The risk of lab-created potential pandemic influenza

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Abstract

In 2017, considerable new data became available that calls for a new calculation of the risk of release into the community of lab-created potential pandemic pathogens.

This study focuses mainly on lab-created avian-influenza viruses that have been modified to be transmissible in mammals through the air. These are the most worrisome potential pandemic pathogens because a highly transmissible strain released from a lab into the community could seed a pandemic with substantial worldwide fatalities.

There are at least fourteen facilities worldwide that have created such viruses, here dubbed the "Research Enterprise." It is calculated that there is about a 15.8% probability of a release into the community from the Research Enterprise for five years of research. Combining the likelihood of community release with the estimated not-insignificant probability of 5% to 40% such a virus could seed a pandemic if the released virus is highly transmissible in humans, we have an alarming situation with a real risk to human lives.

Those who support this research either believe the probability of community release is infinitesimal, or the benefits in preventing a pandemic are great enough to justify the risk. In the author's opinion, it would take extraordinary benefits and significant risk reduction via extraordinary biosafety measures to correct such a massive overbalance of highly uncertain benefits to potential risks.

No one can be sure how virulent or airborne transmissible in humans these potential pandemic viruses would be if released into the community. In the best-case scenario, they would soon die out with little to no sickness and no deaths; however, just the possibility of a pandemic dictates that we must proceed with the utmost caution. Put another way; the Precautionary Principle should apply.

The strategy in the analysis is to calculate the probability of release into the community from the Research Enterprise and subsequently to calculate the probability of a pandemic using, wherever possible, conservative numbers in the calculations so as not to exaggerate the risk.

Introduction

The 2011 announcements of the creation of live H5N1 avian viruses transmissible in mammals through the air (matH5N1) in two laboratories[1, 2] began the debate over whether this research is too dangerous to conduct. This debate continues today.

Until 2017, there were almost no relevant quantitative data available to calculate the probability of an accidental release into the community; nonetheless, some analyses were carried out with the meager available data. More lab-incident data are needed to quantify the risk. Estimates of the community release probability and the probability that a release sparks a pandemic are important data for discussing international guidelines or regulations for this research.

Past risk analyses

In 2014, Klotz and Sylvester calculated the probability of a community release[3] based on a CDC observation that four undetected or unreported laboratory-acquired infections (uuLAIs) entered the community outside the lab when the lab worker leaves the lab at the end of the workday. These uuLAIs occurred in Federal Select Agent Program (FSAP) labs during the years 2004-2010[4]. The Klotz and Sylvester publication showed that even this small number of releases into the community was large enough to cause significant fatalities if a pandemic occurred.

During the White-House-ordered deliberative process[5], Gryphon Scientific was retained to carry out a "Risk and Benefit Analysis of Gain of Function Research" that included a risk analysis of the pandemic potential for a lab release of a lab-created avian influenza virus[6]. (This author's discussion of the Gryphon report may be found on the Cambridge Working Group website[7].) Gryphon ended up having to guess at the probability of a lab-acquired infection in influenza research laboratories:

> "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... For influenza, 100 labs and an observation period of twenty years (for a total of 2,000 lab-years) was assumed…If the assumption is made that three LAIs have surreptitiously occurred, then an LAI is expected to occur from once every three years to once every 20 years."

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 lab-acquired infections (LAIs). Why might this be the case? If a researcher is infected with seasonal influenza, it might be attributed to a community infection, not from the lab. Furthermore, reporting it as possibly an LAI could lead to time-consuming follow up. While the author has no evidence, it could be an unspoken policy in seasonal influenza research labs to not report infections of uncertain origin given that the infected person will be well in a week. It is difficult to believe that there were no LAIs from these highly contagious, airborne-transmissible viruses in 100 mostly BSL2 labs in 20 years, especially since they should cause LAIs more frequently as BSL2 researchers usually do not use respirators or HEPA face masks.

In opposition to the analysis and opinions expressed here are the arguments of Fouchier[8, 9], where he suggests that his enhanced BSL3 lab (BSL3+) is at least ten-fold safer than a typical BSL3 lab from which almost all release data in this analysis are obtained.

This analysis aims to show that the probabilities of the release of a mammalian-airborne-transmissible highly-pathogenic avian influenza (matHPAI) and a subsequent pandemic could be

high enough to cause significant fatalities even for influenza viruses of moderate case-fatality rates. The main reason for significant fatalities is that a pandemic virus can spread throughout the world, exposing more than 7 billion people.

Case-fatality rates from infections with H5N1 and H7N9 viruses

The H5N1 avian flu virus has killed nearly 53 percent[10] of humans diagnosed with infection (455 fatalities in 861 cases between 2003 and mid-2019) from contact with poultry, but it is rarely transmissible among humans[11]. Over the last year or so, human H5N1 fatalities have almost disappeared[12], but it is not known if this will continue. However, there remains a concern over a release into the community of the older lab-created mammalian-airborne-transmissible highly pathogenic H5N1 strains still retained in laboratories.

As of October 2018, there have been 1,567 laboratory-confirmed human cases and 615 deaths (39% fatality rate) from H7N9 infections since March 2013, when the strain was first detected in people.[13] There are also many fewer H7N9 infections in chickens at present compared to the recent past, which is likely due to a successful chicken vaccination program in China[14].

Results of the analysis

Estimating the number of entities in the Research Enterprise

The number of entities (facilities) with laboratories creating and conducting research on matHPAI must be estimated to quantify the potential risk to the community. Here, the words "entity" and "facility" have the same meaning. They are the words used by the Federal Select Agent Program (FSAP). Each entity may have several high-containment laboratories. It is an entity official, not laboratory principal investigators, who report incidents to the FSAP and NIH. One entity official might have all the institution's labs he/she is responsible for; and a PI, who reports to the entity official, might be responsible for only one lab. It is useful to know the credentials of entity officials who report incidents.

The greater the number of entities in the Research Enterprise, the greater the risk of release into the community from at least one member of the Enterprise; and subsequently, the greater the risk that the release seeds an outbreak or pandemic. A minimum estimate of the number of entities is all that is needed to make the argument that a release from at least one lab in the Research Enterprise is too likely.

Here, Research of Highest Concern (RoHC) is defined as lab-creation of or subsequent research with mammalian-airborne-transmissible (mat) highly pathogenic avian influenza viruses (HPAI), in particular, matH5N1 and matH7N9. RoHC also includes a few human pandemic viruses.

The PubMed search included avian influenza viruses other than matH5N1 and matH7N9 that have caused (occasional) infections in humans. If they are made mammalian-airborne-transmissible, they could be considerably more dangerous. The employed search terms along with the number of PubMed abstracts found (in parentheses) were: mammalian transmissible HPAI (9), mammalian transmissible H5N1 (95), mammalian transmissible H7N9 (63), mutagenesis 1918 H1N1 (24), mutagenesis 1957 H2N2 (4), mammalian transmissible H5N6 (3),

mammalian transmissible H10N8 (2), reassortant HPAI (68), recombination HPAI mammals, (33), reassortant HPAI mammals (43), mammal transmissible avian influenza (123), reverse genetics H5N1 mammalian transmissible (5), and reverse genetics H7N9 mammalian transmissible (3).

Many of the PubMed abstracts appeared more than once, so extra copies were deleted. The remaining abstracts were quickly scanned to delete the irrelevant ones. The remaining Abstracts were read; and for each, the full publications were downloaded, and relevant text read to verify that the research was indeed research that created or researched the mammalian airborne transmissible avian influenza viruses of interest and the few lab-created human pandemic viruses of interest.

The findings from the PubMed search are presented in an unpublished paper posted on the Center for Arms Control and Non-Proliferation website[15]. The key finding is that the search found fourteen Research Enterprise entities, the number to be used in the calculations here.

The PubMed search should have identified most publications but could miss a few. What might be missed?

- Unpublished research.
- Research missed by the employed search terms.
- Publications in languages other than English may not always be listed in PubMed, in particular, some Chinese and other Asian research. Asia is the source of most human fatalities from H5N1 and H7N9 avian influenza infections, so much of the recent research seems to be carried out there.

The weeks of extra effort to identify more Research Enterprise entities is not necessary as the illustrative calculations presented here will show the risk of a pandemic already to be intolerably high in an Enterprise with as few as fourteen entities. Thus, the fourteen entities used in subsequent calculations are conservative.

The focus is the recent past from 2012 as an indicator of the present and future Research Enterprise. There are publications of concern from years before 2012; however, the focus of many of us has changed since the 2011 revelations about creating matH5N1. With this new focus in mind, pre-2012 research is not discussed.

<u>The probability of a uuLAI from the Research Enterprise</u>

uuLAIs are a main source of release of pathogens into the community. For estimating the probability of community-release, the present analysis utilizes the Federal Select Agent Program (FSAP) summary incident reports for the years 2004-2017 made publicly available in 2017. Specifically, the data is from the FSAP yearly reports to Congress and more recently from their annual reports. None of the reported laboratory-acquired infections (an example of confirmed releases in FSAP terminology) were influenza viruses. Almost no influenza viruses are Select Agents, so it is not surprising that there are no data on laboratory-acquired infections of influenza viruses.

The analysis also uses full incident reports for the years 2004-2017 obtained from the NIH Office of Science Policy through the author's 2017 FOIA request. The analysis provides other

data and calculations necessary to make illustrative pandemic risk calculations and to support the analysis.

Analysis of FSAP/CDC Reports to Congress

The official name of the summary reports is "The Department of Agriculture and the Department of Health and Human Services Report to Congress on Thefts, Losses, or Releases of Select Agents or Toxins."[16] The reports covered the years 2003 through 2015 and were provided to The Black Vault by the CDC under the Freedom of Information Act (FOIA). The Black Vault is a non-government clearing-house for FOIA documents. The years 2015, 2016 and 2017 are the Annual Reports[17] of the Federal Select Agent Program.

Some definitions require discussion. In FSAP language, a "release" is defined as "a discharge of a select agent or toxin outside the primary containment barrier due to a failure in the containment system, an accidental spill, occupational exposure, or a theft. Any incident that results in the activation of a post exposure medical surveillance/prophylaxis protocol should be reported as a release."[18] In the FSAP reports to Congress, a "confirmed release" is defined by the following FSAP quote; "For human select agents, in this context, confirmed [release of a select agent] means that an exposure occurred that resulted in occupational illness."[19] A confirmed release is called an LAI in the terminology here. Only some LAIs are uuLAIs (see Table 1). uuLAIs represent release into the community, which differs from the FSAP definition of a release. In this analysis, "release" always means a release into the community.

Both the FSAP reports to Congress and the FSAP Annual Reports provide only brief descriptions of LAIs and no explicit discussion of which LAIs are uuLAIs leading to releases into the community. A FOIA request for the actual incident reports was denied, citing confidentiality. Thus, whether an LAI is indeed an uuLAI must be inferred from the brief FSAP descriptions. The FSAP descriptions and this author's italicized comments on the descriptions are presented in PART 1 of the Supplementary Material. As indicated in the author's comments, a few FSAP descriptions are not clear enough to decide whether those LAIs can be classified as uuLAIs. The Supplementary Material is appended at the end of this analysis.

A summary of the FSAP LAI data is presented in Table 1.

