RMS WHITE PAPER

INFLUENZA PANDEMIC RISK
THE CONTRIBUTION OF LABORATORY PATHOGENS TO EXCESS MORTALITY RISK

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The announcement that scientists have succeeded in creating a transmissible form of the avian flu virus in the laboratory has caused an international outcry because of the dangers posed by a man-made pandemic. This paper explains the background to the experiments, and analyzes the mechanisms by which a dangerous virus could trigger a pandemic through accidental or malicious release. It quantifies the impact of scenarios of pandemics that could result, and considers the implications for excess mortality risk assessments, for life insurers concerned with quantifying tail risk for economic capital reserves or Solvency II excess mortality risk capital requirements.

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EXECUTIVE SUMMARY

On January 23, 2013, influenza bioscientists lifted their self-imposed moratorium and resumed research into how highly pathogenic avian influenza (HPAI) H5N1 viruses might gain transmissibility and virulence. The research moratorium was triggered last year, following the first successful laboratory creation of airborne transmissible H5N1 virus which prompted security fears of a man-made pandemic.

In nature, H5N1 has infected over 600 people, typically from direct contact with an infected bird, killing around 60% of those infected. The H5N1 influenza virus is rapidly mutating, and public health officials fear that if it naturally acquired transmissibility, it could trigger a severe pandemic. The research is intended to improve understanding of the evolutionary mechanisms and to prepare vaccines and other medical treatments in case of a pandemic.

Two research teams independently revealed results in which they forced mutation mechanisms to enable airborne transmission of H5N1 in ferrets. In both cases the transmissible strains had low virulence. With the lifting of the moratorium, a community of researchers is now set to continue pursuing gain-of-function research, trying to increase the virulence and transmissibility of H5N1. The heart of the debate is the level of safety in carrying out this type of laboratory research. H5N1 research currently requires biosafety level three (BSL-3) laboratories, rather than the maximum security BSL-4. Researchers resisted calls to increase security to BSL-4 for gain-of-function research, arguing that this will slow up research progress.

RMS provides analysis and independent advice to insurance clients with financial exposure to severe losses from excess mortality shocks, including pandemic. To help inform the debate, RMS has used its epidemiologically-based infectious disease model to simulate two scenarios for pandemics that could result from the escape of a virus from a research laboratory, calibrated with plausible values to assess the impact of a high-virulence pandemic. Both scenarios assume that the H5N1 virus loses virulence from its current level in becoming transmissible. Scenario A sees the virus halve in virulence, Scenario B sees it reduce by an order of magnitude. The age mortality distribution of known avian flu is mirrored in the pandemic modeling – a concern because this affects young adults. Other assumptions, such as time taken to instigate a mass vaccination program, and the effectiveness of anti-viral drugs are varied between the scenarios. The scenarios are available in the RMS® Infectious Disease Model for life insurers to run on their own portfolios using the RMS LifeRisks™ Platform.

Scenario A results in 50 million deaths worldwide. Scenario B results in 18 million deaths worldwide. Life insurance portfolios will see high excess mortality in the age range of 20 to 50, and losses will depend on the make-up of the portfolio. These scenarios illustrate the potential severity of a man-made pandemic.

Pursuing gain-of-function research will increase the chance that an H5N1 pandemic will occur by a small amount. Biosafety measures can be expected to fail occasionally. If a pandemic were to occur as a result of a laboratory escape, there is a wide range of potential outcomes. Even a mild epidemic with limited mortality can have catastrophic economic impacts. H5N1 has the potential to cause a societally-crippling event, resulting in tens of millions of premature deaths and global economic disaster.

However the research also holds out the potential for great reductions in risk, if the research can generate improvements in vaccination capability for public health officials to combat future pandemics. RMS models suggest that risk from future severe pandemic events could be reduced by about a third with faster vaccine availability and improvements in the capabilities to perform mass-vaccination programs.

As with many things that threaten public safety, a precautionary principle should be followed to ensure the public good. The potential severity of such an outcome makes it imperative that a full risk assessment is carried out, weighing the potential threat and benefits of allowing future research, to maximize the security of HPAI H5N1 research and focus it on the direct public health benefits that it promises.

H5N1 research increases pandemic risk, and could become significant with a gain-of-function breakthrough. Insurers may want to apply stress tests to their risk assumptions. The expected change in frequency from laboratory research remains within the uncertainty bounds of the current RMS infectious disease model. However, for risk managers looking for a reasonable sensitivity test on Solvency capital requirements, RMS models indicate a 5% increase at the 1-in-200 level, using best-estimate escape probabilities and the RMS standard viral characteristics distribution.

1   THE FOUCHIER-KAWAOKA VIRUSES

1.1   Letting the Ferret out of the Bag

Nature works randomly, and it usually takes generations to evolve new strains of viruses. Scientists can give nature a helping hand and accelerate the process, directing it towards specific objectives.

The feared H5N1 strain of avian influenza has been of particular concern to public health authorities, the life insurance industry, and society in general. Cases started occurring in 2003 and have been reported every year since. The cumulative tally to date is 610 human cases of which 360 died[1] – a case fatality rate of 59%, making it the most virulent strain of influenza ever observed.

The vast majority of these cases have been traceable to the individual contracting the virus directly from poultry or wild fowl, but a few cases of human-to-human transmission are known. Fortunately for mankind, the H5N1 influenza virus has not adapted to spread easily between people in the way that other strains of influenza can, through airborne transmission. If the H5N1 virus were to undergo genetic mutations to adapt and acquire the ability to transmit easily between humans, it could potentially create a catastrophic pandemic with a very high mortality rate. Virologists and epidemiologists have debated what mechanisms might lead to this possibility, and what the probabilities might be. The fact that no observable cases occurred in nature over nearly a decade suggested that it might be complex and of low probability.

The mutation of an influenza virus into a highly pathogenic and transmissible disease is one of the extreme scenarios that form the tail risk of an excess mortality assessment for a life insurance portfolio. The RMS influenza pandemic risk model is parameterized with detailed studies and assessments of the current state of science in order to assess the probability of viruses occurring with various characteristics.

Two separate groups of researchers have now succeeded in creating laboratory versions of the virus that previously had just been hypothesized: an H5N1 strain that can be transmitted through airborne transmission between mammals. Ron Fouchier, virologist at the Erasmus Medical Center, Rotterdam, announced his breakthrough at a conference in Malta in September, 2011. Yoshihiro Kawaoka at the University of Wisconsin published his research in a commentary online in *Nature* on January 25, 2012. After months of international debate over biosecurity issues, their work has been published in leading scientific journals. Research of this type is intended to help clarify the number and types of genetic mutations required for transmission to occur, and to help develop vaccines if it did.

Both set of experiments examined how the genetics of the H5N1 virus could change to make it a human-to-human transmissible virus. This is known as 'gain-of-function' research. To speed up the mutation process, both scientific teams used laboratory ferrets, which are considered the best animal model for the study of influenza transmission between humans. Macaque monkeys are also used as an animal model to study influenza, and have been used, for example, in experiments with the reconstructed 1918 pandemic influenza virus. The use of ferrets for research purposes is less restricted than macaque monkeys, which have special primate protection. This is important, because the more animals that are used in flu trials, the more extensive the exploration of the mutation domain.

Fouchier started with making a few genetic substitutions to H5N1. He then greatly accelerated the mutation rates that occur in the virus through ten cycles of artificial cross infections in ferrets. Kawaoka started with the naturally infectious but mild 2009 pandemic H1N1 virus and genetically engineered it to splice in the key H5 hemagglutinin (HA) gene, before exposing the hybrid virus to ferrets. The separate experiments produced significantly different types of virus, but both showed that it is possible for transmissible variants of H5N1 to occur. With only a handful of mutations required to achieve this transformation, the end goal was easier to attain than expected.

