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Cache Valley virus: A scoping review of the global evidence

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Abstract

Cache Valley virus (CVV) is a mosquito-borne RNA virus detected throughout North America, Central America and parts of South America. A limited number of human case reports have described severe illness. CVV infection has been associated with outbreaks of congenital defects in small ruminants in Canada and the United States. A scoping review was conducted to identify, characterize and summarize research on CVV, and to identify research gaps. A structured search was conducted in eight electronic databases, with additional search verification and grey literature investigation. All captured studies were independently appraised by two reviewers for relevance and data characterization. The review captured 143 relevant studies investigating CVV epidemiology (n = 104), pathogenesis (n = 37), viral characteristics (n = 24), transmission (n = 14), diagnostic test performance (n = 8) and mitigation strategies (n = 2). Evidence of CVV infection was found in mosquito studies (n = 47), and serological evidence of exposure was demonstrated in animals (n = 41), as well as human (n = 20) studies. In sheep, five outbreaks of birth defects following asymptomatic dam CVV infection during the first 50 days of pregnancy were reported. Only six human cases of CVV-associated illness were captured, with case symptoms described as initially non-specific, progressing to more severe clinical signs (e.g., meningitis). No research was identified investigating treatment, societal knowledge and risk perception, economic burden or predictive models related to the impact of climate change on CVV. CVV circulates in mosquito and animal species across a large area of the Americas. Small ruminants are the only animals in which CVV-associated clinical disease has been extensively studied. It is likely that human cases are under-reported or misdiagnosed. Future research should focus on the impact of CVV infection in human and animal populations.

KEYWORDS

vector-borne diseases, viral pathogens, zoonoses

1 | INTRODUCTION

Cache Valley virus (CVV) is a mosquito-borne virus belonging to the Bunyamwera serogroup of the *Orthobunyavirus* genus. The virus was first isolated from *Culiseta inornata* mosquitoes in Cache Valley, Utah, in 1956 (Holden & Hess, 1959). Since then, other closely related viruses have been identified. The Bunyamwera serogroup was created in 1960 by grouping together related viruses demonstrating

some level of cross-reactivity (Casals & Whitman, 1960). Currently, recognized CVV subtypes include Tlacotalpan and Playas, identified in Mexico and Ecuador, respectively (Armstrong, Andreadis, & Anderson, 2015; Blitvich, Lorono-Pino, Garcia-Rejon, Farfan-Ale, & Dorman, 2012; Yang, Chan, et al., 2018). Similar viruses, such as Maguari and Xingu, have been categorized as genomically distinct from CVV (Armstrong et al., 2015; Blitvich, Lorono-Pino, et al., 2012; Dunn, Pritlove, & Elliott, 1994; Groseth et al., 2017). Reassortant Bunyamwera viruses have been isolated, including Cholul virus and Potosi virus; both of these reassortants are also categorized as distinct from CVV (Armstrong et al., 2015; Groseth et al., 2017).

Cache Valley virus circulates in mosquitoes and mammals throughout North America, Central America and parts of South America (Armstrong et al., 2015). However, there have only been a small number of cases of human illness attributed to CVV infection (Wilson et al., 2017). Most of the reports of mammalian pathology attributable to CVV infection in mammals describe infection in pregnant sheep and goats (McConnell, Livingston, Calisher, & Crandell, 1985; Rodrigues, 2011; Shapiro et al., 2012). While CVV has been detected in multiple mosquito species, little research has investigated the epizootic cycle of CVV, or the relative importance of the major vectors responsible for transmission (Andreadis, Armstrong, Anderson, & Main, 2014; Ayers et al., 2018; Yang, Chan, et al., 2018).

A scoping review (ScR) on CVV was prioritized to identify, characterize and summarize the available primary research on CVV, and to identify knowledge gaps. The ScR is a research synthesis methodology that aims to describe and map the research underpinning a broad research question or emerging research area in a reproducible and updateable manner (Peters et al., 2017). Bias is minimized through a rigorous process and the use of a study protocol developed a priori. To the best of our knowledge, a ScR on CVV has not previously been conducted.

Impacts

- Cache Valley virus (CVV) circulates in mosquito and animal species across a large area of North, Central and South America.
- The impact of CVV infection has only been extensively studied in small ruminants in the United States of America (USA) and Canada; foetal death or severe malformations may occur whether exposure occurs early in pregnancy.
- There are only six published records of human CVV-associated illness; however, serological studies indicate exposure may be common in some areas, in both humans and small ruminants.

2 | METHODS

2.1 | ScR protocol and team

A study protocol was drafted a priori to document the rationale for the ScR and the search strategy, as suggested by Peters et al. (2017). The protocol also includes the appraisal tools and the analysis plan, which are provided in Appendix S1.

This manuscript conforms to the requirements of the PRISMA extension for ScRs (Tricco et al., 2018). The ScR team included seven individuals with expertise in knowledge synthesis, vector-borne disease, zoonotic disease and library science.

2.2 | Research question

The research question was "What is the global evidence on CVV?" The relevant context for the research question included the

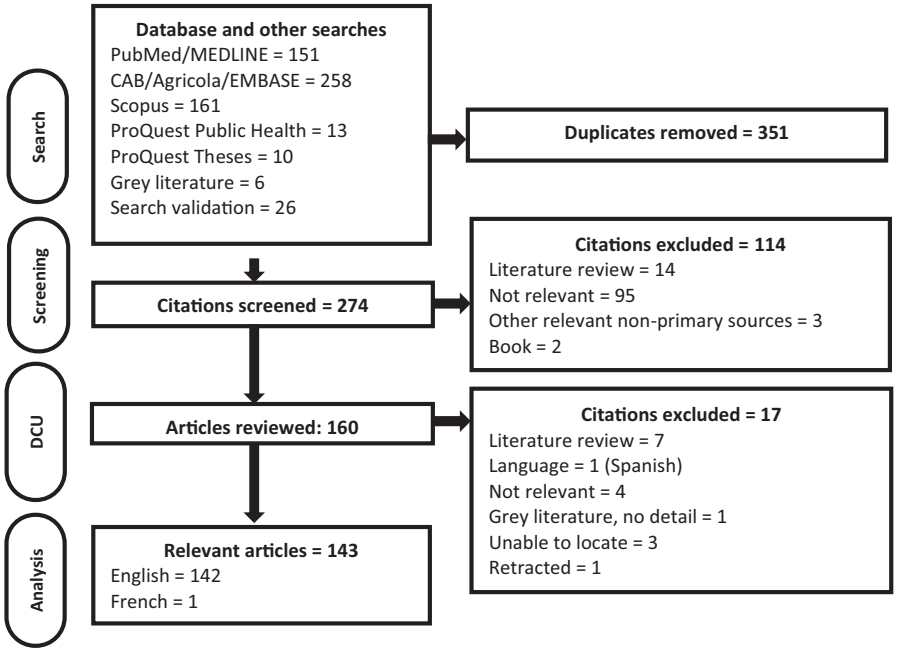

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the citations and articles throughout the scoping review process

identification of all primary research from any settings ranging from insects and animals sampled in their natural environments, to species studied in laboratory settings, to in vitro studies of CVV. All populations which might potentially be sampled for demonstration of CVV or exposure to CVV were deemed relevant, including potential vectors, animal populations and human populations.

2.3 | Search strategy

The pretested search algorithm was implemented on 16 May 2017 and updated 7 January 2019 in eight electronic bibliographic databases to capture publications relevant to the ScR: PubMed/MEDLINE, CAB, Agricola, EMBASE, Scopus, ProQuest Public Health, ProQuest Theses and Dissertations, and the COCHRANE library: ("cache valley" OR playas OR tlacotalpan) AND (virus).

