

MERS-CoV and SARS-CoV Infections in Animals: A systematic review and meta-analysis of prevalence studies

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SUMMARY

Introduction: Coronaviruses are zoonotic viruses that include human epidemic pathogens such as the Middle East Respiratory Syndrome virus (MERS-CoV), and the Severe Acute Respiratory Syndrome virus (SARS-CoV), among others (e.g., COVID-19, the recently emerging coronavirus disease). The role of animals as potential reservoirs for such pathogens remains an unanswered question. No systematic reviews have been published on this topic to date.

Methods: We performed a systematic literature review with meta-analysis, using three databases to assess MERS-CoV and SARS-CoV infection in animals and its diagnosis by serological and molecular tests. We performed a random-effects model meta-analysis to calculate the pooled prevalence and 95% confidence interval (95%CI).

Results: 6,493 articles were retrieved (1960-2019). After screening by abstract/title, 50 articles were selected for

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full-text assessment. Of them, 42 were finally included for qualitative and quantitative analyses. From a total of 34 studies (n=20,896 animals), the pool prevalence by RT-PCR for MERS-CoV was 7.2% (95%CI 5.6-8.7%), with 97.3% occurring in camels, in which pool prevalence was 10.3% (95%CI 8.3-12.3). Qatar was the country with the highest MERS-CoV RT-PCR pool prevalence: 32.6% (95%CI 4.8-60.4%). From 5 studies and 2,618 animals, for SARS-CoV, the RT-PCR pool prevalence was 2.3% (95%CI 1.3-3.3). Of those, 38.35% were reported on bats, in which the pool prevalence was 14.1% (95%CI 0.0-44.6%).

Discussion: A considerable proportion of infected animals tested positive, particularly by nucleic acid amplification tests (NAAT). This essential condition highlights the relevance of individual animals as reservoirs of MERS-CoV and SARS-CoV. In this meta-analysis, camels and bats were found to be positive by RT-PCR in over 10% of the cases for both; thus, suggesting their relevance in the maintenance of wild zoonotic transmission.

Keywords: Coronavirus, SARS-CoV, MERS-CoV, serology.

■ INTRODUCTION

Rationale

Since 2002, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), became an essential zoonotic pathogen, after the recorded epidemics of SARS taking place in China and other countries across East Asia. A decade later, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), originating in Saudi Arabia, emerged as the second most relevant zoonotic coronavirus [1, 2]. Currently, SARS-CoV, taxonomically, shares species level with other SARS-related coronaviruses within the subgenus *Sarbecovirus*. The subgenera *Embecovirus*, *Hibecovirus*, *Merbecovirus*, and *Nobecovirus*, are all included within the genus *Betacoronavirus* (order *Nidovirales*; suborder *Cornidovirineae*; family *Coronaviridae*; subfamily *Coronavirinae*); while the MERS-CoV is part of the subgenus *Merbecovirus* [3-7].

As expected with other coronaviruses, SARS and MERS CoVs share many ecological and zoonotic aspects, as well as several clinical, epidemiological, and management features of the disease [8-11]. Structurally, these viruses are positive-strand RNA enveloped isolated from bats that share a high degree of sequence homology with human isolates, suggesting their role as likely natural hosts and reservoirs [4, 12-15]. The aforementioned raises the issue of the role and implications of animals as natural hosts and reservoirs for these viruses [10, 16, 17]. Thus, a better understanding of the frequency and transmission dynamics across the wild, suburban, and urban settings, from animals to humans (spillover), is of utmost importance [18-21]. Despite multiple

studies, conducted mainly in humans, animal studies are still scarce, particularly addressing all available evidence on the prevalence of SARS-CoV and MERS-CoV in different animal hosts [22, 23] concisely.

Such findings would be of extreme importance to extrapolate in light of the ongoing expanding epidemics of the third highly relevant zoonotic coronavirus (SARS-CoV-2), currently causing the Coronavirus Disease 2019 (COVID-19), which is also believed to have originated from animals [22, 23], mostly bats in China [24-27]. For these reasons, we carried out a systematic review and meta-analysis to consolidate what has been found from each study assessing infection in animals with MERS-CoV and SARS-CoV by serological and molecular techniques.