This discovery has shed new light on viral mechanisms to pave the way for improved surveillance and an eventual vaccine, but it has also unleashed a storm of controversy about accidentally or maliciously triggering a catastrophic pandemic.

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[1]   World Health Organization, 17 Dec 2012

1.2 Controversy

The announcement of the results of the research was controversial and stoked a major debate in the scientific community around gain-of-function research into highly pathogenic avian influenza. The U.S. National Science Advisory Board for Biosecurity (NSABB) requested that details of the scientific methodology and specific viral mutations should not be published openly. NSABB concerns are that the danger represented by the research, posed by the chance of virus escape, either by accident or malice, could be a significant threat to public safety.

Experts convened by the World Health Organization (WHO) have supported the open publication of the research, arguing that it has benefits for flu surveillance: evidence of similar genomic signatures in animal or human viruses may provide early warning for an impending pandemic.

Kawaoka, Fouchier and others signed an agreement to suspend studies on H5N1 viruses that can transmit in mammals. Kawaoka went on record to strongly disagree with efforts to limit future work and its full publication[2]. "As the risks of such research and its publication are debated by the community, I argue that we should pursue transmission studies of highly pathogenic avian influenza viruses with urgency," he wrote in *Nature*. "Because H5N1 mutations that confer transmissibility in mammals may emerge in nature, I believe that it would be irresponsible not to study the underlying mechanisms."

The moratorium lasted throughout 2012 but after an international workshop of experts at the National Institutes of Health (NIH) convened in mid December 2012 to review the issues[3], it was finally lifted on January 23, 2013, with the setting of new tighter rules by the U.S. Department of Health and Human Services (DHHS) for the scrutiny and funding of gain-of-function research into highly pathogenic avian influenza (HPAI) viruses[4].

1.3 Research at the Fouchier Laboratory

For years, virologists have been conducting experiments on influenza viruses to see whether a deadly transmissible virus can be created. There are so many combinations of genetic changes that might lead to such a virus that theoretical biologists thought it would be extremely difficult and take many years to achieve. Safety concerns over this kind of research have been mitigated by a record of persistent failure until 2010 when researchers working in a high security lab in Beijing demonstrated that a single amino acid substitution in the HA protein would change the pathogenicity of the 2009 H1N1 virus[5].

In humans, avian flu viruses attach and replicate primarily in the lower respiratory tract, which makes it harder for them to transmit from person-to-person. Seasonal strains of influenza are more readily transmissible between people, because the virus is adept at attaching to the upper respiratory tract. If an avian flu virus could replicate in the upper airways, it would be more likely to be released in an aerosol, and might be more transmissible. Some eminent virologists thought that the H5N1 avian flu virus could never become airborne between mammals. Ron Fouchier has now demonstrated this to be too optimistic, confirming that H5N1 is a potentially transmissible virus between mammals.

Fouchier's path to discovery involved making just a few genetic substitutions to the H5N1 virus, enabling it to affix to human nose and trachea cells in laboratory cultures. However, when tests were performed on ferrets, there was still no airborne viral transmission. Fouchier then devised a simple method to make a pathogen adapt to a new host: he manually passed the virus from one ferret to another. The mutated H5N1 virus was swabbed into the nose of one ferret. Then a sample of nasal fluid from this ferret was swabbed into the nose of another ferret. The tenth round of ferrets shed an H5N1 strain that spread to ferrets in separate cages.

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2 Kawaoka, commentary in Nature and to ScienceInsider
3 National Institutes of Health International Consultative Workshop, Bethesda, Maryland, December 17-18, 2012, on Gain-of-Function Research on Highly Pathogenic Avian Influenza H5N1 Viruses
4 US DHHS, 2012, Draft communiqué, December 12, 2012, for National Institutes of Health *International Consultative Workshop*, Bethesda, Maryland, December 17-18, 2012.
5 Xu, 2010

Significantly, none of the ferrets that were infected via airborne transmission died, suggesting that the infectious version of the virus was less virulent. The virus was only lethal if administered in large doses directly into the trachea or nasal passages of a ferret. Thus, contrary to early press reports, and indeed Fouchier's own remark that "this is one of the most dangerous viruses", it is entirely possible that the airborne version that he produced is relatively mild. It may be that the mutation process has greatly reduced the virulence of the virus, so that it might not pose a great danger to the public if accidentally released.

1.4   Research at the Kawaoka Laboratory

In their pioneering research to discover if H5N1 could evolve into a virus that was easily transmissible between humans, Yoshihiro Kawaoka and his team of virologists at the University of Wisconsin, Madison, began by randomly mutating its haemagglutinin (HA) gene. This was a major undertaking, with no guarantee of any success, rather like picking a giant combination lock. But perseverance and industry were rewarded. Of the 2.1 million different strains they created, one was found to be significant in recognizing the human-type receptors instead of the avian ones. Just two HA mutations were necessary for this adapted recognition.

Next, Kawaoka fused the mutated HA gene with seven other genes from the H1N1 2009 pandemic virus, and ferrets were then exposed to the resultant hybrid virus. Within a week, one ferret was found to have tens of thousands times more virus than the other ferrets. On sequencing this particular virus strain, the researchers found that it had acquired a third HA mutation, which enabled the virus to spread between the ferrets. The next step was obvious: exposing yet more ferrets to the new mutant strain. This was effective. Several ferrets picked up infections from neighbors they had no direct contact with. A fourth mutation was thereby discovered, which facilitated airborne spread of the virus. However, similar to the Fouchier end result, the transmissible virus did not kill any of the ferrets it infected. Furthermore, it was slower to spread than the 2009 pandemic H1N1 strain, caused less severe damage in the lungs, and was susceptible to both Tamiflu and a prototype H5N1 vaccine. The Kawaoka experiments resulted in a transmissible version of avian flu, but one that does not appear to be a particularly dangerous virus.

In order to release their genetic material, it is necessary for flu viruses to merge their membranes with the membranes of their host cells. The mutations in Kawaoka's new virus allowed for this to happen prematurely, and reduced the virus' ability to spread. Kawaoka's key discovery is that a fourth mutation was found to be responsible for stabilizing the protein, allowing the virus to be more transmissible. Still, many research questions remain unanswered. For example, it is unclear whether the virus could spread between humans as well as it did between ferrets, or whether the four HA mutations would confer the same ability on a purely H5N1 virus.

1.5   Not Deadly Yet

Both sets of experiments, by Fouchier in Rotterdam and Kawaoka in Wisconsin, appear to have resulted in avian flu viruses that are transmissible but that are a lot less virulent than their non-transmissible parent, at least in ferrets. The exact level of virulence for ferrets has not been established, and although ferrets are good representatives of humans in influenza research, it is difficult to be certain what impact the mutant viruses would have on humans.

Both sets of researchers still believe that it is possible for a highly pathogenic transmissible virus to occur in nature and that laboratory experimentation will help to elucidate the mutation processes that will give rise to it. They have expressed an intention to continue their search for more deadly forms of the transmissible virus. The techniques that they have developed have proven to be very successful in causing directed mutations towards a goal. The U.S. DHHS charter for HPAI H5N1 gain-of-function research from 2013 onwards is directed towards imposing stricter conditions on the next wave of research anticipated to "increase pathogenicity, virulence, and/or transmissibility of a virus in mammals"[6].

