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The Monster at Our Door

The Global Threat of Avian Flu

Mike Davis

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that Pranee had contracted it only because of sustained intimate contact with her daughter's body fluids. But, as the lead researchers pointed out, "this should not be a rationale for complacency"; "the person-to-person transmission of one of the most lethal human pathogens in the modern world should serve as a reminder of the urgent need to prepare for a future influenza pandemic."[5]

The essence of the avian flu threat, as we shall see, is that a mutant influenza of nightmarish virulence—evolved and now entrenched in ecological niches recently created by global agro-capitalism—is searching for the new gene or two that will enable it to travel at pandemic velocity through a densely urbanized and mostly poor humanity. This is a destiny, moreover, that we have largely forced upon influenza. Human-induced environmental shocks—overseas tourism, wetland destruction, a corporate "Livestock Revolution," and Third World urbanization with the attendant growth of megaslums—are responsible for turning influenza's extraordinary Darwinian mutability into one of the most dangerous biological forces on our besieged planet. Likewise, our terrifying vulnerability to this and other emergent diseases has been shaped by concentrated urban poverty, the neglect of vaccine development by a pharmaceutical industry that finds infectious diseases "unprofitable," and the deterioration, even collapse, of public-health infrastructures in some rich as well as poor countries. The evil that visited Ban Srisomboon, in other words, was not some ancient plague awakened from dormancy, if such can exist independent of historical circumstance, but a new form in whose creation we have inadvertently but decisively intervened. And that, as the villagers in Ban Srisomboon avowed, is surely a "sign."

1

Evolution's Fast Lane

In essence, it's a destructive form of molecular burglary; flu gets into the building, cracks the safe, takes what it wants; and wrecks the place on its way out.[6]

Pete Davies

The most ferocious of man-eaters is an innocuous companion of wild ducks and other waterfowl. At the end of every summer, as millions of ducks and geese mass in Canadian and Siberian lakes for their annual migration, influenza blooms. As researchers first discovered in 1974, the virus replicates harmlessly but vigorously in the intestinal tracts of juvenile birds and is copiously excreted into the water.[7] Other birds ingest this viral soup until as many as one-third of the young ducks and geese are producing influenza. In northern lakes, moreover, diverse strains of influenza coexist in the same population, even within an individual duck; one study in Alberta found twenty-seven different subtypes in a community of mallards, pintails, and bluewinged teals.[8]

During their migrations to the Gulf Coast and southern China, the birds continue to shed virus in their feces for as long as one month, increasing the likelihood of the infection spreading to

other species of wild and domestic birds. By late fall, however, duck influenza fades to invisibility. Some virologists believe that enough smoldering infection survives in the birds to be rekindled the following August. Others surmise that influenza is tough enough to survive winter under lake ice. In any event, ducks and influenza both return to the same lakes year after year. The cycle, in fact, may be hundreds of thousands, perhaps millions, of years old. In the opinion of one textbook, it is "a classical example of an optimally adapted system."[9] Influenza prospers while ducks remain otherwise unharmed.

Influenza in humans, pigs, and other mammals, on the other hand, is far from such a happy equilibrium; indeed, it is a radically different system of host–parasite interaction due to a variety of factors. In the first place, the virus usually infects the respiratory tract rather than the gut and spreads by an aerosol rather fecal–oral route. Second, it is highly pathogenic, causing an acute respiratory infection that sometimes kills the host. Third, in contrast to genetically stable wild-duck influenzas, the species-jumping versions are extraordinary shape-shifters that constantly alter their genomes to foil the powerful immune systems of human and mammalian hosts. The pandemic threat stems especially from this capacity for ultrafast evolutionary adaptation.

Influenzas are classified into three major genera: A, B, and C. Influenzas B and C have been domesticated by long circulation in human populations. "Genetic studies," a leading expert explains, "suggest that [they] . . . diverged from the avian influenza A viruses many centuries ago."[10] Influenza C is a cause of the so-called common cold, while B produces a classic winter flu, especially among children. Neither is a pandemic threat, although B

is responsible for some of the annual influenza mortality in susceptible populations. Influenza A, on the other hand, is still wild and very dangerous. Although its primary reservoir remains among ducks and waterfowl, it is in the early stages of crossing over to humans and other bird and mammal species. Compared to other human pathogens, it is also evolving at record-breaking speed; from year to year its proteins change amino acids to create modified strains requiring new vaccines, a process called *antigenic drift*. Moreover, every human generation or so, a bird or pig version of influenza A will swap genes with a human type of influenza, or more drastically, acquire mutations that permit it to vault over the species barrier. This revolutionary event is called *antigenic shift*, and it signals the imminence of a pandemic. In effect, influenza A reinvents itself as a new disease against which we have no protective immunological memory. In epidemiological parlance (and in contrast to more stable viruses like smallpox), it is a "constantly emerging disease."[11]

