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Date: February 23, 2016

Commentary for the March NAS meeting on GOF: Toward absolute probabilities for escape from a laboratory

Summary and conclusion

This Commentary presents a calculation of "direct" or "absolute" probability[1] of escape from a laboratory of a potential pandemic pathogen, specifically mammalian-airborne-transmissible, highly-pathogenic avian influenza viruses (matHPAI). Absolute probabilities are necessary to calculate the probability of a laboratory escape and subsequently the likelihood of a pandemic from an escape, a key goal of Gryphon Scientific's risk-benefit (RBA) analysis.

Gryphon employed a relative probability approach that in the end failed to arrive at an absolute probability of an escape. Thus, this key part of their analysis ended up where it started, not accomplishing its goal of estimating the risk of the research (risk = likelihood x consequence). Gryphon acknowledges this failure.

Here, I will argue that Gryphon went down a wrong path by pursuing a relative probability approach. I will further show that it is possible to estimate absolute probability of escape by actually carrying out the calculation using laboratory incident data reported under the NIH reporting guidelines for BSL3 or BSL4 laboratories. Since all steps of my analysis are explicit and transparent to the reader, it provides a basis for focused discussion and assessment of each step.

In comparison, Gryphon's analysis does not explicitly provide the exact data employed or direct references to it, and Gryphon often provides little detail of the steps in its various analyses. This lack of transparency makes it difficult to verify Gryphon's conclusions. Furthermore, Gryphon fails to define the meanings of or labels for various variables. For instance, if they report a value for a lab-related accident probability, they fail to say if the probability represents one lab for one year, one lab for many years, etc.

This failure to define precisely key variables adds to the lack of transparency and the ability to assess their RBA.

My analysis concludes that the probability of escape and likelihood of a potential pandemic is much too high, with an expected "fatality burden" of 512 fatalities per year for each lab conducting this research. 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 512 fatalities per year.

Dr. Marc Lipsitch, in his presentation at the January 2016 National Science Advisory Board for Biosecurity (NSABB) meeting, described published research to understand how HPAI may become airborne transmissible in humans that does not require live matHPAI viruses. Many mutations that contribute to airborne transmission have already been identified by this research without employing live virus. Thus, there is little to be lost by banning the live virus research.

I conclude that NIH should not fund this specific matHPAI research and should also not fund any other research with comparable risk. Since the NSABB mandate is very narrow, only whether NIH should fund the research, the NSABB should strongly recommend that the U.S. ban the research regardless of funding source, and recommend that the State Department make a serious effort at an international agreement to ban the research.

Two approaches for estimating absolute probabilities of a lab escape and subsequent pandemic

To estimate the likelihood (probability) of a pandemic beginning with a laboratory escape of a matHPAI, there are two general approaches:

(1) A "bottom-up" approach where probabilities are obtained for significant mechanical/equipment failures or for human error that can lead to laboratory acquired infections (LAIs) and other escape paths into the community. Then, add them all up. This appears to be Gryphon's approach. The approach here is bottom-up as well, but it starts with laboratory incident data reported under the NIH reporting guidelines for BSL3 or BSL4 laboratories, a starting point and path forward different from Gryphon's.

(2) The "top-down" or "real-data" approach. A number of us have been arguing that Gryphon should have taken into account real data as well (for instance, the probability of escape into the community of undetected or unreported LAIs calculated from the 2013 CDC report). Gryphon's valid criticism of the CDC data is that the LAIs were for bacterial pathogens, and certainly not for matHPAI viruses.

Gryphon could have carried out a "control" calculation to demonstrate that its approach can produce probabilities of escape through LAIs comparable to those calculated from the 2013 CDC data. If the two calculations end up with greater than one or two orders-of-magnitude difference, there is a problem with their data used in the bottom-up approach. In a conversation with Gryphon's Managing Director, Rocco Casagrande, he pointed out the data they have collected is not relevant to bacterial select agents, so the control calculation could not be done. But they could and should have collected the missing data as part of their risk-benefit analysis (RBA) to gain confidence in their bottom-up approach data.