The next round of scientific experimentation is likely to be directed towards increasing the virulence of transmissible viruses.

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[6]   United States Department of Health and Human Services (US DHHS) 2012.

1.6   Age Profile of H5N1 Cases

The overall virulence of the H5N1 avian flu virus is of sufficient concern in its own right, but an additional dimension of concern is the strong impact of the virus on young adults. Currently, the number of H5N1 cases is markedly higher in children and young adults, with the modal age of cases at 20 years. The number of people over the age of 60 who have been infected is low. Seasonal influenza typically causes higher mortality in the very young and the very old. The H5N1 virus has a very different age mortality profile. The age bias is consistent across all the countries where H5N1 cases have occurred.

The number of infected people at different ages could be explained by behavioral factors – such as only young people coming into contact with infectious birds. But the proportion of cases that die, or the case fatality rate (CFR), is also markedly higher in the younger age groups, as shown in Figure 1. An immune response known as a cytokine storm has been used to explain this demographic pattern. Cytokines are chemical messengers that signal immune cells to activate cells at infection sites. In a cytokine storm, a positive feedback loop is established between cytokines and immune cells, so that the reaction becomes uncontrolled. Too many immune cells activated at one location can potentially result in significant damage to body tissues and organs and can lead to death.

Another potential explanation for the age profile is that the older populations may have a greater immunity to the virus. It is possible that older individuals may have acquired some degree of immunity, possibly from being exposed to previous strains of a genetically-similar influenza virus.

If this age profile of victims were reflected in a pandemic, the death count and illness rates would be particularly marked in the economically-productive workforce and in the portfolios of life insurance companies, which tend to have concentrations of policyholders in the age range of 30 to 60. The overall population mortality from a pandemic might be less significant than the infection rates and subsequent mortality in the working population. Insurance companies could find themselves experiencing higher mortality rates in their portfolio than the general population. The economic impact of a pandemic resulting from an H5N1 virus could be much more significant than pandemics from other strains.

Figure 1: Cases and Deaths by Age, Analysis of 407 Human Cases of H5N1[7]

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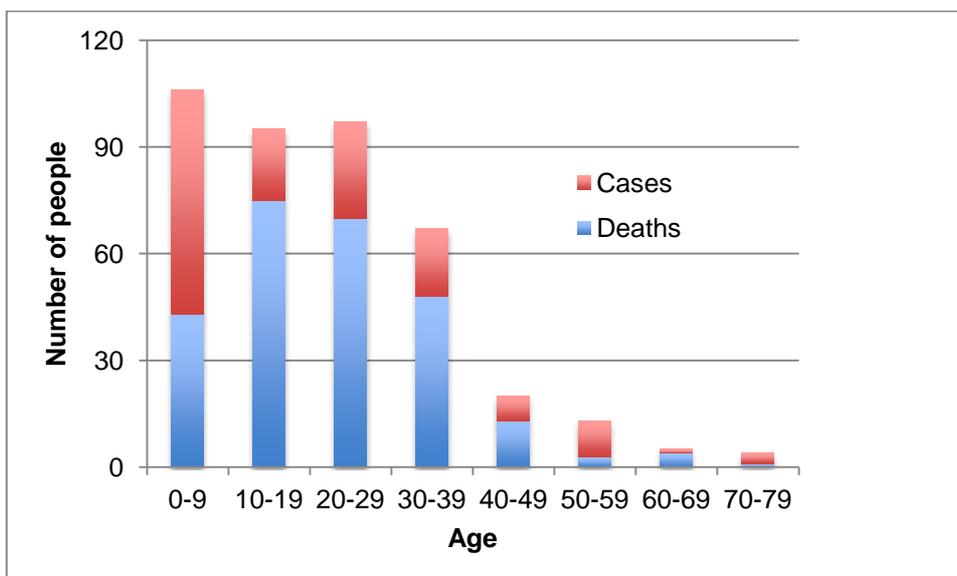
[7]   Dudley, 2009.

1.7   No Change in Timeline to the Next Pandemic

H5N1 strains in Egypt and some other countries in the Middle East already carry the mutations that enable the virus to bind to human-type receptors. Some also have a mutation that is associated with effective virus replication in mammals. Kawaoka's research shows that all that is missing is a further stabilizing mutation. Does this suggest that the next natural pandemic is imminent?

In Kawaoka's laboratory, this additional mutation emerged from within a close group of infected ferrets. The identification of the mutation process is helpful to improve the quality and targeting of surveillance of naturally occurring strains in the Middle East and elsewhere. Public health measures to minimize the spread of H5N1 are already aggressive, and for example, involve the wholesale eradication of infected domestic poultry populations. Containment and eradication measures could be expected to become even more aggressive if a new strain with the feared characteristics were detected. The WHO takes an active role in resourcing and coordinating H5N1 surveillance, and has supported the publication of the papers by Kawaoka and Fouchier because of the perceived surveillance benefits. Early detection of a new strain with the feared characteristics would trigger a substantial effort to contain and eradicate the virus before it could spread widely in the human population. Once in the human population, however, the containment and quarantine process is complex, and it is difficult to prevent major spread. Past pandemics, including the 2009 H1N1 pandemic, have been impossible to contain at their source. Many epidemiologists and health care specialists expect that if a mutation occurs in rural areas or countries with less well-developed healthcare systems, viral spread into the human population will not be preventable through surveillance and containment[8]. It would be pragmatic to assume that the laboratory discoveries will not reduce the risk of a new mutation turning into a pandemic.

The risk of a naturally-occurring pandemic is largely unchanged from before this research was undertaken. We now know that the mutation is possible and that the evolutionary steps may not be as complex as previously thought, but this does not change the overall assessment of the potential or likelihood of the process occurring naturally through random evolutionary processes. Quite apart from Kawaoka's stabilizing mutation, there are likely to be others, as yet unknown, that might also trigger a pandemic. There is nothing in the knowledge that has been gained from the recent discoveries to suggest that the actual time interval to the next natural pandemic is any shorter than previously thought.

2   POTENTIAL ESCAPE FROM A LABORATORY

The completion of this piece of science confirms the existence of a type of virus that before was only hypothesized. An infectious version of avian flu now exists and samples are being held in several laboratories. The successful experiments will encourage other scientists to replicate the process, and also to carry out more experiments along similar lines.

The intention of the research was to explore the possibility of a hybrid that was transmissible and highly virulent. This round of research does not seem to have produced that. Instead both experiments produced a hybrid that was transmissible but probably mild in its virulence. The fact that the laboratory viruses produced are not as dangerous as originally was perceived from press reports is one of the reasons for the non-redacted, open publication of their scientific papers.

Once published, the advancement in scientific knowledge is irreversible. Experimentation is continuing and high virulence is still a goal. Now that it is known to be possible to generate mutated H5N1 strains that have some degree of transmissibility and lethality, the range of mutant strains will be explored by other scientists.

Many countries now have sophisticated biological research laboratories handling dangerous pathogens, as biotechnology develops rapidly as a global industry. These laboratories are run with high safety standards, but they are complex systems with inherent risks. Even in advanced technological societies like the United States, new laboratories have been challenged and criticized as posing unnecessary threats to populations. In less well-developed countries, there is potential for increasing, rather than decreasing, biological threats through

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8   Lipsitch et al., 2012.

the establishment of high biocontainment laboratories. There is no global control system for these laboratories, and efforts are being made to stop further expansion. Many countries lack even basic legal and regulatory systems that would govern such facilities. The proliferation of biological labs is a matter of significant concern for many scientists.[9] Marc Lipsitch and Barry Bloom from the Harvard School of Public Health have said that H5N1 viruses that are transmissible between mammals pose "a greater threat to public health than possibly any other infectious agent currently under study in laboratories, because of such viruses' likely combination of transmissibility and virulence to humans."

