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African Horse Sickness Virus: History, Transmission, and Current Status

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Abstract

African horse sickness virus (AHSV) is a lethal arbovirus of equids that is transmitted between hosts primarily by biting midges of the genus *Culicoides* (Diptera: Ceratopogonidae). AHSV affects draft, thoroughbred, and companion horses and donkeys in Africa, Asia, and Europe. In this review, we examine the impact of AHSV critically and discuss entomological studies that have been conducted to improve understanding of its epidemiology and control. The transmission of AHSV remains a major research focus and we critically review studies that have implicated both *Culicoides* and other blood-feeding arthropods in this process. We explore AHSV both as an epidemic pathogen and within its endemic range as a barrier to development, an area of interest that has been underrepresented in studies of the virus to date. By discussing AHSV transmission in the African republics of South Africa and Senegal, we provide a more balanced view of the virus as a threat to equids in a diverse range of settings, thus leading to a discussion of key areas in which our knowledge of transmission could be improved. The use of entomological data to detect, predict and control AHSV is also examined, including reference to existing studies carried out during unprecedented outbreaks of bluetongue virus in Europe, an arbovirus of wild and domestic ruminants also transmitted by *Culicoides*.

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PERSPECTIVES AND OVERVIEW

Introduction

African horse sickness virus (AHSV) is a double-stranded RNA virus that occurs in nine antigenic types within the genus *Orbivirus* of the family Reoviridae (50). AHSV causes African horse sickness (AHS), an infectious, noncontagious disease of equines (99). The clinical disease caused by AHSV is usually classified into four forms according to characteristic pathology and varies according to host species as well as prior exposure to the specific serotype of AHSV (98). The least severe form is horse sickness fever, which results in a transient pyrexia and edema of the supraorbital fossae. This form occurs only in (*a*) horses that have recovered from a previous infection with an AHSV serotype or are naturally resistant to infection or in (*b*) the primary maintenance reservoirs of AHSV, species of zebra (*Equus quagga*; *E. grevyi* and *E. zebra*) and the African donkey (*E. africanus*) (51, 98). The three more severe forms of AHS occur in naive horses (*E. ferus*) and European and Asiatic donkeys and cause impairment of the respiratory and circulatory systems resulting in effusions and hemorrhage (8, 30, 93). All forms of these diseases can occur during an outbreak, and combined rates of fatality in naive horse populations can reach 80-90%, which ranks AHS as among the most lethal of viral infections known in horses (27, 53). Seroconversion following infection with AHSV has also been reported in dogs, camels, and wildlife other than equids. It is unclear whether these infections are also important in the persistence and spread of the virus (3, 11, 97).

Recent changes in the epidemiology of bluetongue virus (BTV), an orbivirus closely related to AHSV, but that infects wild and domestic ruminants, have highlighted uncertainty about the variables controlling the spread and persistence of *Culicoides*-borne arboviruses (29, 85). The widespread and devastating incursions of BTV within Europe have raised concerns that AHSV may also mount similar incursions (41, 56, 92, 101). In this review, we examine the history and the transmission potential of AHSV with a view to understanding those factors limiting its distribution. We also compare and contrast modern studies of AHSV ecology in the African republic of Senegal and the Republic of South Africa (RSA), where research has characterized transmission within the endemic range of the virus. Finally, we provide recommendations regarding future research directions that may assist in understanding and predicting the emergence of AHS, drawing on past epidemic and endemic outbreaks.

Impact and Control of African Horse Sickness Virus

The socioeconomic impact of AHSV falls primarily on two distinct equine populations within Africa. Morbidity and mortality from AHS within working equids may constrain the draft power these animals provide in low-income countries, thereby affecting food security, poverty alleviation, and gender equality (42, 86, 102). Quantitative investigation of this impact has not been conducted, largely because accurate recording of clinical disease and collection of samples for AHSV diagnosis in working horses is rarely achieved (42). In contrast, AHSV is also a major threat to the equine sport and companion animal industries, which involve, in part, the production of high-performance animals. This threat occurs both in endemic regions of AHSV transmission, where breeding and export of horses is a major trade (e.g., in the RSA), and in regions at risk of epidemics from importation (e.g., Europe and the Middle East). The economic value of horse racing is considerable. In 2009 alone, more than 160,000 thoroughbred races took place across 47 countries, amounting globally to several hundred billion dollars (57). The value of horses as companion animals is less well defined but can provide physical and psychological benefits to owners and riders (17, 18, 25).

