Reviewing the Ecological Evidence-Base for Management of Emerging Tropical Zoonoses: Kyasanur Forest Disease in India as A Case Study

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Abstract

Background Zoonotic diseases disproportionately affect poor tropical communities. Transmission dynamics of zoonoses are complex, involving communities of vector and animal hosts, with human behaviour and ecosystem use altering exposure to infected vectors and hosts. This complexity means that efforts to manage and prevent human spillover are often hampered by a poor ecological evidence base and intervention strategies tend to focus on humans (e.g. vaccination, preventative drug treatment). However, integrating ecological and evolutionary understanding of multi-vector and host transmission, human and environmental factors into disease control policy is essential. Recent frameworks have been developed to guide appropriate design of "ecological interventions" which have the potential for being more long-term, effective and economical approaches to managing human disease.

Results We extended new frameworks to identify the hierarchical series of barriers that need to be overcome by a vector-borne pathogen to facilitate human spillover, focusing on an emerging, tick-borne zoonotic pathogen in India, Kyasanur Forest Disease Virus (KFDV). Current management recommendations focus on human barriers, through personal protection and vaccination, as well as targeting vector control on cattle and at the sites of monkey deaths. Assessment of the validity of current management practices for KFD through literature review and interviews with disease managers found the efficacy of interventions difficult to quantify, due to poor empirical evidence and a lack of understanding of KFDV-vector-host ecology, particularly regarding the role of cattle in amplifying tick populations and the spatial scale of risk arising from ticks infected via monkeys, which are considered to be amplifying hosts for KFDV. The spraying of malathion around dead monkeys and the burning of vegetation to reduce tick abundance were particularly unfounded interventions. The need for community guidance and education in best practice for tick-prevention and improved vaccine efficacy and surveillance were also identified. We highlight 18 urgent research priorities and identify those which could refine current management strategies or facilitate ecological interventions targeting vectors and host barriers to spillover in the future.

Conclusions We emphasise that inter-disciplinary One Health approaches involving collaboration across diverse disciplines including ecology, epidemiology, animal and public health, health systems and social sciences, and with meaningful involvement of local communities, are necessary to refine predictive models of spillover, develop new interventions and target vaccination strategies and surveillance more effectively. Applying such approaches to understand the complex ecological systems involved in zoonotic spillover, and refine and develop appropriate management interventions, including ecological interventions targeting non-human barriers, will ultimately lead to more sustainable and long-term reductions in human cases of neglected zoonoses in the future.

Introduction

Zoonotic diseases disproportionately affect poor tropical communities [1–3], resulting in 26% of Disability Life Adjusted Years lost to infectious diseases in Lower Middle Income Countries (LMICs, Grace *et al.* 2012). Their burdens and impacts are evolving worldwide due to wide-ranging socio-political, ecological and environmental change [4]. Most zoonotic diseases have complex transmission cycles involving communities of vector and animal hosts, with disease dynamics highly dependent on the ecology and evolutionary biology of the hosts [5, 6]. Further complexity arises since human behaviour and ecosystem use alters exposure to infected vectors and hosts [7], making it challenging to predict human infection risk and develop effective control strategies.

Despite this known complexity, and the worldwide development of the "One Health" initiative (that recognises the interconnectedness of human and animal health, and the environment [8]), many zoonotic disease control programmes utilise interventions that are focussed on humans (e.g. vaccination, preventative drug treatment) rather than considering animal hosts, or the environmental settings in which spillover to humans occurs [5, 9]. This is particularly true of neglected zoonotic pathogens in tropical settings, for which there are widespread examples of effective disease control being hampered by a poor ecological evidence-base or limited application of existing evidence into policy and practice. Among the major gaps in ecological evidence-base is the lack of knowledge of how different vector and host species contribute to transmission and human-spillover events [5]. Indeed, better mechanistic understanding of ecological and environmental drivers of transmission has the potential to lead to more targeted, long-term, effective and economical approaches to managing human disease cases. In the case of Nipah virus for example, knowledge of transmission mechanisms, reservoir and amplifying hosts and human social factors driving infection risk led to the development of practical intervention strategies. *Pteropus* spp. of bats are known to be the reservoir hosts for the Nipah virus, but pigs are amplifying hosts [10–12]. Human spillover arises through direct ingestion of fruit contaminated by bats or by pigs, which are also infected via ingestion of infected fruit or contamination with bat faeces or urine [13–15]. Therefore, management strategies being practiced and developed include surveillance in pigs in areas where pig farming overlaps with *Pteropus* spp. distributions to facilitate early intervention, restrictions on fruit trees near pig farms and education and measures to prevent human consumption of infected plant products [16, 17]. The potential for developing more ecological intervention strategies for managing disease has recently been highlighted [9].

Integrating ecological and evolutionary understanding of multi-vector and host transmission, human and environmental factors into disease control policy is now thought to be essential to reducing the impact and probability of emergence of zoonotic diseases [5, 6, 9]. New frameworks are being developed to guide appropriate design of “ecological interventions” to prevent and manage human disease by identifying and strengthening barriers to pathogen spillover [9, 18]. To inform operationalisation of such frameworks in real-world settings, we focus on an emerging, tick-borne zoonotic pathogen in India. This paper reviews current management strategies and the current state of the empirical ecological evidence underpinning such strategies. We review how current strategies adhere to new framework guidelines relating to ecological interventions, and assesses the research priorities that would facilitate future effective, integrated management.

Globally, India ranks high in terms of the burden and diversity of endemic and emerging zoonotic diseases [19, 20]. Kyasanur Forest Disease Virus is a tick-borne virus (KFDV; family Flaviviridae, genus Flavivirus) that causes debilitating and potentially fatal haemorrhagic disease in people in the Western Ghats region of south India, with mortality rates reaching up to 10% in unvaccinated communities, and up to 500 people affected each year [21]. Historically, KFD cases were restricted to only a small number of districts in Karnataka state since the disease was first described in 1957 [21, 22]. Human cases of KFD have increased since 2005, with a recent dramatic spread to neighbouring states of Goa, Tamil Nadu, Maharashtra and Kerala [23]. Serological evidence from humans further suggests KFDV circulation across a broad spatial area, including Gujarat, West Bengal and the Andaman and Nicobar islands [24], revealing potential for more widespread outbreaks in humans. Thus, there is an urgent requirement for empirical understanding of the conditions and mechanisms underpinning transmission cycles in reservoirs and spillover to humans. The disease primarily affects low-income rural forest communities such as small-holder farmers, plantation and forestry workers, and tribal groups living in and around forests and reliant on harvesting of non-timber forest products [25–27]. As well as affecting diverse forest users, KFDV has a broad vector and host range, with a complex transmission cycle in which various tick species (principally of the *Haemaphysalis* genus, but also *Ixodes*) and vertebrate hosts have been implicated, including wild rodents and shrews, monkeys and some birds [21]. Humans contract KFDV when bitten by an infected tick but are incidental hosts for the disease and are not involved in onward transmission [28]. Thus like the Lyme disease agent, *Borrelia burgdorferi*, KFD is a "spillover pathogen" for which almost every human case represents a spillover event from a wildlife reservoir via the infected tick vector. However, we lack empirical knowledge of the role of different species of vector and hosts in the KFDV transmission cycle and how human behaviour and environmental changes like deforestation and are leading to disease outbreaks. Monkeys, principally the black-footed grey langur (*Semnopithecus hypoleucos*) and the bonnet macaque (*Macaca radiata*), are thought to act as amplifying hosts, by infecting large numbers of larval ticks with the virus [29]. Cattle do not amplify KFDV since they do not develop viraemia of long duration [30, 31], but are hypothesised to amplify tick population density through their importance as a blood meal host [32, 33]. The lack of robust testing of these latter two hypotheses in the field, is indicative of the significant gaps in our empirical knowledge of the ecology of the KFDV system. Even though spillover of KFDV to humans has been widely linked to human modification of the forest ecosystem through deforestation [22, 34, 35], empirical data collection on host-vector-pathogen interactions is restricted to disease emergence events that occurred last century in the 1960s and 1980s and has not been updated for current, further degraded forest conditions or areas where KFD has more recently emerged .

To consider how current KFD management fits in with new frameworks to prevent and manage human disease by identifying barriers to pathogen spillover, we first extended the framework of Sokolow et al. [9] to consider additional barriers that operate for vector-borne zoonotic diseases compared to those that are directly transmitted (Fig. 1). Vector-borne pathogens not only have to evade the immune systems of reservoir hosts and humans to effect spillover but also have to overcome several tissue barriers and immune responses within the body of the arthropod vector in order to survive and replicate to transmissible levels [See review by 36]. A key pre-requisite for spillover of vector-borne human pathogens is that their biological arthropod vectors are sufficiently abundant, widespread [37] and overlap in the same habitat with key reservoirs involved in transmission and with people [38]. Furthermore, spillover host exposure depends not only on how human activities within the ecosystem interface with reservoir habitats and behaviour but also how these activities overlap with vector habitats [39] and whether vectors prefer to bite both people and reservoirs [40].

Mapping the aims of current management recommendations for KFD in India, originating from the public health sector, namely the National Centre for Disease Control and the Department of Health and Family Welfare Services, Government of Karnataka (DHFWS), onto this extended framework of barriers to spillover (Fig. 1), it is clear that current recommendations are largely focussed on humans as the spillover host: (i) reducing exposure through community education and tick-bite prevention and (ii) reducing the number and severity of cases in humans through vaccination. A formalin-inactivated tissue-culture vaccine was developed has been used in Karnataka since 1990 [27]. This vaccine is known to give protection against KFD if the correct dose procedure is followed [41, 42]. However, duration of immunity from the vaccine is poor, requiring multiple repeated doses, and anecdotal evidence from more recent outbreaks suggests that vaccine efficacy was reduced compared to previous outbreaks (Table S1). The effectiveness of vaccination strategies has been further hampered by limited seasonal vaccine availability and poor acceptance and coverage of the required doses of the vaccine in some areas [26, 27]. This highlights the importance and urgency in developing complementary disease prevention measures alongside vaccination that follow the new framework for disease prevention set out in Fig. 1. Measures for reducing tick populations at perceived infection hotspots and monitoring disease events in monkeys as a sentinel vertebrate host are also encompassed in existing government KFD management recommendations.