2.1 Accidents Do Happen

The possibility of a dangerous virus escaping from a laboratory and triggering a human pandemic is of major concern. However diligent Fouchier and Kawaoka have been, hundreds if not thousands of researchers may eventually handle the new flu strains or others like them.

Accidents do happen, even in high-security laboratories. It is estimated that some 5,000 people have suffered from laboratory-acquired infections (LAIs) since 1930, and nearly 200 have died. Although infections and escapes have reduced over the years, the proliferation of research laboratories across the world has raised concerns for increased regulation and controls. Over 100 incidents have been reported to federal regulators in the U.S. since 2003, involving scratches from plague-infected monkeys, broken vials of an encephalitis-causing pathogen, Ebola needle sticks, and missing plague-infected mice. Breaking the law also happens: a Texas Tech professor carried a vial of plague bacteria onto a passenger jet. International security is only as strong as its weakest link: three escapes of the SARS virus occurred in Asian laboratories. There are significant biosafety concerns for laboratories in the developing world. Unlike SARS, the spread of flu is harder to control because people may be contagious without being symptomatic

A 2008 U.S. Department of Homeland Security (DHS) review report of U.S. and international laboratory incidents, involving BSL-3 and BSL-4 labs from 1974-2008, identified 9 incidents involving BSL-3 and BSL-4 labs from 1974-2008, where a pathogen left a secure facility and was not immediately identified. One incident, involving SARS in China, led to the death of an individual not affiliated with the lab: the mother of a laboratory worker. Not all of these lab releases involved pathogens that have pandemic potential, but they were notable because they initially went undetected.

Unnecessary regulation is acknowledged to be a threat to good science, and there is recognition that there is a need for a balance between public safety and regulations. Research on H5N1 and the new strains has so far been conducted at what is classified as Biosafety Level 3 labs (see Table 1). Calls have been made for research into new strains of H5N1 to be conducted under the maximum security of Biosafety Level 4, which is typically reserved for highly lethal pathogens for which there is no known cure. The engineered H5N1 strains might yet turn out to be in this category. Agents requiring BSL-4 security include smallpox, Ebola and hemorrhagic fevers. Most of the BSL-4 categorized agents primarily threaten people who work directly with them, and fortunately are not very transmissible when they get into the environment. The reclassification of new-strain H5N1 research to BSL-4 requirement would add significantly to the cost of doing research, but would reduce the likelihood of accidental release.

2.2 The Likelihood of Accidental Escapes and Outbreaks

There are a wide range of views of the likelihood of escapes and the potential for an escape to turn into a pandemic. In a paper published August 2012[10], Klotz identifies at least 42 laboratories currently working with potential pandemic pathogens (PPPs) – i.e. H5N1 viruses, live versions of the 1918 influenza virus, or the SARS virus. He estimates from the history of past escapes from BSL-3 laboratories and government risk assessments for biolabs that a conservative assessment of the frequency of virus escapes from each BSL-3 lab is 0.003 (i.e. 0.3%) per year, which translates to an 80 percent likelihood of escape from one of the existing 42 labs every 12.8 years.

Klotz also notes that although security levels are significantly higher in BSL-4 laboratories, intuitively, the probability of escape from these labs should be lower, but the statistical evidence shows that the escape

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9   National Academy of Sciences, 2012, Biosecurity Challenges of the Global Expansion of High-Containment Biological Laboratories

10   Klotz and Sylvester, 2012, 'The Unacceptable Risks of a Man-Made Pandemic'.

frequency at BSL-4 may be of a similar order of magnitude to that at BSL-3. Although the number of laboratories is much smaller, making the data more susceptible to random events, there have been four documented escapes from the 50 or so BSL-4 laboratories operating since 1990, a frequency of around 1 in every 150 lab-years of operation or 0.67%.

Table 1: Security Requirements for Different Grades of Biosafety Laboratories[11]

Biosafety Level BSL	BSL 1	BSL 2	BSL 3	BSL 4
Agents	Only agents that do not cause diseases in immunocompetent adult humans	Agents associated with human disease. Hazard: percutaneous injury, mucous membrane exposure, ingestion	Indigenous or exotic agents with potential for aerosol transmission; disease may have serious or lethal consequences; diseases for which treatments exist	Dangerous or exotic agents which pose high risk of life threatening disease, aerosol-transmitted lab infections; or related agents with unknown risk of transmission
Examples of Agents:		Mumps, measles, influenza A, C. difficile, hepatitis, Lyme disease, Salmonella, MRSA	Yellow Fever, SARS coronavirus, Bacillus anthracis, Mycobacterium tuberculosis, West Nile virus, Salmonella typhi	Smallpox, hemorrhagic viruses, Marburg virus, Ebola virus, Lassa virus
Practices	Standard microbiological practices	BSL-1 practices plus: biohazard warning signs; sharps precautions; waste decontamination; medical surveillance policies	BSL-2 practices plus: decontamination of all wastes; decontamination of lab clothing before laundering; baseline serum	BSL-3 practices plus: clothing change before entering; shower on exit
Access Controls	None required	Limited Access	Controlled Access	Secure Access
Personal Protective Equipment (PPE)	Gloves and eye protection recommended as good practice	Gloves and eye protection recommended as good practice	Laboratory coats, gloves, respiratory protection as needed	Full-body, air supplied, positive pressure suit
Primary Barriers (Safety Equipment)	None required	Physical containment devices used for all manipulations of agents that cause splashes or aerosols of infectious materials	Class I or II biosafety cabinets or other physical containment devices used for all manipulations of agents	All procedures conducted in Class III biosafety cabinets
Secondary Barriers (Facilities)	Open bench top, sink required	BSL-1plus: non-fabric chairs and other; furniture easily cleanable	BSL-2 plus: physical separation from access corridors; self-closing double door access	BSL-3 plus: separate building or isolated zone
Air Handling			Exhaust air not recirculated; negative airflow into laboratory	Dedicated supply/exhaust air system, with vacuum and decontamination system
Decontamination	Sink required	Autoclave required; eyewash readily available	Hands-free handwashing-sink; eyewash readily available in lab	All material decontaminated on exit from facility; decontamination of all air exhaust
Estimates of Total Number of Labs			Worldwide more than 5,400; 1,356 registered with CDC in US in 2007	Around 50 identified worldwide, 15 registered in US with CDC in 2007

Not all escapes would result in a pandemic. Only a few recorded cases of escapes have resulted in widespread epidemics, but one such example is the 2007 outbreak of foot-and-mouth disease in cattle in England as a result of a virus escape from the Pirbright BSL-4 research laboratory[12]. There is some possibility that the 1977 Russian flu epidemic may have emerged from a laboratory virus escape[13].

For an epidemic to result from an influenza virus escape, the initial infected individual would need to infect others who would spread the disease in the community faster than the public authorities could identify the outbreak and quarantine all the infected people.

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[11] Centers for Disease Control, 2007, *Biosafety in Microbiological and Biomedical Laboratories*; Estimates of total numbers of laboratories from GAO, 2007; and National Academy of Sciences, 2012.

[12] The 2007 Foot and Mouth outbreak was caused by incomplete decontamination of viruses in discharge from centrifuges in the BSL-4 research laboratory, combined with overflowing drains that infected vehicles that spread the disease to neighboring farms in Surrey, Sellers (2007). At least 39 animals were infected, some 19 km (12 mi) away from the laboratory. A quarantine protection zone and major livestock cull contained the outbreak.

