Global One Health – a new integrated approach

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Executive summary

Infectious diseases, as well as non-communicable diseases in humans, animals, and plants, are inherent to life on Earth. During human history, much has been achieved in the control of diseases, leading to significant advances in human health and agricultural productivity. What we have gained with effective disease control and prevention has been of great benefit both to the developed and the developing world. However, new diseases continue to emerge and these diseases are major stumbling blocks to prosperity. As such, they are an important measure of inequality in the world: in the developing countries there are more human disease threats and fewer opportunities for trade because of the lower health status of animals and plants, compared to developed economies. The latter enjoy a better health status and have more resources to invest in disease prevention and the scientific research needed for effective disease control. However, countries are interconnected. Lowering the disease burden should be a worldwide goal, and requires us to further improve our approach towards managing diseases. This is a challenge, as even preventing an increase of the current disease burden requires a considerable effort because new problems continue to emerge. Moreover, considering today's highly interactive global linkages, it is not enough to deal with single issues for single diseases. Clearly, a systems approach is called for, in which complex systems are studied within various disciplines and at various scales..Hence, we need to consider important interactions between, for example, human and animal diseases, the environment and human diseases, domestic animal and wildlife diseases, social changes and disease burden, economic development and diseases, and trade and diseases. These interactions have gained cognition in the current One Health Concept and Global Health Concept. We propose a wider approach, namely ***Global One Health*** (GOH), to emphasize the interdependence of human health with the health of animals, plants and sustainable ecosystems from a global perspective. True prosperity and security will only be reached if we weigh all possible effects of interventions on the health of humans, animals, plants and the environment, while taking global ecosystem sustainability into account. The GOH approach uses multiple disciplines to seek transnational solutions for improving the health of humans, animals and plants, and ultimately, the sustainability of the ecosystems of planet Earth. This paper outlines the principal components that contribute to Global One Health, and provides a platform for developing a systems approach through which policy and science can be developed for global one health.

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Introduction

In the 20th century, many infectious diseases in humans, farmed animals (including fish and shellfish), and plants were successfully controlled through the discovery of new drugs and pesticides, food hygiene, sanitary improvements and better nutritional status. People living in the advanced and industrialized (OECD) countries benefited most from these developments, while those living in poorer countries continued to be exposed to many high-impact infectious diseases as well as lack of clean drinking water and good sanitation. The green revolution, aided by the intensive use of fungicides and insecticides, increased the world agricultural production to an extent that, on average, all inhabitants on earth can be fed sufficiently in terms of calories. However, other inequalities in health have become apparent, with the developed economies being mainly exposed to non-communicable diseases associated with wealth, and lesser developed societies (mostly) with communicable diseases linked to poverty and, increasingly, also to non-communicable diseases resulting from the spread of high-fat and energy-dense food for relatively low prices, the 'global nutrition transition' (Popkin et al. 2012).

In developed economies, where infectious diseases have been eliminated or are managed by medical interventions such as vaccines and drugs, attention has shifted to emerging infectious diseases. The recent outbreak of Ebola in West Africa, for example, caused fear that the disease might affect other parts of the world and stringent measures were taken to prevent the spread of the disease (Arwady et al. 2015, Bogoch et al. 2015, Kennedy and Nisbett 2015). Continuing outbreaks of avian influenza demand attention at the medical front, but also politically as this is an example of an emerging disease that could rapidly affect large parts of the global society (Sundstrom et al. 2014, Watanabe et al. 2014). These examples demonstrate that modern society needs to stay alert to the risk of emergence of diseases that require rapid responses to limit their impact.

Greater food availability, due in part to the control of pathogens in domesticated plants and animals, has contributed to improved health. It has been argued that a reduction of communicable diseases will lead to less poverty and fewer poverty-related diseases on the one hand, and to an increased prevalence of non-communicable disease on the other (Murray and Lopez 2013). Although impressive progress in disease control has been made, infectious and chronic diseases continue to affect societies and need to be dealt with in order to achieve the health-for-all objective as outlined in the UN Millennium Development Goals and the soon to be adopted Sustainable Development Goals. Furthermore, the importance of healthy, well-functioning ecosystems for human well-being has been widely recognized since the Millennium Ecosystem Assessment. The goal of having healthy people in a healthy environment requires an integrated approach, including not only health specialists, but also ecologists, nutritionists, sociologists and economists, etc. This position paper outlines how this can be accomplished and launches a novel approach termed Global One Health, as an extension of previous approaches around Global Health and One Health.

The One Health concept

The idea that human, animal and environmental health are linked goes back to very old times. The Greek physician Hippocrates (460 - 370 BCE) in his text "On Airs, Waters, and Places" already promoted the concept that public health depended on a clean environment. The great discoveries in the 16th century and evolving international trade not only introduced spices, potatoes and tomatoes to the European food culture, they simultaneously highlighted the importance of fruits and vegetables in preventing scurvy (long before vitamin C was known) during the long overseas journeys and the endemic food-related micronutrient deficiencies in tropical countries (B1, niacin, others). Along with the sailors, measles travelled to the Americas, while syphilis was introduced into Europe (Wolfe et al. 2007). Similarly, animal pests entered Europe (e.g., rinderpest in the Netherlands in the 18th century). At the local level, the intimate relationship between societal and environmental ecosystem and health was evident, for example from the water supply system being a source of exposure to the as yet undiscovered cholera bacterium (Cameron and Jones 1983). The term One Medicine was apparently coined by Calvin Schwabe (1927-2006), an American veterinarian who wrote extensively about the relationship between animal and human diseases (Schwabe 1968), which is one of the bases of the One Medicine concept.

The modern age wake-up call that human and animal health have to be seen in conjunction came with the outbreak of Bovine Spongiform Encephalopathy (BSE). It was clear from comparative pathology that the sheep disease scrapie and the human variant Creutzfeldt-Jacobs Disease (vCJD) were similar. However, the risk of transmission between individuals of one species and between individuals of different species was (and still is) not well understood. Nevertheless, it was very soon decided that transmission between cattle was due to meat and bone meal in cattle feed (Wilesmith et al. 1988). Initially, the risks to humans were considered to be negligible. However, this turned out to be not entirely correct, as the BSE epidemic gave rise to several hundred variant CJD cases, which are now considered to have been caused by BSE exposure. This resulted in European governments and the EU looking again into which is the responsible authority for initiating and conducting risk assessment and risk management of those diseases that affect both humans and animals. Ultimately, the BSE crisis created conditions for the foundation of a common European Food Safety Authority in 2002 (Budka 2011). It also drew attention, for the first time, to the complexities of the food chain supporting meat production. The One Health concept was further embraced around 2004, at a time when it was feared that the highly pathogenic H5N1 avian influenza could cause a pandemic.

One Health recognizes that humans do not exist in isolation, but are part of a larger whole, a living ecosystem, and that activities of each member affect the others. Whereas One Medicine historically implied linkages between veterinary and human medicine, One Health considers health as a whole: the humans, animals, plants and the environment with which they interact. Nowadays, the expression One Health has been adopted by epidemiologists, physicians and veterinarians and also by wildlife specialists, environmentalists, anthropologists, economists and sociologists, among others, and also by international organizations working on the control of zoonoses such as the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) as well. With the broader involvement of people and institutions promoting health through interdisciplinary study and action, many different definitions of "One Health" have come into use. Most of these definitions fit rather well with the one published by the One Health Commission (www.onehealthcommission.org): "One Health is the collaborative effort of multiple health science professions, together with their related disciplines and institutions – working locally, nationally, and globally – to attain optimal health for people, domestic animals, wildlife, plants, and our environment".

The Global Health concept

In contrast to One Health, Global Health is a relatively new concept in medicine. The first article with "global health" in the title was published in 1966 (Niblett 1966), addressing global health factors affecting the Canadian mobile forces. The upsurge in global health research starts in the 21st century, with 1250 articles published in 2010 (Marušić 2013).

The concept of global health has evolved during the past 50 years from a narrow view of ecologically and geographically restricted health challenges to a broad and comprehensive approach to health in the world as a whole. The term global health has replaced such earlier terms as international health and tropical medicine. Tropical medicine developed in the late 19th and early 20th centuries, an era when many countries of the southern hemisphere were colonized by countries of the northern hemisphere. It focused on diseases associated with warm climates. To prevent and treat these diseases, training in tropical medicine became a priority in preparing northern professionals for overseas service. Infectious and parasitic diseases, maternal and child health, and nutrition were the most common components of these early international health efforts (De Cock 2011). There are several definitions of global health currently available. The definition of Koplan et al. (2009), is widely used:

"Global health is an area of study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide. Global health emphasizes transnational health issues, determinants, and solutions; involves many disciplines within and beyond the health sciences and promotes interdisciplinary collaboration; and is a synthesis of population-based prevention with individual-level clinical care".

Global health as defined by Koplan et al. (2009) broadens the agenda internationally and considers health at the global level. For example, it includes strengthening and supporting the systems required to implement health interventions as well as mechanisms for coordinating public health activities. It includes health education and prevention and extends to overseeing clinical at local level. Global health recognizes the reality of globalization and prioritizes public health challenges that transcend individual country boundaries and require collective action, such as threats from infectious agents like HIV, but also from environmental and climate change, rapid and widespread urbanization, and changes in socioeconomic conditions, diet, and lifestyles. Global health is guided by epidemiological science and has as core values concepts of justice, decency, human rights, and health equity. It also recognizes the overwhelming relevance and importance of policy, politics, and diplomacy (De Cock 2011).

Examples of complex health problems and the lessons learnt

The complexity of human, animal and ecosystem interactions can best be understood by reviewing a number of recent high profile health cases and the lessons that could be drawn from them for an integrated approach.

Influenza A H5N1

Avian Influenza (AI) can be transmitted to a wide variety of host species. Especially the transmission to and from wild birds, farmed poultry and humans is important. Wild birds, particularly migratory water birds, form a natural reservoir of AI viruses. They pose a special risk for introduction of AI viruses of all subtypes to poultry. AI virus infections in reservoir hosts are usually asymptomatic. In poultry, AI normally causes only mild or no disease. Low pathogenic avian influenza viruses (LPAI) of the H5 and H7 subtypes have the potential to mutate to highly pathogenic avian influenza viruses (HPAI) and are therefore notifiable to the OIE. Avian influenza is a zoonotic disease and past influenza pandemics were caused by viruses that were at least partly derived from AI viruses. One particular lineage of Influenza A H5N1 has been observed to circulate the globe since it was first observed in May 1997 in Hong Kong (Claas et al. 1998). It circulates mainly as a highly pathogenic avian influenza (HPAI) strain among poultry, but it is also seen as a HPAI in wild birds (which was only observed once before), and as a virus that causes infections and a high case mortality rate in humans (which was never observed before to this extent).

As there have been severe human cases, AI control in poultry by (local) eradication or mitigation is required. In Europe the virus has been eradicated in poultry by strict measures, and several countries where the strain is endemic have attempted vaccination (e.g., Indonesia, Egypt and Vietnam). Vaccination is now considered to have only a mitigating effect and it does not lead to eradication. Also, it has to be noted that a descendant of the aforementioned H5N1, a linage of HPAI H5N8, has started its global spread from South-Korea and has been observed in Europe, Japan and North America. This H5N8 linage is not as pathogenic for humans as H5N1 but it again occurs as a HPAI in wild birds (Kim et al. 2015).

This epidemic was managed by applying an eradication strategy imposed by the Special Administrative Region (SAR) of Hong Kong. This strategy was not followed by mainland China and thus there was a system in place to test imported live poultry to prevent reintroduction into the SAR. Europe likewise adopted an eradication strategy, but as introductions in each country most probably originate from migratory birds, prevention of introduction is difficult. Consequently, we now see that the descendant strain H5N8 was introduced into several European countries, Japan and North America. Countries in Asia (e.g., Indonesia) and Africa have not been able to eradicate the virus and have resorted to vaccination.

Malaria

The estimated number of yearly malaria cases worldwide is 198 million, with 584,000 deaths (WHO 2014a), which is of another order of magnitude than for example vCJD, human cases of H5N1, or Ebola, although the latter diseases often receive much more attention. Malaria is a disease that occurs as an acute or recurrent fever and it was already known in ancient times. In those days, e.g., the period of the Roman empire it was associated with bad air and marshlands. Until the discovery of the parasite and the role of mosquitoes in its transmission (Ross 1897), effective malaria control was not possible and the disease has claimed millions of lives of people worldwide. Since then, with the development of effective drugs and preventive measures, significant advances have been made in malaria control, leading to the eradication of the disease from temperate industrialized countries. In (sub)tropical countries, however, the disease continues to pose a huge burden on human health.

The recent successes in malaria control were achieved with a high dependency on insecticides, applied as indoor residual spray or impregnated onto bed nets (WHO 2014a). However, the continuous selection pressure placed on the mosquitoes by exposure to these insecticides has caused large-scale resistance (Ranson et al. 2011, Wang et al. 2013), threatening the advances made. This requires urgent attention, for example by developing integrated vector management strategies that are based on non-insecticidal tools such as biological agents, water management and behavioral manipulation (Chanda et al. 2008, van den Berg and Takken 2009). With such an integrated approach, insecticides can continue to be used for malaria vector control, but at a much reduced scale, delaying the onset of further resistance (Takken and Knols 2009, Thomas et al. 2012).

While malaria on its own often causes severe disease, leading to mortality or lasting impairments, the disease is much aggravated by iron deficiencies. Iron deficiency often co-exists with infectious diseases such as malaria. Iron deficiency and iron deficiency-anemia are estimated to be the most widespread of all nutritional deficiencies and, as a consequence, iron is probably the most widely administered of all compounds both through preventive campaigns involving mass administration and by individual prescription (Prentice 2008). However observations in affected populations suggest that optimizing iron status may involve a very delicate balance: a deficit of iron will impair host-function (including immunity), but an excess may favor the growth and pathogenicity of microorganisms such as those causing malaria (Doherty et al. 2002).

For malaria, complex vector-parasite-host relationships exist, and these are influenced by the ecology, genetics and behavior of various vector species and parasites, and are influenced by environmental factors that operate over a range of spatial and temporal scales (White et al. 2014). This is one of the reasons that malaria is still abundant and difficult to eradicate despite enormous efforts.

It is hypothesized that ill health due to malnutrition and/or infectious disease impacts on the labor productivity of women especially, as they not only are in poor health themselves, but often need to care for sick children. Hence, iron deficiency and malaria are associated with reduced work capacity (Haas and Brownlie 2001), but the impact on time use, and agricultural production as a result of integrated interventions that lead to better nutrition and less malaria are not well understood (Zhang and van den Berg 2013).

Food-borne toxins

A large outbreak of the hemolytic-uremic syndrome caused by Shiga-toxin-producing *Escherichia coli* O104:H4 bacteria occurred in Germany in May 2011. Soon, epidemiological field studies suggested that fresh vegetables were the source of infection but it took more than a month before an organic farm producing sprouted seeds was identified as the source of the outbreak. Fenugreek sprouts acted as a transmission vehicle and had been widely consumed in the outbreak area at the time of the epidemic. Close to 4000 people developed a clinical illness characterized by bloody diarrhea, with a high frequency of serious complications, including hemolytic-uremic syndrome (HUS). More than 50 people died of the infection. In June 2011 the German Bundesinstitut für Risikobewertung (BfR) (Federal Institute for Risk Assessment, German Federal Ministry of Food, Agriculture and Consumer Protection), reported that the outbreak was caused by an entero-aggregative *E. coli* (EAEC) strain that had acquired the genes to produce Shiga toxins, present in sprouts of fenugreek (*Trigonella foenum* greacum), a kind of bean (Fabaceae). Seeds of fenugreek imported from Egypt were most likely the source of the outbreak.
In the meantime, the suggestion that fresh vegetables could be the cause of the outbreak led to a ban on cucumbers by consumers. This had huge consequences for trade and indirectly for individual farmers. The case shows the enormous effects of early findings brought into the media. As a precautionary principle it is important to communicate all information as soon as it becomes available although this information may later be shown not to be “correct”. Tracking and tracing is important but may need more time than it initially seems. Entero-aggregative *E. coli* (EAEC) strains present on fresh vegetables such as sprouts can acquire the genes from STECs to produce Shiga toxins. Shiga toxin is released by decaying bacteria in the gut, migrates through the intestinal barrier and is transported via the blood to the target organs, such as the kidney. Treatment and prevention options include antibody and antibiotic treatment and probiotics, although not undoubtedly proven effective. Thorough cooking of foods and hand washing are the main preventive measures. In most of the Shiga toxin outbreaks associated with the consumption of sprouted

seeds, the seed appeared to be the origin of the contamination. As seeds sold for sprouting are often sold as seed mixes and cross-contamination cannot be excluded, consumers are sometimes advised not to grow sprouts for their own consumption , and preferably not to eat sprouts or sprouted seeds unless they have been cooked thoroughly. As some of these vegetables are eaten raw, the latter is not really an option. Therefore microbiological tests should also be carried out on seeds. However, negative test results have been shown not to provide a full guarantee. Moreover, sprouted seeds of beans, radish, alfalfa and fenugreek etc. may be used in the kitchen at the same time, making it more difficult to trace back the origin of a contamination.

