Rationale and Science Behind Likelihood-weighted Consequences as a Measure of lab-created Influenza Risk (pandemic update)

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INTRODUCTION

Seasonal influenza viruses are a concern because they spread throughout the world in a year or two, infecting ten- to twenty-five percent of the world's population. Seasonal influenza causes 290,000 to 650,000 respiratory fatalities worldwide. With a world population of about 8 billion, the fatality rate is from 0.0036% to 0.0081%. With such low fatality percentages, no wonder seasonal influenza does not seem particularly dangerous to most of us. If influenza virus was created inside a lab and somehow released into the community, spread worldwide, and caused 290,000 to 650,000 deaths, we would be outraged that some lab caused these deaths.

This article focuses on lab-created, highly pathogenic avian influenza virus that have been made mammalian airborne transmissible. The abbreviation used for these lab-created viruses is matHPAI. This research is an example of particularly worrisome gain of function (GOF).

Every facility creating or conducting research on matHPAI must bear the consequences of their contribution to potential morbidity and fatalities from a pandemic sparked by a release into the community. Based on a fatality rate of 2.5%, like the 1918 influenza pandemic, the fatality burden for a single facility for each year it conducts research is 10,664 fatalities. Even if the fatality rate is as low as typical seasonal influenza, the fatality burden per facility per year is 107 fatalities. And even if BSL3+ labs (BSL3 labs with enhanced mechanical safety features) are at least 10-fold safer than typical BSL3 labs as Professor Ron Fouchier has sometimes suggested, the yearly fatality burden is 10.7.

Fouchier makes strong arguments that the mechanical safety of his lab is much greater than 10-fold, but human error is the main cause of release of pathogens into the community which questions Fouchier's estimates of the overall safety of his lab.

Likelihood-weighted consequences (LWC) is perhaps the best way to think about pandemic risk posed by such a virus. LWC is defined as the product of the probability of the consequences times the consequences:

LWC = [probability of the consequences] x [consequences].

LWC analysis is a standard method for assessing risk; and in this author's opinion, it should be at the center of the lab-created potential pandemic influenza research debate. The American

Chemical Society provides a clear explanation of the value of LWC in assessing risk: which they call Risk Rating. Quoting from the ACS document:

> "Many risk assessments use "probability of occurrence" and "severity of consequences" scales to rate risks associated with laboratory experiments. They are comprehensive assessment tools and provide greater differentiation of risks based on actual laboratory operations.
>
> Using this kind of scaling, laboratory hazard risk rating is calculated as follows:
>
> Risk Rating (RR) = Probability of Occurrence (OV) x Severity of Consequences Value (CV)
>
> As the formula indicates, the higher the assessed probability of occurrence and severity of consequences, the greater the risk rating will be."

The primary advantage of LWC is that it provides a relatively simple method for assessing the risk posed by an activity with severe consequences but a low or high probability of occurring.

No Institutional Review Board (IRB) tasked with assessing human-subject research would approve a research project with a potential for perhaps tens to thousands of fatalities. Maybe an IRB could approve the research if it could be assured with almost absolute certainty that there will never be a release into the community or that the released virus would neither be airborne-transmissible, virulent, nor fatal. "Almost absolute certainty" is an almost impossible requirement to meet.

This article was written in late 2019 and early 2020 before we were aware of the COVID-19 pandemic. Throughout the pandemic, many web sites and news stories for COVID-19 infections and deaths have reported that 1.5% to 2% of infections result in deaths. In the UK in the week preceding April 29, 2021, there were 15,140 positive tests and 132 deaths; so, the fatality rate was 0.9%. Even though a more contagious and more virulent variant of COVID-19 commonly known as B.1.1.7 dominates, the fatality rate was low which could be due to vaccines and better therapy. Still, there should be grave concern over a future, more highly contagious and deadly variant that is vaccine resistant and resistant to current therapy.

In comparison, deadly strains of H5N1 and H7N9 avian flu cause a high percentage of deaths in poultry workers who become infected. The H5N1 avian flu virus has killed nearly 53 percent of humans diagnosed with infection (454 fatalities in 860 cases between 2003 and mid-2019) from close contact with poultry, but is rarely transmissible among humans. As of October 2018, there have been 1,567 laboratory-confirmed human cases and 615 deaths (39% fatality rate) from H7N9 infections since March 2013 when the strain was detected in people.

Even though the fatality rate from COVID-19 is much lower than that from H5N1 and H7N9, a natural pandemic sparked by a future highly contagious and highly virulent variant of COVID-19 is as much concern as matHPAI. But it still must be shown that matHPAI should be of concern, the subject of this article.

