The Human Fatality Burden of Gain of Function Flu Research:
A Risk Assessment

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Synopsis

The voluntary research moratorium on mammalian-transmissible highly pathogenic avian influenza virus has ended, and research is resuming. These mammalian-transmissible, gain-of-function (mtGOF) flu strains may already be highly contagious in humans, with the threat of accidental release from research labs seeding a pandemic.

In August 2013 letters to the journals Science and Nature, 22 virologists have notified the research community of their intent develop and research mtGOF strains of the H9N7 influenza virus that has caused over 130 human infections and 43 fatalities in China. Among the research on live flu strains that the virologists would like to see performed are "transmission studies to identify mutations and gene combinations that confer enhanced transmissibility in mammalian model systems (such as ferrets and/or guinea pigs)." The wild-type H9N7 strain is only mildly transmissible among ferrets, and human infections seem to have tapered off.

Is a pandemic from a lab release from mtGOF flu research a possibility? The simple likelihood-weighted-consequence analysis (LWC analysis) presented here can provide insight into the answer for this question. Among the consequences of a release are fatalities, severe illness, and economic loss. Each lab working with mtGOF flu strains carries with it the burden of these consequences. To simplify the analysis, fatalities from a pandemic are considered to be the only consequence, here called the "fatality burden." The fatality burden has three components:

the probability of a mtGOF flu strain release from a lab, the probability that release leads to a pandemic, and the number of pandemic fatalities.

The analysis is focused on an infected lab worker spreading infection to strangers during commutes to and from work on public transportation in an urban setting. The lab worker could infect both known persons (e.g., spouse, children, coworkers, friends) or strangers (e.g., casual brief contacts, contacts during commutes), all of whom could become infected and further spread infection. Strangers can spread infection for some time as they cannot easily be traced and identified for quarantine or other control measures, the reason for the focus here.

The analysis finds that *each lab in each year* it conducts this research carries with it the burden of 180 to 1,100 fatalities. To put these numbers in perspective, no Institutional Review Board tasked with assessing human-subjects research would approve a proposed research project with estimated fatalities of 180 to 1,100 per year. Furthermore, perhaps twenty labs will carry conduct the research for ten year, which would increase the likelihood of lab release and a pandemic by nearly 200-fold.

It would take extraordinary benefits and significant risk reduction with extraordinary biosafety measures to correct such a massive overbalance of risk over unclear benefits.

All analyses of this type must rely to some extent on uncertain data, making results uncertain. But we need only to estimate fatality burden within one or two orders of magnitude to reach meaningful conclusions. Here, very conservative to reasonable estimates of all factors were chosen so as to not bias findings toward larger fatality burdens.

Introduction

In 2009 we witnessed a pandemic from an H1N1 flu virus that swept over the world, infecting an estimated 24% of the world's population according to the World Health Organization. The virus turned out not to be particularly deadly. Nonetheless, the number of world-wide fatalities may have been over 1 million,[1] based on the fatality rate of 0.02%.

mtGOF flu strains could be as contagious as the 2009 flu virus and could carry with them a fatality rate of 30% to 60%. A lesser 10% fatality rate will be used in this analysis. A world-wide pandemic seeded by a lab release of mtGOF flu strains could kill over a hundred-million people.[2]

The financial toll would be huge. Consider only the average cost of loss of a single human life that is valued at $1.8 million in the U.S., totaling over $8.5 trillion dollars[3] for fatalities in the U.S. population.

Likelihood-weighted consequence analysis

Likelihood-weighted consequences (LWC) are 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 should be at the center of the mtGOF research debate.

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[1] Based on a fatality rate of 0.02%, 24% infected, and a world population of 7 billion

[2] Based on a fatality rate of 10%, 15% infected, and a world population of 7.0 billion

[3] Economists estimate the dollar value of a year of human life to be the gross domestic product per capita. In the U.S., the GDP per capita is about $48,000. A person of average age of perhaps 40 years old would have his/her life cut short by about 38 years, a value of lost life of 38 x $48,000 = $1.8 million. For anticipated pandemic deaths in the U.S. of 4.7 million, the economic toll of lost life will be $8.5 trillion in the U.S. alone.