Obesity and diabetes

The risk of non-communicable diseases such as cardiovascular diseases, diabetes, osteoarthritis and cancers increases with overweight and obesity. Changes in diet, caused by the increased availability of energy-dense foods alongside lower levels of occupational and other physical activities, have resulted in a worldwide epidemic of obesity and diabetes. Diabetes risk increases exponentially with increasing Body Mass Index (BMI). The diagnosis of type 2 diabetes at a young age results in many developing micro- and macrovascular complications. Overweight (BMI≥25) and obesity (BMI≥30) are defined as abnormal or excessive fat accumulation that may impair health (WHO 2000).

Overweight and obesity are linked to more deaths worldwide than low weight, and most of the world's population live in countries in which excess weight and obesity kill more people than underweight does (this includes all high-income and most middle-income countries). The worldwide prevalence of obesity more than doubled between 1980 and 2014 (Harvard School of Public Health 2014). Many low- and middle-income countries are facing a "double burden" of disease. While they continue to deal with the problems of infectious disease and under-nutrition, they are experiencing a rapid increase in risk factors for non-communicable diseases such as obesity and overweight, particularly in urban settings (Boutayeb 2006). Although obesity is a risk factor for developing diabetes type 2, it is not the sole cause of this condition. Therefore, alternatives to preventing diabetes 2 should be investigated, for example via drug treatments (Knowler 2002).

Elaborating present and future linkages between ecosystems, food chains, and plant, animal and human health

Health and Global Change

Historically, many infectious diseases have their roots in natural aquatic or terrestrial ecosystems, where interaction between biotic and abiotic factors has led to the emergence and transmission of often-deadly diseases of man and animals. Global changes such as caused by deforestation, anthropogenic encroachment into forest zones, environmental pollution, and climate change increasingly lead to outbreaks of "new" diseases as well as allow "ancient" scourges such as leishmaniasis, malaria and TB to thrive (McMichael and Lindgren 2011). The rapid urbanization of the world, with ultimately the vast majority of the population living in cities, and increases in human population densities, has created additional and unparalleled health problems. In tropical and subtropical countries, mega-cities lead to new opportunities for infectious disease outbreaks, aggravated by unhealthy environmental conditions from pesticides, insufficient sewerage and polluted air (Semenza and Menne 2009, Kovats et al. 2014). In many climate zones, burning of fossil fuels as well as car exhausts cause new health risks for the urban population. The depopulation of the countryside in certain parts of the world leads to denser vegetation and increased numbers of wildlife, which may be followed by higher burdens of infectious disease vectors (mosquitoes, ticks, midges etc.) (Cutler et al. 2010). Risks of animal and human diseases can thereby increase as well. To understand the impact of these changes, we need to consider in a comprehensive way the various aspects that contribute to changes in health risk.

Emerging infectious diseases

An emerging infectious disease can be defined as "a pathogen that is newly recognized or newly evolved, or that has occurred previously but shows an increase in incidence or expansion in geographical, host or vector range". Emerging infectious diseases are caused by newly identified species or strains (e.g., MERS and SARS CoV, AIDS) (Fauci 2005), that may have evolved from a known infection (e.g., influenza) or spread to a new population (e.g., West Nile virus) or to an area undergoing ecologic transformation (e.g., tick-borne encephalitis). Emerging infections account for at least 12% of all human pathogens (Taylor et al. 2001) and emerging infectious disease events are dominated by zoonoses (60.3%), the majority of these originating from wildlife (Jones et al. 2008).

EBOLA OUTBREAK AND GLOBAL ONE HEALTH

In 2014, an Ebola virus outbreak occurred for the first time in West Africa, where it caused an epidemic of epic proportions. The index case was located in south-east Guinea. Because the local authorities were not aware of the seriousness of a highly contagious and fatal disease such as Ebola, the disease spread rapidly, affecting large parts of Guinea, but also neighboring Sierra Leone and Liberia (Arwady et al. 2015). Eventually, more than 26,628 people became infected, of which 11,020 died. In April 2015, Liberia was officially declared free of the disease, but cases continued to occur in Sierra Leone and Guinea (http://apps.who.int/ebola/en/ebola-situation-reports; 13 May 2015)

Health authorities in the affected region were unable to control the disease, and a huge international effort was initiated to assist with medical as well as logistical staff. By September 2014, these efforts resulted in a prevention of further spread of the epidemic, eventually leading to a situation in which the disease was no longer considered a threat to global one health.

This Ebola outbreak should be considered as the emergence of an infectious disease that went out of control. Indeed, several cases of the disease were diagnosed outside of Africa, where they caused much concern among the general public as well as governments.

Was the 2014 Ebola epidemic a threat to global one health? Given the high virulence of the virus, with a case fatality rate of 42%, any region that is unprepared for such an infection may have suffered a disease incidence similar to that in West Africa. On the other hand, the stringent international preventive measures, with quarantine facilities for patients, would likely have led to a rapid extinction of the disease. The disease caused so many victims because there was no effective treatment or vaccine available and local authorities were unprepared to rapidly and effectively inform the local population about how to handle sick and deceased individuals so that these could be placed in quarantine. The lessons learnt from this epidemic clearly demonstrate that a) the world was unprepared for an outbreak at this scale; b) effective treatment and vaccine were not available and c) the international bodies that could have coordinated the control of the epidemic were late in responding effectively.

At the start of the 20th century, infectious diseases were the principal cause of death in human societies. The discovery of micro-organisms, development of disease epidemiology and the introduction of public health measures such as piped drinking water and controlled sewage systems have caused an unprecedented reduction in morbidity and mortality, especially in industrialized countries. Better food hygiene and, for example, pasteurization of raw products such as milk have also reduced the spread of infectious diseases. Scientific advances in pharmacology and immunology produced drugs, in particular antibiotics, that could be used for the effective control and/or prevention of many infections and infectious diseases. Global introduction of synthetic antimalarial drugs such as chloroquin (Resochin®) allowed malaria in North America, Europe and Australia to be eliminated, as well as significantly reducing malaria in tropical countries. The discovery of penicillin has been hailed as perhaps the most significant contribution to global health. Vaccines against poliomyelitis, smallpox, measles and other viral diseases have saved millions of lives, and even led to a global eradication of smallpox in humans and rinderpest in cattle. With the introduction of the expanded program of immunization by UNICEF in 1974, children in countries all over the world were ensured of a safer life (Henderson 1984, Duclos et al. 2009) and it seemed that health for all could be attainable within one generation. Indeed, it was predicted that infectious diseases could be effectively conquered so that they would no longer pose a burden on human societies. Although there are indications that humans are winning the war on infectious diseases (Behrman et al. 2009), the two leading diseases in humans still are infectious diseases – lower respiratory infections and diarrheal diseases (Lopez and Mathers 2006).

In the final decade of the 20th century, however, following a series of unprecedented events, this earlier optimism turned into concern. In the late 1990s, outbreaks of cholera, a disease that can be well controlled with antibiotics and proper public health measures, were recorded in several tropical countries. In Peru, these outbreaks were associated with pollution of the coastal seawater, which was rich in organic waste from the mega-city of Lima (Jutla et al. 2013). In Zimbabwe, thousands of people suffered from cholera resulting from inadequate health care and poor maintenance of the water supply system (Ahmed et al. 2011). More recently, the dramatic earthquake in Haiti caused the loss of the public health infrastructure, including provision of safe drinking water and sanitation, leading to one of the largest outbreaks of cholera in modern history.

Hence, many of the “emerging” infectious diseases have in fact not recently been discovered, but have been around for many centuries and should be considered as re-emergence of diseases that were controlled several decades ago. These include Q-fever (the Netherlands, 2007-2009), measles (the Netherlands, 2013), TB (global), antibiotic resistant microbes (ARM) especially in health care settings but also in the wider community (Knol et al. 2013). Other infectious diseases are emerging from hitherto limited areas of distribution and spreading into other global regions. Many emerging diseases are vector-borne, such as dengue, West Nile virus, Crimean-Congo Hemorrhagic Fever (CCHF), tick-borne encephalitis (TBE) and chikungunya. A third group are novel infectious diseases often with a wildlife origin such as SARS, MERS, HIV-AIDS, Usutu virus, EHEC and Ebola (Raj et al. 2014). The livestock industry has also experienced outbreaks of newly emerged infectious diseases, which include bovine spongiform encephalopathy (BSE, causing vCJD in humans), Porcine Respiratory Reproduction Syndrome virus (PRRSV), bluetongue, Schmallenberg virus and several variants of influenza A, such as the H5N1 high pathogenic avian influenza (H5N1 HPAI) lineage, which caused many human influenza fatalities worldwide, and the H1N1 reassortant influenza virus that has caused a human pandemic. Likewise, many well-known infectious diseases of animals have continued to cause problems, for example classical swine fever, African swine fever, foot and mouth disease virus, *Mycobacterium bovis*, *Brucella abortus*, *Neospora caninum*, and virulent BVDV strains. The latter have huge economic consequences and affect national and international trade (Koenraadt et al. 2014).

It should be noted that certain diseases are not specifically emerging or are not appearing as major outbreaks, and therefore receive less attention, although they are still very relevant to public health. Emerging issues, outbreaks and new diseases often draw significant attention, and may also cause public health impacts, and even create widespread panic as in the case of Ebola. More dispersed disease outcomes and old foes receive less attention and create less fear, but can still represent a large public health burden.

Health and climate change

Recent predictions of climate change suggest an average increase in global temperature between 0.5 and 2.5°C, depending on the latitude, and large variations in precipitation, causing flooding and/or drought (Pachauri and al. 2014). These climate changes are predicted to lead to significant impacts on ecosystems, in particular vegetation structure and composition of floral and faunal communities. Poikilothermic species such as micro-organisms and invertebrates, including insect (pest) populations as well as predators of plant pathogens, are likely to be most affected (Myers and Patz 2009). As animal, human and plant health are all affected by abiotic factors such as temperature and rainfall, climate change is expected to cause significant changes in health: plant pests and diseases can proliferate under increased temperatures, arthropod vectors of infectious disease express higher vector competence and hence are better vectors and may increase survival, and vectors of livestock diseases such as bluetongue can expand their distribution range and/or phenology because of more favorable environmental conditions. Increased rainfall can cause catastrophic flooding, which may trigger microbial diseases such as cholera to erupt readily in otherwise weakened human populations. Water accumulation resulting from excessive rain may lead to increased malaria risk because mosquitoes benefit from the extended water bodies. Warming of the oceans due to global change may increase the risk of microbial diseases that are associated with polluted water, especially in countries that are prone to periodic flooding or subject to the effects of sea-level rise (Rose et al. 2001). Wildlife diseases, as with human and livestock disease, may be equally affected by climate change as pathogen-associated vectors thrive better at higher temperatures (Acevedo-Whitehouse and Duffus 2009, Billinis 2013). Furthermore, higher temperatures and humidity may be conducive to food-borne diseases, especially in poor tropical countries.

Urbanization and overpopulation

Global population growth and associated development has led to an unprecedented expansion of urbanized areas as well as the emergence of mega-cities such as São Paulo, Mexico City, Cairo, Jakarta and Beijing. In some countries the expansion of these cities occurs with little or no planning, leading to conditions in which many people end up living in huge urban slums. These are characterized by poor housing, inadequate sanitation and unsafe provision of drinking water. In combination, these conditions are a recipe for disease outbreaks (Guerrant and Blackwood 1999, Kovats et al. 2014). For example, poor sanitation and unplanned human waste deposits are a haven for disease-carrying rodents, reservoirs of leptospirosis, hantavirus, *Salmonella* and *Campylobacter* spp., for example (Meerburg and Kijlstra 2007). In the tropics, human and animal waste is also an excellent substrate for the development of synanthropic flies, which may carry bacteria causing trachoma, a serious eye disease (Emerson et al. 2001, Tian et al. 2015). Tropical mega-cities often harbor vegetable gardens where crops are grown to be sold on urban markets. Apart from the heavy use of pesticides and associated health risks posed by these chemicals, water storage tanks and irrigation ditches serve as the nurseries for mosquitoes, resulting in urban malaria and filariasis (Donnelly et al. 2005, Klinkenberg et al. 2008), an issue compounded by their use as open-air gutters and sewers. Other vector-borne diseases in urban areas are dengue and chikungunya. Indeed, both are rapidly increasing in incidence, with annually >500,000 people suffering from dengue, mostly in urban areas (Bhatt et al. 2013, Weaver 2013). Urban farms may also house livestock such as poultry and pigs. Unless strictly regulated, animal husbandry in densely-populated cities can be a main source of infectious-disease risk, for example avian influenza acquired from chickens at live markets, but also food-associated bacterial disease. This applies in particular to warm climates, where stocks of animal food and waste can be highly conducive to the introduction and the establishment of pathogenic micro-organisms (Sims and Peiris 2013). Apart from infectious disease, urban living also exposes residents to exhausts from cars and/or the burning of coal for heating. Many urban slums are situated along the edge of highways and industrial areas, where exposure to dangerous aerial pollutants is high. Climate change is expected to exacerbate this situation (McMichael and Lindgren 2011).

Health, large scale production and innovation

Modern innovations can contribute to significantly improved health and reduction of disease risks. For example, the introduction of air-conditioning has allowed for improved living conditions, also decreasing the indoor abundance of disease-carrying insects such mosquitoes. Pharmaceutical research, including molecular genetics, has been exploited for the discovery and development of new vaccines against a score of viral diseases. The discovery of a method to store vaccines at room temperature has significantly contributed to the success of the expanded program of immunization (EPI). Even children living in remote places can now be vaccinated safely, whereas previously they depended on expensive and logistically complex cold-chains. The use of electronic communication devices, text messaging and twitter, has caused a revolution in public health. For example, by rapid exchange of health information between program managers and health-care staff, the malaria control program in Tanzania became vastly more effective when stocks of anti-malaria drugs were monitored weekly through mobile telephone exchanges; allowing for a rapid redistribution of drugs to ensure that clinics that needed them could be adequately supplied (Zurovac et al. 2012).

Innovations in livestock production allow for scaling up the livestock industry to mega-farms, more easily meeting the protein demands of the growing global population. Gene exchange and the discovery of gene functions in livestock and fish have been used for the creation of animals with qualities that can meet increasing market demands. Animals are also used as bioreactors for the production of human medicines, for example insulin, which can be produced by bovids that have undergone selective, heritable gene insertions (Chance and Frank 1993).

Not all innovations lead to health benefits. The massive use of antibiotics in animal and human health has led to high, and sometimes, irrevocable, levels of pathogen resistance (Carbon 2000, Levy and Marshall 2004). In hospitals, the difficulty of eliminating MRSE and MRSA bacteria have caused grave concern, as increasingly, patients do not survive infection with these pathogens. Wide-scale use of antibiotics in the livestock industry has led to rapidly increased microbial resistance levels, requiring the adoption of alternative, expensive, farming methods. The use of pesticides in salmon farms has led to high resistance levels in sea lice, causing high economic costs for these farms; integrated control strategies are required that rely less on pesticides (Murray and Peeler 2005). In general, urbanization is associated with a rapidly growing demand for animal products and hence increased public health issues from antibiotics and zoonotic diseases.

Pesticides link human health to health of agro-ecosystems

Healthy and sufficient food is necessary for human health and well-being; therefore food security (sufficient food) and food safety (i.e., free of toxicants) are of great concern to governments worldwide. Most of our food is produced in agriculture, and the technologies used in food production in agriculture must be safe for workers and consumers. There is ample legislation and regulation on many aspects of the safety for human health of agricultural practices, but some level of risk to health is unavoidable (Hamilton and Crossley 2004). Such risks exist both in animal and plant production. In animal production, some of the main risks include emergence of new pathogens (or pathogen genotypes) and selection for antibiotic resistance, with downstream effects on the introduction of bacteria with resistance genes to human populations via the food chain or through farm workers. In plant production, the occurrence of toxic substances in food is of concern (D'Mello 2003). These can be of microbial origin (e.g., aflatoxin in peanuts produced by the fungus *Aspergillus flavus*, or mycotoxins produced by *Fusarium* spp. in wheat), but they can also be man-made.