[13] Kilbourne, 2006. Analysis of the 1977 Russian flu virus showed that it was implausibly similar to an influenza virus of the 1950s, implying that it had come from concealed experimentation with live virus in a research laboratory.

This probability is very difficult to estimate. With influenza, symptoms typically show between one and four days after infection ('the incubation period'), and carriers become infectious to others about a day before they experience symptoms. This makes it possible for unknowingly-infected people to travel widely and infect others before they ever exhibit symptoms of being sick, which is why influenza is such a difficult disease to contain. The containment of infectious disease outbreaks is proving increasingly difficult in our modern, highly-mobile society.

2.3 Malicious Release

In addition to accidental release from a research laboratory, there is the potential for deliberate release of a pathogen for malicious reasons. There are several precedents:

One of most significant malicious releases of a deadly pathogen from a research laboratory occurred when military-grade anthrax was sent through the post in 2001, in the months following the World Trade Center terrorist attack, to addresses in New York City and Washington, D.C. The Federal Bureau of Investigation (FBI) claims these anthrax letters were distributed by a microbiologist at USAMRIID, Fort Detrick's bioweapons defense institute. The chief suspect was plagued by mental health problems, and he took his own life shortly before he was due to be interrogated by the FBI. The failure of security systems and background checks on personnel is a major cause of concern for similar recurrence with a potential pandemic pathogen.

There have been a number of other historical incidents, for a variety of motives. During the 1960s, unscrupulous landowners in Brazil released pathogens, including influenza, amongst indigenous tribes with the intent of taking over their grazing land.

Regrettably, there are numerous scenarios for the intentional misuse of man-made pandemic influenza. Paul Keim, acting chair of the U.S. National Science Advisory Board for Biosecurity (NSABB) has identified some of these in a *Nature* editorial[14]: "mad lone scientists, desperate despots, members of millennial doomsday cults, nation states wanting mutually assured destruction options, bioterrorists, and the random acts of craziness of single individuals". Humanitarian hope that highly trained bioscientists would ultimately step back from any act of mass murder should be offset by the grim recollection of the 1995 sarin gas attack on the Tokyo subway—a former heart surgeon participated in the attack.

Although individuals with access to these dangerous agents undergo strict vetting procedures, confidence that this security measure will prevent intentional release is undermined by the history of security breaches.

The more labs that have access to the technical information about the Fouchier and Kawaoka's methods, the greater the risk of malicious release. These two research teams are only a subset of the labs that have been concurrently manipulating H5N1 in the effort to better understand the virus. The community of researchers that could become involved in gain-of-function research into HPAI viruses could be even larger than this, now that the moratorium has been lifted.

We cannot know the likelihood of any individual lab worker perpetrating a malicious release, but if severe mental disorders are an associated factor, the prevalence of these in the general population would give cause for concern. If there was a one-in-a-thousand chance that any one of the HPAI researchers is deeply emotionally disturbed, and a one-in-a-hundred chance that such a vulnerable individual might commit a malicious release in a given year, this would be of the order of an annual 1% chance of a malicious release[15].

Given that a major malicious release of a pathogen has already happened in the 21st century, the idea that a malicious release of a man-made pandemic virus might be possible in the coming decades does not seem excessively pessimistic.

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[14] *Nature* editorial, 2012. 'Flu papers warrant full publication'.
[15] Woo, 2012.

3   WHAT KIND OF PANDEMIC MIGHT RESULT?

To assist the life insurance clients of RMS with understanding the threat posed by laboratory pathogens, and also to contribute to societal debate around the value and dangers of HPAI research, RMS has modeled some scenarios of possible pandemics resulting from laboratory escapes.

The RMS® Infectious Disease Model estimates the impact of pandemics on populations and life insurance portfolios by simulating the international spread of a pathogen and how public health authorities would respond. There are a number of variables that would affect the impact of a pandemic, so RMS is making plausible assumptions, documented here, based on current science and public health. The most likely scenario would be a single case or small epidemic. For the pandemic scenarios in the table below to occur, researchers must first be successful in increasing the transmissibility of a highly virulent virus. The preferential binding of virulent virus to the lower respiratory tract and transmissible viruses to the upper respiratory tract is indicative of a natural tradeoff that may exist between virulence and transmissibility.

Table 2: Scenarios of Laboratory-Triggered Highly Pathogenic Avian Influenza Pandemics

	Scenario A	Scenario B
RMS® Infectious Disease Model Event ID	10996	11218
Description	H5N1 reassortment, virus retains high virulence and transmissibility increases similar to 1918 pandemic strain	H5N1 reassortment, virulence significantly reduced to levels similar to 1918 pandemic strain, high transmissibility
Transmissibility (R_0)	2.0	2.25
Virulence (Case Fatality Rate)	30%	2.5%
Age Profile of Deaths	Elevated in young and working age population	Elevated in young and working age population
Vaccination Achieved in yr 1	~30%	~50%
Pharmaceutical Strategy	Antivirals and Supportive Care (Antibiotics have limited effect, most deaths from viral pneumonia)	Antivirals, Antibiotics, and Supportive Care
Total Global Deaths	**50 million**	**18 million**
Global Death Rate	**7 per 1,000 population**	**2.5 per 1,000 population**

Two scenarios are provided here, bracketing some of the more severe outcomes. They are representative of severe outcomes but do not necessarily constitute 'worst-case' scenarios. The scenarios are available in the RMS® Infectious Disease Model. The event IDs are provided, and the events are summarized in Table 2. Users of the RMS LifeRisks™ Modeling Platform can run these scenarios in the infectious disease model to quantify the excess mortality rates that would be likely to occur on their specific life insurance portfolios.

3.1   Viral Characteristics

The primary variables are the characteristics of the virus, in terms of its infectiousness and virulence. For scenario A we assume that the infectiousness would be similar to other viruses that have triggered pandemics, with a basic reproductive number (R_0) of 2.0. An R_0 of 2.0 is on the high end of seasonal flu (R_0 range estimated to be 0.9-2.1) and of similar order to the 1918 pandemic virus, but higher than some

estimates of the 2009 pandemic virus (R_0 estimated to be 1.4-1.6) [16]. Fouchier has estimated that the infectiousness of the virus he created is lower than the 2009 pandemic virus but higher than seasonal flu. Higher R_0 values mean faster spread of the disease, more difficulty for public health authorities in controlling the pandemic and significantly larger proportions of the population likely to be infected during the pandemic wave. Scenario B is an example of a higher transmissibility flu virus, similar to the higher transmissibility observed in certain regions during pandemic outbreaks.

The scenarios also explore the impact of virulence, measured as case fatality rate (CFR) – the ratio of deaths to number infected. The currently circulating H5N1 avian influenza virus has limited human-to-human transmissibility but it has a CFR of nearly 60%. Seasonal flu, by contrast, typically has a CFR of less than 0.1%. The 2009 pandemic was exceptionally mild, with a CFR estimated to be <0.05% for cases in United States and Europe.

It is possible, and theoretically likely, that the genetic changes required to make the virus transmissible, involving enabling the virus to attach to the upper respiratory tract instead of the lower, would cause the virus to reduce in virulence. This trade-off of virulence for infectiousness is an uncertain part of the estimation.