To appreciate the true genius of influenza A, it is necessary to know a little about its macromolecules and their stunning evolutionary capabilities. Like all viruses, influenza is a parasitic genome traveling in the company of clever proteins. Under an electron microscope it is revealed to be a spheroid bristling with tiny spikes and mushrooms, rather like an infinitesimal dandelion. The spikes consist of three intertwined molecules of hemagglutinin, an amazing protein that derives its name from its ability to agglutinate red blood cells. The square-headed mushrooms, fewer in number, are powerful enzymes known as neuraminidase. The outer surface of the virus also has a few M2 proteins that function as proton pumps; these allow the virus to adjust the relative acidity of its interior. Inside the virus's lipid jacket—stolen

from a host cell—is its strange genome. All living cells, of course, are programmed by the instructions contained in their DNA double helices. Influenza's genetic software, however, consists of single-stranded RNA packaged in eight separate segments known as ribonucleoprotein complexes (RNPs). Inside each of these complexes, an RNA molecule is coiled tightly around a nucleoprotein and bound together with the polymerases required for its synthesis. Inside the host, the virus also produces a nonstructural protein (NS1) which interferes with the cellular interferon-based immune response. Finally, a matrix protein called M1 fills the remaining space, cushioning the RNPs like so much styrofoam popcorn.

This highly competent little assembly is chemically inert until the hemagglutinin spikes make contact with appropriate receptors (actually sialic acid residues) on the surface of certain cells. While hemagglutinin (hence: HA) is the molecular key that influenza uses to unlock and enter host cells, different key configurations are needed to open different cells. Avian influenza HA, for example, generally only unlocks the intestinal cells of waterfowl, while human HA has been refashioned to break into cells in the mucous lining of the respiratory system. This difference in lock and key configurations is generally considered to be the species barrier that prevents avian influenzas from easily circulating among mammals. Recent research has shown, however, that slight amino substitutions in avian HA—perhaps even the change of a single glutamine to leucine—may suffice to unlock human cells.[12]

Once influenza's HA has docked with a host cell, actual entry requires that the big HA molecule be cleaved down the middle to expose key amino acid complexes; some virologists

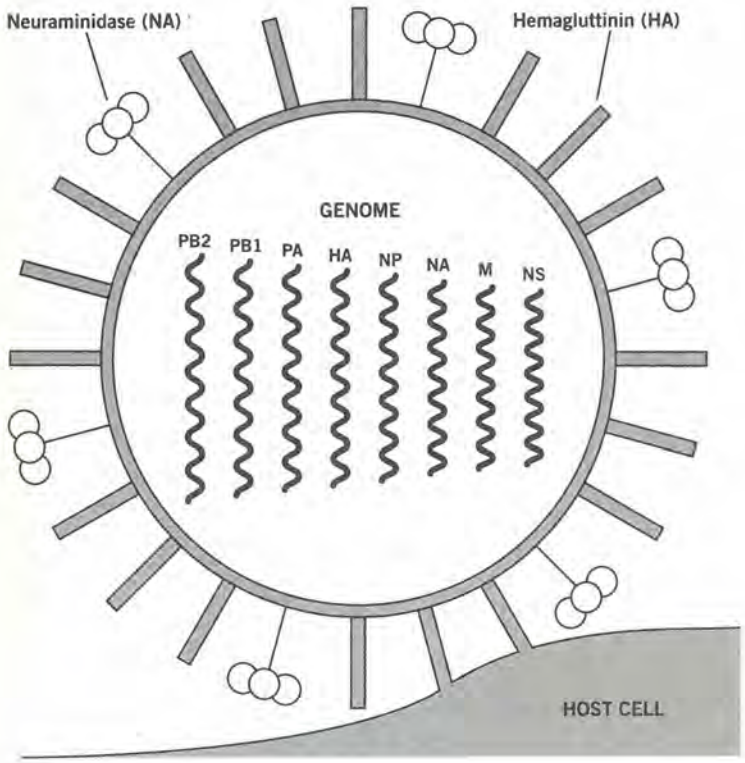

Figure 1 The Influenza Virus

compare this to opening a Swiss army knife. This cleavage is catalyzed by proteases, protein-hungry enzymes in the host organism. Most influenza HAs are fussy in choosing proteases, but some are more promiscuous. The latter probably have faster rates of attack and are correspondingly more virulent. In any case, HA's success at breaking and entering is the *sine qua non* of an influenza infection, and it is the primary target (or *antigen*) of immune response and vaccination. Pandemic influenza is usually defined as the emergence or reappearance of an HA subtype against which most people have no prior immunity.