It is essential to mention that still, to May 15, 2020, there is a lack of data for SARS-CoV-2 prevalence in animals. Some studies have focused on the phylogenetic analyses of SARS-CoV-2 regarding animals [28, 29], such as bats and pangolins [30]. Even more, some case reports and small series of natural infection of SARS-CoV-2, especially in cats, have also reported, and shortly a systematic review of SARS-CoV-2 disease in animals is highly expected.

Objectives

- To summarize the frequency of infection of animals reported on currently available observational studies for MERS-CoV and SARS-CoV.
- To examine the differences between the pool prevalence by technique, animals, and countries.
- To compare the significant differences in the

frequency of infection between SARS-CoV and MERS-CoV in animals by main serological and molecular techniques.

■ METHODS

Protocol

This protocol follows the recommendations established by the PRISMA statement [31].

Eligibility criteria

We included published peer-reviewed articles that reported infection in animals with serological or molecular confirmation of SARS-CoV or MERS-CoV. For serological tests, we considered Enzyme-linked Immunosorbent assay (ELISA), Indirect Immunofluorescence test (IFI), Immunofluorescence Antibody test (IFAT), pseudo-particle Neutralization test (ppNT), micro-neutralization test (mNT), and the MERS-CoV antigen assay (MERS-CoV Ag assay). For molecular-based testing, Reverse Transcription Polymerase Chain Reaction (RT-PCR), and the Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP) were included. Article language limit was not set, and we included publications from January 1, 2002, until the date the search was finalized and completed (February 1, 2020). Review articles, opinion articles, and letters not presenting original data were excluded from the study, as well as studies reporting on cases with incomplete information.

Information sources and Search Strategy

We conducted a systematic review using Medline/PubMed, Scopus, and Web of Sciences. The search terms used were as follows: “coronavirus”, “SARS coronavirus 2019”, “SARS-CoV”, “MERS coronavirus 2019”, “MERS-CoV”. The searches were concluded by February 1, 2020, and four different researchers independently evaluated search results.

Study Selection

The results of the initial search strategy were first screened by title and abstract. The full texts of relevant articles were examined for inclusion and exclusion criteria (Figure 1). When an article reported duplicate information from the same patient, the data of both reports were combined to obtain complementary data, counting only as a single case. Observational studies that reported

the frequency of animals infected due to SARS-CoV or MERS-CoV were included for quantitative synthesis (metanalysis).

Data collection process and data items

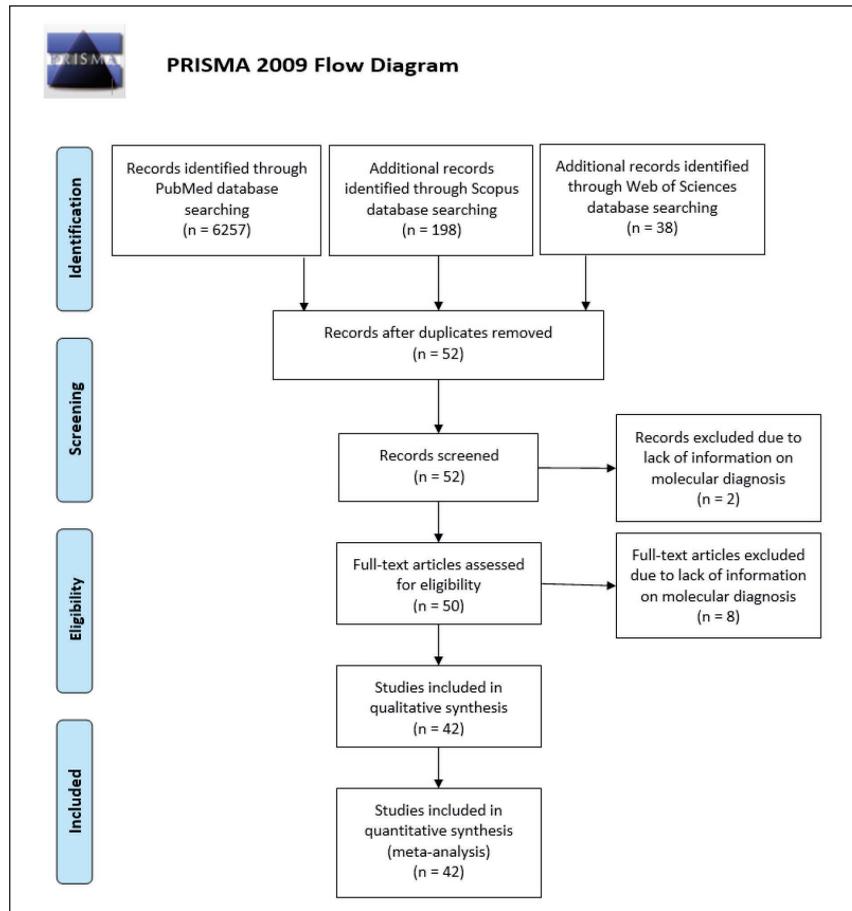
Data extraction forms, including information on the type of publication, the publishing institution, country, year, and date of publication, as well as the number of infected animals assessed by serological or molecular tests, were filled independently by four investigators. A fifth researcher checked the article list and data extractions to ensure there were no duplicate articles or duplicate information of the same study and also resolved discrepancies about study inclusion.