In its RBA, Gryphon notes that human error far exceeds mechanical failure. This is borne out by NIH reported incident data (see below) and by the highly publicized recent incidents of human errors leading to escapes into the community.

It is a hypothesis of this Commentary that likelihood of human error will be similar in laboratories researching matHPAI and in laboratories researching other less dangerous select agents. A further hypothesis is that absolute probabilities of escape can be estimated from data already publically available and can be supplemented by data gathered easily. This is a more useful and different approach from Gryphon's approach that employs relative probabilities.

Toward absolute probabilities: A flow chart analysis of paths for escape from a laboratory

To determine the absolute probability of escape for a matHPAI virus from a BSL3 laboratory, a number of events must occur, beginning with an incident that can involve mechanical or equipment failure or human error. The flow chart in Figure 1 describes the events and connections among events, and it lists symbols for probabilities[2] that would eventually lead to an escape. For a matHPAI virus, an escape could lead to a pandemic.

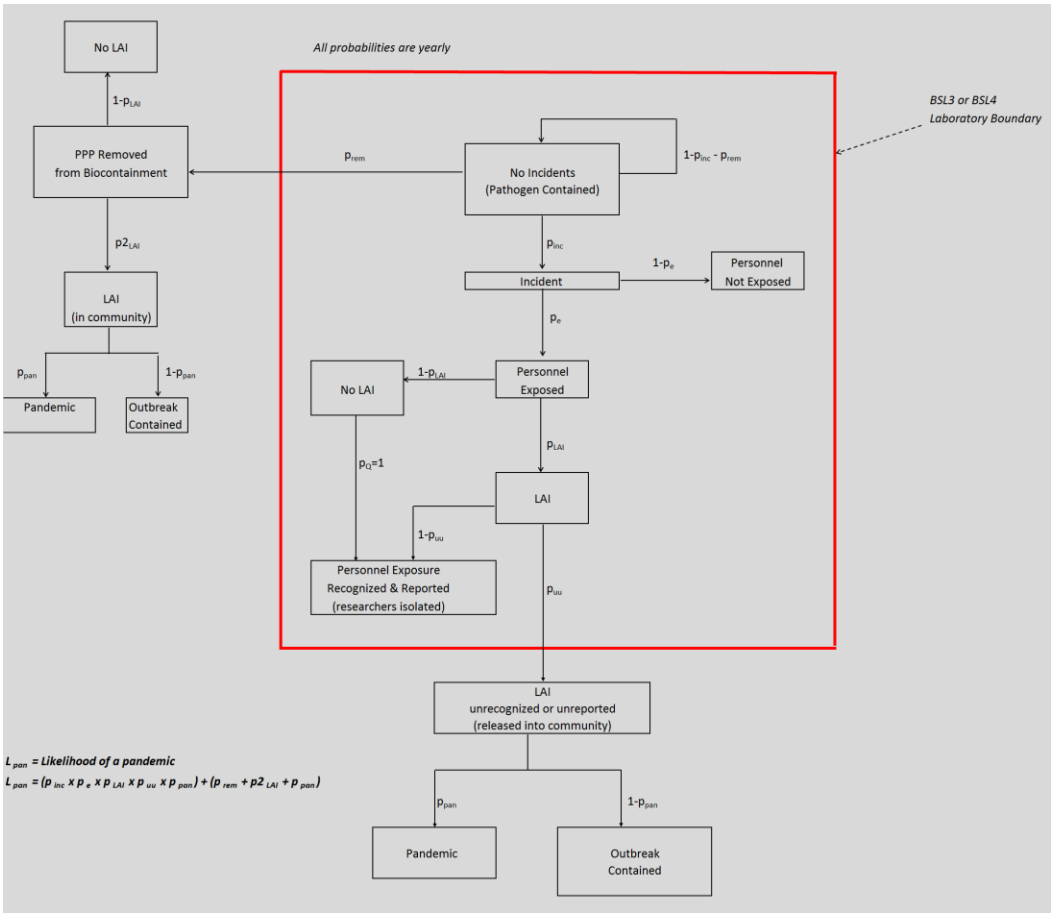

Figure 1. Flow chart of events leading to a lab escape and a pandemic.