After HA turns the lock, the influenza virus enters the host cell clothed in some of the host's own plasma membrane. The M2 channel protein then pumps ions into the interior of this capsule (*endosome*). The increased acidity dissolves the membrane and releases influenza's genome segments (the RNPs) into the host cell. The RNPs then flock to the nucleus, where viral RNA replication takes place. Like all viruses, influenza hijacks the host's biosynthetic machinery to produce several hundred copies of itself; in human influenza, the virus also issues instructions to stop making the proteins that the host cell requires for its own survival.

The complex details of RNA transcription and replication are best left to a good virology textbook, but two general aspects of influenza's reproduction are key to understanding its success as a pathogen. First, RNA synthesis is radically error prone. All cellular life (as well as some viruses) depends upon the scrupulous accuracy of DNA polymerase in duplicating genetic information; like an obsessive scholar, it proofreads and corrects every copy of DNA, and the resulting error rate (in bacteria and humans) is thus less than one mistake in every billion nucleotides

copied. RNA polymerases, on the other hand, are careless hacks who do not proof or correct their copy. As a result, the error rates in influenza and some other RNA viruses are 1 million times greater than in DNA-based genomes. Each new strand of RNA is a mutant, differing on average from its parental template by at least one nucleotide. (Its progeny are often characterized as a "mutant swarm" or "quasi species" because of their extreme variability.) Influenza, in fact, lives at the very edge of what evolutionary biologists call "error catastrophe." If the error rate were any higher, information integrity would be lost, and the genome would decay into utter gibberish.[13]

To aficionados of complexity theory, then, influenza is an outstanding example of a self-organized system on the edge of chaos.* Such perilous fine-tuning is supposed to optimize complexity and enhance evolutionary fitness, but for what purpose? In wild ducks, genetic hypervariability has seemingly lost its *raison d'être*; older strains of influenza find it easy to earn a living, and different subtypes can coexist peacefully with another. Evolution, according to Robert Webster and William Bean, has resulted in stasis as "the long-term survival of the avian viruses appears to favor those that have not changed, and selection is primarily negative."[14] In humans and other secondary hosts, however, influenza comes under ferocious attack from sophisticated immune systems. This generates intense selective pressure, which in turn kicks evolution into fast forward. "The molecular clocks

* Some scientists find influenza's sudden mutations and dramatic shifts too extreme to accept as mere results of RNA genetics. Most famously, the astrophysicist Sir Fred Hoyle and his associate Chandra Wickramasinghe have proposed an extravagant theory positing that influenza is literally extraterrestrial; that it episodically hitchhikes to earth on cosmic dust particles scattered in the tail of comets.

of RNA viruses," writes evolutionary biologist John Holland, "can spin at blinding speeds as compared to those of their hosts." Indeed, their rates of evolution "proceed up to millions-fold faster than that of their hosts."[15]

Influenza A's extraordinary heterogeneity thus becomes a resource for resisting the immune-system onslaught. As rapidly as antibodies defeat one influenza strain, others, more resistant, emerge to take its place—a single amino acid substitution can suffice to thwart an antibody attack. This irresistible drift of influenza's antigenic characteristics ensures its survival in the face of the antibody blitz. Indeed, according to leading researchers, "it may be that human influenza A is unique in that it is able to produce a series of antigenically selected mutants that are as fit as the parental population and is the only virus that undergoes true antigenic drift."[16] Yet if these point mutations ensure influenza viability as a disease from season to season, they do not totally outwit immunological memory. "[T]he high level of partial immunity remaining in the community," Dorothy Crawford explains, "ensures that antigenic drift will not cause a pandemic."[17]

The influenza genome, however, has a second, even more extraordinary, trick up its sleeve: because its RNA is packaged in separate segments, a co-infection of a host cell by two different subtypes of influenza can result in a *reassortment* of their constituent genes. Under the right circumstances, influenzas can trade replicating RNPs like kids swap baseball cards, with the resulting hybrids having gene segments from different parents. Thus the pandemic Asian flu of 1957 contained three avian segments (including a novel HA) along with five RNPs from the previously circulating human subtype. Likewise, the pandemic Hong Kong subtype of 1968 retained six segments of the 1957

genome while adding new avian genes for HA and one of the polymerases. In both cases, the *reassortants* combined avian surface proteins with human-adapted internal proteins; this enabled them to overcome what Taubenberger and Reid characterize as "the twin challenges of being 'new' to its host, while being supremely well adapted to it."[18]

