

A framework for evaluating animals as sentinels for infectious disease surveillance

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The dynamics of infectious diseases are highly variable. Host ranges, host responses to pathogens and the relationships between hosts are heterogeneous. Here, we argue that the use of animal sentinels has the potential to use this variation and enable the exploitation of a wide range of pathogen hosts for surveillance purposes. Animal sentinels may be used to address many surveillance questions, but they may currently be underused as a surveillance tool and there is a need for improved interdisciplinary collaboration and communication in order to fully explore the potential of animal sentinels. In different contexts, different animal hosts will themselves vary in their capacity to provide useful information. We describe a conceptual framework within which the characteristics of different host populations and their potential value as sentinels can be evaluated in a broad range of settings.

Keywords: sentinel; surveillance; infectious diseases; epidemiology

1. INTRODUCTION

The dynamics of infectious disease systems are inherently variable. The outcome of any infection depends on multiple factors relating to pathogen characteristics, host susceptibility, infecting dose and routes of transmission, all of which can vary widely for any particular infectious organism. Many of the major diseases of medical, veterinary and conservation importance (such as highly pathogenic avian influenza (HPAI), foot-and-mouth disease, bluetongue and rabies) are caused by pathogens with wide host ranges (Woolhouse & Gowtage-Sequeria 2005), which introduces further complexity.

While the complex epidemiology of multi-host pathogens presents considerable challenges for understanding infection dynamics and implementing disease control, heterogeneities in host range and infection outcome also provide opportunities for disease surveillance. In this paper, we develop a conceptual framework that can be applied to examine those characteristics of host populations that influence their potential value as sentinels for disease surveillance in different ecological and epidemiological settings.

Surveillance is defined by the World Health Organization as ‘the ongoing systematic collection, collation, analysis and interpretation of data and the dissemination of information to those who need to know in order for action to be taken’ (World Health Organization 2001). The aim of disease surveillance is

to identify changes in the infection and/or health status of animal and human populations and is essential to provide rigorous evidence of the absence of disease or to determine the prevalence of a pathogen when present (Salman 2003). A critical element of surveillance is that an identified response is made on the basis of the surveillance data generated to allow appropriate action to be taken. Sentinel surveillance is one form of surveillance in which activities focus on specific subpopulations to enhance detection of disease and/or improve the cost-effectiveness of surveillance (McCluskey 2003). The aim of the sentinel surveillance is to obtain timely information in a relatively inexpensive manner rather than to derive precise estimates of prevalence or incidence in the general population (Centers for Disease Control and Prevention 2002). It has long been recognized that animal populations have the potential to act as sentinels for environmental health hazards (CAMEH 1991), but, given the importance of domestic and wild animal hosts in emerging human diseases, it is clear that surveillance in animals is also critical for understanding and managing emerging disease threats (Kuiken *et al.* 2005; Woolhouse & Gowtage-Sequeria 2005; Kahn 2006). Animal sentinels almost certainly represent an important but underused surveillance tool (Rabinowitz *et al.* 2005) that may be capable of accommodating and capitalizing on the variability that exists in infectious disease processes.

Animal sentinels may potentially be used to address a range of surveillance questions including (i) detection of a pathogen in a new area, (ii) detection of changes in the prevalence or incidence of a pathogen or disease over time, (iii) determining the rates and direction of

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Table 1. Summary of applications of animal sentinels for environmental and infectious hazards.

type of sentinel	example	reference
individual animal	coal miner's canary used to detect the presence of carbon monoxide	Burrell & Seibert (1916); Schwabe (1984)
herd/population	sentinel cattle herds and chicken flocks used to monitor the distribution of arboviruses and their vectors in Australia and the USA	National Arbovirus Monitoring Program (2003–2004); Loftin <i>et al.</i> (2006)
same species	unvaccinated chickens placed within vaccinated flock to detect HPAI	Suarez (2005)
different, more susceptible species	feral pigs released into New Zealand to detect the presence of bovine TB—more susceptible than possums; coal miner's canary (as above)	Nugent <i>et al.</i> (2002)
sentinel application	example	reference
deliberately placed (experimental)	standard laboratory mice sentinel programmes using outbred mice, sacrificed and tested to detect presence of a panel of rodent pathogens in the core experimental or breeding colony	Institute of Laboratory Animal Resources (US). Committee on Infectious Diseases of Mice and Rats (1991)
	use of sentinel chickens to evaluate the effectiveness of cleaning and disinfection procedures for eradication of Newcastle disease	McCluskey <i>et al.</i> (2006)
in natural habitat (observational)	wildlife as detectors of DDT and PCB toxicity	CAMEH (1991)
	evaluation of white-tailed deer as natural sentinels for <i>Anaplasma phagocytophilum</i> , the cause of human granulocytic anaplasmosis	Dugan <i>et al.</i> (2006)
sentinel unit	mesothelioma in pet dogs associated with exposure of their owners to asbestos	Glickman <i>et al.</i> (1983)
	equine premises used to investigate presence of vesicular stomatitis in Colorado	McCluskey <i>et al.</i> (2002)