Assessment of methodological quality and risk of bias

For quality assessment, we used the Quality Appraisal of Case Series Studies Checklist of the IHE and specifically the critical appraisal tool to assess the quality of cross-sectional studies (AXIS) [32, 33]. Publication bias was evaluated using a funnel-plot. A random-effects model was used to calculate the pooled prevalence and 95% CI, given variable degrees of data heterogeneity, and given the inherent heterogeneity in any systematic review of studies from the published literature. Besides, Egger’s test was performed.

Statistical approach

Unit discordance for variables was resolved by converting all units to a standard measurement for that variable. Percentages and means \pm standard deviation (SDs) were calculated to describe the distributions of categorical and continuous variables, respectively. Since individual patient information was not available for all patients, we report weighted means and SDs. The baseline data were analyzed using the Stata version 14.0, licensed for Universidad Tecnológica de Pereira. The meta-analyses were performed using Stata, and the software Open Meta[Analyst] [34] and Comprehensive Meta-Analysis ve.3.3® licensed for Universidad Tecnológica de Pereira. Pooled prevalences and their 95% confidence intervals (95% CIs) were used to summarize the weighted effect size for each study grouping variable using the binary random-effects model (the weighting took into consideration the sample sizes of the individual studies), except for median age, where a continuous random-effect model was applied

Figure 1 - Study selection and characteristics.

(DerSimonian-Laird procedure) [35, 36]. A random-effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical, but follow some distribution. For random-effects analyses, the pooled estimate and 95% CIs refer to the center of the distribution of pooled prevalence but do not describe the width of the distribution. Often the pooled estimate and its 95% CI are quoted in isolation as an alternative estimate of the quantity evaluated in a fixed-effect meta-analysis, which is inappropriate. The 95% CI from a random-effects meta-analysis describes uncertainty in the location of the mean of systematically different prevalence in the various studies.

Measures of heterogeneity, including Cochran's Q statistic, the I^2 index, and the tau-squared test, were estimated and reported. We performed subgroup analyses by techniques, animals, and

countries. And meta-analyses for each of the variables of interest. Publication bias was assessed using a funnel-plot. A random-effects model was used to calculate the pooled prevalence and 95% CI, given variable degrees of data heterogeneity, and given the inherent heterogeneity in any systematic review of studies from the published literature.

■ RESULTS

Study Selection and Characteristics

A total of 6,493 articles were retrieved using the search strategy. After screening by abstract and title, 50 articles were finally selected for full-text assessment. Of these, eight were excluded due to lack of information on molecular diagnosis, and 42 were finally included for final qualitative and quantitative meta-analysis (Figure 1). Our review included

42 studies that were published between January 1, 2002, and December 31, 2019, most of them from Kenya (18%), Saudi Arabia (16%), Egypt (10%), and Qatar (10%), including a total of 23,807 animals assessed by RT-PCR, and 8,604 by ELISA, 37 studies for MERS-CoV and 5 for SARS-CoV [37-77]. All the studies were cross-sectional. We analyzed 16 variables for the meta-analyses (Table 1). Publication bias was assessed with a funnel plot for the standard error by logit event, with no evidence of bias for MERS but with evidence for SARS. Additionally, the Egger test suggested that there was no notable evidence of publication bias on MERS ($P=0.6708$), but significant for SARS ($P=0.0103$).