In the Figure 1 rendering, there are two independent paths for escape: (1) the undetected or unreported LAI path (top to bottom) and (2) the purposeful removal from containment path (to the left).

For path (1), the likelihood (probability) of a pandemic is $L1_{pan} = p_{inc} \times p_e \times p_{LAI} \times p_{uu} \times p_{pan}$. Here, p_{inc} is the probability that there is an incident is the first place. p_e is the probability that the incident involves exposure of one or more lab personnel. p_{LAI} is the ratio of LAIs to exposures (not strictly a probability because it includes multiple LAI from each exposure). p_{uu} is the probability that the LAIs are undetected or unreported, so infected persons leave the laboratory into the community. In the flow chart, the undetected or unreported LAI moves outside the red laboratory boundary into the community. Finally, p_{pan} is the probability that a pandemic results.

For path (2), the likelihood of a pandemic is $L2_{pan} = p_{rem} \times p2_{LAI} \times p_{pan}$. Here, p_{rem} is the probability that a matHPAI is purposely removed from the laboratory. This could happen for a number of reasons, a common reason being that a researcher has mistakenly believed that the pathogen has been made inactive and is removed for research in a BSL2 lab or removed for transport to another facility.

The overall rate at which pandemics occur (effectively, the probability of generating a pandemic per calendar year) is

$$L_{pan} = (p_{inc} \times p_e \times p_{LAI} \times p_{uu} \times p_{pan}) + (p_{rem} \times p2_{LAI} \times p_{pan})$$

All probabilities in this analysis should be estimated for one year and one lab, as this is the basic probability from which many-lab, many-year escape probabilities can be readily calculated.

Determining values for the probabilities

For path (1), start with p_{inc}. It is a probability that should be obtainable with reasonable accuracy from incident data for many labs over many years. Gryphon should already have this data. I would guess that it is possible that every lab would experience some reportable incident each year, for instance a spill. So, p_{inc} might be 50% or greater. To be a bit more conservative, I will assume that p_{inc} =0.2, which assumes a lab will experience on average one incident every five years (1/0.2). This is likely a generous probability reduction.

In a telephone conversation with Rocco Casagrande, he commented that only 2% of incidents result in personnel being exposed. In analyzing incidents that result in LAIs[3] (Table 1), clearly exposure has occurred.

Thus, the probability that an incident escapes containment and a lab worker is exposed is p_e = 2% = 0.02. So 98% of the time incidents involve no personnel exposure (1-p_e = 98%) and no LAI could occur. Gryphon should be able to comment on the accuracy of the 2% number--that is, how much data supports it. This is a key number.

To estimate the other probabilities, I turn to a table of reported lab incidents collected for the *Final Supplementary Risk Assessment for the Boston University National Emerging Infectious Diseases Laboratories (NEIDL).* (http://www.bu.edu/neidl/files/2013/01/SFEIR-Volume-III.pdf) This 2,716 page risk assessment is abbreviated as the SFEIR (Supplemental Final Environmental Impact Report).

An informative table in the SFEIR is Table D-7, "Recent Reported Incidents Involving U.S. BSL-3 laboratory Facilities." The table is 27 pages long and lists and summarizes 118 incidents, with 23 incidents involving viruses. The table does not report the number of laboratories reporting and their years of operation, so probabilities for each of the different kinds of incidents cannot be ascertained (the frequently encountered "denominator" problem). However, it does provide a way that allows the probabilities downstream of p_e in Figure 1 to be estimated, using as denominator the 118 incidents.