But, given the species barrier raised by HA specificity, how do co-infections of avian and human viruses ever occur? Until the 1997 outbreak, it was generally believed that antigenic shift required the intermediary of pigs: "[F]or influenza viruses, the species barrier to pigs is relatively low when compared with the barrier between birds and humans."[19] Cells in the respiratory systems of swine have the right receptors for both avian and human HA and thus can contract diverse subtypes of influenza A—they are ideal viral blenders. Their critical role, moreover, is supported by epidemiological history: influenza epidemics and pandemics usually emerge first in southern China (especially in Guangdong and the Pearl River Delta) where huge numbers of pigs, domestic ducks, and wild waterfowl live in traditional ecological intimacy.

It should be stressed, however, that reassortment, like mutational drift, is a scattershot process. As a leading researcher at the National Institutes of Health explains, "the vast majority of reassortants between avian and human (or mammalian) influenza viruses contain a gene . . . or gene constellation that prevents the virus replicating efficiently in primates." Nevertheless, "some 25 percent of the resulting recombinant viruses would still be potentially virulent for humans if one of the two parents is a human influenza virus."[20] On rare occasions, it is also possible for novel influenza subtypes to emerge through *recombination*: the

splicing together of parts of genes (coding for the same protein) from different species. In a controversial 2001 article in *Science*, three Australian researchers proposed that the devastating 1918 pandemic was triggered by a recombination event involving the HA gene. The spike head, they argued, derived from a swine lineage, while the stalk was encoded by a human gene. This recombinant hemagglutinin, they suggest, may have had "an unusual tissue specificity, such that it spread from the upper respiratory tract to the lungs."[21] (Later, to make matters more complex, we will examine two other possible mechanisms of pandemic emergence: dormancy and direct species jump.)

Whether or not recombination is part of influenza A's repertoire, few other human pathogens—apart from the HIV retrovirus (world champion at wily mutation) and the chief malaria parasite, *Plasmodium falciparum*, seem so invincible. Yet influenza does have its weak points, as can be seen as we complete our sketch of its progress through a host: next, the progeny viruses must be assembled and then execute their escape from the dying host cell. Although research shows that the M1 protein is probably the "major virus assembly organizer," the complex choreography that produces new viral particles out of the separately replicated gene strands and proteins is incompletely understood.[22] The final assembly takes the form of a budding of the new viruses from the cellular membrane. This is sticky business; the problem is that the strong affinity of the HA molecules for the external neuraminic acid residues—the very property that made viral entry possible—now blocks the exit. Neuraminidase (henceforth: NA) overcomes this dilemma by attacking and removing the neuraminic acid residues—if HA is the burglar, NA is the escape artist. Their complementary roles are

so important that virologists classify influenza A subtypes by their specific HA and NA: the formula adapted in 1980 is H*x*N*y*. (Please remember this. It will avoid confusion later on when you meet a series of bad characters named H3N2, H9N1, H5N1, and so on.)

However the NA mushrooms are more vulnerable than are the HA spikes to antivirals that imitate neuraminic (sialic) acid residues and plug strategic portals in their three-dimensional structures. The development of powerful neuraminidase inhibitors—zanamivir (Relenza) in 1993 and oseltamivir (Tamiflu) in 1997—has been a major breakthrough in the treatment of annual influenza. More importantly, zanamivir and oseltamivir are the *only* medications that are thus far effective in preventing or moderating the acute onset of avian flu (or, for that matter, lab-made clones of the deadly 1918 strain).[23] Because of the difficulties of administering zanamivir—it requires an inhaler—oral oseltamivir tablets are seen as the only practical alternative for mass prophylaxis. Indeed, until (and if) avian flu vaccines become widely available, oseltamivir, as *Science* points out, "would be the world's only initial defense against a pandemic that could kill millions of people."[24] For several years the world's top influenza experts have been urging a crash program to increase oseltamivir production; it is currently manufactured by Roche in a single factory in Switzerland. An international stockpile could then be set aside for emergency use by the WHO. These warnings, as we shall see later, have largely been ignored, and oseltamivir inventories remain woefully insufficient to meet the pandemic needs of a single American state, much less the entire nation or the rest of the world.