Individual study characteristics

The mean of the number of included animals for RT-PCR per study was 384 and 374 for ELISA, with positive rates ranging from 0 to 100% in both coronaviruses.

Serological findings

Regarding the ELISA, the pool prevalence for MERS-CoV derived from 15 studies, including 7,648 animals, was 73.0% (95%CI 63.8-82.2%) (Table 1). In the case of SARS-CoV, with seven studies, with 947 animals, it was 3.0% (95%CI 0.4-5.5%) (Table 1).

The results for MERS-CoV with the IFI/IFAT techniques were similar, 83.9% (95%CI 66.0-100.0%) (no significant difference with the ELISA) (Table 1). Not enough studies with these techniques were available for meta-analyses of SARS-CoV. However, for SARS-CoV, the pool prevalence with the Western Blot, from 2 studies, with 44 animals, was 65.0% (95%CI 0.0-100.0%). Similarly, for MERS-CoV, there were not enough studies with Western Blot available for meta-analyses (Table 1).

Molecular findings

Regarding the RT-PCR, the pool prevalence for MERS-CoV derived from 34 studies, including

Table 1 - Meta-analysis outcomes (random-effects model)*.

Coronavirus, technique, animals, countries	Number of Studies	Pool Prevalence (%)	95%CI	n	Q^{\dagger}	I^2	t^{28}	p
<i>MERS Studies</i>								
ELISA	15	73.0	63.8-82.2	7,648	1271.924	98.899	0.032	<0.001
IFI/IFAT	4	83.9	66.0-100.0	322	53.402	94.382	0.031	<0.001
RT-PCR	34	7.2	5.6-8.7	20,896	1719.949	98.081	0.001	<0.001
Camels	20	10.3	8.3-12.3	20,330	1705.777	98.89	0.011	<0.001
Qatar	5	32.6	4.8-60.4	177	110.178	96.37	0.01	<0.001
United Arab Emirates	4	16.0	5.8-26.2	8,166	100.376	97.01	0.01	<0.001
Saudi Arabia	5	15.4	0.0-37.2	2,509	799.239	99.5	0.01	<0.001
Egypt	3	7.7	0.0-16.5	4,013	175.581	98.86	0.01	<0.001
Kenya	13	0.4	0.2-0.6	3,830	7.724	0.0	0.01	<0.001
ppNT	9	26.8	6.2-47.4	1,066	6788.447	99.882	0.099	<0.001
Protein MicroArray	8	73.1	56.1-90.2	1,265	957.284	99.269	0.059	<0.001
mNT	15	41.8	21.0-62.6	4,837	9678.135	99.855	0.167	<0.001
<i>SARS Studies</i>								
ELISA	5	3.0	0.4-5.5	947	19.327	68.955	0.001	<0.001
RT-PCR	5	2.3	1.3-3.3	2,618	78.037	66.682	0.001	<0.001
Bats	2	14.1	0.0-44.6	1,004	77.578	88.37	0.005	0.003
Western-Blot	2	65.0	0.0-100.0	44	15.815	93.677	0.221	<0.001

*95% CI = 95% confidence interval. † Cochran's Q statistic for heterogeneity. ‡ I² index for the degree of heterogeneity. § Tau-squared measure of heterogeneity.

ELISA, enzyme-linked immunosorbent assay; IFI, Indirect Immunofluorescence; IFAT, immunofluorescence antibody test; RT-PCR, reverse transcription-polymerase chain reaction; ppNT, pseudoparticle neutralization; mNT, microneutralization test.

20,896 animals, was 7.2% (95%CI 5.6-8.7%) (Table 1). From the total number of animals, 97.3% corresponded to camels, in which pool prevalence was 10.3% (95%CI 8.3-12.3). In the case of SARS-CoV, with 2,618 animals in from 5 studies, the RT-PCR pool prevalence was 2.3% (95%CI 1.3-3.3). Of them, 38.35% were bats, in which the pool prevalence was 14.1% (95%CI 0.0-44.6%) (Table 1).