Year	No. Registered Entities	Is confirmed release a BSL3 uuLAI?	How many infected?	Pathogens Involved and likely risk-group
2003-2006	241.3	no		Newcastle disease virus, RG2
2003-2006		no		Newcastle disease virus, RG2
2003-2006		yes	3	*Francisella tularensis, RG3*
2003-2006		maybe	1	*Brucella melitensis, RG3*
2003-2006		yes	1	*Brucella melitensis, RG3*
2007	283	yes	1	*Brucella melitensis, RG3*
2008	279	not relevant		*Brucella sp, RG3*
2008		yes	1	*Brucella melitensis, RG3*
2009	285	no		*Francisella tularensis, RG3*
2010	285	maybe	1	*Brucella suis, RG3*
		maybe	1	*Brucella suis, RG3*
		not relevant		Classical Swine Fever virus, RG unk
2011	285	no		*Francisella tularensis, RG3*
2012	285	no		no reported confirmed releases
2013	285	maybe	1	*Burkholderia pseudomallei, RG3*
		no		*Brucella mellitensis, RG3*
2014	285	no		*Coxiella burnetii, RG2, RG3*
		yes	1	*Coxiella burnetii, RG2, RG3*
2015	291	yes	2	*Coxiella burnetii, RG2, RG3*
		yes	1	*Brucella abortus, RG3*
2016	276	no		no reported confirmed releases
2017	263	no		no reported confirmed releases

Table 1. Summary of FSAP data on confirmed releases (LAIs) from registered laboratories for the years 2003 through 2017. In FSAP terminology, a laboratory-acquired infection is an example of a confirmed release. See PART 1 in the Supplementary Material for reasons why confirmed releases are classified as "yes" (for an uuLAI)[20], or "maybe" (where the confirmed releases may or may not be an uuLAI). The three *F. tularensis* uuLAIs in 2004 were researched in a BSL2 laboratory but should have been researched in BSL3, so are counted as a "yes" in Table 1. A fully annotated version of this table is found in PART 2 of the Supplementary Material.

The key number to be calculated from Table 1 is the probability, p_1, of a community release through a uuLAI per entity per year for a single entity (entity-years). From p_1, it is a simple matter to find the probability p_{NY}, the probability of at least one community release from N Research Enterprise labs in Y years (see below).

The most conservative calculation assumes the number of uuLAIs is the number of "yes" entries in Table 1, which is 10. The total number of entity-years for the years 2003 through 2017 is the sum of the No. Registered Entity column in Table 1, which is EY=4,067. (Approximate total number of entities for the years 2003 through 2006 is estimated to be 4x241.3=965. The total number of entities for the years 2007 thru 2017 is 3,102. Thus, the total number of entities for the years 2003 thru 2017 entity-years is estimated to be 965+3,102=4,067.) Then,

p_1=uuLAI/EY=10/4,067=0.00246 or 0.246% per entity-year.

The less conservative calculation assumes the number of uuLAI is the number of "yes" entries plus the number of "maybe" entries in Table 1, which is 14. Then,

p_1=14/4,067=0.00344 or 0.344%.

From most conservative to less conservative, the calculation of p_1 from the FSAP data falls in a small range. The conservative value $p_1 = 0.00246$ from the FSAP data will be used in subsequent calculations.

An aside on determining entity-years conservatively

One reader observed that the entity-years (EY) number used above in the denominator of the p_1 equation is too large because some entities might not be working on particular pathogens at all times throughout the year. While that observation is correct, it doesn't affect the goal in this analysis of employing conservative numbers in calculations. It is assumed in the above calculation of p_1 that all entities were working on pathogens throughout the whole year, thereby maximizing the number of entity-years and conservatively decreasing p_1. Furthermore, how could any outside observer determine the fraction of the year a lab was working on particular pathogens?

Analysis of FOIA-obtained incidents reported to the NIH Office of Science Policy

The incident reports from the author's FOIA request to the NIH Office of Science Policy cover the period from 2004 through 2017 and are for BSL3 and BSL4 laboratories, not BSL2. (The analysis is based on 187 total FOIA reports delivered in three batches: December 2017, July 2018, and February 2019.) The reports provide extremely detailed descriptions of incidents from the entities.

There were 13 uuLAIs from 187 incident reports over that period. Descriptions of the uuLAIs are presented in PART 3 of the Supplementary Material.

Next, the number of entity-years for the denominator of p_1 must be determined. To estimate the number of entity-years (EY) from the NIH data, one assumption is that once an entity files its first incident report, it will report all future incidents as required by NIH. Here are two examples of calculating entity years from this assumption:

(1) Suppose entity 1 first reported an incident in 2010. Thus, through 2017 EY(1)=2017-2010+1=8 entity-years.
(2) Another entity 2 first reported an incident in 2014, so EY(2)=2017-2014+1=4 entity-years.

For the two entities, EY=8+4=12 entity-years. In total, there have been 58 different entities that have reported incidents in BSL3 or BSL4 laboratories over the years. Summing the EY values over those 58 entities gives a total of 458.3 entity-years. Windows metafile images of the spreadsheet used to calculate total entity-years for all entities are presented in PART 4 of the Supplementary Material. The spreadsheet images also contain additional information on all 187 reported incidents. The probability of a uuLAI per entity-year, p_1=uuLAI/EY=13/458.3=0.0284 or 2.84% uuLAIs per entity per year.

Toward a too conservative estimate of p_1: If we assume that each of the 58 BSL3 entities has been researching the BSL3 pathogens since 2004, the total entity-years would be EY = 58 x (2017-2004+1) = 812 entity-years. Further, assuming that they had no uuLAIs over their earlier non-reporting years, then $p_1 = 13/812 = 0.016$ or 1.6% over the years 2004 through 2017. The range for p_1 is 1.6% to 2.8% per facility-year. Both numbers may be conservative because of the assumption that the labs were working on the pathogens throughout the whole year (see above).

This range is about 5-times to 10-times greater than the p_1 values found from the FSAP data. How can that be? While there is no obvious reason in the data that would explain this large difference, some possibilities come to mind:

(1) Perhaps laboratory workers working with less virulent BSL3 pathogens become infected more easily as they are not as cautious as they should be. The recombinant DNA in some of the NIH incident reports is designed to make the pathogens less virulent.

(2) Of the thirteen uuLAIs, four were exposure and subsequent latent infection with *M. tuberculosis*, but no active infections. Tuberculosis is highly contagious by the airborne route, so it might be easier to acquire a TB infection in the lab. Some individuals have TB infections but show no symptoms, that is, latent or dormant TB [21]. Unfortunately, TB infections in the NIH data might be an indicator of what could occur in research on other airborne-transmissible pathogens like matHPAI compared to pathogens that infect by other means. *M. tuberculosis* is not a select agent, so incidents are not reported to FSAP.

(3) Since some FSAP enforcement is conducted by the FBI, there may be more diligent biosafety practices for labs that research select agents. Of the NIH-reported incidents, only two incidents (with four uuLAIs) were select agents so were also reported to FSAP. Nine were reported only to NIH.

The reasons for the large difference between p_1 for the FSAP and NIH data remains a mystery. But the high p_1 value from the NIH incident reports is real, so must be kept in mind although not used in risk calculations here. Only the much more conservative FSAP data value for p_1 will be used.

Human error is the main cause of laboratory incidents

A major route to release into the community are laboratory incidents that result in uuLAIs. A big source of laboratory incidents is human error[22], which can only be limited, not eliminated, by careful laboratory design. Depending on the data source, the percentage of incidents due to human error is 72.7% (NIH) and 79.3% (FSAP). How these percentages were determined is presented in PART 5 of the Supplementary Material.

In a 2015 publication[23], Fouchier describes the careful design of his BSL3+ laboratory in Rotterdam and its standard operating procedures, which he contends should increase biosafety and reduce human error. Most of Fouchier's discussion, however, addresses mechanical systems in the laboratory. Given the many ways by which human error can occur,[24] it is doubtful that Fouchier's human-error-prevention measures can eliminate the release of airborne-transmissible avian flu into the community through uuLAIs.

In defense of surrogate data

A key observation is that human error is mostly independent of pathogen type and biosafety level. Said another way, human errors leading to uuLAIs could occur at a similar rate in select agent laboratories and laboratories working on matHPAI. Determining the likelihood of release from laboratories researching less virulent or transmissible pathogens, therefore, can serve as a reasonable surrogate for potential pandemic pathogens. We are forced to deal with surrogate data

because there are little data on the release of potentially pandemic pathogens. In particular, surrogate data allows us to determine with some confidence the probability of release of a potential pandemic pathogen into the community through uuLAIs.

Arguments that support the use of surrogate data are:

(1) Human error is the cause of most laboratory incidents.

(2) PART 3 of the Supplementary Material describes the 13 uuLAIs from the FOIA NIH incident reports: Reports #2 (3uuLAIs), #30 (1 uuLAI), #109 (1 uuLAI) describe five uuLAIs that were caused by human error. For the other eight uuLAIs where active infections developed or antibody titers indicated a past infection, the incident leading to the infections could not be identified. All that entity officials could say was the infection likely occurred in the lab. The five identified uuLAIs where the cause is known are a small data set but support the use of surrogate data.

(3) Many reported incidents in BSL3 labs are "one-off" meaning that they are almost impossible to predict in advance, so labs working on lab-created matHPAI would unlikely be able to train for them in advance, and new SOPs could not be designed to prevent them. Many examples of "one-off" human errors are presented in PART 5 of the Supplementary Material.

(4) Many non-human-error incidents involve defective labware such as centrifuge tubes that leak in use and defective flasks used in shakers. The defects perhaps cannot be seen with naked-eye inspections. Defective labware incidents would occur with similar frequencies in both BSL3 and BSL3+ labs.

Using surrogate data to determine the numbers of uuLAIs is not a conservative assumption for calculating p_1= uuLAI/EY for BSL3+ labs working with matHPAI. However, it could be close to being accurate, perhaps within a factor of two. Couple this with the observation that EY may be too large, the value for p_1 could be representative of BSL3+ labs. It is the author's opinion that using surrogate p_1 values are reasonable for illustrative calculations of risk.

Furthermore, employing Fouchier's "guesstimate" that his BSL3+ lab is ten-fold safer (p_1 is ten-fold less) still does not ease our concern over the risk of this research especially when likelihood-weighted risk is used to measure potential fatalities. See below for a discussion and calculations of likelihood-weighted risk.

Size of FSAP and NIH data sets

FSAP and NIH data sets are large enough to determine the probability of a lab release with precision high enough for illustrative risk calculations. The following 95% confidence limit table illustrates this point.

		Required β						
		10%	25%	50%	60%	75%	100%	200%
	$N_{obs:}$	400	64	16	11	7.1	4	1

Table 2. The size of the data set, N_{obs}, necessary to have 95% confidence that N_{obs} is within β-percent of N_a. N_{obs} is the number of observed uuLAIs, and N_a is the expected average number of uuLAIs. The mathematical analysis of confidence limits for the Poisson distribution is presented in PART 6 of Supplementary Material.

We do not need high precision to make the case that the release risk is too high. Precision within 60% of the real value is sufficient. The surprising result here is that if we want to be 95% confident that N_{obs} = the observed number of uuLAIs is within 60% of the actual number of uuLAIs, we need only a small data set of 11 events. Both the FSAP data set (N_{obs} = 10 uuLAIs) and the NIH data set (N_{obs} = 13 uuLAIs) are clearly large enough to come close to actual values.

