Feature

Veterinary Record
Towards One Health

ONE HEALTH

Emerging infectious diseases: opportunities at the human-animal-environment interface

Infectious diseases pose a serious threat to the wellbeing of both human and animal populations. Here, in the fifth in *Veterinary Record*'s series of articles promoting One Health, Mathew Dixon, Osman Dar and David Heymann examine lessons learned from previous disease outbreaks; they also consider current threats and how a better understanding of underlying risk factors could stimulate a paradigm shift from treatment to prevention of zoonotic infectious diseases


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A nurse working in a hospital in Taipei, Taiwan, being fitted with protective clothing during the SARS pandemic in 2003. The pandemic is estimated to have cost the global economy between US$30 to 100 billion

EMERGING infectious diseases (EIDs) range from novel zoonotic infections to infective organisms with new patterns of antimicrobial resistance. In the modern age, the speed at which infections can spread globally and transition into deadly pandemics means that surveillance must be able to monitor infections that have the potential to cause outbreaks and also to capture unknown threats that may emerge from a wide variety of sources. Because infections can travel both ways at the interface between animals and people, animal health is intrinsically linked to human health. Zoonotic influenza viruses, for example, are not only transmitted from animals to people, but can be transmitted in the other direction into animals, causing illness through recombination in either group. Bringing the human, animal and environmental sectors together is therefore critical to improving our collective ability to combat EID threats.

Mechanisms for the emergence of new infections at the human-animal interface are complex, as both wild and domesticated animal populations may be implicated. Furthermore, a range of environmental and human drivers play a significant role, making the task of understanding dynamics at the interface and tracking emerging infections incredibly complicated. While outbreaks of emerging and re-emerging infections are often short-term events, they can cause substantial and long-lasting damage to national and global markets. For example, the cost of bovine spongiform encephalopathy (BSE) to the UK economy has been estimated at £3.7 billion, with 3.3 million cattle slaughtered during the crisis between the mid-1980s and late 1990s (Beck and others 2007).

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The costs of EID outbreaks are often felt across multiple sectors, ranging from animal production and agriculture to international trade, human healthcare and tourism. The devastating Rift Valley fever outbreaks that occured in Kenya in 2007 have been estimated to have caused over US $32 million in damage to the Kenyan economy through severe losses to agriculture, human health and other sectors, such as transport (Rich and Wanyoike 2010). A key feature of many national EID epidemics in developing countries, where 'hotspots' of emergence activity exist, is that the impact is greatest among the poorest farmers and communities, particularly in rural settings – thus disproportionately affecting the least resilient people in these societies (Grace and others 2012). On a global scale, pandemics such as the severe acute respiratory syndrome (SARS) pandemic of 2003 to 2004 cost the global economy approximately US $30 billion to $100 billion from decreased commerce, travel and tourism, equating to around $3 million to $10 million per SARS case (Smith 2006, Keogh-Brown and Smith 2008).

Historical approaches to surveillance

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A farmer feeds his cows in Scotland in March 2006, just before the worldwide ban on British beef exports, implemented for a decade due to the BSE outbreak, was lifted

Photo: AP/Press Association Images

Face masks placed on pet dogs in China in 2006 following reports of dogs being infected with the H1N1 influenza virus in the region

have focused on identifying new infections in people and developing an appropriate response. Given the ability of EIDs to readily cross international borders, especially in the age of widespread global travel, a clear need for an international surveillance system was recognised in the late 20th century.

In 1997, a global surveillance system, coordinated by the World Health Organization (WHO) and called the Global Outbreak Alert and Response Network (GOARN) was established and fully formalised in 2000. The network has over 100 partners globally, linking scientific institutions in member states, medical and surveillance initiatives, regional technical networks, networks of laboratories, United Nations' organisations and a range of charities with the capacity to contribute to an outbreak response (WHO 2014). GOARN responds to over 50 outbreaks annually in developing countries; however, a key factor in enhancing the overall timeliness of reporting notifiable diseases is the adoption of the International Health Regulations (WHO 2005). These act to raise awareness of the importance of timely reporting among member states (Tsai and others 2013).