The purpose of this review is to: 1. Identify current management recommendations to prevent human KFD cases; 2. Review the empirical evidence underpinning each management recommendation; 3. Review evidence for the effectiveness of the current management practice; and 4. Identify knowledge gaps that currently prevent evaluation of management options and progress towards "ecological interventions" that can be integrated into KFD management.

Current Management Recommendations And Empirical Support

Current management practices undertaken to prevent human cases of KFD were identified based on a number of guidance documents and sources originating from the Indian National Centre for Disease Control and the DHFWS: a guidance bulletin [43] and a manual on KFD [44]. Empirical evidence for these management practices for the KFD system, or for related tick-borne disease systems, was reviewed in available peer-reviewed and grey literature.

Full details of the current management practices recommended for preventing human cases of KFD in the Western Ghats area of India are given in Table S1. It includes the main assumptions underpinning management advice, in terms of how such practices could reduce human transmission via infected tick bites, indicates the empirical support for the assumptions made, and summarises whether the recommended management practice is justified or could be improved. Finally, we also summarise experiences and views of disease managers in implementing and engaging with local communities on specific current recommended management practices. Though Table S1 is not included in the main text of the paper due to space constraints, we hope this detailed table will provide a key reference document for practitioners involved in KFD management.

We supplemented the documentary review with a series of key informant interviews conducted (between July and August 2019) with district and taluk managers (N = 11) from Shivamogga headquarters, Sagar and Thirthahalli taluks in Karnataka, directly responsible for KFD management. The selection of interviewees was based on purposive and snowball sampling process, with interviews conducted in Kannada or English based on participant preference. The interviews mainly revolved around participants' views and experiences with KFD surveillance and control, which were transcribed and analysed using an open thematic coding approach as described by [45]. In addition, we also collated and analysed messages shared on our MonkeyFeverRisk WhatsApp platform primarily questions posed to researchers by participants about KFD management (Table S3). Identified patterns and contradictions from the textual data were coded and organised into emergent themes which were subsequently analysed and triangulated with the secondary data collated based on which recommendations for effective and integrated management are made [46]. Participation in this study was voluntary and interviewees gave their full prior informed verbal consent before the conduct of the interviews, which lasted between 30 and 45 minutes. The interview data were anonymised to protect the confidentiality of participants. Table S1 outlines the main themes and exemplar quotes identified through the key informant interviews and Table S2 identifies key informants.

The overall assessment of the validity of current management practices is summarised in Table 1, in which each recommendation is scored using separate traffic light scales for degree of empirical support and management effectiveness. The research and surveillance priorities arising are shown in Table 2, targeted at addressing knowledge gaps (a) to improve the existing management practices (short-term priorities) or (b) to allow more integrated or ecological interventions to be implemented in the future (long-term fundamental research priorities). Below, we summarise the validity of measures and research priorities, for each spillover barrier in turn.

Table 1

Overall assessment of the validity of current management practices for KFD. Empirical support underpinning each management recommendation are assessed based on a traffic light scale at both the local level (Western Ghats of India for KFD) and also at a more global scale if evidence for this management being effective has been observed in other tick-borne disease systems (left blank if not applicable). **Red** indicates no or poor support; **amber** indicates some support from observations and laboratory studies but lacking rigorous empirical data in a field setting; and **green** indicates good support including rigorous empirical field data. Management effectiveness was also scored on a traffic light scale: **red** indicates that the management practice is unlikely to significantly reduce human cases of KFD; **amber** indicates that it is unknown whether the management practice will reduce human cases; and **green** indicates that the management practice will reduce human cases of KFD.

Current management recommendations for KFDV	Local empirical evidence	Evidence from other systems	Rationale for evidence score	Effectiveness of management practice	Rationale for effectiveness assessment	Recommendation
Personal protection measures (PPMs) should be taken (long clothes covering neck, chest, back and legs) before going to the forest.			Good evidence from multiple systems that protective clothing can reduce tick bites.		Only effective in conjunction with application of effective repellents, washing the clothes and body and effective checking and removal of attached ticks.	PPMs should be recommended for any activity where persons may brush against vegetation that may harbour ticks, not just forests and should include covering the feet and tucking in clothes.
People living in the forest or visiting forest areas should use tick repellents (DMP oil, DEET, local herbs) before going to the forest. Permethrin-based repellents should be used on clothing.			Good evidence that repellents prevent tick bites, but efficacy of locally available repellents may be poor or untested.		Locally available repellents may have poor efficacy. Only effective in conjunction with appropriate clothing, washing the clothes and body and effective checking and removal of attached ticks.	Recommend applying repellents during any activity where persons may brush through vegetation that may harbour ticks, not just forests and guidance on reapplying repellents regularly.
People should wash their clothes and body with hot water and soap after returning from the forest.			Good evidence from other systems that washing can remove unattached ticks, but more limited local evidence and people use cold water.		Only effective in conjunction with wearing of appropriate clothing, application of effective repellents and effective checking and removal of attached ticks.	Recommend that additional education is needed to inform people that washing alone will not remove attached ticks from the body.

Current management recommendations for KFDV	Local empirical evidence	Evidence from other systems	Rationale for evidence score	Effectiveness of management practice	Rationale for effectiveness assessment	Recommendation
The spraying of insecticide (malathion) may be carried out in areas where monkey deaths have been reported within a radius of 50 feet around the locationof the monkey death. It is also effective on forest tracks frequently visited by people for various activities.			Insecticides may be effective over the area of spraying in the short-term but effectiveness untested locally and little known about resistance.		Infected ticks likely to be found across broader habitats associated with monkey deaths so spraying a small area is likely ineffective. Malathion resistance may be problematic.	Not recommended without empirical evidence of effectiveness and better knowledge of the scale of infection risk.
Application/injection of insecticide on/into cattle can prevent ticks and the transportation of ticks from forests to dwelling premises.			Acaricides can be effective at lessening tick burden on livestock (though caution needed due to resistance), but no evidence that they prevent tick movements.		May well prevent tick movements but no empirical evidence that cattle are associated with higher prevalence of human KFDV cases. Untested whether cattle might operate as diluting hosts for KFDV.	Need more evidence before recommending as KFDV preventative measure but need to consider prevention of other tick transmitted infections too.
Controlled burning of the dry leaves and bushes in the forest boundaries, premises of human habitats.			Conflicting evidence about the temporal scale over which this lowers tick abundance, lack of data on whether forests are main KFDV-risky habitat.		Unclear whether this may increase tick abundance in the longer term.	Not recommended without empirical evidence of effectiveness and better knowledge of the scale of KFDV infection risk.

Current management recommendations for KFDV	Local empirical evidence	Evidence from other systems	Rationale for evidence score	Effectiveness of management practice	Rationale for effectiveness assessment	Recommendation
Burning of monkey carcass.			No empirical support that dying or dead monkeys create hotspots of infected ticks.		Infected ticks likely to be found across broader habitats and burning monkey carcass unlikely to be important for preventing KFD.	Recommended as is a good way of disposal of carcasses which may pose a general risk to human health. Robust post-mortems and sample collection protocols needed prior to burning.
Vaccination of people within a 5 km radius of outbreak.			Substantial evidence that vaccination reduces human cases of KFDV.		Vaccine efficacy and formulation needs to be improved. Vaccine uptake is poor as administration is painful, requires three initial doses and annual boosters to confer immunity. Modelling is needed to optimise the spatial scale over which vaccination is targeted.	Urgent need for a more effective vaccine with fewer doses required and better education to increase uptake. Need better understanding of the scale at which risk operates.
Educate the villagers to avoid the forests areas where monkeys have died. Don't visit the area where recent monkey death is been reported, especially an area where case of KFDV has been reported in the past.			Evidence that monkeys may act as sentinels of human disease but poor empirical evidence over the mechanism for outbreaks and spatial scaling.		If monkeys are effective sentinels then avoiding forests may help prevent human cases.	Need better empirical evidence of tick-habitat associations and better knowledge of the scale of infection risk. Education needed on effective PPM and risk associated with brushing against vegetation, not just in forests.

Current management recommendations for KFDV	Local empirical evidence	Evidence from other systems	Rationale for evidence score	Effectiveness of management practice	Rationale for effectiveness assessment	Recommendation
Don't bring the leaves of trees from KFDV infected area to the village for cattle bedding material.			Ticks have been found in leaf litter but survival times in such litter are unknown.		May prevent the spread of infected ticks but need for better empirical evidence. Alternative sources of bedding may not be available.	Need better empirical testing of the risks posed by leaf collection from different habitats, and the levels of tick infestation in leaf litter used for animal fodder and bedding. Also need more education on appropriate PPM.
Don't handle the infected monkey carcass by bare hand without personal protective equipment.			Good evidence from multiple systems that protective clothing can reduce tick bites but needs to be more than wearing gloves.		Only effective in conjunction with application of effective repellents, washing the clothes and body and effective checking and removal of attached ticks. Needs to be undertaken not just when handling monkey carcasses.	Monkeys should not be handled by members of the public. PPM should be recommended for any activity where persons may brush against vegetation that may harbour ticks, not just when handling monkeys.
Highlighting risky activities: for example to not sit on the ground or in bushy areas of the forest.			Evidence that ticks move onto humans when they brush against vegetation, some species actively quest. Limited empirical quantification of questing behaviour in vectors associated with KFDV in the wild and of the risk associated with different habitats and human activities.		Difficult to judge effectiveness without further empirical data on how activities in different habitats increase KFD risk and on tick-habitat associations. Emphasis should not just be on forests without better empirical data on risk.	Reasonable to keep recommendation but to expand to be aware that risk of ticks may occur in habitats other than forests and that effective PPM, use of repellents and checking for ticks is essential.