Complete descriptions of each electronic search are presented in Appendix S1. In addition, a grey literature search was conducted (May 2017 and January 2019) in the Centers for Disease Control and Prevention (CDC) Stacks Public Health Database using the same search algorithm. Two Google searches were conducted, one using the original algorithm and one using ("cache valley" OR playas OR tlacotalpan) AND (virus) AND (outbreak); sequential hits were screened until hits were deemed irrelevant, in order to identify any additional grey literature reports. All potentially relevant citations not captured by the database search were added to the ScR.

A search verification strategy was executed to ensure that all relevant publications were identified. Reference lists from 15 selected CVV literature reviews were hand searched for potentially relevant references missed by the electronic search. Additionally, 10 CVV primary research studies were identified as "key studies," and a search for studies citing these key studies was conducted in Google Scholar. Results were then cross-referenced with those captured by the database search, and any potentially relevant citation was added to the ScR. A complete list of the literature reviews and key studies included in the search verification is presented in the study protocol (Appendix S1). Search verification was stopped at the point of saturation, when no additional new references were identified.

2.4 | Relevance screening

Relevance screening, performed on the abstracts, titles and keywords of citations captured by the search, consisted of assessment of each citation with one question ("Does this citation describe primary research on CVV, or a predictive model examining the impacts of climate change on CVV") to rapidly identify potentially relevant research (Appendix S1). All citations describing primary research on CVV or CVV subtypes Tlacotalpan virus and Playas virus were deemed relevant and promoted to the next review level of data characterization, and the full article was procured.

2.5 | Study characterization

The second level of assessment, study characterization, was performed on full articles and captured data pertaining to the study focus, design, populations/samples and outcomes of the study. Exclusion criteria included publication in a language other than English or French, or study outcomes not pertaining to CVV or a subtype of CVV. A complete list of the characteristics captured at

TABLE 1 General characteristics of 143 included publications

Category	Count
Type of citation	
Primary peer-reviewed research	124
Thesis	8
Grey literature with primary data	8
Conference proceeding	3
Language	
English	142
French	1
Continent[a]	
North America	125
USA	104
Canada	12
Mexico	11
Central America/South America/Caribbean	16
Europe	2
Australasia	1
Date of publication	
1950–1959	1
1960–1969	20
1970–1979	17
1980–1989	25
1990–1999	30
2000–2009	17
2010-Present	33
Study design[a]	
Observational	110
Prevalence	74
Cross-sectional	12
Surveillance or monitoring programme	12
Case-series or case report	7
Outbreak report	6
Case–control	2
Other	7
Experimental	48
Challenge trial	31
Molecular characterization	13
Controlled trial	1
Other	9
Evaluation of diagnostic tests	8

[a]Total may sum to more than 143 studies as some studies contributed to more than one category.

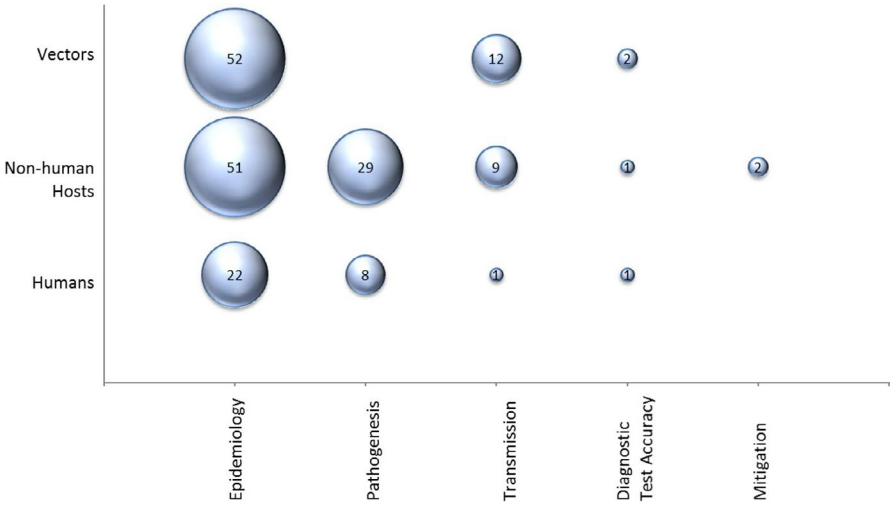

FIGURE 2 Bubble plot of 126 studies sampling humans, non-human hosts and vectors, categorized by study focus. The sum of studies across categories may be larger than the category total as some studies cover more than one population or focus [Colour figure can be viewed at wileyonlinelibrary.com]

the data characterization level is presented in the data characterization tool (Appendix S1).

2.6 | Data management and analysis

Citations captured by the search were uploaded and managed in Endnote X7© (Thomson Reuters). Duplicate citations were removed from the database prior to uploading the list of unique citations to DistillerSR (Evidence Partners, Ottawa, ON, Canada), a web-based systematic review management platform. Each article was screened and characterized within DistillerSR independently by two reviewers; any conflicts between reviewers were resolved by consensus. The final data set was exported from DistillerSR to an Excel spreadsheet (Microsoft 365, Microsoft Corp.) where the descriptive analysis was conducted.

3 | RESULTS

3.1 | General characteristics

Two hundred and seventy-four unique citations were screened at level one of the ScR for relevance, with 160 relevant studies promoted to second-level study characterization (Figure 1). General characteristics of the 143 included relevant studies that were characterized in this ScR are described in Table 1. Most of the research originated from North America (*n* = 126 studies) and was published in English (*n* = 142) in journals (*n* = 123). Only one Spanish study was excluded due to language of publication. Eight reports were classified as grey literature containing primary data and included government surveillance reports (*n* = 6) and laboratory reports (*n* = 2). Overall, a median of two (range 0–7) studies on CVV have been published annually since the first CVV investigation was published in 1959 (Table 1).

The most common research focus was epidemiology (*n* = 104 studies), of which nine studies reported surveillance activities; multiple studies investigated more than one population category (e.g., animals and mosquitoes from same location). Pathogenesis or case reports of CVV in human (*n* = 8 reports describing a total of six cases) and non-human hosts (*n* = 29), in vitro studies of the virus (*n* = 24) and CVV transmission (*n* = 14) were also common foci for investigation. Fewer studies evaluated the performance of diagnostic tests for CVV (*n* = 8) or described the evaluation of mitigation strategies for CVV (*n* = 2) (Figure 2). No studies were captured addressing the treatment of clinical cases of CVV infection, societal knowledge and risk perceptions, economic burden of CVV or predictive models examining the impact of climate change on CVV. Forty-one of 143 included studies reported more than one focus of investigation (e.g., CVV prevalence survey with characterization of isolates recovered).

3.2 | Viral characteristics

Across 82 studies reporting on viral characteristics including genome and antigenicity of CVV, or CVV isolation, 108 different isolates of CVV were identified, as well as seven isolates of Tlacotalpan virus, and three isolates of Playas virus, with additional banked CVV isolates included in phylogenetic analyses (Appendix S3). Of 24 in vitro studies of CVV, the majority focused on viral characterization through immunological and molecular testing (*n* = 21/24 studies) of various CVV strains and other Bunyamwera viruses. Studies (*n* = 14) also focused on CVV transmission characteristics. Phylogenetic analysis was conducted on CVV sequences in 11 studies investigating the relationship among CVV isolates and between CVV and other closely related Bunyamwera viruses (Appendix S3).

