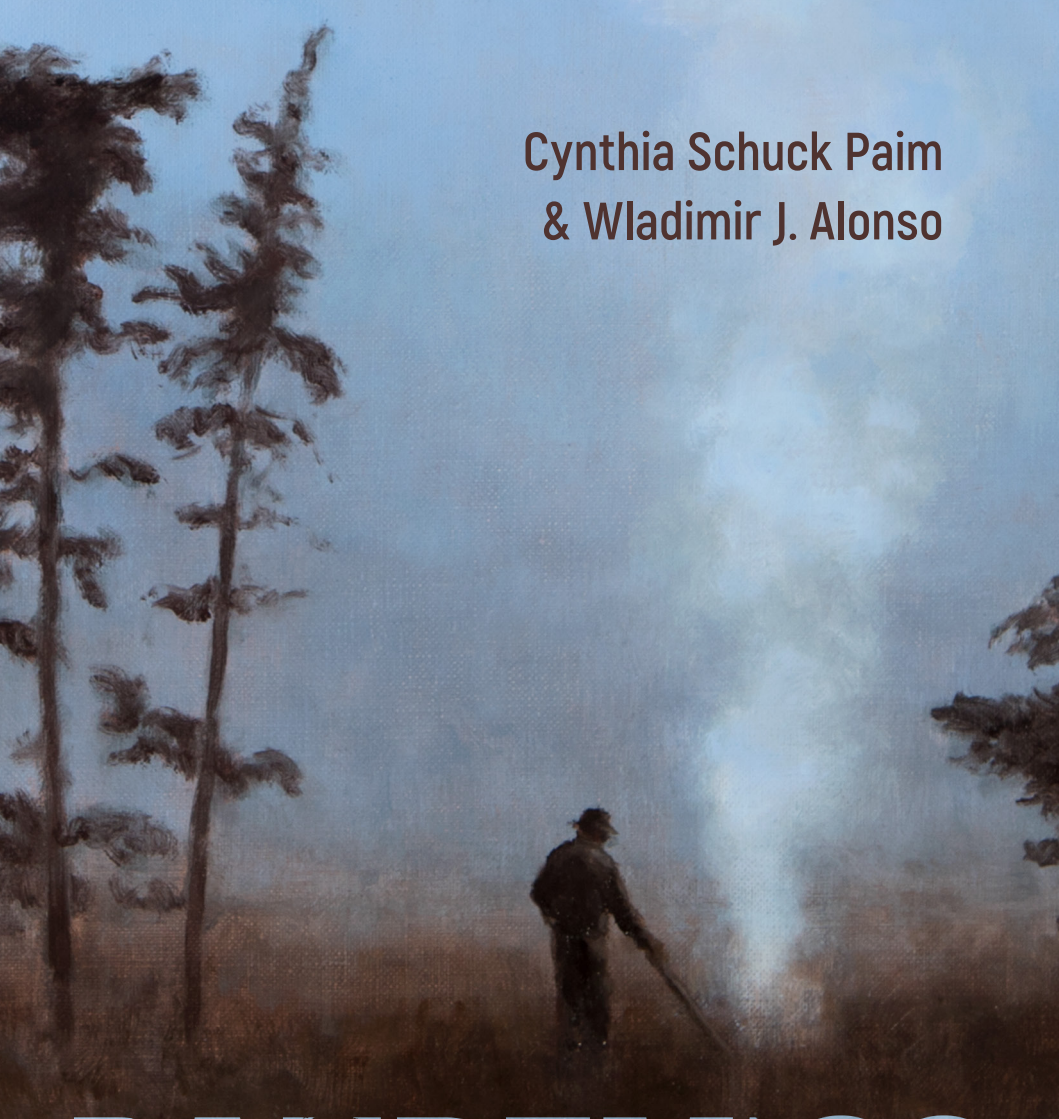
Cynthia Schuck Paim
& Wladimir J. Alonso



PANDEMICS,

global health and consumer choices



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global health and consumer choices

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contato@criaeditora.com.br



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General Director: Nádia Alonso
Editorial Director: Marcelo R. Alonso

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To our family, with love

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Introduction

Are pandemics and infectious disease outbreaks comparable to natural disasters, such as earthquakes and hurricanes, for which little can be done other than preparing for the worst? Should our civilization resign to live under the looming possibility of highly pathogenic pandemics, and simply have plans in place to mitigate their effects when they happen? The enormous burden of these diseases in terms of human suffering and loss of lives, along with their major economic and social impacts, begs the question.

Fortunately, there are ways to reduce the chances that these events keep taking their toll on humanity. The large diversity of pathogens in the wild that are potentially harmful cannot easily find their way to human beings. Some special conditions are needed, particularly in increasingly urban societies, when we mingle in the wilderness only sporadically, with boots protecting us from the soil, bug repellents and our own food and water. In those brief visits to the natural world we, wisely so, come with what our distant ancestors would see as spacesuits.

So, if most of us are not in direct contact with this wellspring of pathogens, why do they keep spilling over to us in deadly epidemics like Ebola and HIV, or in pandemics such as those of influenza and coronavirus? Here we focus on identifying the structural causes favoring the emergence of many pandemics and infectious diseases epidemics. These causes frequently overlap with those leading to the loss of millions of lives every year to common infectious diseases, and to the erosion of the power of antibiotics. Addressing

the drivers of these global health threats is essential if we are to have a shot at protecting lives, improving our well--being and making our economies and future safer.

As we will see here, we can all have a positive role in this process: our choices as consumers are, fortunately, decisive in this regard.

Direct contact with wild viruses

Deep in the jungle

On July 20, 2014, a 40-year-old man collapsed on his arrival at the Lagos airport, in Nigeria, on his way to another Nigerian city where he was supposed to give a lecture. This little-known event is perhaps one of the luckiest strikes of our civilization in modern times [1,2]. Had he made his way out of the airport, the world would probably be a different place now. The man, Patrick Sawyer, was coming from Liberia, after caring for a family member who had died from Ebola 12 days before. He had also been diagnosed with Ebola three days before the flight, and despite medical advice, left the hospital. And took the plane to Lagos, the largest city in Nigeria, with nearly 12 million people at the time. Nigeria recently overtook India as the country with the largest number of people living under extreme poverty [3]. There, at a place where millions of people use as a transportation hub within Africa and to the rest of the world, but where infrastructure and the public health system are overstretched, Ebola would had found an ideal ground to replicate the calamitous scenario that was taking place at

that very moment in Liberia, Sierra Leone, and Guinea, but at a continental – and perhaps global – scale. Fortunately, the swift actions of the Nigerian officers and international partners prevented it from happening [1,2,4].

The brutality of Ebola (its death rate and the dreadful course of the illness on patients) is well known. Ebola is one among many other infectious diseases that find its way into humans when we expose ourselves to the large diversity of viruses that are tolerated by wild animals, but that can be harmful if they spill over to people. In the case of the Ebola outbreak in West Africa, such a jump was traced back to a two-year-old boy from Meliandou, a small village in Guinea. The boy used to play with other children in a hollow tree where bats live. According to the villagers, children would sometimes catch them, and perhaps even roast their catches on sticks to fix a snack [5].

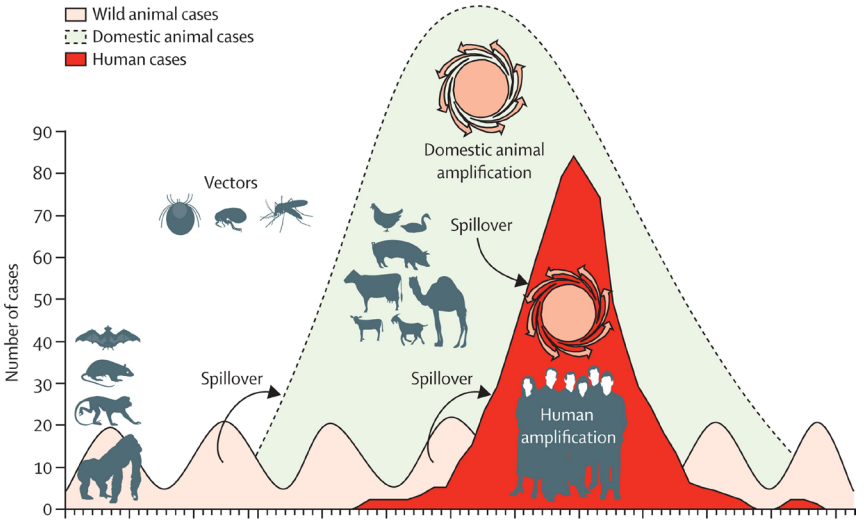


Figure. In this illustration, we can see how a pathogen can "spillover" from wild animals directly into people (pale pink to red), or first infect livestock (pale pink to green), which can then amplify its capacity of transmission to human beings (green to red) (reproduced with permission from the authors – Karesh et al, Lancet 2012).

There are many ways through which pathogens can find their way to human beings. Drinking contaminated water, breathing dust from highly contaminated environments (such as caves), eating food chewed by infected animals or having close physical contact with those animals are among them. Another popular means of human infection is through a vector –such as a mosquito or a tick– through which the pathogen makes its way from one individual to another, belonging either to the same (or different) species. In this case, because every infection transaction requires the intermediation of a middle-man (the vector), the spread of the disease is restricted to the geographic distribution of the vector, it cannot go further [6]. In contrast, diseases that find their way to a person, and from that single human case (the 'patient zero') can be transmitted from human-to-human in a sustained way are more likely to become pandemic, especially if transmission occurs through behaviours that are common (such as physical greetings, sharing of objects, close proximity and sex). And here we find a route that has been particularly important in recent pandemics: the use of wild animal species as food [7].

The origin of most Ebola outbreaks – which still happen, mainly in Central Africa – is believed to be associated with the consumption of bushmeat [8]. It is not so much the consumption of a cooked animal that is risky, but the process of hunting and butchering the animal. In this (literally) bloody affair, plenty of opportunities exist for the direct exposure of vulnerable human tissues (skin wounds, mucosa) to the pathogens and cross-contamination of other

food items with the bodily fluids of the infected animal. Humans were most likely infected with precursors of the human immunodeficiency virus (HIV) in this way, when hunting chimpanzees for meat [9]. Interestingly, chimps got infected in the same way, when hunting two other smaller species of primates [10]. HIV infection, which leads to the acquired immunodeficiency syndrome (AIDS), has spread to all corners of the globe since the 1980s, with 39 million people killed of HIV/AIDS-related complications as of 2018 [11].

Based on those accounts, one could hope that the prevention of infectious diseases imported from wildlife would be just a matter of addressing these practices and the standards of life of populations on the fringes of urban societies. Unfortunately, the influenza pandemics, the outbreaks of SARS in 2002-03 and the 2019 pandemic remind us that the problem is much wider.

In the heart of the big cities

The outbreak of the new coronavirus (SARS-CoV-2) is giving the world a taste of what a respiratory virus pandemic is capable of. If in the age of steam engines the 1918 flu virus spread quickly around the world, it is not surprising that at a time of massive global travel this respiratory virus made its way to all corners of the world in a few weeks. To slow down the infection rate and avoid widespread illness and the collapse of health systems, measures previously only imagined in science fiction movies have been announced

in multiple countries. At the time of writing (March–April 2020), one third of the human population is now under quarantine, imposed by restrictive lockdown measures [12]. If on the one hand the number of direct victims that this virus will make is still unknown, on the other there is less doubt about the economic disaster that is likely to unfold in the most vulnerable nations.

Fortunately, the case-fatality rate of SARS-CoV-2 (the proportion of deaths compared to the total number of people who were infected) is not as high as that of some prior coronavirus outbreaks. For example, in the case of the 2002–03 Severe Acute Respiratory Syndrome (SARS) epidemic, the overall case fatality rate was around 10%, reaching more than 50% in the elderly population. Swift action and scientific collaboration at an unprecedented level across the globe were decisive factors to stop it [13,14]. It is difficult to imagine the consequences that such a high lethality would have if combined with the high transmissibility of SARS-CoV-2.

These outbreaks can be also traced back to the consumption of wild animals, but not only in small villages from poor rural areas of developing countries: both SARS and SARS-CoV-2 emerged in the wet markets of vibrant urban centers in China [4,13,15–17]. In the case of SARS-CoV-2, the origin has been pinpointed to Wuhan, the most populous city in Central China, with approximately 11 million people*.

