Comparative Pandemic Risk:
A Natural Influenza Pandemic *vs.*
The PPP Research Enterprise

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Summary and Conclusions

The analysis presented here compares pandemic risk from natural influenza pandemics with the risk from a laboratory release from the "Potential Pandemic Pathogen Research Enterprise," the group of laboratories that create and research potential pandemic pathogens (PPPs). Lab-created PPPs are not present in the community unless they are somehow released from a Research Enterprise laboratory.

Of greatest present-day concern and the focus of this analysis is laboratory-created, mammalian-airborne-transmissible, highly pathogenic avian influenza (matHPAI). One example of a highly pathogenic avian influenza is the H5N1 virus. This virus kills 60% of people who become infected by direct contact with infected poultry. Unless an HPAI is made airborne-transmissible like seasonal human influenza virus, other means such as direct contact are necessary to transmit infection.

From the analysis here, the likelihood of a pandemic from a laboratory release of a lab-created matHPAI virus is likely within an order of magnitude of the likelihood of a natural pandemic. Consequently, concern over a pandemic from a laboratory release should rival our grave concern over a natural pandemic. The difference is that a pandemic from a lab release might be prevented; whereas, it is difficult to impossible to prevent a natural pandemic.

Each lab in the Research Enterprise must bear the burden of its contribution to potential fatalities, called the "fatality burden." In one sample calculation, a single lab performing ten years of matHPAI research could be responsible for 45,000 fatalities. To put this fatality burden number in perspective, no Institutional Review Board tasked with assessing human subject research would approve a proposed ten-year laboratory research project with even a dozen potential fatalities, much less 45,000 potential fatalities.

Alternative methods that do not employ live HPAI virus are likely faster at finding mutations responsible for airborne transmission in mammals. However, these methods do not prove transmissibility, they only suggest it. But that disadvantage is more than offset by the fact that pandemic risk from a lab release is essentially eliminated.

Simply moving this research to BSL4 facilities will not substantially reduce the risk. There have already been seven reported releases of pathogens from BSL4 containment since 1990, and six of the seven are due to human error.

Pandemics know no boundaries, so are an international threat. The world cannot afford to ignore the Potential Pandemic Pathogen Research Enterprise. The Parties to the Biological Weapons Convention (BWC) could be the catalyst to launch discussions for a different international treaty on proactive oversight and regulation of creation and research on these highly dangerous agents. Since enacting new treaties is an uncertain and lengthy process, in the meantime parties to the BWC should pass legislation in their own nations.

Some matHPAI creation and research should be banned, especially given alternative methods for finding mutations responsible for airborne mammalian transmission. This is an urgent concern.

The analysis

Yearly likelihood of a natural influenza pandemic from historical data

In the 20th century and so far in the 21st century there have been four influenza pandemics (Table 1) with widely varying fatalities.

	Year	Virus Type	Worldwide Fatalities (millions)
	1918	H1N1	50
	1957	H2N2	2
	1968	H3N2	1
	2009	H1N1	0.28

Table 1. The four 20th century and the 21st century influenza pandemics.
References: https://wwwnc.cdc.gov/eid/article/12/1/pdfs/05-0979.pdf
https://www.globalsecurity.org/security/ops/hsc-scen-3_pandemic-1918.htm
https://www.globalsecurity.org/security/ops/hsc-scen-3_pandemic-1957.htm
https://www.globalsecurity.org/security/ops/hsc-scen-3_pandemic-1968.htm
http://www.cidrap.umn.edu/news-perspective/2012/06/cdc-estimate-global-h1n1-pandemic-deaths-284000

Starting with the year 1920 just after the 1918 pandemic[1] to the present, 97.8 years have passed and there have been three pandemics. The probability of a pandemic in any single year is, p_1(natural) = number of pandemics/number of years passed = 3/97.8 = 0.031.

Yearly release probability and pandemic likelihood from the PPP Research Enterprise

The term "Potential Pandemic Research Enterprise" has been coined to describe the collection of laboratories that create and research potential pandemic pathogens (PPPs). Lab-created PPPs are not present in the community unless they are somehow released from a lab.

From an LK analysis[2] of the Federal Select Agent Program's yearly reports to Congress, the probability of release into the community of select-agent pathogens is p_1(single lab) = 0.0028 for a single lab in a single year. The reports cover accidents and incidents that involve potential human exposures, laboratory-acquired infections (LAIs), and releases into the community. The FSAP select-agent labs mainly research bacterial pathogens and are mainly BSL3 labs.

Calculations from the reports should approximately apply to other pathogens such as matHPAI. The main reason for this assertion is that most lab accidents and incidents are caused by human error, which likely will be similar in all settings. Human error is discussed and quantified in the LK analysis.