In Scenario A, we assume that the virulence of the avian influenza virus is reduced from the current apparent case-fatality rate of nearly 60% (unreported or asymptomatic human H5N1 cases would result in an overestimation of the current case-fatality rate). In Scenario B we assume that when the virus achieves transmissibility the virulence is an order of magnitude lower than that of current H5N1, resulting in a CFR of 2.5%, similar to the estimated CFR of the 1918 pandemic strain. There are no published estimates of the virulence of the virus that Fouchier has produced, but the virulence is assumed to be relatively low. The next phase of planned research is likely to explore how higher levels of virulence might be achieved in nature.

Most of the laboratories where gain-of-function research is likely to take place are in the U.S. and Europe, so an escape is more likely to occur in countries with good surveillance systems and resources to improve the chances of containing a potential outbreak. There are a few laboratories in other countries where surveillance might be weaker. Once the outbreak has evaded containment for more than a couple of weeks it is likely to be unstoppable and to become a global pandemic.

The age relativity profile of deaths in the population caused by the new virus is assumed to be similar to the age profile already seen in H5N1 cases, described earlier, and illustrated in Figure 1. Currently, the number of human H5N1 cases and deaths is skewed toward young adults. This offsets the more common age profile seen in influenza, of higher mortality in the infants and the elderly. The age profile assumed in both scenario A and scenario B is relatively flat, but with elevated mortality rates in the age range 20 to 50, peaking in the mid-30s. Mortality rates are lowest for the age group assumed to have a level of residual immunity, 60 to 80, and then rise again in the over 80s.

The full event set contained in the RMS infectious disease model incorporates over 2,000 influenza pandemics with permutations across the full range of viral and response characteristics, including R_0 (1.25 to 3.0) and CFR (0.05% to 30%). Insurers wanting to explore the impacts of alternative scenarios can select a range of viral characteristics to quantify the spectrum of potential impacts on their portfolios.

3.2 Pandemic Response and Pharmaceuticals

The very high virulence of the pandemic scenarios is unprecedented in modern society. For the initial months of the pandemic, before a vaccine is available, there will be little to prevent the disease causing deaths in a large number of cases. The fear of the disease will cause behavioral changes in the world's population. Social contact will reduce to a minimum. Schools and places of public assembly will close, and many places of work will see high levels of absenteeism. Commercial activity and productivity will drop. The social withdrawal will have the effect of slowing down the spread of the disease. At some point, a vaccination program will begin that will contain and eventually stop the spread of the pandemic, but the disease spread and the vaccine development will be in a race. The overall death toll depends on the

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[16]   Coburn BJ, 2009, 'Modeling influenza pandemics and pandemics: insights into the future of swine flu (H1N1)'.

relative progress of these two processes – the reduction of social contact and the progress in developing a vaccine. For these high virulence viruses in Scenarios A and B, the assumption is made that all social contact is reduced to an absolute minimum, and that most commercial activity ceases during the pre-vaccine period. The world's economy is badly hit as a result.

Pharmaceuticals and vaccines are the chief methods of combating pandemics. The majority of influenza mortality is a result of secondary bacterial infections, such as pneumonia. For these, antibiotics are effective treatments and countries with large supplies of antibiotics will be able to use them to reduce mortality levels. The mortality mechanism in the H5N1 pandemic scenarios is assumed to be the same as the current H5N1 virus which causes the majority of its deaths from the primary viral pathogen, and so antibiotics are of limited use. The main pharmaceutical weapons required to combat the pandemic are antivirals such as Oseltamivir/Tamiflu and Zanamivir/Relenza. Only countries with large antiviral supplies – typically those with advanced medical healthcare systems – will have much effectiveness in combating the mortality from the pandemic before the arrival of the vaccine. Without these antivirals, the only medical response strategy is 'supportive care' – standard nursing procedures to alleviate suffering.

The scenarios would be more severe if the virus were to mutate to acquire antiviral resistance. If the resistant strain became the dominant strain in circulation, then the antiviral drugs that some countries have available would be of limited effectiveness. The scenarios here assume that this does not happen.

The speed of development and manufacture of the vaccine, vaccine efficacy, and the ability to implement a vaccination campaign across the general population are all variables in the modeling. The vaccine needs to be developed to target the specific strain that emerged as the pandemic spread. Although some 'pre-pandemic' H5N1 generic vaccines have been developed and licensed, and there have been various proposals to develop a WHO stockpile for first responders in less well-developed countries, only minimal supplies exist today. The scenarios assume that a highly prioritized mass production process is put into place to manufacture vaccine once the outbreak is identified as a major public health hazard, similar to that seen in the 2009 H1N1 pandemic. This process can be expected to take several months, and there are potential complications that could delay this. As quantities of the vaccine become available, the process of administering a prioritized, universal vaccination program also takes time. The metric used to indicate the successfulness of vaccination is the percentage of the population that have immunity, either residual or vaccine-acquired prior to the peak of the pandemic in that region. In Scenario A we assume that approximately 30% of the population is successfully vaccinated. In Scenario B we assume that the existing generic H5N1 was reasonably well matched and approximately 50% of the population had immunity at the peak of the pandemic. These represent the range of achievable vaccination success with a highly prioritized and very well resourced campaign. It is possible to envision outcomes where much lower levels of vaccination success are achieved. For example, if the virus was too virulent, it would make the current manufacturing process of incubating doses in chicken eggs unfeasible. Alternatively, a low-efficacy vaccine could be produced, or front-line healthcare workers could become so depleted by illness that they would be unable to carry out the vaccination program.

The pandemic scenarios A and B are simulated across a population model for the world. The pandemic wave passes around the world in a matter of months, peaking at slightly different times in different locations. When the vaccine is available, the implementation of mass-vaccination gradually suppresses the further spread of the pandemic. High levels of seasonal flu could be expected in subsequent years as the pandemic virus becomes the endemic seasonal influenza strain, and these could potentially be seen as second or third waves of the pandemic. The subsequent waves are excluded from the mortality estimates of the first pandemic wave, which exhausts within the initial 12-month period.

Scenario A causes 50 million deaths worldwide and Scenario B causes 18 million deaths. In both scenarios death rates are significantly higher in countries with less-well-developed healthcare systems. The deaths are highest among working-age adults. These death tolls are consistent with other estimates of what an avian flu pandemic could achieve[17].

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[17] United Nations System Coordinator for Avian and Human Influenza put out an estimate that an outbreak of avian influenza could kill between 5 million and 150 million people worldwide. UN (2005).

Scenario Narrative: Scenario A

An H5N1 gain-of-function research project at a BSL-3 laboratory in Washington, D.C. results in a highly virulent and transmissible strain of influenza. The laboratory assistant in charge of ferret husbandry does not realize that he has become infected. Two days later, he takes the Metro to the airport for his scheduled Christmas trip to Central America. Three days into his vacation he develops a high fever, shortness of breath, and severe gastrointestinal illness. He is treated in a local hospital and recovers, but given his unusual presentation and lack of severe respiratory symptoms, influenza is not suspected as the cause of his illness. During his travels he was contagious although he had not yet started to display symptoms.

Over the course of the next week, 2 people in Washington, D.C., 2 in Asia, 1 in Europe, and 5 hospital workers in Central America develop severe cases of influenza. Flu season normally occurs in early January in the northern hemisphere, and given the geographic diversity in the cases, no public alarms are triggered initially. The following week, 3 of the 5 hospital workers die from severe pneumonia and an additional 12 of their close contacts have developed high fevers and respiratory symptoms. A major containment exercise is initiated in the hospital, with an attempt to trace all contacts. H5N1 is identified as the agent and the Central American hospital becomes the first location for a cluster of infections. The WHO outbreak investigation team begins work to determine the cause of the outbreak.

