Government Office for Science

Foresight

Prediction for biological hazards

Commissioned Review

Foresight, Government Office for Science

Contents

Prediction of biological hazards

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27 November 2012

Report produced for the Government Office of Science, Foresight project ‘Improving Future Disaster Anticipation and Resilience’

1. Introduction

In 2010 just 3 human infectious diseases (HIV, malaria and TB) caused 3.5 million deaths, more than ten times the total number of deaths from all natural disasters combined that year (Guha-Sapir *et al* 2011). Because of the definition of epidemics used to count biological natural disasters in the EM-DAT database, none of these three major killers counts as a disaster. An epidemic must show "an unusual increase in the number of cases…" in order to count as a disaster, so the majority of deaths from infection will simply be classified as part of some grinding, on-going misfortune. Under this tight definition of a disaster caused by an epidemic there were 41 disasters caused by biological hazards in 2010 (all of them epidemics). Those epidemics killed 10,000 people that year, with 8,500 of those deaths caused by just three outbreaks: Cholera in Haiti, Meningitis in Burkina Faso and Dengue in the Philippines. Disastrous epidemics of infection in livestock or crops are simply not mentioned in the records in the database for 2010. Thus deaths from infection overwhelm deaths from disasters, but in reports attributing deaths from disasters to different classes of causes, biological hazards are either shown as a rather small subset of all disasters (Kellett and Sparks 2012) or simply excluded (Guha-Sapir *et al* 2011).

These issues with classification do not change the way science works to predict, control or prevent infections that cause disasters, which is little different from the science of the "everyday" infectious disease killers. However the low profile of biological disasters in the collated data may have an adverse impact on perceptions in policy-making and in formulating actions to reduce the impact of disasters.

In what follows we review the science of infectious disease prediction and prevention for three classes of hosts: humans, livestock and crops. We start with a discussion of the expected future occurrence of outbreaks of infection in each host type. In section 3 we review the current cutting edge of science and technology for disaster prediction and preparedness. In section 4 we look ahead to the way emerging science and technologies can be expected to drive better predictions, preparedness and control in the future. In section 5 we discuss the potential road-blocks that lie between here and that better future.

2. Expected future occurrence

2.1 For diseases of humans

Increasing host population density is the most important driver of future disease occurrence. This is true for human, livestock and crop diseases. Dense, urbanised populations of people, particularly those living in informal settlements are at substantial risk of disastrous disease outbreaks. When parts of cities grow without proper supplies of water or sanitation the risk of infection can be very high. For example, in informal settlements around Nairobi the mortality rate for children under 5 and for infants is higher than it is in rural areas of Kenya (Patel and Burke, 2009). This is true for mortality in "normal" times and reveals a population that would be at very high risk if faced with an outbreak of a severe infection. It is important that data from cities is gathered from such informal "slum" settlements and disaggregated so that the heterogeneous nature of city populations is clear.

In general, closer contact amongst more people implies the potential for more infectious disease spread. However not all people are the same and falling birth rates bring a shift in the age distribution away from the very young who are usually the most susceptible. As this shift continues to populations with more and more elderly people they will become the largest group at high risk during disease outbreaks.

Alongside population growth and urbanization, rapid global travel is an important driver of the spread of infection. In 1918 it was possible for Australia to exclude pandemic influenza for several months by imposing strict maritime quarantine (McLeod *et al* 2008). As passenger travel by plane developed after the Second World War such isolation became impossible. Paying passengers currently fly around 5 billion kilometres each year and this amount is expected to grow at 5% per year for at least the next 20 years. It is well documented that the global spread of both SARS and 2009 H1N1 pandemic influenza closely followed the density of travel across the global aviation network (Hufnagel *et al* 2004, Bajardi *et al* 2011). As traffic on that network grows we should expect the global spread of infection to become even faster than it is now.

The pathogens that cause infectious disease have short generation times that allow rapid evolution under the selection pressures imposed by control measures. For humans the WHO

states as an opinion that the current most intense threat is from the evolution of antibiotic resistant bacteria (WHO 2012).