Pesticides (including insecticides, fungicides, herbicides, acaricides, rodenticides, nematicides, molluscides, and bactericides) are man-made toxins that are deliberately applied in agriculture to suppress pests, diseases and weeds. The most important classes of pesticides are herbicides (49% of worldwide sales), insecticides (25%) and fungicides (22%) (Pretty 2004). Exposure to pesticides is of great concern to human health, both for workers in agriculture being exposed directly and for consumers via residues in the food or drift into the (rural or urban) environment. Pesticides also affect the health of the ecosystems in which they are used, as a result of direct exposure of biota within agricultural fields or in the wider environment of those fields, across field borders through drift or leaching, and through movement in the food chain (Pretty 2004). Currently, approximately 800 active ingredients are on the world market, and it is estimated that 2.56 billion kg of active ingredients are used yearly (Pretty 2004). The total area of cropland is 1.45 billion ha worldwide (Fischer et al. 2014) but not all of the pesticides are used on cropland, as some are used on pastures, on turf grass or around the home. The World Health Organization (WHO 2010) has distinguished four toxicity classes for pesticides according to acute toxicity to the rat, the standard test organism in toxicity studies. Many of the most toxic pesticides are insecticides. In recent decades, governments in the developed world have banned many of the more toxic active ingredients (e.g., methyl bromide), which pose the biggest risk of acute poisoning as well as being persistent and lipid-soluble active ingredients which tend to accumulate in food chains (e.g., the insecticides DDT and dieldrin). This phasing out has greatly improved the safety of agricultural workers, consumers and ecosystems in developed countries. Nevertheless, environmental exposure to insecticides may still be pervasive, for example with the recent widespread adoption of neonicotinoids for seed treatment in agriculture (Simon-Delso et al. 2005) for which side effects are now being reported (e.g., (Hallmann et al. 2014). Pretty (2004) demonstrated that the population collapses of several species of birds of prey in the 50's, 60's and 70's was caused by bio-accumulation of lipid-soluble, persistent insecticides that worked as endocrine disruptors. While the risk of exposure of workers in agriculture to acute pesticide poisoning is nowadays small in developed countries, the risks associated with long-term exposure of consumers are more difficult to estimate, as is the cumulative effect of exposure to multiple contaminants in food produce and the environment.

In developing countries, and especially in tropical regions, highly toxic pesticides continue to be used in agriculture, exposing workers and rural communities to risks of acute poisoning. Protective clothing is often not available, not affordable, or simply too uncomfortable to wear in hot tropical climates. Moreover, workers may lack the ability to wash immediately following pesticide application. Thus, pesticides continue to pose risks to human health in developing countries where more toxic compounds are still available, and technology to apply them safely is not used. The developed world accounts for 70% of the worldwide market for pesticides but this market is no longer growing, whereas usage is growing in the developing world (Pretty 2004). Integrated pest management (IPM) is promoted as a pathway towards reducing the use of pesticides, and hence mitigating their effects on health (Radcliffe et al. 2009). IPM combines genetic resistance in plants, cultural controls, and biological control with natural enemies, and uses pesticides only as a second line of defense if needed. IPM without pesticides is difficult to achieve, though notable successes have been obtained in glasshouse agriculture (van Lenteren 2012). One of the major challenges of integrated pest management is to maintain and augment natural enemy populations, without resorting to the use of pesticides that negatively affect these enemies if biological control at some time is not effective enough. Use of pesticides tends to negatively affect natural controls and can therefore offset a pesticide treadmill, causing lock-in in a pesticide-based model for pest management (Eveleens 1983, Hansen 1986).

Genetic modification of crop plants by expression of genes conferring resistance to pests and pathogens has been heralded as a strategy for protecting crops that is safer to workers and to the environment than the alternative of using pesticides (Shelton et al., 2002). Indeed, major reductions in pesticide usage have been recorded upon wide acceptance of resistant cotton genotypes in developing countries such as China and India, reducing farmer exposure to pesticides as well as the number of cases of farmer intoxication by pesticides (Qaim and Zilberman, 2003; Hossain et al., 2004; Huang et al., 2005; Pray et al., 2010; Qiao et al. 2012, Huang et al. 2015). News stories (e.g., in the Guardian[1]) indicated that costs of GM cotton seed had driven Indian farmers to suicide; however, this news was rated as "false" by Nature magazine (Gilbert, 2013). Genetic modification of crops for insect resistance has been shown to be compatible with biological control, and has much smaller harmful side effects on the functioning of agro-ecosystems than pesticides (Romeis et al. 2008, Lu et al. 2012). However, consumers remain distrustful of the "big industry" that produces GM seed, and the public remains concerned about the safety of GM food (Andreasen, 2014; Struik, 2014). Furthermore, engineered genetic resistance against one pest may not be sufficient to take away the need for pesticides because other pest species, not susceptible to the engineered resistance, may come up and raise pesticide use to levels similar to those before adoption of GM insect-resistant crops (Lu et al. 2010), highlighting the continued need for integrated pest management rather than reliance on a single technology.

Continued efforts are therefore needed to develop agricultural production systems that rely as much as possible on genetic, cultural and ecological approaches for managing pests, diseases and weeds, in order to mitigate the risks for health of humans and ecosystems associated with the use of pesticides.

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[1] http://www.theguardian.com/global-development/gallery/2014/may/05/india-cotton-suicides-farmer-deaths-gm-seeds

managing pests, diseases and weeds, in order to mitigate the risks to human and ecosystem health associated with the use of pesticides.

Increased travel and trade

Travel and trade has always been accompanied by the accidental spread of disease. Well-known examples are the introduction of malaria and yellow fever to the Americas as a result of the slave trade (17th-18th century). The parasite (malaria) and virus (yellow fever) were most likely carried by Africans that had been sold on the slave markets which flourished along the African coast. Following several devastating epidemics, both diseases have since become endemic in South and Central America, aided by a favorable climate and the presence of competent mosquito vectors. The industrial revolution, which started in the early 19th century, was accompanied by a strong increase in global travel and trade: steamships enabled the massive and economic import and/or export of agricultural produce and other commodities over huge distances. Air travel has only led to further increases in the mass exchange of people, livestock, wildlife (e.g, pet industry) and plant and animal products across continents (Tatem et al. 2012). For example, one can travel from London via Los Angeles to Sydney in less than 24 hours, carrying any undiagnosed micro-organism, which may remain undetected until well after arrival. The latter can therefore infect many others before disease symptoms become apparent. In this way, the spread of SARS from S.E. Asia to Canada in 2002 occurred by airline travel and caused a serious epidemic in Toronto (2006). The global spread of the Asian tiger mosquito, *Aedes albopictus*, is known to be caused by the trade in used tires, which serve as reservoir of (dormant) mosquito eggs. Upon arrival on a different continent, the mosquitoes hatch, triggered by rainfall and suitable environmental conditions. *Aedes albopictus* was found to be a highly competent vector of chikungunya virus in La Reunion, where in less than one year >250,000 people became infected (Renault et al. 2007). The chikungunya virus was accidentally introduced into the Caribbean in late 2013, presumably by an undiagnosed traveler who infected resident *Aedes aegypti* mosquitoes on a Caribbean island (Conn 2014). Other examples of the introduction of exotic pathogenic organisms are the outbreak of bluetongue in Italy in 1998 (Purse et al. 2008), and its subsequent establishment in north-western Europe (Faes et al. 2013); both outbreaks were the result of separate introductions, as they concerned different viral strains, demonstrating the potential frequency of such disease introductions. The establishment and dispersal of West Nile virus in North America was presumably caused by the arrival of an infected bird (Murray et al. 2010). It is important to note that in all cases of the introduction of a vector-borne disease such as yellow fever, dengue or bluetongue, competent vectors must already be present. In the Americas these were various *Aedes* spp., vectors of yellow fever and *Culex* spp., vectors of WNV. In Italy, the accidental introduction of the bluetongue vector *Culicoides* imicola from North Africa preceded the arrival of bluetongue virus. However, indigenous *Culicoides* spp. have since also been found to be competent for the virus, allowing virus circulation in the absence of an exotic vector species (De Liberato et al. 2005, Savini et al. 2005).

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Since the first description of the H5N1 virus in S.E. Asia, this virus has made numerous incursions into Europe and North Africa (see distribution map H5N1, CDC site) and continues to be considered a serious health risk, due to its highly virulent nature. Here, dispersal of the virus appears to follow natural pathways, being transported by migratory birds.

The recent jump of African swine fever to the Russian Federation, and the rapid global spread of avian influenza show that a thorough understanding of the movement of vectors, parasites and infected hosts is required in order to understand global changes in the distribution of diseases.

Loss of biodiversity

Global changes in biodiversity as a consequence of human impact can also affect disease risk. Each species is host to a wide variety of parasites, so areas with a higher species richness (such as around the tropics) often hold more parasites (Keesing et al. 2010), or have a higher risk of emerging diseases (Jones et al. 2008). For example, 60.3% of all emerging diseases come from animal populations (Jones et al. 2008). Human impact that leads to a lower species richness, through the local extinction of species, or a lower abundance of a particular species, can therefore lead to a lower parasite richness. However this lower species richness may also increase the risk of infection for humans (Ostfeld and Keesing 2000).

The supposed buffering effect of species diversity on disease prevalence suggests a lower disease risk in areas with a higher species richness, the so-called dilution effect (Ostfeld and Keesing 2012). A potential reduction in disease risk in species-rich systems is an important ecosystem service. The dilution effect has been reported for a wide variety of diseases and hosts, for animal and plant parasites, and is based on the differences in the susceptibility of a species to a particular parasite. Human impacts that reduce species richness do not affect the different host species equally. Species that are vulnerable, such as larger species, or slowly-reproducing species, are often species that are not competent hosts, because they tend to invest in immunological responses and are well-defended; on the other hand, species that tolerate human disturbance, such as small rodent species, are often competent hosts (Huang et al. 2013). Therefore human-induced shifts in the community composition towards assemblages that hold fewer species and more competent hosts, can increasing the disease risk for e.g., hanta viruses (Suzán et al. 2009), Lyme (Schmidt and Ostfeld 2001), West Nile virus (Swaddle and Calos 2008), *Batrachochytrium dendrobatis* (Bd; (Venesky et al. 2014) and bovine tuberculosis. Hence, land use changes such as landscape fragmentation, pollution, species extinction, or other anthropogenic impacts can trigger cascading effects that change the disease risk of people, animals and plants. It is plausible that measurable economic benefits can be derived from biodiversity through its effect on disease risk (Bonds et al. 2012).

Waste management

The management of human and animal waste has become a growing concern due to their rapid increase in volume and the high costs incurred for safe and adequate waste disposal. In less developed countries, waste disposal is often not well organized, leaving thousands of people to earn a living by sifting through waste dumps, in search of food or saleable items. Human and animal waste constitutes a health risk because of the rich assemblage of micro-organisms that may thrive on the organic contents of the waste. For example, more than 150 bacteria may be prevalent in waste dumps, and are the cause of dysentery or other diarrheal disease (Gerba and Smith 2005). Disease-carrying rodents are commonly present in these habitats as well, contributing to additional health risks for those frequenting them (Hamer 2003).

Health and other socio-economic changes

The health effects of global change will vary between countries. Adverse health effects of infectious diseases or environmental/climate changes are much more likely in low-income countries and vulnerable subpopulations. Health risks are commonly associated with poverty, such as low body weight, unsafe water, and poor sanitation and hygiene. Reports on infectious diseases show that poverty and inequality create conditions for the transmission of infectious diseases. Poverty contributes to differential exposure and susceptibility to infectious disease, as well as access to care and treatment once exposure occurs (Quinn and Kumar 2014). Clearly, social class affects people's level of exposure to health-damaging factors and their ability to cope. These disparities may well increase in the coming decades, not only because of regional differences, but also because of exacerbations of differentials in economic conditions, levels of social and human capital, political power, and local environmental dependency (McMichael et al. 2008). Good health enables people to participate in education, on the labor market and in society in general, with potentially positive consequences for the economic performance of countries (Marmot and Commision on Social Determinants of Health 2007).

Although not all governments perceive inequalities in wealth and health to be something the public sector can or should address, all governments are interested in improving economic growth. The evidence base to support the wealth-creating potential of improved health is far less substantial than the evidence relating poor health to poverty. Put differently, the causal links between poverty and health run in both directions and poverty eradication is a prerequisite to global health (Leon et al. 2001).

Nutrition and Health

Since the end of the last century, awareness has been growing of the intricate links between health and diet. The effects of caloric, protein, vitamin and mineral insufficiencies were long known under conditions of scarcity; kwashiorkor and overall stunting and wasting, as well as major deficiencies, were all documented early in the last century. Poverty leads to under-nutrition and disease, famine even more so.

Food insufficiency is rarely simply related to environmental stress such as drought, but generally triggered by natural disasters and displacement of populations during civil war. The latter may be caused in turn by ecological stress. While under-nutrition still is an issue for about 11% of the world population, and mineral and vitamin deficiencies for double that number, we increasingly see the emergency of patterns of abundant high calorie nutrition, even in the poorest countries. The complex effects of diets in middle and affluent classes are only being gradually understood. Globalization, urbanization and large-scale food production have led to an unprecedented access to relatively cheap food that is abundantly available at nearly every street corner. In combination with the decline of manual labor and advent of motorized transportation, this has favored unbalanced diets with high intakes of fatty acids, sugar and salt. Nearly without exception, the middle classes now tend to live in obesogenic environments that promote the imbalance between energy intake and expenditure. Urban environments without green zones, safe walking spaces and sport facilities on the one hand and fast food outlets on the other are both a symptom and a cause of drastic changes in living conditions.

Notwithstanding the lengthy intercontinental food chains, on average food has become safer in terms of pathogen loads and contamination with heavy metals or chemical residues, because of the enforcement of strict international food safety and hygiene standards and fraud control. Nevertheless, in poorer countries industrial water and air pollution, the quality of slaughterhouses and irrigation leave much to be desired and food adulteration is a recurrent phenomenon. Small-scale food production in urban slums continues to be a source of serious disease risk. The rapidly rising demand for animal proteins has led to pressure being placed on natural ecosystems through feed production and fish and shellfish farming, increased zoonotic risks, the use of excess antibiotics and bio-chemicals and pathogen infections from slurry. Agricultural and food storage systems, while contributing to food abundance and lower prices that benefit the urban poor, are in themselves a source of multiple health risks.

Energy and micronutrient deficiencies and risks to infectious diseases are still dominant in emerging economies, and excess energy nutrition together with deficiencies in hard-to-reach groups and the elderly prevail in affluent and ageing societies. Emerging economies are often confronted with increasing socioeconomic and urban/rural differences in food patterns, resulting in simultaneous under-nutrition and over-nutrition, and differently affecting the burden of infectious and chronic diseases. Increasingly, preventing the adverse effects of macronutrients (e.g., saturated fat, sugar) and micronutrients (e.g., vitamin A, folic acid), as well as high saturated fats, salt and sugar apply to the full age range of populations. Reduction to acceptable levels is expected to reduce the global burden of disease by reducing atherosclerosis, CVD, blood pressure, CVA, obesity and diabetes (Yach et al. 2004). Excess weight is an indicator of an imbalanced diet or – when the life expectancy of populations starts to increase -- as a risk factor for subsequent development of diabetes, CVD, and cancer as well as functional impairments. It has been estimated that up to 30-40% of chronic diseases can be prevented (or postponed) by a supply of high-quality foods. Ultimately, food consumption is an individual act, but the freedom of choice is restricted through lack of knowledge, individual purchasing power and accessibility.

The Global One Health approach

Infectious and non-communicable diseases continue to pose a huge burden on societies worldwide. Until recently, disease prevention and control were usually organized from a single disease perspective, through hygienic measures such as installation of tap water and sewage collection, as well as by the provision of drugs, vaccines or insect control (in the case of a vector-borne disease). Better nutrition promoted significant gains in general health and disease resistance. In many countries, these measures led to significant improvements in health, but were followed by the emergence of non-communicable diseases, requiring a new approach to public health. Elsewhere, however, infectious disease is still highly prevalent, while here too, non-communicable diseases are on the rise. Past experience proves that it is not enough to deal with single issues for single diseases but it is better to use a systems approach, in which complex systems are studied within various disciplines at various scales. In our Global One Health approach, the cause of poor health is not only considered from a bio-medical angle, but also in connection with the natural environment and the anthropogenic influences upon it.

DEFINITION OF GLOBAL ONE HEALTH (GOH)

Global one health is the combined effort of multiple disciplines to improve the health of humans, animals and plants within sustainable ecosystems at global level by using an integrated systems approach to come to transnational and global policy, research and practices.