Lessons from pandemics in the 21st century

The first two pandemics of the 21st century, SARS and influenza A (H1N1), demonstrated that, while progress has been achieved in national and global surveillance systems, there are still limitations to current arrangements.

SARS was first detected as a severe atypical pneumonia in Guangdong province in China. It rapidly spread from hospitals in the province to the wider community through unsuspecting hospital workers. During a visit to Hong Kong, one of these health workers (a medical doctor) exposed a number of guests in the same hotel to infection (Chan-Yeung and Xu 2003). In turn, some of these individuals travelled while the infection was still in the incubation period, and as the illness developed they were admitted to hospitals in Hong Kong, Singapore, Canada and Vietnam where they in turn became sources of infection.

SARS was GOARN's first test in response to a pandemic. The initial detection of the virus came from patient specimens examined by GOARN's partners (the WHO's Global Influenza Surveillance Network laboratories). Initially, in November 2002, this network picked up media reports of an influenza outbreak in Guangdong that was later confirmed as influenza B virus. A further respiratory infection outbreak in early February 2003 raised concerns of a fresh influenza outbreak; however, on this occasion influenza virus was ruled out as the causative agent. Once further evidence became available, the true epidemiological and clinical nature of the new infection – the novel SARS virus – was elucidated, enabling GOARN to draw upon its wide expertise and partners to provide real-time information to the WHO (Stöhr 2003). Careful monitoring of the situation allowed authorities to develop rapid, evidence-based guidance for clinical management and identify protective measures for hospital settings (Heymann and Rodier 2004).

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Retrospective epidemiological analysis later confirmed that the first wave of SARS infection in people occurred concomitantly with the influenza outbreak in late 2002. These findings indicated that there was a significant delay in detecting the initial outbreak and possible emergence of the virus in people (Heymann and Rodier 2004). GOARN was not equipped to detect the initial emergence of the virus in people; only retrospective molecular and epidemiological investigation suggested that the infection of the index case (who was never identified) was a one-time event. As more information became available, it was further hypothesised that this initial infection was due to close contact with an infected animal, possibly a civet cat, in one of the province's many live animal markets. The animal host was thought to have been a carrier of a coronavirus that mutated while replicating, either in the animal or an infected person, in such a way as to cause severe illness in people (Wang and Eaton 2007).

A similar unfolding of events occurred with pH1N1 (swine influenza), with the likely mechanisms of pH1N1 emergence in people being elucidated through retrospective epidemiological and molecular analysis. Further work has shown that the virus evolved as a result of a triple reassortment event, combining genes from swine, avian and human influenza A viruses over what may be multiple introductions between animals and people. While the global surveillance system could not detect the initial emergence and earliest stages of pH1N1 transmission in people, the presence of a global surveillance network certainly supported a faster detection and international response to the pandemic, especially in Mexico and the USA where the virus was first detected. A number of new actors in the field of surveillance such as ProMED Mail, a non-governmental programme that uses information from various sources, were responsible for this improved response. Ultimately, however, detection and response lagged behind the international spread of the virus (Tsai and others 2013, Zhang and others 2013a).

In both the SARS and pH1N1 pandemics, the role of animal reservoirs in the emergence of disease in people was clearly demonstrated. While our responses have improved through enhanced surveillance systems and improved laboratory capacity, it is likely that, in the current configuration, our surveillance systems and hence our responses will always be playing a game of catch-up with infections that are able to rapidly spread across the globe.

Understanding risk factors to shift the paradigm

The lessons from previous pandemics and large national EID epidemics are clear. If it became possible to identify infectious agents carried by wild and domestic animals and to predict if, when and where they would emerge in people, and if these animals could then be somehow removed from contact with people or cleared of infection, human sickness and death could be prevented and economies protected. Numerous research initiatives and studies are underway with the aim of identifying and characterising infectious organisms in wild animals in places where emerging infections are known to have occurred in the past (known as 'hotspots') (Grace and others 2012). Although it is possible through these studies to understand the variety of infectious agents carried by wild animals, it is not yet possible to predict which organisms will emerge in human populations using genetic sequencing or other methods.