Based upon more recent phylogenetic analyses, some of the early isolates collected from South America have been reclassified primarily from CVV to Maguari; the original studies of these virus isolates indicated that they seemed antigenically indistinguishable (Casals & Whitman, 1960; Downs, Spence, Aitken, & Whitman, 1961). These included the first isolates from Brazil (BeAr 7272) and Trinidad (Tr20659) and described around the same time as the first isolate reported in the

TABLE 2 Summary of the 44 mosquito species from which Cache Valley virus (CVV) was detected in at least one sample (47 studies) across 52 observational studies or which were evaluated in 12 experimental studies

	Total	Observational studies		Experimental studies	
Mosquito species	No. of Studies	No. of Studies (# reporting CVV)	CVV Strains isolated	No. of Studies	Competence description
Aedes aegypti	5	4 (0)		1	
Aedes albopictus	9	7 (3)	IL95–1704	2	Disseminated infection in 1.2% of mosquitoes. No transovarial transmission
Aedes cantator	7	7 (1)		0	
Aedes cinereus	12	11 (2)		0	
Aedes japonicus	5	4 (3)		1	Able to transmit the virus. After a 14-day incubation, CVV was present in 28% of saliva samples
Aedes scapularis	6	5 (2)	TR 20659[a] BeAr 7272[b]	1	Able to transmit CVV to mice[1]
Aedes sollicitans	17	16 (6)	M273/61 M291/61 M303/61 M424/61 M515/61 M1724/63	1	Able to transmit CVV to mice
Aedes taeniorhynchus	14	13 (8)	63B10 63B54 63B84 63B141 CVV–478 CVV–390 CVV–213 CVV–078 CVV–002 M517/61 M1727/63 M1728/63 M2410/64 M2522/64 Tr48736	1	Able to transmit CVV to mice
Aedes trivittatus	1	1		0	
Aedes vexans	28	27 (6)	SMIS 708	1	Able to transmit CVV to mice

(Continues)

TABLE 2 (Continued)

	Total	Observational studies		Experimental studies	
Mosquito species	No. of Studies	No. of Studies (# reporting CVV)	CVV Strains isolated	No. of Studies	Competence description
Anopheles albimanus	4	4 (1)	61C1	0	
Anopheles crucians complex	2	2 (1)	M600/61	0	
Anopheles freeborni	2	2 (1)		0	
Anopheles grabhami	1	1 (1)	J 7998	0	
Anopheles punctipennis	19	18 (6)	AR 4381	1	Able to transmit CVV to mice
Anopheles quadrimaculatus	21	17 (6)	AR 531	3	Able to transmit CVV to mice
Anopheles walkeri	10	10 (2)		0	
Coquillettidia perturbans	20	18 (4)		2	Able to transmit to mice and rabbits
Coquillettidia venezuelensis[c]	4[d]	3 (0)		1	Maintained virus for at least 10 days[a]
Culex corniger	3	2 (0)		1	Maintained virus for at least 22 days[a]
Culex fatigans	2	1 (0)		1	No transovarial transmission
Culex nigripalpus	8[d]	7 (0)		1	Able to transmit CVV to mice[a]
Culex pilosus	1	1 (0)		1	
Culex pipiens	13	12 (1)		1	
Culex quinquefasciatus	7	6 (0)		1	Able to transmit CVV to mice after the 4th passage[a]
Culex restuans	15	15 (1)		0	
Culex salinarius	15	15 (2)		0	
Culex tarsalis	16	16 (3)	WMC 72 WMC 216	0	

(Continues)

TABLE 2 (Continued)

Mosquito species	Total	Observational studies		Experimental studies	
	No. of Studies	No. of Studies (# reporting CVV)	CVV Strains isolated	No. of Studies	Competence description
Culiseta inornata	22	21 (8)	6V–633 OM 123 SMIS 381 SM 43 SMIS 436 SMIS 483 SMIS 833 SMIS 1035 SMIS 976 SMIS 1057 SMIS 1049 SMIS 160 SMIS 679 SMIS 735 SMIS 662 WM165 WM-247-71		Able to transmit CVV to mice. Demonstrated a low level of transovarial transmission
Culiseta melanura	9	9 (1)		0	
Mansonia arribalzagai	1	0 (0)		1	Maintained virus for at least 10 days[a]
Mansonia perturbans	1	1 (1)		0	
Mansonia titillans	4	4 (1)	61D240	0	
Ochlerotatus canadensis	17	17 (3)		0	
Ochlerotatus communis	8	7 (0)		1	No infection and did not transmit to mice
Ochlerotatus dorsalis	14	14 (3)		0	
Ochlerotatus fitchii	6	6 (1)	85-0708	0	
Ochlerotatus serratus	3	2 (0)		1	The virus had difficulty propagating. Low level of transmission to mice[a]
Ochlerotatus sticticus	9	8 (0)		1	Low level of infection demonstrated and did not transmit to mice
Ochlerotatus stimulans	10	10 (1)		0	
Ochlerotatus triseriatus	20	18 (4)	Ar-560-79	2	No infection demonstrated and did not transmit to mice
Ochlerotatus trivittatus	17	17 (5)		0	
Psorophora cingulata	2[d]	2 (2)	BT-2368	0	

(Continues)

TABLE 2 (Continued)

Mosquito species	Total	Observational studies		Experimental studies	
	No. of Studies	No. of Studies (# reporting CVV)	CVV Strains isolated	No. of Studies	Competence description
Psorophora ferox	14[d]	14 (2)	AR 4249	0	
Aedes/Ochlerotatus genus, species not specified	14[d]	14 (1)		0	
Anopheles genus, species not specified	6[d]	6 (1)		0	
Genus and species not specified	13	13 (4)		0	

[a]Isolate TR 20659 was isolated in Trinidad 1958 and was originally classified as CVV, but is now considered indistinguishable from BeAR7272 which is a Maguari virus isolate (Downs et al., 1961; Groseth et al., 2017).
[b]Isolate BeAr 7272 was isolated in Brazil in 1954 and was originally classified as antigenically indistinguishable from CVV isolate 6V-633 {634 Casals}, but has since been reclassified as Maguari virus (Groseth et al., 2017). This isolate came from a pool of mixed species: *Aedes scapularis*, *Ae. serratus*, *Ae. sexlineatus*, *Mansonia* sp., *P. ferox*.
[c]Mosquito *Coquillettidia venezuelensis* has also been referred to as *Mansonia venezuelensis* in studies from the 1960s (Aitken & Spence, 1963; Peralta et al., 1966; Galindo, Srihongse, De Rodaniche, & Grayson,1966).
[d]The isolate in one study included in this data set (Peralta et al., 1966) was confirmed as CVV using two isolates TR20659 and BeAr 7272 now categorized as Maguari virus.

USA (6V-633) (Causey, Causey, Maroja, & Macedo, 1961; Holden & Hess, 1959). CVV isolates BeAr 7272 and 6V-633 formed the basis of most antigenic testing in studies performed during the 1960s, with five studies from this period exclusively applying the Brazilian isolate (BeAr 7272) to analysis of samples from the USA (*n* = 3), Panama (*n* = 1) and Argentina (*n* = 1) (Buescher et al., 1970; Collins, 1965; Peralta, Shelokov, Vogel, & Longfellow, 1966; Sabattini, Shope, & Vanella, 1965; Work, 1964). More recent phylogenetic analyses have identified genetic mixing occurring among the related viruses; however, to date, Maguari or Maguari-like viruses have been identified in Brazil, Argentina and Peru, whereas CVV isolates were identified in the USA, Canada, Mexico and Colombia, as well as CVV subtypes in Ecuador (Playas virus) and Mexico (Talactopan virus) (Groseth et al., 2017). Thus, the range of CVV and its subtypes may include all of North and Central America as well as some northern areas of South America.