Outbreaks of AHSV are controlled by quarantine of equines moving from endemic and epidemic AHS regions to virus-free areas, vaccination, and stabling. The impact of quarantine falls primarily on endemic regions of transmission that are involved in horse racing and breeding, most

notably in the RSA. In 1997, a 140-km^2 area of the Western Cape where AHS was rarely recorded was established as regionally free of AHSV (20, 45, 46). A combination of vaccination, zonal quarantine (with designated surveillance, protection, and free zones), and stabling was used to enable direct shipment of horses to Europe and other AHSV-free horse-racing and -breeding markets, with a high degree of biosecurity and traceability (95). A concern, however, has been intermittent outbreaks of AHSV in the outermost zones of the system (in 1999, 2004, 2011, 2014). As a result, trade has ceased for significant periods of time during which the scheme has been implemented, and AHSV-free third-party countries such as Mauritius have been increasingly used for quarantine prior to onward shipment.

Vaccination with live attenuated strains of AHSV is the primary means of controlling AHS in both endemic and epidemic scenarios (4, 38, 39). Concerns have been raised regarding live attenuated vaccines in their possible reversion to virulence, transmission by vectors, and reassortment with field AHSV strains. The inability to differentiate between infected and vaccinated animals is also a concern (56, 65, 108). Nevertheless, these vaccinations are used widely in Africa both to reduce the impact of AHS in endemic regions and to eradicate AHS during epidemics (34, 92). Although a monovalent serotype 4–inactivated vaccine was developed and made commercially during the early 1990s (36), this approach has not been pursued largely because of a lack of outbreaks outside the endemic range of the virus. A wide range of other vaccine candidates have been trialed, including some that may provide cross-serotype protection against AHSV, but none have been used in the field to date, primarily owing to a lack of commercial viability (68).

Prior to the development of vaccines, stabling of horses overnight in mosquito-proofed housing was used to protect horses from AHS in southern Africa (84). Stabling has practical limitations related to keeping horses enclosed for long periods, endophilic behavior in some AHSV vector species (59), and measuring the effectiveness of screening that can be provided (9, 79). However, stabling remains a useful way to mitigate AHSV transmission in both endemic and epidemic scenarios, particularly as part of quarantine measures associated with long-distance horse movements (9, 79, 80).

HISTORY OF AFRICAN HORSE SICKNESS VIRUS

The lethality of AHSV infection and the high emotional and economic value placed on horses in human history make this virus identifiable in records as early as the fourteenth century (47). The earliest documentation is heavily biased toward incursions of AHSV into the Middle East, but later reports of AHS occurred following the introduction of horses into central and southern Africa during the seventeenth century. Here, outbreaks of AHS had a significant impact on both civilian and military transport. Notable epidemics include the loss of 70,000 horses in the Cape of Good Hope, representing approximately 40% of the local horse population at that time (13), and the loss of almost 1,000 horses in Namibia (54). The resultant social impacts acted as significant drivers in the development of veterinary science in affected regions (24, 43).

Endemic transmission of AHSV occurs in a broad band across Africa south of the Sahara Desert from Mauritania to Somalia, although surveillance for the virus is usually limited to periodic, single-country surveys. At times, however, AHSV has emerged northward and eastward from these areas into regions with largely naive horse populations (63). The most devastating AHS epidemic in modern times was initiated by the emergence of a strain of AHSV serotype 9 (AHSV-9) into the Persian Gulf region of Iran in 1959 (49). The incursion and rapid spread of AHSV were blamed largely on the movement of nomadic tribes and their equine livestock along riverine trade routes, which involved approximately two million people in Iran alone. During 1959–1961, AHSV expanded eastward from Iran to Afghanistan, Pakistan, and India and westward to Iraq,

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Syria, Lebanon, Turkey, Cyprus, and Jordan (6, 49, 51, 53). The outbreak resulted in the death of an estimated 300,000 equines, most of which were associated with subsistence workers. In severely affected areas, such as the Iran-Iraq border, the presence of numerous decaying horse carcasses in rivers also raised public health concerns (49). This epidemic halted in 1962, probably through a combination of factors, most prominent of which were the deployment of mass vaccination campaigns as well as the mortality and slaughter policies that rapidly reduced availability of susceptible hosts (6, 49, 51).