pathogen spread, (iv) testing specific hypotheses about the ecology of a pathogen, and (v) evaluating the efficacy of potential disease control interventions (McCluskey 2003). The appropriate use of animal sentinels can facilitate the early detection and identification of outbreaks that is of critical importance for the success of control and prevention efforts (Chomel 2003; Kahn 2006) and reducing the magnitude of subsequent outbreaks (Ferguson *et al.* 2005). However, the potential of animal sentinel surveillance can only be realized if the information provided from animal populations is acted upon. For example, in an Ebola outbreak in central Africa, few preventive health measures were taken despite warnings of an imminent human outbreak being provided from monitoring of Ebola deaths in primate sentinels (Rouquet *et al.* 2005).

The term 'sentinel' is widely used in both epidemiological and veterinary clinical literature and is implicitly understood but rarely defined. While all uses invoke the common concept of standing guard or keeping watch, existing definitions tend to be context-specific. The classic example of an animal sentinel is that of the coal miner's canary. In this case, an individual animal of a different species is deliberately selected and placed in a situation where it can provide evidence of increased risk to the human population on the basis of its greater sensitivity and obvious observable response to the presence of carbon monoxide. Since the mid-twentieth century, it has been recognized that animals can act as important sentinels for a wide range of environmental health hazards (CAMEH 1991). For example, domestic dogs and the tumours they develop may facilitate identification of environmental

carcinogens that affect humans (Thrusfield 2005). Sentinels can vary from individual animals to herds or larger populations, from animals of the same species to different, more susceptible, more expendable or more accessible species, and from animals deliberately placed or introduced to those already existing in a particular location. The sentinel concept can also refer to a physical location, such as a farm, abattoir, veterinary practice or laboratory (the 'sentinel unit') which is selected to monitor a particular disease (table 1). Throughout this paper, we use 'animal sentinels' as an umbrella term for the topic in general and 'sentinel population' to refer to the unit of observation in a particular case.

Despite the apparent potential for animal sentinels to inform decisions about risk to both human and animal populations, animal sentinels appear underutilized, particularly in the context of infectious disease surveillance (Rabinowitz *et al.* 2005), and their value has been discussed primarily in the context of environmental health (CAMEH 1991). A basic lack of integration between disciplines, most noticeably between human and veterinary medicine and also between different branches within these fields, is likely to have contributed to this underuse of animal sentinels (Rabinowitz *et al.* 2005). There are currently no standard criteria which are applied for the evaluation of animal sentinels, limiting the ease with which data can be transferred between disciplines (Rabinowitz *et al.* 2005). The existing infectious disease literature regarding animal sentinels consists largely of descriptive studies that have generated hypotheses regarding animal sentinel use (Rabinowitz *et al.* 2005), but as yet includes few studies that were

Box 1. West Nile virus surveillance in North America: animal sentinel case study.

West Nile virus (WNV), an arbovirus of the genus *Flaviviridae*, is maintained in a mosquito–bird–mosquito cycle primarily involving *Culex* sp. mosquitoes (Campbell *et al.* 2002). Humans and other mammal species are incidental dead-end hosts. The majority of human infections with WNV are asymptomatic or result in transient febrile illness but in a small proportion of cases, meningoencephalitis can occur (Mostashari *et al.* 2001). The geographical range of WNV has historically included Africa, Europe, Asia and Australia (Campbell *et al.* 2002). In 1999, the first North American cases of WNV were reported in New York and since then the virus has spread across the continental United States and into Canada, Latin America and the Caribbean (Hayes & Gubler 2006). The surveillance of WNV in North America has included investigation of the utility of different animal sentinels. Some of the findings of these studies are described below with reference to the sentinel framework.

Sentinel response to pathogen

A number of North American bird species including corvids, house sparrows, house finches and grackles are competent reservoirs for mosquito infection with WNV (Komar *et al.* 2003). Among these potential sentinel species, corvids and specifically American crows (*Corvus brachyrhynchos*) are particularly susceptible to infection with WNV and have a high mortality rate (McLean *et al.* 2001; Komar *et al.* 2003; Yaremych *et al.* 2004). In 2000, it was established that dead crow reports preceded both the confirmation of viral activity (through laboratory analysis) and the onset of human cases by several months (Eidson *et al.* 2001b). Subsequent spatial analyses using data collected in New York have identified a positive association between the risk of human disease caused by WNV and elevated local dead crow reports in the previous one to two weeks (Mostashari *et al.* 2003; Eidson *et al.* 2005; Johnson *et al.* 2006). The thorough characterization of this temporal association ensures that the observation of crow deaths can be acted upon immediately without the need for time-consuming laboratory analyses. The observation of clusters of high crow mortality can therefore be used to predict human risk early enough to implement targeted mosquito control and personal protection warnings (Mostashari *et al.* 2003; Eidson *et al.* 2005; Johnson *et al.* 2006).