Comparing the findings by countries, Kenya, Qatar, Saudi Arabia, United Arab Emirates, and Egypt, reported three or more studies for MERS-CoV in animals using RT-PCR (Table 1). The highest prevalence was found in Qatar (Figure 2), with five studies, including 177 animals, with 32.6% (95%CI 4.8-60.4%), followed by United Arab Emirates (UAE) (Figure 2), with four studies, including the highest number of animals, 8,166, for a pool prevalence of 16.0% (95%CI 5.8-26.2%) (no significant differences between both countries). Saudi Arabia yielded 15.4% and Egypt 7.7% (Figure 2). The lowest pool prevalence derived from Kenya (Figure 2), with 13 studies and 3,830 animals, with 0.4% (95%CI 0.2-0.6%), significantly lower than Qatar and UAE (Table 1).

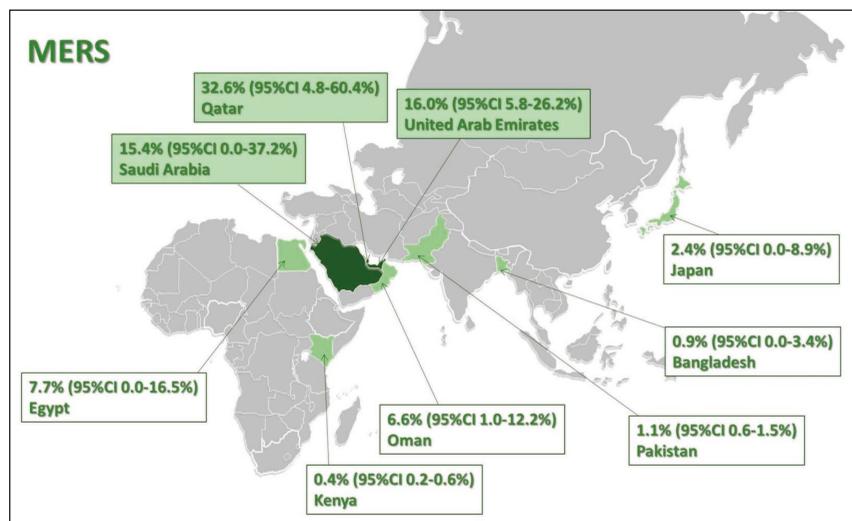
DISCUSSION

A considerable number of studies have shown that the proportion of infected animals testing positive by molecular techniques, is an essential condition to consider the relevance of individual animals as reservoirs of MERS-CoV and SARS-

CoV [8, 17, 78-80]. In this meta-analysis, positivity amongst camels and bats by RT-PCR was found in more than 10% of the evaluated animals, suggesting their possible role and importance in the maintenance of wild zoonotic transmission [40].

In 2012, the MERS-CoV was first detected in humans, and it wasn't until mid-2016 that 1,733 laboratory-confirmed human cases and 628 deaths were reported to the World Health Organization (WHO) from 27 countries [61]. The majority of these cases were reported from the Arabian Peninsula, but imported cases to other countries have also caused significant hospital-linked outbreaks, such as in South Korea, in 2015. Severe respiratory disease and death rate was higher in infections among older patients and those with preexisting conditions. Dromedary camels have been identified as a potential reservoir for the virus following the detection of the virus in camels in Saudi Arabia, Oman, and Qatar, and the detection of high seroprevalence levels of MERS-CoV antibodies in camel populations from a broader range of countries including countries in the Middle East and Africa. Most MERS-CoV infections in humans are not linked to camel exposure and are thought to be due to human-to-human transmission, particularly in health-care settings. The low frequency of camel-to-human infections is supported by the fact that MERS-CoV seroprevalence among the general human population in Saudi Arabia is less than 0.5%, with significantly higher seropositivity amongst camel shepherds (2.3%) and slaughter-

Figure 2 - Pooled prevalences of MERS-CoV in animals, by countries, obtained from the meta-analysis by the random-effects model.



house workers (3.6%) [61]. Nevertheless, results from 20 studies have shown that prevalence in camels is approximately 10.3%, ranging from 8.3 to 12.3 (95%CI); thus, incriminating camels instead as potential animal reservoirs.