---

* As an interesting sidenote, it has been estimated that around five tonnes of bushmeat per week is smuggled from Africa to Europe in personal baggage through the Roissy-Charles de Gaulle airport in Paris.[18]

Wet markets are places where animals are sold for consumption, along with other perishable goods. Described this way, they would not be different from countless other grocery stores or street markets around the globe. What makes some of those places different is not only the large diversity of animal species that are sold, but also the way in which many are kept on display, to be butchered on site on the customers' request. Cages and stand spaces are so limited that animals are mostly crammed into tight spaces, piles and shelves, where lower levels are constantly flooded with the droppings of upper ones. Wild animals (such as turtles, bamboo rats, badgers, hedgehogs, otters, civet cats, snakes, bats, pangolins) might have been taken directly from the wild, but more often they are raised in the numerous farms run by family enterprises. Many pathologists and virologists have warned authorities of the public health dangers that these conditions represent [4,13,19]. The regular mixing of a high diversity of pathogens, from wild and domestic species, in an environment of acute stress for the animals and poor sanitary conditions, and where hosts from all species meet, creates the perfect conditions for the emergence of novel pathogens that can make their way to humans, be it through a wound, the cross-contamination of food or by the air, through the aerosolization of organic material.

China had already banned the trade and consumption of wildlife following the 2002-03 SARS outbreak, but the prohibition was short-lived, and while lasting led to the explosion of the illegal market, as it did when the ban was attempted

in 2013-14, in response to avian influenza H7N9 (paradoxically, in parallel with the ban of the trade of wild animals due to the SARS-CoV-2 pandemic, the Chinese government also recommended the use of bear bile for its treatment [20]).

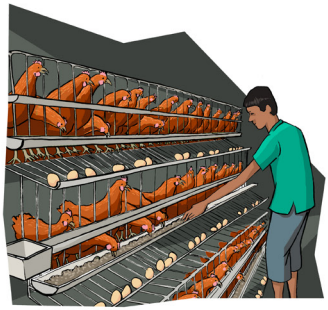
Although more prominent in China and Southeast Asia, wet markets are present in many parts of the world, and in many cases have drivers other than tradition. In Bangladesh, for example, live-bird markets are the main hub for poultry sales [21], as refrigeration in the production, transport and selling facilities is limited. This is not surprising, considering that a fraction of humanity - 13% in 2016 [22] - still had no or very unreliable access to energy (lack of energy also plays a role in rural areas and poor urban centers in China [23]). In these Bangladeshi markets, birds come from multiple places, from backyard producers to industrial poultry farmers.

Backyard poultry breeding is a common practice in rural Bangladesh (a), but industrial facilities are also present (b: laying hens are confined in so-called battery cages). Birds are transported on boats, trucks, and rickshaws (c, d) to wet markets, still the most common method of poultry commercialization, where they are sold, slaughtered and processed (e). The remains are recycled by the poor (f). Processing and consumption of the meat at home (g,h) (artwork: Leandro Lopes)

a



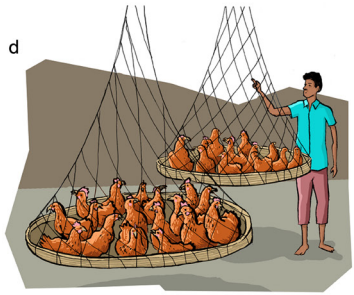
b



c



d



e



f



g



h



Back in 2014, when one of us went to Dhaka, the capital of Bangladesh, to work on a research collaboration, we conducted a study to identify "epidemiological hotspots" in the population where highly-pathogenic avian influenza (HPAI) strains had a higher risk of spilling over to humans. One of these strains, influenza A (subtype H5N1), was first reported in humans in 1997 (killing six people out of 18 infected [24]), and then re-emerged in 2003. Since then, HPAI (or 'bird flu') infections have been reported in millions of birds from more than sixty countries. In Bangladesh, more than 500 outbreaks were reported in poultry from 2007 until 2013 [25]. It was clear that the opportunities for human transmission are many, but the risk seemed particularly high during the slaughter and processing of chickens, as well as the recycling of leftovers by the poor population (figure above). Compliance with protective measures such as the use of gloves and other devices [26] was not realistic, so we proposed the vaccination of wet market workers against various influenza strains, including of course H5N1 (together with other beneficial vaccines, like the one for tetanus) as a short-term solution to reduce the risks of of HPAI crossing the bird-human barrier once more and, at some point, achieving sustained human-to-human transmission. This type of immunization is not yet implemented and remains as an important gap in this area [4].

Another emerging viral disease that has made the headlines in many Asian countries since its emergence in 1998 is that caused by the Nipah virus. In September 1998, an outbreak of an unusual disease was reported in some pig-farmers in the Perak state of Malaysia. Soon later, two other outbreaks

were reported, one in the town of Sikamat, and another in the area of Bukit Pelandok [27]. Many of those who succumbed to the virus were adult males directly associated with pig farming – overall, Nipah killed about 40% of the people who got infected. In this case, pigs functioned as an intermediate host for the transmission of Nipah to humans, enabling the 'aerosolization' of viruses that are usually transmitted in other ways in the wild. In Malaysia, flying foxes (a type of fruit bat) that arrive at the mango plantations in the flowering and fruit seasons can infect pigs that are bred in the region with their saliva and faeces. Once pigs are infected, they can transmit the virus among themselves (particularly in places with a high density of pig farms) and to humans, like any respiratory disease [28]. The Nipah virus disease is an important public health threat *"owing to its broad host and geographical range, high case fatality, potential for human-to-human transmission and lack of effective prevention or therapies"* [28]. Fortunately, the outbreak was contained before spreading further.

The work performed by public health workers in Bangladesh [25], Malaysia, and similar settings around the world is truly remarkable, along with that of field and lab researchers who conduct the surveillance of pathogens in wildlife, livestock and humans [29,30]. We all depend on them. But as we will see in the next section, the global threat posed by a pandemic and major epidemics is not restricted to the wet markets of the world. It is much closer to us.

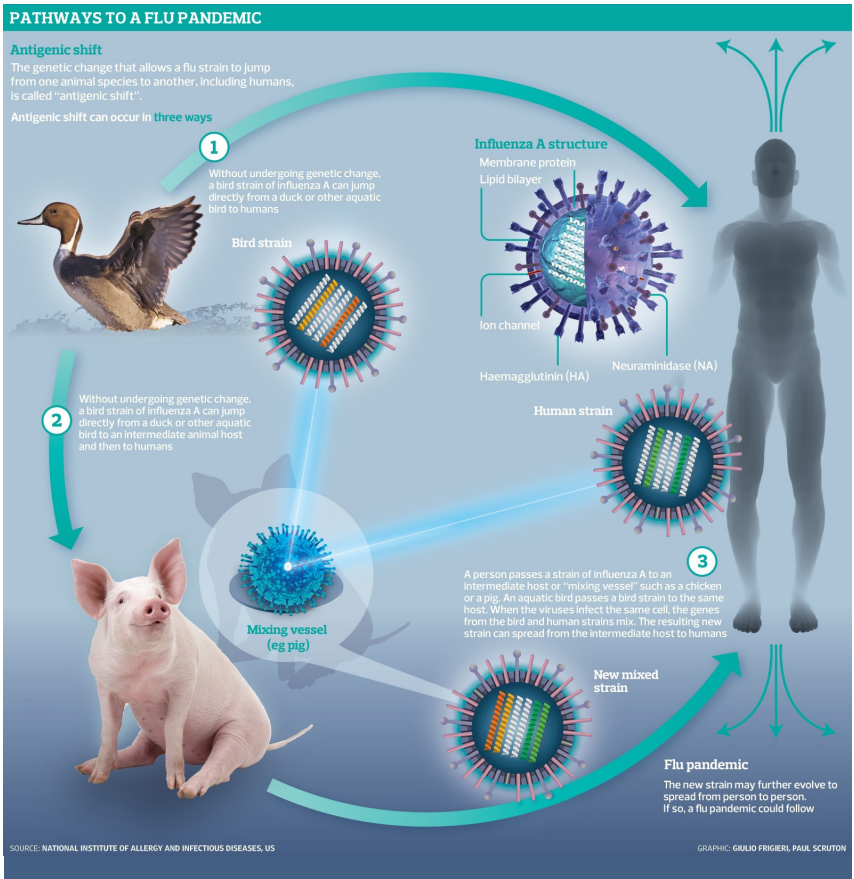
Cooking up highly pathogenic bugs

La Gloria is a small town in the province of Veracruz, Mexico. The afflicted landscape that surrounds the village, the bell tower of the church that attends to the spiritual needs of what are mostly poor farmers and the stoic resignation that transpires the broken walls of its buildings all seem to have come from the mexican writer Juan Rulfo's "The Plain in Flames" stories. In one of the town's squares there is a bronze statue of a five-year-old boy, Edgar Hernandez, holding a frog, a symbol of victory over one of the deadly plagues of Egypt. Edgar, now a student in a technical agriculture school, was an ephemeral worldwide celebrity back in 2009. An outbreak of a respiratory syndrome that caused 120,000 to 250,000 deaths around the globe in one year [31] was traced back to him as "patient zero". That syndrome was later called (H1N1)2009 pdm or simply "swine flu", for reasons that will become clear (though they probably already are) to the reader in this section.

There are many types of influenza viruses circulating in wild animal species, mainly waterbirds. The spillover from those species to humans is not a trivial task. Several key mutations are needed so that viruses that replicate in the digestive system of birds and are carried by the water can effectively infect the human lung and be transmitted instead through the air. The perfect conditions for the selection and spread of mutations that have made the transmission of

Representation of antigenic shift. Image credit: Giulio Frigieri & Paul Scruton, courtesy the National Institute of Allergy and Infectious Diseases

influenza so effective among humans have been achieved instead in the intermediate hosts between aquatic animals and humans: the birds and pigs we breed for consumption [15]. The high densities and sheer number of animals kept in intensive animal farming systems, where most of the pig and chicken meat sold to the population is produced, has enabled different strains of avian influenza to mix up in the same cells and combine their genetic material (a process called antigenic shift), which time and again has led to the emergence of viruses that can also infect humans. Pigs are particularly fit for this purpose, since their upper respiratory tract contains receptors for both avian (SA-alpha-2,3) and swine/human (SA-alpha-2,6) influenza viruses [32].



Intensive animal farming systems, also known as factory farms, have indeed created the perfect breeding ground for the emergence of highly pathogenic viral strains, along with the ideal conduit for the infection of human beings [33]. As put forward by a group of virologists from the Netherlands and Italy *"The unprecedented crowd conditions are undoubtedly major drivers of the emergence and spread of pathogens in domestic animal populations, allowing their increasingly more frequent cross-species transmission to humans"* [34]. The cramming of large populations of animals at high stocking densities in barren and closed environments promotes the development of high levels of pathogenicity in multiple ways. First, by facilitating the rapid animal-to-animal movement of multiple viral strains and the mixing and recombination of their genetic material. Additionally, viruses are faced with hosts that are incredibly susceptible to infection, where pathogens can multiply rapidly to high levels. For example, high levels of aerial pollutants such as ammonia and fecal dust, which naturally result from the presence of high volumes of animal waste, are often found in these closed facilities. Not surprisingly, the respiratory function of animals and their first barriers of defense against infection are often compromised [33]. Moreover, immunosuppression induced by chronic stress, whereby individuals lose partially the immune response that protects them against infection, is a reality in these systems (see next section).

Importantly, in these farming systems, viruses that become so pathogenic to the point of quickly killing their hosts can still spread: given the high density and close proximity of

animals, the transmission from severely sick or dead animals to live animals is possible. In contrast, under extensive, outdoor conditions, high virulence is more likely to be costly to the virus, which may stop spreading as soon as its host dies [33]. In such cases, contact with other animals may be interrupted. Also, viral survival in an outdoor environment tends to be lower. For example, influenza viruses are rapidly inactivated by sunlight and desiccation, impairing their ability to spread efficiently. Under such circumstances, the development of high virulence levels is less likely [33].

Interestingly, it has been hypothesized that it was in fact the concentration of a high number of stressed and immunosuppressed soldiers of the First World War under the filthy conditions experienced in the war camps and trenches (i.e. conditions to a large extent akin to those experienced by animals raised in intensive production systems) that provided the breeding ground for the emergence of the 1918 Spanish Flu, the deadliest pandemic in human history in absolute numbers [35]. The 1918 Spanish flu killed around 50 million people of the estimated 500 million who got infected [36].

That's why so many people are worried about the pandemic potential of influenza viruses, such as the H5N1 bird flu, which so far has killed more than half of the people infected with it [37]. One of the scenarios that takes the sleep of virologists and public health officials everywhere is the possibility of a combination of the genes of the H5N1 strain (or similar) with another that enables rapid and sustained

human-to-human transmission [4,15,34,35,38]. Fortunately, this hasn't happened yet, but it might be a matter of time. The number of birds involved in HPAI outbreaks has increased many-fold in the last decades. As we saw in the case of Bangladesh, avian influenza viruses have become entrenched in poultry populations in several Asian and northern African countries. The H5N1 strain, specifically, has been one the most geographically widespread and costly, resulting in the loss of hundreds of millions of poultry in 68 countries [39]. Ideally, vaccinating workers from factory farms would also be highly advisable [40] , for the same reasons that the vaccination of wet market workers described before was suggested as a short-term solution to reduce the risk of human infection.Of course, as with any influenza vaccine, vaccination programs must be periodical given the high rates of viral mutation, and efficacy is not guaranteed.