Relationship between sentinel and target populations

Domestic dogs have also been evaluated as sentinels of WNV presence (Komar *et al.* 2001; Kile *et al.* 2005). This sentinel choice is informed by the particular relationship that domestic dogs have with humans, which means that they are well suited to act as indicators of the infectious disease risks that their owners are likely to encounter. North American domestic dogs consistently show higher seroprevalence of anti-WNV antibodies than humans (Komar *et al.* 2001; Kile *et al.* 2005) and one analysis revealed that outdoor dogs were nearly 19 times more likely to have seroconverted to WNV than indoor-only pet dogs (Kile *et al.* 2005). The pattern of human exposure to the arthropod vectors of WNV is likely to be more similar to that of indoor-only dogs, but within the context of broad spatial association with humans; this divergence from the human niche means that outdoor-only dogs are more sensitive sentinels of WNV presence and human risk than indoor-only dogs (Kile *et al.* 2005).

Transmission route

The role played by different mosquito species (predominantly of the genus *Culex*) in the transmission of WNV between birds and to humans is apparently quite variable (Kilpatrick *et al.* 2005; Molaei *et al.* 2006). At one study site in Maryland and Washington DC, over 90% of all *Culex* mosquitoes identified were of the species *Culex pipiens* (Kilpatrick *et al.* 2006). At this site, the rise in human WNV cases that occurs in late summer and early autumn is apparently caused by a marked shift in the feeding preferences of this vector species from birds to humans (Kilpatrick *et al.* 2006) that is associated with the dispersal of a preferred host, the America robin (*Turdus migratorius*). This temporal variation in vector feeding preferences means that the transmission of WNV to bird hosts (including corvids) occurs earlier in the season than transmission to humans and explains the capacity for bird die-offs to provide an early warning of human risk. A similar shift in feeding patterns associated with a rise in human cases is also seen in *Culex tarsalis* mosquitoes in Colorado and California (Kilpatrick *et al.* 2006).

Detectability

Although the pathogenicity of WNV to birds including crows has been demonstrated within the historical geographical range of WNV (Work *et al.* 1955), bird die-offs are not typically associated with human WNV outbreaks within this historical geographical range and the very high mortality seen in American corvid populations is apparently unusual (Eidson *et al.* 2001a). Clearly, this difference may limit the application of corvids as useful sentinels of WNV to contexts within the Americas. Even within North America, there is variation in the suitability of corvids to act as a sentinel for WNV activity according to the density of human populations. A study using decoy crows revealed that both detection and reporting rates were lower in rural areas compared with urban areas (Ward *et al.* 2006). Spatial analyses have also identified reduced capacity of dead crow density measures to forecast human infections in rural areas (Eidson *et al.* 2005). These effects are seen because the capacity of crows to act as useful sentinels depends upon the likelihood that bird deaths are observed and reported by people. The power of dead crow sentinel surveillance to predict human risk is greatly reduced in rural areas as a consequence of a reduced detectability of the sentinel response.

purposefully designed to evaluate their potential. The major exception is the extensive research that has been carried out into the use of animal sentinels in the surveillance of West Nile virus (WNV) in North America (see box 1). The utility of different animal sentinel populations varies enormously according to both the ecological context and the aim of the surveillance programme, and in many cases animal sentinels may not prove a useful surveillance tool.

2. IDENTIFYING AND ASSESSING ANIMAL SENTINELS

For any population to be useful for surveillance, it must be under observation and must be capable of developing a detectable response to a particular pathogen. Sentinel populations are distinguished from other populations by having attributes that enhance detection of the disease or of the etiological agent and/or improve the

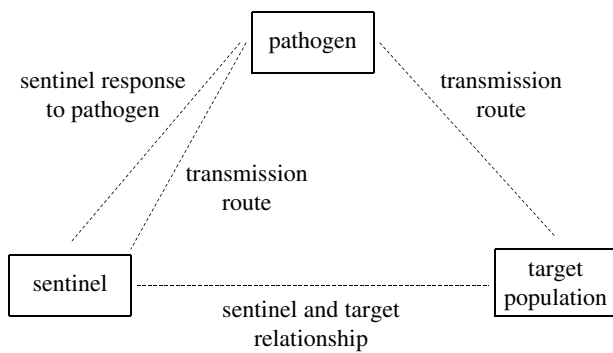


Figure 1. Key components and attributes of the sentinel framework.

cost-effectiveness of surveillance (McCluskey 2003). In most cases, this means that the sentinel population is more likely to be exposed to, or to respond to the pathogen than other populations. This sentinel concept encompasses the variety of uses described above and can refer to any level of grouping from an individual to a larger unit, such as a herd or even a species.