LWC = fatality burden = (basic probability of release) x (probability release leads to pandemic) x (number of pandemic fatalities)

or in symbols

$$\text{fatality burden} = p_1 \times S \times N_f \tag{1}$$

The basic probability of release, p_1, is defined as the probability of release from a single lab in a single year; therefore, the fatality burden estimated here will be for a single lab for a single year. The probability, S, that a release leads to a pandemic has three components: the probability, T, that the infected lab worker commutes by public transportation; the probability, I, that the lab worker infects a stranger during his/her daily commutes; and the probability, $1-F$, that the infection does not fade out so a pandemic is seeded. Thus,

$$S = T \times I \times (1-F) \tag{2}$$

Estimating the basic probability of release, p_1

A 2013 Centers for Disease Control (CDC) report is a significant source of recent data on laboratory-acquired infections (LAIs). The report documents four undetected or unreported LAIs in registered US select-agent high-security BSL3 labs between 2004 and 2010. The report identifies an average of 292 registered US select-agent high-security BSL-2, BSL-3 and BSL-4 labs over those seven years, for a total of 292 x 7 = 2,044 lab-years. The study does not break down numbers of labs into BSL-2, BSL-3, and BSL-4.

The basic probability is calculated as 4 LAIs / 2,044 lab years = 0.002 or 0.2% per lab per year. This is clearly an underestimate since BSL-2 and BSL-4 labs contribute to the denominator. This basic probability is based on the considerable CDC data for current laboratory practices and is consistent with that for the SARS releases through LAIs and with releases from BSL-4 labs.

We will assume the more conservative, order-of-magnitude basic probability of release of 0.1% per lab per year.

As the analysis will show, this order-of-magnitude basic probability is more than high enough to make strong arguments for banning mtGOF flu research. Furthermore, the analysis considers only probabilities of accidental releases through LAIs. It does not consider additional risk such as containment failure, deliberate releases by disturbed or disgruntled laboratory workers (as occurred in the 2001 US anthrax mailings), by a terrorist organization, or by a hostile nation. It also does not consider that labs will be researching mtGOF flu strains for several years, increasing the probability of release. It also does not consider agricultural impact through infection of livestock, particularly swine.

Estimating the probability that a release leads to a pandemic, S

To calculate, S, begin with the calculation of I, the probability that the lab worked infects a stranger during his/her daily commutes. The lab worker could infect both known persons (e.g., spouse, children, coworkers, friends) or strangers (e.g., casual brief contacts, contacts during commutes on public transportation). It is assumed that known victims are quarantined so do not spread infection, but strangers can spread infection for some time as they cannot easily be traced and identified for quarantine or other control measures. The focus here will be on only one particular situation, the infection of strangers by an infected lab worker during commutes on public transportation in an urban setting.

What is the probability of infecting one or more strangers during an urban commute to and from work on a bus or subway? Five example commuting scenarios were analyzed. They

include a short commute on a non-rush hour subway or bus, where six persons are exposed for

five minutes each trip, a typical length of time between a subway or bus stop. In this scenario,

over three days with commutes to and from work, an infected lab worker would expose 36

persons to infections.

Four other commuting scenarios were analyzed as well, including crowded (rush hour)

subway or bus commutes where there may be twenty strangers within six feet of the infected lab

worker. The example commutes are summarized in Table 1.

Commuting Details for the Infected Lab Worker	Total Number Exposed	Contagiousness of Virus	Likelihood of Infecting at Least One stranger
5 minute commute each way (one stop), 3 days, 6 strangers exposed per trip	36	$\tau=3.5\times10^{-4}$ $R\sim1.4$	6.10%
5 minute commute each way (one stop), 4 days, 20 strangers exposed per trip	160	$\tau=3.5\times10^{-4}$ $R\sim2$	24.4%
5 minute commute each way (one stop), 4 days, 20 strangers exposed per trip	160	$\tau=5.7\times10^{-4}$ $R\sim3$	36.6%
20 minute commute each way (five stops), 4 days, 6 strangers exposed per trip	48	$\tau=3.5\times10^{-4}$ $R\sim2$	28.5%
20 minute commute each way (five stops), 4 days, 20 strangers exposed per trip	160	$\tau=1.0\times10^{-4}$ $R\sim0.66$	27.4%

Table 1. Several example scenarios of commuting patterns for an infected lab worker
with a contagious pathogen with different reproductive numbers. (The meanings of R and τ, the mathematics,
and assumptions for calculating the numbers in the table are presented in the Technical Supplement.)

The rule of thumb is anyone within six feet of a person with influenza is exposed to

infection. In one scenario, longer commutes using the Eubank's lab lower contagiousness

number ($\tau \sim 1 \times 10^{-4}$, see Technical Supplement) was modeled. A typical commute may be much

longer than a single subway or bus stop, for example, five subway stops at four to five minutes

per stop or 20-minute exposure. A 20-minute commute is not unusual for someone who works in

a city and commutes to a suburban or a rural home. Such commutes may also involve other

public transportation for a half-hour to hour as well, which is not accounted for in the modeling.

