The Human Fatality and Economic Burden of a Man-made Influenza Pandemic: A Risk Assessment

Version 1/5/2014

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Synopsis

In August 2013 letters to the journals Science and Nature, 22 virologists have notified the research community of their intent to develop and research mammalian-transmissible, gain-of-function (mtGOF) flu strains of the H7N9 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 H7N9 strain is not aerosol transmissible among humans and shows only limited respiratory aerosol transmission among ferrets, so the aim is to confer what is known as gain of function by making the virus mammalian transmissible. H7N9 caused more than 130 human infections, including 43 fatalities, from handling poultry in China. Those infections tapered off last summer but may be picking up again as the new flu season progresses.

The voluntary research moratorium on man-made, mtGOF H5N1 avian influenza virus has ended, and research has resumed. These flu strains may already be highly contagious in humans, with the threat of accidental release from research labs seeding a pandemic.

From now on, these mtGOF flu strains will be referred to as potential-pandemic-pathogen or PPP flu strains. PPPs are all extremely deadly, highly contagious (or potentially highly contagious) in humans, and not currently present in human populations, meaning it would be a disaster to introduce or reintroduce them into the population. In addition to PPP flu strains, PPPs would include SARS and the resurrected 1918 pandemic flu.

Is a pandemic from a lab release from PPP flu strains 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 PPP flu strains carries with it the burden of these consequences. Fatalities and economic loss, "fatality burden" and "economic burden," are both considered in the analysis. The fatality and economic burdens have two common components: the probability of a PPP flu strain release from a lab and the probability that release leads to a pandemic. Fatality burden has the additional component, the projected number of world-wide pandemic fatalities, and economic burden adds in cost for treatment of victims and the costs for the many disruptions to society from a pandemic. Fortunately, world-wide cost has been estimated by a number of groups, so the task here is to apply those costs to the probability a pandemic will occur. To differentiate this fatality and economic analysis from others discussed below, it will be referred to as the FEB analysis. (A lay-level version of the fatality burden analysis may be found in The Scientist.)

The main FEB scenario 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 that focus here. In this scenario it is assumed that persons acquainted to the infected worker are quarantined quickly, so cannot spread infection, a very conservative assumption.

The analysis finds that *each lab in each year* it conducts this research carries with it the burden of 180 to 1,100 projected fatalities. In the worst -case scenario where both acquaintances and strangers spread infection, which is discovered too late to prevent a pandemic, the projected fatality burden is 30,000 per lab per year.

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 30,000 per year. Furthermore, perhaps twenty labs will conduct PPP flu research for ten years, which would increase the likelihood of lab release and a pandemic by nearly 200-fold.

The economic analysis finds that each lab in each year it conducts this research carries with it the economic burden from $2.3 million to $390 million world-wide cost, for conservative and worst cases. 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 pandemic risk must rely to some extent on uncertain data, making results uncertain. But fatality and economic burdens need only to be estimated within one or two orders of magnitude to reach meaningful conclusions. Here, very conservative to reasonable estimates of all elements 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 336,000,[1] based on the fatality rate of 0.02%. A late 2013 analysis suggests fatalities between 123,000 and 203,000 for the 2009 pandemic flu.

PPP 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 is used in this analysis. A world-wide pandemic seeded by a lab release of PPP flu strains could kill over a hundred-million people.[2]

As of the date of this writing, there appear to be only two analyses of the risk of a pandemic from a release of a PPP flu virus from a laboratory through a *single* infected lab worker: this FEB analysis and the analysis published in December 2013, "Containing the accidental laboratory escape of potential pandemic influenza viruses," which is a well thought through, exhaustive study from two mathematical epidemiology labs, one in Italy and the other in the U.S. The analysis traces infections as they spread through a synthetic population starting in Rotterdam and spreading to the rest of the Netherlands (the Netherlands study). It finds one million infections with control measures and ten million infections with no control measures, which when extrapolated to the world population yields 420 million to 4.2 billion infections, and 42 million to 420 million fatalities, based on the Netherlands population of 16.8 million; and at 10% fatality rate. The FEB study finds potentially 100 million fatalities based on one billion infections. Given the assumptions and approximations of these risk analyses, both fatality estimates are in the same range.