However we are not powerless in the face of these threats. Many technologies are used on a daily basis to reduce the burden of infectious disease: clean water, vaccination, drug therapy and protection from disease bearing insects have all had major impact in reducing the mortality and morbidity arising from infection. For example, deaths from measles fell by 74% between 2000 and 2010 as a result of increased vaccination coverage (Simons *et al* 2012).

In sum, the potential for future disasters caused by infectious disease of humans is increased by increasing human population density, rapid travel and the potential for pathogen evolution. However better surveillance, better analytical tools and ever-increasing methods to prevent and treat infections provide a formidable battery with which to predict, prevent and counter diseases caused by infectious diseases of humans.

2.2 For diseases of crops

Crop plants, reared in vast, genetically uniform monocultures are particularly susceptible to the emergence of aggressive new pathogen strains. The biggest threats are posed by fungi and the fungus-like Oomycetes (Fisher *et al* 2012). There are substantial programmes of disease control, but significant amounts of major crops are still lost to disease. Since the green revolution, breeding for disease resistance has focussed on single dominant resistance genes (R) rather than on suites of genes, which would be more likely to offer durable disease resistance to a broad range of pests and pathogens but which may lower yields. 40% of global agricultural land is covered rice, wheat and maize; these three crops alone provide 50% of human calories. In the developed world such crops are grown in huge fields of genetically uniform plants. These conditions offer up ideal conditions for emergence of new aggressive pathogen strains able to overcome inbred plant disease R genes and for the naissance of fungicide resistant strains, a problem exacerbated by our overuse and reliance on single target-site antifungals. Each of these major food crops suffers from persistent crop losses, despite mitigation, and from epidemic outbreaks of infection. Losses caused by the Rice Blast fungus, *Magnaporthe oryzae*, Wheat Stem Rust by *Puccinia graminis* and Maize Smut by *Ustilago maydis*, even at low persistent levels of infection account for sufficient food to feed 6.3% of today's world population some 2000 calories per day for a period of one year: a staggering loss of around £60 billion US dollars. The risk of simultaneous outbreak of epidemic disease in these three crops is apocalyptic but very remote. However, resource-rich farming practices

have thus far provoked emergence of two significant threats. First, a strain of wheat rust that can infect previously rust-resistant wheat varieties (Ug99), which can be controlled with fungicides, but if it were to spread to countries where small farmers cannot afford such measures it could have a devastating impact (Pennisi 2010). Second, an aggressive fungicide resistant strain of potato late blight, *Phytophthora infestans* (A2Blue13) in UK in 2005 which has spread like “wild-fire”

Predicted climate change over the coming decades could act on plant diseases in various different ways. There is evidence that plant diseases could be expected to be more severe under expected climate change conditions (Madgwick *et al* 2011) and that some pathogens are shifting their geographical range in response to global warming (Gregory *et al* 2009).

A third major driver of crop disease is the global trade in seeds and whole plants (Brasier 2008). Potato late blight has been introduced into Europe on infected Mexican tubers at least twice, causing the devastating Irish Potato Famine in the 1840s and, more recently, when the *P. infestans* A2 mating type appeared outside of Mexico in the 1970s. Disease carried on human clothing has also occurred, with wheat yellow rust arriving from Europe in Australia in 1979 and thence spreading to New Zealand (Brown and Høvmoller 2002).

Outbreaks of infectious disease in crops can have devastating consequences for the people who rely on them. The combination of accelerated pathogen evolution, climate change and global trade present a troubling picture for the future.

2.3 For diseases of livestock

As for humans and for crops, so for livestock: more animals more densely housed is a strong positive driver towards increased infectious disease amongst livestock. The risks are different for small holdings and for large-scale production. In small holdings numbers and densities of animals tend to be low, but bio-security is usually weak. Disease thus enters flocks and herds comparatively easily, but outbreaks are only small. In contrast, in large-scale production, bio-security and surveillance are usually better, but if biosecurity fails very large numbers of animals are affected.