WHAT IS NEEDED TO DEMONSTRATE THAT matHPAI ARE A MAJOR CONCERN

There are several steps required to show that matHPAI is a major concern.

The first step is to determine how lab-created potential pandemic viruses could be released into the community. While there are three ways a release could occur, only for one scenario is there enough data to estimate release probabilities. That scenario is an undetected or unreported laboratory-acquired infection (uuLAI) where the infected lab worker leaves the lab into the community at the end of the workday.

The next step is to determine probabilities and other data that lead to an intolerable pandemic risk. This includes the mathematical derivation of likelihood of at least one community release for N labs for Y years creating or conducting research on matHPAI. Then, the probability that a release can lead to a pandemic is obtained from the literature. This would include a summary of the large percentage of human error data leading to community release. Human error calls into question the considerable mechanical safety measures in BSL3+ and BSL4 labs.

Once the pandemic risk probability is determined and deemed too high, the likelihood-weighted consequences expressed only as fatalities, not morbidity, are analyzed.

The article concludes that most creation of and research on matHPAI that cause human fatalities should not be carried out.

CONTRIBUTION TO THE GOF LITERATURE

This article contributes to the GOF literature in several ways. It provides considerable new data for determining risk of a release into the community and provides new data from the author on types and magnitudes of human error. It introduces and demonstrates the value of LWC analysis and provides calculations showing the risk of a pandemic from the large number of labs creating and researching matHPAI.

HOW LAB-CREATED POTENTIAL PANDEMIC VIRUSES COULD BE RELEASED INTO THE COMMUNITY

There are at least three ways a lab-created virus could be released into the community, but only for one way is there enough data to estimate probabilities of release from a lab:

(1) An undetected or unreported laboratory-acquired infection (uuLAI) where the infected lab worker leaves the lab and enters the community at the end of the workday. This is the one release scenario for which there are considerable data, so it is possible to estimate the probability of release from a lab for this scenario.

(2) Mischaracterizing a virus as harmless, so it is purposely removed from biocontainment or moved to lower biocontainment (e.g., from Biosafety Level 3 to Biosafety Level 2) for further research. Research in BSL2 does not require sophisticated personal protective clothing; so, for

instance, the virus could escape from the lab on clothing, skin, hair, etc. when the researcher leaves the lab at the end of the day.

(3) Purposeful release into the community by a mentally unstable lab worker or by someone with evil intent.

The focus here is on uuLAIs for lab-created, highly pathogenic avian influenza (HPAI) that have been modified to be mammalian airborne transmissible. The two HPAIs of primary concern are H5N1 and H7N9. A 2013 paper by Fouchier, Kawaoka and many others have proposed that matH7N9 experiments should be carried out.

The H5N1 avian flu virus has killed nearly 53 percent of humans diagnosed with infection (454 fatalities in 860 cases between 2003 and mid-2019) from close contact with poultry, but is rarely transmissible among humans. Over the last year or so, human H5N1 fatalities have almost disappeared but this may not continue. There remains a concern over a release into the community of the older lab-created matH5N1 strains still retained in labs.

As of October 2018, there have been 1,567 laboratory-confirmed human cases and 615 deaths (39% fatality rate) from H7N9 infections since March 2013 when the strain was first detected in people. There are also many fewer H7N9 infections in chickens at present compared to the recent past, which is likely due to a successful chicken vaccination program in China.

The 2011 announcements of the creation of live H5N1 avian viruses transmissible in mammals through the air (matH5N1) in Professor Ron Fouchier's and Professor Yoshihiro Kawaoka's labs began the debate over whether this research is too dangerous to conduct. This debate continues today.

Fouchier's lab genetically modified a wild type H5N1 virus by site-directed mutagenesis and subsequent serial passage in ferrets. The virus acquired four amino-acid substitutions in the host receptor-binding protein hemagglutinin and one in the polymerase complex protein basic polymerase 2 that were consistently present in ferret airborne-transmitted viruses. The capacity for airborne transmission between mammals in this lab-created virus occurred without recombination with another virus, so the matH5N1 alone provides a possible path to a pandemic.

PROBABILITIES AND OTHER DATA THAT LEAD TO AN INTOLERABLE PANDEMIC RISK

A detailed, full analysis of the probabilities of a release of matHPAI and of a pandemic was calculated from considerable data in the manuscript "The risk of lab-created potential pandemic influenza". Here, the relevant probabilities are only stated without comment.