[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

Furthermore, the Italian/U.S. analysis supports our concern over spread of disease in an urban environment: "Containment depends on population density and structure as well, with a probability of giving rise to a global event that is three to five times lower in rural areas."

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 PPP flu research debate.

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

or in symbols

$$\text{fatality burden} = p_1 \times S \times N_f \qquad (1)$$

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,

$$S = T \times I \times (1-F) \qquad (2)$$

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 PPP 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 PPP 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, and friends) and strangers (e.g., casual brief contacts and 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~1.4	6.10%
5 minute commute each way (one stop), 4 days, 20 strangers exposed per trip	160	$\tau=3.5\times10^{-4}$ R~2	24.4%
5 minute commute each way (one stop), 4 days, 20 strangers exposed per trip	160	$\tau=5.7\times10^{-4}$ R~3	36.6%
20 minute commute each way (five stops), 4 days, 6 strangers exposed per trip	48	$\tau=3.5\times10^{-4}$ R~2	28.5%
20 minute commute each way (five stops), 4 days, 20 strangers exposed per trip	160	$\tau=1.0\times10^{-4}$ R~0.66	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 range from about I = 6.1% to 36.6%. 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 T x I = 0.61% to 3.66% 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[3]. For R_0=2 the probability that a single infectious case will seed a pandemic ranges from 10% (highly heterogeneous) to 80% (no heterogeneity).[4] Since there is no information on the degree of heterogeneity for PPP flu strains, we take an intermediate value of 1-F=30% that an infectious lab worker will seed a pandemic.[5]

Then, for R_0=2, S = 0.0061x0.3= 0.0018 or 0.18% to S = 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

[3] 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.
[4] See Figure 4A in the study
[5] From the blue curve in Figure 4A for R_0=2

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 PPP 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.

The "worst-case" scenario

The worst case would occur when the infected lab worker's spouse, children, coworkers, and other acquaintances, along with strangers, could transmit infection to others. It is quite possible that control measures might not be put in place fast enough to stop a pandemic. This could happen, for instance, with a 10% fatality rate if the first several victims do not die. The infections may be mistaken for a severe, yearly flu. All that may be required to seed a pandemic

is that the laboratory-release origin of the outbreak is not recognized and acted upon for a few weeks when dozens of people become infected.

The decision to shut down a city because all victims cannot be traced could take a few weeks if it is made at all. Even if this drastic action were successful in curbing the outbreak, the economic cost would be high, and even a small number of deaths may incite a call for drastic measures against all infectious disease research. The worst-case scenario is not improbable.

Without control measures or measures taken too late, the likelihood that an infected lab worker seeds a pandemic is simply S =1-F and was estimated before to be 0.3 or 30%. So fatality burden becomes

Yearly fatality burden per lab = 0.001 x 0.3 x 100 million = 30,000 fatalities.

Even though we cannot put a probability on whether control measures are too late, this scenario and its extraordinarily high fatality burden must also be in our thinking about risk *vs.* benefit of PPP flu research.

The Italian/U.S. analysis supports our concern over a budding pandemic not being detected until it is too late. If finds "…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."

The impact of control measures

What is the role of control measures to reduce pandemic fatalities? While the focus of the 2011 study "The Global Economic Effects of Pandemic Influenza" was the world-wide cost of pandemics, it did allow for calculation of fatalities with and without control measures

(interventions) for its two pandemic scenarios. Quoting from this Risk Management Solutions, Inc./Monash University study (the "RMS/Monash study") for the first scenario:

> "Scenario 1 is a virus comparable to a transmissible version of SARS. Overall attack rates are low, in the range of 3% of the global population and it takes 6 months to develop an effective treatment beyond standard antibiotics, antivirals, and supportive care such as ventilators. The case fatality rate without intervention is 10%, similar to SARS. The virus has a disproportionate mortality effect on the working age population, comparable to the 1918 pandemic. The virus causes serious illness in most individuals and 90% of those affected require physician treatment or hospitalisation."