If we now assume that the PPP Research Enterprise is comprised of 10 labs around the world, the probability of a release from a laboratory in the Research Enterprise in a single year is approximately,

$$p_1(\text{enterprise}) = 10 \times p_1 = 0.028 \text{ per year}^3.$$

There are likely at least 10 laboratories creating or conducting research on live matHPAI, and many laboratories making seasonal flu viruses more virulent. This will be documented in a subsequent analysis of published scientific papers reported in Pub Med.

Another perhaps more intuitive way to look at the 0.028 number is what is the probability, E, that at least one release occurs in Y=10 years.

$$E = 1 - [1-p_1(\text{enterprise})]^Y = 1-[1-0.028]^{10} = 0.247 = 24.7\%$$

Thus, there is almost a 25% chance that there will be at least one release in ten years.

Will a release into the community seed a pandemic?

Assume that a lab-created PPP (e.g., matHPAI) is as capable of human to human airborne transmission as an historical pandemic strain; that is, $R_o \geq 2.0$. From Figure 4 in the Lipsitch et al. (2003) paper, the probability that a pandemic is seeded from a single release is about 50% (green curve in Figure 4a, R_0=2 and k=2). Or being more conservative, taking k=10, the probability that a pandemic is seeded from a single release is about 20% (magenta curve in Figure 4a, R_0=2 and k=10).

The graphs were generated using branching theory, a pure mathematical construct, which requires only two parameters, the mean R_0 (the reproductive number or the average number of people an infected person infects) and the variance to mean ratio k, which measures the variation in number of people each infected person infects. It does not take into account any mitigation measures, such as quarantine of the few exposed when the outbreak in its early stages.

In another approach, where movement of infection through the community is simulated[4], Merler, *et al.*, found that "that there is a non-negligible probability (5% to 15%), strongly dependent on reproduction number and probability of developing clinical symptoms, that the escape event is not detected at all" so that a pandemic results.

We will use an intermediate value of 15% from branching theory and simulation (with a range of 5% to 50%) in the calculation of the likelihood of a pandemic below.

With these assumptions, the probability that the Research Enterprise seeds a pandemic in a single year,

$$pan_1(\text{enterprise})=0.15 \times 0.028=0.0042 \text{ per year.}$$

This conservative number is about seven-fold less than the probability of a natural pandemic, where $p_1(\text{natural})=0.031$ per year. Thus, concern over a pandemic from a lab release should be as much of a grave concern as a natural pandemic. The difference is that a pandemic from a lab release might be prevented; whereas, it would be difficult to impossible to prevent a natural pandemic without a long warning.

Pandemic likelihood from the PPP Research Enterprise over the next ten years

It is reasonable to assume that creation of and research with matHPAI will be carried out for at least 10 years. Starting with $pan_1(\text{enterprise})= 0.0042$ after ten years the probability of release from at least one lab, $p_{10}(\text{enterprise})$, is found from the following equation:

$$pan_{10}(\text{enterprise}) =1- [1- pan_1(\text{enterprise})]^{10} =1-(1-0.0042)^{10} = 0.041 \text{ or } 4.1\%$$

4.1% is an uncomfortably high probability for a pandemic over a time period of 10 years, especially for matHPAI since for instance wild type H5N1 avian influenza virus kills 60% of poultry workers who become infected through close contact with infected poultry. The H7N9 avian influenza virus kills up to 30% of poultry workers.

Looked at yet another way, in ten years the probability of a natural pandemic is

$$pan_{10}(\text{natural}) =1- [1- pan_1(\text{natural})]^{10} =1-(1-0.031)^{10} = 0.27 \text{ or } 27\%$$

So, we are creating a lab-release risk in the same ballpark, six-fold less, than the risk of a natural pandemic.

Speculations on fatalities

From Table 1, fatalities for natural pandemics vary widely, from the very deadly 1918 H1N1 flu (50 million fatalities) to the unexpectedly mild 2009 H1N1 flu (284 thousand fatalities). We can only guess at

the number of fatalities from the next natural pandemic. The one thing that we may be sure of is that there will be a *next* pandemic.

For a lab release of a matHPAI H5N1, H7N9, or other lab-created PPPs, we also can only guess at their transmissibility and virulence. To date airborne transmission of matHPAI has been observed only in small mammals (ferrets and mice). In humans, the number of fatalities could be as high as 60% or could be close to 0% of those infected. The worst-case scenario: 25% of the world population infected with 60% fatality rate is in theory possible, but with unknown likelihood. The probability is likely not zero, so we must exercise extreme caution when creating and researching matHPAIs.

Global risk of a ten-year, ten-lab matHPAI Research Enterprise

Restricting consequences to fatalities, likelihood-weighted fatalities, LWF, is calculated from the equation

LWF = (probability of a pandemic) x (consequences of a pandemic).

As a sample calculation of LWF, take an intermediate case: assume 15% of the world's population is infected and the fatality rate is 1%. This fatality rate is about half of the 2% for the 1918 pandemic flu and one-sixtieth of the 60% for poultry workers and others infected by H5N1 from handling poultry. Under these assumptions, with a world population of 7.5 billion people, the consequences are

consequences = $0.01 \times 0.15 \times 7.5 \times 10^9 = 11$ million fatalities.

