Domesticated animals as hosts of henipaviruses and filoviruses: A systematic review

Emma E. Glennon [a]*, Olivier Restif [a], Silke Riesle Sbarbaro [a], Romain Garnier [a], Andrew A. Cunningham [b], Richard D. Suu-Ire [c], Richard Osei-Amponsah [d], James L. N. Wood [a], and Alison J. Peel[e]

[a] *Department of Veterinary Medicine, University of Cambridge, Cambridge, UK*
[b] *Institute of Zoology, Zoological Society of London, Regent's Park, London, UK*
[c] *Accra National Zoo, Accra, Ghana*
[d] *Department of Animal Science, University of Ghana, Accra, Ghana*
[e] *Environmental Futures Research Institute, Griffith University, Nathan, Australia*
*eeg31@cam.ac.uk; +44 01223 337701

Abstract

Bat-borne viruses carry undeniable risks to the health of human beings and animals, and there is growing recognition of the need for a "One Health" approach to understand their frequently complex spillover routes. While domesticated animals can play central roles in major spillover events of zoonotic bat-borne viruses (for example, the swine-amplified Malaysian Nipah virus outbreak of 1998-1999), the extent of their potential to act as bridging or amplifying species of these viruses has not been systematically characterized. This review aims to compile current knowledge on the role of domesticated animals as hosts of two key types of bat-borne viruses: henipaviruses and filoviruses. A systematic literature search of these virus-host interactions in domesticated animals identified 72 studies globally, which were categorized by year, location, design, and type of evidence generated. We then focused on Africa as a case study, comparing research effort in domesticated animals and in bats with the distributions of documented human cases. Major gaps remain in our knowledge of the potential ability of domesticated animals to contract or spread these zoonoses. Closing these gaps will be necessary to fully evaluate and mitigate spillover risk of these viruses, especially in light of global agricultural intensification.

Keywords: Emerging zoonoses; Henipaviruses; Filoviruses; Domesticated animals; Bat-borne viruses

Introduction

The list of bat-borne viruses known to cause morbidity and mortality in domesticated animals, wildlife, and people continues to grow (Moratelli and Calisher, 2015). Many such viruses have pandemic potential and cause severe disease in recipient hosts, raising concern for public health, agriculture, and conservation (Calisher et al., 2006; Plowright et al., 2015). The routes of associated spillover events vary widely: from sporadic bat-to-human Nipah virus (NiV) spillover events over at least the last 15 years in Bangladesh (Luby et al., 2009; Lo et al., 2012) to the 1998-1999 pig-amplified NiV outbreak in Malaysia and Singapore, which resulted in the culling of over one million pigs and the deaths of more than one hundred people (Chua et al., 2000; Chua, 2003). In Australia, outbreaks of disease caused by Hendra virus (HeV), which together with NiV and the closely related Cedar virus comprises the genus *Henipavirus* (Marsh et al., 2012), have resulted from bat-to-horse transmission with occasional spread among horses or transmission from sick horses to their veterinarians and handlers (Middleton, 2014). Henipavirus disease outbreaks have been characterized by stuttering chains of transmission, as have most outbreaks of filovirus diseases caused by Marburg virus (MARV) and ebolaviruses (Lloyd-Smith et al., 2009; Plowright et al., 2015). In contrast, the West African outbreak of Ebola virus disease (EVD) in 2013-16 was characterized by sustained human-to-human transmission on an unprecedented scale. This outbreak, which caused a massive death toll and societal impact, may have resulted from a single bat-to-human spillover event (Baize et al., 2014; Carroll et al., 2015; Spengler et al., 2016).

Domesticated animals used as food sources, companions, or workforce, are able to act as bridges for viral transmission between wildlife (including bats) and people (Reperant et al., 2016). Such animals link "the field" and "the home," often having closer physical contact with both wildlife and people than wildlife and people typically have with one another. The context of intensive agriculture, in which livestock are held in large, dense, and highly-connected populations, provides an ideal opportunity for viral amplification (Cleaveland et al., 2001; Hudson et al., 2002), thereby increasing the risk of otherwise improbable spillover events to people as well as causing significant economic and animal health costs.