The virus is of particular concern, because it is quickly killing previously healthy individuals and antibiotics are ineffective in treating the viral pneumonia. Over the next month, researchers compare the viral genetics of known H5N1 strains and are able to trace the outbreak to the Washington, D.C. laboratory. By this time, clusters have emerged throughout the globe and authorities are acknowledging that they cannot contain the outbreak. The WHO declares pandemic stage 5 and governments around the world move to implement their pandemic response plans.

Analysis suggests that the initial reproductive number of the virus is around 2.0 – each case is infecting another two cases on average, but a handful of super-spreaders, like the index case, have ensured the virus has taken hold globally. First estimates indicate that in the absence of intervention, around a third of the cases die. This is about half the fatality rate of the original H5N1 virus, but is more virulent than any historical influenza pandemic. Antiviral drugs are effective in treating cases, provided that treatment is received within 48 hours of symptoms. Government stockpiles of Tamiflu are released.

The fatality rate is particularly high among economically-active young adults between the ages of 20 and 40. Infection and death rates in people over the age of 60 are lower, possibly due to immunity built up from exposure to previously-circulating similar viruses.

Hospitals and primary healthcare physicians are quickly overwhelmed by demand. Fear of the disease and government advice causes the closure of all public venues. People shun contact with each other and stay home. Absenteeism at work is very high and many companies choose to close their businesses for the duration. The economy is badly hit by work closures and lack of demand for goods and services. Stock markets fall and investment assets devalue.

Even before the beginning of the outbreak, the bioresearch industry has been highly focused on developing a vaccine for the virus. H5N1 research has been underway for years, the virus is well-understood, and a vaccine culture is quickly available. Some small stockpiles of a vaccine for a similar H5N1 virus already exist and are used to inoculate first-line healthcare workers. Biotech factories around the world ramp up their manufacturing capacity and within 4 weeks are producing 100 million doses a month. The factories have orders from the major G20 countries but allocate a proportion of their output to developing countries. It takes several months to manufacture sufficient vaccine to supply the vaccination programs of the major countries of the world.

Mass vaccination programs begin as vaccine arrives, with people queuing for their injections. It takes 6 weeks to inoculate enough people to slow the spread of the pandemic. The number of reported new cases each week starts to fall three months after the outbreak began. Confidence is gradually restored and businesses reopen. Cases and deaths continue for several more months. Vaccine is gradually re-prioritized towards the countries with the worst death counts.

By the end of the year, the WHO estimates that over 50 million people have died from the pandemic worldwide. The global economy has suffered significantly from 2 months of near-complete disruption and over 6 months of dysfunction and reduced demand.

3.3   Escape Scenario

Scenario A, a laboratory-acquired infection (LAI) triggering a pandemic escape scenario is given a narrative in the section below.

3.4   It Could Be Even Worse

The scenarios here are chosen to be severe but not the most extreme examples imaginable. There are several ways that a real H5N1 pandemic could be more severe. The values for transmissibility and virulence could be higher or the virus could develop antiviral resistance. The competence of the responding authorities has been assumed to be exemplary – there are many ways that global and national responses could be compromised. The pandemic is assumed to be the main focus of the world's attention and highest priority for resources, but compounding problems could distract and complicate the issues to make the impact harsher. If the pandemic occurred at a time of geo-political crisis, such as a major war or sectarian division, this could fragment and weaken the global response. Healthcare conditions could be complicated by some other additional circulating diseases, a harsh winter, or extreme respiratory conditions.

4   ARE THE BENEFITS WORTH THE RISKS?

The key debate is whether gain-of-function research is worthwhile, and whether the moratorium should continue, or under what conditions should it proceed? We explore two divergent viewpoints using RMS modeling and scenario A to illustrate the potential impacts of an H5N1 pandemic.

4.1   Viewpoint 1: H5N1 Research is Too Risky

It is reasonable for the world to demand higher security standards, to put into place global regulation frameworks, and to be stringent on what research is really of net value to our society. While it is true that unnecessary regulation is a threat to good science, the benefits of proceeding with gain-of-function research need to be weighed against the potential risks in order to maintain a balance between public safety and scientific freedom. As with many things that threaten public safety, a precautionary principle should be followed to ensure the public good.

H5N1 influenza research currently requires biosafety level three (BSL-3) laboratories, rather than the maximum security BSL-4. Researchers are resisting upgrading to BSL-4 for gain-of-function research, arguing that this will slow up research progress. According to a 2009 U.S. Government Accountability Office (GAO) report, the number of BSL-3 labs is increasing, and there are more than 1350 BSL-3 labs registered to the Division of Select Agents and Toxins (DSAT) in the U.S. alone. Many more exist globally. There is no strict oversight for the regulation of BSL-3 labs, so there is no way to know for certain how many of these laboratories exist and how many people are working with BSL-3 pathogens.

Lab accidents are not uncommon, and many go unreported. It is estimated that as many as 5,000 people have suffered from laboratory-acquired infections since 1930. This number is probably an underestimate, as labs may be disincentivized to report accidents, due to the negative publicity for the laboratory and individuals involved, as well as the increased scrutiny from funding sources following violations of procedures. In this paper we have provided examples of known escapes resulting in outbreaks, and malicious releases.

The benefits of gain-of-function research are limited. Progress towards improved surveillance and vaccine development, though helpful in improving our readiness, would not prevent a pandemic from occurring. The potential severity of a pandemic makes it imperative that a full risk assessment is carried out, weighing the potential threat and benefits of allowing future research, to ensure that gain-of-function HPAI H5N1 research is well-controlled and only carried out under appropriate security levels.

A high-end and extremely conservative estimate of the impact probability of laboratory-escape pandemic would be to take the figures from the 2008 DHS review cited earlier, which documented 9 incidents in 34 years, or a 26% annual probability of a laboratory release of a pathogen. This would be conservative for

human pandemic risk because it is for both animal and human pathogens, and includes all pathogens, not only just those with pandemic potential.

The more difficult aspect to estimate is the probability of an epidemic or pandemic, given the release of a pathogen with pandemic potential. RMS specializes in the quantification of tail risk for the insurance and financial industry, so the remainder of the analysis will focus on the potential for a global pandemic, rather than a localized epidemic. Statistical methods alone cannot be used to estimate the probability of a global pandemic, since a laboratory-caused pandemic has never before occurred been confirmed. From the few escapes of infectious agents that have caused outbreaks, a conservative estimate of the probability of an escaped HPAI H5N1 virus causing a pandemic would be in the range of 5% to 10%.

If an annual probability of laboratory release were conservatively taken at 26%, and combined with a likelihood of it triggering a pandemic of 8%, then the annual probability of a laboratory-triggered pandemic would be 2% (1-in-50). If the pandemic potential escape probability was considered to be around 2% a year[18], and the likelihood of it triggering a pandemic being 5%, then the annual probability would be 0.1% (1-in-1000).

Table 3 shows how these assumptions about the probability of triggering a pandemic impact the risk metric for an extreme event, such as the excess mortality loss occurring with a 0.5% annual probability (1-in-200). The RMS model provides 1-in-200 level losses for the U.S. population from naturally-occurring pandemics, and table 3 shows how this risk metric would increase for different assumptions of the probability of laboratory-triggered pandemics, for 2%, 1%, and 0.1% a year. Taking scenario A as the benchmark, and considering this with the range of probabilities this shows that the 1-in-200 metric would be increased by a factor ranging from 1.1 (a 10% increase) to 3.25.