Current management recommendations for KFDV	Local empirical evidence	Evidence from other systems	Rationale for evidence score	Effectiveness of management practice	Rationale for effectiveness assessment	Recommendation
Human disease surveillance-surveillance of fever cases between December and May with sera screened for KFDV antibodies in order to target vaccination.			Surveillance is a useful way of monitoring past and present outbreaks.		Surveillance needs to be undertaken strategically across areas both within and outwith the historical outbreak regions.	Recommended but improvements could be made to how surveillance effort is targeted.
Tick surveillance-surveillance is undertaken within 5 km of areas where human cases were recorded in the previous year (for up to five years) or within 5 km of areas with current monkey deaths. Surveillance is not undertaken if current human cases are recorded.			Surveillance of ticks can be an effective way of monitoring past and present outbreaks.		Effectiveness difficult to judge without better empirical knowledge of KFDV infection-tick-host-habitat associations so that surveillance can be effectively targeted. Surveillance needs to be undertaken strategically across areas both within and out with the historical outbreak regions with more systematic sampling of habitats and across seasons.	Valuable management tool. Needs better underpinning by empirical evidence to enable better targeting of habitats and seasonality. Need additional information on hosts to be able to determine best surveillance strategies in terms of habitats and spatial scale, and hosts (e.g. rodents) to target.

Current management recommendations for KFDV	Local empirical evidence	Evidence from other systems	Rationale for evidence score	Effectiveness of management practice	Rationale for effectiveness assessment	Recommendation
Monkey disease surveillance-testing of dead and dying monkeys for KFDV infection.			Monkeys are known to be amplifying hosts for the virus so are useful sentinels that may give warning of impending human infections.		Stratified proactive sampling of monkeys is not undertaken, just reactive sampling of dead or dying monkeys.	More stratified sampling of monkey blood for both antibodies and active infection with KFDV at sentinel sites. Better education about reporting dying/dead monkeys and faster response and sampling of monkeys and sampling for ticks around carcasses and the broader environment is recommended.

Table 2
Key research priorities under each of the barriers that could be targeted to prevent KFD spillover to humans (Fig. 1) and how these would inform and improve existing management strategies (a) and facilitate the development and future implementation of integrated, ecological interventions in the long-term (b)

Research priority	**a. refines current management or surveillance** **(short-term)**	**b. facilitates future ecological interventions** **(long-term)**
Barrier: Preventing tick-bites on people through personal protective measures		
1. Systematically review and test the efficacy of natural repellents being used against ticks by people in the Western Ghats alongside chemical repellents recommended by the Indian Government and by the World Health Organisation		X
2. Develop standard assays, including *in vivo* and *in vitro* toxicity tests, to assess safety and efficacy of repellents in the laboratory and under field conditions against local tick vector species	X	X
3. Determine whether ticks survive washing and drying of clothes and then pose a risk to humans through rigorous experiments with different washing and drying regimes	X	
Barrier: Vector density, distribution, habitats and behaviour		
4. Quantify abundance and infection rates of tick vector species across different habitats within the agro-forest mosaic (integrate into stratified tick surveillance)	X	X
5. Determine whether cattle are amplifying and spreading tick species or acting to dilute infection by comparing tick burdens and KFDV-infection rates on cattle, wildlife hosts and people, in settings varying in host densities	X	X
6. Quantify abundance and infection rates of ticks found in different types of dry leaf litter, used for animal fodder and bedding, under different treatments in villages	X	X
Barrier: Vector host associations: contact rates with people		
7. Quantify effectiveness of different acaricide formulations, doses and frequencies of application in reducing tick burdens on cattle, for those species involved in KFDV transmission and for natural as well as chemical repellents	X	

Research priority	a. refines current management or surveillance (short-term)	b. facilitates future ecological interventions (long-term)
8. Determine whether acaricide resistance is widespread in tick populations in India, in tick species involved in KFDV transmission, for acaricides applied both to animals and to the habitat.		X
Barrier: Human activities in ecosystems		
9. Quantify rate of contact between people and ticks during different activities in and around the forest	X	X
Barrier: Pathogen prevalence, infection intensity in reservoirs and pathogen availability to vectors		
10. Determine role of dead and dying monkeys in generating hotspots of transmission: quantify burdens, age structure, feeding history, and infection rates of ticks found on dead and dying monkeys, small mammals and in nearby habitats and people at the same time as measuring host infection levels	X	X
11. Determine role of live monkeys in transmission through infection of larvae via systemic circulation and/or supporting co-feeding between nymphs and larvae: quantify burdens, age structure, feeding history (via blood meal analysis), and infection rates of ticks found on live monkeys, small mammals, and nearby habitats and people at the same time as measuring host infection levels		X
12. Determine role of small mammals in transmission through infection of larvae via systemic circulation and/or supporting co-feeding between nymphs and larvae: quantify burdens, age structure, feeding history, and infection rates of ticks found on live monkeys, small mammals, and nearby habitats and people		X
Barrier: reservoir density, distribution, habitats and behaviour		
13. If monkeys are confirmed as important amplifying hosts for KFDV and contributing to transmission risk via-infected ticks to humans, quantify their habitat associations, movement rates and interactions with people across agro-forest landscapes	X	X
14. If small mammals are confirmed as important reservoirs for KFDV and contribute to transmission to humans, quantify their habitat associations, movement rates and interactions with people across agro-forest landscapes	X	X

Research priority	a. refines current management or surveillance (short-term)	b. facilitates future ecological interventions (long-term)
Barrier: susceptibility of spillover host		
15. Investigate social and cultural barriers to uptake of the current and potential future improved vaccines across the range of affected communities in south India		
16. Test the efficacy in inducing protective immunity and assess duration of immunoprotection for the current vaccine		
17. Investigate the potential efficacy of novel vaccines and alternative vaccines such as those available for closely related viral infections		
18. Develop correlative and mechanistic predictive models of social, environmental and ecological factors influencing spillover to better target vaccination and surveillance in the landscape		

Preventing tick-bites on people through protective measures (spillover host exposure)

Recommended protective measures to prevent tick bites on people, such as wearing long clothing during visits to the forest, application of tick repellents to the body and clothing, and washing the body and clothing after returning from the forest, are supported by robust empirical data from other tick-borne disease systems, which show that such measures can prevent exposure to ticks (refs in Table S1). These measures are endorsed by health organisations such as the World Health Organisation (WHO) for other tick-borne diseases systems. However, there is limited empirical data for the KFDV system on whether these measures prevent tick bites, with uncertainty around the effectiveness of locally available repellents, leading to several short-term research priorities (Table 2). Indeed, there is an urgent need to systematically review the natural repellents currently used by people in the Western Ghats [47] and test their efficacy compared to repellents, primarily dimethyl phthalate (DMP) oil, recommended and distributed by the Indian Government (DHFWS), or the WHO (Priority 1). Natural repellents such as Malabar catmint *Anisomeles malabarica* have good efficacy against *Haemaphysalis bispinosa* ticks but have not been tested robustly on *H. spinigera* and other known KFDV vectors [for review of promising natural repellents globally see 48–50]. Numerous studies have assessed repellence of natural remedies and report variation in efficacy between tick species but comparisons between studies are hampered by a lack of robust standardised tests [48, 51]. Standardised assays are needed (Priority 2), including toxicity tests [via in vivo and in vitro methods; see 51, 52], to assess safety and tick repellent efficacy of substances in laboratory and field conditions against tick species relevant to KFDV transmission. Such testing would require development of a bioassay facility in which pathogen-free colonies of potential tick vector species in the Western Ghats can be reared and used for the repellent efficacy trials. Furthermore, rigorous experiments are needed (Priority 3) to determine whether ticks survive washing of clothes, whether such ticks pose a risk to humans if they then drop off clothes that are being dried in the environment around houses, and for what length of time clothes need to be hung up outside under different conditions before they are free of ticks and safe to be worn again. Overall, we recommend an integrated approach at the local community level to prevent KFDV infection from tick bites, combining use of protective clothing and tick repellents; checking the entire body daily after having been in tick-infested habitats; and prompt and effective removal of any attached ticks (Table 2). Educational leaflets and videos should be developed jointly between the health department and local communities, that give guidance on best practice for preventing tick bites and removing ticks (recent community guidance material has focussed on disease symptoms and vaccination and less on tick bite prevention) whilst also taking account of potential trade-offs between recommendations and community livelihood and health priorities (Table S1 & S2). Current management recommendations and surveillance strategy assume that people only need to protect themselves from exposure to infected nymphal ticks within forests. However, evidence from other (sylvatic) tick-borne disease systems indicates that fragmented and ecotonal habitats at the interface with human habitation may pose a risk of infection to humans, due to such habitats supporting reservoir hosts or substantial densities of infected vectors [53–56]. Other habitats featuring in the agro-forest landscape mosaic of the Western Ghats such as fallow land, paddy and plantation, may also pose a risk but there is little empirical evidence on comparative densities of vectors and hosts in these habitats. A key research priority therefore (Priority 4, Table 2) is to quantify the abundance and infection rates of different tick vector species across a broad spectrum of habitats within agro-forest mosaics, including human habitation, to understand how risk of exposure to infected ticks extends out from forests. Results of such empirical research in two affected districts in the Western Ghats is forthcoming from the MonkeyFeverRisk project of which this evaluation of management strategies is a part (https://www.monkeyfeverrisk.ceh.ac.uk/). Current tick surveillance simply targets forests [as in 57], but stratified tick surveillance sampling and analysis by habitats and season could be integrated into the routine tick surveillance of DHFWS.

