

A Commentary and Analysis of Chapter 6 in Gryphon Scientific's Report: Risk and Benefit Analysis of Gain of Function Research

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With less than a month to analyze and comment on the thousand-page report before the December 31 "soft" deadline for the NABCC January meeting, it would be nearly impossible for anyone to follow in detail Gryphon's analysis and comment on all the chapters. I chose, therefore, to limit my comments and analysis to only Chapter 6, the Biosafety Risk Assessment.

Summary

Based largely on Gryphon's numbers, I estimated the likelihood-weighted fatalities for a pandemic seeded by a laboratory-acquired infection (LAI) from an mtHPAI (a mammal-adapted airborne-transmissible highly pathogenic avian influenza virus). Along the way, comments on aspects of Gryphon's Chapter-6 analysis will be made.

Generally, likelihood-weighted pandemic risk equals probability of a pandemic times consequences of the pandemic. The probability of a pandemic from a lab escape through an LAI for ten labs conducting research on mtHPAI strains for ten years was found to be 1.8×10^{-5} using Gryphon's numbers that an LAI lab escape leads to a pandemic. Ten labs for ten years is my estimate of the "research enterprise" that already is or will be conducting research with these strains.

In my analysis, consequences were restricted to fatalities. The case-fatality rate was chosen to be 5%, which is twelve-fold less than the World Health Organization's accepted case-fatality rate of 60%. For a pandemic infecting 25% of the world's population, the number of fatalities would be 90 million. With these numbers, the Likelihood-weighted fatalities for the research enterprise are

$$\text{likelihood-weighted fatalities} = (1.8 \times 10^{-5}) \times (90 \times 10^6) = 1,640$$

For a single lab for a single year, the likelihood-weighted fatalities are 10x10-fold less or 16.4, which I call "the fatality burden" for the lab. To put this fatality burden in perspective, no Institutional Review

Board tasked with assessing human subject research would approve a proposed research project with an expected 16.4 fatalities per year.

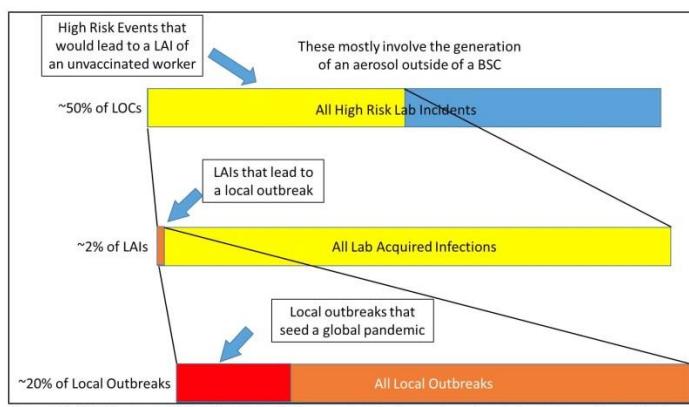
This 5% case fatality rate is much higher than the small fraction of 1% claimed by [Morens and Taubenberger](#). But airborne-transmissible mtHPAI, a key focus of the NIH deliberative process, are not wild type viruses. They infect lung to lung via the airborne route. We do not know the case -fatality rate for these strains. It could be quite high, perhaps over 60%. Arguments over case fatality rate for wild-type HPAI are likely moot. Since we don't know, and the potential consequences in morbidity and mortality are so high, caution dictates instituting a ban on making and researching live airborne-transmissible mtHPAI. This will be discussed a bit more at the end of my Commentary.

The Gryphon report seems to dismiss gain-of-function studies in SARS and MERS, by assuming that mitigation measures such as quarantine should prevent a large outbreak. SARS has about an eight-day incubation period before an infected person can transmit infection, a fair amount of time to quarantine those exposed to an infected person. Timely and strong mitigation measures may be possible in developed nations, but we need only to look at the Ebola epidemic in the poor and war-torn African nations to understand the potential for large outbreaks. GOF studies in SARS and MERS should be looked at very carefully and perhaps many banned as well.

Details of and rationale for my analysis

In describing my analysis and the rationale for the numbers and estimates used, I will rely on quotes and data from the Gryphon risk assessment. Also, I will reproduce here relevant tables and graphs from the Gryphon RA as a convenience to you.