The overall risk also depends on how much trade-off there will be between the virulence and the transmissibility as the virus becomes more transmissible during the research. In this example, virulence remains high. As virulence reduces, the corresponding increase in 1-in-200 excess mortality risk will also decrease.

Table 3: Impact of Laboratory H5N1 Pandemic on 1 in 200 Excess Mortality Loss by Laboratory H5N1 Escape Probability

Annual Lab-Originated Pandemic Probability:	2%	1%	0.1%
Loss for scenario A assuming the following: • High virulence and transmissibility • Mean CFR=30% • Mean transmissibility $R_0 = 2.0$	3.25x	2.1x	1.1x

Results are in multiples of RMS' 1 in 200 infectious disease loss for the U.S. population and will vary by portfolio specifics.

4.2 Viewpoint 2: The Benefits Outweigh the Risks

Pursuing gain-of-function research does not materially change the risk of a H5N1 pandemic occurring. A world unprepared for an H5N1 pandemic presents a much more significant public health threat than the risk laboratory research creates.

Historically, there is a ~3.5% annual risk of a naturally emerging flu pandemic, which is higher than even the most conservative assumption for laboratory escape. Without a well-matched vaccine, we have very few weapons to effectively prevent transmission. RMS' models indicate that as few as 50 geographically-diverse cases are enough to start a global pandemic. Unlike smallpox or SARS, individuals are often infectious prior to being symptomatic, so public health interventions like ring vaccination and tracing and quarantining close contacts are not likely to be effective with flu. The 2009 H1N1 pandemic first occurred in April, a month that is typically outside the normal flu season, in an area with typically low levels of influenza, so it

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18 Woo, 2012.

was easy to identify unusual caseloads of flu-like symptoms quickly. Even so, the virus spread globally and it took over 6 months for vaccination to begin to stem the spread.

Modeling the impact of vaccines on the severity of pandemics shows that varying vaccine effectiveness can change the 1 in 200 excess mortality loss rate by approximately 30%, This impact on risk is far larger than the additional risk contributed by realistic assessments of the probability of a laboratory-originated pandemic.

If H5N1 were to become naturally human-to-human transmissible during a bad flu season, it would be too late to contain by the time an unusual mortality pattern was identified; given the high virulence, there is a high likelihood vaccine development would be difficult, as flu vaccine is manufactured using chicken eggs. With current vaccine development timelines, if a H5N1 vaccine, even a partial match, does not exist at the onset of a pandemic, it is unlikely to play a significant role in preventing morbidity and mortality from a highly transmissible virus.

Nature is as capable as, if not more capable than, researchers when it comes to creating viral mutation. Given the hundreds of untyped strains of influenza currently circulating around the globe, it seems that knowing whether creating an airborne-transmissible H5N1 is possible in a controlled laboratory—and using this understanding to create an arsenal against a potential pandemic—is far more prudent than stopping research because of the incremental risk of laboratory escape.

Natural evolution of the influenza virus, not laboratory accident, is the highest-probability mechanism for the occurrence. Thus far, research laboratories have not been able to overcome the tradeoff in virulence for increased transmissibility when conducting experimentation with H5N1. At this point, there is no reason to believe that a laboratory-created virus would be more virulent than a naturally-emerging transmissible H5N1 strain.

The key value of gain-of-function research is in developing effective and very early availability of vaccines. If this is the focus of research, and there is a high likelihood that this outcome will result, then the benefits will outweigh the risks. The emphasis for debate in favor of continued research is the potential of vaccine advances to greatly reduce the severity of the full range of extreme pandemics.

Supporting the science that can provide better surveillance, create better vaccines, and elucidate the genetic changes necessary to yield highly virulent and transmissible viruses is prudent risk management and good public health.

4.3   Life Insurers' Risks

Life insurance companies need to set aside appropriate capital reserves for excess mortality shock. Some companies have assumed that mortality levels reported from the 1918 influenza pandemic represent a "worst-case" shock scenario. With the advent of laboratory HPAI, it is clear that worse scenarios than 1918 are feasible. Insurers need to incorporate extreme scenarios of excess mortality into their risk management processes.

The tail of extreme mortality shock is long and although likelihoods may be low, there is potential for very severe events. The RMS influenza pandemic risk model is used for insurers to assess the frequency-severity distribution of their life insurance payouts and use this to assess the capital reserves that they need to maintain for mortality shocks. In Europe, Solvency II regulations due to come into force in 2015 require companies to hold solvency capital requirements (SCR) for a 1-in-200 (99.5%-ile) event.

The current viruses that have been produced in the laboratory do not yet constitute a significant threat. However, as gain-of-function research continues, and if it is successful in producing new forms of the virus that are more virulent and transmissible, then the possibility of these escaping and triggering a pandemic will become real. Insurers will need to add risk capital to cover the additional risk of excess mortality events.

Laboratory research does increase pandemic risk, at least until it results in protective vaccine benefits and could become significant with a gain-of-function breakthrough. Insurers may want to apply stress tests to their risk assumptions. The expected change in frequency from laboratory research remains within the uncertainty bounds of the current RMS® Infectious Disease Model. However, for risk managers looking for a

reasonable sensitivity test on Solvency capital requirements, RMS models indicate a 5% increase at the 1 in 200 level, using best-estimate escape probabilities and the RMS standard viral characteristics distribution.

The successful laboratory creation of a highly transmissible and virulent virus would alter the probabilistic distribution and lead to a significant increase in infectious disease mortality risk at all return periods. This has not yet happened. The translation of the gain-of-function research into vaccine technology, combined with the development of stockpiles and preparedness measures for mass-vaccination would cut the risk dramatically, and in the longer run, require life insurance companies to hold less risk capital.

RMS will continue to monitor the research, notify its clients if progress is made towards to developing a high virulence virus, and is conducting a full risk assessment, quantitatively weighing the potential threat and benefits of conducting gain-of-function research, in order to help better inform the debate.

4.4 Conclusion

Perhaps the heart of the debate should not be whether this type of research should be carried out, but rather how to ensure an appropriate level of safety to balance the increased risk with the public health benefit. The framework currently proposed by the U.S. Department of Health and Human Services for gain-of-function research is marked by poorly defined criteria, such as the research must address a scientific question of "high significance to public health" and risks will be "sufficiently mitigated and managed". Unfortunately, guidelines like these are likely to create additional barriers to scientific research that are unlikely to provide benefits to security and will likely slow up research progress. Public health would be better served by requiring actionable safety guidelines such as moving H5N1 influenza research from their current BSL-3 into maximum-security BSL-4 laboratories if and when a highly transmissible and virulent strain is created, and by requiring tangible precautionary measures, such as minimal vaccine development for all mammal-to-mammal airborne transmissible strains that cause fatalities.

The focus of the research to maximize benefits should be on vaccines being made available earlier and more readily available.

The research community alone should not be solely responsible for decisions that impact societal risk. We are all stakeholders in the decision to proceed with H5N1 research, and it is prudent to ask policymakers for cross-disciplinary oversight and pre-defined stringent security guidelines in the event laboratory research does result in a virulent and transmissible H5N1 virus. The H5N1 influenza virus is highly virulent and rapidly mutating and could pose the most significant pandemic threat of the modern era. Its evolution, through both natural and laboratory means, should be closely monitored as part of a comprehensive risk management program.

RMS continues to assess and monitor the contribution of man-made laboratory pathogens to excess mortality risk. By publishing an objective view of the facts, and a model of the potential impact, RMS hopes to contribute to the debate, and help identify how science can best contribute to public safety without increasing the chances of catastrophe.

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