Brucella* spp. have largely been controlled in domesticated animals with infrequent spillover events from wildlife sources (Schumaker, 2013). *Coxiella* cases are more common with frequent spillovers from small ruminants (Georgiev et al., 2013). However, major outbreaks are rare but still occur (Hackert et al., 2012). Where large-scale immunization and outbreak control measures are prohibitively expensive or logistically infeasible, all three pathogens can remain endemic causing intermittent, severe outbreaks. This includes much of East Africa where pastoralists and many small livestock operations lack resources to deploy husbandry, immunization, quarantine or culling protocols to reduce disease burden (Franc et al., 2018; Njeru et al., 2016; Seleem et al., 2010).

Extensive animal husbandry, where animals are allowed to roam and interact with wildlife and other livestock herds, complicates pathogen control measures (Racloz et al., 2013). While wildlife and local transmission ecology of these pathogens is not fully understood, the dynamics of all three pathogens are affected by the wildlife–livestock–human interface (Britch et al., 2013; Godfroid et al., 2013; González-Barrio & Ruiz-Fons, 2019). Small ruminants and camels commonly raised in extensive livestock production systems in pastoral areas can serve as reservoirs or amplification hosts of these EDPs (Beechler et al., 2015; Khoo et al., 2016; Lai et al., 2009; Leahy et al., 2020) (Table 1). Goats and camels are particularly important reservoirs of *C. burnetii* and *B. melitensis*, one of the more virulent *Brucella* species (Khoo et al., 2016; Lai et al., 2009; Leahy et al., 2020; Nahed & Khaled, 2012). It is recognized that African buffalo are a reservoir of *B. abortus* in many countries of subsaharan Africa, leading to infection risk in livestock through habitat overlap and in humans through the consumption of bushmeat (Godfroid et al., 2013). Additionally, *C. burnetii* has been found in over 100 wild mammal species from very divergent orders including Carnivora, Artiodactyla, Diprotodontia, Lagomorpha and Rodentia (González-Barrio & Ruiz-Fons, 2019). *Coxiella burnetii* genotypes that are common in wildlife also occur in livestock, indicating transmission between the two groups (González-Barrio & Ruiz-Fons, 2019). Because *C. burnetii* can infect a broad mammalian host range and ticks are known vectors, *C. burnetii*, and potentially other tick-borne pathogens, may transmit from wildlife to livestock wherever they share habitat.

RVFV can infect a broad range of mammals, but the role of wildlife during epidemics is unclear (Rostal et al., 2017). Compared to other hosts, small ruminants can amplify RVFV transmission by maintaining high viral loads in their tissues, increasing both viral shedding via infected tissue and the probability of transmitting the virus to feeding mosquito vectors (Beechler et al., 2015). Seroprevalence of several wildlife species increased during the 2006–07 RVFV outbreak in Kenya indicating similar drivers of infection dynamics as human and livestock (Britch et al., 2013). Wildlife may function similar to livestock, amplifying local vector-borne transmission and increasing the probability of downstream spillover into humans (Olive et al., 2013). Despite the few studies mentioned above, research directly addressing transmission from wildlife to livestock is relatively scarce (Rostal et al., 2017).

Abattoirs (slaughterhouses) are important sources of infection for many zoonotic diseases, since many of them are transmitted by direct contact of infected animal tissues (Klous et al., 2016; Pal et al., 2013; Swai & Schoonman, 2012). Abattoirs have been listed as a potential source of transmission to humans for all three of these diseases since they can all be transmitted to humans through contaminated droplets and aerosols (Pal et al., 2013) (Table 1). These areas of direct exposure represent a critical surveillance and control point for the timely identification of potential diseases that may have an impact on public health. High exposure rates also make abattoirs and their workers a logical target of coinfection studies.

4 | SIGNIFICANCE OF COINFECTIONS IN HOST INDIVIDUALS

Infection with multiple pathogens has dramatic effects on disease dynamics and outcomes. Many theories predict that infection with multiple pathogens will result in the evolution of increased virulence (Alizon & Van Baalen, 2008; Clay & Rudolf, 2019; May & Nowak, 1995). Likewise, multiple infections may lead to worse host outcomes regardless of evolutionary stable strategies, such as in disease emergence or epidemic settings, which is highlighted by studies of human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (Pawlowski et al., 2012); helminths (*Heligmosomoides polygyrus*) and bacteria (*Bordetella bronchiseptica*) (Lass et al., 2013); and *Mycoplasma* spp. and *Borrelia burgdorferi* (Berghoff, 2013). These effects are especially pronounced if the pathogens involved are genetically dissimilar (Gleichsner et al., 2018). Infection with multiple pathogens often leads to worse health outcomes (Griffiths et al., 2011), exacerbating strain on clinical and veterinary infrastructure. Furthermore, a majority of coinfection studies shows higher within-host pathogen abundance, possibly increasing downstream transmission to new hosts drastically altering epidemiological parameters (Griffiths et al., 2011).

Host immune resources are limited and responding to one pathogen can lead to trade-offs in the response to a second and is illustrated by two concepts. The first is immunodominance, where competing clonal T-cell and B-cell proliferation narrows the adaptive immune repertoire to strongly target a few immunogenic epitopes (Abbott & Crotty, 2020; Berzofsky, 1988; Das et al., 2008). The second is antagonistic T-helper cell responses, where T-helper cells differentiate into mutually exclusive subtypes to fight different pathogen classes. Specifically, Th1 targets intracellular pathogens and Th2 targets large extracellular pathogens such as helminths. Both of these immune mechanisms strengthen the response to one pathogen type at the expense of responding to a second (Abbott & Crotty, 2020; Ezenwa & Jolles, 2011; Kenney et al., 2015).

While the above factors seem to be general principals of viral, bacterial and macroparasite coinfections, the extent to which they alter disease outcomes during coinfections involving *Brucella* spp., *C. burnetii* or RVFV is largely unknown and warrants further work, which would include experimental coinfection studies. Because all three pathogens can successfully infect mice, the considerable immunological and genetic resources for lab mice infections are available. Additionally, because mice have been developed as a model for a broad range of pathogens, testing the generality of immunomodulatory and morbidity/mortality effects of coinfections with many different pathogens are feasible. These studies will include tests of virulence and immune parameters for individual infections compared to coinfections. Specifically, testing immune effects of coinfection will focus on relative strengths of innate/adaptive responses, T-helper cell subtype abundances and cytokine quantities. The results of mouse experiments can then be extended to design experimental infection studies in important livestock hosts to test similar hypotheses.

The host immune system plays a major role in coinfection-induced changes in transmission dynamics and altered morbidity and mortality. During coinfection, pathogens which target the same host tissue can interfere with each other by increasing the local innate immune response of host cells, making the cells resistant to infection. For instance, lymphocytic choriomeningitis virus replication in the liver can abolish Hepatitis B virus replication in the same tissue (Guidotti et al., 1996). Alternatively, infection by one pathogen can cause immunopathology and immunogenic overload allowing opportunistic infection by a second, such as influenza and pathogens that cause bacterial pneumonia (Morris et al., 2017). Pathogens that subvert host innate immunity for their own replication can increase the chances that a second pathogen establishes an infection in the same tissue, often resulting in worse health outcomes (Bonagura & Rosenthal, 2020; Sun & Metzger, 2014; Unger et al., 2012).