Changing diets in developing countries are driving increased demand for meat products which will in turn lead to burgeoning growth in the livestock industry in these countries and a move towards more intensive production. Much of this growth is in pig and poultry production. For

example from 1992 to 2002 poultry meat production in Asia increased one and a half fold, and there was a 30% total increase in pork production worldwide (de Haan *et al* 2010).

We can expect considerable variability in the way these growing populations of livestock are farmed and consequently can expect an increased likelihood of exposure to new sources of infection. It may be possible to decrease the risk associated with known infectious threats through the use of animals bred for disease resistance. However, threats via poorly anticipated pathways may prove to have greater impact. For example the emergence of Nipah virus in Malaysian pigs in 1997-1999 may have been exacerbated by increased pig and fruit tree production in ways that it would have been very difficult to anticipate before the events occurred (Pulliam *et al* 2012)

Although infectious disease outbreaks in livestock can have disastrous economic consequences they are less likely to cause a humanitarian disaster on their own because they are not staple crops. However the potential for cross-over of infection from livestock into humans does exist for some pathogens, most notably for influenza. There is continuing unease about the possibility of a global pandemic caused by the H5N1 strain of influenza which is currently an infection of birds but is known to have the potential to be transmitted amongst mammals (Imai *et al* 2012). The role of livestock as a source of zoonotic infections is extremely important, either as the actual source or as a route for infections from wild animals to humans via livestock.

3. Recent Innovations and Current Interventions.

3.1 Early Detection

Early detection and identification of epidemics in humans and livestock has greatly improved in recent decades. Two recent examples are the rapid identification of the SARS and Schmallenberg viruses.

SARS is now known to be a member of the coronavirus family. In the early spring of 2003 the name “Severe Acute Respiratory Syndrome” was given to a new disease that was circulating in Hong Kong and spreading around the world through the air travel network. On 12 March 2003 the World Health Organisation issued a global health alert concerning the new disease. On April 16 of the same year it was announced that the causative agent of the disease – the SARS coronavirus – had been identified. To identify a new agent causing a severe disease in just a few months was an unprecedented achievement. The fact that this was done when the new virus failed to grow in standard laboratory conditions made it particularly noteworthy.

Several facts about the detection of the SARS epidemic and the identification of the causative virus have lessons for other epidemic outbreaks. First the existence of the epidemic first came to the notice of the world through informal, internet-based channels. It was a series of posts on an internet-based horizon scanning forum called ProMED mail on February 10 2003 that brought the existence of a serious epidemic in China to the attention of the world (Madoff 2004). Second, the new disease spread rapidly around the world, carried by air passengers. Third the global system for monitoring influenza viruses – Flu Net – played a crucial role in detecting early cases and in identifying the causative agent. Flu Net is a network of 110 laboratories in 84 countries that collects samples and analyses them using standard protocols. Its normal role is to search for new strains of influenza. The fact that it was already in existence and had a standing system for rapid communication was crucial to the success of the early identification of the SARS coronavirus. It was this same network of laboratories that identified the 2009 H1N1 pandemic influenza before it had left the Americas.

Schmallenberg virus is a newly emerging infection of sheep and cattle. It was first detected when a number of calves were born with deformities across Northern Europe in the late summer of 2011. Blood samples were taken in October 2011 and the causative agent, a newly

discovered virus, was identified in November 2011 (Hoffman *et al* 2012). The rapid identification of this new virus is an example of the use of metagenomics - the study of the genetic make-up of entire microbial communities - to find unknown pathogens in samples.

3.2 Understanding patterns of mixing and transmission

A second area of current progress is in using quantitative descriptions of human and livestock mixing to improve predictions of the spread of infections. The use of airline network data to predict the spread of SARS and 'flu was discussed above. To date, these methods have made their successful "predictions" after the fact and should still be seen as experimental, scientific tools. In time, however, they have the potential to become real predictive tools, guiding policy through a profound understanding of human patterns of behavior and how they drive the spread of disease.