According to the Food and Agriculture Organization (FAO), the world population of camels in 2001 was 19 million, of which, 17 million were dromedary camels, and approximately 65% of these were found in the eastern African countries of Sudan, Somalia, Ethiopia, and Kenya [61]. Kenya was found in this systematic review to have a pool prevalence of 0.4% for MERS-CoV, considering more than 3,800 animals. Even though the majority of dromedary camels are in Africa, no cases of MERS-CoV in humans have been reported in Africa, except for a cluster of three family members in Tunisia, back in 2013, which was linked to an imported index case with no history of exposure to camels [81]. Such findings may be related to the low frequency of infection among camels, as observed revealed in this systematic review. In such contexts, comparative genomics and phylogenetic studies focusing on viral sequences derived both from human hosts and dromedaries are essential to trace and link possible zoonotic transmission of MERS-CoV from dromedaries to humans [37].

A retrospective study carried out in Kenya detected MERS-CoV antibodies in more than 90% of camels from different regions of the country [43, 61]. A more recent study that analyzed > 1,000 human sera among pastoralists who did not keep camels reported two likely asymptomatic (< 0.2%) positive human cases for MERS-CoV by neutralizing antibodies detection [61, 82]. To better understand the risk of transmission between camels and humans living in close contact, more studies are needed, including more serosurvey or seroprevalence investigations amongst camels and humans within the same households to determine the prevalence of MERS-CoV antibodies as well as to determine the frequency of infection by molecular techniques and also establish which are the possible risk factors associated with seropositivity in camels and humans. Studies involving follow-up of herds of camels from time of calving through the first year of life with serial blood samples together with oral and rectal or fresh fecal swabs would better help define the ecology of the MERS-CoV-like virus infecting these animals

and provide virus isolates for genetic characterization [53]. Another concerning issue is that the MERS-CoV is not only shed by nasal secretions and feces but also from milk (viral RNA), raising the possibility of food-borne transmission of MERS-CoV [65]. Also, a high proportion of camels presenting for slaughter in some studies show evidence for nasal MERS-CoV shedding [46], thus increasing the likelihood of potential air-borne transmission. A recent systematic review, including studies published before December 31, 2018, reporting measures of seroprevalence or prevalence of hCoV-EMC or MERS-CoV RNA in dromedary populations was published [83]. Nevertheless, this systematic review did not proceed with the corresponding meta-analysis. In Saudi Arabia, they included studies ranging from 0.12-56%, which overlaps with our findings (95%CI 0-37.2%). For UAE, similarly, they reported 0-29%, also overlapping with the current report (95%CI 5.8-26.2%). And for Qatar, they reported 22-79%, while now we estimated the 95%CI in 4.8-60.4% [83]. Although consistent, our findings are more robust, pooled, and accurate.

Evidence suggests that MERS-CoV was present and circulating in camels some decades ago before MERS emerged, causing epidemics in the Middle East, as found in a study assessing blood samples from 1992, finding low-frequency antibodies (4.5%) in the Rift Valley of Kenya [43]. In another retrospective study surveying countries in Africa, (Somalia, Sudan, and Egypt) it was found that 189 archived serum samples from camels tested positive for MERS-CoV antibodies, as far as 1983, with 80% in Somalia and 86.7% in Sudan in 1984 and 85.2% in Somalia and 81.4% in 1997 in Egypt [59]. Also, camels have tested positive to MERS-CoV by serological and molecular-based methods (including genome sequencing) in different studies outside the Arabian Peninsula, and across Africa [42, 67]. In those countries, imported infected camels have also been a matter of concern, even in recent years [37]. For that reason, studies have also been carried in Australia and Japan [52]. However, preliminary data suggest that nor Australian or Japanese dromedaries are exempt from MERS-CoV infection, demanding further confirmatory studies [52, 70].

In addition to camels, the role of other animals in MERS transmission remains largely unknown. Molecular investigations have suggested that