Many determinants of Global One Health are shaped by the diversity of animal and plant species of the world's ecosystems. For example, evolutionary processes have led to a rich diversity of animal and plant species, including pathogenic micro-organisms. Climate and geography affect the growth of species by providing abiotic and biotic conditions in which species can thrive. Anthropogenic activities have led to the selection and cultivation of food crops, which in turn provide nutrients for humans, and have led to economic diversification of human societies, including food-borne diseases. Health, as shaped by a safe and secure food supply, suitable climate and stable economy, is often compromised by the emergence of pathogenic organisms, which can affect food security (outbreaks of plant and animal diseases), as well as the stability of human societies (deaths caused by virulent pathogens). The many determinants that affect Global One Health thus interact dynamically: the temporal imbalance of one factor can trigger a cascade of effects that lead to highly undesirable, often insufferable, health situations at local, regional and even continental scale (Figure 1). A thorough understanding of the factors that contribute to Global One Health is therefore essential so that adequate and effective policies can be devised, aimed at the prevention of health imbalances and leading to a safer, healthier world.

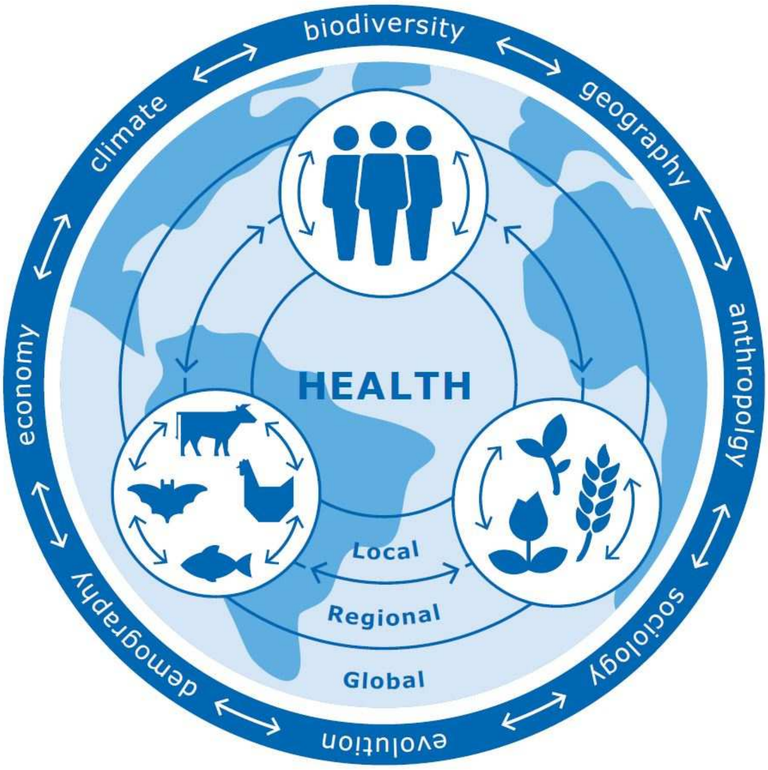

Figure 1 – Determinants of Global One Health and their interactions

Natural, agricultural and social ecosystems

Ecosystems, defined as the community of living organisms (plants, animals and microbes) interacting with the non-living components of their environment (air, water and mineral soil) are controlled both by external factors of which climate is the most important, and internal factors (Schulze and Mooney 1994). Energy from the sun enters ecosystems through photosynthesis. Other external factors include time and potential living organisms. The different components of an ecosystem are linked together through nutrient cycles and the energy flows within networks of interactions among organisms, and between organisms and their environment. Living organisms such as animals play an important role in the movement of matter and energy: Animals may feed on plants and influence the quantity of microbial biomass and the circulation of microorganisms. Whereas resource inputs are generally controlled by external processes of the ecosystem such as climate, internal factors such as decomposition, species competition or shading influence the availability of resources within the ecosystem. Humans are part of the ecosystem in which they live, but their combined influence is large enough to modify external factors such as climate.

Humans may modify ecosystems for their own benefit: terrestrial (farms, pastures, gardens and urbanized areas) or aquatic (fish tanks, dams, and man-made ponds). Demographic pressure and rising income lead to greater demands on agriculture, animal husbandry, land use and wildlife, affecting the interactions between humans and animals, plants and other organisms in the ecosystem (Tylianakis et al. 2008). Mitigations within one smaller (artificial) ecosystem may influence a larger ecosystem. For example, inactivation of microorganisms in organic waste to reduce human exposure to pathogens may influence composting. The widespread use of antibiotics in animal husbandry may lead to microbial resistance against common antibiotics, causing severe risks to human health (Pruden et al. 2013). However, to study antibiotic resistance microbes (ARM), we need to look at all sources of ARM and all the ways microbes are exposed to antibiotics, e.g., also the natural occurrence of ARM in natural soil microbiota and the use of antibiotics in plant disease control (Kumar et al. 2005). The Global One Health approach aims to understand these interactions in a coherent way, taking into account the many different relationships within and between ecosystems, anticipating the development of interventions for overall health improvement.

Such an ecosystems approach is increasingly relevant in social health research. Social ecology is a framework for understanding the dynamic interrelations among a variety of human and environmental factors, highlighting the multidimensional structure of human environments in terms of their physical, social and cultural components at different levels, from individual to large communities (McLaren and Hawe 2005, Stokols et al. 2013). The essential role of cognitive and behavioral aspects of human-ecosystem interactions in managing health and disease prevention has been understood only recently (Ross 2013).

Systems approach

Quantification of all these variables in real systems and comparing these to the values calculated using the relationships with known starting conditions through modeling is now a common approach, and can help to identify additional variables that need to be tracked in order to answer the management questions. The advantage of this approach is that systems can be studied at different levels of integration, such as molecular, cell, tissue, organs, individuals, populations, up to ecosystems. The current paradigm is that to understand management questions at one level, measurements and information on the previous, underlying level is necessary. With a systems approach it is always possible for key questions to go even deeper into the underlying mechanisms: for growth of crops, for example, one can study the mechanisms regulating the opening and closing of stomata.

This systems approach is now also increasingly used for managing infectious diseases in animals (Savill et al. 2007, Brooks-Pollock and Keeling 2009), humans (Anderson et al. 2004, Riley and Ferguson 2006) and plants (Cook 2000). In the case of plants, particular attention is given to the development of strategies that prolong the effectiveness of protective or curative agents against pathogens, such as fungicides, by avoiding resistance development in pathogens (e.g., van den Bosch et al. 2014a, van den Bosch et al. 2014b) or to strategies extending the useful life of plant resistance genes against pests and diseases, for instance by breeding plants with multiple resistance genes (“stacks”) or by spatial deployment at a landscape scale (Bates et al. 2005). Due to the integrative nature of systems approaches and modeling, they can help address complex multi-faceted One Health questions. The impact of proposed control measures can for example be tested under controlled conditions and evaluated when used in the field. For infectious diseases, it is important to look not only what happens with the individual who receives curative or preventive treatment, but also to non-treated conspecifics and other species in the ecosystem. The most obvious example of unintended side-effects is the use of antibiotics and the development and dissemination of antibiotic-resistant microorganisms (ARMs). Whereas for an individual patient (animal of human) it can be worthwhile to try antibiotic treatment as it can help that patient, it may be disadvantageous for public health to use a treatment that is not effective as this may lead to more ARMs. When used in production animals, antibiotics may lead to ARMs in the food chain and in the case of a hospital patient, they may lead to dissemination of the ARMs in hospital wards.

In agricultural economics, system approaches are used to model environmental issues and manage infectious (see above) and non-infectious diseases. For example, poverty may lead to undernourishment, which may be aggravated by infections which in turn also are more likely to occur under impoverished conditions and when individuals are not adequately nourished. This results in lower educational enrolment and lower productivity on the labor market on the short term, resulting in long-term poverty, which is often handed over across generations. Because of these complicated interactions, changing one element in the system may not have the desired effects. Another example is the use of impregnated bed nets and drugs (or vaccination) in malaria to impede parasite transmission, but in a population of undernourished people the impact of that intervention may be different from the impact it had on a division of American soldiers on which the intervention was tested originally. Alternatively, trying to improve the nutritional status of a group of people may have a different impact when malnutrition is prevalent.

The Global One Health approach for infectious diseases

Infectious diseases in biological systems are dynamic: new infectious diseases will appear (e.g., HIV, Schmallenberg Virus) as all biological systems are prone to parazitation by infectious agents. Thus even if biological systems initially do not carry infectious agents, parasites can appear to utilize these systems, e.g., bacteria living in the respirator used in the operating room, HIV among sexually active humans, pathogenic *E.coli* (EHEC/EAEC) in fenugreek sprouts, BSE in cattle feed during recycling of animal waste, or white spot syndrome virus in shrimp aquaculture. Any of these new combinations of infectious agent and biological system can be seen as an emerging disease. Often these emerging pathogens lead to further problems in the onward contacts of the newly parasitized system. BSE in cattle has led to human cases with the same causative agent (then called vCJD). The emergence of the H5N1 influenza strain in poultry that became highly pathogenic in poultry has also led to a number of human cases.

Infectious diseases are also dynamic because infectious agents that are controlled, or mitigated, by interventions will develop a way to escape that control measure. We already mentioned antibiotic resistance, but the same applies to any control measure, such as in the case of vaccine escape, when new variants emerge that are no longer controlled by the vaccine applied in that population. The vaccine for whooping cough, caused by the bacteria *Bordetella pertussis*, has become less effective and fails to protect against the disease (de Melker et al. 2000). This escape from control applies to all control measures, including hygienic and biosecurity measures. From disease control in production animals it is known for example that classical swine fever virus strains will become less virulent over the course of an epidemic because control is based on finding and slaughtering all diseased animals.

Given the dynamic nature of infectious agents, it is clear that our fight against them is an example of the Red Queen effect well known from evolutionary biology: we continuously have to develop new management methods and tools only to maintain the same health status. Every improvement, e.g., antibiotic drug or a new production system, is met with changes in the pathogen that cancel out the improvement. For example, this Red Queen race has been very well documented in plant disease management using breeding for resistance (Clay and Kover 1996, Bergelson et al. 2001). However, understanding these evolutionary processes has led to methods of slowing down the Red Queen race, for example in plant breeding by introducing more than one resistance gene, or gene stacking. Similarly, in fighting HIV a new combination therapy (called HAART) has been successful in postponing treatment failure (Finzi et al. 1997, Egger et al. 2002). The control of infectious diseases can be done in two ways. One approach is mitigation, in which preventing the clinical consequences of the infection (for the individual or the population), is the target. In that case, the infection keeps occurring in the population, usually (but not necessarily) at a lower rate. The alternative is eradication, in which at some geographical scale, transmission of the infection is stopped sufficiently so that the infectious agent disappears from that geographical unit, e.g., a hospital, a farm, or a country. Mitigation is often the first strategy, and only when the impact of the infectious disease is high and eradication seems possible is it attempted. For example ARMs are a serious problem for hospitals, especially in intensive care units; however, eradication from hospitals may be very difficult and in some countries some ARMs may be accepted as too difficult to eradicate, e.g., VRE in North America (Bonten et al. 1996). In animal husbandry, eradication of certain (zoonotic) infections may be very desirable but again in some regions and for some microorganisms this seems too difficult to achieve, e.g., *Mycobacterium bovis* in parts of the UK, Republic of Ireland, and New Zealand (Roberts 1996). On the other hand viruses such as smallpox and rinderpest have been eradicated.

Trying to reduce the clinical disease symptoms of a particular infection is often the first approach that is used and this can be sufficient when the infection does not have serious consequences. As we are dealing with infectious diseases, it follows that the decision made on behalf of or by a single patient can have consequences for others. If the patient is an animal, this can also have consequences across species. For example, if eradication of *M. bovis* fails in one infected animal, all infected cattle have to be detected and culled to prevent infection of humans. Mitigation can be done by diagnosing infected animals or humans and treating them with antibiotics or antivirals. It can also be done by preventive treatments with antibiotics, vaccination, or hygiene measures. For example, patients can receive preventive treatment when they undergo surgery or in the case of animals when they are moved from one farm to another. Also some vaccines applied to a whole population (e.g., against *Bordetella pertussis* in humans) or to particular risk groups are only used to prevent clinical symptoms. When vaccination is only applied to a small risk group, the effect on transmission of the infectious agent will be limited due to incomplete vaccination coverage even when such a vaccine could prevent transmission. For example the vaccination of groups at risk for human influenza is not sufficient to stop transmission. There have been attempts to also motivate health care workers to get influenza vaccinations in order to prevent transmission to vulnerable patients that do not respond well to vaccination (Carman et al. 2000). Moreover, there are vaccines both in veterinary and human medicine that even with complete vaccination coverage would not stop transmission, e.g., against whooping cough and the inactivated polio vaccine in humans, PRRSV vaccines in pigs, and coccidiosis vaccines in poultry.

Mitigation is an important control strategy because it can be a way to assure peaceful coexistence of host and pathogens. Especially in plant disease control this seems to be the current opinion, and resistant plants or insecticide applications are nowadays often used on parts of the fields only. In that way, non-resistant parasitic organisms can also survive. In addition, mitigation may be cheaper than eradication because eradication requires stringent application of all control measures by all actors (for example also by backyard farmers or in highly remote areas). Finally if all countries apply the same mitigation strategy for the selected infectious disease, there are no trade consequences. An important disadvantage of this mitigation strategy, however, can be that not everyone has equal access to health care when becoming infected: e.g. *Mycobacterium tuberculosis* in homeless people, rabies in rural areas in Africa, HIV for the poor, or cholera among displaced persons. Thus as a consequence, the less privileged may suffer more when applying a mitigation strategy.

Eradication at some scale has always played an important role in control of infectious diseases. In public health, there have always been attempts to separate infected people from the general population (e.g., leper colonies in the Middle Ages) and thus obtain a population free of the infectious disease. In the case of SARS, this biosecurity strategy worked to eradicate the infection (Podder et al. 2007). Similar measures were enacted to mitigate and stop the exceptionally large outbreak of Ebola in West-Africa.

For many veterinary and plant disease problems the eradication strategy is an important option in fighting diseases. The motivation behind the establishment of a veterinary science has been the possibility to use veterinary inspection and surveillance to obtain and maintain freedom from certain infectious diseases (e.g., rinderpest). The goals are then to maintain animal (and often human) health, maintain production levels and reduce costs for disease mitigation. Also these infectious diseases play an important role in international trade. Trade restrictions can be imposed on other countries when human, animal or plant health is at stake. Thus evading trade barriers, or raising trade barriers for others, can be also reasons to eradicate a particular infectious disease. Although creating trade barriers for other countries after eradication is a legitimate use of the WTO agreements, they may also be misused when for example concerns about the risks of vaccinated animals or insects in horticulture products are considered to be exaggerated by some.

On a global scale, eradication of infectious diseases is a goal of international organizations, such as the WHO for human medicine, the FAO and OIE for veterinary medicine and the FAO for plant diseases. In the human field, global eradication of smallpox is the landmark achievement and, depending on one’s definition of a successful eradication, SARS can also be added to that list. The WHO has as goal to also eradicate polio and measles, and especially the number of polio-endemic countries have been reduced dramatically. In the veterinary field the landmark achievement is the global eradication of rinderpest. The FAO has formulated the full control of foot and mouth disease (FMDV) as their target.

Clearly, eradication is often attempted when mitigation is not (yet) possible (for example in the case of Ebola) and without effective mitigation the consequences of the disease are too high to be acceptable. In animals almost all viral diseases cannot be treated or mitigated in another way and thus eradication is often the strategy of choice. Eradication in a certain region also has the advantage that treatment is not needed and thus problems with resistance cannot occur (e.g., *Salmonella* enteritidis in poultry).

Disadvantages can be the high costs (both economic and in animal welfare) for eradication and for measures to prevent reintroduction of the disease into a geographical area or population. This can especially be the case when there are wildlife reservoirs. For example *Mycobacterium bovis* is a bacterial infection of cattle that has a very wide and diverse host range. In several places in the world it is difficult to keep cattle free of this infection because of its prevalence in wildlife (Gortazar et al. 2012). In New Zealand the wildlife host is the common brushtail possum (*Trichosurus vulpecula*) and in Ireland and United Kingdom the main wildlife host seems to be the badger (*Meles meles*).

Prevention can be undertaken both with a mitigation and with a (local) eradication strategy and is generally the preferred approach. Prevention as part of the mitigation strategy attempts to lower the chances of becoming diseased in a population not free of the pathogen by reducing transmission and increasing disease resistance. Prevention as part of the eradication strategy attempts to lower the introduction rate into free areas by hygiene and biosecurity measures. Prevention can benefit greatly from better understanding how the pathogen is transmitted.