Moving further upstream, the investigation of individual emergence events can identify risk factors, or determinants, that align to cause putative breaches in the animal-human species barrier. If these risk factors could in some way be mitigated, the risk of future emergence could be decreased; animal and human populations spared sickness and death; and economies better protected. The current paradigm of emergency response and the concurrent attempts at prediction and prevention could then be shifted further upstream – to prevention by managing and mitigating the risks that lead to emergence.

In the case of SARS, there was a flurry of field research activity in Guangdong province during and just after the outbreak, but over time funding decreased and research slowed. Among the research that was completed was a study of workers at some of the province's markets that suggested that up to 22 per cent (12 of 55) of those tested had antibody evidence of a coronavirus infection related to the SARS coronavirus, but none had a history of severe respiratory symptoms that resembled those occurring in people with SARS (Guan and others 2003). Further field research might have helped researchers to better understand the risk factors for emergence, but it was not conducted, and the epidemiology of the infection remains unclear. Risk factors for emergence, in addition to being a market worker, might also include being a hunter of wild animals, being a restaurant worker who kills and or butchers/prepares wild animal meat for consumption or being a member of a household that buys live or recently killed wild game meat from a market. From the evidence available from this study, a series of actions outside the human and animal health sectors could be useful in preventing a future outbreak in Guangdong province from another emerging pathogen.

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Photo: Kjell Gunnar Beraas/AP/Press Association Images

Doctors working with Medecins San Frontieres prepare isolation and treatment areas for an ebola and haemmorhagic fever outbreak in Gueckedou, Guinea, in 2014

Recently, analysis of H7N9 zoonotic influenza emergence in China has demonstrated that live bird markets are linked to cases in people. The authorities in China rapidly instigated emergency surveillance in poultry populations to detect the circulation of the virus in these settings, and reported the data in a timely fashion to the World Organisation for Animal Health (OIE) (Hamilton and Swayne 2013). China has been credited with a much improved response to H7N9 in comparison to that observed with SARS, in particular with improved international transparency by rapidly sharing disease information when available (Zhang and others 2013b). However, the emergence of the Middle East respiratory syndrome coronavirus (MERS), has demonstrated the continuing problems with identifying how new infections arise in people, given that neither the zoonotic origin, nor the mechanisms for introduction into human populations, are still fully understood (Raj and others 2014).

The risk of emergence events is elevated in certain sectors such as agriculture, community planning, water and sanitation. Human migratory dynamics, land use approaches, climate and manipulation of natural ecosystems can also amplify known risks and create others. Risk factors for emergence also occur all along the food chain. Growing demand for animal-based foods has led to ever more complex food chains that involve live animal processing and trade networks. Detection of infectious disease emergence through the food chain and agricultural system requires understanding the risks at each step along the pathway from the farm to the fork. At one end of the food chain, certain behaviours associated with sourcing food can place people at high risk of exposure to novel infections. Hunting practices and consumption of bushmeat in central African countries, and particularly rural communities, have led to repeated disease outbreaks, including ebola outbreaks in the Democratic Republic of Congo in 2007 and 2008 (Grard and others 2011), while recent outbreaks of ebola haemorrhagic fever in Kampala and Luweero in Uganda and the ongoing outbreak in Guinea demonstrate the risk to urbanised communities (Mbonye and others 2012).

Food chains in developed countries have also been implicated in disease emergence. BSE outbreaks in cattle led, in May 1995, to the death of a 19-year-old male in the UK, the first human death from what is now known to be variant Creutzfeldt-Jakob Disease (vCJD) or human BSE (Prusiner 1997). Before the outbreaks, modified regulations that inadvertently permitted rendered parts of cattle infected with the BSE-causing prion to contaminate bonemeal used for livestock feed resulted in livestock infection. The most likely source of human infection is thought to be through the preparation or consumption of contaminated meat and/or beef products.