bats in Saudi Arabia are infected with several alphacoronaviruses and betacoronaviruses. A virus isolated from 1 bat showed 100% shared nucleotide identity to a human virus from an index case-patient. An increasing body of research suggests that bats may play a role in human infection [57]. A wide range of CoV species is known to circulate among bats in Saudi Arabia [57]. Although the prevalence of CoVs was high ($\approx 28\%$ of fecal samples), MERS CoV was found in only one bat [57]. A 3.5% MERS CoV infection rate ($n = 29$; 95% CI 0–20%) in *Taphozous perforatus* bats is low compared with that for severe acute respiratory syndrome-like CoV in rhinolophid bats in China (10%–12.5%) but consistent with CoV prevalence among bats in Mexico [57, 84]. Bats are reservoirs of several viruses that can cause human disease, including rabies, Hendra, Nipah, Marburg, severe acute respiratory syndrome CoV, Ebola, rabies, and even some arboviral diseases, such as dengue and Venezuelan Equine Encephalitis viruses [57, 85–90]. Although in the current systematic review, we were not able to find enough prevalence studies of MERS-CoV in bats for a meta-analysis, we did find more studies relating bats to SARS-CoV, in which 14% a pool prevalence was found after analyzing more than 1000 specimens. Cross-species transmission from bats to humans can be direct, through contact with infected bats or their excreta, or facilitated by intermediate hosts, probably also in MERS-CoV, but especially for SARS-CoV [91].

Bat CoVs are typically host specific; however, MERS-related CoVs have reportedly been found in many bat families, including *Vespertilionidae*, *Molossidae*, *Nycteridae*, and *Emballonuridae* (sheath-tailed bats) in Africa, the Americas, Asia, and Europe [57]. In addition to bats and camels, the presence of MERS-CoV in other animals has been investigated, including the alpaca (*Vicugna pacos*), a native *Camelidae* species from South American and a close descendent of the vicuña, which has proved naturally susceptible to MERS-CoV infection. Such findings prompt future studies to determine the role of alpacas as an additional livestock reservoir for MERS-CoV in other areas of the Middle East [68]. In a survey carried out in Qatar, an endemic area for MERS, alpacas were found positive to MERS-CoV-specific antibodies with reciprocal titers ranging from 49 to 773 [68]. These findings raise essential questions regarding

the possibility that some regions of South America would be suitable for MERS-CoV transmission and established endemicity, as well as for other zoonotic coronaviruses. In these same lines, the genus *Vicugna*, which includes the *V. vicugna* (vicuña), another South American camelid, also deserves further investigation regarding its possible susceptibility to infection by MERS-CoV and other coronaviruses. In some countries of South America, the llama, another camelid, widely used as a meat and pack animal by Andean cultures since the Pre-Columbian era, could also prove susceptible to MERS-CoV infection demanding a careful investigation.

In Saudi Arabia, other animals have also been scrutinized, resulting in negative to MERS-CoV, as is the case for sheep, goats, cattle, and chicken [53]. Similar results have been found in Egypt, assessing not only sheep, goats but also water buffalos and cows, testing even negatively [64]. In that same study, more than 93% of camels tested positive for antibodies by ppNT and mNT, exhibiting a high prevalence [64].

In contrast, a study in Egypt following on serum microneutralization assay (mnT) found that one serum sample from a sheep (1/51, 2%) revealed 1:640 neutralizing titer [38]. This same study found negative results from other domestic animals such as cattle, goats, donkeys, buffalo, and horses, but also bats. Using the mnT, they found 84% positivity in camels, with RT-PCR positive confirmation of around 4% [38]. Sheep were also found to test negative for MERS-CoV in a study from the United Arab Emirates [58].

Interestingly also primates, such as the *Papioanubis*, rodents such as *Acomyskempis*, *Acomyspercivalli*, *Elephantulus rufescens*, *Gerbilliscus robustus*, *Aethomys hindei*, *Myomyscus brodernani*, *Grammonys dolichorus*, and *Saccostomus meamsi*, were screened for MERS-CoV in a study from Kenya, testing all negative by RT-PCR [47]. Unfortunately, the authors of this study did not assess blood samples of those animals by serological tests. In a similar study from Kenya, using IFI/IFAT, authors found seropositivity rates as high as 94% in camels [43].

Data derived from a longitudinal study in camels performed in Saudi Arabia, provided evidence for reinfection of previously seropositive camels, suggesting that prior infection does not provide complete immunity from reinfection. This finding is relevant to camel vaccination strategies as

a means to prevent zoonotic transmission [51]. These results may be of interest for MERS-CoV and other coronaviruses in humans, as is the case of Coronavirus Disease 2019 (COVID-19), in which there is also a concern for possible reinfections in humans throughout the ongoing 2020 outbreak in China. In the specific case of MERS-CoV in camels, it appears that infections do not elicit long-lasting (mucosal) immunity [46, 56].