Various authors have compiled lists of attributes of an 'ideal' sentinel (CAMEH 1991; Komar 2001), but these have invariably been created with a particular sentinel application in mind and there exists little or no consensus about the common characteristics or defining features of 'the sentinel'. This ambiguity, of course, reflects the fact that there is no innate quality of sentinel suitability that particular species or populations have. Instead, the criteria against which the usefulness of a given sentinel population is assessed are influenced by the aim of surveillance and the context in which the sentinel would be used. We describe a conceptual framework which we believe can be used to evaluate potential sentinel populations for any combination of surveillance aim and ecological context (figures 1 and 2).

3. THE SENTINEL FRAMEWORK

Within any surveillance context, the sentinel population must always interact with both the pathogen and the target population and it is essential to consider and describe the interactions between these fundamental components (figure 1). The following are the three components of the sentinel framework.

- *Pathogen*. The pathogen that is under surveillance.
- *Target population*. The population of concern to which information gathered from the sentinel is applied.
- *Sentinel population*.

This framework is not intended to represent the transmission dynamics of a pathogen, but rather the ways in which the components are associated. Three critical attributes of this system must be considered in order to assess the utility of a potential sentinel for a particular surveillance aim and in any given ecological context: (i) the sentinel response to the pathogen, (ii) the relationship between sentinel and target populations, and (iii) routes of transmission to both target and sentinel populations. The conceptual issues raised

are discussed with reference to the surveillance of WNV in North America (box 1).

3.1. Sentinel response to pathogen

The sentinel response to a pathogen can range from the production of antibody in an otherwise healthy individual, through morbidity and ultimately to mortality. It may also be possible to detect the presence of the pathogen in a sentinel population before other responses develop and sentinel responses can therefore include the following.

- Current infection/presence of pathogen.
- Seroconversion.
- Morbidity.
- Mortality.

There is a clear intuitive distinction between sentinel populations that develop high levels of morbidity or mortality in response to pathogen exposure and those that remain healthy. Sick or dying sentinels show an obvious and dramatic response to a pathogen and provide a readily appreciable signal of the presence of a pathogen within an ecosystem (see the discussion of crow mortality as a sentinel of WNV presence in box 1). At the other end of the spectrum, apparently healthy sentinels that develop a subclinical response are often more useful for investigating the maintenance patterns and transmission dynamics of a pathogen within the sentinel and target populations. Following the consumption of prey infected with rabbit haemorrhagic disease virus (RHDV), foxes in northern Germany developed antibody responses that declined after just two weeks. Serosurveillance of this fox population therefore reveals the proportion of the population that has been exposed in the one to two weeks prior to testing. These serological data can provide a good indication of the incidence patterns of RHDV in the sympatric rabbit population (Frölich *et al.* 1998). In cases in which healthy sentinels are used, it may be desirable to resample the same individuals or populations over time. It is also important that the observation and sampling of the sentinel population, and perhaps also the sentinel response itself, has minimal impact upon the study system.

This example also demonstrates the influence of the temporal characteristics of the sentinel response to a pathogen upon the choice and application of sentinel populations. Sentinel populations which respond to a pathogen prior to the exposure of the target population may be useful for those surveillance programmes that aim to prevent the exposure of the target population. For other sentinel uses, the rapid development of a response may not be required. The duration of the potential sentinel's response can also influence the types of question which can be usefully addressed. An equivalent sentinel population (to that of the foxes) that developed a longer lasting antibody response in the above RHDV example would be of limited use for investigating the incidence of disease in the rabbit population on this immediate time-scale.

The sentinel response can be viewed as a test for the presence of the pathogen within the target population

and as such has properties that are analogous to test sensitivity and specificity.

- *Sentinel sensitivity.* The sensitivity of the sentinel refers to its capacity to respond to the presence of the pathogen in the target population and effectively translates as susceptibility to infection. An insensitive population would be unlikely to display evidence of infection with the pathogen even if it were present in the target population and would therefore be poorly suited for use as a sentinel.
- *Sentinel specificity.* The specificity of the sentinel response relates to the ease with which a sentinel response can be interpreted and attributed to a particular pathogen. Specificity is thus closely linked to the response type. Morbidity and mortality are generally less specific indicators of the presence of a particular pathogen than molecular responses that are observed using a test or assay unique to the pathogen in question. Across parts of rural Africa and Asia, for example, bird die-offs due to pathogens other than H5N1 avian influenza virus can be relatively common occurrences, reducing the specificity of bird mortality as an indicator of H5N1 presence (World Health Organization 2005).

Whatever the type of response a particular sentinel population mounts to a pathogen, it is important that the individual members of that population are consistent in the development of the response. Excessive variation within a sentinel population would greatly complicate the interpretation of surveillance findings and it may therefore be important to ensure that members of the sentinel population are of similar age, sex or other relevant characteristics, depending upon the type of response measured.