The probability of a pandemic in the LWF equation is assumed to be the probability of a pandemic from a matHPAI release from a 10-lab Research Enterprise over 10 years, which was calculated to be 0.041. The likelihood-weighed fatalities are

LWF = $0.041 \times 11 \times 10^6 = 450$ thousand fatalities.

Fatality burden for a single lab in the matHPAI Research Enterprise

Each lab in the Research Enterprise must bear the burden of its contribution to potential fatalities, called the "fatality burden." On a per lab basis, the number of expected fatalities over the ten years is about $4.5 \times 10^5/10 = 4.5 \times 10^4$ fatalities. To put this fatality burden number in perspective, no Institutional Review Board tasked with assessing human subject research would approve a proposed ten-year laboratory research project with 14,500 potential fatalities.

Alternative methods for finding mutations responsible for airborne transmission

Alternative methods that do not employ live HPAI virus are likely faster at finding mutations responsible for airborne transmission in mammals. However, the methods do not prove transmissibility; they only suggest it. But that disadvantage is more than offset by the fact that pandemic risk from a lab release is essentially eliminated. There are a number of publications that compare creating live matHPAI viruses with alternative methods for finding mutations (for instance see, here, here, here, and here).

Concluding remarks

Should some matHPAI creation and research be banned, especially given alternative methods for finding mutations responsible for mammalian airborne transmission? The many scientists who signed the Cambridge Working Group statement feel that studies such as these should be "curtailed" until further reviewed:

> "For any experiment, the expected net benefits should outweigh the risks. Experiments involving the creation of potential pandemic pathogens should be curtailed until there has been a quantitative, objective and credible assessment of the risks, potential benefits, and opportunities for risk mitigation, as well as comparison against safer experimental approaches."

Given the horrific toll and staggering economic consequences of a potential pandemic from a lab release, even a relatively small likelihood of release should not be tolerated. In a world of many and varied risks, following the "precautionary principle" strictly and universally can stand in the way of accomplishing worthwhile goals. But the precautionary principle should apply to creation and research with live matHPAI viruses because of the intolerable possible consequences of their release into the community.

Simply moving this research to BSL4 facilities will not substantially reduce the risk. There have already been seven reported releases of pathogens from BSL4 containment since 1990. In the not too distant past, there were three releases: a Marburg virus LAI at the Vector facility in the Soviet Union in 1990, a foot and mouth disease virus release from the Pirbright facility in England infecting many cattle in the nearby countryside, and a SARS virus LAI from a BSL4-rated biosafety cabinet in a Taiwan laboratory.

More recently, the Government Accountability Office has uncovered four releases from BSL-4 labs. Those releases involved the deadly Ebola and Marburg viruses. In three releases, lab workers failed to deactivate the viruses before transferring them to a low containment facility. A fourth release occurred in 2014 at the laboratories operated by the Centers for Disease Control and Prevention (CDC), when live Ebola virus samples were inadvertently switched with inactivated samples.

The cause of all but one of the seven releases was human error.

If creation of research on live matHPAI viruses is deemed necessary in some circumstances, the research community must require an additional level of biosafety -- call it BSL-4-plus -- that adds special protections for laboratory work with potential pandemic pathogens such as matHPAI.

As it stands, researchers create and study potential pandemic pathogens in BSL3 and augmented BSL3 laboratories, ignoring National Institutes of Health guidelines that clearly state: " Biosafety Level 4 is

required for work with dangerous and exotic agents that pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening disease that is frequently fatal, for which there are no vaccines or treatments, or a related agent with unknown risk of transmission."

Conclusions

The world cannot afford to ignore the Potential Pandemic Pathogen Research Enterprise. Late last year, the White House's Office of Science and Technology Policy (OSTP) published a set of guidelines for proactive review of lab-created PPP research in the U.S. It is unclear whether the OSTP is prepared to follow through on its recommendations in the current Administration.

Furthermore, pandemics know no boundaries, so are international in scope. The Parties to the Biological Weapons Convention (BWC) could be the catalyst to launch discussions for a different international treaty on oversight and regulation of creation and research on these highly dangerous agents. In the meantime, since enacting new treaties is an uncertain and long process, Parties to the BWC should pass legislation in their own nations.

This is an urgent matter.

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[1] Any other starting date would be arbitrary.
[2] Unpublished. Draft available from Lynn Klotz
[3] This approximate calculation is accurate for probabilities much less than 1. In mathematical notation, $p<<1$
[4] Stefano Merler, Marco Ajelli, Laura Fumanelli and Alessandro Vespignani, *Containing the accidental laboratory escape of potential pandemic influenza viruses*, BMC Medicine 2013, 11:252
http://www.biomedcentral.com/1741-7015/11/252