While clear examples exist for henipaviruses, the potential role of domesticated animals as bridging species for most filoviruses is less clear. This lack of clarity can be attributed in part to the different ecological and agricultural contexts of regions of documented henipavirus and filovirus spillover events. For example, the kind of intensive livestock production that facilitated NiV spillover in Malaysia and possibly *Reston ebolavirus* (RESTV) spillover in the Philippines (Barrette et al., 2009) is uncommon in sub-Saharan Africa, where most MARV disease and EVD outbreaks have occurred (Gilbert et al., 2015). Also, evidence for non-domesticated wildlife, such as apes and duikers, as bridging species for ebolaviruses has made study of domesticated animals as hosts a less urgent priority (Leroy et al., 2004; Rouquet et al., 2005). Understanding the potential role of domesticated animals in filovirus transmission is important nonetheless, particularly given ongoing intensification of livestock production and its encroachment into new wildlife habitats in Africa (Gerber, 2005; Tilman et al., 2011; Herrero and Thornton, 2013; Perry et al., 2013; Pan et al., 2014).

The emergence of bat-borne henipaviruses and filoviruses has prompted frequent calls for a "One Health" approach to mitigating their risk to people and animals (Plowright et al., 2015; Roess et al., 2015; Lo Iacono et al., 2016; Rural Industries Research and Development Corporation, 2016), involving multidisciplinary collaboration to connect the health of wildlife, domesticated animals, people, and the environment. Despite the importance of such an approach to zoonoses with complex life histories, few studies have explicitly considered the role of domesticated animals in the spillover of bat-borne viruses. This omission creates a major gap in our understanding of the epidemiology and ecology of these viruses.

Here we systematically review the available literature on domesticated animals as hosts of two sets of bat-borne viruses with zoonotic potential: the henipaviruses NiV and HeV and the filoviruses MARV and ebolaviruses. We summarize the existing evidence for the abilities of domesticated animal species to host, sustain intraspecific transmission, and act as interspecific spillover species for each virus. In addition, we use our quantitative review to understand where research effort has focused and to identify understudied domesticated animal species, regions, and viruses, as well as more general knowledge gaps. Finally, we present a case study of filoviruses in Africa considering the context of global capacity challenges, agricultural intensification, and zoonotic disease emergence.

Materials and methods

We gathered articles from a Web of Knowledge search using the following terms and criteria:

(TS=(morbillivirus OR Nipah OR Hendra OR henipavirus OR Ebola OR ebolavirus OR Marburg OR filovirus) AND TS=(pig OR swine OR porcine OR cattle OR cow OR bovine OR sheep OR ovine OR goat OR caprine OR horse OR equine OR camel OR dog OR canine OR cat OR feline OR livestock OR domesticated OR pet OR poultry OR chicken OR galline OR duck OR anatine OR buffalo OR bubaline OR donkey OR asinine)) AND LANGUAGE:(English) AND DOCUMENT TYPES:(Article OR Note)

This search produced 1276 results as of March 27, 2017, of which 72 studies[1] fit the following inclusion criteria:

1) They pertain to henipa- or filovirus infection in our selected set of domesticated animals (e.g., excluding laboratory rodents).
2) They are not comment, opinion, or review articles.
3) They have not been retracted or followed by an expression of concern.