In 1965, AHSV-9 reemerged, this time in southern Morocco, and spread eastward to Algeria and Tunisia (63). This incursion was also attributed to the movement of nomadic tribes and their donkeys from Mali and the Republic of Niger across the Sahara Desert to North Africa (22). For the first time in recorded history, the virus recrudesced in North Africa in 1966 after a winter pause and then entered Europe via the Straits of Gibraltar in Spain. By October, it had infected horses in the Spanish province of Cadiz. However, AHSV was eradicated from Spain within a few weeks through the rapid deployment of vaccination and slaughter policies. Following the winter of 1966–1967, AHSV-9 failed to recrudesce in North Africa, despite having successfully overwintered in the area from 1965 to 1966. Thus, the incursion ended. Though recommended in reports published during these outbreaks, entomological studies during 1959–1962 and 1965–1966 were extremely limited and did not include attempts to implicate vectors or measures that would prevent vector access to susceptible hosts (52).

Following a period of more than 20 years without outbreaks in Europe, AHSV again appeared in Spain in 1987, subsequently spreading into Portugal and Morocco in 1989. Unlike previous incursions, the index case is thought to have arisen from the importation of 10 zebras by sea from Namibia to Spain, rather than via transhumance across the Sahara Desert. The virus serotype involved was AHSV-4, which was the first recorded occurrence of any serotype other than AHSV-9 outside Africa. In addition, and uniquely, AHSV-4 overwintered in Spain for three years until it was eradicated during late 1990 by a combined vaccination and slaughter policy (63). Approximately 3,000 equids were killed during the outbreak. The route of entry of this outbreak in Europe and North Africa led to a reevaluation and tightening of procedures for importation of equids and equine products from Africa to Europe, and no further incursions of AHSV have occurred.

It is uncertain how AHSV-4 survived in Spain over three successive winters (from 1987 to 1990); each overwintering bout followed a long "silent" interepizootic period of up to 11 months duration (116). However, the ability of AHSV-4 to overwinter is clearly connected to the seasonality of the major vector *Culicoides imicola* Kieffer, which is not present in the adult phase in central Spain for approximately four months during winter, but is continually present throughout the year in southern Spain (89). Overwintering of AHSV-4 occurred only in southern Spain, never in central Spain, where the virus initially arrived (65). The long interepizootic silent periods between successive bouts of disease in horses are more difficult to explain but may be related to the fact that vaccination in Spain initially concentrated on the more valuable, disease-sensitive horse population. As a result, AHSV continued to circulate covertly and at low levels in the large, disease-resistant donkey population in southern Spain. Presence of the virus (i.e., disease) would then be detected only in late summer, when vector populations peak and the virus spills over into unvaccinated horse populations (116).

The AHSV-4 outbreak in Spain led to a substantial entomological investigation of transmission. Light-suction trap surveys of the distribution and seasonality of *Culicoides* biting midges were performed in Spain (75, 76, 87), Portugal (26), and Morocco (21). Climatic data and satellite imagery from Morocco were integrated into preliminary analyses of distribution of the primary vector of AHSV involved in the epidemic, *C. imicola* (16). The presence of *C. imicola* populations

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correlated with certain values of the Normalized Difference Vegetation Index, which provides estimates of soil moisture and hence the availability of suitable larval habitats.