Travel by air is not the only human behavior to be quantified and used to improve our understanding of the spread of infection. Detailed data on age-dependent patterns of mixing of people in a number of European countries have recently been gathered and now offer a rich resource for exploring the spread of infection in family, school and community settings (Mossong *et al* 2008).

In animal health there are large datasets that describe animal movements as they are traded between farms. These are now mined to reveal the network of contacts amongst farms and the implications of those contacts for the spread of infections like avian infulenza (Nickbakhsh *et al* 2011)

These are all examples where social science data about patterns of mixing between cities, between individuals or between farms are harnessed to improve our understanding of the spread of infection. In time, there is every reason to expect that such data can be built into tools that give a much clearer understanding of the spread of infection under normal mixing patterns. That will leave the problem of knowing how mixing patterns change under extreme circumstances – and data on such circumstances can only be gathered as extreme events occur.

3.3 Global surveillance networks

Mention has already been made of ProMED mail and Flu Net. These are two global

surveillance networks, but there are many others. GPHIN is an internet-based horizon scanning system that crawls the web searching for information about infectious disease outbreaks. Its underlying technology is the ability to process natural language in text sources and so search for news about infectious events. Healthmap, Biocaster and EpiSpider are similar web-based event-driven surveillance systems. These different systems vary in the sources they monitor, the languages they use and the parts of the world upon which they focus. EMPRES-i performs the same role but focused upon animal diseases. These networks have transformed the availability of information about infectious disease outbreaks. As more information about individuals' health status is shared in electronic form this kind of internet based bio-surveillance is set to gain in importance.

4. Emerging technologies

4.1 Gene sequencing

Rapid, cheap gene sequencing is transforming all of the life sciences and underpins multiple new technologies for detecting pathogens. Such technologies are an important addition to on-going progress in the early detection of epidemics, epizootics and outbreaks of plant infectious disease. Gene sequencing technology is now so far advanced that the bottle-necks in generating information lie at the point of gathering biological material to sequence and, after the sequencing has been performed, developing tools to turn sequence data into useful information.

4.2 Genuine prediction

The holy grail of infectious disease surveillance would be the ability to predict the occurrence of epidemics that have not yet even started. Such predictions are most advanced for infectious diseases of humans, and are at different stages of advancement for different classes of pathogens.

There are some pathogens whose biology is so simple and well-understood that we can predict the future occurrence of epidemics based on our understanding of how epidemics are triggered by the build-up of a pool of susceptible individuals. This has been most-notably successful for measles epidemics that have been successfully predicted in both the UK and New Zealand. However, such predictions are formed on the basis of extensive characterisation of population levels of immunity. Such characterisation is acquired through measuring antibody levels in large collections of blood samples collected across the population.

There are other pathogens which we know well but for which we still cannot predict future incidence with precision. A prime example is influenza for which we do not have a good enough understanding of the relationship between the immunity we can measure and the chance that individuals will become infected, infectious or sick.

Drug resistant variants of known pathogens pose a substantial future threat. Domesday predictions are common, but it is frequently unclear how fit the drug resistant new variants are and hence how easily they will spread. Without such information it is not possible to make

reliable predictions of the future threat posed by drug resistance. Intense vigilance is then the only sensible response.

The “unknown reservoirs” of pathogens in wild animals are just beginning to be explored. The current state of the art is to collect and analyse samples to identify new pathogens (mostly viruses). The outcome of these studies will be new inventories of potential threats. Classifying them according to the degree of threat they pose is not yet possible because we cannot tell from a gene sequence alone which newly detected pathogens can: (i) infect people, (ii) be transmitted between people, (iii) be transmitted efficiently enough to cause an epidemic, (iv) make people sick or kill them if they are infected. We do not have well developed laboratory assays to measure these vital parameters of newly discovered pathogens, or indeed of new variants of well-known ones.

Two new major US government projects address some of these issues. USAID’s “predict” program aims to characterise new infectious agents in high-risk wildlife populations. Darpa’s (the Defense Advanced Research Projects Agency) “prophecy” program aims to predict the natural evolution of viruses. Both are new (2010) and it is too soon to know if their ambitions will be realised. It is sobering to note that even if we had known about the existence of SARS before it arose we would not have been able to predict its behaviour in terms of its ability to infect humans, spread around the globe and cause widespread mortality.