Calculation of probability of community release from the Research Enterprise

The probability of at least one community release from an uuLAI for N Enterprise entities in Y years is

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

As found before, the probability of a community release from a single Enterprise entity in a single year is p_1=0.00246 to 0.00344 from the FSAP data. The number of entities, N, in the Research Enterprise is at least fourteen.

Some illustrative calculations are presented in Table 3.

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

N = 14 (number of Enterprise entities)

Data Source	p_1	Y=years 1	2	5	10
FSAP	0.00246	0.0339	0.0666	0.1584	0.2917
FSAP	0.00344	0.0471	0.0920	0.2143	0.3827
NIH	0.01600	0.2021	0.3634	0.6767	0.8955
NIH	0.02840	0.3319	0.5537	0.8669	0.9823
Fouchier (FSAP min/10)	0.00025	0.0034	0.0069	0.0171	0.0339

Table 3. The body of the table is probability, p_{NY}, of at least one community release from an uuLAI for a Research Enterprise of N=14 entities for various values of the probability of release for a single entity in a single year, p_1, and for various years, Y, of research.

The Fouchier row-entries are from his guess that his BSL3+ laboratory is at a minimum ten-times safer than the average BSL3 lab researching surrogate data. Then, for the Fouchier entry, p_1=0.000246 was used for the calculation of P_{NY}.

Taking the conservative estimate p_1=0.00246, the probability of at least one community release from an Enterprise entity is p_{NY}=0.1584 or 16% in five years of research, the author's estimate of the typical length of a research project. This likelihood of a release is uncomfortably high.

The Fouchier guess of 10-fold minimum reduction for p_1 may be a reasonable guess for mechanical failure, but it is likely too large a reduction when human error is considered. Thus, the p_{NY}=0.0171 or 1.7% is likely much too conservative but still uncomfortably high given the possible millions of fatalities from a lab release.

Probability of a lab-created pandemic

The next step is to provide an illustration of the probability of a pandemic from a release into the community from a uuLAI using a typical reproductive number for a pandemic influenza. For this probability, Figure 4 graphs in the Lipsitch and coworkers 2003 paper[25] was consulted and reproduced here for the readers convenience.

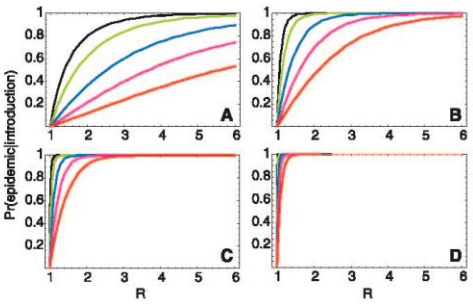

Fig. 4. The probability of an outbreak of SARS in a susceptible population for a range of values of *R*, approximated by the probability of nonextinction of a branching process (22) in which the number of secondary cases is given by a negative binomial distribution with a mean of *R* and a variance-to-mean 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.

Figure 1. Reproduction of Figure 4 from *Transmission Dynamics and Control of Severe Acute Respiratory Syndrome* in Transmission Dynamics and Control of Severe Acute Respiratory Syndrome.

The graphs were generated using branching theory, a purely mathematical construct, which requires only two parameters, the mean R_0 (the reproductive number; that is, the mean number of people infected by an infected person) and the variance to mean ratio k that measures the variation in R_0.

As an illustration, assume that a lab-created matHPAI is as capable of human-to-human airborne transmission as a historical pandemic strain[26]; that is, R_o ~ 1.5. The probability that a pandemic is seeded from a single release might be as high as 40% (green curve in Figure 4a where the variance to mean ratio k/R_o=1, for R_0=1.5). Or being more conservative by taking k/R_o=10, the probability that a pandemic is seeded from a single release is about 10% (magenta curve in Figure 4a for R_0=1.5).

In a very different approach, where the progress of infection from person to person through the community is simulated, Merler and coworkers[27] found that "that there is a non-negligible probability (5% to 15%) that a pandemic results. The probability is strongly dependent on

reproduction number, probability of developing clinical symptoms, and that the release event is not detected at all".

Even if the reader is uncomfortable with mathematical approaches, observing how the 2009 H1N1 pandemic virus spread quickly throughout the world should convince everyone that it is nearly impossible to stop an influenza pandemic once it appears in the community.

In what follows, an intermediate value of the probability of a pandemic, pan =15%, will be used. Then, the probability that the Enterprise seeds a pandemic in a single year is

$$pan_{14,1}(\text{Enterprise})=0.15\text{x}0.0339=0.0051 \text{ or } 0.51\% \text{ per year},$$

where the 0.0339 probability is from Table 2 for an Enterprise of N=14 entities and Y=1 year.

For Y=5 years, the probability of a pandemic increases to

$$pan_{14,5}(\text{Enterprise}) = 0.15\text{x}0.1584 = 0.0254 \text{ or } 2.5\%,$$

a worryingly high percentage. This is a key analysis result.

One qualifier is that it can't be known how virulent or airborne transmissible in humans a matHPAI virus would be when released into the community because the experiment can't be done. In the best-case scenario, infection would soon die out with little to no sickness and no deaths; however, just the possibility of a pandemic dictates that we must proceed with the utmost caution.

Likelihood-weighted consequences and fatality burden

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 potential pandemic influenza research debate.

Here, only fatalities will be considered as consequences; so, for likelihood-weighted consequences, we substitute the term fatality burden, LWC = FB.

FB = (probability of a release) x (probability of a pandemic) x (number of pandemic fatalities)

$$FB_{NY} = p_{NY} \text{ x pan x } F, \qquad (2)$$

where pan is the probability of a pandemic and F is the number of fatalities for the pandemic.

To calculate the number of fatalities, first note that the human case-fatality rate could be as high as 53%, the rate for the highly pathogenic H5N1 strains used in creating matH5N1. To be conservative, assume that the case-fatality rate is 2%, similar to the 1918 pandemic flu.

The number of fatalities, F, is then

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

$F = 7.7x10^9$ x 0.15 x 0.02 = 23.1 million

where a typical seasonal influenza epidemic infects about 15% of the world's population, and the 1918 pandemic flu had about a 2% case-fatality rate.

Consider three cases: The fatality burden for (1) a single Research Enterprise entity in a single year; (2) a 14-entity Enterprise for a single year; and (3) a 14-entity Enterprise for five years of research. The fatality burdens for the three cases are illustrated in Table 4.

$p_{NY} = 1-(1-p_1)^{NY}$						
$FB_{NY} = p_{NY}$ x pan x F						
		p_1 =	0.0025	(the FSAP minimun value)		
		pan =	0.15			
		F =	2.31E+07			
	N	**Y**		p_{NY}		**FB**
	1	**1**		0.00250		8.7E+03
	14	**1**		0.03444		1.2E+05
	14	**5**		0.16073		5.6E+05

Table 4. Fatality burden for Research Enterprises of either 1 or 14 entities and for 1 or 5 years of research on matHPAI or mctHPAI. The body of the table is fatality burden, FB. N is the number of entities in the Research Enterprise and Y is the number of years the Enterprise is conducting research. F is the number of assumed fatalities.

Each entity in the Research Enterprise must bear the burden of its contribution to potential fatalities. Using the numbers in the top row of Table 4, each year that a single entity conducts research, it carries with it the burden of 8,700 fatalities according to one illustrative calculation.

What if the released virus is no more deadly than a typical seasonal influenza virus? According to the World Health Organization, for a typical seasonal influenza epidemic[28] "Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290,000 to 650,000 respiratory deaths." Using the lower number, F=290,000 fatalities, the fatality burden for a single Enterprise entity in a single year is

FB = p_1 x 0.15 x 290,000 = 0.0025 x 0.15 x 290,000 = 109 fatalities

Fouchier's suggests[29] that his enhanced BSL3 lab (BSL3+) is at least ten-fold safer than a typical BSL3 lab from which most release data are obtained. Fouchier's 10-fold safer lab would yield 870 fatalities. Another illustration, with a much more conservative case-fatality rate, would yield potential fatalities of 10.9 per year for Fouchier's safe lab.

Conclusion

Should we be willing to risk a 2.5% likelihood of a pandemic from the Research Enterprise for five years of research? Other than alerting us that these avian viruses can be made mammalian

airborne transmissible, a useful fact to know, matHPAI creation may yield little practical results in the author's opinion.

Perhaps likelihood-weighted consequences, here expressed as fatality burden, is the best way to think about pandemic risk. To help put fatality burden in perspective, no Institutional Review Board (IRB) tasked with assessing human-subject research would approve a research project with a potential of a hundred to perhaps thousands of fatalities. Perhaps an IRB could approve the research if it could be assured that there will never be a release into the community or that the released virus would neither be airborne-transmissible, virulent, nor fatal. The key phrase is "almost absolute certainty."

Each entity in the Research Enterprise must bear the consequences of its contribution to potential fatalities from a pandemic sparked by a release into the community. Based on a case-fatality rate of 2%, similar to the 1918 influenza pandemic, the fatality burden for a single Enterprise entity for each year it conducts research is 8,700 fatalities. Even if the case-fatality rate is as low as typical seasonal influenza, the fatality burden per entity per year is 109 fatalities. And even if BSL3+labs are 10-fold safer than typical BSL3 labs as Fouchier suggests, the yearly fatality burden is10.9. Every one of these fatality burdens is unacceptable.

In some nations, scientists who do this research may not be subject to proactive oversight and regulation. Even in the U.S., it is unclear if the recently instituted review process is sufficient. The review applies only to NIH-funded experiments and is certainly not transparent.[30] If the right to unfettered experimentation costs lives, that is a high price to pay.

The risk of lab-created potential pandemic influenza

(Supplementary Material)

PART 1

(Lab-acquired infections for registered laboratories
In the FSAP program for years 2003 through 2017)

First, a few definitions: The FSAP defines a "release" as "an occupational exposure or release of a select agent outside of the primary barrier of the biocontainment area." Thus, a release implies a possible exposure, so a lab worker could become infected. A "confirmed release" means that an exposure resulted in occupational illness (laboratory-acquired infection, LAI). In this document, release into the community is the focus. Thus, the reader must be careful to differentiate a "community release" from an uuLAI or other means from the FSAP definitions of "release" and "confirmed release."

The following discussion of seroconversion is modified from FSAP descriptions. Seroconversion is the development of detectable specific antibodies to microorganisms in the blood serum as a result of infection or immunization. Seroconversion itself meets the criteria for confirmed release. A seroconversion to a select agent is quantified as a four-fold rise in antibodies associated with infection from an agent. Seroconversion would signify a release into the community if it was discovered at some date later than the actual infection, for instance during yearly serological screening.

The summaries of confirmed releases in FSAP registered laboratories

CDC/FSAP reports to Congress February 7, 2003, (the effective date of the interim final rule) and December 31, 2006

• There were 5 confirmed reports of releases of a select agent. These releases were identified by illnesses in 7 laboratorians that had occurred as a result of working with these materials.