3.2. Relationship between sentinel and target populations

The relationship that exists between the sentinel and target populations may include behavioural, epidemiological or spatial aspects or any other form of ecological association. Detailed understanding of the associations between the sentinel and target populations is not required to address all questions. However, a comprehensive understanding of the relationship between a sentinel and a target population will allow for the investigation of more complex epidemiological questions and better-informed interpretation of the data collected through surveillance of that sentinel. The minimum association that must exist between a sentinel and a target population is a spatial association. This need not imply spatial overlap however. If the pathogen is spreading on a wavefront or emanating from a focal source, then a sentinel population may be selected on the basis of its closer proximity to the focus at the target population.

At the other extreme, the sentinel population may consist of a specific subset of the target population, ensuring a very close relationship between the two populations. A subpopulation that experiences high-transmission risk, or is particularly sensitive to infection with a particular pathogen, may serve as a sentinel

for the wider population and can clearly provide a more accurate assessment of risk to the target than a population occupying a dissimilar ecological niche and consequently experiencing a very different pattern of exposure to the pathogen (e.g. unvaccinated sentinel birds are used to detect the presence of HPAI viruses within the otherwise vaccinated flock; Suarez 2005). The sentinel and target population may also be epidemiologically linked such that the sentinel may act as a source of infection for the target population, as is the case with arthropod vector surveillance.

3.3. Transmission routes

This attribute is essentially a component of the relationship between the sentinel and target populations that explicitly considers the route or routes through which the two populations can become infected with the pathogen. In circumstances where the target and sentinel are exposed to infection via the same route, the relative intensity and patterns of exposure of the two populations to the source of infection are important (Estrada-Franco *et al.* 2006). It may be desirable to select a sentinel that has higher levels of exposure and which is therefore more likely to show evidence of a pathogen if it is present than to directly survey the target population itself. For pathogens that are transmitted by a vector or vectors, the feeding preferences of the vector(s) can therefore be important in informing sentinel selection. Domestic dogs are the preferred source of blood meals for *Triatoma infestans*, one of the main vectors of *Trypanosoma cruzi* in Mexico. A comparative serosurvey revealed overall anti-*T. cruzi* IgG prevalence of 16% in dogs compared with a 2% prevalence in humans, and a strong positive correlation between human and dog seropositivity within the study area. These data suggest that the feeding preferences of this vector make the domestic dog population a good sentinel for identifying areas of human seropositivity and monitoring prevalence in this context (Estrada-Franco *et al.* 2006).

There are also circumstances in which the route of exposure of the sentinel and target population may differ. A number of emerging zoonoses, including WNV and HPAI H5N1 viruses can be transmitted through the ingestion of infected material (Komar *et al.* 2003; Austgen *et al.* 2004; Rimmelzwaan *et al.* 2006). Carnivore and scavenger species that are exposed through consumption of infected prey may prove useful sentinels for a wide range of pathogens, specifically because of this additional route of exposure that is not shared with the target population (Cleaveland *et al.* 2006). A single predator or scavenger typically consumes material from multiple individuals, increasing the probability of exposure to pathogens circulating within the prey population. Predators and scavengers can effectively sample from the prey population, leading to a 'bioaccumulation' effect whereby pathogens present at relatively low prevalence in the prey population may be detected at higher prevalence in the predator/scavenger species (Cleaveland *et al.* 2006). An understanding of the predator-prey relationships between the target population and potential sentinels may prove useful in sentinel selection. The principal

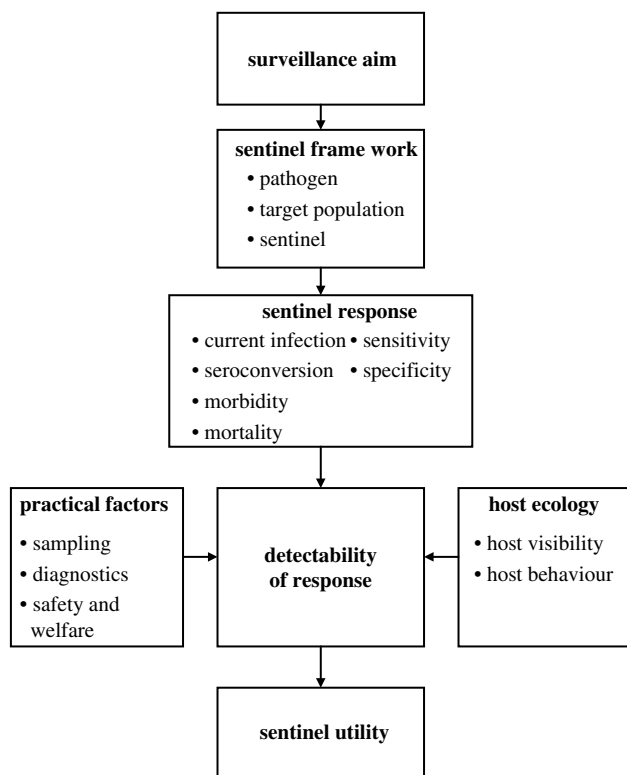


Figure 2. The sentinel framework in context.

transmission route of bluetongue virus, which infects wild and domestic ruminants across East Africa, is via *Culicoides* midge vectors. Serosurveillance of free-ranging African carnivores revealed that both the seroprevalence and the virus serotype identified varied dramatically across carnivore species (Alexander *et al.* 1994). This study suggested that the most probable route of infection of carnivores with bluetongue was via consumption of infected prey, and that the variation seen between species was attributable to dietary differences. Different carnivore species may therefore vary in their utility as sentinels for the presence of bluetongue virus in different ruminant species.