Another major interface for pathogen interaction during coinfection is resource use. For instance, *Plasmodium* spp. and bloodsucking hookworms, which both use erythrocytes, compete for the same niche; thus, coinfection reduces pathogen load, morbidity and mortality (Budischak et al., 2018). For intracellular pathogens, such as the three EDPs discussed here, that resource is host cell type. When pathogens use the same host cell type for replication, they can interfere with each other and reduce the total amount of pathogen replication and reduce associated symptoms (Burivong et al., 2004; Coffin et al., 2007). *Brucella* spp. and *C. burnetii* both target host antigen presenting cells (APCs) including mononuclear phagocytic cells (e.g. macrophages and blood monocytes) for replication (He, 2012; Melenotte et al., 2016). Because viral pathogens commonly use APCs for replication and to disseminate throughout the host body (Goutagny et al., 2003; Guerreiro-Cacais et al., 2004; Hofmann-Winkler et al., 2012; Wahid et al., 2005), *C. burnetii* and *Brucella* spp. could interfere with a wide range of viral pathogen infections and subsequent transmission.

5 | COINFECTIONS INVOLVING *BRUCELLA* spp., *COXIELLA BURNETII* OR RIFT VALLEY FEVER VIRUS

Few studies have investigated these three pathogens regarding coinfection and host immunological responses. Recent serological studies conducted in northeastern Kenya showed that up to 11% of humans and about 5% of livestock hosts had antibodies for multiple EDPs (B. Bett, unpublished data). Due to high seroprevalence and increased severity of symptoms and transmission opportunity, studying these EDP's in the context of coinfection is imperative. Moving from co-exposure (serology) to coinfection studies of these diseases is critical for disentangling ecological determinants of exposure risks from one pathogen driving the prevalence of another.

All three focal pathogens in this review have the capacity to actively subvert host immune mechanisms. *Coxiella burnetii* induces expression of the anti-inflammatory cytokine IL-10

(Melenotte et al., 2016), RVFV blocks pro-inflammatory interferon α/β signalling and virus sensing PKR function (Bouloy et al., 2001; Habjan et al., 2009), and infection with *Brucella* spp. reduces innate immune surveillance by blocking TLR2/4 signalling (Salcedo et al., 2008). Furthermore, *Brucella* spp. and *C. burnetii* infect macrophages and monocytes, respectively, both of which are professional APCs integral to innate and adaptive immunity (He, 2012; Melenotte et al., 2016). Both pathogens reduce or alter the infected APC's ability to activate and secrete pro-inflammatory cytokines and likely interferes with their ability to aid in detecting and fighting other infections (Benoit et al., 2008; Jiménez De Bagüés et al., 2004). Infections of these EDPs are therefore predicted to severely impair a host's immune response, limiting its ability to control coinfecting pathogen proliferation and environmental contamination. As stated above, experimental coinfection studies in mice and livestock could be used to identify immunological effects of single verse multiple infections, specifically, if the known immune modulatory effects of these pathogens exacerbate symptoms of infection and increase shedding of coinfecting pathogens.

6 | POPULATION LEVEL TRANSMISSION EFFECTS OF COINFECTION

A question of critical importance is whether coinfection leads to altered transmission dynamics. If prevalence of one pathogen has population level effects on the prevalence of another, public health interventions can lead to unintended consequences; wildlife vaccination campaigns against one pathogen could exacerbate the public health consequences of another. Infection with one pathogen can alter the within-host replication of a second by many mechanisms, but how this translates to differences in transmission dynamics among individual and populations of hosts is still obscure. During a 2008 outbreak of RVFV, tuberculosis (bTB) positive buffalo in Kruger National Park were more likely to become infected with RVFV (Beechler et al., 2015). There was also increased RVFV induced morbidity when buffalo were also infected with bTB.

While increased pathogen replication due to coinfection may be predicted to increase shedding of reproductive stages, increased morbidity/mortality associated with increased pathogen replication can lead to unexpected population level consequences. In a model describing individual and population effects of coinfection with bovine tuberculosis and brucellosis, the authors find that brucellosis increases the transmissibility of bTB, yet at the population level, coinfection-induced mortality leads to a decrease in the overall prevalence of bTB (Gorsich et al., 2018). These studies highlight that pathogen community ecology at the individual host level can scale up to unexpected changes in epidemiology at the population level, underscoring the importance of considering coinfections in risk management.

7 | SURVEYING THE LITERATURE

We searched published literature for articles of coinfection involving *Brucella* spp., *C. burnetii* and RVFV in humans and terrestrial animals using Google Scholar, Los Alamos National Laboratory (LANL) Research Library and PubMed published from 2004 to August 2020. We used the following search terms: "coinfection", "co-infection", "concurrent infection", and "concomitant infection" to find multiple infections. We searched these databases from June to August 2020. These terms were paired with various forms of our primary disease and pathogen search terms: "Brucellosis", *"Brucella"*, "Rift Valley Fever", "Rift Valley Fever virus", "Q Fever", "Q-Fever", and *"Coxiella burnetii"*. These terms allowed us to perform a comprehensive search for coinfections involving our primary zoonotic pathogens and other pathogens. Those publications that investigated infection in humans, livestock, vectors or wildlife that explicitly stated positive results for multiple pathogens with at least one being RVFV, *Brucella* spp. or *C. burnetii* contributed to our analysis. We did not restrict our analysis to any specific taxa; we included all known parasites and pathogens that were involved in coinfections. Since no new data are generated with this manuscript, ethical approval is not required.

Each publication was analysed, and the following information was extracted: the coinfecting pathogens and the diseases they cause, the mode of pathogen transmission, location of the study, species of host(s) and whether direct pathogen detection methods were used (microscopy/PCR). Modes of transmission of the pathogens within each study were sorted into not vector-borne and vector-borne, in which case the type of vector was determined (e.g. mosquitos, ticks, fleas, etc.). We also determined whether the pathogens are known to be zoonotic. Hosts were categorized as humans, livestock and wildlife. We also identified the methods and types of analysis used in the study (e.g. serological studies versus direct pathogen detection). These data were extracted directly from the cited papers.