- Two of these reports involved exposure to Newcastle disease virus (velogenic) and resulted in conjunctivitis.
  [*AUTHOR'S note: Was this an uuLAI, or was the exposure detected in the lab at the time of the incident? Newcastle disease virus was reported to APHIS, not CDC and is a Risk Group 2 agent, so most likely studied at BSL2.*]
- One of these reports involved exposure of 3 laboratorians to a virulent strain of *Francisella tularensis*. This resulted from an error in the identification of the strain, which led the laboratorians to manipulate the strain under Biosafety Level 2 conditions, which in turn failed to protect the workers from possible aerosol exposure.
  [*AUTHOR'S note: From news reports, the three F. tularensis infections were uuLAIs as illness was detected weeks later, so it is an uuLAI.*]

• Two of the reports involved exposure to *Brucella* that resulted in illness. One of these two reports involved an exposure to a virulent *Brucella melitensis* strain in a diagnostic laboratory. As with the *Francisella tularensis* incident, a significant factor in this release was the incorrect identification of the organism. In this case, prior to its identification as *Brucella*, this strain was handled in conditions that did not protect the worker from potential aerosol exposure.
[*AUTHOR'S note: The organism hadn't been identified at the time of the incident implies an uuLAI, but was the research mistakenly conducted at BSL2? Will be designated as a "maybe".*]
The second report involved the exposure of a laboratorian to *Brucella* in a research laboratory in which the exact incident involving the exposure was not determined.
[*AUTHOR'S note: The exact incident involving the exposure was not determined, implies that it is an uuLAI*]
• In all cases, the individuals involved have recovered from their illnesses.

CDC/FSAP reports to Congress 2007

There was one (1) confirmed report of a release of a select agent. This release was identified by an illness in a laboratorian that occurred as a result her working with *Brucella melitensis* under conditions that failed to protect her from an aerosol exposure. This report involved an apparent non-compliance with the Select Agent Regulations and was referred to HHS OIG for further investigation and enforcement.
[*AUTHOR'S note: This confirmed release was identified only when the lab worker became ill, so is a presumed uuLAI.*]

CDC/FSAP reports to Congress 2008

"There were two (2) validated reports of a release of a select agent. One (1) release was identified as a result of a routine annual laboratory test of cattle for *brucellosis*. One (1) cow in an adjacent *brucellosis*-free herd at a facility with ongoing brucellosis research tested positive for *brucellosis* and was destroyed. The report was referred to IES for apparent non-compliance with the Select Agent Regulations and resulted in USDA and HHS suspending the entity's research. In addition, IES imposed a civil money penalty of $425,000. [*AUTHOR'S note: Brucellosis is caused by Brucella sp. Since the release was detected during a routine annual test, it is an uuLAI. It involved an animal (a cow), not humans. Animals will not be included in the statistics for uuLAIs.*]

The other report was identified by an illness in a laboratory worker that occurred as a result of her working with *Brucella melitensis*. This report is still under investigation to confirm the cause of the laboratory worker's illness. No additional cases have been identified in association with this incident.
[*AUTHOR'S note: The cause was not known at the time of the illness, so implies it was an uuLAI*.]

CDC/FSAP reports to Congress 2009

One confirmed release of a select agent or toxin
There was one confirmed report of a release of a select agent. This release resulted in the infection of a laboratory worker with *Francisella tularensis*. The laboratory worker received medical treatment and

has recovered from this infection. [*AUTHOR'S note: Was this an uuLAI, or was the exposure detected in the lab at the time of the incident? To be conservative, assume it was not an uuLAI.*]

CDC/FSAP reports to Congress 2010

There were three (3) confirmed reports of a release of a select agent. These releases resulted in two laboratory workers who were infected with *Brucella suis* in two separate states. Both laboratory workers received medical treatment and both recovered from their illness.
[*AUTHOR'S note: The description indicates that the lab workers became ill in the two separate incidents, indicating that they may be uuLAIs. However, there is not enough information to determine whether the incident was detected in the lab when it occurred. To be conservative, it will be classified as a "maybe."*]

There was one confirmed release of a select agent involving, Classical Swine Fever virus which resulted in clinical illness in two (2) animals. Both animals were euthanized.
[*AUTHOR'S note: It involved two animals, not humans, so will not be included in the statistics for uuLAIs.*]

CDC/FSAP reports to Congress 2011

One (1) confirmed release of a select agent or toxin
There was one (1) confirmed report of a release of a select agent. The release involved a confirmed occupational illness with *Francisella tularensis* that occurred within a privately-owned veterinary clinic, which is an exempted laboratory. The worker in this case made a full recovery and returned to work and there was no evidence of spread beyond this one worker.
[*AUTHOR'S note: Since the incident occurred in an exempted laboratory, not a registered laboratory, it will not be included in the uuLAI statistics. Also, the laboratory is likely BSL2. It is a "no" for statistical purposes here.*]

CDC/FSAP reports to Congress 2012

Zero confirmed releases of a select agent or toxin.

CDC/FSAP reports to Congress 2013

Two confirmed releases of a select agent.
There were two confirmed releases identified by serological testing in 2013. These incidents occurred at two different facilities at different times during the year.
• One case involved an exposure to *Burkholderia pseudomallei*. Exposure to this microorganism was detected prior to the onset of symptoms. This worker was given prophylactic antibiotics to prevent the onset of illness and has returned to work.
[*AUTHOR'S note: If it was routine yearly serological testing, it implies the worker left the facility to enter the community, so it would be an uuLAI. However, since the phrase "prior to the onset of symptoms" may imply that the facility officials knew of the potential exposure when it occurred. It is classified as a "maybe."*]

• The second case involved exposure to *Brucella mellitensis*. While under medical observation after a suspected release event, serological testing detected the presence of antibodies against *B. mellitensis*. Shortly thereafter, symptoms consistent with brucellosis were reported by the worker, and the infection was confirmed by isolation of the microorganism from the patient's blood. Antibiotic therapy was quickly initiated and resulted in the successful recovery of the worker, who has also returned to work.
[*AUTHOR'S note: This was a suspected release event, so this would not be an uuLAI, even if the worker was allowed to leave the laboratory because there was no concern that an infected worker would transmit the infection. It is classified as a "no."*]
• There was no secondary transmission of these infections to other persons identified for either Incident.

CDC/FSAP reports to Congress 2014

Of the 168 reports of releases that met the regulatory criteria for a release, USDA and HHS confirmed that occupational exposure resulted in laboratory-acquired infection in three of them.
Please see below for a description of each incident.
1) Two workers at a veterinary medical teaching hospital (exempt entity) were exposed to *Coxiella burnetii* and became ill with Q fever. USDA and HHS confirmed the release with serological testing. Both workers were treated, made a full recovery, and returned to work with no restrictions. All potentially exposed individuals were notified of the potential exposure. There was no evidence of transmission to other workers.
[*AUTHOR'S note: Exempt, not a registered, entity. Not to be counted as an uuLAI in these statistics.*]

2) A worker at a veterinary diagnostic hospital (registered entity) tested positive for *Coxiella burnetii* by serological testing during the annual screening process. Occupational health professionals monitored the worker for an extended period of time. The worker never demonstrated symptoms for Q fever and continues to perform daily work with no restrictions. All potentially exposed individuals were notified of the potential exposure. There was no evidence of transmission to other workers.
[*AUTHOR'S note: Infection detected during annual serological testing so it is an uuLAI.*]

CDC/FSAP reports to Congress 2015

In CY 2015, two entities submitted reports of seroconversion identified through annual screening in a total of three workers:
1) Two workers at a federal government laboratory demonstrated seroconversion to *Coxiella burnetii* during an annual screening. No laboratory incident or event was identified to explain the seroconversion. These workers conducted other duties outside the laboratory that included working with sheep. It was determined by the occupational health professional working for the facility that there was no evidence of laboratory-acquired illness. Neither worker received therapy for a presumed infection, and both workers remained asymptomatic during the 3-month monitoring period and continue to perform their work without restrictions.
[*AUTHOR'S note: The comment that the occupational health professional working for the facility determined there was no laboratory-acquired illness does not imply that the worker did not become*

infected in the laboratory. Seroconversion indicates exposure to the pathogen in numbers that would elicit an antibody response. This is an uuLAI.]

2) One worker at a university research laboratory demonstrated seroconversion to *Brucella abortus* during an annual screening. No laboratory incident or event was identified to explain the seroconversion.
Occupational health professionals monitored the worker for an additional 4 months. It was determined by the occupational health professional working for the facility that there was no evidence of laboratory-acquired illness. The worker received no therapy for presumed infection and remained asymptomatic during the monitoring period.
[*AUTHOR'S note: Both seroconversion during annual screening and no identified incident implies this incident is an uuLAI*]

CDC/FSAP reports to Congress 2016
[*AUTHOR'S note: No confirmed releases, implies no uuLAI releases into the community*]

CDC/FSAP reports to Congress 2017
[*AUTHOR'S note: No confirmed releases, implies no uuLAI releases into the community*]

PART 2

(Fully annotated version of Table 1 from the main text)

This table provides sources of data and other relevant information on the data.

Year	No. Registered Entities	Is confirmed release a BSL3 uuLAI?	How many infected?	Pathogens Involved and likely risk-group [g]
2003-2006[a,b]	241.3	no		Newcastle disease virus, RG2
2003-2006[a,b]		no		Newcastle disease virus, RG2
2003-2006[a,b]		yes[h]	3	*Francisella tularensis, RG3*
2003-2006[a,b]		maybe[i]	1	*Brucella melitensis, RG3*
2003-2006[a,b]		yes[j]	1	*Brucella melitensis, RG3*
2007[b]	283	yes[k]	1	*Brucella melitensis, RG3*
2008[b]	279	not relevant[l]		*Brucella sp, RG3*
2008[b]		yes[m]	1	*Brucella melitensis, RG3*
2009[c]	285	no[n]		*Francisella tularensis, RG3*
2010[c]	285	maybe[o]	1	*Brucella suis, RG3*
		maybe[o]	1	*Brucella suis, RG3*
		not relevant[p]		Classical Swine Fever virus, RG unk
2011[c]	285	no[q]		*Francisella tularensis, RG3*
2012[c]	285	no		no reported confirmed releases
2013[c]	285	maybe[r]	1	*Burkholderia pseudomallei, RG3*
		no[s]		*Brucella mellitensis, RG3*
2014[c]	285	no[t]		*Coxiella burnetii, RG2, RG3*
		yes[u]	1	*Coxiella burnetii, RG2, RG3*
2015[d]	291	yes[v]	2	*Coxiella burnetii, RG2, RG3*
		yes[w]	1	*Brucella abortus, RG3*
2016[e]	276	no		no reported confirmed releases
2017[f]	263	no		no reported confirmed releases

[a] The number of entities for 2003 was not reported. the average is for 2004 through 2006

[b] Number of registered enities from GAO report, Sept 2009 (GAO-09-574)

[c] Number of registered entities not reported by either FSAP or GAO
Thus, the numbers are calculated as the average for years 2008 and 2015= (279+291)/2

[d] 2015 Federal Select Agent Program Annual Report (Figure 1)

[e] 2016 Federal Select Agent Program Annual Report

[f] 2017 Federal Select Agent Program Annual Report

[g] Risk Group 3 (RG3) is assumed to be BSL3

[h] This was the highly publicized Boston University incident where infection was discovered a few months afer exposure
The pathogen was mistakenly studied in BSL2, should have been BSL3, so will be counted as an uuLAI here

[i] The incident occurred in a diagnostic laboratory, so may or may not be a registered entity

[j] The exact incident involving the exposure was not determined, which implies it originally was an uuLAI

[k] The infection was identified only when the lab worker became ill, so is a presumed uuLAI.

[l] Brucellosis is caused by Brucella sp. Since the release was detected during a routine annual test, it is an uuLAI.
It involved an animal (a cow), not humans. Animals will not be included in the statistics for uuLAIs.

[m] The cause was not known at the time of the illness, so implies it was an uuLAI.