4. PLACING THE SENTINEL FRAMEWORK IN CONTEXT

The sentinel response can be viewed as the output of the sentinel framework. The nature of this response, in combination with other sentinel host factors and practical influences which depend upon the context in which surveillance is conducted, determines the overall detectability of the sentinel response (figure 2). Unlike the attributes which operate within the sentinel framework, detectability is a quality of the interaction between the sentinel and the observer. The overall utility of any potential sentinel can only be assessed by considering both the sentinel framework and the influences of the context in which it would be applied (figure 2; box 2).

The visibility of any animal population is determined by the morphology, behaviour, distribution and abundance of the individual animals of which it is comprised. The detectability of the

sentinel response includes both the visibility of the animal and its response to a pathogen. The type of response that an animal mounts will directly affect the ease with which it is detected by the observer. For example, lions are being used as sentinels for canine distemper in the Serengeti National Park in Tanzania, as a result of their high visibility to observers and the dramatic manifestations of clinical disease, which include grand mal seizures (Roelke-Parker *et al.* 1996). Information from lion sentinels would be used to increase disease detection efforts within other wild carnivore populations of the park to establish the extent and impact of any epidemic and initiate a risk–benefit assessment for possible interventions (such as vaccination) for protecting threatened wildlife populations. A wide range of other carnivore species such as hyaenas, bat-eared foxes and leopards are known to be susceptible to canine distemper (Roelke-Parker *et al.* 1996), but are less suitable as sentinels for disease in the Serengeti owing to ecological and behavioural factors that reduce visibility (e.g. nocturnal behaviour, small body size, den-living characteristics, lower levels of tourist observation). Widespread morbidity or mortality within a sentinel population are more readily appreciable than seroconversion or current infection/presence of pathogen, which can only be detected by the observer after first sampling the sentinel population and then conducting laboratory analysis. In the case of overt sentinel responses such as mortality, the existence of a reliable network of ‘observers’ and a mechanism through which data are reported are crucial. It is equally important to consider the available capacity to detect any less overt responses including the existence of a reliable sampling protocol and a diagnostic test (McCluskey 2003). The majority of diagnostic tests for human and livestock pathogens have not been validated for use in non-target species and the sensitivity and specificity of tests can vary hugely between species (Greiner & Gardner 2000). The existence of a suitable negative control population and recognition of the time required to identify and validate diagnostic tests must be considered in any proposed sentinel surveillance programme.

The practical difficulties involved in sampling any potential sentinel population must also be evaluated and it may often be difficult to reconcile the use of a theoretically ideal sentinel with such practicalities. For a sentinel population to be useful, it must be both logistically feasible and safe to sample sufficient numbers of the population (CAMEH 1991). Since sentinels are often selected on the basis of increased likelihood of exposure to a pathogen, sentinel surveillance can enable targeting of resources and often has improved cost-effectiveness as compared, for example, with more comprehensive cross-sectional surveys (McCluskey *et al.* 2003). The bioaccumulation effect discussed above suggests that evidence of exposure to a pathogen may effectively accumulate within carnivore populations (Cleaveland *et al.* 2006). The identification of the presence of a pathogen within a particular area can therefore be achieved by sampling relatively few carnivore sentinels, as compared to an exhaustive and costly survey of the prey population

Box 2. Simplified application of the conceptual framework represented in figures 1 and 2 to the evaluation of potential sentinel populations for the surveillance of HPAI H5N1.

Surveillance aim

To establish if H5N1 viruses have been introduced into a country with underdeveloped disease surveillance and reporting structure.

Should sentinels be used?

- Cross-sectional survey—may be expensive and time consuming.
- Sentinel surveillance—potentially cost-effective alternative



Sentinel framework

pathogen=HPAI H5N1 virus.

target population=the national poultry population.

Potential sentinels

- Backyard chicken populations in areas of perceived high risk of virus introduction, e.g. close to areas of wild bird congregation or to livestock markets.
- Backyard ducks in similar locations.
- Wild bird populations.
- Domestic cats.
- Domestic dogs.

Other potential sentinels are excluded altogether on the basis of a lack of response to the pathogen or of any type of meaningful relationship with the target population.

Relationship between sentinel and target populations

Chickens

- Subset of target population.

