Rebecca Law, of Georgetown University Department of Microbiology and Immunology on animals as sentinels

# All along the watchtower

In May 1956, a five year old girl has presented to a health clinic with ataxia, convulsions and difficulty speaking. Two days later, her younger sister and eight other children in the neighbourhood presented with the same syndrome. An urgent investigation began but the cause of Minamata disease was not discovered until months later - mercury poisoning. Could this have been prevented? In the course of the investigation, local residents revealed that the area's wildlife and specifically stray cats had begun displaying strange behaviour - termed 'dancing cat disease' - seen as early as 1950. Crows fell from the sky, seaweed no longer grew on the seabed, and dead fish floated on the surface.[1] Like miners' canaries, these animals could have provided a warning of dangerous environmental conditions and many fatalities and cases of debilitating disease could have been prevented.

In another example, thousands of wild crows and zoo birds died from neurologic disease concurrently with a string of encephalitis cases in horses, months before a similar outbreak in humans. Thought to be St Louis encephalitis, which does not typically cause illness in birds, the connection between the outbreak of West Nile virus in birds and the encephalitis outbreak in humans was only made months later by an astute veterinarian. The many factors that contributed to the delay need to be addressed, including poor communication between the human and animal sectors, exclusion of wildlife (including captive zoo animals) from surveillance efforts, and weak diagnostic capacity at state natural resources departments.

Adopting a One Health approach by understanding that the health of humans, animals, and the environment are interconnected, and using animals as sentinels for health means that proper intervention (eg mosquito control, pollution controls) and treatment can be applied faster to effectively predict, prevent, detect and respond to global health issues and pandemics. Due to a shared risk for many diseases, animal health can be a strong indicator for human health. These capabilities allow the US to prevent and respond to pandemics and potential bioterrorism attacks quickly and effectively. Conversely, ignoring these indicators hinders early detection of pathogens and toxins affecting human populations.

## Zoonoses and beyond

Because of a shared risk for many diseases and environmental hazards, the health of animals can be a strong indicator of human health. According to Stephen K Ritter: "For a plant or animal to be considered a good sentinel species [of environmental effects], it must be relatively common, easily handled, and have consistent and regularly measurable responses to environmental changes."[10] A well-known instance of using animals as sentinels is the presence of canaries in coal mines as indicators for toxic gases, eg carbon monoxide and methane. Because canaries need immense quantities of oxygen to fly, their anatomy allows them to take in oxygen when they inhale and exhale by holding the air in extra sacks, thereby delivering a 'double dose of air and any poisons the air might contain.'[3] This among other factors causes the canaries to sicken more quickly than humans and other animals in the same situation.

Canaries tend to show easily recognisable symptoms, like falling off their perches and appearing visibly ill[4], thus allowing for rapid warning and sufficient time for miners to evacuate and/or don protective respirators. Animals are often more sensitive to environmental factors and changes and thus may signal a chemical or biological attack or provide further information on the effects of radiation after a radiological or nuclear attack or of climate change, pollution and natural disasters, etc. Ignoring these indicators hinders early detection of pathogens and toxins affecting human populations.

A paramount example of the importance of One Health is zoonotic diseases, ie pathogens that can be transmitted from animals to humans and vice versa. Zoonoses are noteworthy because six out of 10 diseases are zoonotic and three out of every four new or emerging and infectious diseases are transmitted from animals.[5] It is easy to focus on the danger in our vulnerability to infection from animals during zoonotic spillover, but zoonoses present a unique opportunity if viewed through the lens of shared risk. The aforementioned West Nile virus outbreak is a clear example of shared risk.

Avian influenza, high and low pathogenicity, is one example where animals have been used successfully as sentinels. Across the world sentinel flock are deployed and regularly tested for a number of diseases, but primarily for emerging or reemerging strains of avian influenza. This monitoring provides early warnings so livestock and humans can be protected from deadly strains.

Furthermore, one study explored the capabilities of animals as sentinels for bioterrorism agents. As most priority bioterrorism agents are zoonotic the aim was to determine whether animals

## Hypothetical scenario with context and the effects of One Health policies

### Scenario

- On 15 March 2018, a patient in Raleigh, North Carolina presents to her physician with acute fever, chills, malaise, myalgia, a productive cough and associated chest pain.
- Approximately a week earlier, a number of pet cats in the area had been brought in to veterinarians in Raleigh with fever, swollen lymph nodes, vomiting, diarrhoea, depression, anorexia and lung infection. After extensive lab work, all tested positive for Yersinia pestis, ie plague.
- Dozens of other patients concurrently and subsequently present with similar symptoms.

### Case A: With a One Health Approach

- The physicians had been alerted to the outbreak of plague in cats the previous week and obtained thorough patient health history including animal contact. The patient's cat had been diagnosed a week earlier and she disclosed this information, was diagnosed properly, and received antibiotics for the infection and recovered fully.
- Pet owners with plague-infected cats took proper precautions,ie quarantine and post-exposure prophylaxis (PEP), preventing their own infection and further spread of the disease. Additionally, the public avoided direct contact with wild cats.
- Patients are appropriately quarantined and treated with antibiotics and recover fully. An epidemic is avoided due to contact tracing and quarantine.

### Relevant Policy Improvements Involved

- Improved communication between physicians and veterinarians and an understanding of shared risk.
- The inclusion of domestic animals in disease reporting mechanisms.
- An extensive One Health public education campaign made the public aware of zoonotic risks from pets and wildlife.

