Supplemental Information— Detailed Descriptions of the Fault Tree Analyses

1.1 Reduction Factors

In this fault tree analysis, like others,[1] a reduction factor (RF) is applied to each branch between the nodes of the tree. During a single Monte Carlo trial, Each RF encountered on a single path through the tree is multiplied by the material available for release (MAR), the total amount of infectious material that could be released, to get the Q value, the actual amount released. Generally, the MAR represents the amount of material a worker is handling during the experiment in which the incident occurs, and is frequently reduced a significant amount by containment features (e.g. BSCs), personal protective equipment (e.g. gloves), and physical properties of the material (e.g. the aerosolized fraction, the small amount of liquid aerosolized in a drop or spill). A RF of 1.0 means that branch has no effect on the overall MAR, and an RF of 0.0 means that no material can be released regardless of what happens in later branches. In the fault trees modeled here, some events can lead to multiple routes of exposure (e.g. aerosols and fomites) and a node may reduce one, both, or none of the potential exposure routes. For example, if the primary container in a shipped infectious package does not break, no liquid or aerosolized material can escape, and all modes of exposure are prevented. In comparison, wearing a PAPR may reduce the amount of aerosolized material a worker is exposed to, but will not reduce the size of the fomite should a worker contaminate his or her hands.

Some branches of the tree may have a RF of 1.0 for counterintuitive reasons. While a branch may eliminate exposure at a certain node (e.g. a glove tear or leak), if the total amount of MAR of the same category (e.g. fomites) is still available via another node further down the tree, then it is not reduced at the current stage. This occurs when, for example, a worker's gloves do not fail and material cannot contaminate hands via glove tears or leaks, but the worker may still contaminate his or her hands with the material on the gloves during removal. As a result, because all of the material is still available for release, the reduction factor for gloves that do not tear or leak is 1.0.

In other instances, nodes may only determine which downstream outcomes are possible without reducing the material available for release. For example, in the shipment tree, whether a trained individual receives a package does not affect the amount available for release upon opening the package. However, it does obviate the possibility that a non-laboratory worker will open the package. Because these types of nodes have no effect on the MAR, they are all assigned a RF of 1.0.

1.2 Types of Probability Distributions

Except in limited circumstances where extensive and directly applicable data were available to build a complete probability distribution, as in hand washing efficiency, probability distributions that approximated the range and uncertainty of the event were used. If only minimum and maximum failure probabilities were available, but no estimate of the typical event or its probability could be obtained, a uniform distribution was used. If, however, a typical circumstance and probability of failure in that circumstance were available, a triangular distribution was used instead. These triangular distributions ranged from the minimum to the maximum probability of failure, with a mode equal to the probability of failure of the typical event. If the range of the distribution was less than or equal to an order of magnitude, a linear uniform or triangular distribution was used. If the distribution ranged broader than that, a log

[1] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility

uniform or log triangular distribution (i.e. uniformly or triangular distributed on the exponent) was used instead, in order to prevent biasing the density of the distribution to the higher numbers. For example, if a distribution ranged from 1E2 to 1E8, perhaps representing a virus titer, and was distributed uniformly and linearly, the midpoint of the density would be the arithmetic average of the extremes, or 5E7, and half the values would fall on either side. In contrast, if the same distribution were log uniformly distributed, the midpoint of the density would be the geometric mean of the endpoints, or 1E5, 500-fold lower. The log distribution more accurately represents the underlying data, as the many dilutions a researcher may use result in values less than 1E5 as likely as values above it. Also note that, in the case of uniform distributions both distributions have the same probability that *a specific point* is drawn, as is the definition of a uniform distribution: $P(X = x) = P(X = y)$ for both log and linear uniform distributions for any possible x and y within the range. Instead, it is the *density* that changes: $P(x \leq X \leq y)$ differs between them.

Distributions incorporating zero as a possible value were treated specially. First, zero was treated as having a zero-order exponent, such that distributions ranging from 0 to 1 were scaled linearly and treated as within an order of magnitude. Second, for log scaled distributions, zero was not an allowable point (i.e. there is no x such that $\log(x) = 0$). Although one can come arbitrarily close to zero by using negative exponents of arbitrarily large magnitudes, doing so can significantly scale the median. For example, a log uniform distribution from 0-1E8 that replaces zero with 1 will have a median of 1E4, but a distribution that replaces zero with 1E-8 will have a median of one, and half of the density will be less than or equal to one. In this analysis, most cases where zero was a possible value involved viral concentrations; with one IU replaced zero IU in order to both avoid reducing the median and avoid creating significant probability density below one IU, as concentrations below one IU are rarely encountered during the course of containment lab research. This change had an insignificant effect on the probabilities of infection after exposure.