4.3 Remote Surveillance

Predicting the occurrence of epidemics before they arise remains, for now, a long-term ambition. Early detection and efficient monitoring of disease spread is very much a burgeoning technology of our time.

Existing internet-based event-driven surveillance systems were described above and are clearly an area of rapid development. The google flu-trends system that was able to detect influenza-like illness through patterns of word use in online search engines is a recent addition. Its results were in close agreement with official government figures from the CDC, but were available with a reporting lag of one day, one or two weeks before the official surveillance figures (Ginsberg *et al* 2009). The future for such technologies is to broaden the base of information they trawl.

One potential source is crowd sourced information about outbreaks – for example Healthmap’s

“Outbreaks Near Me” mobile phone app includes the capacity for users to report new outbreaks. The app disseminates real-time, location-specific infectious disease outbreak data to mobile phones and in addition lets users report outbreaks.

Many ‘phones log their current location. This generates large amounts of data about where their owners are which has great potential to inform studies of normal human behaviour and of behaviour during epidemics. For livestock there are biosensors that can be attached to individual animals and provide real-time readings of each animal’s location or stomach pH and temperature. Such biosensors provide real-time animal-health monitoring to rapidly identify early clinical signs of disease. Although such products are already available they are expensive and it is unclear if temperature is a measure that is sufficiently sensitive to give early warning of infection. These devices that locate individuals (humans or cows) generate huge amounts of data. New tools of analysis that can extract useful signals from such enormous datasets will have to be developed.

As well as detecting where hosts are from the devices they carry, it is becoming possible to detect where pathogens are with devices that regularly sample the environment. As part of their drive for homeland security the US government tried to establish a network of air-sampling devices to filter air in fixed locations searching for particular pathogens that might be used in a bioterrorist attack. The machines are called Biowatch devices and in their current iteration the filters are collected daily and analysed in local laboratories. The next iteration of this technology – so called “Generation 3” - was planned to perform molecular analysis of samples automatically, on site and in less than four hours to provide close to real-time reporting (Kman and Bachmann 2012). However, after repeated false alarms and in the face of escalating costs, in the autumn of 2012 the US Government Accountability Office called for a pause before commissioning Generation 3 with grave doubts about the viability of the whole scheme (GAO 2012).

Remote sensing at a different scale is provided by satellite images. These can be used to detect environmental drivers of pathogen spread. This has greatest potential for waterborne and vector borne diseases in which environmental variables have such a clear impact on transmission. Remotely sensed sea surface temperature, sea surface height and chlorophyll A levels gives good predictions of Cholera outbreaks in Bangladesh, and although these are still research tools, their predictive power is very promising (Ford *et al* 2009).

4.4 Novel Diagnostics and Pharmaceuticals

Cheap and rapid gene sequencing is driving new tools for detecting pathogen genomes in biological samples so making cheaper faster, diagnostic tools. But sequencing is not the only new technology driving novel diagnostics. The field of microfluidics has the potential to generate high resolution, low-cost devices that could be used in a field setting to process blood samples instantly. Such devices use small differences in air pressure to drive a liquid sample across a range of sensors (Dimov *et al* 2011). Such devices are small and if they were cheap could make “bed-side” detection of infection a reality. Better technology is also being developed to more rapidly identify known viruses, by coating light scattering nanoparticles with antibodies, and then analyzing the light scatter properties of, for example, serological samples (Driskell *et al* 2011). The development of novel diagnostic tools is a broad field which was reviewed in depth for the Foresight project on infectious disease (Foresight 2006) and by the US National Academy of Science (Lemon *et al* 2007).