For a matHPAI, the full analysis finds the average probability of a community release from a single facility (with one or many labs) in a single year is $p_1 = 0.00246$ or 0.246% per facility-year. Combining the likelihood of community release with the estimated not-insignificant probability of 5% to 40% that such a virus could seed a pandemic, we have an alarming situation with a real risk to human lives.

Using an intermediate 15% value for the probability of seeding a pandemic, the probability that a single facility in a single year seeds a pandemic is

pan_1 = (probability of a release into the community) x (probability that the release seeds a pandemic)

pan_1 = 0.00246 x 0.15 = 0.000369 or 0.0369%

There are at least fourteen facilities worldwide that have created matHPAI, here dubbed the "Research Enterprise."

The probability of at least one community release from a uuLAI for N Research Enterprise facilities in Y years of research in each facility is derived as follows:

$1-p_1$ = the probability of no community releases per facility

$(1-p_1)^{NY}$ = the probability of no community releases in N facilities in Y years

$$p_{NY} = 1 - (1-p_1)^{NY} \qquad (1)$$

where p_{NY} is the probability of at least one release from N facilities in Y years

From equation (1) with N=14 and Y=5, there is a probability of 0.158 or 15.8% of at least one release into the community from the Research Enterprise in five years. Thus, the probability that the Enterprise seeds a pandemic is

pan (Enterprise) = 0.158 x 0.15 = 0.0237 or 2.37%,

a worryingly high percentage. If the released virus is highly transmissible in humans, we have an alarming situation.

QUANTIFYING FATALITY RATES FOR HUMAN PANDEMIC INFLUENZA VIRUSES

TABLE 1 summarizes data from over the last century to calculate the case fatality rate for pandemic influenzas.

Years of Pandemic	Pandemic Virus Strain	World Population (billions)	Worldwide Fatalities (millions)	Case Fatality Rate (percent)
1918-1919	H1N1	1.6	50	3.1%
1957-1958	H2N2	2.87	1.1	0.04%
1968	H3N2	3.56	1.0	0.03%
2009-2010	H1N1	6.9	0.16	0.0024%

TABLE 1. Summary data for pandemics over the last century. Case fatality rate equals (world-wide fatalities)/(world population). General reference for all data except for the 2009-2010 pandemic, where worldwide fatalities for the 2009-2010 pandemic were obtained.

The 2009-2010 pandemic was particularly mild, approximately the same as seasonal influenza. The 1918 pandemic flu was particularly deadly, with a 2.5% to over 3% fatality rate.

LIKELIHOOD-WEIGHTED CONSEQUENCES AND FATALITY BURDEN FOR matHPAI

Likelihood-weighted consequences (LWC) is defined as the product of the probability of the consequences times the consequences:

LWC = [probability of the consequences] x [consequences] (2)

LWC analysis is a standard method for assessing risk and should be at the center of the potential pandemic influenza research debate value of LWC in assessing risk.

Here, only fatalities will be considered as consequences. To indicate this change, we replace LWC with fatality burden, FB.

FB = [(probability of a release) x (probability release leads to a pandemic)] x [number of fatalities] (3)

As a first example, assume that the fatality rate is 2.5%, the often-quoted rate for the 1918 pandemic flu. Then, the number of fatalities, F, is

F = (world population) x (fraction of population infected) x (fatality rate)

$F = 7.7 \times 10^9 \times 0.15 \times 0.025 = 28.9$ million

where it is assumed that a typical influenza epidemic infects about 15% of the world's population. (Note that the human fatality rate could be as high as 53%, the rate for the highly pathogenic H5N1 avian strain used in creating matH5N1.)

Each facility in the Research Enterprise must bear the burden of its contribution to potential fatalities. For a single facility in a single year where $p_1 = 0.00246$

$FB = [0.00246) \times (0.15)] \times [28.9 \times 10^6] = 10{,}664$

where the probability of starting a pandemic is estimated to be 15%.

From this illustrative calculation, each year that a single facility conducts research, it carries with it the burden of 10,664 fatalities. Fouchier suggests that his enhanced BSL3 lab (BSL3+) is at least ten-fold safer than typical BSL3 labs from which most release data here were obtained. A 10-fold safer lab would yield a fatality burden of 1,066 fatalities.

Fouchier points to several mechanical safety features that led him to the at least10-fold-safer conclusion. Among the features are work on influenza virus transmission is carried out in class 3 isolators or class 3 biosafety cabinets, which are airtight boxes with negative pressure to ensure inward flow in case of leakage. Air-tight gloves fitted to the front of these cabinets are used for

manipulations inside the cabinet. Air released from the class 3 units is filtered by high efficiency particulate air (HEPA) filters and then leaves directly via the facility ventilation system, again via HEPA filters. In most BSL3 labs, work is performed in open-front class 2 biosafety cabinets with directional airflow to protect the environment from release of pathogens and laboratory workers from exposure. In these labs, workers could be directly exposed to pathogens if there is an accident inside the cabinet.