Ecology, the environment and human demographics are further significant forces that underpin EID dynamics. Emergence may occur among people living and working in small rural farming communities in tropical rainforests, savannah, mountains and deserts that are in close proximity to wild animals, or to domestic animals they tend that have been in close proximity to wild animals. Outbreaks of nipah and ebola reston virus infection in pigs raised in unprotected environments in Malaysia and the Philippines, respectively, are examples, and both outbreaks spilled over into human populations (Miranda and Miranda 2011, Daszak and others 2012). New studies conducted in the forests of south-east Asia indicate that *Plasmodium knowlesi*, now recognised as the fifth malaria-inducing parasite in people, is emerging more widely in human populations as a result of excessive deforestation activities and increasing human population in areas previously abundant in tropical rainforest (Lee and others 2011). Factors associated with larger urban communities can also play a role in emergence, where human contact with animals is limited to a few farm animals in close proximity to households, to domestic pets, or to rodents and other animals that have adapted to the urban environment. Animals come into contact with people or other animals as they range (for example, cows and chickens in parts of Asia) or browse (for example, urban foxes and rodents). The continued high rate of contact between people and poultry in both smaller backyard farms and larger market system farms continues to permit repeated human exposure to the H5N1 influenza A virus that is endemic in poultry stock (Hogerwerf and others 2010). Both children and adults are thought to have been infected by contact with living chickens in backyards, and adults have been shown to become infected at some point during the process of raising or slaughtering/butchering chickens.

> 'Climate change appears to be a key ecological factor in the emergence of human infection'

Climate change also appears to be a key ecological factor in the emergence of human infection. Rainfall associated with the El Niño/southern oscillation in East Africa, for example, has contributed to frequent outbreaks of Rift Valley fever as a result of flooding that increases breeding sites of the mosquito vector (Anyamba and others 2009). The frequency of *Leptospira* transmission from rodents to people has been shown to increase in Latin America, Bangladesh and India following heavy rains and flooding (Lau and others 2010).

Importantly, overuse of antibiotics in livestock animals is now also thought to be a risk factor for the emergence of antimicrobial-resistant bacteria in animals. Strategies to combat microbial stresses imposed on piglets during early weaning formerly included the administration of antibiotic growth promoters, raising concerns about emerging antibiotic resistance (Vondruskova and others 2010). However, the ban on antibiotics as growth promoters in the EU since 2006 has limited this practice. Outside of the EU – particularly in the USA and other large animal-exporting countries – the widespread use of antibiotics still occurs. There remains debate in the scientific community as to the contribution of antibiotics in farming systems to the rise of antibiotic resistance, and the possible implications for emerging antibiotic resistance in downstream human populations is even less well understood (Barton 2000). However, there is general consensus that farming systems are likely to contribute to the flow of antibiotic-resistant microbes in the wider ecosystem and in people via effluent and runoff into water used or consumed by people, especially in economically poor settings where farming communities exist alongside densely populated human environments with poor sanitation and sewage systems (Segura and others 2009, Abraham 2011). Clearly, cross-sector action is required to mitigate these risks. The recent emergence and spread in people from the Indian subcontinent of New Delhi metallo-β-lactamase 1 (NDM-1) Gram-negative Enterobacteriaceae with carbapenem resistance demonstrates the constant threat posed by antimicrobial resistance (Kumarasamy and others 2010). The role of the environment, not only in harbouring bacteria carrying the NDM-1 gene, but also acting as a driver to enable spread to people, particularly in the urban environment, may be an important component of the story of global emergence (Mohapatra 2013). Finding alternative strategies to antibiotic use in farm animals could help to curb the increasing rates of antimicrobial resistance in animals, an approach that has been adopted in Norway following a shift to vaccination of salmon. This has resulted in a 98 per cent reduction in the use of antibiotics, while also reducing costs to the consumer through increased salmon production (Davies and Verde 2013).