3.3 | Vectors of CVV

Findings of 52 observational studies sampling various mosquito species and 12 laboratory-based experiments of transmission and vector competence of selected mosquito species are presented in Table 2. Investigators sampled 146 wild-caught mosquito species (Appendix S4), with 47 of 52 studies reporting CVV detection in at least one sample. Eight laboratory-based studies examined mosquito species for competence as a vector of CVV (defined as the ability of a vector to be infected with, replicate and transmit CVV). Natural infection with CVV and confirmed competence in experimental studies were reported for several species from the *Aedes*, *Anopheles*, *Coquillettidia* and *Culiseta* genuses including *Ae. japonicus*, *Ae. scapularis*, *Ae. sollicitans*, *Ae. taeniorhynchus*, *Ae. vexans*, *An. punctipennis*, *An. quadrimaculatus*, *Co. perturbans* and *Cu. inornata* (Table 2). Five additional mosquito species reportedly maintained experimental CVV infection although their ability to transmit CVV was not studied or demonstrated (*Aedes albopictus*, *Coquillettidia venezuelensis*, *Culex corniger*, *Culex quinefasciatus* and *Mansonia arribalzaggi*). One study reported maintenance of experimental CVV infection in *Culex nigripalpus*; however, no reports of CVV detection in wild-caught *Cu. nigripalpus* were identified in this ScR. CVV was also detected in mosquito species from three other studies; however, vector competence was not an evaluated outcome in these studies (Table 2).

Reports of North American mosquito surveillance, describing programmes operating between 1964 and 2016, were captured; sampling included Iowa, New York and across the USA and in the Canadian provinces of Manitoba and Saskatchewan (Appendix S3). One study demonstrated a correlation between quantity or load of circulating CVV, and the number of different mosquito species from which CVV could be isolated (Andreadis et al., 2014).

Other arthropods from which CVV was not detected include midges (*Culicoides sonorensis*, *Culicoides variipennis* and other species), sandflies (*Lutzomyia diabolica* and other species), ticks (*Amblyomma americanum* and *Dermacentor variabilis*), horseflies (*Chrysops* species, *Diachlorus* species, *Hybomitra* species and *Tabanus* species) and stable flies (*Stomoxys calcitrans*) (Appendix S3). One experimental

transmission study concluded that *Cu. sonorensis* is not a competent vector of CVV (Reeves & Miller, 2013).

3.4 | Non-human hosts of CVV

Fifty-one observational studies and 26 challenge trials examined the epidemiology, pathogenesis and mitigation strategies for CVV in infected animal hosts (Appendix S3). The hosts studied included the following: sheep, goats, cattle, horses, chickens, pigs, dogs, cats, rats, mice, squirrels, deer, rabbits, foxes, reptiles, primates and birds, as well as other rodents and wild animals. Challenge studies investigated CVV pathogenesis and transmission in sheep, goats, mice, cows, chickens, hamsters, deer, guinea pigs, opossums, donkeys, rabbits, raccoons and pigs (Appendix S3).

3.4.1 | CVV studies in sheep and goats

The impact of CVV on small ruminants has been the focus of most of the non-human host CVV literature (*n* = 31 studies), as CVV

TABLE 3 Clinical signs and pathology reported in offspring of Cache Valley virus-infected ewes and does across nine observational and eight experimental studies

	Number of studies reporting the sign			
Outcomes of CVV infection	No. of observational studies	Proportion (%) subjects affected	No. of experimental studies	Proportion (%) subjects affected
Clinical signs				
Appetite loss	1	100.0		
Depression	1	100.0		
Disorientation			1	NR[a]
Dystocia	1	NR[a]	1	5.6
Fever			2	NR[a]
Muscle spasms			1	NR[a]
Seizure			1	NR[a]
Suckling difficulties			1	NR[a]
Tremors			1	NR[a]
Congenital defects				
Ankylosis	1	15.0		
Ataxia	1	NR[a]		
Arthrogryposis	5	50.0–80.0	5	12.5–41.6
Concave spinal flexion			1	6.3
Encephalopathy	3	93.3–100.0	1	NR[a]
Hydranencephaly	1	NR[a]	2	2.8
Hydrocephalus	1	NR[a]	1	NR[a]
Inability to walk	1	5.0		
Incomplete diaphragm	1	NR[a]		
Kyphosis	2	NR[a]	2	5.6–12.5
Limb stiffness	1	NR[a]		
Micromyelia			1	NR[a]
Mummification	2	NR[a]	3	11.1–27.8
Muscular abnormalities	5	NR[a]	1	NR[a]
Scoliosis	5	NR[a]	2	5.6
Skeletal abnormalities	3	5.0–19.2		
Low birthweight	1	NR[a]		
Stillbirths	5	5.0–50.0		
Torticollis	5	NR[a]	3	11.1–12.5
Vertebral malformations	1	NR[a]	1	NR[a]
Weak/small trachea	1	5.0		
Generalized weakness	1	50.0		

[a]NR = proportion affected by symptom not reported in one or more articles.

TABLE 4 Seroprevalence of Cache Valley virus (CVV) reported in populations of sheep and goats in 16 studies from Argentina, Canada, Mexico and the USA

Location	Study date	Host species	Seroprevalence +/N (%)	Screening type	References
Argentina					
Córdoba	1962–1963	*Capra aegagrus*	1/34 (2.9%)[a]	General Population	Sabattini et al. (1965)
Mexico					
Coahuila, Nuevo Leon & Tamaulipas	1989	*Ovis musimon*	1/6 (16.7%)	General Population	Aguirre, McLean, Cook, and Quan (1992)
Nuevo Leon	1988	*Ovis aries*	5/44 (11.4%)	Ewes with adverse birth outcomes	Chung (1992)
Yucatan	2007–2008	*Ovis aries*	3/31 (9.7%)	General Population	Blitvich, Saiyasombat, Da Rosa, et al. (2012), Blitvich, Saiyasombat, DaRosa, et al. (2012)
USA					
California, Oregon and Washington	2011	*Ovis aries*	12/686 (1.7%)[b]	General population	Meyers et al. (2015)
Colorado	1981	*Ovis aries*	1/8 (12.5%)	General population	Chung (1992)
Colorado, Idaho, Kansas, Montana, New Mexico, South Dakota, Texas, Utah & Wyoming	2011	*Ovis aries*	130/2459 (5.3%)[b]	General population	Meyers et al. (2015)
Illinois	1988	*Ovis aries*	6/6 (100%)	Ewes with adverse birth outcomes	Chung (1992)
Indiana	1992	*Capra aegagrus*	3/4 (75.0%)	General population	Blackmore (1996)
Iowa, Kentucky, Michigan, Minnesota, Missouri, New York, Ohio, Pennsylvania, Virginia and Wisconsin	2011	*Ovis aries*	319/2005 (15.9%)[b]	General population	Meyers et al. (2015)
Kansas	1981	*Ovis aries*	3/21 (14.3%)	General population	Chung (1992)
Kansas and Texas	1991–1992	*Ovis aries*	336/1100 (30.5%)	General population	Shelton et al.. (1994)
Maryland and Virginia	1962	*Capra aegagrus*	4/13 (30.8%)[b]	General population	Buescher et al. (1970)
Maryland and Virginia	1962	*Ovis aries*	6/22 (27.3%)[b]	General population	Buescher et al. (1970)
Maryland	1990	*Ovis aries*	9/9 (100%)	Ewes with adverse birth outcomes	Chung (1992)
Michigan	1986	*Ovis aries*	9/10 (90%)	Ewes with adverse birth outcomes	Chung (1992)
Montana	2013–2014	*Ovis aries*	1/104 (1.0%)	General population	Johnson et al. (2014)
Nebraska	1987	*Ovis aries*	15/19 (78.9%)	Ewes with adverse birth outcomes	Chung (1992)
New York	1989	*Ovis aries*	2/5 (40%)	Ewes with adverse birth outcomes	Chung (1992)
Oklahoma	1988	*Ovis aries*	5/17 (29.4%)	Ewes with adverse birth outcomes	Chung (1992)
Texas	1981	*Ovis aries*	7/20 (35.0%)	General population	Chung et al. (1991), Chung (1992)
Texas	1981	*Ovis aries*	1/61 (1.6%)	General population	McConnell et al. (1985)
Texas	1981	*Ovis aries*	1/1 (100%)	General population	McConnell et al. (1985), McConnell, Livingston, Calisher and Crandell (1987)
Texas	1983	*Ovis ammon*	2/2 (100%)	General population	McConnell et al. (1987)