Information regarding geographical location of sampling or study region was extracted from papers with an attempt to find the highest specificity, that is coordinates, city, region and/or country. We examined the distributions across 8 biogeographic realms (Nearctic, Palearctic, Afrotropic, Neotropic, Indo-Malay, Australasia, Oceanic and Antarctic) and 14 terrestrial biomes. The terrestrial biomes are defined by similar climatic and geographical conditions and thus share habitat type and ecologies. For both realm and biome assignment, region definitions from Olson et al. (2001) were used. For biome assignment, the HHMI's interactive biome viewer at (https://media.hhmi.org/biointeractive/biomeviewer_web/index.html) was an invaluable resource. If the country of origin for the study contained multiple biomes (Israel or Iraq), the city (i.e. Tel Aviv, Israel) or region (i.e. central Iraq) was used to infer biome. In some cases, sample collection location was not given and the country of origin contains several biomes. In this case, we assumed the institutional address in author affiliations to be the study location. If a study explicitly stated sample collection sites across different biomes, all relevant biomes were recorded. For several studies, the likely

location of disease exposure differed from the location samples were obtained (e.g. travellers on vacation, which were sampled upon returning home). If this likely disease contraction location was explicitly stated, it was taken as the coinfection location rather than the sampling location. Several studies investigated both *Brucella* and *Coxiella* infections. In these cases, the paper's geographical information counts towards both in Figures 1c,d, and 2a,b.
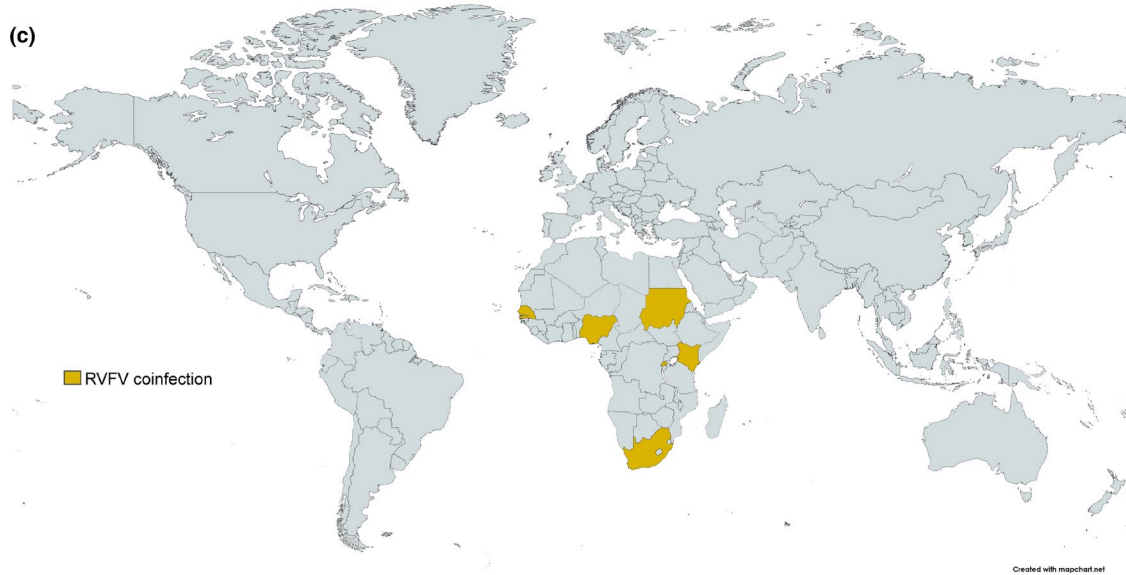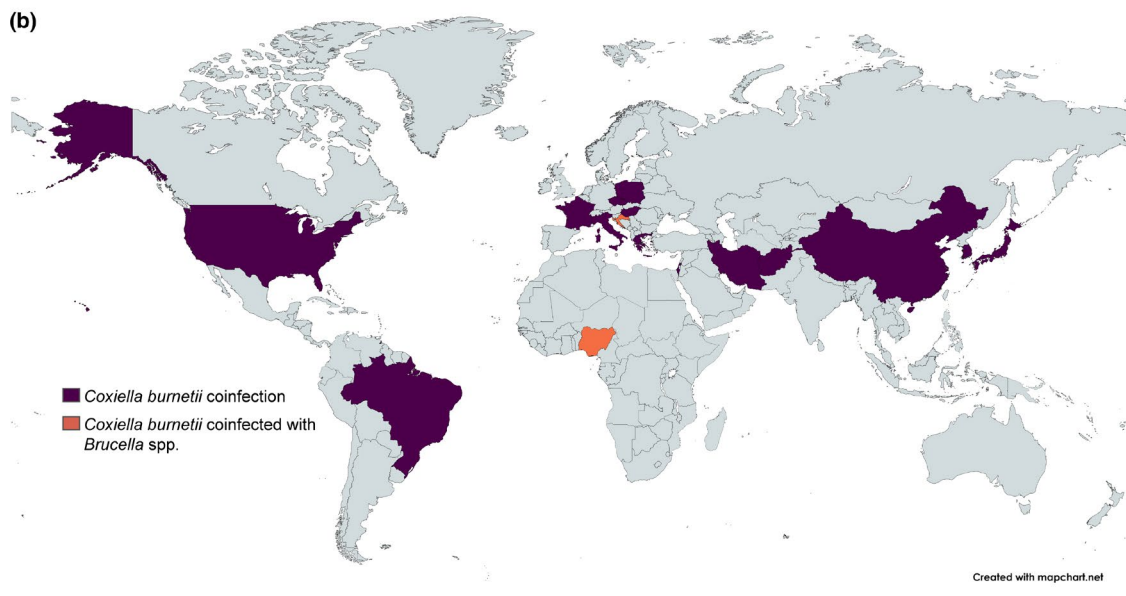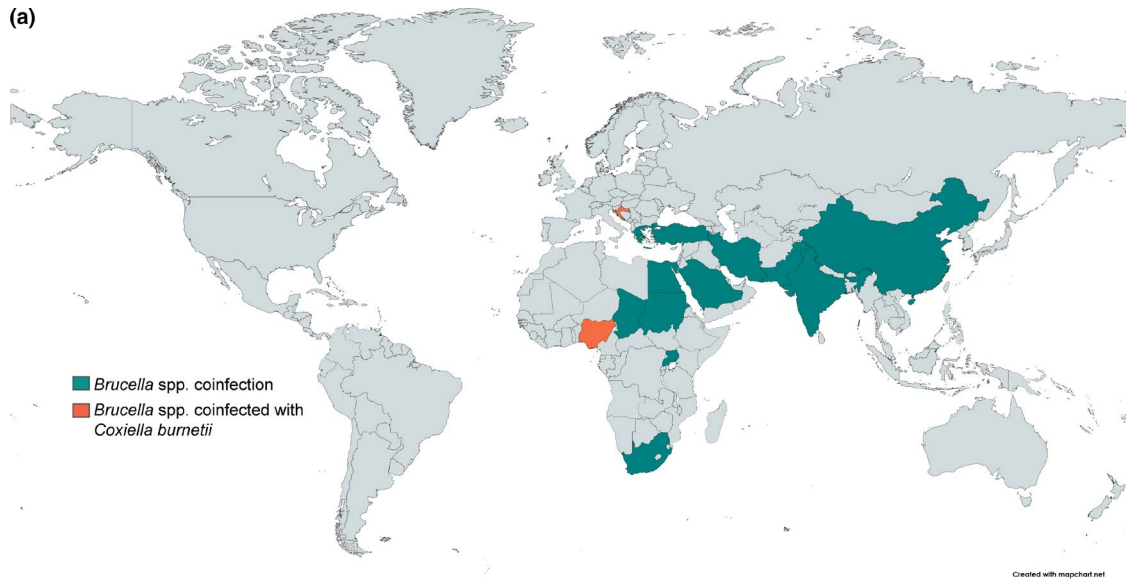
This literature survey illustrates the research effort put into testing for specific pathogens. Thus, the results are a representation of researcher and funding source interest in certain pathogens. Research effort could be skewed based on which pathogen assays have previously been developed, are locally available and are easily performed in the author's laboratory. For instance, a researcher that routinely does serological studies might choose to investigate pathogens with commercially available antibody tests, as opposed to

designing a novel PCR test for a more relevant pathogen. Therefore, the results presented here are strongly affected by public/private interests, reagent availability and researcher expertise.