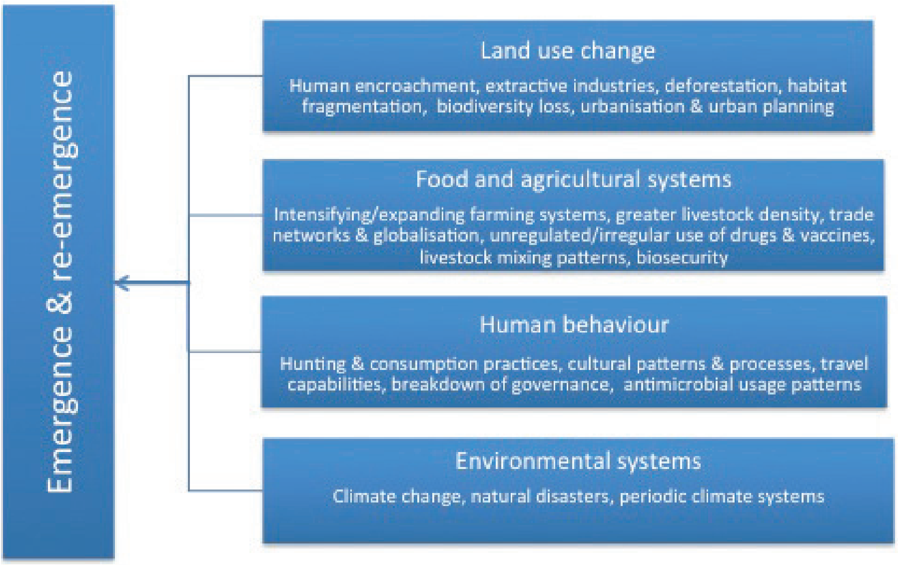

FIG 1: Disease emergence pathways at the human-animal-environment interface. Adapted from Heymann and Dixon (2013)

Fig 1 highlights the various routes that drive emerging infectious disease dynamics at the human-animal-environment interface.

Improving surveillance

Mitigation of the risk factors for disease emergence includes surveillance activities and thus requires a focused and collaborative effort across multiple disciplines – a One Health approach. The One Health approach is defined by the American Veterinary Medical Association as: 'The collaborative efforts of multiple disciplines working locally, nationally, and globally, to attain optimal health for people, animals, and our environment.' This definition encourages research and control/prevention activities to adopt an interdisciplinary approach, linking human health, animal health and environmental sectors. A key step in this process is recognising the need for collaboration across sectors at every level.

To this effect, progress has been made at the global level, with the tripartite agreement between the WHO, Food and Agriculture Organization (FAO) and the OIE. The high-level technical document produced as a result of this agreement outlines the steps that are required to develop an environment where effective collaboration can take place, which extends to surveillance activities such as producing joint risk assessments, sharing data across sectors and developing integrated systems (WHO and others 2011). Ecological risk factors are also of critical importance, and it is therefore imperative that more is done to seek input from ecologists and the environmental sector.

In the context of the argument for shifting the paradigm, surveillance activities would need to be carefully aligned to shift