As a sparsely populated and economically depressed region, the land near La Gloria was one among countless similar landscapes where intensive animal production facilities have been established in the world. A few kilometers from the town there was a massive complex of animal production plants belonging to one of the large North American companies installed there following the free-trade Nafta treaty. Local inhabitants complain of the strong stench that the wind brings to their homes, which often causes them nausea and vomit and gives, for many, a reason to emigrate [41]. But when the breeze turns into wind storms, more than just the stench can be carried to the town. Aerosolized matter from open slurry pits, that is, liquid manure reduced into

tiny droplets by the wind, can travel miles (as can the flies from the pits where dead bodies of sick or injured pigs are left to decompose [41]). That's the same manure frequently sprayed onto crops as fertilizer. This may have been how the boy Edgar Hernandez got infected, sparking a pandemic that only ten years ago killed a quarter of a million people, mostly young adults.

Fragile meat-making machines: making life easy for pathogens

After World War II a dramatic shift in the way domesticated animals are raised started taking place. Rapid population growth, rising income levels and a large appetite for meat created the ideal incentives for the expansion and intensification of animal agriculture, while new technologies in animal breeding and nutrition unlocked the potential for tinkering with the biology of farm animals, a process that had dramatic effects on their well-being. Gains in productivity stemmed mostly from the selection of fast-growing and highly productive breeds, helped by the development of diets designed to maximize the conversion of animal feed into meat, milk and eggs.

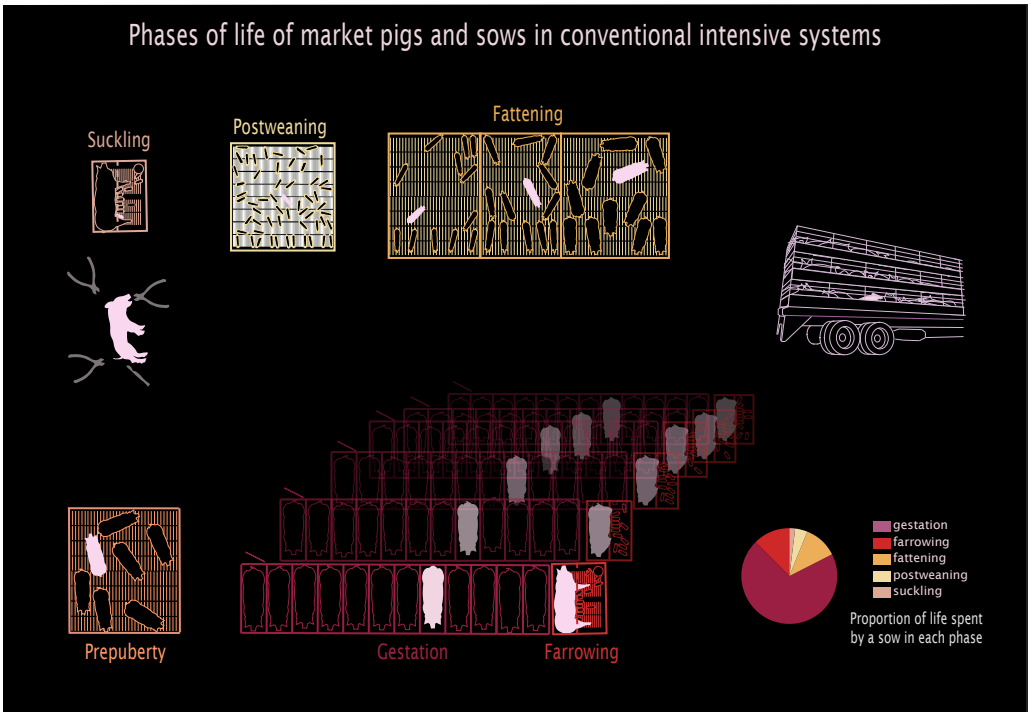
The welfare and health costs that this process imposed on farm animals can be grasped by looking at how their physiologies were transformed in a few decades. In the pork industry, sows (female breeders) can start breeding with less than six months of age and have two to three pregnancies per year. In each pregnancy, they give birth

to more than 12 piglets, which are then weaned at only 21 days, in some cases earlier. Sows are culled at less than 3 years of age, when reproductive, locomotory and metabolic problems make her unfit to keep breeding. The biological limits of farm animals were stretched even further in the poultry industry. Broiler chickens (those used for meat) gain on average more than 400 grams (around 20 percent of their final body weight) per week. They are slaughtered at 40 days of age. Laying hens were not spared either: they now lay eggs nearly every day, compared to a frequency of about one egg per week not so long ago or one egg per month in the case of its ancestral, the red jungle fowl.

This intensification process took a heavy toll on the health of animals, who now suffer routinely from multiple ailments. Many of these are referred to as 'production diseases', that is, diseases that become more prevalent, or severe, in proportion to the productivity of the animal [42]. For example, most laying hens are found to suffer from osteoporosis and bone fractures by the end of their lives: their physiologies were pushed so hard to produce more eggs (and egg shells) that a large proportion of calcium is removed from their bones [43]. Meat chickens suffer from leg abnormalities and lameness. Because they gain weight so rapidly, the growth of bones and internal organs cannot keep pace with it; heart failure and respiratory insufficiency are thus also common.

Over-selection for productivity, poor welfare and both chronic and acute stress have made factory farmed animals incredibly susceptible to infection [44,45]. Like humans, animals can succumb to disease more easily when living

under constant stress [46]. That is why in periods of stress we are more prone to respiratory infections [47] and Herpes blisters. Believe it or not, wounds also take longer to heal [48]. The outcome of stress on the immune system is most commonly suppressive, weakening the defenses against external threats like virus and bacteria [44,45]. In the case of viruses, for example, an impoverished immune function not only facilitates their replication, but also increases the likelihood that vaccines used to prevent important diseases will not work properly [49].



Typical life phases of market pigs (those used for their meat) and sows (females who give birth to market pigs) in conventional intensive systems. The suckling, postweaning and growing/fattening phases (upper part) are similar to market pigs and sows, lasting together about 6 months. The prepuberty, gestation and farrowing phases (lower part) are exclusive of sows. As shown in the pie chart, following pre-puberty, sows spend all of their remaining lives (about two years) in crates where they cannot move (artwork: Wladimir J Alonso).

Genetic selection for productivity adds to the problem, as energy that would otherwise be used for defense is diverted to growth and reproduction [33,50]. The association between higher productivity, immune dysfunction and susceptibility to disease has been indeed shown in multiple species, including chickens, pigs, cattle and dairy cows [33]. Such an increased susceptibility to infection is not only a risk for the emergence of highly pathogenic strains but, as we will see, represents a major risk for food security, increasing the likelihood of food-borne illnesses caused by enteric pathogens like Escherichia coli, Salmonella, and Campylobacter [51].

Biosecurity

Although large animal production facilities can rely on various biosecurity protocols and sanitary standards to prevent and control the transmission of infectious diseases, the sheer scale of the outputs of these systems (excrements, feed, animals, their bodily fluids), the dependence on multiple players in the production chain, the transport of live animals nationally and across borders, and the possibility of contamination of the final animal products during slaughter and processing makes it unlikely that those measures are sufficient, even if they were strictly implemented.

And they aren't. Poor compliance with biosecurity is an endemic problem in the livestock industry. Whenever surveyed, flaws in biosecurity practices are found to be widespread, even in countries where compliance is expected to be higher, such as Sweden, Canada, the United States and Australia [52–55]. This is even more concerning since the

level of implementation of biosecurity measures is often overestimated in surveys, with a large gap between the levels of compliance reported by farmers and the actions actually implemented at the farms and abattoirs [56].

The situation is worse in resource-limited settings, where a large proportion of farms fails to meet even minimal standards. Not only is biosecurity expensive, it also requires producers and stock personnel to clearly understand strict technical guidelines and behavioral protocols. Serious risk practices, such as the unsafe disposal of carcasses of dead animals, are common in many places. For example, amidst a series of outbreaks of highly pathogenic avian influenza in Egypt, an investigation conducted by researchers from the Food and Agricultural Organization of the United Nations found that the usual means for the disposal of poultry carcasses included feeding them to dogs and the throwing of dead birds into watercourses. Some growers even reported the selling of diseased poultry for human consumption [56].

These practices are unlikely to be exceptions, particularly in light of the sheer number of animals that die prior to slaughter in every nation. For example, nearly 1.5 billion pigs are slaughtered for food in the world every year, or about 4 million per day. Pre-slaughter mortality rates in the industry are about 5-10% during the suckling phase, 3% following weaning and an extra 3% during growing [57]. This translates into about half a million carcasses of dead pigs per day that must be disposed of. In the broiler industry, the numbers are more impressive: over 60 billion broiler chickens are killed annually for food. Assuming a mortality rate of 5%, this means that over 8 million birds per day die

before being sent to slaughter. Not every farm will have the proper means of ensuring that dead carcasses (often of sick animals) are disposed of following the proper biosecurity standards. The situation gets even worse during infectious disease outbreaks, when the number of animals that must be culled often exceeds the capacity of proper disposal and recycling facilities. In these cases, it is not uncommon for hundreds of animals to be hauled to landfills.

Food-borne infections

Prof. David Rogers, head of the TALA (Trypanosomiasis And Land-use in Africa) research group in Oxford, pioneered the use of a technique widely used by engineers (Fourier analysis) to analyse the seasonality of infectious diseases such as malaria and the African sleeping sickness. The group was applying this technique to find the environmental causes for the temporal changes in the number of cases and deaths from many of these diseases, using satellite imagery and meteorological data. Interested in this technique, a team from the Department of Epidemiology of the University of Wales sought the help of this research group in 2003, at the time one of us was finishing his doctoral thesis at TALA. They had data collected from 85 health authorities in England and Wales on human cases of infection by Campylobacter for several years, and wanted to understand why the number of infections peaked during spring and summer, as this could lead to better prevention.

Campylobacter is the main cause of foodborne illness in the United Kingdom, causing sickness in more than 300,000 Bri-

tish people each year [58]. It is also the most common bacterial cause of human gastroenteritis in the world [59]. Although in most episodes of this disease symptoms are restricted to intestinal inconvenience and abdominal cramps, in some cases the illness can involve life-threatening complications. Also, because the cell surface proteins (proteins in the cell wall that enable their adhesion to the body tissues of their hosts) of this bacteria are very similar to those in cartilaginous tissues, in some cases the immune system of infected patients turns against them, attacking their joints and leading to chronic arthritis. Similar surface proteins are on the myelin sheath of the nerves (an insulating layer around the nerves). If they are attacked by the immune system, patients develop the Guillain-Barré syndrome, a progressive paralysis of the body and of respiratory capacity.

Chickens are a natural host for Campylobacter species. When the chicken is slaughtered, it is very difficult to prevent the contamination of muscles, blood and bones with its gut content and fecal matter. So to prevent the cross-contamination of cooking surfaces and other foods a rather counterintuitive recommendation is often given: to avoid washing chicken meat before cooking it, so Campylobacter (and other pathogens present in the chicken's gut) does not spread further in the meat and to other parts of the kitchen [60,61]. But if the consumption and handling of chickens is associated with most cases [58] (though contamination can also occur through red meat and milk consumption), why was the number of cases peaking during certain months of the year, when the demand for fresh poultry meat was not particularly high?

Despite all the analyses and close inspection of meteorological and satellite data, we were puzzled and could not find an answer. The likely answer came from an elegant study using the same dataset, which showed that the increase in the fly population during spring and summer was enabling the cross-contamination of foods [62]. By visiting contaminated food items (mainly in warmer months, when people open their windows and prepare barbecues), those insects carry the bacteria to other food products (many eaten in raw form) in the same way contamination occurs when salad is prepared with the same kitchen utensils used to cut raw chicken meat. It has been also suggested that flies were also a source of contamination of chicken production houses [63]. As Dr. Gordon Nichols recently told us, *"Sadly fly transmission (non-biting ones) has been an area that has been somewhat neglected by microbiologists and epidemiologists over recent decades, despite being an area of interest to environmental health experts".*

Virtually every food, when spoiled, contains toxins and/or pathogens that can cause illness. There are also some products that need careful processing to be suitable for consumption (cassava, the third most important source of calories in the tropics, releases the deadly poison cyanide unless properly processed) [64]. But when we are talking about human infections caused by the consumption and handling of food, animal-sourced products vastly dominate the landscape [65].

Before the discovery of the ubiquitous existence of microorganisms, and the implementation of the sanitation and

hygiene standards most of us enjoy today, food of virtually any kind were certain carriers of many pathogens. There were plenty of opportunities for pathogens to make their way onto the surfaces of fruits, vegetables, meat and seafood during their farming, transport, delivery, sale and processing. We were left with little more than natural selection to keep us going: many people died (mostly children) from food-borne infections. It was only with the adoption of personal and kitchen hygiene practices (propelled by knowledge of the existence of microorganisms and advancements such as indoor plumbing), that pathogens catching a ride on food surfaces could be washed away (no doubt, a great leap forward in terms of public health).