(Continues)

TABLE 4 (Continued)

Location	Study date	Host species	Seroprevalence +/N (%)	Screening type	References
Texas	1986	*Ovis aries*	9/104 (8.7%)	Outbreak population	Chung et al. (1991), Chung (1992)
Texas	1986	*Ovis aries*	(5%)[c]	Outbreak population	Edwards et al. (1988)
Texas	1987	*Ovis aries*	(78%)[c]	Outbreak population	Edwards et al. (1988)
Texas	1987	*Ovis aries*	3/5 (60%)[d]	Outbreak population	Edwards et al. (1988)
Texas	1988	*Ovis aries*	5/44 (11.4%)	Outbreak population	Chung et al. (1991), Chung (1992)
Texas	1989	*Ovis aries*	64/89 (71.9%)	Outbreak population	Chung et al. (1991), Chung (1992)
Wyoming	1981	*Ovis aries*	1/3 (33.3%)	General population	Chung et al. (1991) Chung (1992)
Canada					
Saskatchewan	2013–2014	Ovis aries	84/130sheep (64.6%) 47/50 flocks (94.0%)	General population	Uehlinger et al. (2018)

[a]The isolate used to make the antigenic test in this study was BeAr 7272, which has been reclassified as Maguari virus.
[b]Number of positive cases estimated from data provided in the study.
[c]N value not reported.
[d]CVV was isolated from all three seropositive ewes.

infection during pregnancy results in a range of negative birth outcomes from reproductive failure to major congenital defects. Eleven studies describing twelve challenge trials were conducted in the USA in sheep (*n* = 8 trials) and goats (*n* = 4) from 1969 to 2013, studying CVV pathogenesis (Appendix S3). Sixteen studies described the adverse foetal outcomes associated with CVV infection in small ruminants during early pregnancy (days 1–50 of gestation), the hallmark of which is a range of congenital defects of the skeletal and central nervous systems (Table 3). Six studies reported pathology in sheep naturally infected with CVV (Appendix S3). One study estimated the interval of time between CVV exposure and development of viremia in sheep (Chung, Livingston, Jones, & Collisson, 1991), with another describing the duration of viremia in CVV-infected goats (Kokernot, Radivojevic, & Anderson, 1969).

Five outbreaks of clinical disease caused by CVV infection in sheep populations were described in six papers, occurring in the USA (in Texas, 1986–1988 and North Dakota, 1990) and in Canada (in Ontario, during 2011 and 2016, and Québec, 2013) (Appendix S3). These outbreaks were reported between the months of December and February, during lambing season, presenting with an unusually high prevalence of stillbirths and foetal deformities.

Sixteen studies reported the seroprevalence of CVV in sheep (*Ovis aries* 12/16, *Ovis ammon* 1/16, *Ovis musimon* 1/16) and in goats (*Capra aegagrus* 3/16), sampling animals during an outbreak (*n* = 3 studies), dams of lambs with congenital defects (*n* = 1) or selected healthy populations (*n* = 14) (Table 4, Appendix S3). The single study quantitatively investigating the association between housing and CVV exposure in sheep described a significant ($p < 0.05$) positive association between seroprevalence of CVV and sheep kept outside, relative to sheep kept in housing with four walls, a roof and a door closed most of the time (Meyers et al., 2015). This finding was consistent with a field experiment conducted in Texas, where sheep housed indoors remained CVV seronegative despite high seroconversion in pastured sheep (Crandell, Livingstone, & Shelton, 1989). Other potential risk factors identified for CVV seropositivity included: various flock management factors; increasing age, sex and breed of animals; year of sampling and location in Eastern USA states (Meyers et al., 2015; Shelton, de la Bermejillo, Willingham, & Mock, 1994).

3.5 | CVV studies in other non-human hosts

Seroprevalence of CVV was investigated in 33 studies sampling deer, rabbits, horses, swine, cows, foxes, dogs, raccoons, woodchucks, rats, voles, mules, wild birds, chickens, mongooses and monkeys (Appendix S5). Researchers reported isolation of CVV in Michigan from naturally infected horses in two studies conducted during a 1980 epizootic of eastern equine encephalitis (McLean et al., 1985; McLean, Calisher, & Parham, 1987). A study conducted in Maryland reported 45% of cattle sampled developed CVV neutralizing antibodies over a 6-month study period (Yuill, Gochenour, Lucas, Collins, & Buescher, 1970). An association between increasing age and odds of CVV seropositivity was reported in studies sampling white-tailed deer (*n* = 2 studies), horses (*n* = 1) and swine (*n* = 1) (Blackmore,

1996; Blackmore & Grimstad, 1998; McLean et al., 1987; Neitzel & Grimstad, 1991).

Challenge experiments (n = 15) were conducted in cows, guinea pigs, opossums, horses, chickens, hamsters, mice, deer, rabbits, raccoons and swine (Appendix S6). Most of these studies investigated the pathogenesis of CVV in animals (12/15) and/or the transmission of CVV to and from competent vectors (9/15). Researchers also evaluated the influence of vitamin A on the immune response to CVV in deer (Blackmore, 1996). Only one study reported pathology (failure to litter in mice) resulting from CVV infection in an animal host other than sheep or goats (Nowicki, 1996). Several aspects of experimentally induced CVV infection were described, including time of onset of CVV viremia post-exposure in rabbits, swine, goats and calves (Blackmore & Grimstad, 2008; Kokernot et al., 1969) and duration of viremia in deer, hamsters, mice, guinea pigs, rabbits and calves (Blackmore & Grimstad, 1998; Edwards, Higgs, & Beaty, 1998; Kokernot et al., 1969). White-tailed deer were identified as a potential reservoir for CVV, with reservoir defined as a population in which CVV naturally persists (Blackmore & Grimstad, 1998).