Preventing Tick Spread By Cattle Through Protective Measures

The application of acaricides to reduce tick loads on cattle and to prevent transportation of ticks from forests to areas of human habitation is recommended in current management guidance (Table S1, Table 1). Cattle do support high loads of ticks, including adults and *H. spinigera* (the putative main vector species), although the commonest ticks found on cattle have not yet been incriminated in the KFDV transmission cycle [32, 33]. Hence, cattle may act both as an amplifier of tick numbers and as a disperser of ticks between habitats. Moreover, correlative modelling found that the spatial risk of human KFD cases was associated with the density of cattle in areas long-affected by KFD [58]. Conversely, cattle may act to dilute infection, since they do not show systemic infection with KFDV [30, 31]. There is evidence from other tick-borne disease systems that increased density of ungulate hosts, which can amplify ticks but do not have systemic infection, may dilute pathogen transmission by diverting tick bites from competent hosts [59, 60]. Resolving these contrasting potential roles of cattle in KFDV transmission, by comparing the abundance, composition and infection rates of tick burdens between cattle, wildlife hosts and people, in varying ecological settings is therefore an urgent research priority (Priority 5). It is clear from the experiences of disease managers (Table S1), farmers cannot always keep their cattle out of the forest to avoid tick exposure, since the resulting shortages of fodder can lead to animal health and livelihood impacts. This highlights the imperative to identify effective personal protective measures for animals and people that cannot avoid the forests due to livelihood or health impairments. From an operational stand-point, though acaricides are known to reduce tick burdens on cattle, further testing of the effectiveness of different formulations, including optimal doses and frequency of application is needed, including for natural repellents that may be more available and commonly used within Western Ghats communities (Priority 7, Table 2). It is also essential to ascertain whether acaricide resistance is widespread in tick populations in India, in those species involved in KFDV transmission, for acaricides applied both to animals and to the habitat [see review in 61 ; Priority 8].

Avoidance Of Human Activities In The Ecosystem

Several of the current management recommendations for KFD seek to reduce human exposure by setting out activities within the ecosystem that should be avoided (Table S1, Table 1) including visiting forests where monkeys have died (see next section), not sitting or lying on the ground or in bushy areas of forest, and avoiding bringing dry leaves, that can harbour ticks from KFDV-infected forests into villages for use as bedding and fodder for cattle. Dry leaf litter is important not only for animal bedding and fodder but also for fertilising crops where alternatives are not available [62] and the importance of this practice constituted a key theme of questions from disease managers in Table S4). Whilst there is some empirical support that forests support tick species implicated in KFDV transmission [57] and thus that reducing these activities could reduce human cases, further quantification of tick habitat associations, encompassing non-forest habitats, (Priority 4) is needed to refine these recommendations. Although correlative modelling suggests that the presence of piles of dry leaves around the compounds of the house were associated with human disease cases [27], empirical data is needed on the abundance, infection rates and survival of ticks found in different types of dry leaf litter, used for animal fodder and bedding, and subject to different treatments in villages (Priority 6, Table 2). More generally, the rate of contact between people and ticks during different activities in and around the forest should be quantified (Priority 9, Table 2) to obtain a clearer picture of which activities cause highest exposure [63 ; https://www.monkeyfeverrisk.ceh.ac.uk/].

Measures To Reduce Density And Distribution Of Infected Ticks

The measures currently recommended to reduce the density and distribution of infected ticks, include: controlled burning of dry leaves and bushes in forests and around houses; dusting of insecticide (malathion) within 50 feet of a monkey carcass; and burning of monkey carcasses. Such measures are perhaps the least supported by empirical evidence among all the recommendations for KFD management and are the least likely to be effective at reducing human cases (Table 2). The latter two measures are predicated on the assumption that humans become exposed to infected nymphal ticks mainly at hotspots around monkey deaths, where infected ticks leave a dying or dead monkey with high KFDV viraemia, and then go onto seek a new host and bite humans, either within the same stage if they are partially fed nymphs, or, if they are larvae, following moulting to the nymphal stage (all within 50 feet). The measures further assume that insecticide or burning will kill these partially fed ticks before they bite people (Table S1). KFDV-infected monkeys are known to have high titres of virus [64] and are likely to bear infected ticks. Although, partially-fed nymphs have been found in areas around monkey carcasses [65], and engorged ticks have been observed to move up to 30 cm [66], no empirical data exist showing that successful interrupted feeding occurs in tick species commonly found to transmit KFDV in the wild. In other tick-borne disease systems, ticks generally feed on only one host in each of their life stages [67] and interrupted feeding (intra-stadial feeding) has very rarely been recorded and most often under laboratory conditions and in *Rhipicephalus* spp. where male ticks actively seek female ticks with which to mate [68, 69]. Experimental transmission studies on partially-fed ticks collected from areas close to monkey deaths suggest that these have limited potential to transmit virus by feeding on a second host [65]. Thus, though dead KFDV-positive monkeys undoubtedly indicate ongoing KFDV transmission in an area, there is no direct evidence that locations of monkey deaths are hotspots of host-seeking infected ticks, compared to surrounding areas of habitat where monkeys or small mammal hosts have spent time. Moreover, evidence is building of malathion resistance in tick populations and off-target effects on human and animal health, such as increased cancer risk, elsewhere in India [Priority 8; 70–72].

The confusion surrounding the role that monkeys play in KFDV transmission, compared to alternative small mammal hosts, highlights the need for fundamental ecological research. Although it seems very unlikely that only the immediate area around a dead or dying infected monkeys supports high density of KFDV-infected partially fed ticks or fully-fed larvae (which would then feed again as nymphs after moulting) that may pass infection to humans, this should be confirmed empirically. Priority should be given to quantifying the tick burden on dead and dying monkeys, assessing the number, species, stage and KFDV infection rate of these attached ticks, as well as determining the number, KFDV infection rate and blood meal identity [73] of ticks sampled from the habitat or off people near the monkey death site. (Priority 10, Table 2). It also needs to be ascertained whether and how quickly partially fed ticks begin to quest, the distances they can cover and the survival rates of non-questing partially-fed nymphs and larvae that moult to the next life-stage (Priority 10, Table 2). Similar sampling of ticks from monkeys, small mammals and people over broader areas of habitat would indicate whether monkeys are sentinels of infection occurring in the broader environment or whether they contribute to KFDV transmission across broader spatial scales, by feeding and infecting larvae numbers of larvae via systemic circulation, and by feeding both larvae and nymphs simultaneously, allowing co-feeding transmission to occur (Priority 11, Table 2). Though small mammals are neglected completely in current management recommendations, given their central role in amplifying transmission in other tick-borne systems through processes such as co-feeding [74], it is equally important to clarify their role in the KFDV transmission, by sampling them in similar ways alongside monkeys and humans (Priority 12, Table 2). If small mammals and monkeys are confirmed as being important reservoirs and amplifying hosts for KFDV, then empirical data on their movements and habitat associations is required in order to quantify how far they tend to travel in the landscape (when healthy or sick for monkeys), in which habitats they interact with people and ticks, and the predictability of their movements in time and space (Priority 13 and 14, Table 2). This is vital for matching the scale of surveillance, awareness raising and vaccination to the scale over which spillover from monkeys or small mammals occurs.

As for controlled burning of vegetation in forests and human habitation as a means to reduce tick abundance in the habitat, there are no studies of the impacts of burning regimes on potential tick vectors of KFDV in India. Evidence from other disease systems shows that burning can both reduce or increase tick abundance and infection rates, that impacts may vary with time and with complex local responses of hosts, vectors and vegetation [75, 76]. Experimental investigations of the impacts of burning regimes on densities of infected nymphal ticks and their contact rates with people over short- and long-time scales should be conducted in the Western Ghats.

Measures to reduce susceptibility of people as the spillover host

The strategy of vaccinating people within a certain radius of known outbreaks or circulation of KFDV in ticks or monkeys is well underpinned by evidence. The vaccine is known to protect against KFDV if the correct dose procedure is followed [42, 77], though acceptance of the vaccine and coverage rates has been poor in some areas [26, 42] due to social and cultural factors that need to be further investigated [78, 79 ; Priority 15]. Moreover in recent outbreaks there is some evidence that vaccine efficacy was reduced compared to prior outbreaks [26, 42], necessitating robust testing of efficacy and duration of protection offered by the current vaccine (Priority 16, Table 2) and parallel development of novel vaccines or alternative vaccines for closely related infections which may offer cross-immunity [80] (Priority 17, Table 2). There are opportunities to refine scaling and targeting of vaccination and surveillance activities, through predictive modelling of social, environmental and ecological factors influencing spillover (Priority 18, Table 2). At first these model frameworks will be correlative, developed by statistically matching patterns in potential risk factors with observed patterns in human cases [58] but, in the longer term, could incorporate improved knowledge of the habitat associations, movements and interactions of vectors, reservoir hosts and people (e.g. Priorities 4, 9–14, Table 2) around agro-forest landscapes to predict spillover more robustly under different intervention scenarios [39, compare to 81].