[n] From NIH full report, all personnel in the laboratory at the time of the spill were wearing appropriate PPE

[o] The description indicates that the lab workers became ill in the two separate incidents, indicating that they may be uuLAIs.
However, there is not enough information to determine whether the incident was detected in the lab when it occurred.
To be conservative, it will be classified as a "maybe."

[p] It involved two animals, not humans, so will not be included in the statistics for uuLAIs.

[q] Incident occurred in an exempted laboratory

[r] Exposure to this microorganism was detected prior to the onset of symptoms.
prophylactic antibiotics to prevent the onset of illness. Maybe the potential infection
was detected in the lab.

[s] This was a suspected release event, so would not be an uuLAI

[t] The incident occurred in an exempt entity, a diagnostic laboratory.

[u] A worker at a veterinary diagnostic hospital (registered entity) tested positive during annual serological testing

[v] Seroconversion indicates exposure to and infection with the pathogen in numbers that would elicit an antibody response, an uuLAI.

[w] Both seroconversion during annual screening and no identified incident implies this incident is an uuLAI

PART 3
(Detailed descriptions of the 13 uuLAIs from the FOIA NIH incident reports)

The descriptions here are for the thirteen uuLAIs from all FOIA-requested NIH OSP incident reports. Some of the involved pathogens were not particularly virulent or contagious. If the involved pathogens were potential pandemic influenza pathogens, the outcomes below could have been catastrophic.

Report #2. Entity B, November 2004 (uuLAIs=3)

Laboratory researchers believed they were working with the [attenuated] Live Vaccine Strain (LVS) of *Francisella tularensis*. The LVS stock used by the researchers was contaminated with Type A *F. tularensis*, a wild-type, virulent form of the organism. The source of the virulent strain has not been identified to date. Three cases of Tularemia (1 confirmed, 2-probable) were reported to the City's Public Health Commission. Three researchers had become ill in 2004 (two in May and one in September) with symptoms consistent with pneumonic tularemia. Serologic testing confirmed antibodies to *F. tularensis*. The experiments required BSL3, but researchers did not know they were working with an infectious strain so were working in a BSL2 lab.

The investigation into the source of the wild-type strain is ongoing.

Report #10. Entity X, April 2006 (uuLAIs=3)

Three lab workers were found to have high *Coxiella Burnetti* [antibody] titers. (Base line titers are performed annually.) This agent causes Q-fever. All three individuals were offered prophylaxis. None of individuals involved could recall any incident in the laboratory where exposure could have occurred and none had any clinical signs of illness.

The Biological Safety Officer made several recommendations, including following up with the Occupational Health Program, decontaminating the laboratory, and reviewing the laboratory safety procedures, including the use of personal protective equipment. The IBC was kept informed of the incident and subsequent investigation.

When it became aware of the infections, The University did not conduct a thorough investigation into their cause. Because this was not done, it was impossible to determine the precise source of exposure. The University nonetheless does not believe the titers were indicative of a laboratory exposure or infection. [*AUTHOR'S comment: It would seem highly unusual that three laboratory workers researching Coxiella Burnetti would have become infected anywhere else.*]

Report #30. Entity B, October 2009 (uuLAIs=1)

A researcher acquired a laboratory *Neisseria meningitides* infection. The Entity's *ad hoc* committee's conclusion regarding the root cause of this exposure was that the researcher did not remove and dispose of his gloves after directly handling opened sample containers in the biosafety cabinet (BSC) and subsequently touched his face with the contaminated glove. Also, there is the possibility that the researcher may have been exposed to aerosol during centrifugation of samples. The researcher was

subsequently placed on an IV antibiotic regimen for suspected septicemia. Personnel who may have had casual contact with the researcher were placed on a "symptom watch."

This researcher's inconsistent donning of appropriate personal protective equipment (PPE) while performing research was only discovered during the course of the investigation into his laboratory-acquired infection. The Institutional Biosafety Committee (IBC) temporarily suspended research on biological agents in the laboratory; the Principal Investigator was allowed to continue with research not involving *Neisseria meningitides.* The PI indicated that the researcher was not going to conduct lab work. The researcher was instructed to work 100% time on a manuscript that is in preparation.

Report # 36b. Entity AA, March 2009 (uuLAI=1, additional tests for TB confirmed exposure)

A student who works in BSL3 containment with *M tuberculosis* tested positive in a routine bi-annual PPD test[31] after repeatedly testing negative over the course of several years. The student did not have a spill, accident, PPE tear, or any other incident in the BSL3 lab that could cause obvious exposure to *M tuberculosis*.

The underlying cause of the PPD positive test result is therefore unknown. Prior to testing positive, the student was classified as somewhat reactive with the PPD test. It is therefore possible that repeated PPD tests over the course of several years caused the student to have an escalated response leading to what is now a positive result. Alternatively, the student may have been exposed to *M tuberculosis* in the outside environment. This report is being filed in the case that exposure did occur in the BLS3 lab in a manner that was not noticed.

The student was advised to seek medical consultation. The student met with a campus medical professional, given additional tests for *M tuberculosis* immunoreactivity, and counseled regarding options for prophylactic drug treatment. The student opted to take a course of prophylactic antibiotics as recommended. The student has not experienced any health problems.

Report #76. Entity AA, September 2012 (uuLAI=1)

A lab member recently went to the Occupational Health Clinic for his semi-annual T-spot test[32] for *Mycobacterium tuberculosis* and received a positive result. There has been no known exposure or spill in the lab to cause this conversion. The lab member always wore full PPE in the BSL3 facility which included closed front gown, booties, double gloves and a Powered Air Purifying Respirator (PAPR). All procedures are conducted within a biosafety cabinet and there have no known mechanical failures related to labs HV AC or equipment. This lab member is known to be exceptionally meticulous.

Other members of the lab have been advised to consult with Occupational Health. However, several other members were tested around the same time as this individual and no others were positive. We believe this to be an isolated incident. Based on our evaluation of the conversion, we were unable to find a direct exposure or root cause of the positive test. However, as the individual's highest risk for acquiring TB during the last 6 months was from the lab, we must assume that this a lab acquired infection. The individual is being treated by our Occupational Health Clinic.

Report # 109. Entity BD, December 2016 (uuLAI=1)

This is a case of an unreported LAI, not an undetected one; thus, details about how the infection occurred were available. A graduate student grazed her finger with a needle while administering an antibody to mice infected with *Chikungunya virus* (CHIKV). She was wearing appropriate PPE. Including double gloves, but the needle broke through both pairs of gloves. She immediately washed her hands with soap and water. The student did not see any blood from the scratch so she did not report it or seek medical attention. Two days after the incident, the student developed a fever with severe body aches. Three days later, she presented with a macular rash which worsened throughout the day. That evening she reported her symptoms and the needle stick to the principal investigator (PI) and went to the hospital. She was kept in hospital overnight for observation, and the following day was seen by an infectious disease specialist who sent blood to the state laboratories for CHIKV testing. She was released from hospital that day. A few days later, the fever and rash had gone and the student did not develop arthralgia or arthritis which is often associated with Chikungunya fever. However. she did receive positive CHIKV qPCR results.

In response to this incident, the PI met with all laboratory personnel to discuss the proper reporting of personnel exposures and the processes in place for reporting incidents. The Department of Environmental Health and Safety will add additional slides about sharps safety to the annual laboratory training. The student may require additional hands on training on how to safely handle sharps. Needles should be discarded in an appropriate sharps container immediately after use to minimize the potential for a stick. The use of safety needles. where the needle can be sheathed immediately after use should also be considered.

Report # 110. Entity AJ, January 2012 (uuLAI=1)

A potential laboratory-acquired infection (LAI) of a medical school researcher. The researcher had a positive result from a purified protein derivative (PPD) tuberculosis test taken October 1, 2012. A chest X-ray and a T-spot test were performed later that day. The chest X-ray was negative, but the T-spot test came back positive. Based on these results, a diagnosis of latent tuberculosis was made. The researcher's previous PPD test was negative, indicating that the exposure to *Mycobacterium tuberculosis* occurred in the past year.

After discussing possible routes of exposure with the researcher, it was determined that the only opportunity for the researcher to have been exposed to *Mycobacterium tuberculosis* was when the BL3 facility experienced a power outage in December 2011. At the time of that incident, the researcher was working with *Mycobacterium tuberculosis* in a biosafety cabinet. However, the researcher was wearing all appropriate personal protective equipment, including an N95 respirator. No other instances of potential or overt exposure could be identified by the researcher. While it is possible that the *Mycobacterium tuberculosis* infection was community acquired, the University of Massachusetts Medical School is treating this as a potential LAI.

Report # 138. Entity BB, April 2012 (uuLAI=1)

A student who needed a purified protein derivative (PPD) skin test for tuberculosis (TB). PPD conducted for his work with a local home health company tested positive through our student health services program. His chest x-ray was negative. They administered the Quantiferon Gold test to the student at a later date which also was positive. At that time, our state department of health was notified. The

student has worked in a lab that handles mycobacterium bovis as well as mycobacterium avium but the student indicated that he never directly worked with these agents.

Report # 150. Entity X, May 2015 (uuLAI=1)

A researcher who had undergone a routine annual exam with serology for Brucella received notice from the occupational medical provider that the Brucella antibody titer was elevated. The researcher was not symptomatic for Brucella and the titer did not meet the fourfold increase which would confirm disease by the Centers for Disease Control and Prevention (CDC) criteria. The elevated titer also did not meet the criteria for presumptive evidence of infection. The researcher's prior titers had been normal. The biological safety officer met with the researcher and principal investigator in an effort to determine whether a specific incident, accident, or research-related activity in the laboratory might have resulted in an exposure. No incident could be identified. It is possible that the elevated titers reflect the presence of cross-reactive antibodies to organisms other than Brucella species, or a false-positive test. It is possible that the antibody titers observed in this researcher may have resulted from an exposure in the BSL-2 lab while working with Risk Group 2 vaccine strains of Brucella or with heat-killed preparations or may indicate the presence of cross-reactive antibodies.

PART 4

Windows metafile images of key data from NIH incident reports

(organized by entity name coded by letters A, B, C,…, AQ)

Key to the Metafile spreadsheet images below

The Windows metafile image just below supplies definitions of spreadsheet entries, describe the key calculation of entity-years for any entity. The many pages that follow are metafile images of the spreadsheet summarizing the 185 reports to NIH of all incidents in BSL3 labs through 2017. A few BSL2 lab incidents are included because they represent research that should have been carried out in BSL3.

The totals at the end of the last image provide the data for calculation of p_1 from totals for data in the Table.

The actual spreadsheet is available upon request from the author.

For a particular facility with one or more reported incidents, the time period, T_{ri}, for reportable incidents begins at the first reported incident and ends at the end of 2017, so the frequency of a reportable incident per year, $F_{ri} = N_{ri}/T_{ri}$ where N_{ri} is the total number of reported incidents for that facility.

The assumption here is that once a facility reports an incident, it will report all incidents in the future. If it doesn't report some incidents, then N_{ri} estimated here is less than it really is, so the estimate here of F_{ri} is lower and thus consevative.

T_{ri} = (2017 - (year of first incident) + 1) - (month/12) + (0.5/12) in years

The 0.5 assumes incidents happen in the middle of the month to crudely take into account that incident dates are randomly distributed throughout the month.