3.6 | Transmission of CVV

Fourteen studies reported investigation of one or more broad aspects of CVV transmission, including vector-to-host transmission (n = 6 studies), host-to-vector transmission (n = 3), vector-to-vector transovarial only transmission (n = 3) and host-to-host transmission (n = 2). Four studies investigated more than one mode of transmission (Blackmore, Blackmore, & Grimstad, 1998; Blackmore & Grimstad, 2008; Corner, Robertson, Hayles, & Iversen, 1980; Saliba, DeFoliart, Yuill, & Hanson, 1973). Successful transmission of CVV to mice was demonstrated from eight species of mosquito: *Ae. scapularis*, *Ae. sollicitans*, *Ae. taeniorhynchus*, *Ae. vexans*, *An. punctipennis*, *An. quadrimaculatus*, *Co. perturbans* and *Cu. inornata* (Table 5). In one study, eastern cottontails (*Sylvilagus floridanus*) were successfully infected by *Co. perturbans* but did not experience sufficient viremia to transmit CVV back to the mosquito (Blackmore & Grimstad, 2008). In contrast, CVV transmission from hosts to mosquitoes was successful in studies using Syrian hamsters (n = 1) and mice (n = 3) (Table 5). One study demonstrated an interaction between detectable CVV infection in mice following a challenge and exposure to mosquitoes (Edwards et al., 1998). Eight studies investigated determinants of vector competence such as dose, extrinsic incubation period, infection rate, dissemination rate and transmission rate under experimental conditions (Aitken & Spence, 1963; Ayers et al., 2018; Blackmore et al., 1998; Miller, 1997; Reeves & Miller, 2013; Saliba et al., 1973; Yang, Chan, et al., 2018; Yuill & Thompson, 1970).

Successful transovarial transmission of CVV in *Cu. inornata* was reported in one study (Corner et al., 1980). However, unsuccessful transovarial CVV transmission attempts were reported in *Ae. albopictus* and *Culex fatigans* species, two species categorized to have limited competence as vectors of CVV (Table 5). In hosts, vertical transmission of CVV was demonstrated in mice, but adults did not become infected from the consumption of viremic pups and other contaminated bodily fluids (Blackmore, 1996; Edwards & Hendricks, 1997; Nowicki, 1996).

3.7 | CVV studies in humans

Six human clinical cases of CVV were captured by this ScR; all attributed to CVV exposure occurring in the USA. The first case was reported in 1995 in North Carolina (CDC, 1996; Sexton et al., 1997), followed by single cases occurring in Wisconsin in 2003 (Campbell et al., 2006), New York in 2011 (CDC, 2012; Nguyen et al., 2013) and Missouri 2015 (CDC, 2017). More recently, in 2016 two immune-compromised men from New York and Australia, the latter with travel history to the USA, were diagnosed with CVV-associated meningoencephalitis (Wilson et al., 2017; Yang, Qiu, et al., 2018b). Researchers hypothesized that the Australian patient's exposure likely occurred in 2013, but the diagnosis of CVV infection did not occur until 2016 after several years of chronic neurological deficits, eventually diagnosed as chronic meningoencephalitis (Wilson et al., 2017). The clinical pathology of these severe human CVV cases was reported in journal articles, except for the Missouri case, which was only described in a surveillance report with limited case information (CDC, 2017).

Symptoms of CVV infection reported from five of the six published cases include non-specific clinical signs: fever (reported in 5/5 cases), headaches (3/5), nausea (3/5), vomiting (3/5), appearance of rash (2/5), body aches (1/5) and confusion (1/5). Three patients experienced long-term symptoms including persistent headaches (reported in 2/3 cases), difficulty in word finding (1/3), memory loss (1/3) and motor control deficits (1/3) (Campbell et al., 2006; Nguyen et al., 2013; Sexton et al., 1997). The Australian patient eventually diagnosed with CVV chronic meningoencephalitis displayed 6 months of progressive memory decline, slowing of speech and mood disturbance, predominantly anxiety; the diagnosis was made via metagenomic next-generation sequencing of the patient's cerebrospinal fluid and brain biopsy tissue (Wilson et al., 2017). CVV illness was ultimately fatal, either directly or due to other complications, in three of five CVV cases for which outcome data were reported (Sexton et al., 1997; Wilson et al., 2017; Yang, Qiu, et al., 2018b).

Twenty human CVV serosurveys conducted in North and South America, reported human CVV seroprevalence ranging from 0% to 50%, in studies published from 1956 to 2010 (Table 6). As with non-human animal hosts, increasing age was associated with increasing odds of seropositivity in some studies (Blitvich, Saiyasombat, Talavera-Aguilar, et al., 2012; Heard, 1997). Two case–control studies investigated the potential association between the presence of maternal CVV antibodies and congenital malformations in their babies. While one study did not detect any CVV antibodies in the sample population (Edwards & Hendricks, 1997), the second case–control study had a very small sample size, but did report a significant association between CVV antibodies in mothers and the occurrence of macrocephaly or microcephaly in their newborns (Calisher & Sever, 1995).

3.8 | Diagnostic test performance

Eight studies assessed the performance of diagnostic tests for the detection of viral RNA or serological evidence of prior CVV

TABLE 5 Transmission of Cache Valley virus reported in vectors and hosts across 10 studies

Transmission type	Original CVV host	Recipient	Transmission successful?	References
	Aedes scapularis	Mice[b]	Yes[c]	Aitken and Spence (1963)
Vector to host	*Aedes sollicitans*	Mice: Charles River albino	Yes	Yuill & Thompson, (1970)
	Aedes taeniorhynchus	Mice: Charles River albino	Yes	Yuill & Thompson (1970)
	Aedes vexans	Mice: Charles River CD1 and HA/ICR strain	Yes	Saliba et al. (1973)
	Anopheles punctipennis	Mice: Charles River CD1 and HA/ICR strain	Yes	Saliba et al. (1)973
	Anopheles quadrimaculatus	Mice: ICR strain	Yes	Blackmore et al. (1998)
	Anopheles quadrimaculatus	Mice: Charles River CD1 and HA/ICR strain	Yes	Saliba et al. (1973)
	Coquillettidia perturbans	Mice: ICR strain	Yes	Blackmore et al. (1998)
	Coquillettidia perturbans	Rabbit: *Sylvilagus floridanus*	Yes	Blackmore and Grimstad (2008)
	Culiseta inornata	Mice[b]	Yes	Corner et al. (1980)
	Culex nigripalpus	Mice[b]	Yes[c]	Aitken and Spence (1963)
	Culex quinquefasciatus	Mice[b]	Yes[c]	Aitken and Spence (1963)
	Ochlerotatus communis	Mice: Charles River CD1 and HA/ICR strain	No	Saliba et al. (1973)
	Ochlerotatus serratus	Mice[b]	Yes[c]	Aitken and Spence (1963)
	Ochlerotatus triseriatus	Mice: Charles River CD1 and HA/ICR strain	No	Saliba et al. (1973)
Host to vector	Syrian hamster: *Mesocricetus auratus*	*Coquillettidia perturbans*	Yes	Saliba et al. (1973)
	Mice[b]	*Aedes scapularis*	Yes[c]	Aitken and Spence (1963)
	Mice[b]	*Culiseta inornata*	Yes	Corner et al. (1980)
	Mice and a feeding device[b]	*Aedes vexans*	Yes	Saliba et al. (1973)
	Mice and a feeding device[b]	*Anopheles punctipennis*	Yes	Saliba et al. (1973)
	Mice and a feeding device[b]	*Anopheles quadrimaculatus*	Yes	Saliba et al. (1973)
	Mice and a feeding device[b]	*Ochlerotatus communis*	No	Saliba et al. (1973)
	Mice and a feeding device[b]	*Ochlerotatus sticticus*	Yes	Saliba et al. (1973)
	Mice and a feeding device[b]	*Ochlerotatus triseriatus*	No	Saliba et al. (1973)
	Rabbit: *Sylvilagus floridanus*	*Coquillettidia perturbans*	No	Blackmore and Grimstad (2008)
Vector to vector: transovarial	*Aedes albopictus*	*Aedes albopictus* (offspring)	No	Miller (1997)
	Culex fatigans	*Culex fatigans* (offspring)	No	Tesh and Gubler (1975)
	Culiseta inornata	*Culiseta inornata* (offspring)	Ye	Corner et al. (1980)
Host to host	Mice: ICR strain	Mice: ICR strain	No	Blackmore (1996)
	Mice[b]	Mice (offspring) [b]	Yes	Nowicki (1996)
	Humans	Humans (offspring)[d]	No	Nowicki (1996)