The three steps to a pandemic are illustrated in Gryphon's Figure 6.2 for seasonal influenza.



The absolute probability of an escape from a single lab in a single year though an LAI or other routes, p_1 , is not shown in the graph. Making a reasonable guess for this absolute probability is the subject of Section 6-8 of the Gryphon report. For the second and third steps, the probability that the LAI will lead to a local outbreak is estimated by Gryphon to be about 2% for seasonal influenza, and the percentage of local outbreaks that will lead to a pandemic is about 20%. The probability that a single lab in a single year seeds a pandemic, pan_1 , is then

$$\text{pan}_1 = p_1 \times 0.02 \times 0.2 = 0.004 p_1 \quad (1)$$

The 0.004 or 0.4% figure is quoted many times throughout Chapter 6 (sometimes Gryphon uses 0.5%). It is the result of their analysis of risk using branching theory and the HHS-BARDA Interactive Influenza Model.

Gryphon's dividing the path from a lab escape leading to a pandemic into two steps--(1) the escape causes a local outbreak and (2) the local outbreak then causes a pandemic--is not necessary. A single infected researcher can seed a pandemic directly. From [Figure 4](#) in the Lipsitch *et al.* (2003) paper, the probability that the single infected researcher can seed a pandemic is 10% to 30% (for $R_0=1.3$ and smaller k values). Thus, the 0.4% value is likely $1/0.02 = 50$ -times higher due to eliminating this intermediate local-outbreak step.

These are two well-established methods; and given Gryphon's high-level mathematical and analytic skills, I will use the 0.4% Gryphon number to stay closer to their analysis. In Gryphon's words,

“Sufficient biomedical and epidemiological evidence exists to develop robust models of the initiation of an outbreak from the primary to the secondary cases and the expansion of this outbreak within a community to eventually spark a global pandemic.”

For a “research enterprise” of $10 \times 10 = 100$ lab years, the probability that some lab in some year will seed a pandemic is approximately $100 \times \text{pan}_1$ or $100 \times 0.004 p_1 = 0.4 p_1$. Clearly, p_1 is the key probability to carry out the analysis with high confidence. The two parts of Gryphon's and my analysis that are uncertain are values for the probabilities p_1 and for the case fatality rate.

To obtain an absolute probability for p_1 , in Section 6.8 Gryphon basically guesses. In Gryphon's words,

“...absolute risk estimates are desired. For this reason, the historical rate of laboratory acquired infections could be used to predict a reasonable upper bound for the frequency with which these incidents occur. However, the research team is unaware of any laboratory acquired infections in laboratories that study influenza or coronaviruses and so an absolute risk analysis will have at its foundation a weak estimate of the frequency at which laboratory acquired infections occur. That being said, this historical rate of laboratory infections can then be combined with calculated rates of laboratory acquired infections leading to secondary infections, local outbreaks and global pandemics from this assessment to produce an estimate of absolute risk.”

The remarkable observation here is that in 100 mostly seasonal influenza BSL2 research labs over 20 years of research, Gryphon was unable to find any reported LAIs. Gryphon offers the following explanation:

"The project team knows of no laboratory acquired infections involving any one of these laboratories. This lack of a laboratory acquired infection could be due to the fact that none have occurred in that time frame or that some have occurred but the project team does not have access to the reports or data."

The report neglects additional possible reasons: asymptomatic or subclinical infections, or misattribution of LAI to the community. If a researcher contracts seasonal influenza, it might not be detected, as a high proportion of seasonal influenza is subclinical particularly among individuals with considerable levels of natural immunity or immunity from vaccinations. If it were detected clinically, it would likely be attributed to a community infection, not from the lab. In any case, reporting it as possibly an LAI would lead to time-consuming follow up. It could be unspoken policy in seasonal influenza research labs to not report infections of uncertain origin given that the infected person will be better in few days. I find it difficult to believe that there have been no LAIs in 100 mostly BSL2 labs in 20 years. That would be inconsistent with rates of LAI in other BSL2 labs, even in settings where [underreporting is known to be a problem.](#)¹

In any event, where Gryphon expected to find statistically-useful real data on LAIs in seasonal influenza labs, it found none. I suspect Gryphon then resorted to historical data from other labs researching other pathogens to obtain its range of zero to ten LAIs. Gryphon raises a valid and important point on using accident data from other pathogens and laboratories.