TRANSMISSION OF AFRICAN HORSE SICKNESS VIRUS

Transmission by *Culicoides* Biting Midges

Transmission of AHSV occurs almost entirely through hematophagous arthropods, which act as biological vectors. Field and laboratory-based trials have implicated *Culicoides* biting midges (Diptera: Ceratopogonidae) as the primary vectors of AHSV. By far the most important species in the field transmission of the virus is *C. imicola* (61, 63), as stated above. This species is present, often in high abundance, across most of Africa, the Middle East, southern Europe, and southern Asia as far as the Wallace Line (58, 61).

More isolations of AHSV have been made from field populations of *C. imicola* than from any other insect species, although this is partially due to greater surveillance in the RSA at sites where this species is highly abundant (72, 100, 104). As a striking example of this work, between 1979 and 1985, 66 isolations of AHSV were made from across the RSA, originating from mixed pools of *Culicoides* (72). Although up to 20 species could have been present in these pools, the dominant species by far was *C. imicola*. Additional AHSV isolations from *C. imicola* have been made in Zimbabwe (19, 83) and Europe (62). AHSV has also been detected using reverse transcription–polymerase chain reaction in pools of *C. imicola* in Namibia (44).

Laboratory findings using multiple field and laboratory reference strains of all nine AHSV serotypes also indicate *C. imicola* in the RSA is susceptible to infection (82, 90, 103, 108, 110, 111). These studies have examined the influence of a wide range of parameters on vector competence and have been enabled by a systematic approach based on feeding blood-AHSV suspensions to *Culicoides* through chick skin membranes (109). Variation in susceptibility of *C. imicola* has been demonstrated according to the population tested (111) and the origin and isolate of AHSV used (110, 111). However, susceptibility for infection with AHSV is often less than 10% of individuals tested, indicating that maintenance of transmission in the field is likely to be reliant on high biting pressure on hosts. Environmental and genetic factors underlying these differences remain entirely unexplored in part owing to the inability of establishing colony lines of *C. imicola* (71, 112).

Two separate series of experiments have used field populations of *Culicoides* and mosquitoes in the RSA to assess transmission of AHSV between viremic and naive horses (35, 115). Results of the 1943 study of AHSV transmission, which were not reported in full, but as a later personal communication (115), described the successful transmission of AHSV to a naive horse following refeeding of seven *Culicoides* that engorged on a viremic horse 12 days earlier. Attempts to repeat this experiment in the same laboratory failed, despite exposure of two naive horses to a far greater number of *Culicoides* putatively infected with AHSV (73 *C. imicola* and 3 *Culicoides milnei* Austen at 10 days postinfection fed on one horse, and 87 *C. imicola*, 2 *C. milnei*, and 1 *Culicoides shultzei* (Enderlein) at 12 to 18 days postinfection fed on the other) (115). This may have resulted from a low level of vector competence in the populations tested, as highlighted in laboratory-based infection trials using artificial membranes.

In addition to *C. imicola*, *Culicoides bolitinos* Meiswinkel, which breeds in African bovine dung, has also been implicated in field transmission of AHSV through isolation of virus from wild populations in the cooler, mountainous region of the central RSA (60). Within this region, *C. bolitinos* was by far the most abundant species on the 14 horse holdings sampled, representing 65% of the total *Culicoides* catch, whereas *C. imicola* accounted for less than 1%. Previous studies have demonstrated that *C. bolitinos* is susceptible to infection with AHSV in the laboratory at a rate broadly comparable with that of *C. imicola*, although this relationship varies with virus strain

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(103, 111). This observation contrasts with similar infection studies with BTV where *C. bolitinos* recorded a consistently greater susceptibility to infection with this virus (109).