The Global One Health approach for Non-Communicable Diseases (NCDs)

Tobacco, alcohol, foods and dietary nutrients have been established as major lifestyle-related risk factors for NCDs. The behavior governing addictive behavior such as smoking and drinking is largely determined by social class, education and the structure of the agricultural and food supply-chain. The latter is directly related to chemical and microbial food safety. Thus social determinants influence both infectious diseases as well as NCDs. Recent reports indicate that disease profiles have changed in the past decades, shifting from infectious to non-communicable diseases (WHO 2014a). This shift occurs in both rich and poor countries and in all segments of society. It is estimated by the World Health Organization that non-communicable diseases currently account for approximately 60% of the global disease burden and trends indicate they will become even more important over the next decades (Behrman et al. 2009). For the onset and maintenance of many infectious and non-communicable diseases and conditions (e.g., diabetes, cardio-vascular diseases, and malignancies), malnutrition is an important risk factor - i.e., both as under-nutrition, hidden hunger, and obesity. Obesity and the obesogenic societal environment is also clearly linked to infectious and chronic disease, leading for instance to impaired immune functions (Karlsson and Beck 2010). Thus, there is a need to confront disparities in health and nutrition simultaneously.

The global supply of foods and drinks and the production of tobacco has had an enormous impact on lifestyle. The prevalence of obesity and associated NCDs points to the imbalance in energy needs and physical activity. These imbalances are in part due to the obesogenic environment, with numerous food outlets and few incentives for physical activity, which is enabled by highly efficient agricultural and industrial production and transportation, coupled with urbanization. Modern crop and animal production practices based on fossil fuels, fertilizer and feed play a large role in anthropogenic emissions of greenhouse gases. At the same time, agriculture and food production also contribute to alternative energy sources such as biofuels, the use of sludge and the retrieval of nutrients from waste. Despite these complex and recursive causal interactions, and despite the fact that history tells us that agricultural and health care systems shape people′s lifestyles, scientific research has tended to focus on smaller sub-systems, e.g., at the molecular, individual and population level rather than the study of factors and actors in the social and built-up environment. Although lower integration levels are important for the biological underpinning of causal subsystems, the prevention of NCDs requires that the complex interaction between the molecular, individual, population, and societal levels of causation also be taken into account. We must deal with the recursive interactions between the agricultural and food production with food supply and energy needs, food safety, food choice and nutrient composition, and eventually functional and physiological implications for a healthy life.

The Global One Health approach for food supply, food security and food safety

Food supply and food security are related to both infectious diseases as well as NCDs, directly through human health and indirectly through the risks associated with food production and supply. In developing economies, local and sudden or seasonal shocks in food supply and purchasing power affect child growth, risk of infectious diseases (e.g., malaria, measles) and child mortality; in affluent countries this aspect of child nutrition is largely overcome and replaced by lack of physical activity and increasing trends towards obesity. Malnutrition of pregnant women leads to low birth weight in developing countries, but gestational diabetes is dominant in westernized societies. At the same time, elderly people in affluent countries may suffer from micronutrient and protein insufficiency, whereas major parts of the population may suffer from excess weight associated with increased risk of infections from both food and seasonal mortality patterns because of the flu or food-borne pathogens, more prevalent in summer. Apart from the biological explanations related to body composition, reproduction and the immune system, these phenomena can also be understood by factors such as technology development, markets and economic development related to urbanization. Preventive approaches that focus on the biology tend to neglect the societal factors.

Indirect risks in global and local food chains of production, transport and retail involve effects on ecosystems and vectors, e.g., irrigation, waste management, as well as pathogens in the food chain. As food security quality and diversity improve, risks may be reduced through better monitoring, but new risks can be introduced, such as antibiotic resistance and vCJD.

Securing food production impacts sustainability. Apart from health implications and economic benefits, the environmental footprint of producing our daily food for the present and future generations must be considered. Aside from using crude metrics for sustainability (e.g., land use, GHG-emissions, biodiversity, fair trade, etc), current research on healthy and sustainable diets does not account for the huge diversity in supply of products in affluent societies or the different food and nutrient profiles within and between societal subgroups within these populations. Reducing losses occurring throughout the food chain through waste, predators, pathogens and inadequate storage as well as consumer carelessness in developed societies will increase sustainability and reduce direct and indirect health risks.

Evidence is accumulating that only part of the health effects of diet can be explained by their nutrient content. Food preparation and industrial production of refined foods from raw agricultural commodities affects the characteristics of the food matrix (e.g., chewing versus drinkable foods, as related to satiation). Availability of nutrients may depend on the food matrix and nutrients simultaneously provided by certain foods (e.g., within meals) may contribute to physiologic interactions and variations in health effects. Increased attention for foods rather than nutrients could help to overcome sometimes conflicting implications for sustainable food production versus nutritional health.

Like prevention of infectious diseases, prevention of chronic diseases is based on the multifactorial etiology of diseases. Although the external exposures (e.g., viruses, nutrients) and societal conditions (e.g., development, wealth) vary hugely on the global scale, host factors within the human system are similar for the human species all over the world. Depending on disease etiology and the prevalence of component causes, the host factors relevant to infectious diseases (acute inflammatory response and immunity) as well as longevity (subclinical inflammation as related to obesity and chronic disease) will need to be tailored to optimal host resistance given the socioeconomic stage of development of the population considered.

Social, cultural, and economic determinants of Global One Health

Global One Health challenges cannot be separated from peoples' social, cultural and economic conditions. Such conditions relate to the complex, integrated, and overlapping social structures and economic systems which influence the health status of populations (WHO 2008). They include socio-economic status and educational level, among other things. Cultural factors, such as race, ethnicity, family systems, and religion, also strongly impact health disparities, particularly gender-specific norms and practices. Cultural norms and practices about the distribution of food, care giving practices and (in)formal health care within households, which are anchored in gender and family stems, vary across ethnic, religious and socioeconomic groups (Gupta 1999, Therborn 2004). In some Indian regions, for instance, the custom of preference for male descendants means that mortality rates of female infants are higher than those of male infants and that girls have a higher prevalence of nutritional status deficiencies, such as being stunted, than boys (Fledderjohann et al. 2014). Health gaps caused by differences in people's social, cultural, and economic conditions are, despite overall progress in global well-being over the last century, persisting and even widening, both in high- and low-income societies (Marmot and Commision on Social Determinants of Health 2007, WHO 2013).

Reports on infectious diseases show that poverty and inequality create fertile conditions for the transmission of infectious diseases. Socio-economic, cultural, and gender disparities are related to differential exposure and susceptibility to infectious disease, disparities in vaccine uptake rates, and differential access to care and treatment once exposure occurs (Quinn and Kumar 2014). In addition this also has indirect effects, as poor people are part of a community of poor people, they have higher risks of getting infected even if they would have the same susceptibility as somebody that has contact with another community.

To make this more specific, a young girl from a poor neighborhood having unprotected sex has a higher chance of contracting a SOA than a similar girl in a richer neighborhood. But social, economic and cultural determinants do not only influence infectious diseases. Also the burden of non-communicable disease, especially cardio-vascular diseases, obesity, diabetes, cancer and chronic pulmonary disease which are traditionally associated with high income countries, is increasingly spreading to middle- and low income countries. Obesity is clearly linked to both infectious and chronic disease, leading for instance to impaired immune functions (Karlsson and Beck 2010). In fact, middle- and low income countries now face a double burden; a combination of communicable and non-communicable diseases. For many infectious and chronic diseases and conditions, malnutrition- i.e., undernutrition, hidden hunger, and obesity - is an important risk factor, both in terms of onset and maintenance of diseases.

Also in animal health, socio-economic circumstances predetermine for a large part the animal health status, within systems as well as between systems. In many developing countries, relatively easy-to-eradicate diseases are still endemic (WAHID 2015, www.oie.int). Reasons for this situation lie both in a lack of resources (economics) as well as weak governmental organizations.

Evidently, the place that people occupy in the social hierarchy affects their level of exposure to malnutrition and health-damaging factors, their ability to cope with them, and their access to adequate health care. To effectively deal with Global One Health challenges it is necessary to integrate social, cultural, and economic determinants of health. Health inequalities do not remain stable over time. Economic and technological developments, social and demographic transformations, climate change, epidemics such as the Ebola crisis, and wars and political conflicts, have an impact on people's health and nutrition security and on the inequalities therein. Important changes also occur during people′s lifetimes, as they age and develop. Morbidity and years of lost life due to premature mortality arise from conditions under which people are born, grow up, live, work, and age, which change throughout their lives (Gortmaker et al. 2011, Bras 2015). Human development and aging, whether biological, physiological, psychological, or social, are lifelong processes. For example, it has now become increasingly recognized that a child's nutritional status during the first 1,000 days of life set the stage for much of its health, cognitive, and social development in adolescence, adulthood, and old age (Eggersdorfer et al. 2013, UNICEF 2013, Hardgrove et al. 2014, Lawn et al. 2014).. While childhood may be the most crucial developmental stage, substantial social changes occur throughout one's life, in health and nutritional status, but also in education, work, and social relationships. Historical and social changes may cause variations during the course of life through so-called cohort effects. Men and women who were prenatally exposed to famine during the Dutch Hunger Winter of 1945, the last year of World War II, for instance, have been found to have higher chances of obesity at age 50 than those born before or after the famine (Ravelli et al. 1999). On the other hand, the influence of time may be uniform across age groups. Technological advances, such as the introduction of a new vaccine for malaria, for instance, have the same implications for everyone in the population regardless of people's birth year. Lifetime behavior takes place in specific contexts that differ in culture, socio-economic circumstances, and social institutions. There are obvious differences in health risks of those born in a western society or in China. But within Chinese society, rural and urban settings are very different in the resources and restrictions to which people adapt their behaviors. Cultural contexts, and their norms, values, and practices, regulate the course of life and cause particular inequalities.

Global One Health challenges are driven by complex forces which require a systems approach, taking all levels, and their linkages, across historical time and lifetime into account. We cannot rely on veterinary, clinical, technical or behavioral interventions only; interventions addressing the social, cultural and institutional context are needed as well. This includes both disciplinary and interdisciplinary knowledge and action (Koelen et al. 2008). The aims of such an approach are to look at the most efficient distribution of scarce resources to obtain the health goals either by a cost-minimization approach when health goals are set or by a cost-effectivity approach when the amount of resources are given (the hard approach). Moreover, soft approaches to improve the intentions of people to implement and sustain preferred actions should be taken into account and should be combined with the hard approach. Systems to predict the combined effect of hard and soft approaches to improve animal and/or human health are not yet available.

Although not all governments perceive inequalities in wealth and health to be something the public sector can or should address, most governments are interested in improving economic growth. The causal links between poverty and health clearly run in both directions (Leon et al. 2001). Economic development may increase health status, but good health also enables people to be educated, be active on the labor market, and participate in society. Better health contributes to increased well-being, social cohesion, environmental protection, increased productivity and economic development. Hence, addressing the social, cultural and economic determinants of health will yield greater, and more sustainable, returns to existing efforts to tackle Global One Health challenges.

Applying the Global One Health approach

Revisiting the earlier examples, we can now add new policy and research dimensions based on the global one health approach.

Influenza A H5N1

Whereas vaccination under controlled circumstances stops transmission (net reproductive number R_0<1) even when the match between vaccine and circulating virus is poor (van der Goot et al. 2008, Poetri et al. 2009), transmission occurs in spite of vaccination in the field if the titers after vaccination are very low. Although the strains in the field do change due to vaccination, that change is not the reason for the vaccine failure (Sitaras et al. 2014). The possibilities for eradication or mitigation in humans if the H5N1 strain would start transmitting among humans (R>1) have also been studied (e.g., Ferguson et al. 2005).The success of control of H5N1 on a local level is also dependent on political and cultural issues. A vaccination strategy to control an AI outbreak will only be effective if sufficient vaccination coverage and a certain level of protective immunity is reached in a relatively short time interval. In practice, this will require the availability of approved high-quality vaccines as well as effective action from producers, traders and the authorities. Moreover, contacts of the public with poultry would have to be reduced significantly. To achieve that, live poultry markets would have to be abolished and household slaughtering of poultry should be discouraged.

Not only HPAI H5N1 is a threat for the poultry industry and public health. Over the last 15 years, Europe has experienced several HPAI outbreaks of other AI subtypes. The outbreaks in Italy in 1999-2000 and The Netherlands in 2003 confirmed that H5 and H7 subtype viruses can increase in pathogenicity and to be prepared for such a threat, a new European control directive was drafted (2005/94/EU). In this new draft, outbreaks of LPAI of subtypes H5 and H7 were included as notifiable. European Member states are obliged to conduct surveillance programs according to the design laid down in the guideline 2010/367/EU. The active serological surveillance complements surveillance aimed at the early detection of notifiable AI. The surveillance can be risk based or based on representative sampling. Concerning risk, this can be based on the location of holdings or the type of holdings (e.g., free-ranging farms). Serum samples have to be tested for the presence of antibodies against H5 and H7 only as a minimum requirement. Since the AI control directive came in place, member states are obliged to report outbreaks of AI as defined in the new directive, to the EU commissions that record them in the Animal Disease Notification System. In total almost 300 LPAI and more than 400 HPAI outbreaks have been reported. Most outbreaks occurred in Italy, Germany and the Netherlands. The relative high number of LPAI outbreaks is explained rather by higher intensity of surveillance (The Netherlands) and secondary spread (Germany and Italy).

On a global level, various factors such as the spatial structure of outbreak patterns (Si et al. 2009, Tian et al. 2015), and the role of host species ecology and impact of environmental variables on infection risk (Si et al. 2013) make that global control of the disease is difficult. Hence, large scale (i.e., international), multidisciplinary and integrated approaches are required to be able to better understand and predict the spatial distribution of the disease, once confirmed cases have been reported. Not only is the host density important in this respect but also (international) movements of migratory birds, for example. Avian influenza could possibly be considered as one of the major candidates for a future pandemic.

Malaria

Fighting malaria, even locally, is a large and complicated struggle. It has to involve not only curative and preventive treatment in human populations, but also small and large scale vector control operations. In addition, agricultural practices need much attention, not only for the improvement of food production and food supply but also regarding land use and water management. Sir Ronald Ross received the Nobel Prize in 1902 for showing that the infection is transmitted by mosquitoes and he also started studying the mosquito and human host populations as a system (Ross 1930). This has led to mathematical model(s) that allow the calculation of whether or not malaria can persist in certain areas by quantifying characteristics of the host and vector populations (Smith et al. 2012). With this set of methods based on a systems approach, further studies can be carried out to evaluate various control measures. A single bullet approach is unlikely to be effective, and a multidisciplinary, trans-boundary approach is required, so that the chances for the emergence of drug-resistant or immunologically different strains are reduced. However more issues have to be included in these models, for example the fact that the parameters for the host may depend very much on whether or not the host is sufficiently nourished. In the Global One Health approach, the reciprocal relationship between malaria, iron status, undernourishment and labor should be addressed in close conjunction to reduce negative consequences of addressing this double-edged sword.

Food-borne toxins: Escherichia coli O104:H4

Tracking and tracing of food-borne agents to quickly identify sources of infection is very important. This also helps to stop media-driven hypes. To prevent Shiga toxin exposure within households, hygienic measurements such as hand washing and thorough cooking of foods are the most important tools. In addition, testing of animal and plant produce for *E.coli* bacteria and toxins, respectively, is recommended. Extra attention should be paid to infants and young children because they are considered to be more susceptible to toxins than adults due to their relatively lower body weight, higher metabolic rate and lower detoxification capacity. Elderly and immuno-compromised people may need extra attention as well. Sprout producers may find that testing seeds for pathogens is advantageous. After the outbreak in 2011, new European regulations were implemented (209/2013 (CEC 2013)). Although a negative result does not guarantee the absence of pathogens, a positive result would allow a producer to avoid using seed lots that have been shown to contain pathogens. As the seed used for sprouting appears to be a primary source of pathogenic bacteria causing sprout-associated illnesses, prevention and intervention methods have focused on eliminating pathogens from the seed prior to sprouting mainly by technologies based on heating and treatment with disinfectants.

Obesity and diabetes

The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Changes in dietary and physical activity patterns are often the result of environmental and societal changes associated with development and lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing, distribution, marketing and education. To reduce the prevalence of obesity, foods with a low energy density should be recommended and physical exercise in everyday life and during leisure should be promoted. This clearly implies changes in lifestyle but there is no scientific evidence to support any particular order of measures to be taken (Wirth et al. 2014).

In addition, research into other mitigating strategies to prevent diabetes and other lifestyle associated diseases should also be continued.

From disease to health and sustainability

Health cannot be approached from the perspective of a single discipline dealing with a single disease. The One Health approach allowed a step forward through the collaborative efforts of health science professionals for infectious diseases. In the Global Health approach the work is extended to cover all diseases, to obtain a synthesis of prevention and clinical care aiming for equity in health for all people worldwide through a full systems approach. It requires not just early responsiveness to incidents but above all, full-fledged prevention taking into account humans and animals, infectious diseases and non-communicable diseases (NCDs), disease mechanisms together with ecological and societal drivers of disease, policy, research and capacity building.