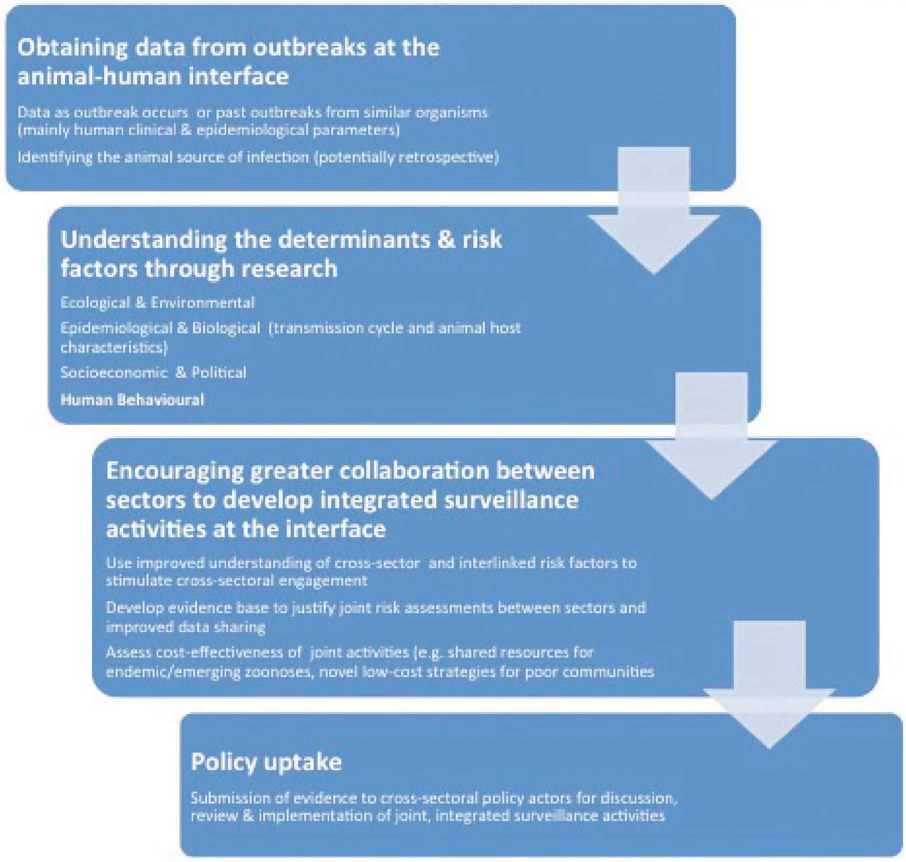

FIG 2: Transforming evidence at the animal/human interface into policy – a simple flow chart for improved surveillance at global, regional and national levels

the focus of detection upstream at source. In order to develop highly sensitive surveillance systems to focus on the upstream processes in the disease emergence continuum, a critical understanding of the risk factors that underpin emergence and transmission into the wider human population is needed (Engering and others 2013). A large amount of scientific knowledge about the risk factors for disease emergence and its mitigation is already available. Much more must be obtained from in-depth study of each emergence event as it occurs. Research must also take into account human behaviour, and ensure that populations most at risk clearly understand the measures required to minimise behaviour that is high risk. Developing systems that focus on surveillance at the animal-human-environment interface will require more research to understand risk factors, which in turn can convince authorities and policy makers that greater collaboration between sectors for surveillance, particularly at the national level, is needed. Clear and easy to understand evidence from cost-effectiveness and other studies identifying risk factors to develop optimal surveillance systems is therefore needed. Fig 2 demonstrates how this process could occur.

Efforts are already underway to get ahead of the curve with respect to disease emergence; for example, the USAID Emerging Pandemic Threats (EPT) programme contains five project areas, two of which are linked to surveillance. These are the PREDICT project, which is a risk-based approach (using modelling and laboratory surveillance methods) to strengthening the capacity to detect emergence in wildlife populations within geographic hotspots; and the IDENTIFY project, which is involved with strengthening diagnostic and laboratory capacity across human and domestic animal/livestock sectors (USAID 2010). This programme offers a first attempt at shifting the paradigm, but significant evaluation will be required before conclusions can be reached about its effectiveness. The strategic aims of the EPT programme all focus on strengthening local capacity, especially given that a significant majority of EID activity occurs in low-income, impoverished community settings (Grace and others 2012). The challenge at both the national and local level for adequately improving and strengthening surveillance activities in these settings is huge, emphasising the need for sustainable systems that will be operated by and, in the long term, financed by national governments (Halliday and other 2012). Opportunities to overcome these problems are beginning to emerge, including the advent of low-cost mobile technology-based platforms to improve surveillance in field settings (Robertson and others 2010, Li and others 2013).

> 'Ecological risk factors are also of critical importance, and it is therefore imperative that more is done to seek input from ecologists and the environmental sector'

The challenge may be huge, but the opportunities are there – the time to act is now.

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doi: 10.1136/vr.g3263

Veterinary Record

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Veterinary Record 2014 174: 546-551
doi: 10.1136/vr.g3263