But mechanical safety misses the observation that human error is the chief cause of potential exposures of lab workers to pathogens. According to my research, statistical data from two sources show that human error was the cause of 73.5% and 79.3% of incidents leading to potential exposures in BSL3 labs. These percentages come from an analysis of years of incident data from the Federal Select Agent Program (79.3%) and the National Institutes of Health (73.5%). Both data sets yield similar values. The categories of error are presented in Table 2.

1. Bite/scratch from infected animal
2. Incidents involving equipment or mechanical failures
3. Needle stick or other through the skin exposures with other potentially contaminated sharp objects
4. Failure or problem with personal protective equipment [*from Gryphon report most are human error*]
5. Potential exposures resulting from non-adherence to safety procedures; deviations from laboratory standard operating procedures
6. Spills of select agents *inside* of biocontaiment laboratories
7. Research labs: Agents manipulated outside of a BSC or other equipment designed to protect exposures to infectious aerosols

TABLE 2. Release categories in the 2009 through 2015 CDC/FSAP reports. The red-highlighted categories are releases caused by human error, not other causes.

Gryphon Scientific provides a useful chart of human error types (see Table 14.1 in Appendix III) of the Gryphon report. The types are skill-based, rule-based, and knowledge-based. Table 14.1 also provides some examples of human errors such as those listed in Table 2 here. The list of human error categories in Table 2 comes directly from the Black Vault FOIA request for Federal Select Agent Program reports.

The numbers of errors in each category are listed in Table 3.

Year	CDC Registered Laboratories No. Reported Releases	No. In Each Release Category 1	2	3	4	5	6	7
2009	94	2	9	12	4	11	34	22
2010	97	3	6	18	5	4	11	50
2011	118	8	13	17	16	12	33	19
2012	108	8	3	14	16	11	37	19
2013	105	4	10	11	17	2	31	30
2014	76	7	3	14	14	6	NR	32
2015	90	4	13	11	26	7	NR	29
	Total (all years): 688	**36**	**57**	**97**	**98**	**53**	**146**	**201**
	Average (per year): 98.3	**5.1**	**8.1**	**13.9**	**14.0**	**7.6**	**20.9**	**28.7**

TABLE 3. Release numbers from registered laboratories from the Federal Select Agent Program (CDC/FSAP) reports to Congress for the years 2009 through 2015. The red-highlighted categories are releases caused by human error. The total number of reported incidents is 688, with an average of 98.3 per year. [red highlighted human error totals]/ [totals for all release .categories] = 71.1/98.3 = 72.3% human error. NR means numbers not reported.

This large percentage of human error, 73.5%, is confirmed by an analysis of results of 185 incidents reported to NIH over the years 1995 through 2010. The spreadsheets summarizing the NIH data are available to qualified researchers from the author.

For CDC/FSAP, a "release" is defined as release of a select agent outside of the primary barriers of the biocontainment area, not release into the community. A release into the community is called a confirmed release. Releases from primary containment are appropriate for determining the percent of human error. Registered laboratories are those registered in CDC/FSAP. Exempted laboratories are not required to register; they include diagnostic and clinical labs.

It should be noted that the CDC/FSAP data are mainly for BSL3 labs and bacterial pathogens, where there may not be as much care to biosafety, since almost all these pathogens are less deadly and less transmissible than matHPAI. From Table 3 and the published paper linked just below, the counter argument to this statement is that 72% or more of lab incidents/accidents are from human error. Human error should not vary much between BSL3 and BSL3+.

Starting in 2016, the FSAP provided publicly available yearly reports. The reports mention most error categories and state that the number of releases outside the primary barriers of the biocontainment area is over 200 for each year from 2016 thru 2018, similar to numbers of releases in the Black Vault reports. Unfortunately, these newer FSAP reports do not provide numbers of releases in each category, so they are useless for expanding Table 2 through 2018 and beyond.