P1 = number of uuLAIs/number of entity years = 0.028 **(see the last page of spreadsheet metafile)**

Report Number	Facility Name/Location	Date: Year	Date: Month	T_{ri}(years)	N_{ri}	F_{ri}	Biosafety Level	Reported to FSAP?	uuLAI, rLAI, pe, peu	Number of uuLAIs
111	A	2014	10	3.21	1	0.31	ABSL3	Yes	peu	
2	B	2004	11	13.13	2	0.15	BSL2	Yes	uuLAI	3
30	B	2009	10				BSL3	No	uuLAI	1
120	C	2012	1	5.96	4	0.67	ABSL3+	Yes	pe	
122	C	2016	6				NA	NA	peu	
123	C	2017	6				BSL3/BSL2	No	pe	
121	C	2017	5				BSL3	Yes	pe	
40	D	2010	5	7.63	1	0.13	BSL3	No	peu	
38	E	2010	3	7.79	6	0.77	BSL3	No	pe	
54	E	2010	3				BSL3	No	pe	
100	E	2014	5				**BSL3**	Yes	pe	
113	E	2014	10				BSL3	No?	pe	
83	E	2015	1				BSL3	Yes	peu	
94	E	2015	5				BSL3	Yes	peu	
85	f	2007	1	10.96	2	0.18	BSL3	Yes	peu	
48	F	2011	3				BSL3	No	pe	
34	G	2010	1	7.96	1	0.13	ABSL3	Yes	peu	
72	H	2012	12	5.04	2	0.40	BSL3	No	peu	
102	H	2017	7				BSL3	No	peu	
32	I	2009	11	8.13	8	0.98	BSL3	Yes	pe	
57	I	2009	11				BSL3	Yes	peu	
107	I	2010	5				BSL2	No	pe	
92	I	2011	9				BSL2, BSL1	No	peu	
71	I	2012	9				ABSL3	Yes	pe	
68	I	2012	9				BSL2	No	pe	
65	I	2015	1				BSL2	No?	pe	
74	I	2015	3				BSL2	No	pe	

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Report Number	Facility Name/Location	Date: Year	Date: Month	T_a(years)	N_a	F_a	Biosafety Level	Reported to FSAP?	uuLAI, rLAI, pe, peu	Number of uuLAIs
101	J	2013	6	4.54	4	0.88	BSL3	Yes	pe	
108	J	2014	8				BSL3-Ag	No	peu	
112	J	2014	9				BL-3 Ag	Yes	pe	
114	J	2016	10				BSL3?	Yes	peu	
11	K	2007	5	10.63	1	0.09	ABSL3	Yes	pe	
104	L	2010	7	7.46	2	0.27	ABSL3	No	peu	
41	L	2010	7				ABSL3	No	pe	
89	M	2011	3	6.79	1	0.15	BSL3	Yes	peu	
64	N	2011	9	6.29	2	0.32	ABSL3	Yes	pe, Q	
106	N	2011	9				BSL3	Yes	pe	
171	O	2015	8	2.38	1	0.42	BSL2+	No	pe	
42	P	2010	7	7.46	4	0.54	BSL3-->BSL2	Yes	pe	
127	P	2015	1				BSL3	No	peu	
141	P	2016	4				ABSL3	No	pe	
125	P	2017	1				BSL3	No	pe	
27	R	2009	10	8.21	1	0.12	BSL2	No	pe	
14	S	2007	9	10.29	2	0.19	BSL3	Yes	peu	
176	S	2008	1				BSL2,3,4	No	***	
185	T	2010	11	7.13	4	0.56	BSL#	Yes	peu	
45	T	2011	12				BSL3/ABSL3	Yes	peu	
166	T	2014	2				BSL3	No	peu	
160	T	2014	8				BSL3->BSL2	No	**	

Report Number	Facility Name/Location	Date: Year	Date: Month	T_a (years)	N_a	F_a	Biosafety Level	Reported to FSAP?	uuLAI, rLAI, pe, peu	Number of uuLAIs
58	U	2011	5	6.63	2	0.30	BSL3, BSL2	Yes	pe	
136	U	2016	3				ABSL3	Yes	pe	
16	V	2008	3	9.79	1	0.10	BSL3	No	pe	
132	W	2015	2	2.88	1	0.35	BSL3+	To USDA	pe	
10	X	2006	4	11.71	16	1.37	BSL2	No	uuLAI	3
15	X	2008	2				BSL3	Yes	peu	
50	X	2008	2				BSL3	Yes	peu	
62a	X	2010	8				BSL3	Yes	peu	
62b	X	2011	1				BSL3	Yes	peu	
52	X	2012	2				ABSL3	Yes	peu	
61	X	2012	6				BSL3	Yes	pe	
151	X	2012	6				BSL3	Yes	peu	
63	X	2012	8				BSL3	No	uuLAI?	
126	X	2013	1				BSL3	No	pe	
146	X	2013	5				BSL3	Yes?	peu	
154	X	2013	6				BSL3	No	peu	
170	X	2013	11				BSL3	No	peu	
148	X	2014	5				BSL3	No	peu	
152	X	2014	6				BSL3	Yes	peu	
150	X	2015	5				BSL3	Yes	uuLAi	1
81	Y	2017	2	0.88	1	1.14	BSL3	No	pe	
47	Z	2009	12	8.04	1	0.12	BSL3 BSC	No	pe	

Report Number	Facility Name/Location	Date: Year	Date: Month	T_a (years)	N_a	F_a	Biosafety Level	Reported to FSAP?	uuLAI, rLAI, pe, peu	Number of uuLAIs
36b	AA	2009	3	8.79	6	0.68	BSL3	No	uuLAI?	1
36a	AA	2009	7				ABSL2	No	pe	
118	AA	2011	2				ABSL3	No	peu	
76	AA	2012	9				BSL3	No	uuLAI	1
80	AA	2016	1				BSL2	No	pe	
67	AA	2016	12				BSL3	No	peu	
56	AB	2010	5	7.63	2	0.26	BSL3	Yes	peu	
49	AB	2011	12				ABSL3	No	peu	
157	AC	1980	7	37.46	1	0.03	BSL3	No	pe?	
172	AD	2015	11	2.13	1	0.47	BSL3	No	pe	
179	AE	2013	11	4.13	2	0.48	BSL3	No	pe	
155	AE	2016	6				BSL3	Yes	peu	
156 a	AF	2010	6	7.54	3	0.40	ABSL3	No	peu	
156 b	AF	2010	6				ABSL3	No	pe?	
173	AF	2014	11				BSL3	No	peu	
143	AG	2017	3	0.79	1	1.26	BSL3	Yes	peu	
97	AH	2013	4	4.71	4	0.85	BSL3	Yes	peu	
98	AH	2013	4				BSL3	Yes	peu	
99	AH	2013	6				BSL3	Yes	peu	
79	AH	2013	9				BSL2, BSL3	No?	pe?	

Report Number	Facility Name/Location	Date: Year	Date: Month	T_a(years)	N_a	F_a	Biosafety Level	Reported to FSAP?	uuLAI, rLAI, pe, peu	Number of uuLAIs
161	AI	2016	8	1.38	1	0.73	BSL3	Yes	peu	
31	AJ	2009	11	8.13	8	0.98	BSL3	No	pe	
110	AJ	2012	1				BSL3	No	uuLAI	1
51	AJ	2012	10				BSL3?	No	peu	
46	AJ	2013	2				ABSL3	Yes	pe	
134	AJ	2014	2				ABSL3	No	pe	
175	AJ	2014	10				BSL3	No	peu	
163	AJ	2015	9				ABSL3	No	pe	
178	AJ	2016	11				BSL3	No	peu	
140	AK	2012	4	5.71	1	0.18	BSL3	Yes	pe	
131	AL	2011	2	6.88	2	0.29	BSL3	Yes	peu	
144	AL	2011	4				ABSL3	Yes	peu	
128	AM	2010	12	7.04	1	0.14	BSL3	No?	peu	
70	AN	2008	10	9.21	13	1.41	BSL3	Yes?	pe	
180	AN	2008	11				BSL3	No	pe	
69	AN	2012	10				BSL3	No	peu	
181	AN	2013	11				BSL3?	Yes	peu	
135	AN	2014	3				BSL3?	Yes?	peu	
159	AN	2014	8				BSL3?	No	peu	
124	AN	2015	1				BSL3	Yes	peu	
142	AN	2015	4				ABSL3	No	peu	
167	AN	2015	10				BSL3	Yes?	pe	
183	AN	2015	11				ABSL3	No?	peu	
133	AN	2016	2				ABSL3	No	pe	
129	AN	2016	2				ABSL3	Yes	pe	
139	AN	2017	4				BSL3	Yes	peu	

Report Number	Facility Name/Location	Date: Year	Date: Month	T_a(years)	N_a	F_a	Biosafety Level	Reported to FSAP?	uuLAI, rLAI, pe, peu	Number of uuLAIs
145	AO	2015	4	2.71	7	2.58	ABSL3	No	pe	
164	AO	2015	9				BSL3	Yes?	pe	0?
169	AO	2015	10				BSL3+	Yes?	peu	
184	AO	2015	12				ABSL3	No?	pe	
158	AO	2016	8				BSL2	No	pe	
130	AO	2017	2				BSL3	Yes	pe	
147	AO	2017	5				BSL3	No	pe	
84	AP	2012	2	5.88	11	1.87	BSL3	No	peu	
88a	AP	2013	10				BSL3	No	pe	
88b	AP	2014	4				BSL3	No	peu	
88c	AP	2014	10				BSL3	No	pe	
91	AP	2015	1				BSL3	No	peu	
88d	AP	2015	4				BSL3	No?	pe	
116	AP	2015	11				BSL3	No	pe	
75	AP	2016	12				BSL3	No	pe	
117	AP	2016	12				BSL3	No	peu	
82	AP	2017	2				BSL3	No	peu	
77	AP	2018	1				BSL3	No	pe	
55	AQ	2008	3	9.79	1	0.10	BSL3	No	pe	
8	AR	2005	2	12.88	3	0.23	BSL3	Yes?	rLAI	
3	AR	2007	5				BSL2?	No	peu	
24	AR	2008	10				BSL3	Yes	peu	

Report Number	Facility Name/Location	Date: Year	Date: Month	T_a(years)	N_a	F_a	Biosafety Level	Reported to FSAP?	uuLAI, rLAI, pe, peu	Number of uuLAIs
7	AS	2007	4	10.71	3	0.28	BSL3	Yes	peu	
25	AS	2009	6				BSL3	Yes	peu	
39	AS	2010	4				BSL3	Yes	peu	
6	AT	2007	4	9.71	7	0.72	BSL3	Yes?	peu	
9	AT	2007	4				BSL3	Yes?	peu	
90	AT	2008	4				BSL3	No	pe	
17	AT	2008	4				BSL3	No	pe	
21	AT	2008	7				BSL3	Yes?	peu	
35	AT	2010	1				BSL3	Yes?	peu	
60	AT	2012	5				BSL3	No	peu	
13b	AU	2002	7	15.46	7	0.45	BSL2	Yes	pe	
13a	AU	2003	7				BSL3	Yes	pe	
13c	AU	2007	5				ABSL3	Yes	peu	
18	AU	2008	5				BSL3	Yes	peu	
20	AU	2008	7				BSL3	Yes	pe	
103	AU	2010	7				BSL3	Yes	pe	
73	AU	2011	12				BSL3	Yes	pe	
5	AV	2006	4	11.71	1	0.09	BSL3	Yes	peu	
26	AW	2009	8	8.38	1	0.12	BSL2	Yes?	peu	
12	AX	2007	4	10.71	5	0.47	BSL3	Yes	peu	
23	AX	2008	8				BSL3	No	peu	
22	AX	2008	10				BSL3	Yes	pe	
33	AX	2010	1				BSL3	Yes	pe	
174	AX	2016	11				BSL3	Yes	pe	