The table covers 1984 through 2010, with most reported incidents after the year 2000. I sorted the table to collect all the LAIs together. The sorted table, including only confirmed LAIs, with a few columns deleted and a few non-substantive changes, is presented in Table 1 below.

LAI Category	Research agent	Description	Results	Action
Detected	West Nile virus (WNV)	A microbiologist working under BSL-3 conditions suffered a finger puncture from a hypodermic needle harboring WNV being harvested from infected mouse brain (Centers for Disease Control and Prevention 2002).	The wound was cleansed and bandaged. Serologic testing showed evidence of acute WNV infection. Mild symptoms developed and resolved.	CDC determined that applicable handling and biocontainment protocols were followed.
Undetected or unreported	Sabia virus[c]	A research virologist discovered a leaking vessel upon opening a sealed aerosol biocontainment centrifuge rotor outside of a BSC. Personal respiratory protective equipment consisted of a surgical mask. The incident was not reported (Altman 1994).	Symptoms began 8 days afterward. Two days later the infection was correctly diagnosed.	Antiviral therapy cured the nearly fatal infection. Two external committees strongly criticized the researcher and institution. The university agreed to implement all recommendations. No secondary infections were found among the 142 subsequent human contacts (ref needed)
Undetected or unreported	*Neisseria meningitidis*	A microbiology researcher at BU sought medical attention for laboratory-acquired bacteremia and meningitis. Molecular typing determined the infecting strain was the same strain he had been working with. Work with *N. meningitis* is conducted at BSL-2 using BSL-3 precautions (respiratory protection provided by Class II BSC) (Boston University 2009; Smith 2009, 2009).	Intravenous antibiotics were administered and the researcher recovered fully.	University experts determined the researcher did not consistently wear appropriate personal protective equipment, and did not consistently follow appropriate safe microbiological practices. It was surmised that the researcher touched his gloved hand to his face while working with the bacterium
Undetected or unreported	*Coxiella burnetii*	Previously undiagnosed exposures to *C. burnetii* are diagnosed in three laboratory workers by serologic testing (Centers for Disease Control and Prevention 2007, 2007). As many as ten workers might have been infected (further information is unavailable (Subcommittee on Oversight and Investigations 2007).	Responsible officials did not report these infections to federal authorities as required by federal law.	CDC issued a cease and desist order to TAMU on April 20, 2007 that was expanded on June 30 to include work with all Select Agents. Other serious violations were found during a site visit inspection in July 2007.
Undetected or unreported	*Brucella melitensis*	A researcher contracted undiagnosed brucellosis during improper disinfection of aerosolization chamber. She later required prolonged administration of intravenous and oral antibiotics (Centers for Disease Control and Prevention 2007, 2007; Subcommittee on Oversight and Investigations 2007).	Responsible officials did not report this infection to federal authorities, as required by federal law, until April 11, 2007 in response to an inquiry from the Sunshine Project. (Texas A&M University 2007)	CDC issued a cease and desist order to TAMU on April 20, 2007 that was expanded on June 30 to include work with all Select Agents. Other serious violations were found during a site visit inspection in July 2007.
Undetected or unreported	*Francisella tularensis*	Researchers were working under BSL-2 biocontainment protocol with what was believed to be a non-infectious vaccine strain of the bacterium. Later, it was determined the bacterial culture also contained the infectious wild-type strain that requires BSL-3 biocontainment precautions. Investigation was unable to determine the cause for the mixed culture (Anonymous 2005; Barry 2005; Lawler 2005; Dalton 2005).	Two researchers became infected with *Francisella tularensis* in May and were not correctly diagnosed until a third scientist became infected with the bacterium in September.	An investigation revealed that researchers had failed to follow proper BSL-2 biocontainment protocol, and that the University failed to identify work- related illness in laboratory staff and failed to immediately report suspicious work-related illness to local and state health departments. Biosafety policies and SOPs were revised accordingly. The Chief of Infectious Diseases was replaced.
Undetected or unreported	*Brucella* species	A laboratory worker became feverish months after handling a culture of *Brucella* sp (The Associated Press 2009).	Infection was confirmed in July by laboratory testing.	It was determined that employee had handled the culture without using proper biocontainment precautions. The employee eventually returned to work.
Detected	West Nile virus (WNV)	A microbiologist, working under BSL-2 conditions using a Class II BSC, lacerated a thumb with a scalpel during necropsy of a bird infected with WNV (Centers for Disease Control and Prevention 2002).	The superficial wound was cleansed and bandaged. Symptoms began 4 days post injury; medical attention was sought 7 days after injury. Infection was self- limiting and was confirmed by serologic testing.	CDC recommends BSL- 3 biocontainment measures for WNV. However, CDC does accept BSL-2 biocontainment facilities that incorporate certain elements of BSL-3 biocontainment measures.