Upon reviewing the search results, it was apparent that the majority of studies used serological evidence as a proxy for coinfection (31/55), meaning only 24/55 studies and 38 of 86 total 'coinfection' pairs were identified with PCR, microbiology or antigen confirmation, even though the literature search terms imply ongoing infections (i.e. co-, concurrent and concomitant infection). Because host antibodies typically last far beyond the duration of an infection, hosts being seropositive indicate a history of exposure; and thus, co-seropositive indicates co-exposure. It is important to note that co-exposure could also include coinfection if antibodies targeting both pathogens are generated and detected during coinfection. For instance, acute *C. burnetii* infection is commonly diagnosed by
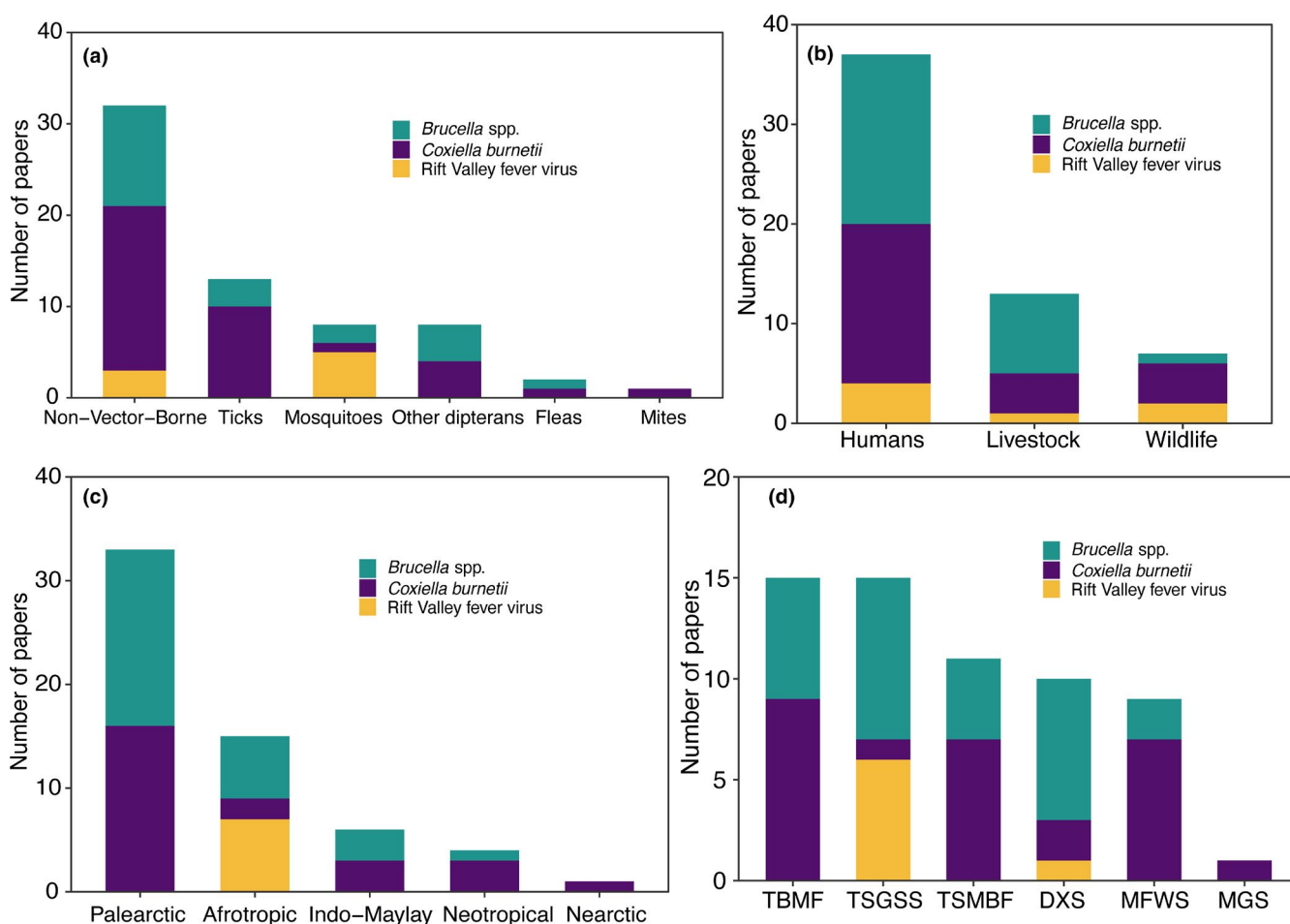
FIGURE 1 (a) Number of pathogens found to coinfect with *Brucella* spp., *C. burnetii* and RVFV according to the transmission mode. 'Other dipterans' refers to non-mosquito dipterans. (b) The number of coinfection articles for each of the three focal pathogens and the host groups (humans, livestock and wildlife) in which the infections were found. A paper that identified coinfections in multiple host groups was counted twice. (c) Distribution of coinfection articles in 5 of the 8 biogeographic realms. Zero studies were found in 3 of the realms and are not included in the graph. (d) Distribution of coinfection articles in 7 of the 14 terrestrial biomes. DXS: Deserts and Xeric Shrublands; TSGSS: Tropical and sub-tropical grasslands, savannas and shrublands; TSMBF: Tropical and sub-tropical moist broadleaf forests; TSDBF: Tropical and sub-tropical dry broadleaf forests; TBMF: Temperate broadleaf and mixed forests; MFWS: Mediterranean forests, woodlands and scrub; TGSS: Temperate grasslands, savannas and shrublands. Zero studies were found in 7 of the terrestrial biomes and are not included in the graph

(a)

Legend:
- *Brucella* spp. coinfection
- *Brucella* spp. coinfected with *Coxiella burnetii*

Created with mapchart.net

(b)

Legend:
- *Coxiella burnetii* coinfection
- *Coxiella burnetii* coinfected with *Brucella* spp.

Created with mapchart.net

(c)

Legend:
- RVFV coinfection

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either high IgM or rising IgG antibodies targeting the pathogen. For the purpose of this review, we did not consider any antibody tests as diagnosing ongoing infection. For simplicity, we will continue to use the literature search term "coinfection" in the following section to describe co-positive pathogen results regardless of detection methods used. In the discussion section, we will further clarify the distinction between co-exposure and coinfection, discussing the strengths and weaknesses of both, highlighting suitability for testing different hypotheses.