Report Number	Facility Name/Location	Date: Year	Date: Month	T_a (years)	N_a	F_a	Biosafety Level	Reported to FSAP?	uuLAI, rLAI, pe, peu	Number of uuLAIs
37	AY	2009	12	8.04	2	0.25	BSL3	Yes	peu	
168	AY	2016	9				BSL3-->BSL2	Yes	pe	
149	AZ	2016	5	1.63	1	0.62	BSL3	OSHA	pe	
4	**BA**	2006	8	11.38	10	0.88	BSL3	Yes?	peu	
29	**BA**	2008	5				BSL3/ABSL3	Yes	pe	
28	**BA**	2009	10				BSL3	No	peu	
43	**BA**	2009	10				BSL3	Yes	pe, Q	
44	**BA**	2010	10				BSL3	No	peu	
105	**BA**	2011	8				BSL3	No	peu	
19	**BA**	2011	8				BSL3	Yes	pe	
177 a	**BA**	2013	11				ABSL3+	Yes	pe	
177 b	**BA**	2013	11				ABSL3+	Yes	pe	
137	**BA**	2016	3				BSL3	No	peu	
96	BB	2010	5	7.63	3	0.39	BSL3	No	pe	
87	BB	2012	3				BSL3	Yes	peu	
138	BB	2012	4				BSL2/BSL3	No?	uuLAI	1
165	BC	2014	10	3.21	2	0.62	BSL3	Yes	peu	
162	BC	2015	9				BSL3	Yes	pe	

Report Number	Facility Name/Location	Date: Year	Date: Month	T_{ri} (years)	N_{ri}	F_{ri}	Biosafety Level Reported to FSAP?		uuLAI, rLAI, pe, peu	Number of uuLAIs
78	BD	2011	2	6.88	7	1.02	BSL3?	No	pe	
95	BD	2013	5				BSL3	No?	pe	
153	BD	2014	6				BSL3	No	pe	
119	BD	2016	9				BSL3?	No	pe	
109	BD	2016	12				BSL3	No	uuLAI	1
93	BD	2017	4				BSL3?	No?	pe	
115	BD	2017	11				BSL3	No	pe	
53	BE	2011	2	6.88	2	0.29	ABSL3	No	pe	
86	BE	2017	3				ABSL3	No	pe	
1	BF	1995	8	22.38	1	0.04	BSL2, ABSL3	FSAP not enacted	peu	
			Sum:	**458.3**	**191**	**0.52 (avg)**			**Number of LAIs:**	**13**

TOTALS:

T_{ri}(years) =	**458.3**
N_{ri} =	**191**

Average frequency of incident reporting per year over all entities = sum (N_{ri}/T_{ri})	**0.417**
Average frequency of incident reporting per year averaging over each facility	**0.52**
No.of different entities reporting	**58**
p_1= (number of uuLAI) / (total entity-years) =	**0.028**

PART 5
(Human Error Rules the Roost in High Biocontainment)

Categorizing human errors

Because of the scarcity of data on human-error incidents in influenza research labs, Gryphon Scientific looked to other sectors to define and understand types of human error[33]. Gryphon summarized their findings in a table[34] in their report. They list three types of human error, summarized here in Table 1 in shortened and modified form.

Human Error Type	Definition	Examples
Rule-based	Errors in following instructions or set procedures, accidentally or purposefully	Omitting a required PPE item, too low biosafety level
Skill--based	Errors involving motor skills involving little thought	Cutting oneself with a sharp object, creating a splash while pipetting
Knowledge-based	Errors stemming from a lack of knowledge or a wrong judgement call made based on a lack of experience	Identifying a pathogen as not hazardous, choosing the wrong centrifuge tube

Table 1. Types of human error. According to Gryphon, much of the data on human reliability comes from the transportation, chemical and nuclear sectors. PPE stands for personal protective equipment.

Many different data sources confirm the idea that human error is the main source of incidents in BSL3 and BSL4 laboratories. Here, the data from various sources are summarized with detailed analysis available from the author.

FSAP/CDC Incident Reports

This following incident data is from the Federal Select Agent Program (FSAP) yearly summary reports to Congress[35] for seven years, 2009 through 2015. During that period there were a total of 749 incidents reported to FSAP from select-agent research laboratories. In December 2016, the percent BSL3 registered select agent labs was about 70%[36] of all labs, a percentage here assumed to be relatively constant over the seven-year period.

The data on incidents were provided to Congress in seven categories listed in Table 2.

Incident Category	Human Error Type	Number of Errors
1. Bite/scratch from infected animal	**Skill-based**	**36**
2. Incidents involving equipment or mechanical failures	Not human error	57
3. Needle stick or other through the skin exposures with other potentially contaminated sharp objects	**Skill-based**	**97**
4. Failure or problem with personal protective equipment	Not human error?	98
5. Potential exposures resulting from non-adherence to safety procedures; deviations from laboratory standard operating procedures	**Rule-based or knowledge-based**	**53**
6. Spills of select agents *inside* of biocontaiment laboratories	**Skill-based**	**146**
7. Agents manipulated outside of a BSC or other equipment designed to protect exposures to infectious aerosols	**Rule-based or knowledge-based**	**262**
	TOTAL (incidents):	749
	TOTAL (human error):	**594**
	Percent human error):	**79.3%**

Table 2. Numbers of incidents for the seven categories reported to Congress by FSAP/CDC for the years 2009 through 2015. The five categories due to human error are highlighted in bold-face type. BSC stands for biosafety cabinet.

The bold-faced categories are likely close to 100% human error. Category 4 could be a mix of human error and personal protective equipment (PPE) defects or failure. To be conservative, assume Category 4 is entirely PPE defects or failure. The second largest incident category is spills, Category 6, a category where some causes could be reduced (see below).

By FSAP rules[37], spills or splashes or other accidents in a BSL3 laboratory where the worker wears personal protective equipment (PPE) including a powered air purifying (PAPR) or the incident occurred in a biosafety cabinet (BSC) are not considered reportable incidents since the worker is not exposed to pathogen. On the other hand, all spills, splashes, etc. are reportable to NIH[38] regardless of whether the worker is protected by PPE or a BSC. The FSAP rules seem more reasonable.

NIH incident reports

The FOIA-requested incident reports from the NIH Office of Science Policy cover the period from 2004 through 2017[39] and cover BSL3 and BSL4 labs. There were no reported incidents from BSL4 labs. Reporting to NIH is required only for incidents involving pathogens that contain recombinant DNA. While there have been incidents in BSL4 labs, they may not have involved strains containing recDNA, so they would not show up in the FOIA NIH reports. BSL2 labs must report incidents as well, but they are of less interest here; thus, the very many BSL2 reports were not requested.

Recombinant DNA research is ubiquitous in molecular biology; and sometimes, pathogens are engineered to contain recDNA. Thus, a wider group of pathogens than FSAP Select Agents would be covered in the FOIA NIH reports. However, there is overlap in reports to FSAP and NIH.

The BSL3 reports provide extremely detailed descriptions of incidents from the facilities where the incidents occurred. The reports are often several dozen pages long, so almost no questions remain about details, and much can be learned about incidents and human error.

The 185 FOIA NIH reports cover 187 incidents. A few reports cover more than one incident. In the 187 incidents, 136 are due to human error, yielding 72.7% human error. 71% of errors are skill based, which is consistent with the FSAP data.

By far, lab workers with potential through the skin exposures, spills-splashes, or dropped-objects are the main causes of human-error incidents. For the few incidents relating to centrifugations and shakers, most are caused by defective labware such as cracked centrifuge tubes, cracked shaker flasks, or other defective labware, rather than equipment failure.

Some human errors are “one-off” errors, meaning they happened once, likely won’t happen again, and would be difficult to anticipate. It is unlikely that one can devise meaningful changes in standard operating procedures (SOPs) for many of them for future prevention. Here are a few examples of potentially one-off errors gleaned from the first few-dozen reports:

> 1) A spill of animal bedding potentially contaminated with recombinant SARS Coronavirus. Cages were stacked next to a -80° C freezer, and when the door was opened a cage tipped over and fell on the floor. This caused the lid of the cage to open and contaminated bedding to fall onto the floor.
>
> 2) A water overflow from an effluent decontamination system (EDS) which handles all the effluent from three high-containment suites in a multi-lab BSL3 facility. Water from the EDS backed up in the BSL- 3Ag suite and, to a lesser extent, the ABSL-3 suite. The backup was primarily caused by a staff member's failure to turn off the sink faucet in the BSL-3 suite, and the EDS could not handle the volume of water produced. A secondary cause was the failure of a high-water-level alarm linked to the EDS to be sent to the appropriate maintenance staff. The water came out of floor drains within the high-containment suites. The BSL-3 suite is located on the main floor above the BSL-3Ag and ABSL-3. While the water produced in the BSL-3 was the cause, this suite was unaffected due to its location.
> Work conducted in one room involves 1918 H1N1 viruses.
>
> 3) A graduate student sustained a superficial abrasion to the right forearm when his hand slipped while closing the sash of a cage change station.
>
> 4) A researcher was exchanging two plastic 24-well plates in the tabletop Sorvall centrifuge. While closing the lid, it was caught on a centrifuge wrench which was accidently placed into the path of the lid. The wrench jumped and knocked one of the removed 24-well plates onto the counter. The plate landed at approximately a 45-degree angle and lost approximately half its contents to the bench top.

> 5) A researcher was using an electroporator to transform *M. tuberculosis* cells when the cap of the electroporation cuvette ejected from the machine and landed on the floor, resulting in a minor spill.

Other errors are frequent, for which there are now changes in SOPs in some facilities to reduce their frequency. For instance, needle sticks can occur using syringes with sharp-metal needles to transfer liquids from one small container to another. Here is an example:

> A researcher was working in a BSC and was transferring inactivated HIV into an ultra-centrifuge tube to layer it over a sucrose gradient. The tube was in a small beaker, and was at an angle to facilitate adding the virus suspension. The tube moved slightly; and to prevent the tube from spilling, he used his left hand to steady it. During this motion, he accidentally moved his right hand, which was holding the syringe, and brushed the tip of the needle over the surface of his left thumb. He felt a small bump or prick, as the needle punctured both gloves on the thumb of the left hand.

For injecting animals, sharp-metal needles are needed; but for liquid transfers, blunt-plastic needles would suffice.

Dropped items sometimes could be prevented using lab carts to transport items from place to place instead of carrying them by hand. Some facilities have changed their SOPs to reflect these ideas.

Failure to inactivate

Failure to inactivate is a major reason for release from high biocontainment into BSL2 labs. Since there are reliable inactivation procedures, failure to inactivate is a human error of the Rules or Knowledge type.

Carrying out research in BSL3 and BSL4 laboratories is difficult, both because of restricted movement in the PPE that must be worn and because of constraints in SOPs to minimize potential exposure to pathogens. It is much easier to carry out research at BSL2, since researchers are much less constrained. When research does not require active pathogens, researchers will inactivate them so they may be researched at BSL2. If the pathogen has not been inactivated, the threat of a uuLAI increases and the probability of other release into the community increases. In BSL2, workers clothing and body parts are exposed to pathogens.