Undetected or unreported	*Bacillus anthracis*	A lab worker used an incorrect disinfectant; failed to wear disposable gloves; and failed to cover a pre-existing skin defect (facial cut from shaving) (Centers for Disease Control and Prevention 2002).	Cutaneous anthrax resulted following skin exposure to a contaminated surface.	Patient was successfully treated using antibiotics. CDC reviewed proper biosafety measures with laboratory personnel.
Undetected or unreported	*Burkholderia mallei*	A research microbiologist routinely failed to wear disposable gloves, and became infected. A primary care physician prescribed antibiotics without knowledge of the specific etiology (Srinivasan et al. 2001; Centers for Disease and Prevention 2000).	The patient improved but relapsed to a life- threatening condition. Culture revealed specific etiology and appropriate antibiotics resulted in cure.	A review of laboratory procedures was conducted but no further information is available.
Undetected or unreported	*Mycobacterium tuberculosis*	PPD skin test conversion was noted for a laboratory technician (Johnson 2009).	Source of infection suspected to be from samples sent by outside laboratories. Samples were to have been inactivated prior to receipt, but validation was uncertain.	Policies and SOPs for sampling handling were revised to assume that samples could be infectious. HVAC systems were upgraded. Air flow alarms were added to BSCs. Aerosol-containment centrifuge was added.
Undetected or unreported	*Chlamydia trachomatis*	Researcher was diagnosed with a lung infection soon after working with the pathogen (Johnson 2009).	Policies and SOPs for safe handling of the pathogen were found to be inadequate.	New requirements for PPE (respiratory protection), use of a BSC to open centrifuge rotors/buckets, and correct use of BSC were instituted.
Undetected or unreported	*Mycobacterium tuberculosis*	A retrospective survey was sent to 56 state and territorial public health laboratories to determine, by skin tests results, the frequency of probable laboratory-acquired tuberculosis.	Seven laboratory workers were determined to have laboratory-acquired infections (Kao et al. 1997).	CDC guidelines for preventing LAI tuberculosis, and recommendations for regular skin testing of laboratory employees, were re-emphasized.
Undetected or unreported	*Brucella melitensis*	A laboratory worker thawed a frozen vial of bacterial suspension and inoculated a plate culture on the open bench top instead of within a BSC (Staszkiewicz et al. 1991)	Eight laboratory workers became infected, one being asymptomatic. The outbreak was most consistent with airborne spread.	The 7 symptomatic workers were given antibiotic therapy. One relapsed and required alternative therapy. Enhancements to laboratory SOPs were recommended by the Department of Epidemiology and the Infectious Diseases Division.
Undetected or unreported	*Mycobacterium tuberculosis*	Three researchers became skin-test positive for tuberculosis after using a newly acquired aerosolization chamber for experimental infection of animals (Washington Department of Labor and Industries 2004).	Infections were sub- clinical. Prophylactic treatment typically is employed in such cases	Investigation revealed multiple faulty seals in the device, and researchers were not fully familiar with proper operation of the device.
Uncertain soure of infection	Venezuelan equine encephalitis virus.	A laboratory worker was found to have a high rise in anti-VEE virus titer. No occupational exposure was confirmed (Subcommittee on Oversight and Investigations 2007).	APHIS/CDC form 3 (Report of Theft, Loss, or Release of Select Agents and Toxins) was filed.	No further information available
Undetected or unreported	H1N1 influenza A virus (swine)	Two people, working in separate ABSL-3 rooms, each became symptomatic and were diagnosed with influenza 1.5 days after collecting nasal specimens from experimentally infected pigs (Wentworth et al. 1997).	Genetic analyses determined the workers had become infected with the same virus used to infect the pigs.	Investigation determined that an incorrect mask had been supplied to the workers for 1 day, and it is possible this error facilitated infection of personnel.
Uncertain whether detected or not	Various pathogens: U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland	A retrospective review of institute records showed that 67 people were evaluated for likely or highly likely exposure to infectious agents (Rusnak, Kortepeter, et al. 2004)	3 LAI from BSL-3 pathogens were confirmed in 3 cases: (Chikungunya virus, Venezuelan equine encephalitis virus, and *Coxiella burnetii*); LAI was likely in a 4th case (*Yersinia pestis*); post-flooding contamination of a lab with *B. anthracis* was detected.	NA (retrospective review)
Undetected or unreported	*Francisella tularensis*	A USAMRIID military scientist was reported to have been diagnosed with tularemia, as a result of her work with *F. tularensis* (USAMRIID United States Army Medical Research Institute of Infectious Diseases 2009, 2009; Bhattacharjee 2009).	Oral antibiotics were started on an outpatient basis, followed by inpatient administration of intravenous antibiotics. Recovery was expected	No further information available