But what about those pathogens that live further down, within the body cavities or tissues of the organisms we use as food? Things then get trickier. As we saw with chicken meat contaminated with Campylobacter, washing might be exactly what we are advised against. To overcome the inner defenses of organisms, those pathogens use sophisticated molecular processes to infect them. As a general rule, the closer we are to another organism in evolutionary terms, the easier it is for a pathogen to infect us. And here lies a simple reason why food-borne infections are mostly relegated to products of animal origin: humans are evolutionarily much closer to animals than to plants. It is extremely difficult for a virus, bacteria or any other pathogen adapted to infect the cells and structures of plants to attack human cells and tissues. Of course, among the fantastic diversity of life forms we can find all sorts of exceptions.

One of them is *Salmonella*, a genus of bacteria that can infect nearly any organism with an intestinal tract. *Salmonella* is responsible for over 50 thousands of deaths every year [66] following the consumption of contaminated chicken, eggs and pork. However, some species of Salmonella can, under very specific circumstances, find a way to infect plants [67]. But fear not: when you watch the news about the discovery of Salmonella in peanut butter, fruits or vegetables, or an E. coli outbreak on romaine lettuce, they can certainly be traced back to the intestines of animals, for example through the use of manure as fertilizer, the contamination of water bodies with animal waste or the contact (direct or indirect) with animal products.

The decomposition process that inevitably follows death (when the organisms' defenses are switched off, allowing the colonization of opportunistic microbes) is another reason for why it is generally much easier for an animal product to be infected with pathogens. The grains, leaves, fruits, roots, tuberculae and stems that we consume are mostly still alive, as their cells and tissues depend less on the integrity of the whole organism to keep functioning. In many cases, we could even start a new viable plant with these foods if we tried. Conversely, a struggle to artificially slow down the decomposition of an animal's body starts at the very moment the animal dies. So it does not come as a surprise that most of the food preservation techniques developed throughout our history – salting, smoking, pickling, cooking, sun-drying, ashing, peppering, fermentation, pasteurization, refrigeration – were developed mainly for products of animal origin.

Of course, a major source of contamination of meat is through the process of evisceration at the slaughter plants, through which internal organs, especially those in the abdominal cavity, are removed. Needless to say, meat comes from animals who once had a gut, and it has proved not so easy to ensure that fecal matter does not contaminate the animal carcass (internally or externally) [68,69] .

Even animal products that are not directly derived from the meat of slaughtered animals, such as milk and eggs, need special attention to avoid contamination due to decay. Milk is a bodily fluid not meant to be lingering around in the external environment for too long, but to be delivered directly from mother to offspring. So different cultures found ways of extending its life through different processes, such as its coagulation and dehydration in the form of cheese. Other animal species packed the nutrients needed for their offspring to grow in a capsule (we call this arrangement egg), enabling their development in the external environment. However, as soon as its content is released, the spoiling process is even quicker than for most other foods of animal origin (that is why homemade mayonnaise must be eaten immediately, unless prepared with pasteurized, irradiated or cooked eggs – or, of course, without eggs).

The impact of foodborne illnesses on global health is far from negligible. It has been estimated that, only in 2010, food contamination episodes of all types caused 600 million cases of illness, resulting in 420,000 deaths worldwide. So even though these illnesses are not the cause of pandemics, they have a cost in terms of human lives affected in the

same order as that of major infectious diseases such as HIV/AIDS, malaria, and tuberculosis [70].

Transport of Live Animals

Over the last decades, the number of live animals exports rose sharply. In 2017, nearly two billion animals were loaded onto ships or lorries and sent on journeys lasting from hours to weeks [71]. As the reader can imagine, the crowding of animals from multiple origins into poorly ventilated, small and stressful environments for long periods of time creates the ideal conditions for the spread of infectious diseases [72]. Not only do pathogens travel with the animals, but animal-to-animal infection is facilitated by the immunosuppressive effects of the stress: as we discussed before, acute and chronic stress weaken the immune defenses of hosts, facilitating the multiplication of pathogens. Additionally, in these journeys animals are in constant contact with their own waste and that of journey companions, increasing even further the likelihood of infection. To make matters worse, long-distance transport can increase the 'fecal shedding' of pathogens (such as Salmonella and Escherichia coli) present in the gut of animals [72], that is, their release into the stool. In general, the more pronounced the stress to which an animal is exposed, the higher the likelihood that high levels of pathogens will be found in their feces [51,73].

Predictably, animal trade has long been an effective way of introducing and spreading infectious diseases of animal origin. For example, the movement of live animals and

their products is a primary driver of the spread of foot and mouth disease across borders [74], a highly infectious disease affecting non-avian livestock species, particularly cattle. Similarly, some reports mention the introduction of bovine spongiform encephalopathy, the 'mad-cow disease', into Canada through the introduction of infected cattle into that country [75].



Livestock carrier with live cattle exported from Brazil, at an intermediate port on its way to the Middle East (photos: Cynthia Schuck)

Still, the most concerning risks of live animal movements relate to the spread of highly pathogenic strains. For example, extensive analysis of genetic data has also shown that the global trade of live pigs strongly predicts the spatial dissemination of influenza A viruses in these animals [76].

Losing the battle to infections: antibiotic resistance

In intensive pig farms, piglets are separated from their mothers, or foster mothers, with only three weeks of age, much earlier than their natural weaning age, approximately three and half months [77]. This is very stressful for these young animals for many reasons, such as the transfer to a new enclosure, the exposure to new pathogens, the stress and fights due to the sudden mixing of many litters, and the rapid change to a new diet at a time when their immune and digestive systems are still immature [78]. Consequently, many pigs at this phase suffer from severe diarrhoea, in some cases fatal. In an effort to prevent this from happening (or reduce the damage), farmers routinely add antibiotics prophylactically to the diets of all animals. Antibiotics such as amoxicillin, tetracyclines and colistin have been common choices [79].

The sudden weaning process described above is one of many practices employed at intensive pig rearing facilities that put the animals at higher risk of infections. The circumstances are different and the risk fluctuates, but it is present along

the entire production process. Of course, the same can be said about all intensively bred species – from farmed fish to cows, from rabbits to chickens [80]. So antibiotics, a treasure for medicine, are used daily on billions of animals to prevent infections resulting from conditions of poor welfare and sanitation. What is wrong with that? Let's see.

Before the development of antibiotics, humanity lived in a very different world. The painting in the figure below is from the Venezuelan artist Cristobal Rojas, a man who had his life surrounded by the loss of loved ones to tuberculosis. Cristobal himself succumbed to the disease in 1890, at the age of 32. At the time, the only treatment available was sunshine and fresh air. From as early as 5,000 years ago until the first half of the 20th century, tuberculosis claimed more victims than any other pathogen [81]. In the turn of the twentieth century, tuberculosis was killing one out of every seven people in Europe and the United States. Other infectious diseases, such as pneumonia, added to that toll, attacking every home, the rich, the poor, the educated and the uneducated. Even something as simple as a paper-cut, if infected, could lead to a fatal septicemia. Surgeries were almost unthinkable. Giving birth was a Russian roulette, as perinatal infections could not be treated. Hospitals were charitable places to provide shelter, food and comfort to the lonely and poor, but little could be done to treat the critically ill. Premature death was a fact of life, affecting virtually every family, from peasants to kings (unfortunately, this is still a reality in some poor regions of the world, where the population does not yet have access to antibiotics [82]).



'The Misery' (1886) by Cristóbal Rojas Poleo shows a husband losing his wife to tuberculosis (image: public domain)

All this changed with the discovery of penicillin in 1928, the first antibiotic, by Alexander Fleming. The treatment of wounds and infections, surgeries, transplants and procedures such as chemotherapy became possible. Coupled with other advancements such as vaccines and sanitation, antibiotics opened the gates to the world as we know today.

But the power of antibiotics to fight infections is eroding at an alarming rate. The emergence of antimicrobial-resistant bacteria is currently deemed as one of the biggest threats to global health [4,80,83]. Pathogens that cause serious

medical problems, or complications from these conditions – such as tuberculosis, many sexually transmitted diseases, urinary tract infections, pneumonia, and hospital infections – have now become resistant to a wide range of antibiotics. According to WHO, *"the world is heading towards a post-antibiotic era in which common infections could once again kill"*. In this unfolding scenario, about 700 thousand deaths per year already occur due to antibiotic-resistant infections, with an estimated 10 million deaths per year due to antibiotic-resistant infections in 2050 (more than cancer or diabetes) if trends continue unchanged [84]. As with pandemics and infectious disease outbreaks, antimicrobial resistance is also a major threat to the global economy. A review commissioned by the United Kingdom estimated this cost at 100 trillion dollars [85]. Our ongoing experience with the 2019 pandemic suggests that dramatic economic downturns due to biosecurity risks should no longer be taken lightly.

How do bacteria become resistant?

Bacteria have been on this planet for nearly 3.5 billion years, and can evolve and adapt to different conditions at an alarmingly rapid rate. They reproduce by a process known as 'binary fission', whereby the bacterial cell divides into two identical daughter cells. Under favorable conditions, some bacteria can divide every 20 minutes. If we do the maths, it means that one bacteria could in theory multiply into 2,097,152 bacteria in 7 hours!

But it is not only by passing their genetic inheritance (and occasional mutations) to their offspring that bacteria evolve. These invisible organisms are also capable of incorporating genetic material from fellow bacteria and from the environment into their genetic makeup. One of the most efficient ways through which this occurs is by the direct transfer of genetic information through small circular pieces of DNA (called plasmids) outside chromosomes that can be transferred from a donor to a recipient bacteria when they are in contact. This confers bacteria with a sort of super power that enables them to adapt to many conditions very rapidly. Not surprisingly, we find bacteria where no one else dares to live, under extreme heat, cold, acidity and radiation. The total weight of bacteria on Earth is in fact greater than the weight of all animals and plants combined [86]. In our own body we have more bacteria than human cells [86], most of which are essential to keep us healthy.

Antibiotics then come into play to treat diseases caused by harmful (pathogenic) bacteria. They act by either killing bacteria directly or reducing their ability to reproduce. However, they can stop working if bacteria find ways of countering their actions, for example by changing their structure so that the antibiotic no longer recognizes them, or by directly neutralizing (e.g. digesting) the antibiotic. These abilities can be acquired fortuitously by mutation, or by the incorporation of genes from other bacteria possessing such abilities. The greater the exposure to antibiotics, the greater the chances that the abilities that confer 'resistance' to antibiotics will spread.

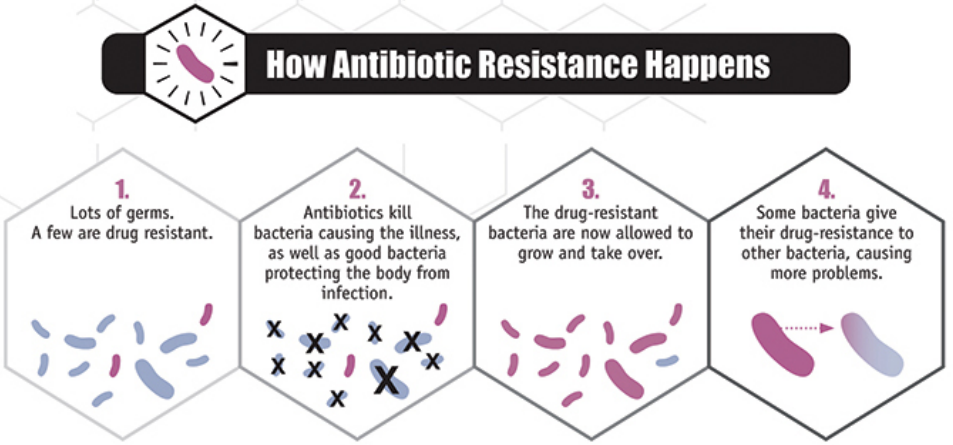


Figure. How development of antimicrobial resistance happens (illustration from the Centers for Disease Control and Prevention, United States; public domain).

Why is multi-drug resistance spreading so quickly?

Because bacteria can rapidly adapt to threatening conditions, antimicrobial resistance – the ability of bacteria to survive in the presence of antibiotics – is expected to emerge naturally when bacteria are exposed to antibiotics. The problem is that we accelerated this process a lot through the misuse and overuse of antibiotics. In the United States, for example, the Centers for Disease Control and Prevention estimated that 30 percent of the prescriptions for antibiotics written in doctor's offices and emergency departments each year are unnecessary [87].