Ducks

- Occupy a very similar niche to target population.
- May act as silent carrier of viruses (Hulse-Post *et al.* 2005).

Wild birds

- May act as source of infection for domestic species.
- May not occupy the same geographical areas as the target population (especially true for large congregations of migratory birds).

Cats and dogs

- Spatial correspondence with target population.
- Cats and dogs may prey upon the target population.

Transmission routes

Chickens, ducks and wild birds

- Bird–bird transmission.
- Environmental contamination.

Cats and dogs

- Consumption of infected birds (Keawcharoen *et al.* 2004; Kuiken *et al.* 2004).
- Horizontal transmission in cats (Rimmelzwaan *et al.* 2006).



Sentinel response

Chickens

- Consistent, rapid and widespread mortality.
- Die-offs provide a prompt indication of virus presence.

Ducks

- Variable pathogenicity and thus mortality (Sturm-Ramirez *et al.* 2005).
- Isolation of virus from healthy birds (Hulse-Post *et al.* 2005).

Wild birds

- Variable pathogenicity (Ellis *et al.* 2004).
- Isolation of virus from healthy birds (Chen *et al.* 2006).

Cats

- Experimental evidence of mortality response (Rimmelzwaan *et al.* 2006).
- Mortality reports associated with bird die-offs (Butler 2006a, Songserm *et al.* 2006a, Yingst *et al.* 2006).
- High seroconversion rates (Butler 2006b).
- Subclinical infections (Leschnik *et al.* 2007).

Dogs

- High seroconversion rates (Butler 2006b).
- Mortality report associated with bird infection (Songserm *et al.* 2006b).

Sensitivity and specificity of responses

Chickens

- ✓✓✓ Highly sensitive but specificity of mortality response is low, as
- ××× chicken die-offs not necessarily unusual where poultry are not routinely vaccinated against other pathogens,

(Continued.)

Box 2. (*Continued.*)

e.g. Newcastle disease virus.

- ✓✓✓ High specificity of laboratory analyses.

Ducks

- ✓/× Variable mortality response limits sensitivity.
- ✓✓✓ High specificity of laboratory analyses.

Wild birds

- ✓/× Variable mortality response limits sensitivity.
- ××× Very low prevalence in healthy birds limits sensitivity (Chen *et al.* 2006).
- ✓✓✓ High specificity of laboratory analyses.

Cats and Dogs

- ✓/× Serological analyses non-specific for distinguishing high- and low-pathogenicity viruses.

+

Host ecology

- ✓✓✓ Domestic species are all highly observable as a consequence of their close association with humans.
- ××× Wild birds are considerably less visible and may occupy relatively remote and inaccessible areas.

+

Practical factors

- Risk to sampling personnel must be considered as a priority when developing all sampling protocols.
- ✓✓✓ Domestic species approachable and handleable.
- ✓/× Distribution of cats and dogs relatively to poultry may vary according to factors such as urbanization and religion.
- ××× Considerable investment of money, time and expertise required to sample sufficient numbers of wild birds.
- ✓✓✓ For the identification of virus presence, standard test protocols include RT-PCR and virus isolation (World Organization for Animal Health 2005) which are generally adaptable across species.
- ✓/× Serological analyses may not be well developed for wild birds, cats or dogs.

↓

Detectability

Chickens

- ✓✓✓ Mortality response easily appreciated.
- ✓✓✓ High visibility within human communities.
- ××× Low specificity of mortality limits detectability.

Ducks

- ××× Mortality response variable.
- ✓✓✓ Additional responses detectable through laboratory analysis.
- ✓✓✓ High visibility within human communities.

Wild birds

- ××× Mortality response variable.
- ××× Low visibility compared with domestic species.
- Logistically complex and time-consuming sampling required.

Cats and Dogs

- ✓✓✓ High visibility within human communities.
- ✓✓✓ Sudden and widespread morbidity or mortality uncommon.
- ✓/× Non-mortality responses less detectable.

In all cases, a comprehensive network of observers is vital and it may be necessary to develop education programmes aimed at improving reporting levels.

↓

Utility

- Domestic chicken and ducks sentinels are likely to provide the most rapid and dramatic response to HPAI H5N1 virus within a country. However, in this context in which mortality in domestic birds is not unusual, this mortality may not be reported and the detectability of the response in the context of this surveillance aim may be very low.
- To best address this surveillance aim, the specificity of the chicken mortality response to HPAI H5N1 presence could be enhanced by using a combination of sentinels such that priority was given to the investigation of chicken die-offs that were accompanied by morbidity or mortality in cats or dogs (Yingst *et al.* 2006).
- Retrospective analysis of sera collected from ducks, cats and dogs could also be used to identify those areas in which an H5N1 virus had been present.

within which the pathogen may circulate at very low prevalence, thereby providing a relatively rapid and inexpensive surveillance option (Frölich *et al.* 1998; Leighton *et al.* 2001; Csángó *et al.* 2004; Cleaveland *et al.* 2006). In addition to consideration of time and cost, the potential risks to research personnel and the public that are associated with the desired sampling strategy must be evaluated, as well as the effects of

sampling upon the sentinel population itself in the context of animal welfare and conservation status (CAMEH 1991).