Besides reinfection, coinfection with other coronaviruses is also a matter of pressing concern. In a 2019 study, results revealed the occurrence of MERS-CoV and HKU8r-CoV co-circulation in camels. The study also suggested the possibility of circulation of a recombinant coronavirus virus with the spike of MERS-CoV and the nucleocapsid of an HKU8r-CoV in Kenya. However, the authors failed to provide molecular evidence of an HKU8r-CoV or a putative recombinant virus [76]. In contrast to MERS-CoV, SARS-CoV has also been detected in studies from different animals, besides bats, in China, and other countries such as Kenya, but also from pigs, implicating such species in possible zoonotic transmission [41, 60, 71, 73]. A study in China reported on the isolation of SARS-CoV from a pig during a survey aimed to determine potential routes of viral transmission short after the SARS epidemic, finding that the animal was in close contact with humans in a suburban area and its extended farming villages, Xiqing County of Tianjin, where a SARS outbreak occurred in late spring of 2003 [41].

The results of this systematic review highlight the importance of animals as reservoirs for coronavirus and their close link as zoonotic diseases, as for the case of MERS and SARS. Also, the increasing need for more field studies aimed to understand the main epidemiological features, ecological/environmental aspects, and the role of wild and domestic animals as drivers of these emerging viral infections [25, 92, 93]. Despite a growing volume of literature, further studies on many aspects of related to MERS-CoV and SARS-CoV are needed. Moreover, with the recent emergence of SARS-CoV-2 causing the COVID-19 epidemics, studies aimed at evaluating the role of animals reservoirs such as bats, camels, and other domestic animals as well as wild game, including pangolins, birds, snakes, and other reptiles and mammals, would be highly relevant, as to drawing the landscape on the origin of these coronaviruses as zoonotic

pathogens, and their potential for global expansion [12, 24, 92, 94, 95].

As previously mentioned, soon will be essential to develop systematic reviews about the SARS-CoV-2 prevalence in different animals, as felines, dogs and other vertebrate seems to be susceptible according to various analyses, with still pending interpretations of the preliminary findings reported in the literature for transmission and endemicity mediated by animals of SARS-CoV-2/COVID-19 [28, 28, 96, 97].

Limitations

This review has several limitations. First, still few studies are available for inclusion, especially for SARS-CoV [98, 99]. It would be better to include as many more studies not only from the Middle East but especially from East Asia. Second, more detailed information on the collected and sample animals, particularly regarding their clinical findings and conditions during collection, was unavailable in most studies at the time of analyses; however, the data in this review permit a first synthesis of the frequency of infection due to MERS-CoV and SARS-CoV in animals, although the need to be more detailed for the last one.

■ CONCLUSIONS

Infection with MERS-CoV and SARS-CoV is considered crucial in animals given their reported frequency [99, 100]. These results, as mentioned, have not only implications for MERS-CoV and SARS-CoV but also the novel SARS-CoV-2, causing the COVID-19. Additional research is needed to elucidate multiple aspects of transmission, reinfection, coinfection, and many other ecological aspects of the disease, including the role of environmental issues related to their natural cycles. Future research should focus on developing studies that contribute to fully characterizing and defining the determinants of coronavirus zoonotic spillover and their linkages to make operational contributions for risk assessment [15]. The phenomenon of cross-species spillover is the defining characteristic of pathogens that transmit from vertebrate animals to humans, zoonoses, as is the case of MERS-CoV, SARS-CoV, and SARS-CoV-2. The public health burden imposed by zoonoses includes outbreaks of those pathogens that can lead to even more significant outbreaks,

as currently with the ongoing COVID-19 [29, 94]. Camels and bats are essential confirmed hosts of MERS-CoV and SARS-CoV, respectively. The role of other animals remains an entirely unanswered question, but a link between these viruses and other mammals remains a latent possibility.

Author contributions

DKBA and AJRM formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript. MCCT, AGB, YHR, ICB, HABA, and LJPC refined the search strategy by conducting iterative database queries and incorporating new search terms. MCCT, AGB, YHR, ICB, HABA, LJPC, DKBA, and AJRM searched and collected the articles. AJRM and DKBA conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

Conflicts of interest

All authors report no potential conflicts, except AJRM. AJRM is a COVID-19 consultant for Abbott Laboratories de Colombia S.A.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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