However, the responsible use of antibiotics in human medicine alone will not solve the problem. Over 70% of the antibiotics sold in the world are not used in humans, but in animals raised in intensive farming systems [88]. In the-

se systems, the primary goal of antimicrobials is not the treatment of sick animals. Instead, they are routinely used for two other purposes. First, to promote the growth of farm animals, by adding them to their feed or water in subtherapeutic (low) doses. The mechanisms by which they make animals grow more are not entirely clear, but evidence suggests that they act by killing a fraction of the gut bacteria that competes for nutrients with the animals, as well as harmful gut bacteria that slows down their growth by causing subclinical disease (disease with no obvious symptoms) [80,89 90]. The notion behind the use of antibiotics

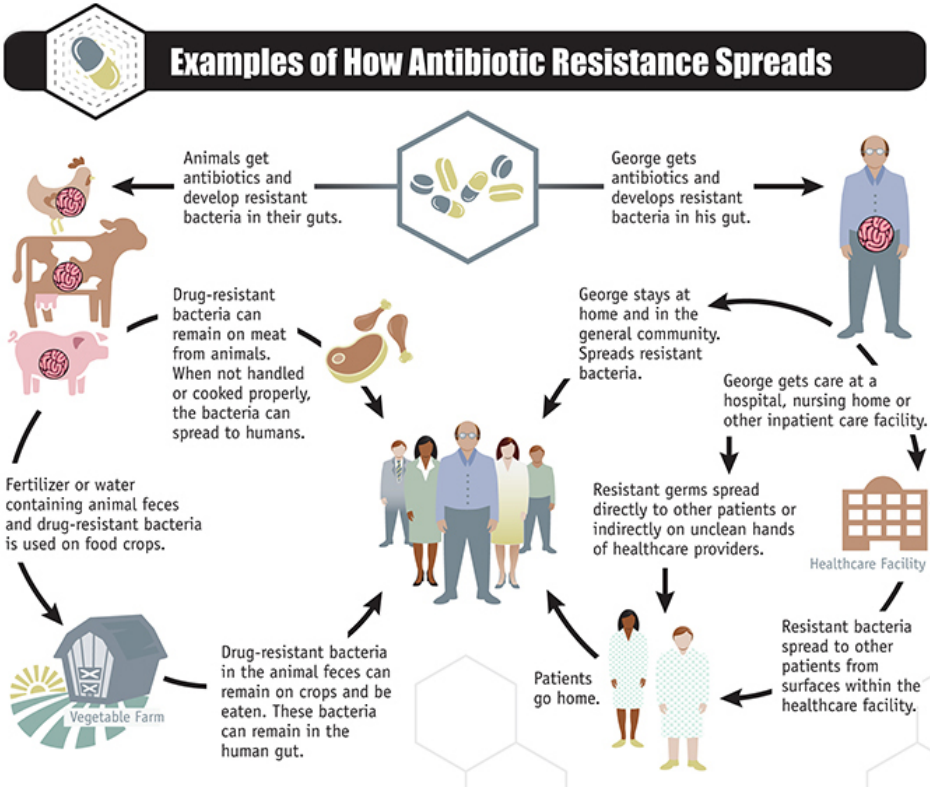


Illustration from the Centers for Disease Control and Prevention, United States (public domain)

as growth promoters is to control the bacterial flora of animals to make digestion more efficient, and divert all possible energy towards growth.

Antibiotics are also used prophylactically, to prevent infections and ensure that animals survive until the slaughter age under the intensive conditions of modern animal production systems [80,89]. As discussed in the previous sections, the living conditions in factory farms create the ideal conditions for infections to spread rapidly, thus an inherent need for disease prevention. Antibiotics are a cheap way to address this issue.

The use of colistin in pig farms is illustrative. After years of use of colistin on a large scale, a plasmid gene that makes bacteria resistant to colistin (the 'mcr-1 gene') has been found in pig farms in China [91], and since then in many other countries [92]. This has raised alarm bells throughout the scientific community, due to the possible loss of effectiveness of colistin to treat multidrug-resistant human infections – colistin is one of the last lines of defence against many life-threatening conditions in humans [93]. As we will see in the next section, there are many ways through which antibiotic-resistance can make their way from food animals to humans and, unfortunately, in the case of colistin it was not different. Since being traced back to pig farms in China [94], the colistin-resistant (mcr-1) gene has been found in human populations in many places [95,96].

As developing nations increasingly intensify the production of animal-sourced foods, resistance to the antibiotics commonly used in animal production is rising rapidly too.

Countries such as China, India, Brazil and Kenya, where meat production increased dramatically over the last decades, are now hotspots of antimicrobial resistance in animals [88]. In general, from 2000 to 2018, the proportion of antimicrobial compounds with resistance rates higher than 50% increased nearly three-fold in chickens and pigs [88] – currently, one third of drugs fail 50% of the time in chicken and one quarter of drugs fail 50% of the time in pigs. Such high rates of resistance are now observed for the antibiotics most commonly used in livestock, many of which are used to treat people too [88].

Antibiotics that are critical for human medicine are also widely used in the intensive rearing of fish (aquaculture), one of the fastest growing food industries on the planet. In these fish farms, where over 100 kilograms of fish per cubic meter of water can be cultivated [97], infectious illnesses triggered by the high stocking densities, poor water quality and chronic stress are fought by adding large amounts of antibiotics to the water. Similarly to other intensive farming systems, intensive fish farming have been designated as "hotspots" for genetic transfer and bacterial resistance [98]. A review from 2015 [99] has shown that most antibiotics commonly used in aquaculture are important in human medicine too.

How antibiotic-resistance makes its way from animals to humans

In 2014, the then Prime Minister of the United Kingdom,

Mr. David Cameron, commissioned a major review on antimicrobial resistance [84] to analyse existing evidence on the problem of rising drug resistance and propose actions to tackle it at a global level. Of the 139 academic studies the review found, the overwhelming majority reported evidence of a link between antibiotic consumption in animals and resistance in humans [85].

Take the example of Escherichia coli ST131, which is responsible for millions of infections each year and sadly has become resistant to multiple drugs [100]. Over the period of a year, a group of researchers collected samples of poultry and pork meat sold from all nine major grocery store chains in the city of Flagstaff, a small and relatively isolated town surrounded by mountains in the middle of Arizona. Simultaneously, they also collected bacterial isolates from urine and blood samples from patients diagnosed with extra-intestinal infections, and which had been sent to the Flagstaff Medical Center. They found that the same E.coli ST131 strains were present both in the patient samples and the fresh meat, a finding that was echoed by the media across the globe. A little earlier, in a much more populous city on the other side of the globe (Hyderabad, India) nearly half of the samples of chicken meat sold at retail stores had been found to be contaminated with a similar superbug [101].

Another example comes from Brazil. Methicillin-resistant Staphylococcus aureus (MRSA) is a common cause of skin infections in athletes, school students and military personnel in barracks, and also underlies some cases of pneumonia in hospitalized patients [102]. In Brazil, MRSA has been identified in milk samples from dairy cows with mastitis [103,104],

an inflammation of the mammary glands often triggered by infection. This means not only that cows suffering from mastitis do not respond to treatment with the antibiotic methicillin, but also that methicillin will be ineffective to treat people who get contaminated with MRSA (for example through the consumption of unpasteurized milk).

The presence of important antibiotic-resistant strains of bacteria in animal-sourced foods has been reported in nearly every published study that sought to investigate it. In general, these pathogens were found to be resistant to multiple antibiotics on the list of the World Health Organization. [99]. To name a few more worrying examples, bacterial strains resistant to multiple drugs, including those triggering episodes of bronchopneumonia and the development of kidney stones, have been identified in pork and chicken meat sold in seven traditional marketplaces in the state of Sao Paulo, in Brazil [105,106]. In China, identical genes conferring antibiotic-resistance to E.coli were detected in retail meat samples and human patients in Guangzhou, the third largest city in China [107]. In that same Chinese city, a gene with resistance to linezoid, the last treatment option for infections caused by MRSA, vancomycin-resistant Enterococci and penicillin-resistant Streptococcus were all found in chicken and pork meat sold in the supermarkets [108]. In the United States, 75 percent of the bacteria the Food and Drug Administration found on grocery store meat was antibiotic resistant [109].

Of course, this is also an occupational hazard to veterinarians, farmers, slaughterhouse workers and food handlers,

who can be contaminated by direct contact with food animals or their bodily fluids (such as blood, urine, feces and saliva) [80]. For example, a strong direct association was found between livestock-associated MRSA (LA-MRSA) and veterinarians in contact with pigs [110].

Environmental contamination is also another route of infection. Bacteria are excreted in the urine and stool of animals still in their active form [111,112]. This creates an enormous problem, as both antimicrobial-resistant bacteria, active antibiotics and their residues make their way to water bodies and the soil and contaminate other agricultural produce through the use of animal waste as fertilizers [113]. Unfortunately the three large bodies of the United Nations that should coordinate efforts on this front – the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) – have not 'walked the talk' effectively yet; their databases on antimicrobial resistance on animals and humans are still not integrated years after the launch of the Tripartite Alliance, preventing the swift transfer of information among those agencies and the rest of the world, hence effective action. Hopefully this will change now [114].

In recent years, many countries have issued policies to regulate the use of antibiotics in livestock, for example by gradually banning their use as growth promoters [80,89]. Although a welcomed policy, the extent to which it will address the problem is unclear, as the line between the use of antibiotics for growth promotion and disease prevention is blurred. Additionally, antibiotic-free animal products are

not necessarily free from antibiotic-resistant bacteria. For example, the prevalence of the dangerous MRSA has been found to be similar in products from pigs conventionally raised (in intensive farms) and labeled "raised without antibiotics" in retail stores in Iowa, Minnesota, and New Jersey, in the United States [115]. Although decreases in antibiotic resistance are likely to follow reductions in the use of antibiotics in livestock, this is unlikely to entirely solve the problem.

Economic Impact

The impact of pandemics and epidemics in terms of human suffering and loss of lives does not only stem from their direct effects on the health of infected people. They also hurt economies. Unemployment follows, along with further loss of health and lives, although more slowly and silently than the losses caused directly by these events. The most vulnerable and poor are bound to suffer disproportionately more the economic consequences of these episodes. For example, a study from the World Bank has shown that economic shocks in the developing world lead to more infant deaths, especially when these shocks are severe and occur in poorer regions [116].

The World Bank had estimated that a global influenza pandemic akin to the 1918 Spanish flu could cost the global economy 3 trillion dollars, or up to 4.8% of the gross domestic product. For a virus of lower pathogenicity, the costs would be approximately half of those figures [117]. And yet, these estimates have been dwarfed by the costs that the

2020 coronavirus pandemic is likely to incur. According to a preliminary assessment by the International Labour Organization [118], the global workforce could lose $3.4 trillion dollars in income in 2020 due to the current coronavirus outbreak (a value corresponding to the sum of the GDP of large countries such as Brazil and Canada [119]), with the increase in global unemployment surpassing that caused by the 2008-9 global financial crisis on some simulated scenarios.

In this equation, the global economic damage already caused by antimicrobial resistance, food-borne illnesses and existing zoonotic diseases should also be considered. For example, in the United States only, antibiotic resistance costs Americans $20 billion dollars in medical costs and over $35 billion dollars in lost productivity each year [120].

A brief account of our history with animals

Animals have served modern humans and our lineage ancestors for hundreds of thousands of years. Cut marks on bones point the scavenging of flesh scraps and marrow from leftovers of kills by other animals to as early as 3 million years ago [121], and more recently (about 200-500 thousand years ago) to the more deliberate hunting of animals as an occasional part of an opportunistic omnivorous diet.

More recently, about 15,000 years ago, some animals started following our hunter-gatherer groups (mostly the ancestors

of dogs) and became our companions. Then soon later, about 10,000 years ago, a new chapter in the association between humans and animals took place with the domestication of the first species of animals along with the emergence of the early agricultural practices. Goats, sheep, chickens, horses and oxen were among the first species used by humans as a predictable source of meat and secondary products (eggs, milk, wool, fur), as well as muscle power for tasks such as plowing and transportation. Uninvited guests (commensals such as rodents) that benefited from human settlements, for example by feeding on refuse around us, also joined the party.

In our interactions with wild animals, companions, livestock and commensals, pathogens commonly known to us were imported: scavenging and hunting gave us tapeworms, and probably hepatitis and poliomyelitis through the hunting of our close relatives, primates; companion animals, rabies; livestock gave us measles, Salmonella, smallpox (one of the world's most feared diseases that fortunately was eradicated 40 years ago) and anthrax (a disease that became famous for its potential use as a biological weapon); commensals, the plague, hantavirus and typhus [34]. Of course, the reverse is also true: many human infectious diseases can also be transmitted to animals [122].

In the late 19th century industrial development overtook agricultural expansion following the industrial revolution. Many advances brought about at this time, such as vaccines, antimicrobials, sanitation and general improvements in life-standards and health care, enabled the control of

many of the infectious diseases that had haunted us until then, granting modern populations with (overall) longer and healthier lives. At some point in the late 1960s, the belief that infectious diseases would be soon conquered was widespread [123].