[1] *Murray et al., 1995a; Murray et al., 1995b; Selvey and McCormack, 1995; Hooper et al., 1996; McCormack et al., 1996; Rogers et al., 1996; Ward et al., 1996; Westbury et al., 1996; Hooper et al., 1997a; Hooper et al., 1997b; O'Sullivan et al., 1997; Paterson et al., 1998; Williamson et al., 1998; Chua et al., 1999; Kudoyarova-Zubavichene et al., 1999; Paton et al., 1999; Chew et al., 2000; Chua et al., 2000; Goh et al., 2000; Hooper et al., 2000; Parashar et al., 2000; Black et al., 2001; Hyatt et al., 2001; Sahani et al., 2001; Chan et al., 2002; Lam and Chua, 2002; Middleton et al., 2002; AbuBakar et al., 2004; Hsu et al., 2004; Allela et al., 2005; Weingartl et al., 2005; Chang et al., 2006; Epstein et al., 2006; Hanna et al., 2006; Mungall et al., 2006; Tanimura et al., 2006; Weingartl et al., 2006; Lahm et al., 2007; Mungall et al., 2007; Berhane et al., 2008; Bossart et al., 2008; McEachern et al., 2008; Barrette et al., 2009; Mills et al., 2009; Morris, 2009; Field et al., 2010; Li et al., 2010; Playford et al., 2010; Sendow et al., 2010; Hayman et al., 2011; Kobinger et al., 2011; Marsh et al., 2011; McFarlane et al., 2011; Conlan et al., 2012; Pulliam et al., 2012; Sayama et al., 2012; Stachowiak and Weingartl, 2012; Weingartl et al., 2012; Nfon et al., 2013; Chowdhury et al., 2014; Pan et al., 2014; Smith et al., 2014; Ching et al., 2015; Halim et al., 2015; Kirkland et al., 2015; Dowall et al., 2016; Han et al., 2016; Freitag et al., 2016; Lo Presti et al., 2016; Pickering et al., 2016; Suerhering et al., 2016; Middleton et al., 2017.*

While reading the papers identified by this search, we found additional unpublished or informally published reports (e.g., on government websites). Results from these additional reports are not included in any summary statistics or figures, but they are noted (and identified as outside of our search) in the results and discussion sections where they provide relevant context.

We categorized Nipah viruses by clade (NiV-B for Clade I NiV originating in Bangladesh; NiV-M for Clade II NiV originating in Malaysia or elsewhere in Southeast Asia (Lo Presti et al., 2016)) and ebolaviruses by species (e.g., *Zaire ebolavirus* (EBOV), *Reston ebolavirus* (RESTV)) where available; otherwise we used the narrowest classification provided by the study. Animal categories included were pigs, horses, cows, small ruminants (i.e., sheep and goats), dogs, cats, buffaloes, donkeys, and poultry (i.e., chickens and ducks). We included one entry in our database per animal-virus pair; as a result, some of the studies and some outbreaks appeared in multiple entries.

For each domesticated animal-virus species pair within each study, we evaluated whether any evidence, even if limited, was sought or provided for the following traits or abilities of the host species: susceptibility, disease phenotype, a physiological or mechanical mechanism for virus transmission, demonstrated virus transmission to conspecifics, demonstrated inter-species virus transmission (and, where relevant, we specified the other species infected), natural (i.e., non-experimental) infection, and a demonstrated role in zoonotic spillover during the course of an outbreak. Studies were considered to provide evidence both for those abilities they directly tested and for those that were prerequisite for their findings (e.g., we considered studies

138 describing HeV transmission between horses as evidence of the susceptibility of horses to HeV).
139 Where possible, we recorded negative findings as distinct from a lack of findings.

140

141 We accessed global domesticated animal counts by country in 2014 from FAOSTAT;[2]
142 this database includes official national data where available, supplemented by estimates from the
143 Food and Agriculture Organization of the United Nations. We accessed filovirus disease
144 outbreak data from the Centers for Disease Control and Prevention to place research effort in
145 Africa in the context of the distribution of past outbreaks (Centers for Disease Control and
146 Prevention, 2014a-2014b). To compare research effort applied to domesticated animals with that
147 applied to bats, we collected studies that fit criteria 2 and 3 above, applied to henipa- or filovirus
148 infection in bats in non-controlled settings in Africa, as returned by the following search terms:
149 *(TS=(Nipah OR Hendra OR henipavirus OR Ebola OR Marburg OR filovirus) AND*
150 *TS=(bat) AND TS=(Africa OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso*
151 *OR Burundi OR Cabo Verde OR Cameroon OR Central African Republic OR Chad OR Comoros*
152 *OR Congo OR Cote d'Ivoire OR Djibouti OR Egypt OR Guinea OR Eritrea OR Ethiopia OR*
153 *Gabon OR Gambia OR Ghana OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar*
154 *OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Namibia*
155 *OR Niger OR Nigeria OR Rwanda OR Sao Tome OR Principe OR Senegal OR Seychelles OR*
156 *Sierra Leone OR Somalia OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR*
157 *Uganda OR Zambia OR Zimbabwe)) AND LANGUAGE: (English)*
158

[2] *See:* http://www.fao.org/faostat

We produced plots using the mapdata, ggplot2, and treemap packages in R.