8 | RESULTS OF THE SURVEY

8.1 | Diversity of coinfecting pathogens

A total of 50 pathogens were reported to coinfect with *Brucella* spp., *C. burnetii* or RVFV (Table 2). Most of the coinfecting pathogens were bacteria (23), but parasites (8) and viruses (16) were also identified as coinfecting with these EDPs. Thirty-two of the 50 pathogens (64%) are known to be zoonotic (Table 2). *Brucella* spp. and *C. burnetii* had 21 and 32 coinfecting pathogens, respectively, while RVFV had far fewer at 8 coinfecting pathogens (Table 2). RVFV is the least studied pathogen out of the 3 focal pathogens examined here in terms of co-infection. We only found 7 total articles dealing with RVFV coinfections compared to 28 articles involving *Brucella* spp. and 25 involving *C. burnetii* coinfections.

Although the three focal pathogens cause overlapping symptoms in livestock and share areas of endemism, there were only 2 articles describing coinfections between *Brucella* spp. and *C. burnetii*, and none involving RVFV coinfections with *Brucella* spp. or *C. burnetii*. Several coinfecting pathogens are investigated in multiple articles. For example, there were 3 separate articles on *C. burnetii* and *Bartonella* spp. coinfections. Additionally, we found 5 articles involving *C. burnetii* and *Rickettsia* spp., which are transmitted by ticks and the most widely studied pathogen in our study. *Plasmodium falciparum*, a causal agent of malaria, is the only pathogen identified to coinfect with all three focal pathogens. Many of the coinfections identified in the literature search (Table 2) are only found in one article or case report, highlighting the need for additional research to understand the prevalence and impacts of these infections. No pattern could be distinguished regarding disease outcomes, such as immune diseases, febrile illnesses, blood-borne diseases, or those that are vector-borne or zoonotic.

8.2 | Pathogen transmission

Pathogens that are found to coinfect with our focal pathogens have various modes of transmission, with some being transmitted directly to new host individuals, and others that require vectors. We categorized pathogens based on their mode of transmission using the following categories: not vector-borne, mosquitos, ticks, fleas, other dipterans (i.e. non-mosquito dipterans) and mites. Pathogens were counted more than once if they can be transmitted by more than one vector and for those that are vector-borne and not vector-borne (Figure 1a). Many of the coinfecting pathogens are directly transmitted and do not require a vector to be transmitted to subsequent hosts (Figure 1a), including *Mycobacterium* spp., *Toxoplasma gondii* and Hepatitis A/B virus. *C. burnetii* coinfects with non-vector borne pathogens along with pathogens transmitted by fleas, mites, ticks, mosquitoes and other dipterans. Of those requiring a vector, *Coxiella burnetii* is most commonly associated with other tick-borne pathogens such as *F. tularensis*, *Rickettsia* spp., *Ehrlichia* spp. and *B. burgdorferi*. *Brucella* spp. are also found coinfecting with pathogens transmitted by these modes, with the exception of mites. Conversely, of the vectored RVFV coinfecting pathogens, mosquitoes are the only mode of transmission.

8.3 | Coinfections in humans, livestock and wildlife

A total of 55 studies were recorded that involved coinfection with *Brucella* spp., *C. burnetii* or RVFV. Thirty-seven of these studies involved humans, 13 involved livestock, and 8 involved wildlife (mammal or arthropod); some studies involved both humans and livestock or humans and wildlife and were counted twice. We found that few coinfection studies were performed in wildlife (*n* = 8), even though they have the potential to spread all three of these zoonotic pathogens to both livestock and humans. *Brucella* spp. is most studied in humans and livestock with 17 and 8 papers respectively. Rift Valley fever has the least amount of coinfection articles in livestock (*n* = 1) and wildlife (*n* = 2) with slightly more in human (*n* = 4) (Figure 1b). The lack of wildlife coinfection studies for all the pathogens is problematic, considering many of these pathogens and those they coinfect with are zoonotic (Table 2). Understanding the effects of coinfections on the wildlife component of these diseases is critical for improved risk management and limiting transmission to humans and livestock.

8.4 | Geographical Distribution of coinfecting pathogen articles

Out of the 8 biogeographic realms, coinfections were found in 5 of them (Figure 1c). Not surprisingly, there were no studies in the Antarctic and Oceanic realms. Most of the coinfection cases took place within the Palearctic and Afrotropic realms (Figures 1c and 2). The Afrotropic realm was the only realms to have cases of coinfection with all three primary pathogens: *Brucella* spp., *C. burnetii*

TABLE 2 Pathogens coinfecting hosts with *Brucella* spp., Rift Valley fever virus and *Coxiella burnetii* (Q fever)

Coinfecting Pathogens	Pathogen vector-borne	Pathogen zoonotic	*Brucella* spp.	*Coxiella burnetii*	Rift Valley fever virus	Host species coinfected	Ref.
Bacteria							
Anaplasma marginale	Yes	No		X		Ticks (*Dermacentor* and *Ixodes* spp.)	(Bonnet et al., 2013)
Anaplasma phagocytophilum	Yes	Yes		X		Ticks (*Dermacentor* and *Ixodes* spp.)	(Bonnet et al., 2013)
Bartonella spp.	Yes	Yes		XXX		Bat (*Artibeus fimbriatus*), Rodent (*Akodon cursor*), Ticks (*Dermacentor* and *Ixodes* spp.)	(Bonnet et al., 2013; Ferreira et al., 2018; Rozental et al., 2017)
Borrelia burgdorferi sensu lato	Yes	Yes		X		Ticks from migratory birds	(Toma et al., 2014)
Brucella spp.	No	Yes		XXX		Cattle, Humans	(Adamu et al., 2018; Peric et al., 2018)
Chlamydia abortus	No	Yes		X		Sheep	(Kreizinger et al., 2015)
Chlamydiales spp.	No	Yes		X		Cattle	(Kreizinger et al., 2015)
Coxiella burnetii	Yes	Yes	XXX			Cattle, Human	(Adamu et al., 2018; Peric et al., 2018)
Ehrlichia spp.	Yes	Yes		X		Ticks from migratory birds	(Toma et al., 2014)
Enterococcus faecalis	No	Yes		XX		Humans	(Rovery et al., 2009; Yahav et al., 2015)
Francisella philomiragia	No	No		X		Ticks (*Dermacentor* and *Ixodes* spp.)	(Bonnet et al., 2013)
Francisella tularensis	Yes	Yes		XX		Humans, Rodents (M. glareolus, A. flavicollis, A. sylvaticus)	(Bártová et al., 2020; Lai et al., 2009)
Haemophilus influenzae	No	No		X		Humans	(Okimoto et al., 2007)
Kingella kingae	No	No		X		Humans	(Kagan et al., 2020)
Leptospira spp.	No	Yes	X	XXX		*Brucella* – Humans *Coxiella* - Cattle, Humans	(Lai et al., 2017; Parker et al., 2007; Wójcik-Fatla et al., 2018; Zanatto et al., 2019)
Mycobacterium avium paratuberculosis	No	Yes	X			Goats	(Singh et al., 2013)
Mycobacterium bovis	No	Yes	XX		X	African buffalo	(Beechler et al., 2015; Cadmus et al., 2008; Gorsich et al., 2018)
Mycobacterium tuberculosis	No	Yes	XX			Humans, African buffalo	(Ozkok et al., 2012; Zou et al., 2018)