5. APPLICATIONS OF ANIMAL SENTINELS

Many of the questions addressed through the use of animal sentinels, such as the assessment of pathogen

control efforts, the monitoring of prevalence fluctuations over time and the demonstration of the absence of a pathogen, require only the basic qualities of a sentinel as defined above. While the more specific requirements of any particular sentinel are unique to the context and aim to which it is applied, there are some general qualities and subtypes of sentinels that correspond to major applications of animal sentinels. For example, sentinels in which the response to a pathogen and the detection of that response occur prior to exposure, or cases in the target population, can provide early warning of pathogen presence. Early warning sentinels are used to provide a predictive signal of risk to the target population. Sentinels that are exposed and which respond to a pathogen before the exposure of the target population may provide an opportunity to implement pre-emptive control measures and to prevent the infection of the target population (see discussion of WNV surveillance in box 1). Other early warning sentinels may respond to the pathogen more rapidly than the target population but not necessarily before the target's exposure (e.g. the coal miner's canary). In such cases, data collected from the sentinel cannot be used to prevent cases in the target population altogether. However, the information they supply can provide advance warning of cases, enabling the prioritization of resources for treatment and the prevention of additional cases. In most cases, early warning sentinels are highly visible and develop a very obvious response to the pathogen. Data provided by sentinels with these qualities can be more rapidly processed, analysed and acted upon than the data from apparently healthy sentinels for which the potentially lengthy processes of sample collection and laboratory analyses must be carried out before any data are available. Ideally, the response of early warning sentinels should also be very specific to minimize the likelihood of false positive responses and consequently improve confidence in decision making based on the sentinel response alone.

Sentinels can also be used retrospectively to provide evidence of the timing of pathogen introduction and spread through a target population. In situations where a number of populations or locations are sampled, this information can be combined to reveal the spatial and temporal pattern of pathogen spread. Following the widespread rinderpest outbreak that occurred in Kenya in 1993–1997, the retrospective serosurveillance of buffalo herds and analysis of age-seroprevalence patterns allowed the estimation of the time of infection in different herds, the identification of the probable point of entry of the pathogen into the wildlife population and the elucidation of where the pathogen had been, how it had spread and where it was likely to move to (Kock *et al.* 1999). In this case, buffalo herds were selected as sentinels on the basis of the increased susceptibility of the species to this virus (Rossiter 1994), and served as sentinels for the larger livestock population in the affected areas. In such circumstances, the appropriate sentinel population must develop a response to the

pathogen that persists and is detectable a long time after exposure. When used retrospectively, it is also important that individuals of the sentinel population can be reliably aged.

6. CONCLUSION

The objective of this paper has been to provide a consistent and inclusive framework that clarifies our understanding of the role of animal sentinels and their potential value in the surveillance of human and animal infectious diseases, as well as providing a conceptual tool that can be applied to assess and characterize potential sentinels in the future. At present, surveillance of many pathogens involves the target population alone; however, the broad host range of many important human and animal diseases provides opportunities for exploiting a wide range of species for surveillance purposes. The variability of host responses to a pathogen, the heterogeneities in pathogen exposure in different populations and the differing relationships between sentinel and target populations indicate that different animal hosts will themselves vary in their ability to act as effective sentinels in different circumstances.

Animal sentinels may not serve as a useful surveillance tool in all contexts. The generic framework that we have developed in this paper describes the attributes of host species that need to be considered to identify appropriate sentinel populations for different surveillance purposes. This same framework should also be used to identify characteristics of potential sentinels that perhaps make them unsuitable in a particular circumstance. For example, sentinels must by definition be intentionally observed. This classification distinguishes the use of animal sentinels from scenarios in which responses of animal populations to novel pathogens are 'noticed'. For this reason, animal sentinels cannot provide the solution to the question of how to carry out surveillance for pathogens that are currently unknown. However, as a consequence of greater awareness of the potential of animal sentinels and improved observation of animal populations, instances of unusual morbidity and mortality in animal populations that result from the emergence of novel pathogens would perhaps be more likely to be noticed and their potential significance to other species recognized.

To date, there has been limited appreciation of the data resource that different animal hosts represent for disease surveillance. This paper aims to highlight the variety of surveillance functions for which animal sentinels may be used, the range of animal host species that may usefully be exploited (particularly for human disease surveillance) and the potential benefits of animal sentinels for enhanced pathogen detection and improved cost-effectiveness of surveillance. The potential value of animal sentinels in disease prevention and control can only be realized with close integration and effective communication between and within human and animal health sectors; information generated from sentinel populations must be disseminated to those who need to

take action, and appropriate responses must be generated as a result of this information to mitigate disease risk.

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