Table 1. Excerpts from Table D-7 from the Supplemental Final Environmental Impact Report

For the 118 reported incidents in Table 1, 19 involved LAIs in laboratory personnel, some incidents with multiple infected persons. These 19 are shown in the table. In my reading of the table descriptions, 15 of the 19 incidents involved undetected and unreported LAIs, where presumably the infected persons left the lab and entered the community before they were later diagnosed with infection; that is, the pathogen escaped the laboratory. *This is contrary to Gryphon's claim that most exposures would be detected, the infected persons would be quarantined until found to be not infected or until the infection cleared.*

A direct estimate of the probability that an LAI is undetected or unreported, p_{uu}, from these data would be 15/19= 79%. A very cautious matHPAI research lab might quarantine those who thought that they *may have been* exposed. For calculation purposes, p_{uu} = 0.20 or 20% will be used. This may be a generous reduction, as laboratory management and researchers may be reluctant to be quarantined based only on a thought.

Backing up on the flow chart to p_{LAI}, of the 118 reported incidents 17 resulted in LAIs. Taking into account that some incidents involve more than one LAI, the total number of LAIs was 38 (red-highlighted in Table 1). No fatalities were reported, which likely would not be the case with matHPAI. Thus, the probability or rate of LAIs per incident is p_{LAI} = 38/118 = 0.32 or 32%.

The probability values are summarized in Table 2, along with their source and rationale for values used in the analysis.