[a]Some studies investigated more than one mode of transmission (Blackmore et al., 1998; Blackmore & Grimstad, 2008; Corner et al., 1980; Saliba et al., 1973).
[b]Species or strain name not specified.
[c]Isolate TR 20659 was isolated in Trinidad 1958 and was originally classified as CVV but is now considered to be indistinguishable from BeAR7272 which is a Maguari virus isolate (Downs et al., 1961; Groseth et al., 2017).
[d]Prenatal transmission determined by the presence of IgM antibodies to CVV in cord blood.

infection. The majority of these papers described initial proof-of-accuracy studies, using CVV-spiked samples at various dilutions and in various media to evaluate the sensitivity of the test; they also employed an array of other viruses to assess test specificity. Among these eight studies, samples used included pooled mosquitoes (n = 2/8 studies), and animal (n = 1/8) or human (n = 1/8) sera. We also captured in vitro experiments (n = 5/8). The captured diagnostic test studies investigated the performance of molecular (n = 5/8) and immunological (n = 3/8) assays, as well as virus isolation techniques (n = 1/8). All five molecular assays were reverse-transcription polymerase chain reaction tests (Appendix S3). Reported performance parameters included analytical sensitivity

TABLE 6 Seroprevalence of Cache Valley virus reported in human populations between 1956 and 2009 in 20 studies

Country/Region[a]	Sampling date	Study design	Population	Positive/*N*	Proportion positive (%)	References
North America						
Canada						
Manitoba	2009	Prevalence Survey	Suspected West Nile cases.	9/55	16.4	Dimitrova et al. (2011)
Saskatchewan	2009	Prevalence Survey	Suspected West Nile cases.	9/216	4.2	Dimitrova et al. (2011)
Mexico						
Chiapas & Tabasco	1969	Prevalence Survey	Outpatients; Men in factories, prisons, and the army	1/46	2.2	Goldsmith et al. (1979)
Coatetelco	1961	Prevalence Survey	Humans age 41–75	0/20	0	Scherer, Campillo-Sainz, Dickerman, Diaz-Najera, and Madalengoitia (1967)
Oaxaca	1969	Prevalence Survey	Outpatients; Men in factories, prisons, and the army	13/493	2.6	Goldsmith et al. (1979)
Tlacotalpan	1961	Prevalence Survey	Humans age 20–41	0/20	0	Scherer et al. (1967)
Tlacotalpan	1961	Prevalence Survey	Humans age 41–75	7/18	38.9	Scherer et al. (1967)
Campeche, Quintana Roo & Yucatan	2007	Prevalence Survey	Febrile patients	18/146[b]	12.3	Blitvich, Lorono-Pino, et al. (2012)
USA						
Alaska	1983–1986	Prevalence Survey	General population	0/90	0	Walters, Tirrell, and Shope (1999)
California	1987	Prevalence Survey	Outpatients; Outdoor workers	0/235	0	Campbell, Reeves, Hardy, and Eldridge (1992)
California	1988	Prevalence Survey	Outpatients; Outdoor workers	0/118	0	Campbell et al. (1992)
Colorado	2008–2009	Prevalence Survey	Rocky Mountain National Park Employees	2/60	3.3	Kosoy et al. (2016)
Florida	1960	Cross-sectional	Humans aged 1–15 living a reservation	2/5	40.0	Work (1964)[c]
Florida	1960	Cross-sectional	Humans age 16 + living in a reservation	12/60	20.0	Work (1964)[c]
Illinois	1964	Prevalence Survey	General population	1/59	1.7	Kokernot et al. (1969)
Indiana	1989–1990	Prevalence Survey	Hospital patients	36/2696	1.3	Heard (1997)
Indiana	1990–1993	Prevalence Survey	Individuals with CNS infections	3/244	1.2	Heard (1997)
Indiana	1993–1994	Cross-sectional	Live birth cord samples	32/1088	2.9	Nowicki (1996)
Kentucky	1965	Prevalence Survey	General population	3/55	5.5	Kokernot et al. (1969)
Kentucky	1966	Prevalence Survey	General population	2/72	2.8	Kokernot et al. (1969)
Maryland	1962–1963	Prevalence Survey	General population	9/180	5.0	Buescher et al. (1970)[c]
Tennessee	2008–2009	Prevalence Survey	Great Smoky Mountain National Park Employees	2/75	2.7	Kosoy et al. (2016)

(Continues)

TABLE 6 (Continued)

Country/Region[a]	Sampling date	Study design	Population	Positive/N	Proportion positive (%)	References
Utah	1956	Prevalence Survey	Humans in the vicinity of the first CVV isolations	0/5	0	Holden and Hess (1959)
Virginia	1961	Prevalence Survey	General population	33/176	18.7	Buescher et al. (1970)[c]
Wyoming	2010	Prevalence Survey	Grand Teton National Park seasonal employees	5/160	3.1	Kosoy et al. (2016)
South America						
Argentina						
Buenos Aires, Mendoza & Tucumán	1961	Prevalence Survey	Healthy males 20–40 years	4/175	2.3	Mettler, Parodi, and Casals (1963)
Córdoba & Litoral	1961–1963	Prevalence Survey	General population	6/213	2.8	Sabattini et al. (1965)[c]
Córdoba	2004–2005	Prevalence Survey	Outpatients	40/638	6.3	Tauro, Almeida, and Contigiani (2009)[c]
Guyana						
Upper Takutu-Upper Essequibo	1956	Prevalence Survey	General population	4/18	22.2	Downs et al. (1961)[c]
Upper Takutu-Upper Essequibo	1959	Prevalence Survey	General population	4/8	50.0	Downs et al. (1961)[c]
Jamaica						
Kingston, Portland, St. Andrew, St. James & St. Thomas	1963–1964	Prevalence Survey	Children and adults; positive results were mainly children under 5	29/531	5.5	Belle, Grant and Griffiths (1966)
Portland, St. Andrew & St. Thomas	1963–1967	Prevalence Survey	Humans age 5–15	0/25	0	Belle, King, Griffiths, and Grant (1980)
Portland, St. Andrew & St. Thomas	1963–1967	Prevalence Survey	Humans age 15+	5/77	6.5	Belle et al. (1980)
NR[d]	1989[e]	Prevalence Survey	Individuals with and without HTLV–1 antibodies	16/200	8.0	Murphy, Calisher, Figueroa, Gibbs, and Blattner (1989)
Trinidad						
Port of Spain	1961[e]	Prevalence Survey	Field staff members of the Trinidad Regional Virus Laboratory	4/11	36.4	Downs et al. (1961)[c]
Sangre Grande	1961[e]	Prevalence Survey	General population	15/46	32.6	Downs et al. (1961)[c]

[a]Region is the state or province studied as described by the author.
[b]Number of positive cases estimated from data provided in the study.
[c]The antigenic test employed was developed using isolate BeAr 7272 (Buescher et al., 1970; Work, 1964), TR 20659 (Downs et al., 1961) and CbaAr- 426 (Sabattini et al., 1965), which have been reclassified as Maguari virus (Groseth et al., 2017). CVV and Maguari virus isolates were shown to be indistinguishable antigenically at the time of these studies (Casals & Whitman, 1960).
[d]NR = data not recorded.
[e]Publication date reported as study date was not available.