Infectious diseases and non-communicable diseases (NCDs) often have the same drivers, which lie outside the domains studied by medical professionals. Thus Global One Health is more than the integration of veterinary and medical approaches to health. For example poverty, through under- and malnourishment or more exposure to pollutants, predisposes for many infectious diseases but poverty will also often lead to NCDs. Moreover, an infectious disease often predisposes for NCDs and vice versa. For example malaria in itself can cause iron deficiency and iron deficiency from malnourishment will enhance clinical disease from malaria. Thus these drivers for disease, the interactions between different diseases, and their overall effects on health need to be studied in conjunction with attempts to control (eradicate or mitigate) particular diseases. Furthermore, economic development has both positive and negative effects on some of these drivers: the modernization of agricultural systems through irrigation may increase malaria, breed resistance in mosquitoes to agrochemicals, affect local weather through higher humidity which increases populations of other pathogens and plant pests, requiring even more chemical control, while at the same time allowing farmers an increased income with better access to food and medical care.

A systems approach can help to make this more than an abstract exercise by singling out those relationships that are quantitatively important for the problem at hand. Such an approach involves modeling (Heesterbeek et al. 2015), and quantifying the relationships to gain insight into which relationships are important

When dealing with health at a global scale, there is not only an important link between infectious diseases and NCDs, and between animal and human health, but there are also common drivers involving environmental and societal issues. For example the massive outbreak of Ebola in West Africa (2014-2015) shows us how relationships between wildlife infections and human disease can change. Whereas it was known earlier that Ebola could be transmitted from the reservoir species (bats) through intermediate hosts (monkeys) to humans, it seems that in this case transmission was directly from bats to a human (Saéz et al. 2015). This index case in a more urban area had consequences for the outbreak. Earlier outbreaks were often in small (remote) village and therefore the number of cases remained limited even with failing transmission control. In contrast, an outbreak starting in a large urban area will increase the likelihood of a massive outbreak. Also the cultural differences between the people in this new area for Ebola (West Africa) compared to the traditional Ebola areas (Central Africa) may have made the situation more difficult for successful control. Note however that there is no a priori reason to think that in the developed world, such an outbreak would have been controlled without many fatalities. Take for example the consequences of BSE for human health, i.e., the occurrence vCJD in humans where it was clear that identifying and controlling new transmission routes may not always be very effective (Hueston 2013).

Finally, the relationship between disease and international trade and other contacts (tourism, refugee movements, human organ trafficking) merits a Global One Health approach as well. These contacts, affected by climate change, civil war and terrorism, are drivers of disease risks. Moreover, disease issues can also have important repercussions for trade and travel (for example the 2002 SARS outbreak, concerns about safety of infant formula in China in 2008, the 2014 Ebola outbreak).

Effect of diseases on trade, economic health and security

Under the WTO agreements, disease issues may restrict trade (or travel) whether they concern diseases affecting humans (WHO), animals (OIE) or plants (FAO). Clearly such trade issues only arise when the possibilities to control the diseases are too limited to manage the disease satisfactorily and local freedom of disease elsewhere can only be maintained by bringing trade and travel restrictions into place. The least developed countries not only suffer more from infectious diseases but they also have an additional burden because such diseases may also exclude them from markets in the developed world. Therefore, it is important that acceptable management strategies for disease problems with global implications, even when the diseases are "only" relevant for plants or animals, be developed and implemented.

That will allow disease management in all countries and will take away the inequality in acceptable health status for developing and developed countries.

The above applies to endemic diseases for which no satisfactory solutions are available. In addition, we must deal with emerging diseases that will occur, both infectious (e.g., SARS, influenza, MERS) and NCDs (e.g., dioxine through animal feed to humans or toxins produced by algae in seafood). By the very nature of these emerging problems there will always be a time lag before adequate management is in place. Laboratory infrastructure, mobile sampling teams, microbiological and toxicological testing, epidemiological capacity, and risk management are needed. Again, global inequality in the extent and quality of these infrastructures may be a further burden on developing countries as can be seen from the H5N1 epidemic and the most recent Ebola outbreak.

Failure to understand the extent of their impact on society can lead to too little attention for these issues, as crisis management is based on optimizing other dimensions, often in the short term. Some examples are the BSE crisis in the EU but also the FMDV crisis in the EU in 2003. Although in the latter case human health was not an issue, the impact on tourism and society in the countryside was enormous and begs the question that had these impacts been taken into account, would not other decisions have been made (Bickerstaff and Simmons 2004)?

Global health governance

More and better options to deal with existing disease problems and better preparedness are needed. Certainly, there are not only national but also global organizations that deal with these disease issues, with a clear division between the affected group of species. The general framework is provided by the WTO and the FAO with the Sanitary and Phytosanitary (SPS) measures agreement which sets the standard for food safety and the protection of human, animal, and plant health including wildlife and wild flora (www.wto.org/sps). The WTO and FAO ask countries to base their measures on scientific evidence and international standards that are set by international organizations. The main international organizations are: the WHO for human health, the FAO/WHO Codex Alimentarius Commission (CAC) for food safety, the Office International the Epizooties (OIE) for animal health, and the FAO International Plant Protection Convention for plant health. However, there is no international framework governing the ecosystem aspects of global health, and only few countries have developed an integrated policy to deal with ecosystem, plant, animal and human health.

The emphasis lies on the health implications for humans. Consequently, human health problems, even when of animal origin, are mainly handled by the organizations for human health (WHO, CDC, ECDC, PAHO, etc.). On the other hand when human health implications are considered to be negligible, disease management is done by the animal health organizations (e.g., BSE). The latter situation may then lead to a real or perceived lack of consideration for human health. During the last decade, veterinary and agricultural health issues have been moved to separate organizations outside the agricultural sector, covering both human health and animal health (UK DEFRA, EU EFSA). The CDC in the USA also plays an international role in risk assessment and management for human health issues. The last decade has seen increased collaboration between public health and veterinary authorities internationally, but there little collaboration still across these sectors.

Animal and plant health issues are managed locally and are used to gain trade advantages over other countries [e.g., *Salmonella* enteritidis (SE)]. Often, solutions must be highly specific: for SE, kitchen hygiene may be the missing factor when looking at mitigation or eradication strategies for this problem. Is eradication useful, or does it only delay the emergence of another bacterium or another *Salmonella* serovar?

Many diseases are very important but never become urgent because they are endemic, especially the neglected tropical diseases. A comparison between Ebola and malaria, vCJD from BSE and human cases from bovine tuberculosis, human H5N1 cases and seasonal influenza immediately make clear that the outbreak diseases receive more attention than their direct impact measured in human fatalities warrants: the first one in each pair causing several hundreds of deaths over their whole period of occurrence and the second one 1000-10,000 times more each year. Examples of other important endemic diseases with a large impact on human and animal health are leishmaniasis, trypanosomiasis, Chagas disease, and diarrhea in young children.

For endemic diseases, it often pays to go from a reactive curative approach to a prevention approach, following the famous saying “an ounce of prevention is worth a pound of cure”. Although following this line of thought, lifestyle changes in humans are to be preferred over cures, it is not easy to achieve those and perhaps it is time to also consider alternative measures such as preventive medication for the obese (Knowler 2002), reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. A comparable issue is preventing the introduction of avian influenza from wild birds into poultry farms. Indoor housing with the right biosecurity can possibly be sufficient, but if perceived animal welfare issues prevail, alternative prevention needs to be considered, such as vaccinating poultry against potential dangerous influenza strains (H5 and H7). Thus we advocate exploiting the GOH approach to take a broader look at possibilities of reducing disease and make clear what are the advantages and disadvantages of various approaches.

Implementation

For the rapid response and control of new and emerging diseases, prompt detection and instigation of control measures such as vaccination is pivotal. This may call for new detection methods and procedures, which may require optimization and validation before they can be deployed in diagnostic laboratories. For pathogen control, methods will need be improved in order to rapidly develop new intervention strategies and new intervention tools, for example vaccines. We do not know which emerging disease or zoonosis will be the next important public health threat. However, as we increase our efforts to improve our capacity to respond to such pathogens we will also increase the likelihood that we can efficiently and effectively respond to new, (re-) emerging pathogens including zoonotic diseases in the long term. Recognition of new emerging disease threats in livestock or human populations starts with knowledge of pathogens, their interaction with hosts and their transmission modes and dynamics. For the analysis of disease potential, zoonotic potential, distribution risks and associated health risks in an early stage of a disease, outbreak countries preferably should have resources in place or should be helped as needed to install a national or international task force to do such analyses within a short time period. For a rapid response in case a disease outbreak turns into a crisis situation, we also should have a strong response force in place to be operated under the United Nations Security Council, supported by a special emergency fund.

The Global One Health approach calls for a different design of health research, health policy-making and health prevention and implementation of interventions. Various intervention strategies need to be evaluated together, even if these interventions fall within the mandate or jurisdiction of different actors. Public health officials may order the culling of animals to prevent spread to humans (e.g., Hong Kong in1997) but they may not have the knowledge needed to know if such measures are effective, for example which animals are selected for culling and which animal (species) are excluded. Conversely, communicating about potential health risks may lead to unwanted human behavior, such as killing suspected animals unnecessarily, moving pet animals that are about to be killed to other areas, or consumer boycotts of certain suspected products (cucumbers in the German pathogenic *E.coli* example discussed above, or beef in the case of BSE.

We not only suffer from diseases that enter the human population (e.g., Ebola) or our food chain (BTB, EHEC) from natural ecosystems, we also introduce diseases into the populations in the ecosystems surrounding us. In the BTB example, we should not consider the transmission into the wildlife reservoirs as being partly independent of the transmission in livestock (Woodroffe et al. 2006), and we need to acknowledge that, as in Africa (Ayele et al. 2004), in the affected countries there is likewise a risk for humans (De la Rua-Domenech 2006). Thus our agriculture and our own living environment, as well as all ecosystems on the planet have to be seen as part of the natural world and if we want to achieve sustainable health for humans and animals, we need to look at the whole system. In many cases, poverty is an underlying causal factor.

In several countries, civil disturbance and poor governance have led to a so-called “failed state” or “limited statehood” status, in which the population is left without a functional government (Brinkerhoff 2005). Often, this leads to severe poverty, and lack of education, health care and malnutrition. The United Nations, the International Red Cross and other NGOs often provide essential help by sending medical staff and emergency food relief. These countries, however, lack a fundamental base for development, remaining at the bottom of the Global One Health status and therefore, require special attention so as not to be left behind.

The Global One Health approach should be an integral part of the education of health professionals, be they medical doctors, veterinarians, or others such as disease ecologists, modelers, epidemiologists, health economists, health geneticists, sociologists, nutritionists, bioinformaticians. In a world of increased specialization, the broader connections must not be forgotten and specialists must be trained to communicate across disciplines. Here there is a clear role for better and more training and education.

Implementing the GOH approach follows procedures similar to risk assessment, starting with a broad inventory of relationships of potential importance, quantifying the impact of these relationships and modeling the effects on health. The quantitatively important relationships are then studied and measured in greater detail, including possible interventions and their expected impact. The whole ecosystem, from pristine natural areas, through agricultural to urban environments, will need to be considered, allowing for clear and open communication to policy-makers and the public, who will then have to decide on approaches to be followed.

It is essential that specialists working on these problems cooperate across fields and across geographical areas and that access to available data but also to the possibility to collect data is assured. An important lesson that we have learned (or should have learned at least) from past outbreaks it is that transparency and exchange of ideas is important for determining the best solutions. In case of a disease outbreak, only the best approaches are acceptable, although what is “the best” depends on available resources and on the goals.

In summary, all necessary elements are available to implement the Global One Health approach to ecosystem sustainability, safety and health assurance in food chains, and human, animal and plant health. This approach can be implemented immediately, and the benefits are beyond doubt – it is a matter of political awareness and international agreement. What is needed is a concerted effort to bring together in research, education and governance, both at national and international level, the actors concerned: ministers of trade, health, agriculture, environment, including water management, and rural development; the private sector ranging from the pharmaceutical industry to food companies, traders and retailers; the development of integrated research programs aimed at early warning, monitoring, risk management and prevention of diseases at all stages, starting at the ecosystem and pathogen levels; the training of healthcare practitioners and the public at large to create a broadly shared awareness of the interconnectedness global one health issues; the development of urban hygiene and food systems that prevent outbreaks of infections and facilitates their management and sustainable and healthy living patterns - and much more. Although daunting, this is not an impossible task, on the contrary, it is a necessary task in a truly globalized world where humans, ecosystems and food systems form intricate, multilevel webs and the health of one is the health of all.

References

Acevedo-Whitehouse, K., and A. L. J. Duffus. 2009. Effects of environmental change on wildlife health. Philosophical Transactions of the Royal Society B-Biological Science 364: 3429-3438.

Ahmed, S., P. K. Bardhan, A. Iqbal, R. N. Mazumder, A. I. Khan, M. S. Islam, A. K. Siddique, and A. Cravioto. 2011. The 2008 Cholera Epidemic in Zimbabwe: Experience of the ICDDR, b Team in the Field. Journal of Health, Population, and Nutrition 29: 541.

Ali, S. H., and R. Keil. 2006. Global cities and the spread of infectious disease: the case of severe acute respiratory syndrome (SARS) in Toronto, Canada. Urban Studies 43: 491-509.

Anderson, P. K., A. A. Cunningham, N. G. Patel, F. J. Morales, P. R. Epstein, and P. Daszak. 2004. Emerging infectious diseases of plants: pathogen pollution, climate change and agrotechnology drivers. Trends in Ecology and Evolution 19: 535-544.

Andreasen, M., 2014. GM food in the public mind - facts are not what they used to be. Nature Biotechnology 32: 25.

Arwady, M. A., L. Bawo, J. C. Hunter, M. Massaquoi, A. Matanock, B. Dahn, P. Ayscue, T. Nyenswah, J. D. Forrester, L. E. Hensley, B. Monroe, R. J. Schoepp, T. H. Chen, K. E. Schaecher, T. George, E. Rouse, I. J. Schafer, S. K. Pillai, and K. M. De Cock. 2015. Evolution of Ebola Virus Disease from Exotic Infection to Global Health Priority, Liberia, Mid-2014. Emerging Infectious Diseases 21: 578-584.

Ayele, W., S. Neill, J. Zinsstag, M. Weiss, and I. Pavlik. 2004. Bovine tuberculosis: an old disease but a new threat to Africa. The International Journal of Tuberculosis and Lung Disease 8: 924-937.

Bates, S. L., J. Z. Zhao, R. T. Roush, and A. M. Shelton. 2005. Insect resistance management in GM crops: past, present and future. Nature Biotechnology 23: 57-62.

Behrman, J. R., J. A. Behrman, and N. M. Perez. 2009. On what diseases and health conditions should new economic research on health and development focus? Health Economics 18: S109-S128.

Bergelson, J., G. Dwyer, and J. Emerson. 2001. Models and data on plant-enemy coevolution. Annual Review of Genetics 35: 469-499.

Bhatt, S., P. W. Gething, O. J. Brady, J. P. Messina, A. W. Farlow, C. L. Moyes, J. M. Drake, J. S. Brownstein, A. G. Hoen, O. Sankoh, M. F. Myers, D. B. George, T. Jaenisch, G. R. W. Wint, C. P. Simmons, T. W. Scott, J. J. Farrar, and S. I. Hay. 2013. The global distribution and burden of dengue. Nature 496: 504-507.

Bickerstaff, K., and P. Simmons. 2004. The right tool for the job? Modeling, spatial relationships, and styles of scientific practice in the UK foot and mouth crisis. Environment and Planning D 22: 393-412.

Billinis, C. 2013. Wildlife diseases that pose a risk to small ruminants and their farmers. Small Ruminant Research 110: 67-70.

Bogoch, II, M. I. Creatore, M. S. Cetron, J. S. Brownstein, N. Pesik, J. Miniota, T. Tam, W. Hu, A. Nicolucci, S. Ahmed, J. W. Yoon, I. Berry, S. I. Hay, A. Anema, A. J. Tatem, D. MacFadden, M. German, and K. Khan. 2015. Assessment of the potential for international dissemination of Ebola virus via commercial air travel during the 2014 West African outbreak. The Lancet 384: 29-35.

Bonds, M. H., A. P. Dobson, and D. C. Keenan. 2012. Disease ecology, biodiversity, and the latitudinal gradient in income. PLoS Biology 10: e1001456.