Thus, the five-minute commute with only six strangers exposed assumptions is quite conservative. The five scenarios yielded probabilities of infecting at least one stranger from about 6% to 37%. The likelihood of infecting a stranger is high enough to be of concern.

The probability, T, that the infected lab worker commutes by public transportation is unknown, but could be obtained through polling workers from BSL3 labs in urban settings. A safe guess is 10%, perhaps more in large cities where driving and parking are difficult (e.g., New York, Boston, San Francisco). Thus, the likelihood of an infected lab worker infecting a stranger during commutes is reduced by a probability of 0.1 to the range from 0.61% to 3.7% for the examples in this analysis, still high enough to be of concern.

The last probability, 1-F, may be calculated from branching theory as a function of reproductive number, R_0. For a single infected person, 1-F has been calculated as a function of R_0 with results depending on heterogeneity of infectiousness[4]. For $R_0=2$ the probability that a single infectious case will seed a pandemic ranges from 10% (highly heterogeneous) to 80% (no heterogeneity).[5] Since there is no information on the degree of heterogeneity for mtGOF flu strains, we take an intermediate value of 30% that an infectious lab worker will seed a pandemic.[6]

Then, for $R_0=2$,

1-F = 0.0061x0.3= 0.0018 or 0.18%

to

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[4] Some infected persons do not transmit infection efficiently or at all to others, while other infected persons must then transmit infection more efficiently to others. This phenomenon is known as heterogeneity of infectiousness. For instance, in a recent study on influenza A viruses, 20% of adults are responsible for 78% to 82% of transmission; that is, about only 20% of lab workers will transmit infection to a stranger during commutes.
[5] See Figure 4A in the study
[6] From the blue curve in Figure 4A for $R_0=2$

1-F = 0.037x0.3 =0.011 or 1.1%

of lab escapes would result in a pandemic.

In their White Paper, *Influenza Pandemic Risk: The Contribution of Laboratory Pathogens to Excess Mortality Risk*, the company Risk Management Solutions (RMS, Inc.) uses 2%, 1% and 0.1% for this probability in their analyses, which encompasses the range found here for our example commute scenarios. RMS advises the insurance industry on management of catastrophe risk. Quoting the White Paper, "RMS' models indicate that as few as 50 geographically-diverse cases are enough to start a global pandemic." For influenza reproductive numbers between 2 and 3, the RMS finding implies only 4 to 6 three-day periods may be all that is required to seed a pandemic, perhaps a too short time period to identify infected strangers and their contacts to stem an outbreak leading to a pandemic. This is an unsettling thought.

Victims infected with influenza viruses become contagious in one to three days, often before showing symptoms themselves. This rapid onset of contagion is a main reason why influenza outbreaks are difficult to control through quarantine--think again of the 2009 H1N1 pandemic.

Calculation of fatality burden

Remembering that

Yearly fatality burden = (basic probability of release) x (probability release leads to pandemic) x (number of pandemic fatalities)

Doing the arithmetic:

Yearly fatality burden per lab = 0.001 x 0.0018 x 100 million = 180 fatalities

to

Yearly fatality burden per lab = 0.001 x 0.011 x 100 million = 1,100 fatalities

So each lab in each year it conducts mtGOF flu research carries with it the burden of 180 to 1,100 fatalities, the larger number more likely since it is derived from reasonable commuting scenarios.

Other points and conclusions

How safe are BSL-3 and BSL-4 labs?

A basic probability of 0.1% could be quite conservative. Experts appointed to a National Research Council committee formed to monitor the Department of Homeland Security's risk assessment for the planned National Bio- and Agro-Defense Facility in Manhattan Kansas estimated a significantly higher basic probability of release. The initial DHS risk assessment found the probability of a release resulting in secondary infections approached 70% over a 50-year period, which can be converted to a basic probability of 2.4%,[7] twenty-four times the 0.1%. The NRC committee commented that even this 70% over 50 years might be too low for "most modern, complex industrial systems."

High containment biosafety labs are indeed complex systems with many components, which means improvements in safety will likely be incremental. Perhaps improved infrastructure and training could make them two to four times safer than current BSL-3 labs. What improvements could make them safer by a factor of ten or more?