"very little data exists on human reliability in life science laboratories, which drives the probability that laboratory acquired infections occur in the first place. Fortunately, the accidents that humans cause (or contribute to) in the laboratory are the same regardless of the pathogen manipulated. That is, workers may overfill a centrifuge tube with the same frequency regardless of the pathogen in the tube, or will slip while working with scissors during a necropsy with the same frequency regardless of the pathogen studied. Because the absolute rate at which these accidents happen and cause infections is not supported by robust data, absolute estimates of the rate of laboratory acquired infections cannot be made using the method described in this report."

Lacking real data, Gryphon makes an educated guess that perhaps three LAIs did occur in the hundred mostly seasonal influenza labs over the twenty years. Gryphon calculates

"Across all 100 laboratories ...if the assumption is made that three LAIs have surreptitiously occurred, then ...a global pandemic could be triggered once every 750-5,000 years."

Gryphon chooses to report its findings as "return periods" in years, not probabilities. Return periods are the reciprocal of probabilities per year. My problem with return periods is that they can fool you into thinking something is safe when it is not when consequences are considered. It is necessary to stick to the more fundamental probabilities for calculations.

For seasonal influenza, with Gryphon's guess of 3 LAIs in $20 \times 100 = 2,000$ lab years, the probability of an LAI (escape) per lab per year is $p_1 = 3/2,000 = 1.5 \times 10^{-3}$. (Three LAIs in over 2,000 lab years seems conservative to me, there were likely more.) Thus, the return period for one lab in one year is $1/p_1 = 667$ years for an LAI to occur. This may seem like the experiments are safe, as they will be completed in

¹ Marc Lipsitch contributed to this paragraph

perhaps 10 years, well short of the return period. But looked at another way, in 20 years this means that there are three LAIs, where each one has a not-insignificant chance of causing a seasonal influenza pandemic. I would not accept those odds.

What is the probability, $p_{1,HPAI}$, for research on mtHPAI? I assume that research on mtHPAI is conducted in BSL3 labs using the level of biosafety for research on SARS, as SARS has a case-fatality rate of around 10% considerable caution is warranted. Gryphon lists relative probabilities compared to work with seasonal influenza in their Table 6.2, reproduced here.

Table 6.2. Relative probability of a laboratory acquired infection for the various pathogens considered in this study as compared to work with seasonal influenza.

Pathogen	Biosafety Level	Relative Probability of an LAI*
Seasonal influenza virus	BSL2	1 (defined)
Pandemic influenza virus	BSL3	0.10 (0.07-0.15)
Avian influenza virus	BSL3	0.43 (0.21-0.90) (mostly of birds)
SARS-CoV	BSL3	0.03 (0.02-0.04)
MERS-CoV	BSL3	0.01 (0.006-0.02)

These data are generated by comparing the sums of the frequency of infection from all loss of containment pathways for each pathogen. In this case, we use the term laboratory acquired infection to include an infection of wild birds to capture the comparative risk of working with avian influenza viruses. The numbers in the parenthesis are the results from the p5 and p95 outputs of the Monte Carlo analysis.

Before using data from Table 6.2, this is a good place to state what I view as a major shortcoming in the Gryphon report. Sources of data and calculations to obtain it are not referenced throughout Chapter 6. Are the sources not referenced in the Supplementary material? In the published literature? In spreadsheets available from Gryphon? In Table 6.2, for instance, the caption could have provided references. Thus, we don't know how solid or significant various pieces of data are, unless Gryphon chooses to discuss it. I suspect that Gryphon could have used much more time in preparing its report.

Furthermore, Gryphon ignores the frequency of accidents over the years in labs researching Select Agents compiled by the CDC in 2013. Gryphon's analysis also ignores the highly publicized recent accidents in the CDC lab. While none of these accidents involved seasonal influenza, somewhere in Chapter 6 they should have been acknowledged and incorporated into their analysis. It is unclear why guesses well below the empiric rate of LAI should be used for a risk analysis. Nonetheless, in what follows, Gryphon's numbers are accepted for the sake of argument.