The development of new drugs and vaccines for infectious diseases is a massive field and much of its research takes place behind closed doors in pharmaceutical companies. A US government review of new approaches to the development of antimicrobial therapeutics identified a number of priorities and promising avenues (Board on Life Sciences 2006). The top priority is to replace the antibiotics whose usefulness is fading because of the evolution of drug resistance (WHO 2012). The development of broad-spectrum antivirals – drugs that could be used to treat a wide range of viral infections rather than acting on one specific virus would be of great benefit (Rider at al 2011). It would be good if the hard lessons learned through the development of drug resistance to antibiotics, antifungals and specific antivirals were applied to the newly emerging class of broad spectrum anti-virals so that the evolution of drug resistance can be delayed. Vaccines have been one of the most effective interventions in infectious disease but there are still many infections for which no vaccine is available, or for which the existing vaccine is inadequate. HIV, malaria, tuberculosis and influenza are all such examples and each has one or more potential vaccines in clinical trial (AVAC 2012, Agnandji *et al* 2011, McShane *et al* 2004, Lambert and Fauci 2010).

4.5 Breeding for disease resistance

For livestock and crop plants breeding variants that are resistant to infection has been a long-standing strategy for infection control. For plant infectious disease some of that breeding has been on a narrow genetic basis that has allowed pathogens to evolve countermeasures to the

plants' resistance. In the future a number of strategies are planned to breed disease resistant crop variants where the resistance is more durable.

Systemic acquired resistance is the plant response which can allow plants to resist or recover from infection. It is a non-specific response, activated by a wide range of pathogens and induces resistance that is effective against a wide range of pathogens. This broad spectrum activity makes these systems attractive targets for crop breeding. Another strategy to ensure that resistance is more durable is to create mixtures and multilines of cultivars so that there is much greater genetic diversity in the crop and the evolution of resistance in the pathogen is slowed (Mundt 2002).

Breeding livestock with disease resistance to specific known diseases is well established, first with traditional breeding programmes, then using gene sequencing to identify resistant individuals from whom to breed and most recently using GM techniques (see for example Lyall *et al* 2011). For both animals and plants there is substantial public unease about genetically modified organisms entering the food-chain. The breeding of livestock for resistance needs to avoid the problems of genetic monocultures that have been encountered in plant breeding.

5. Road blocks to progress

Across all host types (humans, livestock, crops) it remains difficult to predict the future spread of infections for a number of reasons. Predicting the future spread of infection requires a profound understanding of the pathogen's interactions with its host, the hosts' interactions with each other, and interactions of both host and pathogen with the environment. The development of meaningful *in vitro* bioassays able to predict the epidemiological behavior of a pathogen (ability to cross species barriers, ability to transmit between hosts, ability to induce disease) would make a profound difference to our ability to predict the spread of new infections. However, it is unclear when, if ever, such assays might be developed.

If data about the epidemiology of infectious diseases were shared more widely progress would be faster. In the field of gene sequencing there are strict protocols that require that gene sequences are deposited in publicly accessible databases before they are published. Those databases have become repositories for vast amounts of sequence data, open for anyone to work on and annotated so that the data makes sense. In response people interested in the analysis of gene sequence data can develop new methods and test them out on this wealth of data. In contrast epidemiological data are not shared by those who gather it, even though they are often gathered using public funds. The protection of individual privacy is often given as a reason for not making such data public and is obviously an important concern. However it is relatively straightforward to anonymise epidemiological data. Publicly available databases describing past and on-going infectious disease epidemics and the populations through which they pass would allow many more people to work on the development of infectious disease models that were closely tied to data. Better open access to the published literature would also open the field to more players. These would be great advances on the current situation.

A continuing growth in our understanding of the role of travel and trade in the international spread of infection is needed. But we also need to understand which interventions are effective to slow or stop spread through when that trade is such a core activity of globalisation.

As mentioned above, better surveillance, based on better, cheaper diagnostics will enhance our ability to detect new threats. Also mentioned above, further advances in real-time, digital syndromic surveillance have much to offer. However as more and more data of this type are collected the barrier becomes the development of tools to make sense of the data. It is also necessary to build much better records of baseline data to give a much better understanding of

the “normal” diversity of viruses and other micro-organisms that hosts carry. A proper description of background diversity is an essential precursor to the very early detection of novel threats.

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