Results

Susceptibility, clinical signs, and natural infection

Available evidence for the capabilities of domesticated animal species to host, transmit, and contribute to the zoonotic spillover of henipa- and filoviruses showed considerable species biases (Fig. 1). No MARV studies examined any domesticated animal as potential hosts. No studies examined camels, buffaloes, or donkeys as hosts of any henipa- or filovirus. No studies investigated any relationships between cattle or poultry and ebolaviruses or directly tested the susceptibility of cattle or poultry to HeV. Experimental infection studies involving horses, goats, and sheep suggest they are not highly susceptible to EBOV infection (Kudoyarova-Zubavichene et al., 1999). All remaining animal-virus pairs demonstrated some level of susceptibility to henipaviruses or filoviruses (left column, Fig. 1).

Figure 1. Number of studies seeking (white) or providing (color) evidence of domesticated animal species as hosts of each of Nipah virus, unknown henipaviruses (stacked with Nipah virus for visibility), Hendra virus, and ebolaviruses. Marburg virus, camels, buffaloes and donkeys are excluded from the figure as no associated studies were identified. Types of evidence considered are: demonstrated susceptibility to each virus, demonstrated transmission mechanisms thereof, evidence of transmission between animals of the same species, evidence of transmission from a domesticated animal species to some other species, evidence of

natural infection (e.g., immunity during an outbreak or in a natural setting), and evidence of a role of spillover to humans in a confirmed outbreak.

Of all domesticated animal species, pigs showed the most evidence for a significant role as amplifiers of zoonotic henipa- and filoviruses. They are demonstrated amplifiers of NiV-Malaysia (NiV-M), with serological studies of pigs, case-control studies of people, and successful control via culling all supporting their critical role in the 1998-1999 NiV outbreak in Malaysia and Singapore (Chua, 2003). Pigs have also shown high seroprevalence against NiV-Bangladesh (Chowdhury et al., 2014). When experimentally infected with HeV, pigs demonstrate similar clinical signs, including fever and respiratory signs, as when naturally infected with NiV (Middleton et al., 2002; Li et al., 2010). About 5% of pigs blood-sampled from two villages in Ghana tested positive for non-neutralizing antibodies to henipaviruses, suggesting a broad geographical range of natural henipavirus infection in pigs (Hayman et al., 2011). When infected with the filovirus RESTV, which naturally occurs in the Philippines, pigs exhibit no clinical signs (Barrette et al., 2009; Marsh et al., 2011; Sayama et al., 2012; Pan et al., 2014). Upon experimental infection with EBOV, however, pigs develop fever and pulmonary hemorrhage (Kobinger et al., 2011). Mass mortalities of bush pigs in Gabon have been reported concurrent with EVD outbreaks in people and other wildlife, but infection in pigs was not confirmed in these cases (Lahm et al., 2007).

Horses have exhibited susceptibility to NiV-M infection in experimental studies (Chua et al., 2000), and horses naturally infected with NiV in the Philippines have suffered acute neurologic disease, often characterized by circling, ataxia, and sudden death (Ching et al., 2015).

The horse is a well-known host of HeV in Australia, apparently following direct or indirect infection from bats in multiple outbreaks (Halpin et al., 2011; Martin et al., 2015). Infection in horses remains rare, however, with cross-sectional studies of asymptomatic horses and (informally published) investigations of clinically ill horses rarely showing evidence of past or current infection (Rogers et al., 1996; Ward et al., 1996; Animal Health Australia, 2016). HeV infection in horses results in a wide range of signs, often including severe respiratory and/or neurological disease such as pulmonary edema and vascular lesions in the lungs and brain (Hooper et al., 1997a). High viral loads in response to HeV challenge have been confirmed experimentally (Williamson et al., 1998). The horse is not susceptible to EBOV disease (Kudoyarova-Zubavichene et al., 1999).