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[7] This escape probability is calculated from the formulas in "Sharpening Our Intuition on Man-made Pandemics."

Some proponents of mtGOF flu research argue that research should be conducted in BSL-3 labs, since BSL-4 labs are no safer. This argument misses the point: [even BSL-4 labs are likely not safe enough](#).

Many years many labs

The above analysis was based on one lab and a single year. As more labs take up mtGOF flu research, [the threat of a lab release increases dramatically](#). Many more labs are ready to enter this research area. Each additional lab will increase the likelihood of release and shorten the length of time before a release will occur. Assuming 20 labs and 10 years of research the probability of release from at least one lab over those years is

$$1 - (1-p_1)^{20 \times 10} = 0.18 \text{ or } 18\%, \text{ using } p_1=0.001$$

This increases both likelihood of release likelihood of a pandemic, and fatality burden by 180-fold.

For now, restriction to BSL-4 labs would significantly reduce the number of labs that could carry out mtGOF flu research (since there are far fewer BSL-4 labs than BSL-3 labs), an important measure to reduce the likelihood of release.

Risks vs. Benefits

Do benefits outweigh risks? In the case of mtGOF flu research, it would take extraordinary benefits and significant risk reduction with extraordinary biosafety measures to correct such a massive overbalance of risk over benefits.

We already knew prior to any experiments that we should be concerned about the possibility of these viruses becoming contagious among humans. It is quite possible, but there is no persuasive evidence that H5N1 avian flu and H7N9 flu in nature are creeping toward human contagion from aerosols via the respiratory route.

One goal of the research is to find DNA changes (e.g., mutations) that will give us advance warning of a potentially highly human-contagious form of virus. A budding human pandemic will likely be detected in "the old fashioned way," by seeing a sudden increase in the number of victims, some of whom have not had direct contact with infected poultry or intimate contact with an infected victim and even may have, God forbid, traveled to distant, heavily populated areas.

Beyond mtGOF flu research

While mtGOF flu strains are potential pandemic pathogens (PPP) of grave concern, [there are a few others such as the 1918 pandemic flu virus and the SARS coronavirus](#). PPPs are pathogens that are deadly, highly contagious in humans, and currently not present in human populations, meaning it would be a disaster to reintroduce them into the population.

Research with mtGOF flu strains should be banned

Much of mtGOF flu research may be funded by the U.S. and will be conducted in the U.S. if it is not banned. Release from a U.S. lab causing fatalities elsewhere in the world could open up the U.S. to demands for restitution and international criminal and civil charges. If there is an accident, Congress and the President will bear the blame.

The U.S. should take the lead to insist on discussions leading to an international agreement that would require the strictest oversight and the highest biosafety level for most potential pandemic pathogen research anywhere, and carry with it the authority to ban some research. Failure to act implicitly gives permission for the entire world to carry out this dangerous research without regard to consequences.

Whatever number we are gambling with, it is clearly far too high a risk to human lives around the world, so this particular PPP research must be shut down.

Technical Supplement:
Mathematical Rationale for Analysis Results

Calculating the probability an infecting a stranger, S

The equation relating probability of disease transmission to length of exposure is from Eubank's lab.

$$P(B|A) = 1-(1-\tau)^{\Delta_{AB}} \qquad\qquad\qquad\qquad (TS-1)$$

where P(B|A) is the probability that an infected person A transmits the infection to a contact B, Δ_{AB} is the contact time in minutes, and τ is a measure of how infectious the pathogen is, $\tau<1$.

The probability, Q, that no infection is transmitted from A to B is

$$Q = 1 - P(B|A) = (1-\tau)^{\Delta_{AB}} \qquad\qquad\qquad\qquad (TS-2)$$

If there are N exposed potential victims, the probability that none of them is infected is Q^N. Then the probability that there is at least one transmission or infected victim is

$$P(\text{at least one transmission}) = 1 - Q^N = [(1-\tau)^{\Delta_{AB}}]^N \qquad\qquad (TS-3)$$

Equation (TS-3) is used to calculate the likelihood of infecting at least one stranger.

To complete the description, how was $\tau=3.5\times10^{-4}$ used here in the calculations obtained? To do this, a spreadsheet was developed that follows an infected worker as he/she carries out the typical daily activities until bedridden. The daily activities are:

Strangers (not easily identified or traced):

- Commute to and from work

- Casual contacts

Non-strangers (acquaintances of IC who can be readily identified or traced):

- Spouse

- Activities with children

- Coworkers/friends

The first column in Table TS-1 below is the construction of numbers of exposed persons and duration of exposure for each of the infected worker's activities based on four days among potential victims.