TABLE 2 (Continued)

Coinfecting Pathogens	Pathogen vector-borne	Pathogen zoonotic	Brucella spp.	Coxiella burnetii	Rift Valley fever virus	Host species coinfected	Ref.
Orientia tsutsugamushi	Yes	Yes		XXX		Humans	(Jeong et al., 2019; Lai et al., 2009, 2017)
Pseudomonas aeruginosa	No	No		X		Humans	(Okimoto et al., 2007)
Rickettsia spp.	Yes	Yes	X	XXXXX		Brucella - humans; Coxiella – horses, ticks from migratory birds, humans	(Bailey et al., 2011; Brouqui et al., 2005; Lai et al., 2017; Li et al., 2020; Parker et al., 2007; Toma et al., 2014)
Salmonella typhi	No	Yes	X			Humans	(Parker et al., 2007)
Streptococcus gallolyticus	No	Yes		X		Humans	(Rovery et al., 2009)
Streptococcus mitis	No	No		X		Humans	(Rovery et al., 2009)
Trueperella pyogenes	No	Yes	X			Dog and cat on dairy farm	(Wareth et al., 2018)
Waddlia chondrophila	No	Yes		X		Cattle	(Kreizinger et al., 2015)
Viruses							
Batai virus	Yes	Yes			X	Cattle	(Dutuze et al., 2020)
Border disease virus (pestivirus)	No	No	X		X	Sheep	(Şevik, Gülcü, & Doğan, 2017)
Bovine Herpesvirus	No	No		X		Cattle	(Zanatto et al., 2019)
Bovine immunodeficiency virus (BIV)	No	No	X			Cattle	(Mokhtari et al., 2016)
Bovine viral diarrhoea virus (BVDV)	No	No		X	X	Cattle	(Zanatto et al., 2019)
Bunyamwera Virus	Yes	Yes			X	Cattle	(Dutuze et al., 2020)
Capripox virus (lumpy skin disease)	Yes	No			X	African buffalo	(Fagbo et al., 2014)
Chikungunya virus	Yes	Yes			X	Humans	(Baudin et al., 2016)
Cytomegalovirus	No	No		X		Humans	(Hsu et al., 2014)
Dengue virus	Yes	Yes	XXX			Humans	(Ayyub et al., 2006; Bzeizi et al., 2010; Dutta et al., 2017)
Hepatitis A	No	No	X		X	Humans	(Bektaş, 2014; Oltmann et al., 2008)
Hepatitis C	No	No	X			Humans	(Abou El Azm et al., 2013)
HIV/AIDS	No	No	XX	X		Humans	(Abdollahi et al., 2010; Hajiabdolbaghi et al., 2011; Madariaga et al., 2004)

(Continues)

TABLE 2 (Continued)

Coinfecting Pathogens	Pathogen vector-borne	Pathogen zoonotic	Brucella spp.	Coxiella burnetii	Rift Valley fever virus	Host species coinfected	Ref.
Nairovirus (Crimean-Congo haemorrhagic fever)	Yes	Yes	X			Humans	(Duygu et al., 2017)
Ngari virus	Yes	Yes			X	Cattle	(Dutuze et al., 2020)
Sandfly fever virus (phlebovirus)	Yes	Yes	X	XX		Humans	(Bailey et al., 2011; Ellis et al., 2008[b])
Parasites							
Babesia spp.	Yes	Yes		XX		Horses, ticks (Dermacentor and Ixodes spp.)	(Bonnet et al., 2013; Li et al., 2020)
Leishmania infantum	Yes	Yes	XX	X		Humans	(Fakhar et al., 2009; Georgiadou et al., 2015[a,b])
Neospora caninum	No	No	X	X		Brucella - Pakistani water buffalo; Coxiella - Brazilian cattle	(Nasir et al., 2014; Zanatto et al., 2019)
Onchocerca sp. (likely O. guturosa)	Yes	Yes	X			Brazilian cattle	(Soares Filho et al., 2019)
Plasmodium falciparum	Yes	No	XX	X	XX	Humans	(Badiaga et al., 2005; Brouqui et al., 2005; Kolawole et al., 2018; Nabukenya et al., 2013; Sow et al., 2016)
Theileria equi	Yes	No		X		Horses	(Li et al., 2020)
Toxoplasma gondii	No	Yes	X	XX		Brucella - cattle, sheep, goats, camels; Coxiella - Brazilian cattle	(Ibrahim et al., 2016; Wójcik-Fatla et al., 2018; Zanatto et al., 2019)
Trypanosoma vivax	Yes	Yes		X		Brazilian cattle	(Zanatto et al., 2019)

Each X represents an identified pathogen pair coinfection article. The diseases caused by the pathogens are listed in parentheses. Red X's denote pathogen pairs identified with direct detection methods for both pathogens (e.g. PCR, direct antigen tests, microbiology) indicating confirmed coinfection. Many pathogen detection methods are non-specific; thus, the best resolved taxonomic classifications are used. The host species or clade infected by each pathogen pair are also listed.

[a]Detection methods for both coinfecting pathogens not given.

[b]Reference has coinfections with multiple focal pathogens and thus represents multiple (X) in the table.

or RVFV (Figure 1c). *Brucella* spp. coinfections were primarily from the Palearctic and Afrotropic. In accordance with this finding, many countries within the Palearctic and Afrotropic average between 50 and 500 reported *Brucella* spp. cases annually, while countries outside these realms typically have less than 50 (Pappas et al., 2006). *Coxiella burnetii* was identified in coinfections of tick populations within the Afrotropic and Palearctic realms, which vector *C. burnetii* and many of the associated pathogens to wildlife, livestock and humans (Duron et al., 2015). Due to its current range, RVFV coinfection studies are limited to the Afrotropic. It is important to note, however, that Rolin et al. (2013) argue that there is a high risk of RVFV spreading to broader regions due to wide ranges of competent vectors and outbreaks occurring in diverse habitats (Rolin et al., 2013).

Coinfection studies were conducted in 6 of the 14 terrestrial biomes (Figure 1d): desert and xeric scrubland (DXS), Mediterranean forest, woodland and scrubland (MFWS), montane grasslands and shrubland (MGS), temperate broadleaf mixed forest (TBMF), tropical sub-tropical grasslands savannas and scrubland (TSGSS) and tropical sub-tropical moist broadleaf forest (TSMBF). Most studies took place in TSGSS and TMBF with 15 studies each (Figure 1d). Coinfection studies involving the three primary pathogens were found in the DXS and TSGSS terrestrial biomes. Not surprisingly, all studies involving RVFV coinfections were found in those biomes, which are common across Africa. Only coinfections with *C. burnetii* were detected in montane grasslands and scrublands (Figure 1d). There were no studies of coinfection in tropical and sub-tropical coniferous forests; tropical and sub-tropical dry broadleaf forests; temperate coniferous forests; temperate grasslands, savannas and scrubland; boreal forests/taiga; tundra; flooded grasslands and savannas; and mangroves.