There is serological evidence of natural NiV infection of goats, but not sheep, during outbreaks in both Malaysia and Bangladesh (Chua, 2003; Hsu et al., 2004; Chowdhury et al., 2014). Non-neutralizing antibodies of an unknown henipavirus were reported from a sheep and a goat in Ghana (Hayman et al., 2011). No studies have examined or described henipavirus disease in these species. It appears that neither sheep nor goats are susceptible to ebolavirus disease; sheep exhibit a neutralizing antibody response to immunization with EBOV glycoprotein (Dowall et al., 2016), and goats and sheep are insensitive to challenge with live EBOV (Kudoyarova-Zubavichene et al., 1999).

Experimental infections of the domestic cat have demonstrated this species' susceptibility to HeV (Westbury et al., 1996; Hooper et al., 1997b; Williamson et al., 1998) and NiV (Middleton et al., 2002; Mungall et al., 2006, 2007). Cats infected with henipaviruses develop

228 severe respiratory disease, with typical signs including pulmonary edema and interstitial
229 pneumonia (Hooper et al., 1997b). Natural infection of cats with NiV has also been reported;
230 several cats died after eating the meat of NiV-infected horses in the Philippines in 2014 (Ching et
231 al., 2015), and seropositive cats were detected during the index outbreak in Malaysia in 1999
232 (Chua et al., 2000a). In contrast, sixty-four cats were blood-sampled following the first known
233 HeV outbreak in Queensland, Australia, but serum neutralization testing provided no evidence of
234 infection (Rogers et al., 1996). Of two cats sampled in Ghana during a wider study on
235 henipavirus epidemiology, both tested seronegative to henipavirus (Hayman et al., 2011). The
236 only investigation of the susceptibility of the domestic cat to any filovirus infection is an *in vitro*
237 study (Han et al., 2016). This study assessed the glycoprotein-mediated entry of EBOV into
238 primary feline cells, and found they were more susceptible to EBOV entry than canine cells, but
239 less susceptible than human or primate cells (Han et al., 2016). We found no evidence that either
240 natural or experimental infection of the domestic cat with EBOV or any other filovirus has been
241 investigated.
242
243 Several studies have reported high seroprevalences to NiV in the domestic dog during
244 disease outbreaks in Malaysia (where up to 57% of tested dogs were seropositive (Mills et al.,
245 2009)) and the Philippines (where all four dogs with contact with sick horses were seropositive
246 (Ching et al., 2015)) in the absence of clinical disease. Dogs experimentally infected with HeV
247 show few to no clinical signs despite viral replication and the excretion of viable virus in oral
248 secretions and urine (Middleton et al., 2017). To date, however, only two dogs have been
249 demonstrated to be naturally infected with HeV (Petrey, 2011; Kirkland et al., 2015); only one of
250 these cases (Kirkland et al., 2015) was returned by our search. Both animals lived on farms in

Australia where there were HeV outbreaks in horses, showed minimal clinical signs of disease, and were euthanized as a precaution to protect public health (Petrey, 2011; Halim et al., 2015). Post mortem examination was reported for one of these dogs and revealed diffuse vasculitis throughout the body (Kirkland et al., 2015). We could only find one investigation of filovirus infection in the domestic dog. The authors of this study reported a high seroprevalence of EBOV-reactive antibodies in dogs in Gabon in the absence of clinical disease (Allela et al., 2005).

Minimal data exist for both poultry and cattle as hosts of henipaviruses and no data exist for either as hosts of filoviruses. Contact with sick cattle has been associated with NiV seropositivity among people in Bangladesh (Hsu et al., 2004). Chowdhury et al. (2014) tested domesticated cattle in a NiV-prone region of Bangladesh for antibodies to NiV glycoprotein and found 6.5% seropositivity. This is the only attempt, to our knowledge, to test cattle for evidence of NiV infection. We identified two studies which examined NiV infection in poultry; one failed to find serological evidence of infection during NiV outbreaks among a small (n=10) sample of unspecified bird species (Hsu et al., 2004), and one demonstrated mortality in chicken eggs experimentally inoculated with NiV-M (Tanimura et al., 2006). We found one study that looked for evidence of natural HeV infection in cattle and poultry (following the first known outbreak of this disease), and the authors failed to find serological evidence of infection in 276 sampled cattle or 21 combined turkeys, geese, and chickens (Rogers et al., 1996). No studies returned in our search have looked for evidence of susceptibility to, or infection with, filoviruses in either cattle or poultry, but one study that fell outside our search terms reported no evidence of EBOV

infection in tissues from fewer than five chickens collected in the Democratic Republic of the Congo and Cameroon (Breman et al., 1999).