FATALITY BURDEN CALCULATIONS AND THE PRECAUTIONARY PRINCIPLE

What if the released virus is no more deadly than a typical seasonal influenza virus? Using F=290,000 fatalities for seasonal influenza, the fatality burden for a single Enterprise facility in a single year is

$$FB = [0.00246 \times 0.15] \times 290{,}000 = 107 \text{ fatalities}$$

The Fatality Burden calculations for various situations are summarized in Table 4

Data Source	Fatalities (worldwide)	Likelihood of a pandemic	Fatality burden
Resurrected 1918 pandemic flu (2.5% fatality rate)	28.9 million	3.69×10^{-4}	10,664
Typical seasonal flu virus	290 thousand	3.69×10^{-4}	107
Typical seasonal flu virus (10-times safer lab)	29 thousand	3.69×10^{-4}	10.7

TABLE 4. Summary of fatality burden calculations. The likelihood of a pandemic is calculated as follows: For a single facility in a single year, the likelihood or probability of a community release = $0.00246 \times 0.15 = 3.69 \times 10^{-4}$ where $p_1 = 0.00246$ is the probability that a single facility in a single year has a community release and 0.15 is the probability of a pandemic from that release.

No one can be sure how virulent or airborne transmissible in humans these potential pandemic viruses would be if released into the community. In the best-case scenario, they would soon die out with little to no sickness and no fatalities; however, just the possibility of a pandemic dictates that we must proceed with the utmost caution. Put another way; the Precautionary Principle should apply. The Precautionary Principle simply states "the precept that an action should not be taken if the consequences are uncertain and potentially dangerous."

Every one of these fatality burdens is unacceptable. If the right to unfettered experimentation costs lives, that is a high price to pay. In some nations, scientists who conduct this research may not be subject to proactive oversight and regulation, increasing the risk. Even in the U.S., it is unclear if the recently instituted review process is sufficient. The U.S. review applies only to NIH-funded experiments and is certainly not transparent. The review process is not broad enough. "It applies only to research funded by the Health and Human Services Department, and primarily the National Institutes of Health. Research funded by other federal agencies, or by the private sector, is not subject to this review process…gain-of-function research [should] be applied to all researchers, regardless of their source of funding." In addition, it would be

desirable to have a review process that is international in scope, which unfortunately could require years to institute an international rule.

DISCUSSION & CONCLUSION

Should we be willing to risk a 2.37% likelihood of an influenza pandemic for five years of research in the Research Enterprise? Other than alerting us that these avian viruses can be made mammalian airborne transmissible, a useful fact to know, creation of matHPAI viruses may yield little practical results in the author's opinion.

This article explores the likelihood of an uuLAI leading to a pandemic, but could a pandemic also occur by a wild-type H5N1 virus acquiring the five mutations in nature? Is a natural pandemic more or less likely to occur than a release from a lab through a uuLAI? Using a mathematical model of within-host virus evolution, nearly twenty scientists and mathematicians set out to answer this important question Unfortunately, despite their valiant effort, they were unable to find an answer because they needed more data to assess the threat of wild-type H5N1 evolving to human transmission in nature.

Understanding the mutations in H5N1 and H7N9 that make them mammalian airborne transmissible could provide a warning that a matH5N1 or matH7N9 strain is occurring or about to occur in nature. Could vaccines be prepared in advance to protect us?

A recent study by Kaiser Permanente shows that influenza vaccines lose effectiveness during the flu season. The risk of contracting the flu climbs about 16% for every 28 days after vaccination. Two possible reasons for diminishing effectiveness over time are antigenic drift and emergence of virus strains not well matched to the vaccine. The fact that effectiveness diminishes over time in a flu season calls into question making vaccines in advance to protect against matH5N1 and matH7N9 in nature.

Each facility in the Research Enterprise must bear the consequences of its contribution to potential fatalities from a pandemic sparked by a release into the community. As calculated in Table 4, based on a fatality rate of 2.5% for a resurrected 1918 pandemic flu virus, the fatality burden for a single Enterprise facility for each year it conducts research is 10,664 fatalities. Even if the fatality rate is as low as typical seasonal influenza, the fatality burden per facility per year is 107 fatalities. And even if Fouchier's BSL3+ labs are at least 10-fold safer than typical BSL3 labs, the yearly fatality burden is 10.7.

Institutional Biosafety Committees and Institutional Review Boards decide whether a research project presents a risk to experimental subjects. All too often, board members, who have less authority than faculty members, are often bullied into approving a faculty project. Related here are comments from Simon Wain Hobson, the head of Molecular Retrovirology, at L'Institut Pasteur.

"These IBCs and IRBs are full of yes committee types. What we have seen from Madison [Wisconsin] leaves a great deal to be desired. The lying, for it is not spin, is very sad and makes you realize that $ and peer pressure are very much in place." E-mail comment from Wain Hobson to the author.

In light of the high fatatility burden posed by the matHPAI Research Enterprise and the weaknesses in the existing institutional biosafety oversight mechanisms, the most prudent course of action would be to impose a moratorium on this type of research in line with the precepts of the Precautionary Principle.

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