Though to a lesser degree than *C. imicola* and *C. bolitinos*, but given their susceptibility to laboratory infection, other livestock-associated *Culicoides* species have also been implicated in the transmission of AHSV in the RSA (85). The role that these species play in maintenance of AHSV is not known but illustrates that barriers to vector competence for AHSV are unlikely to be the primary determinant of vector capacity. In addition to these species in the RSA, isolations of AHSV were also made during the outbreak of AHSV-4 in Spain (1987–1991) from pools of mixed species of *Culicoides* collected in the province of Cadiz (62). One pool contained 50 *Culicoides obsoletus* complex, 18 *Culicoides pulicaris* (L.), and 5 *Culicoides cataneii* Clastrier, whereas another included 3 *C. pulicaris*, 2 *Culicoides lailae* Khalaf, 1 *C. obsoletus* complex, and 1 *C. cataneii*. The presence of the *C. obsoletus* complex and *C. pulicaris*, which are both widely distributed across stables in central and northern Europe, is cited as a risk factor for transmission of AHSV in this region (63). Members of the *C. obsoletus* complex have also supported the transmission of both BTV (48) and Schmallenberg virus (37) in this region. Schmallenberg virus is an Orthobunyavirus that was first identified in 2011 in Germany and has since become established across Europe (85). Attempts to reinforce these studies with laboratory-based infections with AHSV-9 in Israel failed owing to low rates of successful blood feeding (66).

An advance in exploring AHSV-vector interactions was the discovery that a colony line of *Culicoides sonorensis* Wirth and Jones, a North American species, could become orally infected with and support the replication of the virus to a high titer (64). This enabled later studies of the relationship between temperature and the duration of the extrinsic incubation period of the virus in a vector to be established (114, 117). In addition, the titer of virus developed in *C. sonorensis* that is indicative of a full AHSV infection with dissemination to the salivary glands (i.e., a transmissible infection) was similar to that for BTV (3.0 $\log_{10}$ tissue culture infective doses on a baby hamster kidney cell line) (90).

In contrast, *Culicoides nubeculosus* Meigen, a second colony species, is almost entirely refractory to infection, which was hypothesized as due to a midgut infection barrier (64, 90). However, larval- or pupal-rearing temperatures of 33–35°C significantly increase vector competence of *C. nubeculosus* for AHSV (67). Likewise, this may also result from disruption of the midgut barrier to infection and dissemination, leading to a "leaky gut" where AHSV can pass directly into the hemocoel, even in *Culicoides* that would be refractory to infection under cooler temperatures. The impact of this enhanced vector competence has not been investigated in the field. From studies of BTV and Akabane virus, a *Culicoides*-transmitted Orthobunyavirus that can cause congenital defects in ruminants, transovarial transmission of the virus might not occur in *Culicoides* because the ovarial sheath acts as a barrier to dissemination (5, 74).

Transmission by Other Arthropods

Other arthropod groups have been implicated in the biological transmission of AHSV, although the importance of these in the epidemiology of the virus remains unclear. Initial studies on AHSV transmission by mosquitoes, carried out at the Onderstepoort Veterinary Institute, in Pretoria, RSA, failed to elicit any evidence of AHSV transmission between viremic and naive horses (28). Conversely, later studies carried out in Iran in the 1960s demonstrated that infected mosquitoes could transmit AHSV to naive horses 15 to 22 days after feeding on blood from a viremic horse (77). During these experiments, 14 *Anopheles stephensi* Liston collected locally in the field and two *Culex pipiens* L. from a colony established in Teheran were successfully fed on two horses, and both animals later died of AHS (77).

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These experiments were later repeated with a colony line of *Aedes aegypti* L. originating from a colony established in Florida (78). Here, AHSV produced in tissue culture was mixed with horse blood rather than being taken directly from a donor animal, and transmission to the naive host occurred with successful feeding of nine *A. aegypti*. A subsequent study used a strain of *A. aegypti* and the mosquitoes were infected orally with AHSV via an artificial membrane-based system. It demonstrated infection rates of less than 3%, and transmission was not attempted (23). These early studies of mosquito species as potential vectors of AHSV have not been followed up in more recent times so their significance remains uncertain.

In Egypt, AHSV has been isolated from and may be transmitted between horses by the camel tick *Hyalomma dromedarii* Koch (7, 91). Transstadial transmission of AHSV from larvae to nymphs and from nymphs to adults was demonstrated, but transovarial transmission was not because the virus could not be detected in their offspring (7). Also in Egypt, the brown dog tick *Rhipicephalus sanguineus* Latreille was shown to be able to transmit the virus to naive dogs and horses and demonstrated transstadial persistence but no transovarial transmission. This early work using tick species has not been confirmed elsewhere. Consequently, the epidemiological significance of these experiments and the potential for persistence of AHSV in the environment through infection of ticks remain uncertain. The relatively long feeding periods of a single tick on a host (up to a few days) and the long periods between feeding events also do not fit the dynamic epidemiology of AHSV.