Intra- and interspecific transmission

Figure 2. Summary of suggested routes of interspecies transmission for NiV (yellow), HeV (red), and ebolaviruses (blue) to and from domesticated animals. The species represented are goats, poultry, pigs, dogs, cats, horses, and cattle. Plus symbols indicate known susceptibility to infection of a domesticated animal species, while filled and open/dashed circles indicate intraspecific transmission in natural and controlled settings, respectively. Solid and dashed lines represent transmission that has been observed or suspected in natural and experimental conditions, respectively. Carrion, rather than direct transmission from bats, has been suggested as a source of EBOV infection in dogs (Allela et al., 2005)*. NiV-associated mortality has been demonstrated in chicken eggs, but not in live chickens. Known or suspected direct transmission from wildlife to people is not represented. We found no evidence of transmission from other wildlife host species (e.g. EBOV from nonhuman primates) to domesticated animals.*

All interspecific transmission routes for which we found evidence of domesticated animal involvement are summarized in Fig. 2. Nipah virus circulation among pigs and transmission from pigs to people were well-documented in the 1998-1999 NiV outbreak in Malaysia and Singapore (Chua et al., 1999) but neither have been observed for HeV. Dogs and cats in contact with pigs became infected during this NiV outbreak (Chua et al., 2000). Phylogenetic and serological evidence suggest that RESTV has circulated among pigs for decades (Barrette et al.,

2009), and farmers and slaughterhouse workers in contact with infected pigs in the Philippines have tested seropositive to RESTV antibodies, suggesting pig-to-human spillover (Morris 2009; Sayama et al., 2012). Experimental studies have demonstrated the ability of pigs to transmit EBOV to other pigs (Kobinger et al., 2011) and to macaques (Weingartl et al., 2012).

A 2014 NiV outbreak in the Philippines involved multiple horses and their handlers as well as people, cats, and dogs that consumed horse meat; epidemiological evidence from this outbreak is highly suggestive of horse-to-human spillover but is inconclusive about horse-to-horse transmission (Ching et al., 2015). In addition to infecting their veterinarians and human handlers, HeV-infected horses have infected other horses with which they shared a stable as well as at least one dog (Murray et al., 1995a; Selvey and McCormack, 1995; Williamson et al., 1998; Field et al., 2010; Kirkland et al., 2015). This transmission was likely mediated by human handlers spreading the virus among horses or by environmental contamination, as outbreak reports suggest direct horse-to-horse transmission is relatively inefficient (Field et al., 2010).

No intraspecific transmission has been demonstrated for any henipavirus among goats, sheep, poultry, dogs, or cattle, but we found almost no research effort in this area. There is limited evidence from a questionnaire survey, however, of an association between human NiV cases and exposure to sick cattle in Bangladesh (Hsu et al., 2004), although none of the sick cattle were tested for NiV infection. Dogs have been shown experimentally to be able to transmit HeV to ferrets (Middleton et al., 2017), and HeV-infected cats have infected other cats (Westbury et al., 1996) and horses (Williamson et al., 1998) in experimental settings. No transmission among adult cats or between cats and other species has been shown for NiV,

318 although the isolation of NiV RNA from fetal tissues and placental fluid in an experimentally
319 infected pregnant cat suggest vertical transmission may be possible (Mungall et al., 2007).
320
321 No studies to our knowledge have tried to demonstrate the potential for intra- or
322 interspecific ebolavirus transmission between domesticated animals (other than for pigs, as
323 described above) and any other domesticated or wild species.
324
325 **Research effort**
326
327 A summary of all the studies investigating domesticated animals as hosts for a
328 henipavirus or a filovirus returned by our search is shown in Fig. 3. Pigs and NiV comprised by
329 far the most frequently studied domesticated animal-virus pair (25% of pairs studied). Most of
330 these studies involved either analysis of the 1999 Malaysian NiV outbreak or experimental
331 infection studies in controlled settings. Few studies investigated cattle (3% of studies), poultry
332 (3%), or sheep/goats (7%). We found no studies that investigated filovirus infection in either
333 cattle or poultry. For both henipaviruses and filoviruses, we found no cross-sectional studies of
334 poultry and no experimental studies of cattle. Henipaviruses are much better-represented targets
335 of domesticated animal studies than filoviruses; no study from our search looked at domesticated
336 animals as potential hosts of MARV, and only 19% of studies targeted ebolaviruses.
337
338 Excepting laboratory studies (for which locations were not always listed or relevant),
339 Australia was the best-represented region, comprising 41% of geographically specific studies,
340 followed by East and Southeast Asia with 36%, Africa with 18%, and South Asia with 4.5%.