The second pandemic scenario:

> "Scenario 2 is an extremely transmissible influenza virus with global attack rates of approximately 40%, despite the availability of an effective vaccine within months of the outbreak. The case fatality rate is 0.5%, which is similar to the case fatality rate of the 1957 influenza pandemic. Unlike seasonal influenza, where typically 90% of the fatalities are observed in individuals greater than 65, this virus has an equal case fatality across ages consistent with the 2009 H1N1 pandemic. The majority of cases are subclinical or physician visits and approximately one fifth of those hospitalized require intensive care, analogous to what is observed in seasonal outbreaks."

Both scenarios allow for control measures such as quarantine, antivirals, and a vaccine once it is developed.

Total global fatalities with control measures may be determined by summing the deaths in each nation in the next to last column from Tables 1 and 2 in the RMS study, giving 9.51 million and 6.03 million for scenarios 1 and 2, respectively. For no control measures, the total fatalities for scenario 1 are

3% attack rate x 10% fatality rate x 7 billion world population = 21 million.

So control measures reduce fatalities by 21/9.51=2.21 fold. For scenario 2 with no control measures,

40% attack rate x 0.5% fatality rate x 7 billion world population = 14 million.

Interventions reduce fatalities by 14/6.03=2.32 fold.

Therefore, it is anticipated that control measures will reduce fatality rates by a factor of about two as a rule of thumb, but will not stop a pandemic once it is underway.

Analysis with a few more conservative numbers

Proponents of PPP flu research might argue that a 10% fatality rate is too liberal an assumption; the analysis should have used 2%, the 1918 pandemic flu rate. The 10% was chosen as a compromise between the 2% for the 1918 flu and the greater than 30% for H5N1 bird flu and the H7N9 Chinese flu. Since fatality burden scales linearly with fatality rate, using 2% would reduce fatality burden by a factor of five (10%/2% = 5).

In their comments on the analysis, the Center for Infectious Disease Research and Policy argued that using R_0=2 throughout much of the analysis is also too liberal, so lower values might be more realistic. In Table 1, R_0 = 1.4 was used in one short commute scenario, which yielded a 6.1% probability for disease transmission. This scenario provided the lower bound used throughout the analysis. In the early stages of the 2009 H1N1 pandemic, reproductive numbers were estimated between 1.2 to 3.0, so the R_0 = 1.4 estimate in Table 1 is at the low, conservative end.

The only other place where reproductive number appears explicitly in the analysis is in estimating fadeout probability, F, for the outbreak, or its complement the pandemic probability (1-F). The Lipsitch lab paper calculates values for 1-F for a range of reproductive numbers. From Figure 4A in that paper, the 30% probability is based on R_0=2. For R_0=1.4, the probability is about 15%, so the fatality burden would be reduced by a factor of two.

These less liberal assumptions still yield too high a fatality burden and too high a risk in the risk vs. benefit balance.

Calculation of economic burden

The RMS/Monash study details the impact on the world gross domestic product (GDP) of pandemic influenza for the two scenarios described earlier. The analysis considers "a comprehensive representation of the economy, i.e., as a complete system of interdependent components: industries, households, investors, governments, importers and exporters."

For scenario 1 in the RMS/Monash study, the reduction in global GDP in the year of the influenza pandemic is 0.268%; and for scenario 2, the reduction of global GDP in the year of the pandemic is 3.342%. (There would be minor losses in global GDP for one or two years subsequent to the pandemic, which are ignored in the calculation here.). The base-case numbers used in the calculation of fatalities in the FEB analysis were R_0=2, 10% fatality rate, 15% of the global population infected (100 million fatalities); these numbers are between the two scenarios in the RMS study. For the calculation of economic burden here, the average (0.268+3.342) = 1.81% will be used. Based on a world GDP of $72 trillion in 2012, the dollar loss from the reduction in global GDP is .0181% x $72 trillion = $1.3 trillion.