During early attempts to implicate vectors of AHSV, mechanical transmission was also demonstrated using *Stomoxys calcitrans* (L.) (94). Similarly, research has not followed up on these studies because this form of transmission is not considered epidemiologically important (63). Underpinning this assumption is a reduction in AHS cases observed in the RSA: Horses were not infected with the virus when stabled at night, even when they were in the presence of large biting flies (or ticks) during the day.

STATUS OF AFRICAN HORSE SICKNESS RESEARCH

Republic of South Africa

Studies of AHSV in the RSA have been highly influential in shaping our understanding of the virus (30). This knowledge extends to a detailed characterization of *Culicoides* ecology and the role of these insects in the transmission of AHSV (61). Although transmission of AHSV in the RSA has long been considered "endemic," the distribution of AHS cases is spatially and temporally patchy, occurring across a wide range of biotic and abiotic parameters that relate to interactions among host, vector, and environment. Wide-ranging light-suction trap surveys of *Culicoides* have established that the primary vector species of AHSV, *C. imicola* and *C. bolitinos*, are ubiquitous across the RSA with the exception of western coastal sites (14, 88, 106, 107). Significant differences in the abundance of these vectors, however, occurred according to site and were related to both the severity of winter in each region as well as soil type and aspect, all of which may influence *C. imicola* larval survival (61).

Anecdotal evidence links outbreaks of AHS in the RSA to heavy rains and the cessation of cases to the occurrence of the first winter frosts since the turn of the twentieth century. Such evidence was a primary reason AHSV was identified as an arbovirus (47, 81). More recent studies in the RSA have sought to link adult population abundance and, hence, transmission with both short- and long-term climate trends. Years of major AHS epidemics within recorded history have been correlated with the warm phase of the El Niño Southern Oscillation, particularly those instances when pronounced drought occurs in the early part of the year and is followed by an increase in average rainfall

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between April and June (15). On a shorter temporal scale, *Culicoides* can persist throughout the winter in most areas of the RSA, although its numbers are reduced by several orders of magnitude from its summer peak. Yet, outbreaks of AHSV do not appear to persist through these periods (105, 107).

Another major driver for the distribution and persistence of AHSV in the RSA is the presence of the plains zebra (*Equus quagga* Boddaert: formerly *Equus burchelli*) as a maintenance host. The largest population of these zebra (approximately 23,000 head) resides in Kruger National Park in the northeast of the country. All nine serotypes of AHSV have been isolated from *E. quagga* in this region, where populations foal throughout the year and likely represent the primary ancestral host of the virus (12). Transmission of AHSV between zebras has not been investigated in either the RSA or other countries in detail, although at least one undescribed *Culicoides* species (number 107), related to *C. imicola*, has been found as pupae in their dung (58, 73). Surveillance of clinical AHS throughout the RSA initially led to a still-prevalent hypothesis that outbreaks spread from the northeast to the south and eastward each year (12, 30). Recent outbreaks of AHS have occurred in central, eastern, and southern regions of the RSA lacking *E. quagga* populations and without recorded preceding cases in the north. Some of these areas have a year-round presence of *C. imicola*, but the epidemiology of these cases remains poorly understood and the potential role of other AHSV maintenance hosts such as donkeys remains unclear.

Republic of Senegal

AHS was first described in West Africa during the mid-nineteenth century, and by the turn of the twentieth century its cyclical appearance every 5–6 years was anecdotally correlated with extensions of the rainy season. Formal recognition of AHS, after comparison with clinical cases seen in southern Africa, occurred in 1922 during an outbreak in Dakar. Importation of horses decreased during World War II, leading to a reduction in AHS cases. However, from the 1950s onward, the increased use of breeding to improve draft equids led to a horse population increase and a significant increase in AHSV cases (69). Horse populations within Senegal increased dramatically from 94,000 in 1961 to 545,000 in 2013 as a result of an increased use of draft power. Similar population data are not available for mules and donkeys. However, the total population of equines in Senegal is now thought to approach 1 million, including the import of thoroughbreds and the creation of modern stables in peri-urban Dakar within the Niayes region (40). In contrast to the RSA, no zebra populations are present in the country except for epidemiologically insignificant numbers held within game reserves.