Parameter Symbol Value Used in Analysis	Definition	Direct Estimate & Source	Rationale for Value Used in Analysis
p_{inc} = 0.2 or 20%	probability there is a reportable incident	likely that every lab would experience some incident each year (e.g. a spill with or without a potential exposure)	assumes, conservatively, one incident every five years, years = 1/0.2 per lab
p_e = 0.02 or 2%	probability a lab worker is exposed in incident	probability is 2% according to Rocco Casagrande comment	2% value used in the analysis implies one exposure every 50 years = 1/0.02
p_{LAI} = 0.32 or 32%	rate of LAIs per incident	118 reported incidents with 38 total LAIs; 38/118 rate or LAIs per incident	32% value used in the analysis
p_{uu} = 0.2 or 20%	probability that an LAI is undetected or unrported	from the LAI data 15 of 19 LAIs were undetected or unreported (uu), implies p_{uu} = 15/19 = 79%	cautious lab might quarantine those *who thought* they may have been exposed, so p_{uu} reduced from 79% to 20%
p_{rem} = ?	probability that an matHPAI is purposely removed from the laboratory	difficult to obtain	not used in the analysis
$p2_{LAI}$ = ?	probability that removed matHPAI will result in an LAI	different from and greater than p_{LAI}	not used in the analysis

Table 2. Summary of probabilities used in the analysis.
(http://osp.od.nih.gov/office-biotechnology-activities/biosafety/institutional-biosafety-committees/incident-reporting)

Although not a large data set, there is enough data here to carry out a preliminary estimate of the likelihood or probability of escape from a lab, L_{esc}.

$$L_{esc} = p_{inc} \times p_e \times p_{LAI} \times p_{uu} = 0.2 \times 0.02 \times 0.32 \times 0.2 = 0.000256 \text{ or } 0.025\%$$

In addition, the 0.025% does not include escapes from purposeful removal from a laboratory. For purposeful removal, probability data might be obtainable from a larger number of incident reports than those collected for Table 1. There is one example of purposeful removal in Table 1, and we know of several more from past human errors and for recent human errors at the CDC and Dugway.

The flow chart and the analysis here should identify explicitly those probabilities where more data might be sought. Even though the probabilities can be made better with more data, those used in the analysis here are likely good enough to provide a fair estimate for the absolute probability of laboratory escape and subsequently the likelihood of a pandemic.

It has been argued that labs working with matPAI are designed to be safer mechanically than other BSL3 and BSL3+ labs. I agree. But human errors dominate. Table D-7 in the SFEIR risk assessment bears this out:

- 82 likely human errors
- 19 likely mechanical or equipment failures
- 3 non applicable incidents
- 14 incidents where it was unclear if human error was involved.

So of the 118 incidents, 82 errors or 69% are human errors, not mechanical or equipment failure. In the bulleted list, I say likely because in a few of the incidents, the descriptions are not clear enough to classify them definitely. Nevertheless, my conclusion holds that many more incidents involve human error than mechanical or equipment failure. Comments in the Gryphon RBA also agree that human errors dominate.

In many of the 118 incidents reported in Table D-7, for example needle sticks, animal bites and other clearly direct exposures "no further information was available." These are not shown in Table 1, but some may have resulted in LAIs. Most pathogens were not highly contagious or deadly and easily treatable, so I expect the worker could go home.

All that remains is to determine the likelihood of a pandemic from a lab escape from an LAI in the community. For this probability, I consulted Figure 4 in the Lipsitch *et al.* (2003) paper (http://science.sciencemag.org/content/sci/300/5627/1966.full.pdf). The figure is reproduced below for convenience to the reader.

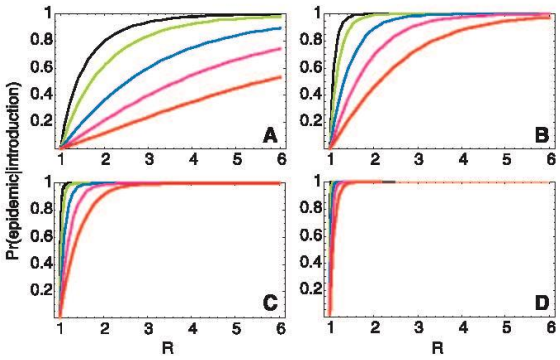

Fig. 4. The probability of an outbreak of SARS in a susceptible population for a range of values of *R*, approximated by the probability of nonextinction of a branching process (*22*) in which the number of secondary cases is given by a negative binomial distribution with a mean of *R* and a variance-to-mean ratio ranging from 1 (for which the negative binomial reduces to the Poisson distribution) to 20 [from left to right: 1 (black), 2 (green), 4 (blue), 10 (magenta), 20 (red)] after the introduction of (**A**) a single infectious case, (**B**) 5 infectious cases, (**C**) 20 infectious cases, and (**D**) 100 infectious cases.