			Probability of No	Probability of No
			Disease Transmission	Disease Transmission
	Number	Time Exposed		
Activity	**Exposed**	**(minutes per person)**	**per person**	**for all exposed**

Number of days an infectious person carries out activities before quarantine or other sequesteration: 4
Number of people initially infected: 1 (for future stranger analysis only)

$\tau = $ 3.50E-04 per min   R ~   2.0146

Contact with strangers

\>> Travel to and from work on the subway
  5   stops   4   minutes between stops
  6   exposed per trip — Number Exposed: 48, Time Exposed: 20, Probability of No Disease Transmission per person: 0.9930, for all exposed: 0.715

\>> Casual contact with   30   people
  0.5   minute per person per day — Number Exposed: 120, Time Exposed: 0.5, per person: 0.99982, for all exposed: 0.979

Contact with people who can be traced

\>> Spouse   12   hrs per day — Number Exposed: 1, Time Exposed: 2880, per person: 0.36488, for all exposed: 0.365

\>> Meals, play, etc. with   2   children
  for   2.5   hrs per day — Number Exposed: 2, Time Exposed: 600, per person: 0.8106, for all exposed: 0.657

\>> Contacts with   8   coworkers and friends
for   1   hour per day per person — Number Exposed: 8, Time Exposed: 240, per person: 0.9194, for all exposed: 0.511

Table TS-1. Probability of disease transmission from the infected worker's activities. For the particular analysis in this table, the infected worker carries out activities for 4 days and $\tau = 3.5 \times 10^{-4}$ (moderately contagious assumption leading to R~2).

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In this particular commute scenario, the exposure of strangers during the infected worker's commute is for a subway commute with 4 minutes between stops, 5 stops, and non-rush-hour travel (only six persons exposed per trip).

The probability that *all* activities lead to no secondary infections is the product of the entries in the last column of Table 1, namely 0.715x0.979x0.365x0.657x0.511 = 0.0857. So the probability that there is at least one secondary infection is 1-0.0857=0.9143. In other words, there is about a 91% chance that the infected worker will transmit at least one infection to someone else, most likely his or her spouse.

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The exact number of secondary infections (transmissions), k, from each of the IC's activities is found from the bionomial probability density function (or approximated by the Poisson density function).

$$P(n,k) = [n!/k!(n-k)!]p^k (1-p)^{n-k} \qquad\qquad (TS\text{-}4)$$

where k is the number of transmissions, n is the number exposed, and p is the probability of transmission per person. The average number of transmissions is np. The values of np for various activities may also be thought of as their contribution to the reproductive number, R_0. In Table TS-2, values of n, p, and np are shown for the various daily activities in the analysis with moderately contagious assumption.

Activity	Number Exposed (n)	Probability of Transmission per Person (p)	Average number Transmissions (np)
Strangers (not easily traceable):			
• Commute to and from work	48	0.00698	0.335
• Casual contacts	120	0.00018	0.021
		$R_S =$	0.356
Non strangers (traceable):			
• Spouse	1	0.63512	0.635
• Activities with children	2	0.18945	0.379
• Coworkers/friends	8	0.08058	0.645
		$R_{NS} =$	1.659
		$R = R_S + R_{NS} =$	2.015

Table TS-2. Values of n, p, and np for the various infected worker's activities for the binomial distribution. for the table $\tau = 3.5 \times 10^{-4}$ and the infected worker carries out activities for 4 days. $R_0 = R_S + R_{NS}$, where S stands for strangers and NS stand for non-strangers.

The reproductive number for all activities is calculated to be $R_0 = 2.015$, obtained by taking the reproductive number for specific activities to be equal to the np values, and summing them.

It is not an accident that the contagiousness measure $\tau = 3.5 \times 10^{-4}$ yields a reasonable reproductive number R~2. This value of τ was purposely chosen to yield R~2 for this set of activities. This value for τ is used the main text to analyze infection transmission during a commute.

The specific activities of the infected worker are typical for a large city. Thus, choosing values for τ that result in reproductive numbers typical for influenza and SARS (R around 2 or 3) is a reasonable method for estimating τ.

I can offer no explanation for how the Eubank lab obtained the smaller range of τ values in the neighborhood of 10^{-4} for their analyses. It is unlikely they were obtained from experiments directly exposing people to someone infected with influenza and it is unlikely such experiments have ever been carried out, and infection transmission studies in animals may not yield values relevant to humans.