Detailed maps of the geographical distribution of coinfection articles are found in Figure 2 and provide information on the type of coinfections at the country level. Most articles on coinfections with *Brucella* spp. are found in North Africa, the Middle East and south/central Asia. Interestingly, there were no *Brucella* coinfection studies from the new world, including South America, where *Brucella* infections are likely common (Figure 2a). *Coxiella burnetii* coinfection articles took place in the United States and Brazil in the western hemisphere. Many *C. burnetii* coinfection studies were also conducted across central Europe and Asia. Unexpectedly, fewer articles have been conducted in Africa (Figure 2b), even though disease burden is likely high across the continent (Vanderburg et al., 2014). Identified RVFV coinfection studies, on the contrary, are not widely distributed and only represent a handful of countries in Africa (Figure 2c). These maps highlight the disconnect between where the focal pathogens are endemic and where coinfection studies have been conducted.

This survey provides a framework and starting point for understanding the macroecology of coinfections with *Brucella* spp. *C. burnetii* and RVFV. *Brucella* coinfections are likely common across Africa, yet have only been identified in 6 countries. Furthermore, Syria and Mongolia have the highest number of annual reported Brucellosis cases, 1600 and 600, respectively (Pappas et al., 2006), yet have no coinfection studies. Infections with *C. burnetii* are found worldwide (Porter et al., 2011), yet coinfection studies are rare, with only a handful per continent. It is clear that RVFV coinfections have only been studied in a few African countries, despite RVFV being endemic across most of the continent (Kenawy et al., 2018). Coinfections with the three focal pathogens are understudied across much of their endemic area, leading to a blind spot for addressing the health and economic implications of their interactions with other endemic pathogens.

9 | RISK IDENTIFICATION AND MITIGATION STRATEGIES IN A ONE HEALTH CONTEXT

9.1 | From co-exposure to coinfection

A major goal of multi-pathogen studies is to address two types of questions: (1) Does prevalence of Pathogen A increase the prevalence of Pathogen B in a population; and (2) Does infection with Pathogen A affect individual morbidity/mortality caused by infection with Pathogen B? Answering these questions will be a considerable challenge, requiring careful experimental design and large study sizes. While answering these questions is a high bar, we focus on them because they are of particular importance to local populations and administrative authorities and are an integration of other more mechanistic effects of coinfection such as epidemiological, immunological, clinical and evolutionary.

Methods used for detection of the three focal pathogens include microbiology, immunohistochemistry, serology, antigen detection and molecular (PCR and sequencing) (Table 3). The most common detection methods used in the coinfection studies cited in this review are serological tests for pathogen reactive antibodies in samples culminating in 23/30, 21/46 and 3/9 pathogen pairs being detected by antibody alone for *Brucella* spp., *C. burnetii* and RVFV respectively (Table 2). These studies show a history of exposure and subsequent immune reaction to multiple pathogens (co-exposure), but lack the ability to diagnose acute infections with multiple pathogens (coinfection). With broad enough sampling, multi-pathogen serology data can show that exposure risk to one pathogen correlates with exposure to a second, but fail to answer questions of altered transmission or morbidity/mortality due to coinfection.

Surveys testing immunological status with respect to multiple pathogens can reveal surprising drivers of co-exposure such as geographical, ecological, behavioural or climactic correlations. A multi-pathogen seroprevalence study in Cambodia quantified concentrations of serum antibodies of 8 endemic pathogens (Arnold et al., 2018). Antibodies targeting 7 of the pathogens correlated strongly, demonstrating overlapping exposure risks. Antibody titres against one pathogen showed very weak correlation with 6 of the 7 others, yet it was strongly correlated with one, hinting that co-exposure serology can identify multiple non-overlapping factors

TABLE 3 Current methods of diagnosis for brucellosis, Rift Valley fever and Q fever using clinical signs, microbiology, serology and molecular methods

	Vet/Clinical Signs	Microbiology	Serology	Molecular	References
Brucellosis	Abortion, retained placenta, stillbirth, orchitis, arthritis in animals and undulant fevers in humans	Lysis concentration (LC), clot culture, Castaneda's blood culture	Indirect ELISA, Rose Bengal Test (RBT), Competitive ELISA, Standard Tube Agglutination Test	AMOS-PCR	(Mangalgi & Sajjan, 2014)
Rift Valley fever	Ruminants: neonatal mortality, abortion, foetal malformation Humans: Fever, headaches, malaise	Many cell culture systems available, including plaque assay, 50% tissue culture infectious dose (TCID50) assay and focus-forming assay	Virus Neutralization Assay (VNA), ELISA, Indirect ELISA	RT-PCR, multiplex PCR-based macroarray assay, RT-LAMP[a], RPA[b]	(Smith et al., 2019)
Q Fever	Fever, rigours, severe headache, acute hepatitis, pneumonia	Shell vial assay	Indirect ELISA, microaggulation, complement fixation, radioimmunoassay	PCR	(Raoult et al., 1990)

[a]RT Loop-mediated isothermal amplification (RT-LAMP).
[b]Recombinase polymerase amplification (RPA).

leading to exposure risk. With sampling from many ecological replicates or time points, co-exposure data can bolster these hypotheses. Co-exposure studies generate crucial multi-pathogen risk factor data for developing models to predict pathogen burden and help target the distribution of anti-pathogen resources based on environmental predictors and, importantly, seroprevalence of strongly correlated pathogens (i.e. local rainfall and malaria prevalence could predict other mosquito-borne pathogens). However, these data fail to disentangle overlapping ecological drivers of exposure risks from one pathogen driving prevalence of another (question 1). Likewise, co-exposure data completely fail to address the second question regarding altered morbidity/mortality when infected with another pathogen. Direct evidence of coinfection is required for answering both questions.

9.2 | Diagnostic methods to detect coinfection

To move from correlation of serological status and course risk assessment to understanding the within-host interactions of coinfecting pathogens, alternative diagnostic methods must be used. Three main classes of methods will detect signatures of ongoing pathogen presence: direct antigen, q-PCR and next-generation sequencing (Table 3). Antigen testing detects pathogen proteins which generally fade shortly after pathogen clearance. These tests require more upfront development (i.e. antibody generation), but require little to no laboratory time or expertise to administer and are much cheaper and accessible once developed.