### Context

- This pathogen is not known to be endemic to Raleigh, North Carolina.
- These symptoms are non-specific and could be indicative of severe influenza, coronavirus, etc.
- In the event of aerosolised exposure, cats have an incubation period of one to two days versus one to seven days in humans, and therefore they could provide sentinel value.

### Case B: Without a One Health Approach

- The first patient is suspected of having influenza and is treated with antivirals. She is sent home and unknowingly infects her family and several others she comes into contact with while picking up her antiviral prescription.
- Her symptoms progress: she has watery mucoid sputum, develops ARDS and begins to show signs of shock.
- She presents to the emergency room as she begins to show signs of shock; samples are sent for diagnostic testing.
- The patient dies without the proper antibiotics/treatment.
- Several other patients present concurrently - some contracted the disease from their infected cats or infected fleas from other pets, others from person to person transmission. Without prompt diagnosis, they are not quarantined and potentially infect others in the hospital, including healthcare workers.
- There is potential for an epidemic/pandemic since pneumonic plague is highly infectious and contagious.

### Where Current Capabilities Failed/Context

- Antivirals are useless on bacteria.
- The connection between the cats is ignored and/or the Centers for Disease Control and Prevention (CDC) and physicians have no knowledge of the outbreak in the cats as household pets are not included in reporting mechanisms.
- These are still misleading symptoms (eg tuberculosis, pneumonia, etc), especially since plague is very uncommon in the US, or typically presents in the more recognisable form, bubonic plague.
- Diagnostics for plague are rapid if ordered, but the rarity of such a disease in the US means the process may be prolonged as they may test for other more common diseases first.
- Without knowledge of zoonoses, cat owners continue close contact with their infected pets.
- Potentially many people die and/or are infected before the disease is correctly diagnosed and thus treated with the correct course of antibiotics, and/or infectious patients are isolated.

could provide early warning of a bioterrorism attack, serve as markers for ongoing exposure risk, and amplify or propagate a bioterrorism outbreak.[6] In the study, three possible reasons for using animals as effective sentinels were identified:

"The animals could be more sensitive than humans to infection with a particular zoonotic disease agent; the animals could have a shorter incubation period than humans once infected; or the animals could be at greater exposure risk than humans by virtue of their feeding habits and more intense environmental exposure."[7]

Ultimately, the study determined that for some agents, humans may

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manifest symptoms before detection is possible in animals. For other agents, active surveillance of wildlife and domestic animal populations after an acute attack could help determine ongoing exposure risks.[8] Therefore, animals as sentinels could be essential to the US's bioterrorism response.

## Desired end state: a case study

The following scenario is hypothetical and highlights the US's ability to respond quickly and effectively to an outbreak with and without a One Health approach. The pathogen involved in this hypothetical outbreak has an incubation period of two to four days and presents with a productive cough and 'flu-like' symptoms, ie fever, muscle aches, myalgia and headaches. Although it presents similarly to the flu, it is a bacteria and thus requires specific antibiotics, not antivirals as are commonly used to treat flu. As the disease progresses, the patient develops adult respiratory distress syndrome (ARDS), pulmonary oedema and signs of shock. Without appropriate treatment it is almost universally fatal[9] within less than 24 hours of severe symptoms. Furthermore, this pathogen has high person to person transmission, is zoonotic - cats mainly, but also dogs, camels, and goats - and can be fleaborne which provides the opportunity for increased transmission without direct contact. While one subtype of this pathogen is endemic in the US southwest, this specific subtype rarely arises naturally in the US and has only seen a recent outbreak in Madagascar.

## Recommendations

The aforementioned detection capabilities are rendered useless if the information is not properly communicated and acted on. Public health officials are blind to the full picture unless they receive data from veterinarians, farmers, ecologists, etc, and thus improved communication channels between physicians, veterinarians, wildlife ecologists, and farmers are needed for a whole system One Health approach. For example, Ebola often becomes epizootic in non-human primates months before an outbreak in humans. Had wildlife veterinarians communicated effectively with local physicians about these infections in local ape populations, outbreaks could have been anticipated and misdiagnosis of the disease as Lassa virus could have been avoided.

The root cause of this disconnect is the professional segregation of doctors and veterinarians beginning in graduate school and into post-doc training. Human doctors are trained to see zoonotic diseases as an 'us vs them' issue, only considering animals as vectors for disease, and the approach is then one of avoidance and elimination of reservoir hosts and insect vectors. This ignores the shared risk of disease for humans and animals, which is key in comparative medicine.[10] It also neglects solutions aimed at understanding how the disease affects animals and how to control it within animal hosts, which can be the best solution for preventing its spread to humans. Medical and veterinary schools need to desegregate professionally, stress the importance of a One Health and shared risk approach at the beginning of the education process and foster collaboration. Alternatively, they might model themselves on the University of Pennsylvania where the veterinary school was created as a department within the medical school in order to mitigate the increasing risk of zoonotic diseases.

Further, the CDC and public health need to increase efforts to educate the public on One Health and zoonotic diseases. Ignorance of a disease's capacity to transfer from animals to humans can cause irresponsible contact, eg physical contact with a rabid animal and/or omitting animal encounters from health history. For example, two dogs from the same household were infected with Rocky Mountain spotted fever (RMSF) and both died as a result. The owner likely did not know the high zoonotic risk of RMSF and so did not take the proper precautions and contracted the disease from his pets. When he sought treatment, he did not inform his physician of the death of his dogs and without a complete health history the physician treated it as a gastrointestinal virus due to the presenting symptoms. The owner died without proper treatment, but had he understood the connection between his pets' illness and his own he may have been able to provide the necessary information for an appropriate diagnosis.


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