In analogy to the fatality burden calculation above, for the conservative scenarios where only strangers can spread infection, yearly economic burden per lab = 0.001 x 0.0018 x $1.3 trillion = $2.3 million projected pandemic cost per lab per year to yearly fatality burden per lab = 0.001 x 0.011 x $1.3 trillion = $14.3 million projected pandemic cost per lab per year. For the worst-case scenario yearly fatality burden per lab = 0.001 x 0.3 x $1.3 trillion = $ 390 million projected pandemic cost per lab per year.

There have been other studies of global GDP reduction from an influenza pandemic, for instance the study by WJ McKibbin and AA Sidorenko from two Australian policy and epidemiology groups. This study reports reductions to the world GDP from 0.8% for a mild

pandemic scenario with 1.4 million fatalities through 9.4%[6] for an "ultra" pandemic scenario with 142 million fatalities. The mild scenario is similar to the Hong Kong flu pandemic of 1968-1969. The ultra scenario is similar to the 1918 pandemic flu "but without the anomalously high elderly survival rates." The 100,000 fatalities in the FEB analysis is closest to the ultra scenario in the Australian study. In the FEB analysis, calculation of economic burden uses the more modest 1.81% reduction in GDP, not the significantly higher 9.4%.

The RMA/Monash and Australian analyses, and therefore the FEB analysis based on their GDP loss calculations, do not consider the cost of loss of human life. For instance, the average cost of loss of a single human life is valued at $1.8 million in the U.S., totaling over $8.5 trillion dollars[7] for fatalities in the U.S. population alone.

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%,[8] twenty-four times the 0.1%

[6] For the ultra scenario, the 2006 study reports a $4.4 trillion reduction to world GDP, which was $46.5 trillion in 2005, so the percent reduction in GDP is 4.4/46.5 x 100 = 9.4%

[7] 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.

[8] This escape probability is calculated from the formulas in "Sharpening Our Intuition on PPP Pandemics."

used in the FEB analysis. 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?

Some proponents of PPP 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.

Why do proponents think the research is safe?

Because the probability for lab release *and* the probability of a pandemic are both low—together ranging from 0.00018 percent for the most conservative commuter-stranger scenario and to the much higher 0.03 percent for the worst-case scenario—supporters of mtGOF research believe it is safe. Such research would be safe for most pathogens; but for PPP pathogens that could seed a worldwide pandemic with tens of millions of deaths, the probabilities are not nearly low enough to judge the research safe.

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

$1 - (1-p_1)^{20x10} = 0.18$ or 18%, using $p_1=0.001$

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

For now, restriction to BSL-4 labs would significantly reduce the number of labs that could carry out PPP 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.

Research with deadly, contagious PPP flu strains should be banned

Much of PPP 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 PPP 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 numbers we are gambling with, it is clearly far too high a risk to human lives and the world's economy, so this particular PPP research must be shut down.

Thanks to Richard Ebright for insightful comments and edits, and to Marc Lipsitch for insightful comments and pointing me to branching theory.

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.

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

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

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

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

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

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

To complete the description, how was $\tau=3.5\text{x}10^{-4}$ 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.

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)

τ = 3.50E-04 per min R ~ 2.0146

Activity	Number Exposed	Time Exposed (minutes per person)	Probability of No Disease Transmission per person	Probability of No Disease Transmission for all exposed
Contact with strangers				
>> Travel to and from work on the subway 5 stops 4 minutes between stops 6 exposed per trip	48	20	0.9930	0.715
>> Casual contact with 30 people 0.5 minute per person per day	120	0.5	0.99982	0.979
Contact with people who can be traced				
>> Spouse 12 hrs per day	1	2880	0.36488	0.365
>> Meals, play, etc. with 2 children for 2.5 hrs per day	2	600	0.8106	0.657
>> Contacts with 8 coworkers and friends for 1 hour per day per person	8	240	0.9194	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).

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.

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).

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

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 $\tau=3.5\text{x}10^{-4}$ 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.