Only one study in East or Southeast Asia investigated ebolaviruses (specifically RESTV). Similarly, all but one study in Australia focused on HeV, and both studies in South Asia (for a total of eight species-specific investigations) focused on NiV in Bangladesh. At least five domesticated animal species were studied per region.

Figure 3. Breakdown of studies returned in quantitative literature review by region, species, and virus studied, where the area of each box is proportional to the number of studies looking at a given animal-virus pair in each region. Some studies cover multiple host-virus pairs and are therefore represented by a greater total area.

Box 1. Case study: filoviruses in Africa

Figure 4. Number of studies studying henipaviruses and filoviruses in bats (A) and domesticated animals (B); number of outbreaks (C) and confirmed human cases (D) of filoviruses by country of outbreak origin; and populations of (E) pigs and (F) cattle by country as reported by the FAO.[2]

Domesticated animals have received less attention as potential hosts of filoviruses than of henipaviruses. Fewer than one fifth of studies returned in this review focused on filoviruses—despite their profound impact on human health as demonstrated by the 2013-16 Ebola outbreak in West Africa (Carroll et al., 2015; Weyer et al., 2015; Spengler et al., 2016). Due to resource constraints and the importance of close-contact human-to-human transmission in outbreak settings, domesticated animals have been relatively low-priority targets of investigation (Spengler

et al., 2016). Case investigations during outbreaks should continue to rule out known sources of EBOV transmission before investigating speculative sources such as domesticated animals, which have never been associated with previous outbreaks. A better understanding of the ecology of domesticated animals in relation to pathogen transmission will nonetheless be critical for long-term control of EVD in West Africa.

Research effort on filoviruses in African bats is fairly well spatially matched to countries where zoonotic spillover has occurred (see Figs. 4-A through 4-D). Investigations of domesticated animals, by contrast, have only been conducted in Ghana (one study on henipaviruses in pigs, goats, sheep, dogs, and cats (Hayman et al., 2011)) and Gabon (two studies on ebolaviruses, one in pigs (Lahm et al., 2007) and one in dogs (Allela et al., 2005)). Our current lack of knowledge about the potential of domesticated animals to host and transmit filoviruses is particularly striking given the ubiquity of large mammal livestock (see Figs. 4-E and 4-F), dogs, and cats across the continent. There is limited evidence of susceptibility of pigs, sheep and goats, dogs, and cats to some ebolaviruses. Pigs are, in particular, a documented risk for RESTV, with observed viral circulation among pigs and indirect evidence of transmission to their handlers in the Philippines (Barrette et al., 2009). Experimentally-infected pigs are also able to transmit EBOV (Kobinger et al., 2011), the ebolavirus that has caused the most human mortality (Carroll et al., 2015; Weyer et al., 2015), and the associated risk has not been adequately evaluated.

Both RESTV spillover in the Philippines and the major Malaysian NiV outbreak occurred in the context of highly intensive, high-throughput swine production (Pulliam et al., 2012). The less intensive livestock production systems in Africa may, for now, reduce the risk of such

amplification events (Gilbert et al., 2015). The potential for amplification, however, is likely to rise along with economic development and global trends of agricultural intensification (Gerber, 2005; Herrero and Thornton, 2013; Perry et al., 2013), and too little is known about the risk posed by either dogs—despite their possible role as asymptomatic hosts—or livestock held in smallholdings.