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Conclusion: Year of the Rooster

We're living on borrowed time.

Klaus Stohr (WHO)[313]

The Year of the Rooster, 2005, began with several more flu deaths in Vietnam. In two cases, the virus was contracted from eating raw duck blood pudding, a local delicacy savoured on ceremonial occasions. Tests showed that GenZ was now endemic amongst the hundreds of thousands of ducks and geese that roam Vietnamese farmyards that are in constant contact with chickens, pigs, and children. Because duck influenza is generally asymptomatic, there was no obvious way—apart from time-consuming and expensive blood testing—to distinguish infected from non-infected birds. Vietnam's desperate efforts at containment through the selective slaughter of poultry were undermined by the emergence of this "silent reservoir." Disoriented local authorities, as a result, grasped at questionable expedients. As the Vietnamese New Year approached, riot police set up checkpoints around Ho Chi Minh City to interdict the expected influx of infected poultry during Tet celebrations.[314] Municipal officials on 1 February also ordered the slaughter of all ducks in the city: a move that Dutch influenza expert Jan de Jong denounced as "really nonsense." He told an American reporter that the only way to stop the outbreak in Vietnam was "a

near-total culling of the region's poultry and curtailment of poultry farming for several years."[315]

Hanoi retorted with justice that it needed more international aid to bolster its surveillance network and to compensate peasants whose flocks were being culled. The country was too poor to afford the destruction of a vital part of its subsistence economy without compensation from the richer nations for whom it was expected to provide an epidemic firewall. Foreign influenza experts working in Vietnam echoed Agriculture Minister Cao Duc Phat's appeal on 2 February for truly serious international assistance. Writing in the *New York Times*, Anton Rychener (the outspoken FAO representative in Vietnam), and Hans Troedsson (his WHO counterpart), pointed out that if the H5N1 outbreak had occurred in a poorer European country, there would have been a vast outpouring of money and medicine. "In the case of Asia, the international community has failed to come forward with enough money to finance desperately needed public health and veterinary measures and research on vaccines."[316] In an earlier interview with *Nature*, Dr. Jeremy Farar of Oxford University's clinical research unit in Ho Chi Minh City had lashed out at the dilettantish behavior of Western scientists: "When there's a problem, everyone flies in, creates a certain amount of havoc, flies out, and leaves nothing behind to change the situation." (He specifically exempted St. Jude's researchers and the crack Hong Kong team from his criticism.)[317] Incredibly, part of the shortfall of aid was most likely due to lobbying by Western poultry interests. With the Bush administration obviously in mind, *Nature* had editorialized in mid-January against the "mindset of protectionism" that obstructed veterinary aid to Vietnam. "Rich governments are disinclined to build up poor countries' ability to keep track of animal viruses, seeing this as economic assistance rather than humanitarian aid."[318]

Although the tsunami catastrophe in the Indian Ocean was the principal agenda item at the WHO executive board meeting on 25 January, the deteriorating flu situation in Vietnam was also on many minds. The Secretariat had circulated a briefing on pandemic preparedness that warned that the "present situation may resemble that leading to the 1918 pandemic." The report emphasized that "changes in the ecology of the disease and behavior of the virus have created multiple opportunities for a pandemic virus to emerge," and that gradual genetic drift, rather than reassortment, might be sufficient to unleash H5N1 on humanity. The Secretariat, underlining the "unprecedented opportunity to enhance preparedness," worried that vaccine development had not advanced "with a speed appropriate to the urgency of the situation."[319]

Some of the rich countries represented on the thirty-two-member executive board, however, were seemingly more concerned to protect pharmaceutical industry profits than to increase the availability of vaccines and antivirals. When Thai delegate Dr. Viroj Tangcharoensathien proposed (with the precedent of AIDS medications in mind) that the poor countries on the frontline of the avian flu battle be allowed to override drug patents in order to produce affordable quantities of Tamiflu, the American and French delegates vehemently objected and ultimately forced the meeting to adjourn without a vote. Dr. Anarfi Asamoa-Baah, the head of the WHO's communicable disease division, gloomily noted that "as a global community we are still ill prepared—and as long as one of us is not prepared, none of us is prepared."[320]