From Table 6.2, the probability of an LAI in a SARS lab is a factor about 0.03 times that of seasonal influenza. Specifically, $p_{1,HPAI} = 0.03 \times 1.5 \times 10^{-3} = 4.50 \times 10^{-5}$ for a SARS or mtHPAI lab where $p_{1,HPAI}$ is the probability of an LAI for a single lab for a single year. The probability of a pandemic from a single lab in a single year, pan_1 , is

$$pan_1 = 0.004 \times p_{1,HPAI} = 0.004 \times 4.50 \times 10^{-5} = 1.8 \times 10^{-7}$$

As an illustration, I conservatively estimate 10 labs conducting mtHPAI research for 10 years (100 lab years),² each with the laboratory safety of a SARS lab. The probability that the research enterprise will seed a pandemic, RE, is approximately

$$RE = 100 \times pan_1 = 1.8 \times 10^{-5}$$

The return period, 1/RE, is 55.6 thousand years, which would seem to make the research very safe if it were not for the potential consequences of millions of fatalities.

The likelihood-weighted pandemic risk, LWR, is given by

$$LWR = (\text{Probability of a Pandemic}) \times (\text{Consequences of a Pandemic})$$

Consequences are restricted to fatalities in this analysis. The case fatality rate was chosen to be 5%, which is twelve-fold less than the World Health Organization's accepted case fatality rate of 60%. For a pandemic infecting 25% of the world's population of 7.3 billion, the number of fatalities, F, would be

$$F = 7.3 \text{ billion} \times 0.25 \times 0.05 = 90 \text{ million.}$$

With these numbers, the likelihood-weighted fatalities, LWF, for the research enterprise is

$$LWF = RE \times F = (1.8 \times 10^{-5}) \times (90 \times 10^6) = 1,640.$$

The Likelihood-weighted fatalities for a single lab in a single year is $1,640/100 = 16.4$, which I call the "fatality burden" for the single lab in a year. As pointed out earlier this fatality burden is likely 1/.02 or 50 times higher. To put this fatality burden in perspective, no Institutional Review Board tasked with assessing human subject research would approve a proposed research project with an expected 16.4 fatalities per year (or $50 \times 16.4 = 820$ fatalities per year, accounting for the 50-fold error discussed above). There are [research approaches](#) not involving live mtHPAI for elucidating the molecular virology of airborne transmission. Such safe research approaches ought to be employed, and research with lab-made, airborne-transmissible, live mtHPAI be banned.

One point still needs to be discussed, case fatality rate. The 5% case fatality rate used in this analysis is much higher than the small fraction of 1% claimed by [Morens and Taubenberger](#). There are well-documented studies (for instance, [here](#) and [here](#)) that claim the case fatality rate is not low but close to the 60% often quoted for wild type H5N1 HPAI. But the airborne-transmissible mtHPAI, a key focus of the NIH deliberative process, are not wild type viruses. They infect lung to lung via the airborne route. We do not know the case-fatality rate for these strains. It could be quite high, perhaps over 60%. So, arguments over case fatality rate for wild-type HPAI are likely moot. Because the potential consequences in morbidity and mortality are potentially high, caution dictates instituting a ban on making and researching live airborne-transmissible mtHPAI.

² Gryphon estimates "approximately 40 research groups in the US because these groups have been performing, or have the capacity to perform, certain types of GOF experiments involving influenza, MERS, and SARS viruses. This maximum number is supported by the case studies examined which showed that a new discovery in virology may proliferate to as few as one and as many as 70 new groups around the world within 10-15 years."

The Gryphon report seems to dismiss gain-of-function studies in SARS and MERS, by assuming that mitigation measures such as quarantine should prevent a large outbreak. SARS has about an eight-day incubation period before an infected person can transmit infection. Timely and strong mitigation measures may be possible in developed nations, but we need only to look at the Ebola epidemic in the poor and war-torn African nations to understand the potential for large outbreaks. GOF studies in SARS and MERS should be looked at very carefully and many perhaps banned as well.