(*n* = 2 studies), specificity (*n* = 3) and limits of detection (*n* = 2). One study investigated both immunological and molecular tests (Brockus,2000).

4 | DISCUSSION

The literature captured in this ScR describes a relatively small, but ongoing area of viral research. Serosurveys of mammals have yielded evidence of CVV exposure in domestic and wild animals across the Americas. The interpretation of the chronologically older surveys is complicated by the relative lack of diagnostic specificity of earlier assays, which could have led to some misclassification of samples (Drebot, 2015). The relatively widespread evidence of CVV exposure in mammals, and detection in a variety of mosquito species across the Americas, makes the very small number of reported cases of clinical illness attributable to CVV infection striking.

Outbreaks of congenital anomalies in lambs born to CVV-infected dams were reported in the USA in the late 1980s (Chung et al., 1991; Edwards et al., 1988). More recently, three outbreaks of CVV-associated reproductive failure in sheep have been reported by diagnostic laboratories in the Canadian provinces of Ontario and Québec (Leboef & Cotê, 2013; Shapiro et al., 2012; Spinato et al., 2016). A serosurvey of domestic animals in the western Canadian province of Saskatchewan found widespread evidence of CVV exposure in sheep, cattle, goats, horses and mule deer (Uehlinger, Wilkins, Godson, & Drebot, 2018). Thus, it is plausible that CVV infection may have been under-diagnosed as a potential cause of reproductive failure and congenital defects in small ruminants in Canada, at least in regions where evidence of CVV exposure has been reported in domestic or wild animals. Given that two of the recent Canadian outbreaks were only reported in a non-indexed producer resource, it is also likely that CVV outbreaks are under-reported or are reported in grey literature media that are difficult to identify in a systematic search. Thus, despite our best efforts, there may be reports of CVV outbreaks in small ruminants that were missed by our search.

There have been a very small number of human clinical cases of CVV-associated illness recorded to date. The scarcity of human clinical cases contrasts with the much larger proportion of humans with serological markers of CVV exposure reported from various populations in the Americas. As with the CVV situation in animals, CVV exposure seems to occur much more frequently than clinical disease. However, there is insufficient evidence to identify the full spectrum of clinical signs during CVV-associated illness, or the degree of under-diagnosis of CVV occurring, or potentially at-risk populations (e.g., 2/6 CVV cases occurred in immune-compromised subjects) (Wilson et al., 2017; Yang, Qiu, et al., 2018b).

In Canada, ongoing "lookbacks" at suspect West Nile virus patients have revealed that some of these subjects have serological markers of CVV exposure, further supporting the possibility that under-diagnosis of CVV in human encephalitis or meningitis patients may occur (Dimitrova et al., 2011). Similarly, the potential impact of CVV infection during pregnancy, currently recognized only in small ruminants, merits further research in other species, given the very small number of studies investigating CVV during pregnancy in humans and mice (Blackmore, 1996; Calisher & Sever, 1995; Edwards & Hendricks, 1997; Nowicki, 1996).

Subgroups, or complexes, within the Bunyamwera serogroup have been proposed, and these subgroups are correlated with the geographic location where the viruses were isolated (Hunt & Calisher, 1979). Based on the most recent phylogenetic analyses, CVV has been identified as being most closely related to Maguari and Fort Sherman viruses, with Tlacotalpan and Playas classified as subtypes of CVV (Armstrong et al., 2015; Blitvich, Lorono-Pino, et al., 2012; Yang, Chan, et al., 2018). The relationship between CVV and these closely related viruses is complex, and overtime has resulted in the reclassification of several isolates; for example, BeAr 7272 and CbaAr-426, originally categorized as CVV, have been reclassified as Maguari or Bunyamwera virus isolates (Groseth et al., 2017).

Reports of recent phylogenetic analyses conclude that some genetic diversity has been reported across CVV strains, but overall CVV is a well-conserved virus across geography and several decades (Armstrong et al., 2015; Blitvich, Lorono-Pino, et al., 2012; Groseth et al., 2017). The emergence of a new CVV lineage in Connecticut, more closely related genomically to CVV strains from Mexico than to other locations in the United States, suggests a possible importation event of a novel CVV strain to a new location (Armstrong et al., 2015). Therefore, the potential exists for future introductions of relatively novel CVV strains into new geographic areas, whether fortuitously in association with human activity, or as the geographic range of vectors expands.

Recent genomic analyses identified that different segments of the viral genome are conserved across similar, but distinct viruses, which explains the antigenic similarities and differences identified between viruses using different antigen-based methods of viral characterization (Groseth et al., 2017). One implication of this finding is that distinguishing between viruses within the *Orthobunyavirus* genus may be difficult with antigenic tests, and even molecular tests need to be comprehensive enough (e.g., target several discerning segments of the viral genome) to distinguish between closely related viruses and any reassortments that may occur (Blitvich, Lorono-Pino, et al., 2012; Groseth et al., 2017). Thus, CVV serological testing across studies may not have distinguished between some distinct, but related viruses, particularly in the early CVV studies from the 1950s and 1960s. Given the evidence for the current geographic distribution of CVV, it is likely that some CVV-positive serological results in the southern areas of South America were detecting exposure to closely related viruses such as Maguari virus (Casals & Whitman, 1960; Peralta et al., 1966; Sabattini et al., 1965). Also, considering the virus' geography, studies conducted in North America in which the antigenic test was developed with a Maguari virus isolate likely represent exposure to CVV rather than Maguari (Buescher et al., 1970; Work, 1964). Across studies presenting serological results, some misclassification of CVV exposure may have occurred with an unknown direction and magnitude, and this contributes some uncertainty about the estimates from these studies.

While we tried to conduct an exhaustive literature search, it is possible that some relevant research may have been missed, especially if it were only reported in grey literature such as producer updates. However, we feel that the potential for language bias in this ScR was low since only one potentially relevant Spanish paper was excluded due to language of publication.

Several knowledge gaps were identified by our ScR, including evidence characterizing the CVV epizootic cycle through studies that identified important vectors and mammalian reservoirs. The factors associated with increased prevalence of circulating CVV in major vectors or reservoirs are unclear. The prevalence of CVV exposure in humans in the Americas in the general population, or within targeted patient groups such as encephalitis patients, lacks representative evidence and therefore also remains somewhat unclear.

Future directions for CVV research therefore include several topic areas. Continued improvement in assays for evidence of CVV exposure, for example, in the area of specificity, that is the correct categorization of samples truly not exposed to CVV, would be useful in the ongoing surveillance of mammalian and human populations. The use of representative sampling frames for serosurveillance could help to identify potential reservoir species and guide additional monitoring for viral detection in reservoir populations. Regular lookbacks for CVV case finding in human populations, such as suspect cases for other viral encephalitides, would help to improve our understanding of the true burden of clinical disease associated with human CVV infection. Similarly, knowledge translation to improve awareness among food animal veterinarians of CVV as a potential cause of reproductive failure and congenital defects in small ruminants could help provide a more accurate understanding of the true burden of CVV infection in these populations.

5 | CONCLUSIONS

Centers for Disease Control circulates in numerous mosquito and animal species across a large area from North to South America. However, clinical disease caused by CVV infection has only been extensively studied in small ruminants in the USA and Canada. Published reports of human disease attributable to CVV infection describe six severe cases; however, CVV-associated illness is likely under-reported or misdiagnosed. Future research should focus on characterizing the impact of CVV infection in human and animal populations.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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