Using PCR to test for current infections requires a priori knowledge of the potential pathogen identity and is low throughput. PCR also requires sequences of pathogen genomes to design primers to specifically amplify a portion of the target pathogen's genome. Primer design and synthesis is relatively fast and inexpensive. However, performing PCR on samples requires experienced laboratory personnel and expensive reagents and instruments. Standard PCR provides qualitative (presence/absence) diagnostic information. The more complex quantitative (q) PCR assay can be used to gain information about quantity of pathogen sequences and infection intensity in samples. The amount of pathogen can inform assignment of pathogen to symptom aetiology. Primer design for q-PCR methods requires much more investment to ensure high PCR efficiency. Additionally, testing samples with q-PCR takes added reagents for standards, expensive instrumentation and more researcher time. PCR protocols designed specifically for the three focal EDPs in this review are outlined in Table 3. One advantage of using q-PCR to detect pathogens is that it provides immediate return on investment. Additionally, investment is dual use because the personnel training and construction of laboratory space is the first step in developing many molecular techniques and next-generation sequencing capabilities.

Finally, an emerging gold standard for pathogen detection is shotgun metagenomics or metatranscriptomics for DNA or RNA pathogens respectively. Shotgun sequencing with next-generation

methods such as the Illumina platform takes no development of testing reagents or knowledge of pathogen identity. The only required a priori knowledge is whether the pathogen of interest has an RNA genome (such as a retrovirus) or not. In fact, a major advantage of shotgun sequencing is that it can be used for diagnosing unknown aetiological agents of disease. Another advantage is that shotgun sequencing will detect a wide range of pathogens in a single reaction and is thus high throughput, avoiding the need to develop and perform q-PCR tests for each pathogen. It can also directly identify coinfecting pathogens in a single sample (i.e. influenza virus and opportunistic bacterial infections in lung samples). Shotgun sequencing also provides pathogen genome sequence information that can be used to place the current infection/outbreak into a phylogenetic context. These data are incredibly powerful in identifying pathogen evolutionary origins, viral receptor usage and deducing transmission networks (Chan et al., 2020; Hadfield et al., 2019).

However, there are several drawbacks to using next-generation sequencing to identify pathogens. Generating sequencing libraries for running on an Illumina instrument (e.g. MiSeq, iSeq and NovaSeq) require PCR expertise along with knowledge and instrumentation for additional molecular techniques (e.g. ultrasonic DNA shearing, magnetic bead nucleotide cleanup and fragment size analysis). Additionally, reagent costs for library preparation can be orders of magnitude higher than reagents for q-PCR. In recent years, the cost per base for Illumina sequencing has reduced significantly and reagents such as transposase-based Nextera reduce the technical complexity of library generation. Oxford Nanopore's MinION instrument dramatically reduce the instrumentation cost ($1000 US) and increase the portability of sequencing requiring just a laptop and USB power, but per-sample costs are still high due to low throughput. Despite the added cost relative to serology and PCR methods, using next-gen techniques to detect ongoing/acute infections allows a greater understanding of pathogen biology and can add to the understanding of multi-pathogen infection dynamics and morbidity/mortality consequences within hosts.

9.3 | Considerations when designing biosurveillance screening strategies

Biosurveillance screening strategies are essential for detecting and preventing outbreaks, which could become larger epidemics and pandemics. Because these three diseases are zoonotic, a One Health approach is necessary to achieve the best health outcomes. Therefore, collecting and testing samples from humans, livestock and wildlife will be important components of a biosurveillance system. Furthermore, understanding how environmental conditions impact disease risk will also aid in decreasing spillover events and host coinfections. Institutional and governmental preparedness and surveillance programmes for early detection are the main defence against any emerging and re-emerging pathogen. A coordinated effort at the international level will be a useful, long-term approach to limit outbreaks and severity of these diseases, alone and as

coinfections. Coordinated responses between countries are critical for control of zoonotic outbreaks, especially where wildlife cross borders or livestock are transported and shared among countries.

Pathogens with low population level prevalence are hard to quantify with direct detection of infections. Because immune reactions typically last far beyond clearance of a pathogen, serology can be thought of as integrating infection risk over the current age of the subject (ignoring variation in immune memory longevity). This means that low prevalence pathogens are more easily detected with serology than with antigen tests, PCR or sequencing. Conversely, estimating differences in disease burden between populations or time points due to high prevalence pathogens can be problematic with serology; most individuals will generate antibodies early in life. For instance, assuming a long-lasting antibody response, a 25% versus 50% risk of infection per year would lead to a difference in seroprevalence of 96.3% versus 99.9% among 10-year-old children. Thus, using seroprevalence to detect differences in disease burden would be problematic, requiring very high sample sizes or sampling schemes skewed towards younger individuals. These considerations are especially important in coinfection studies because their outcomes depend on identifying differences in products of prevalence data for two (or more) pathogens.

Another consideration when designing screening strategies is tissue tropism, which describes the tissues of hosts that support the growth and reproduction of specific viruses and bacteria. Immune reactions against many pathogens will typically lead to a systemic response detectable by serology using blood samples alone. However, using antigen tests, PCR or high-throughput sequencing requires samples that contain pathogen protein or nucleic acid, which can be restricted to few host tissues. This problem is compounded when testing for coinfection because the investigated pathogens do not necessarily share a tissue tropism.

A final consideration is how to choose samples to test. The inexpensive nature of serology allows for broad population level testing of asymptomatic individuals, giving unbiased estimates of seroprevalence or exposure (co-exposure for multiple pathogens). Direct pathogen detection, generally being more expensive, might require prior expectations of infection status to choose samples to screen. Care must be taken to avoid biasing experimental results. For example, if coinfection leads to increased symptom severity, testing based on symptom criteria will bias results to show increased coinfections.

10 | CONCLUSIONS

Brucellosis, Q fever and Rift Valley fever are important zoonotic diseases that have the potential to cause widespread human morbidity and mortality as well as large-scale economic losses in livestock. Being infected with multiple pathogens has dramatic effects on disease dynamics and disease outcomes for host individuals. Few studies have investigated these three pathogens regarding coinfection and host immunological responses. Future work should have the goals of uncovering the immunological responses of hosts to

coinfection with these pathogens, identifying coinfection-induced changes in morbidity and mortality, and testing if coinfection leads to altered transmission probabilities between humans, livestock and wildlife. Currently, little is known regarding the role of wildlife in maintaining the pathogens responsible for these diseases. Since the host ranges of these pathogens are large, future work should address how wildlife mediates transmission to livestock and humans to provide, which would provide information to help reduce disease risk where outbreaks can threaten local human and animal populations.

Moving research efforts from co-exposure to coinfection studies will be key for future work in this area. The diagnostic tests and strategies used to screen hosts for multiple pathogens will involve switching from solely serological tests to incorporate methods such as direct antigen tests, q-PCR and next-generation sequencing to detect signatures of ongoing pathogen presence. We recommend developing direct pathogen detection biosurveillance strategies in countries, especially in places like abattoirs, where coinfections are likely and where they may impact the health of local populations. Researchers should consider designing these studies in a One Health context by incorporating human, livestock, wildlife and ecological data to inform risk mitigation strategies and promote health security around the world. Because of the broad distribution of these pathogens, institutional and governmental preparedness and surveillance programmes for early detection will be the main defence. International efforts will be a key component for long-term risk mitigation and outbreak prevention. This is important for reducing the threat of each disease by itself and the potentially more serious challenge presented by host coinfections.

CONFLICT OF INTEREST
We declare no conflicts of interest.

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