But the advancements in technology and the rapidly growing population were also catalysts of a massive increase of human-animal interactions in a way completely different than those seen in the past. As we discussed here, these conditions created novel efficient routes for the transmission of pathogens that gained, or re-gained, access to human populations, along with the conditions that are paradoxically eroding many of the medical advances achieved so far. We are now in what scientists call the 'third epidemiological transition', characterized by a resurgence of familiar infections along with the emergence of new ones. [4,13,15,65]

In this scenario, new challenges are bound to happen that will test not only our ability to react to these events appropriately, but also to identify (and rectify) the elements that most contribute to their emergence.

A commitment to this and future generations

We tend to approach each new epidemic and public health crisis independently, rather than recognizing their common drivers. Domesticated animals have served humanity for millenia, but in today's modern societies we must be

honest and admit that the way we commonly raise animals is a major threat for global health and the well-being of human populations. Moreover, the extensive human and financial losses associated with infectious disease outbreaks and drug resistance make this an enormous economic and social problem too. As global meat consumption continues to rise even further (it has doubled in the last 50 years, from a global average of 20 kilograms per person in 1961 to around 43 kilograms in 2014 [124]), these risks and costs are expected to increase even further.

The world spends billions every year in the design and implementation of measures to protect us against infectious diseases. In 2015, funding for the investigation of emerging and zoonotic diseases in a single US institution, the Centers for Disease Control, was nearly half a billion dollars [120]. The annual cost of pandemic preparedness alone is estimated to lie somewhere within $ 3 billion to $ 5 billion [125]. Yet it is disturbing that many of the most basic control policies supposed to be well established have failed when tested, even in high income countries such as the United States [120]. Should we insist on making public health safety an exclusively reactive endeavor?

While large investments are currently being poured into the development of vaccines and treatments to control the damage of the 2019 coronavirus outbreak, these (most needed and welcomed) developments are unlikely to shield us from a future epidemic. We must have this same sense of urgency to accelerate the development of modern methods of food production, which include the development of substitutes of animal protein. In fact, this is a revolution

in the food sector that has already started, with a diverse range of products on that menu that include meat-like products made from plants or even grown in vats [126,127]. Ultimately, however, the demand for alternative protein sources must come from the population, and the market will respond appropriately. Just as we exercise our citizenship by adopting the necessary measures to curb the advancement of COVID-19 and protect our communities, we must also exercise it with our wallets at the supermarket, and think how best our purchasing and dietary choices can build a safer future for generations to come.

Personal choices and societal risks

It is widely accepted that we need to consider the societal risks of each energy source. Convenience and price alone are not enough. We are willing to pay more for energetic choices that are safer for this and future generations. And yet, for some reason, this rationale has not been incorporated into the public mindset when we are talking about the risks that different food products (or production systems) impose on society [80,89].

It is of course easy for all of us to have a firm stand on outlawing ritual cannibalism in some remote corners of Papua New Guinea to stop the transmission of Kuru disease, a fatal neurodegenerative disorder acquired through the consumption of the brain of deceased relatives (this prohibition was indeed implemented and had great success in stopping disease spread). And global public opinion is likely to reject the prospect of wet markets of China reopening

(as they did after the 2003 SARS outbreak) following the ongoing pandemic. More difficult though, is *"to be honest with ourselves about what kinds of pandemics we may be brewing through own risky animal-use practices"* [128]

From a health perspective, the costs of some dietary choices falls predominantly on the individual who makes them. That can be said to be the case of excessive consumption of ingredients such as sugar and salt. But it is time to accept that different groups of food products do pose different biosecurity risks and societal costs. One the one hand, we can't be naive and presume that all outbreaks of infectious diseases and other public health threats will emerge exclusively from the consumption of animal-sourced foods. For example, in outbreaks of the Nipah virus disease in Bangladesh, one of the routes of transmission from bats to people has been pinpointed to the contamination of date palm sap with the saliva of Pteropus fruit bats endemic to the region [129], even though, as we saw before, the bridge between bats and humans is also made through pigs [28], as well as cows and goats [129]. But so far there hasn't been a single pandemic in human history that could be traced back to plants, so the data and information summarized along these pages should be food for serious thought.

Additionally, as we saw through several examples, even when personal choices do not contribute to the brewing of an epidemic or global epidemic, they can put others at risk. This is for instance the case of food (and environmental) contamination with animal waste and the development of antimicrobial resistance. Maryn McKenna's excellent book "Big Chicken" [80] walks the reader through several examples

of serious illness and death hitting not only those who ate contaminated meat, but also people (and whole communities) affected by contamination with the by-products of animal production systems, or for whom antibiotics lost their therapeutic value due to their excessive use in farm animals. The public health logic of "passive-smoking" applies here, but on a global scale. The borderless dynamics of zoonotic diseases, food contamination and antimicrobial resistance make all of us, in some sense, "passive bushmeat eaters", "passive wet-market visitors", "passive factory--farm workers" and "passive industrial-meat consumers".

Looking forward

Technology

Technology was pivotal to eradicate and control many of the public health challenges that would otherwise still be taking the life and health of millions of people. Vaccines and antibiotics come quickly to mind, but other non-pharmacological technical advances were also absolutely critical. Some brought us comfort in our daily lives, such as indoor plumbing and sanitation. Others are still considered by many as annoyances, such as seat-belts, smoke restrictions or condoms. And yet, we adopted these interventions for understanding that their benefits greatly outweigh the individual inconveniences.

Once we accept the costs and risks that many products of animal origin represent, and understand that this is a matter to be taken seriously at the personal and collective

level, technology can again lends us a hand. Many people are still unaware that we are amidst one of the greatest technological revolutions of all times: over the last years, incredible progress has been made on the development of animal products that no longer require breeding and raising live animals, as well as animal-like products made from plants. The technologies are diverse: sometimes plant components are combined in ingenious ways to mimic the taste, smell, texture and looks of animal products. Burgers are the most popular example. Since a company pioneered a technique to achieve a "bleeding" plant-based burger with remarkably similar texture and taste to its meat counterpart, several other companies joined the race, perfecting at each new release the plant-based copycat version of the burger.

Another approach is similar to that used to produce, for instance, human insulin for diabetics. In the past, medical insulin was extracted from cattle and pigs, and purified. However, on top of the biosecurity issues that this process represented and that the reader is already well aware of at this point in the book, insulin of animal origin sometimes caused allergic reactions, since it is similar, but not equal, to the insulin produced by the human pancreas. The elegant solution was to copy what viruses do when they invade a cell and hijack its machinery for their own purposes (in their case, to create more viruses). In this case, human genes in charge of producing insulin are inserted into the genome of bacteria, which then became allergen-free human-insulin producing machines. A similar technique is now being used to produce milk, but because milk is a more complex substance, it also uses yeast for the production of the milk

proteins whey and casein [130]. Gradually, the milk produced in this way will have the same composition and properties of regular milk - thus enabling the production of dairy products such as cheese, yogurts, ice-cream (already being commercialized) and ghee with the same methods used to make these dairy products. But it will also provide us with other benefits, as it will not contain any of the unwelcomed elements present in cows' milk, such as traces of animal hormones, antibiotics, and eventual pus (dead white blood cells) and blood from udder infections (for example, in the United States, one in every six dairy cows has mastitis [131]).

A similar emerging technology is the production of cultured meats (also known as lab-grown meat or clean meat). It is real meat, but produced through the cultivation of animal cells instead of relying on the breeding, raising and slaughter of entire animals. In this process, animal cells that have the ability to develop into muscle cells are grown in bioreactors* and then assembled . Because this is a sterile environment, meat produced in this way is free of the many harmful pathogens that we discussed in this book. For the same reason, the use of antibiotics is not needed. Moreover, the technology opens a wide range of possibilities in terms of food production, as it enables the development of animal food products that are diverse (in theory, cells from different species can be cultured), healthier and nutritionally designed to meet different personal needs [126]. The first breakthrough of this technology came in 2013, when a team of Dutch scientists provided the world with a taste test of a cultured beef burger. Since then, production costs have

*Bioreactors already have many applications in the food industry, such as the production of fermented food and beverages, such as beer.

dropped sharply and other alternatives have been added on the menu, including cultured chicken, pork, duck and even fish (bluefin tuna) [132].

These range of new products and technologies attend the demand of a wide spectrum of consumers, from the health- or environmentally-conscious to those worried about the ethical implications of animal farming. As a result, companies in this sector have attracted much investment. It is a safe bet to predict that this sector will include an increasingly larger number of substitutes of animal products, which will become progressively more appealing and accessible to a growing proportion of the population.

And, of course, we should not forget that meat was a scarce resource for most people during most of human history, so thousands of tasty protein-rich recipes from traditional cuisines were developed with little or no meat at all. In a Sunday trip to a prehistoric site, we ended up making friends with a colorful and sweet group of old ladies who, at some point, told us that they didn't enjoy the way people cook nowadays: "far too many 'tropezones', you don't find the chickpeas!". Tropezones are the occasional (hence the name 'stumbles') pieces of meat added to the chickpea stew for taste. Grandmas know best.

A Wealthier World

When just slightly over a century ago steam, combustion and electric engines started to replace animals as a source of mechanical energy, many honest and hard-working pro-

fessionals who depended on the old ways (such as carriages, sakias, mills, trams, horse-breeders) lost their way of living. But a new world of conveniences, new job possibilities and well-being was created. The new machines created the conditions for the improvement of health, sanitation, transportation and many other achievements at unprecedented scales.

The "creative destruction" of the market brought about by technology and innovation brings prosperity and higher standards of life. But during the transition period it may also leave a trail of economic casualties. Big companies and agile enterprises can adapt easily – large meat processing companies are already investing on the production of plant-based protein. However, we should bear in mind the negative consequences that the transition towards safer protein sources may have in the short-term for small-scale producers. These individual financial tragedies can be better envisioned when common folks are suddenly cut short of their way of living in the wake of an epidemic crisis, as was the case for many poor citizens during the lockdown measures implemented in the coronavirus crisis. Therefore, the same ingenuity that is now propelling a revolution in the food sector must be also employed to help smooth out the transition from the existing production practices and supply chains to the new ones, otherwise a wall of resistance will follow.

The rural areas of southern Europe, with their scattered old villages and stone terraces surrounded by patches of oak and pine woods are some of the most picturesque landscapes in the globe, and provide an example of economic opportunities that could bear fruit in what are now largely depopulated regions. In these areas of great beauty, a revival and repopu-

lation of the rural landscape was starting to take place, based mostly on rural tourism, the promotion of outdoor activities and investments on the renovation of traditional properties. However, in several of these regions, these activities have been cut short because of the exponential expansion of factory farms in recent years (most of them facilities to fatten pigs and poultry). Although from the outside they are not necessarily visually aggressive to the landscape, the odour that emanates from those buildings and from the manure lagoons and crop fields sprayed with these residues not only poses some serious environmental and biosafety challenges, but also frustrates any possibility of tourism development within a considerable range, and the repopulation of these areas by those who are not completely dependent on the farms. The opportunity for the diversification and expansion of the economic activity in the region that would come with tourists and more residents, and which would provide an alternative way of living to many, is also missed.



But long-term economic dynamics and social theory are not enough to revert this situation and make local farmers even think of changing their business model. Although the profit margins of the activity are meagre for those in the far end of the production chain (often contracted by larger companies to raise and fatten the animals) these farmers don't see much alternative other than being part of the cheap meat production engines that are fueled by a demand for animal products still on the rise. Solutions for situations like the one described above – or more dramatic ones, as those lived by hunters of bushmeat in very poor corners of the world – must be thoroughly considered, and alternatives presented to make those citizens willing and pleased partners in the transition. Technical and financial counselling for the conversion of their facilities into different production plants, and for the exploitation of the touristic potential of rural areas (that will gain track when animal production plants are converted) would be much needed.

A More Resilient World

In many nations, the greatest difficulty experienced during the 2019 coronavirus pandemic was brought about by the impact it had on unprepared health systems, incapable of meeting the demand of beds, healthcare workers and ventilators needed to absorb the sudden influx of inpatients in need of more intensive care. This should not have happened:

Figure. Landscapes like this, in southern Europe, have come to be dominated by intensive animal rearing facilities, frustrating the development of the tourism sector due to the strong stench that emanates from the waste of a large number of confined animals (Photo: Cynthia Schuck)

in addition to focusing on the difficult task of forecasting which new diseases will emerge, their spread rate and severity, societies must also use simulation tools to exert imaginary stress on its many systems to a range of possible or plausible unpredictable threats, identifying which components are most fragile and which measures most effective to make them resilient [133]. With a few exceptions [134], this approach has been neglected . Had this exercise been performed more frequently, it would have become clear that any outbreak of respiratory disease – caused by coronavirus, influenza or any other respiratory pathogen – would stretch the capacity of health care systems to absorb critically ill patients beyond their current limits.

As we discussed through these pages, one of our biggest fragilities –one which makes us incredibly vulnerable to catastrophic events of biological nature– lies in our food production systems. Promoting and facilitating a transition towards globally safer food sources shall prove to be a worthwhile investment on the health and lives of this and future generations.