Until recently, outbreaks of AHSV in Senegal were characterized only anecdotally, with particularly severe years collated as part of wider records of animal health. In 2007, however, a widespread and severe outbreak of AHSV estimated to have killed approximately 1,169 horses in four months led to an accurate economic assessment of the impact of the virus with a total estimated cost of 900 million FCFA (or approximately 1.5 million US dollars) (2). This AHSV outbreak affected almost the entire country (34) and may have been caused by an AHSV-2 strain, occurring against an endemic scenario where only an AHSV-9 strain was present and where a monovalent, live-attenuated serotype 9 vaccine strain was traditionally used to minimize clinical cases (34). The epidemic was controlled by reintroducing the use of a polyvalent vaccine, and 175,300 horses were vaccinated within a total estimated population of 518,212.

The 2007 outbreak of AHSV was a significant driver in establishing entomological research on *Culicoides* in Senegal and in linking expertise developed within the RSA to the wider African fauna. Differentiation of the cryptic Shultzei group was a major advance in vector implication because these are collected in high abundance alongside *C. imicola* in Senegal and across a broad geographic range from Africa to Asia and Australasia (85). Using specimens collected from Israel, Japan, and Australia, researchers used partial sequencing of the cytochrome oxidase I (*COI*) gene

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and morphological comparison to determine that this group contained four species within Senegal: *Culicoides oxystoma* Kieffer, *Culicoides enderleini* Cornet and Brunhes, *Culicoides kingi* Austen, and *Culicoides nevilli* Carnet and Brunhes (10). The identification of *C. oxystoma* in Africa south of the Sahara implies a very broad geographic range for this potential vector of AHSV that extends to the Oriental and Australasian regions, although the limited evidence of divergence in populations requires further exploration (10). A more recent study has also extended the number of *Culicoides* species described in Senegal from 34 in 1994 to 53 in 2014 (40).

The majority of studies of *Culicoides* ecology in Senegal have been conducted in the Niayes region inland of the coastline of Grande Côte or in the west-central agricultural region (96). There are two main seasons in this region in Senegal: the rainy season (July to October) and the dry season (from November to June). In 2007, AHSV outbreaks began in the dry season in Dakar, but the amplification and diffusion of the disease to the whole country occurred in the wet season. In Senegal, most horses are engaged in transport activities in urban centers, including Dakar, after the end of the rainy season and are returned to rural areas for fieldwork the next winter. Within the Niayes region, *C. oxystoma* predominates from September to November following the rains in collections from both horse-baited drop traps (40) and light-suction traps (33, 40), correlating with peaks of AHSV transmission. However, during the dry season, populations of *C. oxystoma*, *C. kingi*, and *C. imicola* remain similarly abundant. The status of *C. oxystoma* as a potential vector of AHSV remains uncertain.

KNOWLEDGE GAPS AND FUTURE STUDIES OF AFRICAN HORSE SICKNESS VIRUS

Overarching Areas of Research

The development of cross-protective AHSV vaccines that have a long shelf life and that can provide rapid protection and be differentiated from natural infections during outbreaks is rightly seen as the major priority for research (118). Even if these become available, however, a key lesson from both historical and current emergences of *Culicoides*-borne orbiviruses is that the time elapsing from incursion to vaccination can be significant in determining the impact of outbreaks (29). This is particularly the case in regions such as northwest Europe, which have no prior experience with AHS incursion or any licensed vaccine banks with which to respond. Under this scenario, the only measures available to owners to protect horses are based on reducing vector-host contact. These measures have not been effective in preventing BTV transmission in this region (29, 70), but owing to limited host density and greater financial or emotional incentives to conduct multiple integrated measures (e.g., stabling, larval habitat clearance, application of repellent or insecticidal products), they may have a greater impact on AHSV.