Surveillance In Ticks, Monkeys And People To Inform Interventions

Finally, the surveillance that underpins KFD management is well justified by empirical evidence. Human cases tend to be clustered, and surveillance of human fever cases, recommended to take place between December and May with screening for both virus (by RT-PCR) and antibody presence (by ELISA), has been effective in directing vaccination campaigns [26]. Given the shifting pattern of KFD cases, with new geographical hotspots identified each year [82], we additionally recommend that fever case surveillance should be adopted in areas beyond the current known distribution of KFD cases in order to more effectively detect disease outbreaks in new areas. Targeting of human surveillance can again be guided by predictive models (Priority 18, Table 2), as is already happening in Karnataka [77]. Tick surveillance can be an effective way of predicting spillover, as demonstrated in other systems [83, 84], and is valuable locally to monitor whether and where KFDV-transmission persists over time in and beyond outbreak areas and thus help confirm or identify new likely hotspots of infection prior to the outbreak season. However, as mentioned above, tick surveillance methods could be more standardised, rigorous and stratified by habitat (extending beyond forests) to build knowledge of tick vector habitat associations (Priority 4, Table 2) to improve targeting of subsequent interventions and surveillance and should routinely encompass areas beyond the current front of human KFD cases to monitor potential spread into new areas. Similarly, monkey surveillance is currently implemented through passive sampling of dead and dying monkeys, and it is restricted to areas where resources are available and awareness of KFD is high (Table S1). The coverage and value of this passive sampling could be extended by improving education on the importance of reporting dead and dying monkeys (perhaps providing smart-phone based app technology to facilitate such reporting), allowing standardized post-mortems and tick sampling around monkey death sites to be carried out more rapidly than is current practice.

Discussion And Conclusions

We show how the novel barriers framework [9, 18, Fig. 1] can be applied to evaluate the evidence-base for current management practices for reducing zoonotic disease spillover, focusing on tick-borne KFD in India. This approach is particularly powerful for KFD, and indeed for other neglected zoonoses such as scrub typhus and leptospirosis in India and other LMICs, where ecological and social evidence underpinning management strategies is outdated or lacking altogether. We show how this framework can be used to critically evaluate current management interventions and focus recommendations for their improvement, identify knowledge gaps and priority areas for research, and highlight potential opportunities for new interventions.

Current management guidance for reducing the risk of human KFD primarily focuses on practices to reduce human exposure and susceptibility to infection, mainly targeting the final, human, barriers to spillover (Fig. 1). Primary recommendations are for the use of repellents in conjunction with advice for avoiding potentially risky habitats and activities and a targeted vaccination strategy. However, our review clearly highlights the lack of robust, current empirical knowledge on the ecological and social factors leading to human cases of KFD. This lack of empirical evidence means the effectiveness of current management recommendations is questionable. For example, currently the role of cattle in KFDV dynamics is unknown, with cattle having the potential to increase KFDV transmission between susceptible hosts by moving and amplifying tick populations, or alternatively may be reducing spillover into humans by dilution effects (Table 1, S2). Furthermore, the practices of burning monkey carcasses, malathion spraying and controlled burning of vegetation around the sites of monkey deaths are particularly unfounded. Such practices are predicated on the untested assumption that monkey deaths reflect localised hotspots of transmission, as opposed to monkeys being sentinels that indicate KFDV prevalence in the area and more widespread transmission in a range of alternative hosts. However, some of the current guidance can be improved based on available evidence and we suggest detailed ways of doing this in Table S1. For example, current guidance on the use of protective clothing fails to include the need to cover up the feet and does not give guidance on the importance of regular full-body checks for attached ticks or advice on how to effectively remove ticks, and we recommend a more integrated approach. As part of our MonkeyFeverRisk project, we have co-developed community guidance in local languages (Kannada and Malayalam) in order to exchange information about the risk of tick-borne diseases and how to avoid and deal with tick bites (education materials can be accessed here: https://www.monkeyfeverrisk.ceh.ac.uk/kfd). In the short term, current management interventions can be improved through testing and development of locally available tick repellents, education of health workers and the local communities, and identifying vector-host-habitat associations that will be used to inform predictive models of spillover (Table 2).

In the longer term, understanding of the spatial and temporal distribution of infection within vectors and reservoir hosts and their consequent roles in transmission is crucial to predicting spillover and establishing interventions that target non-human barriers [85]. Indeed, the complexity of zoonotic disease dynamics, combined with restrictions imposed by funding and resource availability, favours the focus of most interventions for neglected tropical zoonoses on human barriers to spillover. However, although human interventions may be easier to implement and effective in the short-term, interventions that target vector or reservoir hosts have the potential, in the longer-term, to be both more economical and effective at reducing human spillover [9]. Indeed, even in similarly complex, but well-studied multi-host tick-borne infections such as Lyme Disease, interventions that target non-human hosts are possible: there is evidence that oral bait vaccines that target rodent reservoir hosts are effective at reducing the density of infected nymphs [86–88]. Entomopathogenic fungi such as *Beauveria bassiana* and *Metarhizium anisopliae* have also shown potential as biological control of tick vectors involved in Lyme Disease transmission [89]. Other novel interventions are currently being developed and much may be learned from the testing of such interventions in tick-borne disease systems where transmission dynamics are well elucidated. Vaccinations are being developed, for example, against tick saliva or salivary gland proteins in order to decrease the ability of ticks to feed on reservoir hosts, thus disrupting pathogen transmission [90–92]. With better mechanistic understanding of KFDV-vector-host dynamics, application of new technological advances may be possible in the future. We advocate the continuation of current key management strategies for KFD in conjunction with refined tick surveillance strategies and ecological studies that will inform both existing and future management.

The new framework developed here illustrates the significant number of hierarchical barriers (Fig. 1) that must be overcome in order for humans to become infected by KFDV, further emphasising the need for a cross-disciplinary approach to provide an evidence base and implement appropriate management interventions for tick-borne diseases. Focusing research on a single barrier or barrier type within the hierarchy, within a particular scientific discipline will not be sufficient for understanding spillover risk or implementing effective interventions [18, 93]. For KFD, the ecological processes that underpin seasonal transmission dynamics such as vector and host activity and habitat associations, seasonal resource use and movement need to be quantified alongside the social and cultural processes that influence ecosystem use, livelihoods and exposure of people. For example, the majority of disease managers interviewed highlighted complex trade-offs between restricting forest access to minimise risk of exposure and safeguarding local livelihoods that need to be further investigated as well as diverse social, cultural and techno-administrative barriers to uptake of vaccines, tick personal protection and surveillance measures e.g. post mortems (Table S2). Aligning with the One Health Initiative, inter-disciplinary approaches require collaboration across diverse disciplines including ecology, epidemiology, animal and public health, health systems and social sciences, and would enable predictive models of spillover to be refined, new interventions to be developed and vaccination strategies and surveillance to be targeted more effectively [58].

In order to sustainably and effectively refine management interventions for neglected zoonotic diseases in the face of changing empirical knowledge, environmental and policy shifts, it is vital that strategies and research are co-developed iteratively and reflexively across disciplines, targeting knowledge gaps and prioritising interventions identified by cross-sectoral stakeholders and involving beneficiaries alongside researchers [58, 94]. Within the MonkeyFeverRisk project, empirical research and models were co-created using a co-production approach, that placed stakeholder engagement at the heart of the research, from joint framing of the problem, to knowledge integration and experimentation with resulting knowledge and tools [95–97]. In practice, active science-policy-practice interfaces between a diverse range of stakeholders, researchers and beneficiaries were established and maintained through multi-stakeholder workshops and focus groups, inclusion of decision-makers as active research partners, researcher membership of government technical advisory committees on KFDV and through cross-sectoral WhatsApp groups set up following a direct request from stakeholders at our first workshop

(https://www.monkeyfeverrisk.ceh.ac.uk/sites/default/files/Stakeholder_workshop_report_MonkeyFeverRisk_16012019.pdf). An illustration of the valuable framing of empirical research and subsequent knowledge exchange that can arise through such science-policy-practice interfaces is provided in Table S4, which shows key ecological questions posed to researchers by practitioners through the two recent KFDV transmission seasons. The trade-offs between livelihood benefits and disease dis-benefits from forests, the poor uptake of some interventions for KFD (Table S2) and the wide range of traditional coping methods in use by local communities, highlight the importance of meaningful involvement of local communities in the design of management strategies [97] and this is a key priority for effective management of KFD. Applying the approach to understand the complex ecological systems involved in zoonotic spillover, and refine and develop appropriate management interventions, including ecological interventions targeting non-human barriers, will ultimately lead to more sustainable and long-term reductions in human cases of neglected zoonoses in the future.

Declarations

Ethics approval and consent to participate

The protocols for this study were approved by the Institutional Ethics Committee of the Institute of Public Health (IPH IEC), Bangalore (Study ID, IEC-FR/04/2017) and received a Favourable Ethical Opinion from the Liverpool School of Tropical Medicine Research Ethics Committee (research protocol 17/062). All interviewees were adults and provided informed verbal consent.

Consent for publication

Not applicable

Availability of data and material

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

SJB, BVP, ATV, PNS, MMMC and SLH obtained funding. SJB, BVP, SMS, ATV, PNS, TS and FA contributed to the methodology. SJB, BVP and FA wrote the manuscript. All authors reviewed and edited the manuscript and contributed to discussions leading to the conceptualization of this piece of work.