Bonten, M. J., M. K. Hayden, C. Nathan, J. van Voorhis, M. Matushek, S. Slaughter, T. Rice, and R. A. Weinstein. 1996. Epidemiology of colonisation of patients and environment with vancomycin-resistant enterococci. The Lancet 348: 1615-1619.

Boutayeb, A. 2006. The double burden of communicable and non-communicable diseases in developing countries. Transactions of the Royal society of Tropical Medicine and Hygiene 100: 191-199.

Bras, H. 2015. Inequalities in Food Security and Nutrition. A Life Course Perspective. Wageningen University, Wageningen.

Brinkerhoff, D. W. 2005. Rebuilding governance in failed states and post-conflict societies: core concepts and cross-cutting themes. Public Administration and Development 25: 3-14.

Brooks-Pollock, E., and M. Keeling. 2009. Herd size and bovine tuberculosis persistence in cattle farms in Great Britain. Preventive Veterinary Medicine 92: 360-365.

Budka, H. 2011. Editorial: The European Response to BSE: A Success Story. EFSA Journal 9: e991.

Cameron, D., and I. G. Jones. 1983. John Snow, the Broad Street pump and modern epidemiology. International Journal of Epidemiology 12: 393-396.

Carbon, C. 2000. MRSA and MRSE: is there an answer? Clinical Microbiology and Infection 6: 17-22.

Carman, W. F., A. G. Elder, L. A. Wallace, K. McAulay, A. Walker, G. D. Murray, and D. J. Stott. 2000. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. The Lancet 355: 93-97.

CEC 2013. Comm. Eur. Communities (CEC). 2013. Commission Regulation (EC) No 209/2013 amending Regulation (EC) No 2073/2005 as regards microbiological criteria for sprouts and the sampling rules for poultry carcasses and fresh poultry meat. Official Journal of the European Union L68:19–23.

Chance, R. E., and B. H. Frank. 1993. Research, development, production, and safety of biosynthetic human insulin. Diabetes Care 16: 133-142.

Chanda, E., F. Masaninga, M. Coleman, C. Sikaala, C. Katebe, M. Macdonald, K. S. Baboo, J. Govere, and L. Manga. 2008. Integrated vector management: the Zambian experience. Malaria Journal 7: 164.

Claas, E. C., A. D. Osterhaus, R. van Beek, J. C. De Jong, G. F. Rimmelzwaan, D. A. Senne, S. Krauss, K. F. Shortridge, and R. G. Webster. 1998. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. The Lancet 351: 472-477.

Clay, K., and P. X. Kover. 1996. The Red Queen hypothesis and plant/pathogen interactions. Annual Review of Phytopathology 34: 29-50.

Conn, D. B. 2014. Aquatic invasive species and emerging infectious disease threats: a one health perspective. Aquatic Invasions 9: 383-390.

Cook, R. J. 2000. Advances in plant health management in the twentieth century. Annual Review of Phytopathology 38: 95-116.

Cutler, S. J., A. R. Fooks, and W. H. M. van der Poel. 2010. Public health threat of new, reemerging, and neglected zoonoses in the industrialized world. . Emerging Infectious Diseases 16: 1-7.

D'Mello, J. P. F. 2003. Mycotoxins in cereal grains, nuts and other plant products, pp. 65-90. In J. P. F. D'Mello (ed.), Food Safety Contaminants and Toxins. Cromwell Press, Trowbridge, UK.

De Cock, K. M. 2011. Trends in global health and CDC's international role, 1961–2011. MMWR Supplement,vol. 60: 104-111.

De la Rua-Domenech, R. 2006. Human Mycobacterium bovis infection in the United Kingdom: incidence, risks, control measures and review of the zoonotic aspects of bovine tuberculosis. Tuberculosis 86: 77-109.

De Liberato, C., G. Scavia, R. Lorenzetti, P. Scaramozzino, D. Amaddeo, G. Cardeti, M. Scicluna, G. Ferrari, and G. L. Autorino. 2005. Identification of Culicoides obsoletus (Diptera: Ceratopogonidae) as a vector of bluetongue virus in central Italy. Veterinary Record 156: 301-304.

de Melker, H. E., J. Schellekens, S. Neppelenbroek, F. Mooi, H. Rümke, and M. Conyn-van Spaendonck. 2000. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. Emerging Infectious Diseases 6: 348.

Doherty, C. P., L. T. Weaver, and A. M. Prentice. 2002. Micronutrient supplementation and infection: a double-edged sword? Journal of Pediatric Gastroenterology and Nutrition 34: 346-352.

Donnelly, M. J., P. J. McCall, C. Lengeler, I. Bates, U. D'Alessandro, G. Barnish, F. Konradsen, E. Klinkenberg, H. Townson, J. F. Trape, I. M. Hastings, and C. Mutero. 2005. Malaria and urbanization in sub-Saharan Africa. Malaria Journal 4: 12.

Duclos, P., J. M., M. Okwo-Bele, Gacic-Dobo, and T. Cherian. 2009. Global immunization: status, progress, challenges and future. BMC International Health and Human Rights 9.

Egger, M., M. May, G. Chêne, A. N. Phillips, B. Ledergerber, F. Dabis, D. Costagliola, A. D. A. Monforte, F. de Wolf, and P. Reiss. 2002. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. The Lancet 360: 119-129.

Eggersdorfer, M., K. Kraemer, M. Ruel, M. van Ameringen, H. Biesalski, M. Bloem, J. Chen, A. Lateef, and V. Mannar. 2013. The Road to Good Nutrition, Karger Medical and Scientific Publishers,Basel, Switzerland.

Emerson, P. M., R. L. Bailey, G. E. L. Walraven, and S. W. Lindsay. 2001. Human and other faeces as breeding media of the trachoma vector Musca sorbens. Medical and Veterinary Entomology 15: 314-320.

Eveleens, K. 1983. Cotton-insect control in the Sudan Gezira: analysis of a crisis. Crop Protection 2: 273-287.

Faes, C., Y. van der Stede, H. Guis, C. Staubach, E. Ducheyne, G. Hendrickx, and K. Mintiens. 2013. Factors affecting Bluetongue serotype 8 spread in Northern Europe in 2006: The geographical epidemiology. Preventive Veterinary Medicine 110: 149-158.

Fauci, A.S. 2005 Emerging and Reemerging Infectious Diseases: The Perpetual Challenge. Academic Medicine 80: 1079-1085.

Ferguson, N. M., D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn, and D. S. Burke. 2005. Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature 437: 209-214.

Finzi, D., M. Hermankova, T. Pierson, L. M. Carruth, C. Buck, R. E. Chaisson, T. C. Quinn, K. Chadwick, J. Margolick, and R. Brookmeyer. 1997. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science 278: 1295-1300.

Fischer, T., D. Byerlee, and G. Edmeades. 2014. Crop yields and global food security: will yield increase continue to feed the world?, Australian Centre for International Agricultural Research (ACIAR), Canberra.

Fledderjohann, J., S. Agrawal, S. Vellakkal, S. Basu, O. Campbell, P. Doyle, S. Ebrahim, and D. Stuckler. 2014. Do Girls Have a Nutritional Disadvantage Compared with Boys?

Breastfeeding, Food Consumption, and Mortality among Indian Siblings. The European Journal of Public Health 24: cku162. 060.

Gerba, C. P., and J. E. Smith. 2005. Sources of pathogenic micr oorganisms and their fate during land application of wastes. Journal of Environmental Quality 34: 42-48.

Gilbert, N. 2013. A hard look at GM crops. Nature 497: 24-26.

Gortazar, C., R. J. Delahay, R. A. Mcdonald, M. Boadella, G. J. Wilson, D. Gavier-Widen, and P. Acevedo. 2012. The status of tuberculosis in European wild mammals. Mammal Review 42: 193-206.

Gortmaker, S. L., B. A. Swinburn, D. Levy, R. Carter, P. L. Mabry, D. T. Finegood, T. Huang, T. Marsh, and M. L. Moodie. 2011. Changing the future of obesity: science, policy, and action. The Lancet 378: 838-847.

Guerrant, R. L., and B. L. Blackwood. 1999. Threats to global health and survival: The growing crises of tropical infectious diseases - Our "unfinished agenda". Clinical Infectious Diseases 28: 966-986.

Gupta, M. D. 1999. Lifeboat versus corporate ethic: Social and demographic implications of stem and joint families. Social Science and Medicine 49: 173-184.

Haas, J. D., and T. Brownlie. 2001. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. The Journal of Nutrition 131: 676S-690S.

Hallmann, C. A., R. P. Foppen, C. A. van Turnhout, H. de Kroon, and E. Jongejans. 2014. Declines in insectivorous birds are associated with high neonicotinoid concentrations. Nature. doi:10.1038/nature13531.

Hamer, G. 2003. Solid waste treatment and disposal: effects on public health and environmental safety. Biotechnology Advances 22: 71-79.

Hamilton, D., and S. Crossley. 2004. Pesticide residues in food and drinking water: human exposure and risks, John Wiley & Sons.

Hansen, M. 1986. Escape from the Pesticide Treadmill: Alternatives to Pesticides in Developing Countries: Preliminary Report, Institute for Consumer Policy Research, Consumers Union.

Hardgrove, A., K. Pells, J. Boyden, and P. Dornan. 2014. Youth vulnerabilities in life course transitions. (occasional paper) Human Development Report Office, UNDP, New York, NY (USA).

Harvard School of Public Health. 2014. Obesity Trends. Boston, MA, USA.

Heesterbeek, H., R. M. Anderson, V. Andreasen, S. Bansal, D. De Angelis, C. Dye, K. T. Eames, W. J. Edmunds, S. D. Frost, and S. Funk. 2015. Modeling infectious disease dynamics in the complex landscape of global health. Science 347: aaa4339.

Henderson, R. H. 1984. The Expanded Program on Immunization of the World Health Organization. Reviews of Infectious Diseases 6: S475-S479.

Hossain, F., C.E. Pray, Y. Lu, J. Huang, C. Fan, and R. Hu. (2004), GM cotton and farmer’s health in China: an econometric analysis of the relationship between pesticide poisoning and GM cotton use in China. International Journal of Occupational and Environmental Health 10: 307–314.

Huang, J., R. Hu, S. Rozelle, and C.E. Pray. (2005). Insect-resistant GM rice in farmers’ fields: assessing productivity and health effects in China. Science 308, 688–690.

Huang, J., R. Hu, F. Qiao, Y. Yin, H. Liu, and Z. Huang. 2015. Impact of insect-resistant GM rice on pesticide use and farmers’ health in China. Science China Life Sciences: 1-6.

Huang, Z. Y., W. F. de Boer, F. van Langevelde, V. Olson, T. M. Blackburn, and H. H. Prins. 2013. Species' life-history traits explain interspecific variation in reservoir competence: a possible mechanism underlying the dilution effect. PLoS One 8: e54341.

Hueston, W. D. 2013. BSE and variant CJD: Emerging science, public pressure and the vagaries of policy-making. Preventive Veterinary Medicine 109: 179-184.

Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman, and P. Daszak. 2008. Global trends in emerging infectious diseases. Nature 451: 990-993.

Jutla, A., E. Whitcombe, N. Hasan, B. Haley, A. Akanda, A. Huq, M. Alam, R. B. Sack, and R. Colwell. 2013. Environmental factors influencing epidemic cholera. The American Journal of Tropical Medicine and Hygiene 89: 597-607.

Karlsson, E. A., and M. A. Beck. 2010. The burden of obesity on infectious disease. Experimental Biology and Medicine 235: 1412-1424.

Keesing, F., L. K. Belden, P. Daszak, A. Dobson, C. D. Harvell, R. D. Holt, P. Hudson, A. Jolles, K. E. Jones, and C. E. Mitchell. 2010. Impacts of biodiversity on the emergence and transmission of infectious diseases. Nature 468: 647-652.

Kennedy, S. B., and R. A. Nisbett. 2015. The Ebola epidemic: a transformative moment for global health. Bulletin of the World Health Organization 93: 2-2.

Kim, H. M., C.-K. Kim, N.-J. Lee, H. Chu, C. Kang, K. Kim, and J.-Y. Lee. 2015. Pathogenesis of novel reassortant avian influenza virus A (H5N8) Isolates in the ferret. Virology 481: 136-141.

Klinkenberg, E., P. J. McCall, M. D. Wilson, F. P. Amerasinghe, and M. J. Donnelly. 2008. Impact of urban agriculture on malaria vectors in Accra, Ghana. Malaria Journal 7.

Knol, M., A. Urbanus, E. Swart, L. Mollema, W. Ruijs, R. van Binnendijk, M. Te Wierik, H. de Melker, A. Timen, and S. Hahne. 2013. Large ongoing measles outbreak in a religious community in the Netherlands since May 2013. EuroSurveillance 18: 20580.

Knowler, W. C. 2002. Diabetes prevention. Reply. New England Journal of Medicine 346: 1830-1830.

Koelen, M. A., L. Vaandrager, and A. Wagemakers. 2008. What is needed for coordinated action for health? Family Practice 25: i25-i31.

Koenraadt, C. J. M., T. Balenghien, S. Carpenter, E. Ducheyne, A. R. W. Elbers, M. Fife, C. Garros, A. Ibanez-Justicia, H. Kampen, R. J. M. Kormelink, B. Losson, W. H. M. van der Poel, N. De Regge, P. A. van Rijn, C. Sanders, F. Schaffner, M. M. S. van Oldruitenborgh-Oosterbaan, W. Takken, D. Werner, and F. Seelig. 2014. Bluetongue, Schmallenberg - what is next? Culicoides-borne viral diseases in the 21st Century. BMC Veterinary Research 10.

Koplan, J. P., T. C. Bond, M. H. Merson, K. S. Reddy, M. H. Rodriguez, N. K. Sewankambo, J. N. Wasserheit. 2009. Towards a common definition of global health. The Lancet 373: 1993-1995.

Kovats, S., S. Lloyd, and N. Scovronick. 2014. Climate and health in informal urban settlements.

Kumar, K., S. C. Gupta, Y. Chander, and A. K. Singh. 2005. Antibiotic use in agriculture and its impact on the terrestrial environment. Advances in Agronomy 87: 1-54.

Lawn, J. E., H. Blencowe, S. Oza, D. You, A. C. Lee, P. Waiswa, M. Lalli, Z. Bhutta, A. J. Barros, and P. Christian. 2014. Every Newborn: progress, priorities, and potential beyond survival. The Lancet 384: 189-205.

Leon, D. A., G. Walt, and L. Gilson. 2001. International perspectives on health inequalities and policy. British Medical Journal 322: 591-594.

Levy, S. B., and B. Marshall. 2004. Antibacterial resistance worldwide: causes, challenges and responses. Nature Medicine 10: S122-S129.

Lopez, A. D., and C. D. Mathers. 2006. Measuring the global burden of disease and epidemiological transitions: 2002-2030. Annals of Tropical Medicine and Parasitology 100: 481-499.

Lu, Y., K. Wu, Y. Jiang, Y. Guo, and N. Desneux. 2012. Widespread adoption of Bt cotton and insecticide decrease promotes biocontrol services. Nature 487: 362-365.

Lu, Y., K. Wu, Y. Jiang, B. Xia, P. Li, H. Feng, K. A. Wyckhuys, and Y. Guo. 2010. Mirid bug outbreaks in multiple crops correlated with wide-scale adoption of Bt cotton in China. Science 328: 1151-1154.

Marmot, M., and Commision on Social Determinants of Health. 2007. Achieving health equity: from root causes to fair outcomes. The Lancet 370: 1153-1163.

Marušić, A. 2013. Global health-multiple definitions, single goal. Annali dell'Istituto Superiore di Sanità 49: 2-3.

McLaren, L., and P. Hawe. 2005. Ecological perspectives in health research. Journal of Epidemiology and Community Health 59: 6-14.

McMichael, A. J., and E. Lindgren. 2011. Climate change: present and future risks to health, and necessary responses. Journal of Internal Medicine 270: 401-413.

McMichael, A. J., S. Friel, A. Nyong, and C. Corvalan. 2008. Global environmental change and health: impacts, inequalities, and the health sector. BMJ: British Medical Journal 336: 191.

Meerburg, B. G., and A. Kijlstra. 2007. Role of rodents in transmission of *Salmonella* and *Campylobacter*. Journal of the Science of Food and Agriculture 87: 2774-2781.

Murray, A. G., and E. J. Peeler. 2005. A framework for understanding the potential for emerging diseases in aquaculture. Preventive Veterinary Medicine 67: 223-235.

Murray, C. J. L., and A. D. Lopez. 2013. Measuring the Global Burden of Disease. New England Journal of Medicine 369: 448-457.

Murray, K. O., E. Mertens, and P. Despres. 2010. West Nile virus and its emergence in the United States of America. Veterinary Research 41.