The graphs were generated using branching theory, a pure mathematical construct, which requires only two parameters, the mean R_0 (the reproductive number or the average number of people an infected person infects) and the variance to mean ratio k, which measures the variation in number of people each infected person infects. For instance, some people infected with SARS will infect many other people (super spreaders) and others will infect no one; this implies SARS has a large variance to mean ratio k. I assume for mtHPAI, the subject of this analysis, k will be smaller, perhaps 1 to 2.

Estimating $R_0 = 2$ and k = 2 and a single LAI, the probability of a pandemic, p_{pan}, is about 50% from the green curve in Figure 4a. For more than one LAI entering the community, the probability rises steeply (e.g, Figure 4B for 5LAIs).

Gryphon claims that the probability would not be so high because of public-health efforts to mitigate the spread of community infections. Those of us who watched the 2009 H1N1 pandemic unfold know that such mitigation efforts are likely futile for fast spreading pandemic influenza viruses.

Thus the likelihood or probability of a pandemic for path (1) is estimated to be

$$L1_{pan} = L1_{esc} \times p_{pan} = 000256 \times 0.5 = 0.000128$$

This is the likelihood for a single lab for a single year.

Fatality burden for a single lab in a single year

Assuming the number of fatalities is 4 million, one-tenth of those from the 1918 pandemic flu, the fatality burden for a single lab in a single year is

Fatality burden = 0.000128 x 4 million = 512 fatalities

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 512 fatalities per year.

It should be noted this fatality burden is considerably more than that calculated by me based largely on Gryphon's numbers in my commentary for the January 2016 NSABB meeting. In that calculation, I questioned that their pandemic likelihood was 50% too low, because of an additional 2% probability of unknown origin in the Gryphon analysis. I argue that my calculation using the probabilities estimated here is closer to the true probability of escape. I welcome a response from Gryphon to see if we can reconcile our differences.

For a research enterprise of ten labs conducting this research for ten years, the likelihood of a pandemic is about 100-times greater or 1.28%. I find it very worrisome that laboratory research which could spawn 4 million fatalities has a 1.28% chance of happening in the near future. The assumptions in this analysis are conservative; one reason being that labs in other parts of the world may be much less safe than labs in developed nations.

This live virus research is just too risky to carry out, especially since other means of identifying mutations that lead to airborne transmission in mammals are available. Thus, there is very little to be lost by banning this live virus research.

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[1] "Absolute probability" is the term used by Gryphon Scientific in its risk-benefit analysis (RBA). It seems like a contradiction in terms, since "probability" implies uncertainly, not something absolute. I prefer "direct" probability as it implies leading directly toward a goal. Nevertheless, I will stick with the Gryphon term throughout this analysis.

[2] Each variable p with a subscript is a conditional probability of the event in the chain leading to an accident, given that the previous event in the chain occurred, with two exceptions. p_{inc} is an annual probability (effectively a rate) that an incident occurs. p_{LAI} is a ratio of LAI to exposure, taking into account multiple LAIs in the same exposure event.

[3] Many incidents that must be reported to the NIH involve spills that did not lead to LAIs. The NIH reporting guidelines state "spills or accidents occurring in high containment (BL3 or BL4) laboratories resulting in an overt or potential exposure must be immediately reported." (http://osp.od.nih.gov/office-biotechnology-activities/biosafety/institutional-biosafety-committees/incident-reporting) Potential exposures imply loss of containment to me.