Discussion

We have summarized the current state of knowledge about domesticated animals as hosts of henipaviruses and filoviruses. Our findings have highlighted gaps in the research effort, particularly the near-complete lack of studies of domesticated animals as hosts of filoviruses in Africa (see Box 1). South Asia represents a major geographic gap; direct bat-to-human transmission is a major spillover route in Bangladesh, but given that both studies we identified described evidence of a role of domesticated animals in NiV spillover (Hsu et al., 2004; Chowdhury et al., 2014), further studies are warranted. The dearth of published studies on filoviruses in Oceania or Asia is also notable given the known pig-mediated spillover of RESTV in the Philippines (Barrette et al., 2009). We note that we detected only one study on pigs in China—and none on any other domesticated animal—despite the detection of RESTV in pigs there (Pan et al., 2014), the proximity to known outbreaks of pig-mediated NiV outbreaks (e.g., in Malaysia), and China's housing of an estimated 65% of the world's domesticated pigs, mostly in intensive production settings. It is possible that additional studies in any of the above regions have been published in non-English language journals.

410 The potential role of cats and dogs as intermediate hosts of zoonotic viruses also merits
411 further study. Without isolation of virus or observed clinical signs, observed high
412 seroprevalences in dogs of antibodies to NiV in Malaysia and the Philippines and to EBOV in
413 Gabon do not necessarily indicate any direct risk to human health. Nonetheless, further
414 evaluation of that risk and of the possibility that dogs act as EBOV carriers is warranted,
415 particularly given frequent close contact between people and dogs and the use of dogs to hunt
416 wildlife susceptible to EVD outbreaks, such as duikers (Leroy et al., 2004; Allela et al., 2005).
417 High viral loads and the presence of infectious secretions in HeV-infected dogs pose a potential
418 zoonotic transmission risk. Further study of the pathology and epidemiology of both
419 henipaviruses and filoviruses in these widespread species is justified.
420
421 Clarifying the role of domesticated animals as hosts of henipaviruses and filoviruses (as
422 well as other zoonoses not described here) may help implement proactive strategies to protect
423 against outbreaks of these viruses, such as sentinel surveillance programs. Whether domesticated
424 animals act as amplifying or dead-end hosts of a virus, detection of infection could warn of
425 increased transmission risk to people before any active human infections occur. In many regions,
426 domesticated animal deaths are rarely investigated for emerging or novel pathogens (World
427 Organisation for Animal Health (OIE), 2016). Due to the relative rarity of private veterinarians
428 in much of Central and West Africa (Christopher and Marusic, 2013; World Organisation for
429 Animal Health (OIE), 2015), where filovirus spillover risk appears particularly high, partnerships
430 with government agriculture and veterinary departments and non-governmental organizations
431 may help disseminate advice to farmers and other animal owners. Initiatives such as the
432 PREDICT project of the Emerging Pandemic Threats program or the Dynamic Drivers of

433 Disease in Africa (DDDAC) project could help establish surveillance capacity (Wood et al.,
434 2012; Mandl et al., 2015; Gruber, 2017). In addition to acting as early warning systems, such
435 programs can build human capacity and generate data for additional research into these
436 pathogens.
437
438 Few of the studies returned in our search examined domesticated animals as part of a
439 wider ecosystem, although some studies outside the scope of our search (due to lack of
440 specificity to a virus) have looked at behaviors of people (Mendez et al., 2014) or domesticated
441 animals (Field et al., 2016) that potentially promote contact with bats or bridging species. Guided
442 by a One Health approach, cross-scale studies assessing domesticated animals in the context of
443 their potential interactions with bats, humans, wildlife, and their environment represent another
444 neglected area of research and could help interpret the evidence described in this review.
445
446 **Conclusions**
447
448 Henipaviruses and filoviruses are among the better-studied zoonotic bat-borne viruses,
449 yet we have identified gaps in our knowledge of the past and potential roles of domesticated
450 animals as hosts of these important pathogens. Due to our focus on formally published results,
451 restrictions on the publication types and language included in our search, and a tendency,
452 particularly of multidisciplinary outbreak investigations, to omit negative results, it is likely that
453 we have underestimated the research effort expended on domesticated animal infections with
454 henipaviruses and filoviruses. Nonetheless, the number of open questions remaining in this field
455 is striking and underscores the need for continued emphasis on a One Health approach.

Conflicts of interest

None of the authors of this paper have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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[3] See: ian.umces.edu/imagelibrary/

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