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References

1. Grace D, Gilbert J, Randolph T, Kang'ethe E. The multiple burdens of zoonotic disease and an Ecohealth approach to their assessment. Trop Anim Health Prod. 2012;44 Suppl 1:S67–73. doi:10.1007/s11250-012-0209-y.
2. Halliday JEB, Allan KJ, Ekwem D, Cleaveland S, Kazwala RR, Crump JA. Endemic zoonoses in the tropics: a public health problem hiding in plain sight. Vet Rec. 2015;176:220–225. doi:10.1136/vr.h798.
3. Molyneux D, Hallaj Z, Keusch GT, McManus DP, Ngowi H, Cleaveland S, et al. Zoonoses and marginalised infectious diseases of poverty: where do we stand? Parasit Vectors. 2011;4:106. doi:10.1186/1756-3305-4-106.
4. Jones BA, Grace D, Kock R, Alonso S. Zoonosis emergence linked to agricultural intensification and environmental change' ' . Proc Natl Acad Sci USA. 2013;110:8399–8404.
5. Webster JP, Gower CM, Knowles SCL, Molyneux DH, Fenton A. One health - an ecological and evolutionary framework for tackling Neglected Zoonotic Diseases. Evol Appl. 2016;9:313–333. doi:10.1111/eva.12341.

6. Karesh WB, Dobson A, Lloyd-Smith JO, Lubroth J, Dixon MA, Bennett M, et al. Ecology of zoonoses: natural and unnatural histories. Lancet. 2012;380:1936–1945. doi:10.1016/S0140-6736(12)61678-X.
7. Murray KA, Daszak P. Human ecology in pathogenic landscapes: two hypotheses on how land use change drives viral emergence. Curr Opin Virol. 2013;3:79–83. doi:10.1016/j.coviro.2013.01.006.
8. Lebov J, Grieger K, Womack D, Zaccaro D, Whitehead N, Kowalcyk B, et al. A framework for One Health research. One Health. 2017;3:44–50. doi:10.1016/j.onehlt.2017.03.004.
9. Sokolow SH, Nova N, Pepin KM, Peel AJ, Pulliam JRC, Manlove K, et al. Ecological interventions to prevent and manage zoonotic pathogen spillover. Philos Trans R Soc Lond B, Biol Sci. 2019;374:20180342. doi:10.1098/rstb.2018.0342.
10. Chua KB, Koh CL, Hooi PS, Wee KF, Khong JH, Chua BH, et al. Isolation of Nipah virus from Malaysian Island flying-foxes. Microbes Infect. 2002;4:145–151. doi:10.1016/s1286-4579(01)01522-2.
11. Yob JM, Field H, Rashdi AM, Morrissy C, van der Heide B, Rota P, et al. Nipah virus infection in bats (order Chiroptera) in peninsular Malaysia. Emerging Infect Dis. 2001;7:439–441. doi:10.3201/eid0703.010312.
12. Hooper P, Zaki S, Daniels P, Middleton D. Comparative pathology of the diseases caused by Hendra and Nipah viruses. Microbes Infect. 2001;3:315–322. doi:10.1016/s1286-4579(01)01385-5.
13. Field H, Young P, Yob JM, Mills J, Hall L, Mackenzie J. The natural history of Hendra and Nipah viruses. Microbes Infect. 2001;3:307–314. doi:10.1016/s1286-4579(01)01384-3.
14. Luby SP, Rahman M, Hossain MJ, Blum LS, Husain MM, Gurley E, et al. Foodborne transmission of Nipah virus, Bangladesh. Emerging Infect Dis. 2006;12:1888–1894. doi:10.3201/eid1212.060732.
15. Luby SP, Gurley ES, Hossain MJ. Transmission of human infection with Nipah virus. Clin Infect Dis. 2009;49:1743–1748. doi:10.1086/647951.
16. Pulliam JRC, Epstein JH, Dushoff J, Rahman SA, Bunning M, Jamaluddin AA, et al. Agricultural intensification, priming for persistence and the emergence of Nipah virus: a lethal bat-borne zoonosis. J R Soc Interface. 2012;9:89–101. doi:10.1098/rsif.2011.0223.
17. Gurley ES, Hegde ST, Hossain K, Sazzad HMS, Hossain MJ, Rahman M, et al. Convergence of humans, bats, trees, and culture in nipah virus transmission, bangladesh. Emerging Infect Dis. 2017;23:1446–1453. doi:10.3201/eid2309.161922.
18. Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, et al. Pathways to zoonotic spillover. Nat Rev Microbiol. 2017;15:502–510. doi:10.1038/nrmicro.2017.45.
19. Grace D, Gilbert J, Lapar ML, Unger F, Fèvre S, Nguyen-Viet H, et al. Zoonotic emerging infectious disease in selected countries in Southeast Asia: insights from ecohealth. Ecohealth. 2011;8:55–62. doi:10.1007/s10393-010-0357-3.
20. Sekar N, Shah NK, Abbas SS, Kakkar M, Roadmap to Combat Zoonoses in India Initiative. Research options for controlling zoonotic disease in India, 2010-2015. PLoS One. 2011;6:e17120. doi:10.1371/journal.pone.0017120.
21. Pattnaik P. Kyasanur forest disease: an epidemiological view in India. Rev Med Virol. 2006;16:151–165. doi:10.1002/rmv.495.
22. Nichter M. Kyasanur forest disease: an ethnography of a disease of development. Med Anthropol Q. 1987;1:406–423. doi:10.1525/maq.1987.1.4.02a00040.
23. Gurav YK, Yadav PD, Gokhale MD, Chiplunkar TR, Vishwanathan R, Patil DY, et al. Kyasanur forest disease prevalence in western ghats proven and confirmed by recent outbreak in maharashtra, india, 2016. Vector Borne Zoonotic Dis. 2018. doi:10.1089/vbz.2017.2129.
24. Mourya DT, Yadav PD. Recent scenario of emergence of kyasanur forest disease in india and public health importance. Curr Trop Med Rep. 2016;3:7–13. doi:10.1007/s40475-016-0067-1.
25. Patil DY, Yadav PD, Shete AM, Nuchina J, Meti R, Bhattad D, et al. Occupational exposure of cashew nut workers to Kyasanur Forest disease in Goa, India. Int J Infect Dis. 2017;61:67–69. doi:10.1016/j.ijid.2017.06.004.

26. Kiran SK, Pasi A, Kumar S, Kasabi GS, Gujjarappa P, Shrivastava A, et al. Kyasanur Forest disease outbreak and vaccination strategy,Shimoga District, India, 2013-2014. Emerging Infect Dis. 2015;21:146–149. doi:10.3201/eid2101.141227.
27. Kasabi GS, Murhekar MV, Yadav PD, Raghunandan R, Kiran SK, Sandhya VK, et al. Kyasanur Forest disease, India, 2011-2012. Emerging Infect Dis. 2013;19:278–281. doi:10.3201/eid1902.120544.
28. Murhekar MV, Kasabi GS, Mehendale SM, Mourya DT, Yadav PD, Tandale BV. On the transmission pattern of Kyasanur Forest disease (KFD) in India. Infect Dis Poverty. 2015;4:37. doi:10.1186/s40249-015-0066-9.
29. Work TH, Roderiguez FR, Bhatt PN. Virological epidemiology of the 1958 epidemic of Kyasanur Forest disease. Am J Public Health Nations Health. 1959;49:869–874.
30. Varma MG, Webb HE, Pavri KM. Studies on the transmission of Kyasanur Forest disease virus by Haemaphysalis spinigera Newman. Trans R Soc Trop Med Hyg. 1960;54:509–516. doi:10.1016/0035-9203(60)90024-9.
31. Anderson CR, Singh KR. The reaction of cattle to Kyasanur Forest disease virus. Indian J Med Res. 1971;59:195–198.
32. Rajagopalan PK, Patil AP, Boshell J. Ixodid ticks on their mammalian hosts in the Kyasanur Forest disease area of Mysore State, India, 1961-64. Indian J Med Res. 1968;56:510–525.
33. Balasubramanian R, Yadav PD, Sahina S, Arathy Nadh V. Distribution and prevalence of ticks on livestock population in endemic area of Kyasanur forest disease in Western Ghats of Kerala, South India. J Parasit Dis. 2019;43:256–262. doi:10.1007/s12639-019-01086-7.
34. Walsh JF, Molyneux DH, Birley MH. Deforestation: effects on vector-borne disease. Parasitology. 1993;106 Suppl:S55–75. doi:10.1017/S0031182000086121.
35. Boshell M. J. Kyasanur Forest Disease. Am J Trop Med Hyg. 1969;18:67–80. doi:10.4269/ajtmh.1969.18.67.
36. Kazimírová M, Thangamani S, Bartíková P, Hermance M, Holíková V, Štibrániová I, et al. Tick-Borne Viruses and Biological Processes at the Tick-Host-Virus Interface. Front Cell Infect Microbiol. 2017;7:339. doi:10.3389/fcimb.2017.00339.
37. Randolph SE, Rogers DJ. Tick-borne Disease Systems: Mapping Geographic and Phylogenetic Space. In: Global mapping of infectious diseases: methods, examples and emerging applications. Elsevier; 2006. p. 263–291. doi:10.1016/S0065-308X(05)62008-8.
38. Lambin EF, Tran A, Vanwambeke SO, Linard C, Soti V. Pathogenic landscapes: interactions between land, people, disease vectors, and their animal hosts. Int J Health Geogr. 2010;9:54. doi:10.1186/1476-072X-9-54.
39. Hartemink N, Vanwambeke SO, Purse BV, Gilbert M, Van Dyck H. Towards a resource-based habitat approach for spatial modelling of vector-borne disease risks. Biol Rev Camb Philos Soc. 2015;90:1151–1162. doi:10.1111/brv.12149.
40. McCoy KD, Léger E, Dietrich M. Host specialization in ticks and transmission of tick-borne diseases: a review. Front Cell Infect Microbiol. 2013;3:57. doi:10.3389/fcimb.2013.00057.
41. Dandawate CN, Upadhyaya S, Banerjee K. Serological response to formolized Kyasanur forest disease virus vaccine in humans at Sagar and Sorab Talukas of Shimoga district. J Biol Stand. 1980;8:1–6. doi:10.1016/S0092-1157(80)80041-2.
42. Kasabi GS, Murhekar MV, Sandhya VK, Raghunandan R, Kiran SK, Channabasappa GH, et al. Coverage and effectiveness of Kyasanur forest disease (KFD) vaccine in Karnataka, South India, 2005-10. PLoS Negl Trop Dis. 2013;7:e2025. doi:10.1371/journal.pntd.0002025.
43. National Centre for Disease Control. Kyasanur Forest Disease: a public health concern. 2019.
44. Directorate of Health and Family Welfare Services, Govt of Karnataka. Manual on Kyasanur Forest Disease. Directorate of Health and Family Welfare Services, Govt of Karnataka; 2005.
45. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3:77–101. doi:10.1191/1478088706qp063oa.
46. Cresswell JW, Clark VP. Designing and conducting mixed method research. 2nd Sage.