At a conference in Ho Chi Minh City a month later, this "alarming lack of commitment" from Japan, Europe, and the United States was again a top agenda item as Asian health officials responded to a warning by the WHO's Omi that the region was facing "the gravest possible danger of a flu pandemic." Shocked conferees heard one researcher after another outline fatal flaws in the underfunded avian flu surveillance system. The Japanese National Institute of Infectious Disease, which had retested blood samples from the Pasteur Institute in Ho Chi Minh City, reported that some of the negative results were in fact positive: suggesting that avian influenza, although perhaps not as lethal as suggested by confirmed cases, was actually more widespread and thus statistically closer to reassortment with human influenza. For its part, the Oxford University team in Ho Chi Minh City added fuel to the fire with a case-study of a four-year-old whose GenZ infection imitated acute encephalitis without respiratory symptoms. (Decades earlier, some scientists had associated a strange epidemic of sleeping sickness, *encephalitis lethargica*, with the 1918 H1N1 virus.) How many other similar cases had been misdiagnosed? Disturbingly, the child's stools were also full of H5N1—a warning that avian flu, like SARS two years before, might spread via poor sanitation. There was also nervous discussion of "insect vectors" after a startling announcement by Japanese researchers that they had found H5N1 in flies following the 2004 poultry outbreak.[321]

The gravest concern, however, was focused on the first flu deaths in Cambodia, a country with a corrupt government, primitive health services ($3 per capita annually), and no facility for the sophisticated serological analysis required to identify GenZ. Indeed, the outbreak only came to light when twenty-four-year-old Tit Sokan from Kampot province sought treatment in Vietnam. Earlier, her fourteen-year-old brother had died after Cambodian doctors threw up their hands at his condition. "He had a fever and couldn't breathe normally so we took him to the hospital. The doctors gave him two bags of saline solution, then they told us to take him home. They said maybe we'd done something to offend our ancestors, and we should make an offering to them." Tit Sokan herself was too ill to be saved by antivirals, and after her death WHO investigators learned of border villages full of sick pigs and infected chickens. (In mid-April, another young woman from the same province died of suspected bird flu.)[322]

At the beginning of March, evidence was emerging of a second human-to-human transmission: this time in a Hanoi hospital where two nurses attending a critically ill avian flu patient, and both nurses developed the infection. Warning of the "perfect storm now gathering," *The Lancet* urged the European members of WHO to help Vietnam shut down small-scale free-range poultry production. "If the greatest pandemic in history is indeed on the horizon, that threat must be met by the most comprehensive public-health plan ever devised. That plan presently does not exist."[323] Meanwhile influenza authorities like Albert Osterhaus (University of Rotterdam) and Nancy Cox (CDC) were pleading in the pages of *Science* for the big Western labs to help Vietnam organize a broader, more accurate testing program in response to the troubling "information gap" about the evolution of GenZ.[324]

Researchers were appalled that the bird flu containment campaign in Vietnam was collapsing for lack of relatively trivial financial aid. Yet even on the U.S. home front, where "biosecu-

rity" was supposedly a top priority, the CDC's budget for emergency public-health assistance was slashed by an eighth in fiscal 2005. Although plenty of money was found to increase funding for "abstinence education" (now $193 million per year), child immunization was reduced and preventive-health block grants to the states were eliminated. (A $20 million increase for pandemic vaccine hardly offset the loss of the block grants.) At a time of maximum menace, the CDC altogether lost $500 million in critical funding: a recession that only deepened gloom in an agency suffering, according to top official Robert Keegan, from a "crisis of confidence" that had led to the resignation of a score of top scientists and administrators. In an internal memo revealed by the *Washington Post* in March, Keegan spoke darkly of an "atmosphere of fear" and staff "cowed into silence" in the face of Director Julie Gerberding's autocratic style and her subservience to the administration's ideological agenda. Another CDC official described life in the agency as an "Alice in Wonderland environment where the CDC director is like the Queen of Hearts. You know, 'Off with their heads,' "[325] Meanwhile, an open revolt had broken out against the War on Terrorism's deleterious impact on university-based communicable disease research. Led by two Nobel prize-winners, 758 researchers signed a petition claiming that Washington's obsession with exotic but potentially weaponizable viruses and bacteria had resulted in a 27 percent decline in federal grants for research on tuberculosis and other major non-terror diseases.[326]

With this dissension in the background, Mike Leavitt, the new secretary of HHS, spoke to the National Academy of Sciences on 7 April about his department's strategy for dealing with H5N1. Following on the heels of an unexpected admission by

Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Disease, that a flu pandemic was a greater immediate threat than a bioterrorist attack, Leavitt emphasized that avian influenza had the administration's full attention and that he was receiving daily briefings on the worrisome situation in Asia. He told his scientific audience that an H5N1 vaccine was in the human test stage, and that he had signed a $97 million contract with Sanofi Pasteur to develop new cell-based vaccine production lines.[327]