Myers, S. S., and J. A. Patz. 2009. Emerging threats to human health from global environmental change. Annual Review of Environment and Resources 34: 223-252.

Niblett, D. 1966. Global health factors of importance to Canadian mobile forces with a potential world-wide commitment. Medical Services Journal, Canada 22: 333.

Ostfeld, R. S., and F. Keesing. 2000. Biodiversity and disease risk: the case of Lyme disease. Conservation Biology 14: 722-728.
Ostfeld, R. S., and F. Keesing. 2012. Effects of host diversity on infectious disease. Annual Review of Ecology, Evolution, and Systematics 43: 157.
Pachauri, R. K. et al. 2014. Climate change 2014 - Synthesis Report. 133p. *In*. R. K. Pachauari & L. Meyer [eds.]. Intergovernmental Panel on Climate Change.
Podder, C. N., A. B. Gumel, C. S. Bowman, and R. G. McLeod. 2007. Mathematical study of the impact of quarantine, isolation and vaccination in curtailing an epidemic. Journal of Biological Systems 15: 185-202.
Poetri, O. N., A. Bouma, S. Murtini, I. Claassen, G. Koch, R. D. Soejoedono, J. Stegeman, and M. van Boven. 2009. An inactivated H5N2 vaccine reduces transmission of highly pathogenic H5N1 avian influenza virus among native chickens. Vaccine 27: 2864-2869.
Popkin, B. M., L. S. Adair, and S. W. Ng. 2012. Global nutrition transition and the pandemic of obesity in developing countries. Nutrition Reviews 70: 3-21.
Pray, C. E., L. Nagarajan, J. Huang, R. Hu, and B. Ramaswami, 2011. The Impact of Bt Cotton and the Potential Impacts of Biotechnology on Other Crops in China and India. In C. A. Carter, Moschini and M. Sheldon (eds.) Genetically Modified Food and Global Welfare, pp. 83-114.
Prentice, A. M. 2008. Iron metabolism, malaria, and other infections: what is all the fuss about? The Journal of Nutrition 138: 2537-2541.
Pretty, J. N. 2004. The pesticide detox: towards a more sustainable agriculture, Earthscan.
Pruden, A., D. J. Larsson, A. Amézquita, P. Collignon, K. K. Brandt, D. W. Graham, J. M. Lazorchak, S. Suzuki, P. Silley, and J. R. Snape. 2013. Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. Environmental Health and Perspectives 121: 878-885.
Purse, B. V., H. E. Brown, L. Harrup, P. P. Mertens, and D. J. Rogers. 2008. Invasion of bluetongue and other orbivirus infections into Europe: the role of biological and climatic processes. Review of Science and Technology 27: 427-442.
Qaim, M. and D. Zilberman (2003). Yield effects of genetically modified crops in developing countries. Science 299: 900–902.
Qiao, F., J. Huang, L. Zhang, and S. Rozelle. 2012. Pesticide use and farmers' health in China's rice production. China Agricultural Economic Review 4: 468-484.
Quinn, S. C., and S. Kumar. 2014. Health Inequalities and Infectious Disease Epidemics: A Challenge for Global Health Security. Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science 12: 263-273.
Radcliffe, E. B., W. D. Hutchison, and R. E. Cancelado. 2009. Integrated pest management: concepts, tactics, strategies and case studies, Cambridge University Press, Cambridge, UK.
Raj, V. S., A. D. Osterhaus, R. A. Fouchier, and B. L. Haagmans. 2014. MERS: emergence of a novel human coronavirus. Current Opinion in Virology 5: 58-62.
Ranson, H., R. N'Guessan, J. LInes, N. Moiroux, Z. Nkuni, and V. Corbel. 2011. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends in Parasitology 27: 91-98.
Ravelli, A. C., J. H. van der Meulen, C. Osmond, D. J. Barker, and O. P. Bleker. 1999. Obesity at the age of 50 y in men and women exposed to famine prenatally. The American Journal of Clinical Nutrition 70: 811-816.
Renault, P., J. L. Solet, D. Sissoko, E. Balleydier, S. Larrieu, L. Filleul, C. Lassalle, J. Thiria, E. Rachou, H. de Valk, D. Ilef, M. Ledrans, I. Quatresous, P. Quenel, and V. Pierre. 2007. A major epidemic of chikungunya virus infection on Reunion Island, France, 2005-2006. American Journal of Tropical Medicine and Hygiene 77: 727-731.
Riley, S., and N. M. Ferguson. 2006. Smallpox transmission and control: spatial dynamics in Great Britain. Proceedings of the National Academy of Sciences 103: 12637-12642.
Roberts, M. 1996. The dynamics of bovine tuberculosis in possum populations, and its eradication or control by culling or vaccination. Journal of Animal Ecology: 451-464.
Romeis, J., A. M. Shelton, and G. G. Kennedy. 2008. Integration of insect-resistant genetically modified crops within IPM programs, Springer, Berlin, Germany.
Rose, J. B., P. R. Epstein, E. K. Lipp, B. H. Sherman, S. M. Bernard, and J. A. Patz. 2001. Climate variability and change in the United States: potential impacts on water-and foodborne diseases caused by microbiologic agents. Environmental Health and Perspectives 109: 211.
Ross, H. 2013. One Health from a Social-Ecological Systems Perspective: Enriching Social and Cultural Dimensions, pp. 217-229. In J. S. Mackenzie, M. Jeggo, P. Daszak and J. A. Richt (eds.), One Health: The Human-Animal-Environment Interfaces in Emerging Infectious

Diseases: Food Safety and Security, and International and National Plans for Implementation of One Health Activities, vol. 366.

Ross, R. 1897. On some peculiar pigmented cells found in two mosquitos fed on malarial blood. British Medical Journal 2: 1786.

Ross, R. 1930. Antimalaria Measures. British Medical Journal 1: 797.

Saéz, A. M., S. Weiss, K. Nowak, V. Lapeyre, F. Zimmermann, A. Düx, H. S. Kühl, M. Kaba, S. Regnaut, and K. Merkel. 2015. Investigating the zoonotic origin of the West African Ebola epidemic. EMBO Molecular Medicine 7: 17-23.

Savill, N. J., D. J. Shaw, R. Deardon, M. J. Tildesley, M. J. Keeling, M. E. Woolhouse, S. P. Brooks, and B. T. Grenfell. 2007. Effect of data quality on estimates of farm infectiousness trends in the UK 2001 foot-and-mouth disease epidemic. Royal Society Interface 4: 235-241.

Savini, G., M. Goffredo, F. Monaco, A. Di Gennaro, M. A. Cafiero, L. Baldi, P. De Santis, R. Meiswinkel, and V. Caporale. 2005. Bluetongue virus isolations from midges belonging to the Obsoletus complex (Culicoides, Diptera : ceratopogonidae) in Italy. Veterinary Record 157: 133-139.

Schmidt, K. A., and R. S. Ostfeld. 2001. Biodiversity and the dilution effect in disease ecology. Ecology 82: 609-619.

Schulze, E.-D., and H. A. Mooney. 1994. Ecosystem function of biodiversity: a summary, Springer, Berlin, Germany.

Schwabe, C. W. 1968. Animal diseases and world health. Journal of the American Veterinary Medical **Association 153: 1859-1863.**

Semenza, J. C., and B. Menne. 2009. Climate change and infectious diseases in Europe. The Lancet Infectious Diseases 9: 365-375.

Shelton, A.M., K.-Z. Zhao, and R.T. Roush. 2002. Economic, ecological, food safety, and social consequences of the deployment of Bt transgenic plants. Annual Review of Entomology 47: 845-881.

Si, Y., W. F. de Boer, and P. Gong. 2013. Different environmental drivers of highly pathogenic avian influenza H5N1 outbreaks in poultry and wild birds. PLoS One 8: e53362.

Si, Y., A. K. Skidmore, T. Wang, W. F. De Boer, P. Debba, A. G. Toxopeus, L. Li, and H. H. Prins. 2009. Spatio-temporal dynamics of global H5N1 outbreaks match bird migration patterns. Geospatial Health 4: 65-78.

Simon-Delso, N., s. V. Amaral-Roger, L. P. Belzunces , J. M. Bonmatin, M. Chagnon, C. Downs, L. Furlan, D. W. Gibbons, C. Giorio, V. Girolami, D. Goulson, D. P. Kreutzweiser, C. H. Krupke, M. Liess, E. Long, M. McField, P. Mineau, E. A. D. Mitchell, C. A. Morrissey, D. A. Noome, L. Pisa, J. Settele, J. D. Stark, A. Tapparo, H. van Dyck, J. van Praagh, J. P. van der Sluijs, P. R. Whitehorn, and M. Wiemers. 2015. Systemic insecticides (neonicotinoids and fipronil): trends, uses, mode of action and metabolites. . Environmental Science and Pollution Research 22: 5-34.

Sims, L. D., and M. Peiris. 2013. One Health: The Hong Kong Experience with Avian Influenza, pp. 281-298. In J. S. Mackenzie, M. Jeggo, P. Daszak and J. A. Richt (eds.), One Health: The Human-Animal-Environment Interfaces in Emerging Infectious Diseases: The Concept and Examples of a One Health Approach, vol. 365.

Sitaras, I., D. Kalthoff, M. Beer, B. Peeters, and M. C. de Jong. 2014. Immune escape mutants of highly pathogenic avian influenza H5N1 selected using polyclonal sera: Identification of key amino acids in the HA protein. PLoS One 9: e84628.

Smith, D. L., K. E. Battle, S. I. Hay, C. M. Barker, T. W. Scott, and F. E. McKenzie. 2012. Ross, Macdonald, and a theory for the dynamics and control of mosquito-transmitted pathogens. PLoS Pathogens 8: e1002588.

Stokols, D., R. P. Lejano, and J. Hipp. 2013. Enhancing the resilience of human-environment systems: a social ecological perspective. Ecology and Society 18 (1) 7.

Struik, P.C., 2014. Response to Lotz *et al.*: Genetically modified crops and sustainable agriculture: a proposed way forward in the societal debate. NJAS Wageningen Journal of Life Sciences 70-71: 101-102.

Sundstrom, J., A. Albihn, S. Boqvist, K. Ljungvall, H. Marstorp, C. Martiin, K. Nyberg, I. Vagsholm, J. Yuen, and U. Magnusson. 2014. Future threats to agricultural food production posed by environmental degradation, climate change, and animal and plant diseases - a risk analysis in three economic and climate settings. Food Security 6: 201-215.

Suzán, G., E. Marcé, J. T. Giermakowski, J. N. Mills, G. Ceballos, R. S. Ostfeld, B. Armién, J. M. Pascale, and T. L. Yates. 2009. Experimental evidence for reduced rodent diversity causing increased hantavirus prevalence. PLoS One 4: e5461.

Swaddle, J. P., and S. E. Calos. 2008. Increased avian diversity is associated with lower incidence of human West Nile infection: observation of the dilution effect. PLoS One 3: e2488.
Takken, W., and B. G. Knols. 2009. Malaria vector control: current and future strategies. Trends in Parasitology 25: 101-104.
Tatem, A. J., Z. Huang, A. Das, Q. Qi, J. Roth, and Y. Qiu. 2012. Air travel and vector-borne disease movement. (Special Issue: Dynamics of parasite distributions: modern analytical approaches). Parasitology 139: 1816-1830.
Therborn, G. 2004. Between Sex and Power: Family in the world 1900-2000, Routledge.
Thomas, M. B., H. C. J. Godfray, A. F. Read, H. van den Berg, B. E. Tabashnik, J. C. van Lenteren, J. K. Waage, and W. Takken. 2012. Lessons from Agriculture for the Sustainable Management of Malaria Vectors. PLoS Medicine 9.
Tian, H., Y. Cui, L. Dong, S. Zhou, X. Li, S. Huang, R. Yang, and B. Xu. 2015. Spatial, temporal and genetic dynamics of highly pathogenic avian influenza A (H5N1) virus in China. BMC Infectious Diseases 15: 54.
Tylianakis, J. M., R. K. Didham, J. Bascompte, and D. A. Wardle. 2008. Global change and species interactions in terrestrial ecosystems. Ecology Letters 11: 1351-1363.
UNICEF. 2013. Improving child nutrition: the achievable imperative for global progress, United Nations Children's Fund.
van den Berg, H., and W. Takken. 2009. Evaluation of integrated vector management. Trends in Parasitology 25: 71-76.
van den Bosch, F., R. Oliver, F. v. d. Berg, and N. Paveley. 2014a. Governing Principles Can Guide Fungicide-Resistance Management Tactics. Annual Review of Phytopathology 52: 175-195.
van den Bosch, F., N. Paveley, F. van den Berg, P. Hobbelen, and R. Oliver. 2014b. Mixtures as a fungicide resistance management tactic. Phytopathology 104: 1264-1273.
van der Goot, J. A., M. van Boven, A. Stegeman, S. G. van de Water, M. C. de Jong, and G. Koch. 2008. Transmission of highly pathogenic avian influenza H5N1 virus in Pekin ducks is significantly reduced by a genetically distant H5N2 vaccine. Virology 382: 91-97.
van Lenteren, J. C. 2012. The state of commercial augmentative biological control: plenty of natural enemies, but a frustrating lack of uptake. BioControl 57: 1-20.
Venesky, M. D., T. R. Raffel, T. A. McMahon, and J. R. Rohr. 2014. Confronting inconsistencies in the amphibian-chytridiomycosis system: implications for disease management. Biological Reviews 89: 477-483.
Wang, D. Q., Z. G. Xia, S. S. Zhou, X. N. Zhou, R. B. Wang, and Q. F. Zhang. 2013. A potential threat to malaria elimination: extensive deltamethrin and DDT resistance to *Anopheles sinensis* from the malaria-endemic areas in China. Malaria Journal 12: 164-170.
Watanabe, T., G. X. Zhong, C. A. Russell, N. Nakajima, M. Hatta, A. Hanson, R. McBride, D. F. Burke, K. Takahashi, S. Fukuyama, Y. Tomita, E. A. Maher, S. Watanabe, M. Imai, G. Neumann, H. Hasegawa, J. C. Paulson, D. J. Smith, and Y. Kawaoka. 2014. Circulating Avian Influenza Viruses Closely Related to the 1918 Virus Have Pandemic Potential. Cell Host and Microbe 15: 692-705.
Weaver, S. C. 2013. Urbanization and geographic expansion of zoonotic arboviral diseases: mechanisms and potential strategies for prevention. Trends in Microbiology 21: 360-363.
White, N. J., S. Pukrittayakamee, T. T. Hien, M. A. Faiz, O. A. Mokuolu, and A. M. Dondorp. 2014. Malaria. The Lancet 383: 723-735.
WHO. 2000. Obesity: preventing and managing the global epidemic. World Health Organization, Geneva.
WHO. 2008. Closing the Gap in a Generation: Health Equity Through Action on the Social Determinants of Health: Commission on Social Determinants of Health Final Report. World Health Organization, Geneva.
WHO. 2010. The WHO recommended classification of pesticides by hazard and guidelines to classification 2009.
WHO. 2013. World Health Statistics 2013. . World Health Organization, Geneva.
WHO. 2014a. Global status of non-communicable diseases, pp. 280. World Health Organization, Geneva.
WHO. 2014b. World Malaria Report 2014, pp. 227. World Health Organization, Geneva.
Wilesmith, J. W., G. A. Wells, M. P. Cranwell, and J. B. Ryan. 1988. Bovine spongiform encephalopathy: epidemiological studies. The Veterinary Record 123: 638-644.
Wirth, A., M. Wabitsch, and H. Hauner. 2014. The prevention and treatment of obesity. Deutsches Ärzteblatt International 111: 705.

Wolfe, N. D., C. P. Dunavan, and J. Diamond. 2007. Origins of major human infectious diseases. Nature 447: 279-283.

Woodroffe, R., C. A. Donnelly, H. E. Jenkins, W. T. Johnston, D. R. Cox, F. J. Bourne, C. L. Cheeseman, R. J. Delahay, R. S. Clifton-Hadley, and G. Gettinby. 2006. Culling and cattle controls influence tuberculosis risk for badgers. Proceedings of the National Academy of Sciences 103: 14713-14717.

Yach, D., C. Hawkes, C. L. Gould, and K. J. Hofman. 2004. The global burden of chronic diseases: overcoming impediments to prevention and control. Journal of the American Medical Association 291: 2616-2622.

Zhang, Z. H. A. N. G., and M. van den Berg. 2013. A review of literature on labour and the agricultural productivity, food and nutrition security nexus. Wageningen University, Development Economics Group, Wageningen, The Netherlands.

Zurovac, D., A. O. Talisuna, and R. W. Snow. 2012. Mobile Phone Text Messaging: Tool for Malaria Control in Africa. PLoS Medicine 9: e1001176.