47. Venkatachalapathi A, Sangeeth T, Ali MA, Tamilselvi SS, Paulsamy S. Ethnomedicinal assessment of Irula tribes of Walayar valley of Southern Western Ghats, India. Saudi J Biol Sci. 2016. doi:10.1016/j.sjbs.2016.10.011.
48. Pages F, Dautel H, Duvallet G, Kahl O, de Gentile L, Boulanger N. Tick repellents for human use: prevention of tick bites and tick-borne diseases. Vector Borne Zoonotic Dis. 2014;14:85–93. doi:10.1089/vbz.2013.1410.
49. Adenubi OT, Ahmed AS, Fasina FO, McGaw LJ, Eloff JN, Naidoo V. Pesticidal plants as a possible alternative to synthetic acaricides in tick control: A systematic review and meta-analysis. Ind Crops Prod. 2018;123:779–806. doi:10.1016/j.indcrop.2018.06.075.
50. Benelli G, Pavela R, Canale A, Mehlhorn H. Tick repellents and acaricides of botanical origin: a green roadmap to control tick-borne diseases? Parasitol Res. 2016;115:2545–2560. doi:10.1007/s00436-016-5095-1.
51. Adenubi OT, McGaw LJ, Eloff JN, Naidoo V. In vitro bioassays used in evaluating plant extracts for tick repellent and acaricidal properties: A critical review. Vet Parasitol. 2018;254:160–171. doi:10.1016/j.vetpar.2018.03.008.
52. Dautel H, Dippel C, Werkhausen A, Diller R. Efficacy testing of several Ixodes ricinus tick repellents: different results with different assays. Ticks Tick Borne Dis. 2013;4:256–263. doi:10.1016/j.ttbdis.2012.11.007.
53. Despommier D, Ellis BR, Wilcox BA. The role of ecotones in emerging infectious diseases. Ecohealth. 2007;3:281–289. doi:10.1007/s10393-006-0063-3.
54. Kowalec M, Szewczyk T, Welc-Falęciak R, Siński E, Karbowiak G, Bajer A. Ticks and the city - are there any differences between city parks and natural forests in terms of tick abundance and prevalence of spirochaetes? Parasit Vectors. 2017;10:573. doi:10.1186/s13071-017-2391-2.
55. Kuo C-C, Huang J-L, Shu P-Y, Lee P-L, Kelt DA, Wang H-C. Cascading effect of economic globalization on human risks of scrub typhus and tick-borne rickettsial diseases. Ecol Appl. 2012;22:1803–1816. doi:10.1890/12-0031.1.
56. Borremans B, Faust C, Manlove KR, Sokolow SH, Lloyd-Smith JO. Cross-species pathogen spillover across ecosystem boundaries: mechanisms and theory. Philos Trans R Soc Lond B, Biol Sci. 2019;374:20180344. doi:10.1098/rstb.2018.0344.
57. Naren Babu N, Jayaram A, Hemanth Kumar H, Pareet P, Pattanaik S, Auti AM, et al. Spatial distribution of Haemaphysalis species ticks and human Kyasanur Forest Disease cases along the Western Ghats of India, 2017-2018. Exp Appl Acarol. 2019;77:435–447. doi:10.1007/s10493-019-00345-9.
58. Purse BV, Darshan N, Kasabi GS, Gerard F, Samrat A, George C, et al. Predicting disease risk areas through co-production of spatial models: The example of Kyasanur Forest Disease in India's forest landscapes. PLoS Negl Trop Dis. 2020;14:e0008179. doi:10.1371/journal.pntd.0008179.
59. Bolzoni L, Rosà R, Cagnacci F, Rizzoli A. Effect of deer density on tick infestation of rodents and the hazard of tick-borne encephalitis. II: population and infection models. Int J Parasitol. 2012;42:373–381. doi:10.1016/j.ijpara.2012.02.006.
60. Levi T, Keesing F, Holt RD, Barfield M, Ostfeld RS. Quantifying dilution and amplification in a community of hosts for tick-borne pathogens. Ecol Appl. 2016;26:484–498. doi:10.1890/15-0122.
61. George JE, Pound JM, Davey RB. Chemical control of ticks on cattle and the resistance of these parasites to acaricides. Parasitology. 2004;129:S353–S366. doi:10.1017/S0031182003004682.
62. Davidar P, Arjunan M, Mammen PC, Garrigues JP. Forest degradation in the Western Ghats biodiversity hotspot: resource collection, livelihood concerns and sustainability. Current Science. 2007.
63. Fornace KM, Alexander N, Abidin TR, Brock PM, Chua TH, Vythilingam I, et al. Local human movement patterns and land use impact exposure to zoonotic malaria in Malaysian Borneo. Elife. 2019;8. doi:10.7554/eLife.47602.
64. Shah KV, Dandawate CN, Bhatt PN. Kyasanur forest disease virus: viremia and challenge studies in monkeys with evidence of cross-protection by Langat virus infection. [version 1; peer review: 3 approved]. F1000Res. 2012;1:61. doi:10.12688/f1000research.1-61.v1.
65. Sreenivasan MA, Bhat HR, Rajagopalan PK. Studies on the transmission of Kyasanur forest disease virus by partly fed ixodid ticks. Indian J Med Res. 1979;69:708–713.

66. Bhat HR. Observations on the biology of Haemaphysalis spinigera Neumann, 1897 (Acarina: Ixodidae) under Natural conditions in KFD area. . Journal of Bombay Natural History Societ. 1986;82:548–562.
67. Randolph SE. Tick ecology: processes and patterns behind the epidemiological risk posed by ixodid ticks as vectors. Parasitology. 2004;129:S37–S65. doi:10.1017/S0031182004004925.
68. Wang H, Nuttall PA. Intra-stadial tick-borne Thogoto virus (Orthomyxoviridae) transmission: accelerated arbovirus transmission triggered by host death. Parasitology. 2001;122 Pt 4:439–446. doi:10.1017/S0031182001007478.
69. Little SE, Hostetler J, Kocan KM. Movement of Rhipicephalus sanguineus adults between co-housed dogs during active feeding. Vet Parasitol. 2007;150:139–145. doi:10.1016/j.vetpar.2007.08.029.
70. Brasil VLM, Ramos Pinto MB, Bonan RF, Kowalski LP, da Cruz Perez DE. Pesticides as risk factors for head and neck cancer: A review. J Oral Pathol Med. 2018;47:641–651. doi:10.1111/jop.12701.
71. Kumar S, Sharma AK, Nagar G, Ghosh S. Determination and establishment of discriminating concentrations of malathion, coumaphos, fenvalerate and fipronil for monitoring acaricide resistance in ticks infesting animals. Ticks Tick Borne Dis. 2015;6:383–387. doi:10.1016/j.ttbdis.2015.03.003.
72. Graf JF, Gogolewski R, Leach-Bing N, Sabatini GA, Molento MB, Bordin EL, et al. Tick control: an industry point of view. Parasitology. 2004;129 Suppl:S427–42. doi:10.1017/s0031182004006079.
73. Collini M, Albonico F, Rosà R, Tagliapietra V, Arnoldi D, Conterno L, et al. Identification of Ixodes ricinus blood meals using an automated protocol with high resolution melting analysis (HRMA) reveals the importance of domestic dogs as larval tick hosts in Italian alpine forests. Parasit Vectors. 2016;9:638. doi:10.1186/s13071-016-1901-y.
74. Randolph SE, Miklisová D, Lysy J, Rogers DJ, Labuda M. Incidence from coincidence: patterns of tick infestations on rodents facilitate transmission of tick-borne encephalitis virus. Parasitology. 1999;118 (Pt 2):177–186. doi:10.1017/s0031182098003643.
75. Gleim ER, Conner LM, Berghaus RD, Levin ML, Zemtsova GE, Yabsley MJ. The phenology of ticks and the effects of long-term prescribed burning on tick population dynamics in southwestern Georgia and northwestern Florida. PLoS One. 2014;9:e112174. doi:10.1371/journal.pone.0112174.
76. MacDonald AJ, Hyon DW, McDaniels A. Risk of vector tick exposure initially increases, then declines through time in response to wildfire in California. 2018.
77. Dandawate CN, Desai GB, Achar TR, Banerjee K. Field evaluation of formalin inactivated Kyasanur forest disease virus tissue culture vaccine in three districts of Karnataka state. Indian J Med Res. 1994;99:152–158.
78. Dubé E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J. Vaccine hesitancy: an overview. Hum Vaccin Immunother. 2013;9:1763–1773. doi:10.4161/hv.24657.
79. Oliveira A, Selvaraj K, Tripathy JP, Betodkar U, Cacodcar J, Wadkar A. Kyasanur Forest Disease vaccination coverage and its perceived barriers in Goa, India-A mixed methods operational research. PLoS One. 2019;14:e0226141. doi:10.1371/journal.pone.0226141.
80. McAuley AJ, Sawatsky B, Ksiazek T, Torres M, Korva M, Lotrič-Furlan S, et al. Cross-neutralisation of viruses of the tick-borne encephalitis complex following tick-borne encephalitis vaccination and/or infection. npj Vaccines. 2017;2:5. doi:10.1038/s41541-017-0009-5.
81. Li S, Colson V, Lejeune P, Speybroeck N, Vanwambeke SO. Agent-based modelling of the spatial pattern of leisure visitation in forests: A case study in Wallonia, south Belgium. Environ Model Softw. 2015;71:111–125. doi:10.1016/j.envsoft.2015.06.001.
82. Chakraborty S, Andrade FCD, Ghosh S, Uelmen J, Ruiz MO. Historical expansion of kyasanur forest disease in india from 1957 to 2017: A retrospective analysis. GeoHealth. 2019;3:44–55. doi:10.1029/2018GH000164.
83. Jameson LJ, Medlock JM. Tick surveillance in Great Britain. Vector Borne Zoonotic Dis. 2011;11:403–412. doi:10.1089/vbz.2010.0079.