Another almost entirely unexplored area of research is in understanding how hosts present on farm holdings influence *Culicoides* populations. Mathematical simulation has already identified host preference between equine and ruminant hosts as a key factor influencing AHSV persistence (55). More broadly, however, the *Culicoides* communities associated with equine hosts in Europe in particular are poorly defined, despite substantial light-suction trapping networks for holdings containing ruminant hosts (1, 32). Though global data demonstrate that species assemblages of *Culicoides* are likely to be similar on holdings containing equine and ruminant hosts, variation in abundance according to both the number and type of hosts and husbandry regimes employed (e.g., the degree of dung clearance) has not been quantified at a local or national scale. Such studies would be informative to understand the degree to which surveillance data from ruminant holdings can be extrapolated to those containing equine hosts.

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Research in Endemic Regions

At present, the impact of AHSV on the welfare of horses used for draft power remains unknown because of limitations on reporting and a lack of support for rigorous investigations of welfare and infection status. This is complicated by the fact that immunity of African horse populations with long-term exposure to AHSV and resistance to AHS remains poorly understood. These studies would be best approached in countries within Africa that are heavily reliant on draft power and support AHSV transmission (e.g., Ethiopia, Kenya).

Similarly, even in well-characterized areas of AHSV transmission, such as the RSA, the ecology of endemic maintenance of the virus in zebra and donkey populations is almost entirely unexplored from an entomological perspective. To date, no study has examined adult *Culicoides* populations associated with either of these primary host species in the field, which is a major limitation to understanding maintenance of the virus and predicting an increased probability of spillover into contiguous or overlapping horse populations. Though challenging to perform, these studies would also elucidate the likely impacts of increasing donkey populations for draft power and transport and of restocking zebra populations in game parks throughout the RSA, in particular.

Research in Epidemic Regions

A key area of research in epidemic regions involves identifying potential field vectors of AHSV beyond those already known (*C. imicola* and *C. bolitinos*). The isolation of AHSV from pools of primarily Palearctic species of *Culicoides* in Spain (62) echoes the state of knowledge prior to the recent dramatic extension of BTV into northern Europe. Thus, whether vector competence poses a barrier to movement of AHSV into this region should not be assumed. In addition, outbreaks during the 1960s in India, in particular, were likely not driven primarily by *C. imicola*; rather, *C. oxystoma* has been suggested as a potential vector. Confirmation of the role of *C. oxystoma* in transmission through laboratory infections would be valuable both in elucidating the epidemiology of the most damaging outbreak of AHSV in recorded history and in assessing the risk posed by this species in other regions where *C. imicola* is absent or of low abundance.

Genetic and environmental drivers and modifiers of AHSV vector competence are also poorly explored and almost entirely restricted to *C. sonorensis* (28). Recently, *C. sonorensis* has been the focus of genomic and transcriptomic analyses using infection with BTV, and comparative assessment with AHSV could elucidate the detailed genetic mechanisms for competence (71). Translation of genomic and transcriptomic analysis to other *Culicoides* species is currently limited by a lack of vector species colonies (including *C. imicola*, *C. bolitinos*, *C. oxystoma*, and the *C. obsoletus* complex) (71, 112). Establishing effective blood-feeding techniques outside the RSA would greatly facilitate further studies in this area and provide comparative data from other regions.

Another major issue surrounds the ability of AHSV to spread into new areas and to produce sustained incursions. Even though the movements of susceptible hosts with nomads have been repeatedly invoked to explain outbreaks of AHSV in North Africa, the Middle East, and Asia, no direct studies have been made of this phenomenon. Transhumance in these regions is currently falling as a result of pressures from industrialization, urbanization, and climate change, which may influence the probability of a major epidemic. The association of *Culicoides* populations with nomadic movement as a wider "unknown" in the transmission of viruses has not been addressed in any form. Quarantine measures have been successful in preventing outbreaks of AHSV via imported viremic hosts since the 1987 incursion in Spain, although these remain costly to employ. However, still poorly explored is the risk posed by other forms of entry, not least of which is whether AHSV could also enter into Europe via other unknown entry routes used by both BTV-8 and the Schmallenberg virus (29).

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