But the former governor of Utah did not address the problems inherent in vaccine production—the minuscule scale of the start-up, the long lead times, and the uncertainty whether current templates would match the evolved genome of a pandemic—that CDC Director Julie Gerberding had acknowledged in February at the annual meeting of the American Association for the Advancement of Science. Gerberding—according to a University of Minnesota news source—had warned that it was "nearly impossible to stop an outbreak by quarantining sick people" and "that flu vaccine production remains focused on ordinary seasonal flu, and it would be impossible to switch gears quickly to make a pandemic vaccine."[328] Leavitt also sidestepped widespread complaints about Washington's failure to stockpile Tamiflu in quantities comparable to recent purchases by Great Britain (14.6 million courses) and France (13 million).[329] Nor did he explain why the Bush administration was refusing to provide the aid that Vietnam so desperately needed to keep H5N1 in check.

Moreover, Leavitt's sunny assurances that Washington had public biosafety well in hand were immediately undercut by the startling revelation that a Cincinnati bioscience firm had sent

out more than 5,000 samples of a deadly pandemic strain of influenza. H2N2, the "Asian flu" virus that killed 1 to 4 million people during the 1957 pandemic, had not circulated amongst humans since 1968 and was a grave threat to anyone born afterward. Influenza researchers, chastened by the escape of an earlier "lab fossil" (a strain of H1N1—the 1918 virus) in 1977, had long fretted about the security of H2N2 specimens in lab archives. They were incredulous that Meridian Bioscience—a contractor to the College of American Pathologists (CAP)—had knowingly included H2N2 in the viral test kits routinely used to assess quality control in laboratories across the world. CAP had not been informed of the strain's identity (which was, in any event, mislabeled on customs forms as "H3N2"), and most of the kits had been shipped through the U.S. mail. Although CDC experts had earlier urged the reclassification of H2N2 as a biosecurity level 3 agent, requiring the most stringent lab precautions, the recommendation was never implemented. As a result, "the CDC [did] not have regulatory authority over the distribution of the A (H2N2) influenza virus because it is not classified as a dangerous agent relevant to bioterrorism."[330]

Indeed, it was only thanks to Canadian vigilance that the pandemic threat was discovered at all. At the end of March, the National Microbiology Laboratory in Winnipeg identified H2N2—a strain the Canadians consider too dangerous to use in lab certification tests—in a patient sample sent from British Columbia. Although the Vancouver woman didn't actually have the flu, the contaminated sample was sufficient grounds for worldwide alarm. While Director Gerberding misleadingly reassured the public that "this strain of virus poses a very very low risk of

transmission," the CDC mounted a frantic campaign to track down and destroy the thousands of samples.[331] A few missing test kits in Lebanon, near the epicenter of the Bush administration's fears about bioterrorism, caused considerable anxiety until they were finally accounted for by local labs. Like the Chiron scandal the year before, the H2N2 fiasco demonstrated the public peril of lax federal regulation of production protocols and biosafety standards. How could Washington pretend to defend the nation against the avian flu threat or bioterrorism, when it had allowed a private company to put a potential pandemic in the mail?

While the CDC was chasing the missing H2N2 samples, a joint summit in Paris of experts from the FAO and the OIE was reviewing the campaign against H5N1. Their sobering conclusion was that the virus had become too ecologically entrenched, particularly amongst asymptomatic ducks, to justify the continued economic and ethical costs of culling yet millions more domestic birds. Avian flu, in short, was endemic and inextinguishable. It was also utterly unpredictable: the discovery of a highly pathogenic H7 strain in North Korea in March raised fears of a doomsday recombination with "H5 lethality and H7 transmissibility." Meanwhile, the normally hermetic North Koreans clamored for international assistance to save their fledgling poultry export industry.[332]

As an alternative to the failed culls, the FAO and OIE proposed an ambitious poultry vaccination campaign in affected countries. The plan was a disappointment to experts who advocated the radical elimination of free-range poultry and wet markets. It also faced the formidable technical challenge of how to distinguish between vaccinated and infected birds, since their

antibodies would otherwise be identical. More dauntingly, vaccination would require major financial aid to poor countries like Vietnam, Cambodia and North Korea: "economic subsidies" likely to be opposed by corporate poultry producers and U.S. conservatives. Not surprisingly only a few countries (Japan, Germany, and the Netherlands) were immediately prepared to support the Paris plan with modest contributions.[333]

By late spring 2005, therefore, every biological weathervane was pointing in the direction of an imminent pandemic. The basic WHO assessment of the threat—an inevitable outbreak that could kill millions, even tens of millions—had been accepted by all leading players, including the Bush administration. The rest of the print media had finally caught up with the *New York Times*, and avian influenza was almost daily in the news. Yet a certain quotient of disaster fatigue was also apparent: influenza experts, after all, had been warning of a viral apocalypse since the original Hong Kong outbreak in 1997. Almost nine years later, less than one hundred people had died and the pandemic was still just a prediction. In the meantime, tens of millions had died from AIDS, malaria, and diarrhoeal diseases. Is it possible that the WHO had exaggerated the threat of H5N1?