How often is failure to inactivate responsible for transferring BSL3 and BSL4 pathogens to lower biocontainment? The GAO has weighed in on this question.[40]

> "The total number of incidents involving incomplete inactivation…that occurred from 2003 through 2015 is unknown for several reasons. One key reason is that the [FSAP]…does not require laboratories to identify such incidents on reporting forms." According to the FSAP, "10 incidents occurred from 2003 through 2015. However, GAO identified an additional 11 incidents that the program did not initially identify."

One of the FSAP reported failures to inactivate was Ebola virus (Table 2 in the GAOreport).

Information about the 11 additional incidents is summarized in the GAO's Table 3.

Table 3: Eleven Additional Incidents Involving Incomplete Inactivation of Select Agents from 2003 through 2015 Identified by GAO and Confirmed by the Federal Select Agent Program

Laboratory type	Pathogen	Pathogen type	Method of inactivation	Year of incident
Academic	*Burkholderia pseudomallei*	Bacteria	Physical	2014
Private	*Francisella tularensis*	Bacteria	Chemical	2014
Federal	*Francisella tularensis*	Bacteria	Chemical	2011
Private	*Bacillus anthracis*	Bacteria	Physical and Chemical	2010
Private	Marburg virus and Ebola virus	Virus	Chemical	2009
Federal	*Bacillus anthracis*	Bacteria	Physical	2008
Academic	*Francisella tularensis*	Bacteria	Physical and Chemical	2008
Federal	*Francisella tularensis*	Bacteria	Chemical	2007
Academic	*Francisella tularensis*	Bacteria	Chemical	2007
Federal	*Bacillus anthracis*	Bacteria	Chemical	2006
Federal	Venezuelan equine encephalitis virus	Virus	Chemical	2006

Source: GAO analysis of information from the Federal Select Agent Program, 2016. | GAO-16-842

The GAO further calls attention to a well-publicized, large incident.

> "In May 2015, the Department of Defense (DOD) discovered that one of its laboratories inadvertently sent live Bacillus anthracis, the bacterium that causes anthrax, to almost 200 laboratories worldwide over the course of 12 years. The laboratory believed that the samples had been inactivated…In this case, DOD was inactivating samples to support research on the detection, identification, and characterization of biological threats."[41]

The GAO describes yet another well-publicized incident.

> "Similar incidents have occurred in other countries, including China, where two researchers conducting virus research were exposed to severe acute respiratory syndrome (SARS) coronavirus samples that were incompletely inactivated. The researchers subsequently transmitted SARS to others, leading to several infections and one death in 2004."[42]

Thus, failure to inactivate is likely a major path for deadly pathogens to be released from BSL3 and BSL4 into BSL2 containment, thus increasing the probability of release into the community.

BSL4 laboratory releases due to human error

In BSL4 laboratories, researchers don suits that fully cover their bodies, and they breathe outside-air from hoses tethered to them. The mental image is that of astronauts undergoing a spacewalk fully protected from the cold and vacuum of outer space. Thus, researchers would seem to be protected from uuLAIs.

From 1988 until the recent past, there were two *direct* releases into the community of pathogens (foot and mouth disease virus, Marburg virus) from BSL4 containment, one due to human error. More recently, there have been three releases, Ebola and Marburg viruses, from BSL4 to lower containment labs, all due to human error.

While three releases seem small, the number of BSL4 labs is small compared to the number of BSL3 labs. There are now 22 BSL4 labs worldwide[43]. While the data set is small, the rate of releases from BSL4 labs is comparable to that of BSL3 labs in the U.S.

Here are more details on the two direct releases into the community from BSL4 containment:

(1) In 1990, a 35-year-old junior scientist from the Vektor Laboratory of the Novosibirsk Scientific Center contracted a Marburg virus infection. "[I]n violation of safety regulations, he worked with blood serum of laboratory animals infected with that virus, considering the material to have lost its infectivity in view of its storage at a temperature of 4°C for about 6 months...[F]eeling unwell on April 13th, he went home from work without alerting the laboratory's medical service, and on April 14th he entertained 10 guests

at home. In fact, up until the time he was hospitalized, the patient was in close contact with 12 relatives (his wife and daughter – every day of illness up until hospitalization, and 10 people as guests…)"[44] He ultimately survived, and it is very lucky no one else was infected.

(2) In August of 2007, "An outbreak of foot and mouth disease was confirmed at a farm in Surrey, U.K…It was concluded that the Foot and Mouth Disease Virus likely originated from the nearby Pirbright Research and manufacturing site in Surrey because of construction activities surrounding a leaking drainage pipe." [45] While the NBAF report says "likely," the FMDV outbreak almost certainly came from the Pirbright BSL4 laboratory. This is an example of release from a BSL4 facility through an infrastructure design failure, not human error.

On the web site of Boston University's National Emerging Infectious Disease Laboratories (NEIDL), it is argued that the state-of-the-art design and construction of the NEIDL would prevent pathogens from escaping into the community.

> "The NEIDL is a 192,000-square-foot, seven-story building designed in accordance with the most stringent and protective measures defined by the National Institutes of Health. It was built on the experience of six existing BSL-4 facilities in North America, none of which has ever had a release or community incident… All critical building systems within the NEIDL have a redundant system to ensure safety and uninterrupted operation at all containment levels."[46]

While there is no problem believing that modern BSL4 labs have been designed and built to the state-of-the-art. While technically correct, there is one misleading phrase in the above quote, namely that there has never been a release from a BSL4 lab in North America. As noted above, the GAO has uncovered three recent releases from BSL4 labs, two of the deadly Ebola virus and one of the deadly Marburg virus.[47] These three were due to failure to inactivate the viruses before transferring them to a lower BSL2 containment laboratory.

The release in 2014 from the CDC labs occurred when, in the GAO's words,

> "Scientists inadvertently switched samples designated for live Ebola virus studies with samples intended for studies with inactivated material. As a result, the samples with viable Ebola virus, instead of the samples with inactivated Ebola virus, were transferred out of a BSL-4 laboratory to a laboratory with a lower safety level for additional analysis. While no one contracted Ebola virus in this instance, the consequences could have been dire for the personnel involved as there are currently no approved treatments or vaccines for this virus."

While these are not releases into the community, researchers in BSL2 labs are at a higher risk of a uuLAI than those in higher biocontainment labs or entering the community with contaminated clothing.

The CDC has issued a report[48] on this mix up, and the steps they have taken to avoid this *particular* error in the future.

PART 6
(Precision of Release Risk Calculations)

The main conclusion of the mathematical analysis below is that small data sets of uuLAIs are enough to determine with 95% confidence the probability of community release of an uuLAI, because we do not need high precision to make the case that the release risk is too high. Precision within 60% of the real expected value is sufficient. Both the FSAP data set (4,067 entity-years and 10 uuLAIs) and the NIH data set (458.3 entity-years and 13 uuLAIs) are large enough to come close to real expected value for the release probability, p_1.

The Poisson distribution

Frequencies of events leading to a release from a lab are best described by a Poisson distribution. **(**http://www.intmath.com/counting-probability/13-poisson-probability-distribution.php**)**

The probability distribution of a Poisson random variable X representing the number of "successes" occurring in a given number of trials is given by the formula:

$P(x) = e^{-\mu}\, \mu^x / x!$

Where x=0,1,2,3…; e=2.71828; and μ= mean number of successes.

The mean and the variance of the Poisson distribution are both equal to μ.
$E(X) = \mu$; $V(X) = \sigma^2 = \mu$; the standard deviation by definition is then $\mu^{1/2}$. That is, for the Poisson distribution, only **one** parameter, μ is needed to determine the probability of number of successes.

A "success" here is an observed uuLAI.

Analysis of observed number of events

The number of observed uuLAIs, N_{obs}, and potential precision of N_{obs} as a measure of the real mean number of uuLAIs, N_a, is measured by its standard deviation $N_a^{1/2}$. The mean and standard deviation will depend on the size of the data set. As $N_{obs} \rightarrow \infty$, $N_{obs} \rightarrow N_a$

In this terminology, the Poisson distribution is

$N_{obs}(x) = \exp(-N_a) \times N_a^{\,k} / x!$

Our measure of precision is the ratio of the standard deviation to the mean

$\sigma / \mu = \mu^{1/2} / \mu = N_{obs}^{1/2} / N_{obs} = N_{obs}^{-1/2}$

For values of $N_{obs} > 10$, $N_{obs}(x)$ is basically normally distributed, as the following illustration shows:

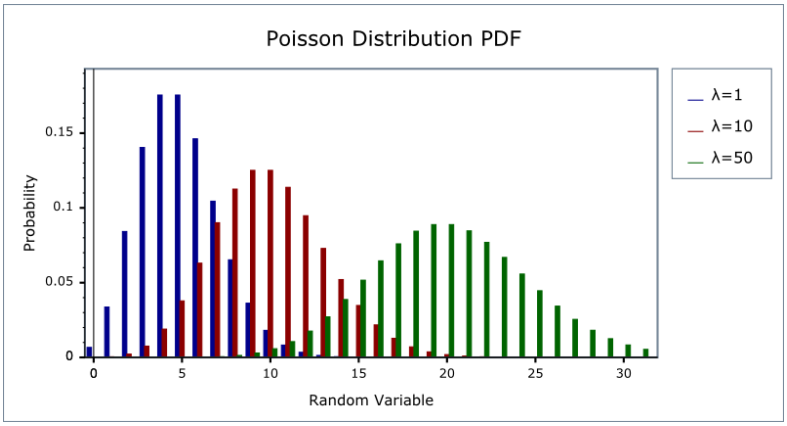

Figure 6-1. Poisson distribution x values (x-axis), and Poisson probability (y-axis). In our terminology, $\lambda=\mu=N_a$. For λ =10, the graph adopts closely the bell-curve shape of a normal or Gaussian distribution.

From a table of normal distribution probabilities, there is a 68% probability that N_{obs} is within one standard deviation from the real expected number of events N_a, and 95% probability that N_{obs} is within two standard deviations (2σ) of N_a. Said another way, for the large uncertainty range ± 2σ, we can be about 95% confident that N_{obs} is within that range around N_a.

If we require precision that we will be 95% confident that N_{obs} is within a fraction

$2N_{obs}^{1/2} / N_{obs} = 2 N_{obs}^{-1/2} \leq \beta,$

where β is the fraction variation from the mean, N_{obs}, how large must N_{obs} be?

$2 N_{obs}^{-1/2} = \beta$ (where β is the fraction, not percentage)

Solving for N_{obs},

$N_{obs} = 4 / \beta^2$

		Required β						
		10%	25%	50%	60%	75%	100%	200%
	N_{obs}:	400	64	16	11	7.1	4	1

Table 6-1. The size of the data set, N_{obs}, necessary to have 95% confidence that N_{obs} is within β-percent of N_a.

We do not need high precision to make the case that the release risk is too high. Precision within 60% of the correct value is sufficient. The surprising result here is that if we want to be 95% confident that N_{obs} is within 60% of N_a, we need only a small data set of 11 events. Both the FSAP data set (N_{obs} = 10 uuLAIs) and the NIH data set (N_{obs} = 13 uuLAIs) are clearly large enough to come close to actual values for the release probability, p_1.

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