Cynthia has a PhD in Zoology from Oxford, and has conducted various research projects on the epidemiology of respiratory diseases and pandemics, animal cognition and in more recent years on farm animal health and welfare. Her published research includes studies on the mortality impact of the 1918 and 2009 influenza pandemics, on the burden of respiratory infectious diseases, the evaluation of the impact of public health interventions using hospitalization data, the impact of the pneumococcal vaccine to reduce mortality in children, studies on animal behavior and a pioneer work on the environmental conditions favoring the evolution of advanced cognition. She has taught workshops on data analysis and scientific capacity building for many years.

Wladimir started his research career on the evolution of biological complexity and biological altruism, and later performed field and lab studies on ecology and animal behavior. After his PhD, he worked on global health issues for over a decade, pioneering the analyses of latitudinal gradients of seasonal parameters of diseases, and the analyses that revealed that the annual vaccination of influenza is administered at the wrong time in the tropics. Wladimir developed Epipoi, a software for the analysis of epidemiological time-series used by many researchers, and taught workshops to audiences of epidemiologists, biologists, physicians and public health professionals around the world. He published more than 70 papers on topics such as vaccination policies, pandemics, catastrophe preparedness, evolution of colors in animals and history of science.

Global timing of influenza circulation by latitude (Alonso et al 2015, Scientific Reports 5: 17214)

Sources

1. Courage, K. H. How Did Nigeria Quash Its Ebola Outbreak So Quickly? Scientific American (2014).

2. Shuaib, F. et al. Ebola virus disease outbreak – Nigeria, July–September 2014. MMWR Morb. Mortal. Wkly. Rep. 63, 867–872 (2014).

3. Adebayo, B. Nigeria overtakes India in extreme poverty ranking. CNN (2018).

4. Osterholm, M. & Olshaker, M. Deadliest Enemy: Our War Against Killer Germs. (Little, Brown Spark, 2017).

5. Quammen, D. & Muller, P. Seeking the Source of Ebola. National Geographic (2015).

6. Alonso, W. J. & McCormick, B. J. J. Urban Ecology and the Effectiveness of Aedes Control. in Dengue Fever – a Resilient Threat in the Face of Innovation (eds. Abelardo Falcón-Lezama, J., Betancourt-Cravioto, M. & Tapia-Conyer, R.) (IntechOpen, 2019).

7. Karesh, W. B., Cook, R. A., Bennett, E. L. & Newcomb, J. Wildlife trade and global disease emergence. Emerg. Infect. Dis. 11, 1000–1002 (2005).

8. Kupferschmidt, K. Hunting for Ebola among the bats of the Congo. (2017) doi:10.1126/science.aan6907.

9. Hahn, B. H., Shaw, G. M., De Cock, K. M. & Sharp, P. M. AIDS as a zoonosis: scientific and public health implications. Science 287, 607–614 (2000).

10. History.com Editors. History of AIDS. HISTORY https://www.history.com/topics/1980s/history-of-aids (2019).

11. Pandey, A. & Galvani, A. P. The global burden of HIV and prospects for control. Lancet HIV 6, e809–e811 (2019).

12. Pleasance, C. Map shows a third of world's population are under coronavirus lockdown. Mail Online https://www.dailymail.co.uk/news/article-8150501/Map-shows-worlds-population-coronavirus-lockdown.html (2020).

13. Peiris, J. S. M., Yuen, K. Y., Osterhaus, A. D. M. E. & Stöhr, K. The severe acute respiratory syndrome. N. Engl. J. Med. 349, 2431–2441 (2003).

14. Snowden, F. Lecture 25 - SARS, Avian Inluenza, and Swine Flu: Lessons and Prospects. videolectures.net http://videolectures.net/yalehist234s2010_snowden_lec25/ (2014).

15. Webby, R. J. & Webster, R. G. Are we ready for pandemic influenza? Science 302, 1519–1522 (2003).

16. Vox. How wildlife trade is linked to coronavirus. https://youtu.be/TPpoJGYlW54 (2020).

17. Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C. & Garry, R. F. The proximal origin of SARS-CoV-2. Nat. Med. (2020) doi:10.1038/s41591-020-0820-9.

18. Chaber, A.-L., Allebone-Webb, S., Lignereux, Y., Cunningham, A. A. & Marcus Rowcliffe, J. The scale of illegal meat importation from Africa to Europe via Paris: Illegal intercontinental meat trade. Conservation Letters 3, 317–321 (2010).

19. Sims, L. D. et al. Origin and evolution of highly pathogenic H5N1 avian influenza in Asia. Vet. Rec. 157, 159–164 (2005).

20. Fobar, R. China promotes bear bile as coronavirus treatment, alarming wildlife advocates. National Geographic (2020).

21. Khan, S. U. et al. Avian influenza surveillance in domestic waterfowl and environment of live bird markets in Bangladesh, 2007-2012. Sci. Rep. 8, 9396 (2018).

22. Ritchie, H. & Roser, M. Access to Energy. Our World in Data (2019).

23. Standaert, M. Appetite for 'warm meat' drives risk of disease in Hong Kong and China. The Guardian (2020).

24. Highly Pathogenic Asian Avian Influenza A(H5N1) Virus | Avian Influenza (Flu). https://www.cdc.gov/flu/avianflu/h5n1-virus.htm (2018).

25. Rimi, N. A. et al. A Decade of Avian Influenza in Bangladesh: Where Are We Now? Trop Med Infect Dis 4, (2019).

26. Noor, M. A. H. & Mostafizur Rahaman, S. Knowledge, attitude and practices survey on avian influenza in three districts of Bangladesh. 14, 27–36 (2016).

27. Sharma, V., Kaushik, S., Kumar, R., Yadav, J. P. & Kaushik, S. Emerging trends of Nipah virus: A review. Rev. Med. Virol. 29, e2010 (2019).

28. Pulliam, J. R. C. et al. Agricultural intensification, priming for persistence and the emergence of Nipah virus: a lethal bat-borne zoonosis. J. R. Soc. Interface 9, 89–101 (2012).

29. One Health: The Human-Animal-Environment Interfaces in Emerging Infectious Diseases: The Concept and Examples of a One Health Approach. (Springer, Berlin, Heidelberg, 2013).

30. Jones, K. E. et al. Global trends in emerging infectious diseases. Nature 451, 990–993 (2008).

31. Simonsen, L. et al. Global Mortality Estimates for the 2009 Influenza Pandemic from the GLaMOR Project: A Modeling Study. PLoS Med. 10, e1001558 (2013).

32. Trebbien, R., Larsen, L. E. & Viuff, B. M. Distribution of sialic acid receptors and influenza A virus of avian and swine origin in experimentally infected pigs. Virol. J. 8, 434 (2011).

33. Greger, M. The human/animal interface: emergence and resurgence of zoonotic infectious diseases. Crit. Rev. Microbiol. 33, 243–299 (2007).

34. Reperant, L. A., Cornaglia, G. & Osterhaus, A. D. M. E. The importance of understanding the human-animal interface: from early hominins to global citizens. Curr. Top. Microbiol. Immunol. 365, 49–81 (2013).

35. Greger, M. Bird Flu: A Virus of Our Own Hatching. (Lantern Books,US, 6 de diciembre de 2006).

36. Taubenberger, J. K. & Morens, D. M. 1918 Influenza: the mother of all pandemics. Emerg. Infect. Dis. 12, 15–22 (2006).

37. Poovorawan, Y., Pyungporn, S., Prachayangprecha, S. & Makkoch, J. Global alert to avian influenza virus infection: from H5N1 to H7N9. Pathog. Glob. Health 107, 217–223 (2013).

38. Webster, R. G. 'Influenza: Lessons Learned from Pandemic H1N1'. https://youtu.be/4zONbkE1J5E (2011).

39. Wu, T. & Perrings, C. The live poultry trade and the spread of highly pathogenic avian influenza: Regional differences be tween Europe, West Africa, and Southeast Asia. PLoS One 13, e0208197 (2018).

40. Saenz, R. A., Hethcote, H. W. & Gray, G. C. Confined animal feeding operations as amplifiers of influenza. Vector Borne Zoonotic Dis. 6, 338–346 (2006).

41. Bacon, D. The Right to Stay Home: How US Policy Drives Mexican Migration. (Beacon Press, 2013).

42. Jones, P. J., Niemi, J., -P. Christensen, J., Tranter, R. B. & Bennett, R. M. A review of the financial impact of production diseases in poultry production systems. Anim. Produc. Sci. (2018) doi:10.1071/AN18281.

43. Perry, G. Welfare of the Laying Hen. (Poultry Science Symposium Series, 2004).

44. Ben-Nathan, D. Stress and virulence: West Nile virus encephalitis. Israel Journal of Veterinary Medicine 68, 135–140 (2013).

45. Humphrey, T. Are happy chickens safer chickens? Poultry welfare and disease susceptibility. Br. Poult. Sci. 47, 379–391 (2006).

46. Moberg, G. P. & Mench, J. A. The Biology of Animal Stress: Basic Principles and Implications for Animal Welfare. (CABI Pub., 2000).

47. Klein, T. W. Stress and infections. J. Fla. Med. Assoc. 80, 409–411 (1993).

48. Ferreira, B. R. & Cardoso, J. C. Herpes and Stress. in Stress and Skin Disorders: Basic and Clinical Aspects (eds. França, K. & Jafferany, M.) 209–225 (Springer International Publishing, 2017).

49. Umar, S. et al. Immunosuppressive interactions of viral diseases in poultry. Worlds. Poult. Sci. J. 73, 121–135 (2017).

50. Norris, K. & Evans, M. R. Ecological immunology: life history trade-offs and immune defense in birds. Behav. Ecol. 11, 19–26 (2000).

51. Rostagno, M. H. Can stress in farm animals increase food safety risk? Foodborne Pathog. Dis. 6, 767–776 (2009).

52. Backhans, A., Sjölund, M., Lindberg, A. & Emanuelson, U. Biosecurity level and health management practices in 60 Swedish farrow-to-finish herds. Acta Vet. Scand. 57, 14 (2015).

53. Racicot, M., Venne, D., Durivage, A. & Vaillancourt, J.-P. Description of 44 biosecurity errors while entering and exiting poultry barns based on video surveillance in Quebec, Canada. Prev. Vet. Med. 100, 193–199 (2011).

54. Dorea, F. C., Berghaus, R., Hofacre, C. & Cole, D. J. Survey of biosecurity protocols and practices adopted by growers on commercial poultry farms in Georgia, U. S. A. Avian Dis. 54, 1007–1015 (2010).

55. Scott, A. B. et al. Biosecurity practices on Australian commercial layer and meat chicken farms: Performance and perceptions of farmers. PLoS One 13, e0195582 (2018).

56. Negro-Calduch, E., Elfadaly, S., Tibbo, M., Ankers, P. & Bailey, E. Assessment of biosecurity practices of small-scale broiler producers in central Egypt. Prev. Vet. Med. 110, 253–262 (2013).

57. ABCS. Producao de Suinos: teoria e pratica (Swine production, theory and practice) - Associação Brasileira dos Criadores de Suínos. (Brasilia, 2014).

58. BBSRC, DEFRA & FSA. UK Research and Innovation Strategy for Campylobacter - in the food chain. https://bbsrc.ukri.org/documents/100717-campylobacter-strategy-pdf/ (2010).

59. WHO. Campylobacter - Key facts. Key facts, World Health Organisation https://www.who.int/news-room/fact-sheets/detail/campylobacter (2018).

60. FoodStandardsAgency. The truth about campylobacter. https://www.youtube.com/watch?v=V3QS_EgEYlk (2014).

61. Channel 4 News. See how the Campylobacter chicken bug spreads in a kitchen. https://www.youtube.com/watch?v=c4wbqWA2qI8 (2014).

62. Nichols, G. L. Fly transmission of Campylobacter. Emerg. Infect. Dis. 11, 361–364 (2005).

63. Djennad, A. et al. Seasonality and the effects of weather on Campylobacter infections. BMC Infect. Dis. 19, 255 (2019).

64. McGee, H. On Food and Cooking: The Science and Lore of the Kitchen. (Simon and Schuster, 2007).

65. Karesh, W. B. et al. Ecology of zoonoses: natural and unnatural histories. Lancet 380, 1936–1945 (2012).

66. GBD 2017 Non-Typhoidal Salmonella Invasive Disease Collaborators. The global burden of non-typhoidal salmonella invasive disease: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect. Dis. 19, 1312–1324 (2019).

67. Wiedemann, A., Virlogeux-Payant, I., Chaussé, A.-M., Schikora, A. & Velge, P. Interactions of Salmonella with animals and plants. Front. Microbiol. 5, 791 (2014).

68. Heuvelink, A. E., Roessink, G. L., Bosboom, K. & de Boer, E. Zero-tolerance for faecal contamination of carcasses as a tool in the control of O157 VTEC infections. Int. J. Food Microbiol. 66, 13–20 (2001).