Alas, a flu pandemic is not a fate we can avoid. To recapitulate an earlier argument: Third World urbanization and the Livestock Revolution have fundamentally transformed influenza ecology and accelerated the evolution of novel recombinants. Moreover, there are multiple pathways to a new catastrophe on the scale of 1918. As we have seen, several subtypes of H7 and H9, in addition to H5N1, are slouching toward Bethlehem with bright prospects of producing pandemic offspring. All the major candidates, in addition, appear to be increasing their evolutionary fitness to spread rapidly through new avian and mammal species. The fifteen HPAI outbreaks since 2000, for example, have killed or led to the culling of ten times as many birds as all earlier known outbreaks combined. ("We've gone from a few snowflakes to an avalanche," an Italian researcher told *Science*.)[334] Even if humanity miraculously dodged H5N1, we would soon be under threat from other virulent avian subtypes.

The rich countries have had nearly a decade—a unique advance warning in the history of disease—to build a network of global defenses against the impending pandemic. But the crash program of vaccine development and antiviral stockpiling, advocated by Robert Webster and others since 1997, has yet to really commence. In Washington, London, and Tokyo, health ministers pay religious deference to pharmaceutical industry patents and profits while failing to assure the elementary provision of lifeline medicines. In Asia, as well as California and British Columbia, governments have covered up outbreaks, lied to international agencies, threatened whistleblowers, and possibly concealed illnesses and deaths. The huge livestock multinationals, with their crony ties to government in Thailand and China, have exploited the crisis to restructure poultry production to their selfish advantage. Although individual foreign researchers and institutions have provided heroic assistance to local authorities, the overall global aid effort has been a disgrace. Most egregiously, the United States—the country with the greatest historical moral obligation to Vietnam—has failed to provide that poor nation with the resources to monitor or contain the outbreak.

Over the last year, to be sure, some progress has finally been made on the vaccine and antiviral fronts. But the chief beneficiaries are a handful of wealthy countries—especially Canada,

Australia, New Zealand, Singapore, and Japan—who have been provident enough to order early and in quantity from Roche. Britain, France, and Sweden have also taken serious steps, but the United States, which has recently spent billions on "biosecurity," lags shockingly far behind its peers. We are better equipped to deal with imaginary anthrax and Ebola attacks than with an avian influenza pandemic. Meanwhile not the slightest effort has been made to protect the truly poor countries of Asia and Africa from the return of history's greatest killer. A "global vaccine" is still a pipedream, and the Tamiflu buying spree by the rich countries has locked up the potential supply.

As with HIV/AIDS and the easily preventable infant diarrhoeal diseases, avian influenza is a fundamental test of human solidarity. Access to lifeline medicines, including vaccines, antibiotics, and antivirals, should be a human right, universally available at no cost. If markets can't provide incentives to cheaply produce such drugs, then governments and non-profits should take responsibility for their manufacture and distribution. The survival of the poor must at all times be accounted a higher priority than the profits of Big Pharma. Likewise, the creation of a truly global public-health infrastructure has become a project of literally life-and-death urgency for the rich countries as well as the poor. The first step—as the editors of *Nature*, *The Lancet*, and other eminent journals have repeatedly emphasized—is a serious aid program to rescue the anti-pandemic campaign in Vietnam and Southeast Asia. On the thirtieth anniversary of the end of its genocidal intervention in Indochina, the United States needs to help the small farmers of Vietnam save the lives of their children.

As the hour hand on the pandemic clock ominously approaches midnight, I recall those 1950s sci-fi thrillers of my childhood in which an alien menace or atomic monster threatened humanity. Scientists try to sound the alarm, but politicians ignore the danger. Ultimately, however, the world wakes up to the peril and unites to defeat the invader. Human species survival overrides the antagonisms of the Cold War and competitive nationalism. Now, with a real Monster at our door—as terrible as any in science fiction—will we wake up in time?

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