84. Ripoche M, Gasmi S, Adam-Poupart A, Koffi JK, Lindsay LR, Ludwig A, et al. Passive tick surveillance provides an accurate early signal of emerging lyme disease risk and human cases in southern canada. J Med Entomol. 2018;55:1016–1026. doi:10.1093/jme/tjy030.
85. Plowright RK, Becker DJ, McCallum H, Manlove KR. Sampling to elucidate the dynamics of infections in reservoir hosts. Philos Trans R Soc Lond B, Biol Sci. 2019;374:20180336. doi:10.1098/rstb.2018.0336.
86. Richer LM, Brisson D, Melo R, Ostfeld RS, Zeidner N, Gomes-Solecki M. Reservoir targeted vaccine against Borrelia burgdorferi: a new strategy to prevent Lyme disease transmission. J Infect Dis. 2014;209:1972–1980. doi:10.1093/infdis/jiu005.
87. Tsao JI, Wootton JT, Bunikis J, Luna MG, Fish D, Barbour AG. An ecological approach to preventing human infection: vaccinating wild mouse reservoirs intervenes in the Lyme disease cycle. Proc Natl Acad Sci USA. 2004;101:18159–18164. doi:10.1073/pnas.0405763102.
88. Tsao K, Fish D, Galvani AP. Predicted outcomes of vaccinating wildlife to reduce human risk of Lyme disease. Vector Borne Zoonotic Dis. 2012;12:544–551. doi:10.1089/vbz.2011.0731.
89. Kaaya GP. Laboratory and field evaluation of entomogenous fungi for tick control. Ann N Y Acad Sci. 2000;916:559–564. doi:10.1111/j.1749-6632.2000.tb05336.x.
90. Contreras M, Villar M, de la Fuente J. A Vaccinomics Approach for the Identification of Tick Protective Antigens for the Control of Ixodes ricinus and Dermacentor reticulatus Infestations in Companion Animals. Front Physiol. 2019;10:977. doi:10.3389/fphys.2019.00977.
91. Contreras M, Alberdi P, Fernández De Mera IG, Krull C, Nijhof A, Villar M, et al. Vaccinomics Approach to the Identification of Candidate Protective Antigens for the Control of Tick Vector Infestations and Anaplasma phagocytophilum Infection. Front Cell Infect Microbiol. 2017;7:360. doi:10.3389/fcimb.2017.00360.
92. Gomes H, Moraes J, Githaka N, Martins R, Isezaki M, Vaz I da S, et al. Vaccination with cyclin-dependent kinase tick antigen confers protection against Ixodes infestation. Vet Parasitol. 2015;211:266–273. doi:10.1016/j.vetpar.2015.05.022.
93. Lloyd-Smith JO, George D, Pepin KM, Pitzer VE, Pulliam JRC, Dobson AP, et al. Epidemic dynamics at the human-animal interface. Science. 2009;326:1362–1367. doi:10.1126/science.1177345.
94. Leach M, Scoones I. The social and political lives of zoonotic disease models: narratives, science and policy. Soc Sci Med. 2013;88:10–17. doi:10.1016/j.socscimed.2013.03.017.
95. Ainsworth GB, Redpath SM, Wilson M, Wernham C, Young JC. Integrating scientific and local knowledge to address conservation conflicts: Towards a practical framework based on lessons learned from a Scottish case study. Environ Sci Policy. 2020;107:46–55. doi:10.1016/j.envsci.2020.02.017.
96. Norström AV, Cvitanovic C, Löf MF, West S, Wyborn C, Balvanera P, et al. Principles for knowledge co-production in sustainability research. Nat Sustain. 2020. doi:10.1038/s41893-019-0448-2.
97. Bardosh KL. Towards a science of global health delivery: A socio-anthropological framework to improve the effectiveness of neglected tropical disease interventions. PLoS Negl Trop Dis. 2018;12:e0006537. doi:10.1371/journal.pntd.0006537.

Figures

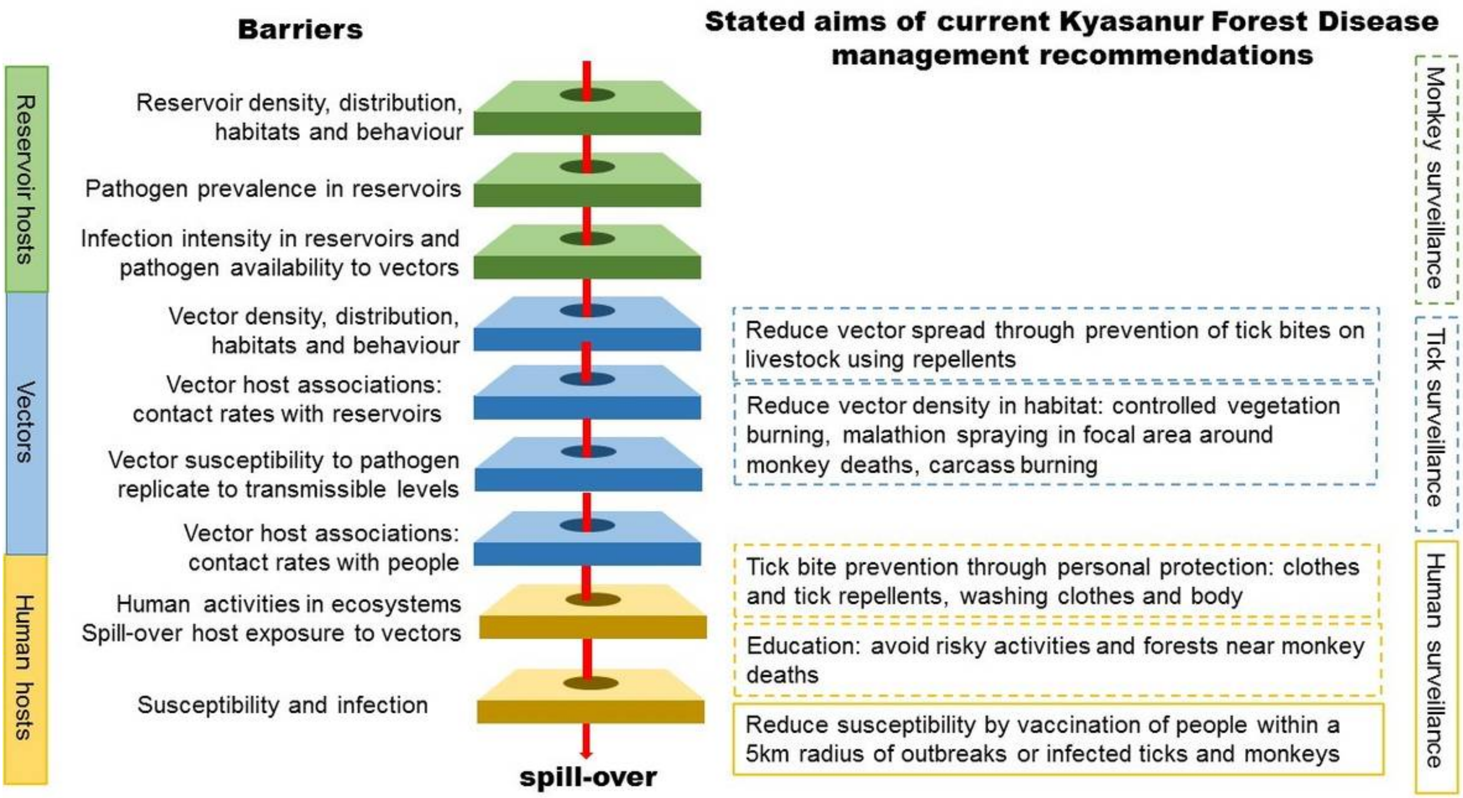

Figure 1

A schematic of the hierarchical barriers to spillover of vector-borne zoonotic diseases to humans, extending the framework set out in [18] and [9]. Management interventions may reduce or prevent spillover by targeting these barriers, with green layers representing reservoir hosts, blue representing the environment and vectors, and yellow the spillover hosts. Current KFD management shown on the right hand side mainly targets the final two barriers associated with the spillover hosts, aiming to reduce human exposure and susceptibility to infection. The dotted outlines of boxes indicate where the empirical evidence for impacts of management interventions is particularly incomplete. Surveillance activity, currently conducted for KFDV in people, ticks and monkeys informs these interventions, with dotted outlines indicating where strategies could be refined to better target interventions.

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