69. Wheatley, P., Giotis, E. S. & McKevitt, A. I. Effects of slaughtering operations on carcass contamination in an Irish pork production plant. Ir. Vet. J. 67, 1 (2014).

70. Devleesschauwer, B., Haagsma, J. A., Mangen, M.-J. J., Lake, R. J. & Havelaar, A. H. The Global Burden of Foodborne Disease. in Food Safety Economics: Incentives for a Safer Food Supply (ed. Roberts, T.) 107–122 (Springer International Publishing, 2018).

71. Levitt, T. Two billion and rising: the global trade in live animals in eight charts. The Guardian (2020).

72. Greger, M. The long haul: risks associated with livestock transport. Biosecur. Bioterror. 5, 301–311 (2007).

73. Freestone, P. & Lyte, M. Stress and microbial endocrinology: prospects for ruminant nutrition. Animal 4, 1248–1257 (2010).

74. Di Nardo, A., Knowles, N. J. & Paton, D. J. Combining livestock trade patterns with phylogenetics to help understand the spread of foot and mouth disease in sub-Saharan Africa, the Middle East and Southeast Asia. Rev. Sci. Tech. 30, 63–85 (2011).

75. Hardstaff, J. L., Häsler, B. & Rushton, J. R. Livestock trade networks for guiding animal health surveillance. BMC Vet. Res. 11, 82 (2015).

76. Nelson, M. I. et al. Global migration of influenza A viruses in swine. Nat. Commun. 6, 6696 (2015).

77. Jensen, P. Observations on the maternal behaviour of free-ranging domestic pigs. Appl. Anim. Behav. Sci. 16, 131–142 (1986).

78. Campbell, J. M., Crenshaw, J. D. & Polo, J. The biological stress of early weaned piglets. J. Anim. Sci. Biotechnol. 4, 19 (2013).

79. Casal, J., Mateu, E., Mejía, W. & Martín, M. Factors associated with routine mass antimicrobial usage in fattening pig units in a high pig-density area. Vet. Res. 38, 481–492 (2007).

80. McKenna, M. Big chicken: the incredible story of how antibiotics created modern agriculture and changed the way the world eats. (National Geographic Books, 2017).

81. Daniel, T. M. The history of tuberculosis. Respir. Med. 100, 1862–1870 (2006).

82. Frost, I., Craig, J., Joshi, J., Faure, K. & Laxminarayan, R. Access Barriers to Antibiotics. (2019).

83. WHO. Global action plan on antimicrobial resistance. (World Health Organization, 2015).

84. Antimicrobial Resistance Review. https://amr-review.org/.

85. O'Neill, J. Antimicrobials in agriculture and the environment: reducing unnecessary use and waste. https://ec.europa.eu/health/amr/sites/amr/files/amr_studies_2015_am-in-agri-and-env.pdf (2015).

86. Bar-On, Y. M., Phillips, R. & Milo, R. The biomass distribution on Earth. Proc. Natl. Acad. Sci. U. S. A. 115, 6506–6511 (2018).

87. CDC. Antibiotic Use in Outpatient Settings, 2017. Centers for Disease Control https://www.cdc.gov/antibiotic-use/stewardship-report/outpatient.html (2017).

88. Van Boeckel, T. P. et al. Global trends in antimicrobial resistance in animals in low- and middle-income countries. Science 365, (2019).

89. Benatar, D. The chickens come home to roost. Am. J. Public Health 97, 1545–1546 (2007).

90. Wegener, H. C., Aarestrup, F. M., Jensen, L. B., Hammerum, A. M. & Bager, F. Use of antimicrobial growth promoters in food animals and Enterococcus faecium resistance to therapeutic antimicrobial drugs in Europe. Emerg. Infect. Dis. 5, 329–335 (1999).

91. Liu, Y.-Y. et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect. Dis. 16, 161–168 (2016).

92. Reardon, S. Resistance to last-ditch antibiotic has spread farther than anticipated. Nature News (2017) doi:10.1038/nature.2017.22140.

93. Rhouma, M., Fairbrother, J. M., Beaudry, F. & Letellier, A. Post weaning diarrhea in pigs: risk factors and non-colistin-based control strategies. Acta Vet. Scand. 59, 31 (2017).

94. Wang, R. et al. The global distribution and spread of the mobilized colistin resistance gene mcr-1. Nat. Commun. 9, 1179 (2018).

95. Gröndahl-Yli-Hannuksela, K. et al. The first human report of mobile colistin resistance gene, mcr-1, in Finland. APMIS 126, 413–417 (2018).

96. Liu, Y. & Liu, J.-H. Monitoring Colistin Resistance in Food Animals, An Urgent Threat. Expert Rev. Anti. Infect. Ther. 16, 443–446 (2018).

97. Garcia, F. et al. Stocking density of Nile tilapia in cages placed in a hydroelectric reservoir. Aquaculture 410–411, 51–56 (2013).

98. Watts, J. E. M., Schreier, H. J., Lanska, L. & Hale, M. S. The Rising Tide of Antimicrobial Resistance in Aquaculture: Sources, Sinks and Solutions. Mar. Drugs 15, (2017).

99. Done, H. Y., Venkatesan, A. K. & Halden, R. U. Does the Recent Growth of Aquaculture Create Antibiotic Resistance Threats Different from those Associated with Land Animal Production in Agriculture? AAPS J. 17, 513–524 (2015).

100. Liu, C. M. et al. Escherichia coli ST131-H22 as a Foodborne Uropathogen. MBio 9, (2018).

101. Hussain, A. et al. Risk of Transmission of Antimicrobial Resistant Escherichia coli from Commercial Broiler and Free-Range Retail Chicken in India. Front. Microbiol. 8, 2120 (2017).

102. CDC. Methicillin-resistant Staphylococcus aureus (MRSA) | General Information. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Healthcare Quality Promotion (DHQP) https://www.cdc.gov/mrsa/community/index.html (2019).

103. Silva, N. C. C. et al. Characterization of methicillin-resistant coagulase-negative staphylococci in milk from cows with mastitis in Brazil. Antonie Van Leeuwenhoek 106, 227–233 (2014).

104. Silva, N. C. C. et al. Molecular characterization and clonal diversity of methicillin-susceptible Staphylococcus aureus in milk of cows with mastitis in Brazil. J. Dairy Sci. 96, 6856–6862 (2013).

105. Silva, K. C. et al. First Characterization of CTX-M-15-Producing Escherichia coli Strains Belonging to Sequence Type (ST) 410, ST224, and ST1284 from Commercial Swine in South America. Antimicrob. Agents Chemother. 60, 2505–2508 (2016).

106. Casella, T. et al. Detection of blaCTX-M-type genes in complex class 1 integrons carried by Enterobacteriaceae isolated from retail chicken meat in Brazil. Int. J. Food Microbiol. 197, 88–91 (2015).

107. Wang, J. et al. Characterization of oqxAB in Escherichia c oli Isolates from Animals, Retail Meat, and Human Patients in Guangzhou, China. Front. Microbiol. 8, 1982 (2017).

108. Zeng, Z.-L. et al. High prevalence of Cfr-producing Staphylococcus species in retail meat in Guangzhou, China. BMC Microbiol. 14, 151 (2014).

109. Undurraga, D. Supermarket Meat Still Superbugged, Federal Data Show. https://www.ewg.org/research/superbugs/ (2018).

110. Graveland, H., Duim, B., van Duijkeren, E., Heederik, D. & Wagenaar, J. A. Livestock-associated methicillin-resistant Staphylococcus aureus in animals and humans. Int. J. Med. Microbiol. 301, 630–634 (2011).

111. Marshall, B. M. & Levy, S. B. Food animals and antimicrobials: impacts on human health. Clin. Microbiol. Rev. 24, 718–733 (2011).

112. Thanner, S., Drissner, D. & Walsh, F. Antimicrobial Resistance in Agriculture. MBio 7, e02227–15 (2016).

113. Founou, L. L., Founou, R. C. & Essack, S. Y. Antibiotic Resistance in the Food Chain: A Developing Country-Perspective. Front. Microbiol. 7, 1881 (2016).

114. OIE. FAO, OIE, and WHO launch a guide for countries on taking a One Health approach to addressing zoonotic diseases: OIE - World Organisation for Animal Health. https://www.oie.int/en/for-the-media/press-releases/detail/article/fao-oie-and-who-launch-a-guide-for-countries-on-taking-a-one-health-approach-to-addressing-zoonoti/.

115. O'Brien, A. M. et al. MRSA in conventional and alternative retail pork products. PLoS One 7, e30092 (2012).

116. Baird, S., Friedman, J. & Schady, N. Aggregate Income Shocks and Infant Mortality in the Developing World. Rev. Econ. Stat. 93, 847–856 (2011).

117. World_Bank. A World at Risk: Annual report on global preparedness for health emergencies. https://apps.who.int/gpmb/assets/annual_report/GPMB_annualreport_2019.pdf (2019).

118. ILO. COVID-19 and the world of work: Impact and policy responses. https://www.ilo.org/wcmsp5/groups/public/---dgreports/---dcomm/documents/briefingnote/wcms_738753.pdf (2020).

119. The World Bank. World Development Indicators. http://datatopics.worldbank.org/world-development-indicators/ (2020).

120. Levi, J., Segal, L. M., Lieberman, D. A., May, K. & Laurent, R. Outbreaks: Protecting Americans from Infectious Diseases. (2014).

121. McPherron, S. P. et al. Evidence for stone-tool-assisted consumption of animal tissues before 3.39 million years ago at Dikika, Ethiopia. Nature 466, 857–860 (2010).

122. Cleaveland, S., Laurenson, M. K. & Taylor, L. H. Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. Philos. Trans. R. Soc. Lond. B Biol. Sci. 356, 991–999 (2001).

123. Fauci, A. S. Infectious diseases: considerations for the 21st century. Clin. Infect. Dis. 32, 675–685 (2001).

124. Ritchie, H. & Roser, M. Meat and dairy production. Our World in Data (2017).

125. Gostin, L. O. Global Health Security After Ebola: Four Global Commissions. Milbank Q. 94, 34–38 (2016).

126. Accelerating breakthroughs in cellular agriculture. New Harvest https://www.new-harvest.org/cell_ag_101.

127. Shapiro, P. Clean Meat: How Growing Meat Without Animals Will Revolutionize Dinner and the World. (Gallery Books, 2019).

128. Shapiro, P. One Root Cause of Pandemics Few People Think About. Scientific American Blog Network https://blogs.scientificamerican.com/observations/one-root-cause-of-pandemics-few-people-think-about/ (2020).

129. Luby, S. P., Gurley, E. S. & Jahangir Hossain, M. TRANSMISSION OF HUMAN INFECTION WITH NIPAH VIRUS. (National Academies Press (US), 2012).

130. Scipioni, J. This $20 ice cream is made with dairy grown in lab—and it sold out immediately. CNBC https://www.cnbc.com/2019/07/16/perfect-day-foods-made-ice-cream-from-real-dairy-grown-in-lab.html (2019).

131. USDA. Dairy 2014 Milk Quality, Milking Procedures, and Mastitis on U.S. Dairies, 2014. https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy14/Dairy14_dr_Mastitis.pdf (2016).

132. Rubio, N., Datar, I., Stachura, D., Kaplan, D. & Krueger, K. Cell-Based Fish: A Novel Approach to Seafood Production and an Opportunity for Cellular Agriculture. Frontiers in Sustainable Food Systems 3, 43 (2019).

133. Alonso, W. J., McCormick, B. J., Miller, M. A., Schuck-Paim, C. & Asrar, G. R. Beyond crystal balls: crosscutting solutions in global health to prepare for an unpredictable future. BMC Public Health 15, (2015).

134. Johns_Hopkins. Event 201, a pandemic exercise to illustrate preparedness efforts. Johns Hopkins Center for Health Security, World Economic Forum, Bill and Melinda Gates Foundation. Event 201 http://www.centerforhealthsecurity.org/event201/ (2020).

This short book was written in late March 2020, during the coronavirus pandemic that has shaken humanity out of its routine. As we write these lines, we join billions of people in the hope that the losses brought about by this crisis in the coming weeks, and months, be as low as possible.

This book also addresses this pandemic, but it does not contain formulas or advice on how to overcome it. What we do, in the following pages, is to take the opportunity to foster a discussion on how to reduce the chances of this type of catastrophe occurring again in the future, and how each of us can play an active role in this regard.

The good news is that – as the reader will see – even when discussing the threats posed by emerging pandemics, epidemics, and infectious disease outbreaks, there is reason to be hopeful and optimistic. Fortunately, reducing many of the risks posed by new pathogens and other global health challenges depends on human action. And humanity has already proven to be ingenious enough to successfully overcome even more difficult challenges when we rise to the occasion.

We hope you enjoy the book,

Cynthia e Wladimir

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