1.3 Centrifuge Event Tree

In this scenario, a worker is centrifuging virus-containing material and either uses the wrong tube or overfills the tube, resulting in the tube leaking or breaking. The scenario is examined twice, as it applies to BL2 and BL3 conditions. Exposure occurs through direct aerosol exposure to the worker (personal aerosols) and aerosols escaping through the exhaust stack (environmental aerosols), as well as hand contamination (fomites) generated when the worker attempts to clean up any spilled material.

Based on interviews with researchers regarding centrifuge use rates, the opportunity frequency is set to once every other work day to five times per work day, resulting in 125-1250 centrifugation events per year, per laboratory. The concentration of material centrifuged was set to a log uniform distribution from 1E2 to 1E8 IU/mL, and a total centrifuged volume ranging uniformly 1-10mL, both from the same interviews. The available volume for fomites was reduced to 1mL, based on an assumption that a glove could not hold more than 1mL of liquid on its surface at a given time. As a conservative assumption, workers are presumed to always contaminate the gloves with the maximum of 1mL.

The fraction of material aerosolized came from a collection of three centrifuge exposure scenarios examined by Bennett and Parks,[2] assuming a 100mL total volume centrifuged for the "Centrifuge Bucket A" scenario. Because no sources documented the types and relative frequencies of centrifuge spills and accidents occurring the laboratory, a log uniform distribution over all sourced aerosolized fractions was used, resulting in a log uniform distribution from 2E-9 to 5.9E-6.

[2] Bennett A, Parks S (2006) Microbial aerosol generation during laboratory accidents and subsequent risk assessment. *Journal of applied microbiology* 100**:** 658-663

1.3.1 Aerosol Generation and Reduction

Worker aerosol exposures may or may not be reduced by the use of a BSC, depending on whether the containment features of the centrifuge cup, such as the seal and lid, are in use and work, and whether the worker opens the cup inside a BSC. As a conservative assumption, if any of the aerosol containment equipment is omitted or fails to work, the worker is exposed to the entirety of the material aerosolized, which may be reduced by a working personal respirator if the work is performed under BL3 conditions.

Environmental aerosol exposures may be reduced by a BSC based on the same circumstances. Because directional, filtered airflow is not a standard requirement in BL2 conditions, no further reductions are made to the environmental aerosol under these conditions, and, as a conservative assumption, all of the material is presumed to escape the building into the surrounding environment. Under BL3 conditions, the aerosol may be further reduced by the HEPA filters present in the airflow exhaust stack, which are presumed to have an alarm notifying workers of any failures. Because double HEPA filters are not a standard requirement for BL3 conditions,[3] they are assumed to be absent.

1.3.1.1 HEPA Filtration Efficiency

The *Updated Site-Specific Biosafety and Biosecurity Risk Assessment (USSRA) for the National Bio and Agro-Defense Facility* (NBAF)[4] compiles several sources measuring or specifying the efficiency of working HEPA filters present in biocontainment labs. In this report, it was assumed that a working filter would meet the minimum standards specified in the HEPA definition of 3.0E-4, but may work as well as the highest measured efficiency of 2.0E-6. Two of the cited studies in the USSRA, Wang et al.[5] and Kowalski et al.[6], give a measured efficiency of 3.0E-5, and a third study by Arunkumar[7], gives a similar efficiency of a new filter of 1.5E-5. Based on that partial consensus, the HEPA efficiency of a working filter was set to a log triangular distribution from 2.0E-6 to 3.0E-4, with a mode of 3.0E-5.

HEPA filters can fail in several ways, including pinholes, large filter tears, or the complete absence of a filter if a replacement was accidentally forgotten during a maintenance change. Pinhole leaks and other minor failures are likely to only marginally reduce the filter efficiency, whereas a complete failure would prevent the filter from working entirely. The USSRA compiles several historical analyses of HEPA filter failures, and, in the most comprehensive source the USSRA authors reviewed, no total filter blowouts had been recorded, though several filters had degraded performance.[8] Based on those data, it was presumed that should a filter fail to work, it is partially degraded and will perform close to the required standards of a working filter. As a result, the efficiency of a failed HEPA filter was set as a log triangular distribution with a minimum overlapping the maximum of the working filter, 3.0E-4, to a maximum of a completely failed filter, 1.0, with a mode of 3.0E-4.

[3] Wilson D, Chosewood L (2009) Biosafety in microbiological and biomedical laboratories (BMBL). 5. *Centers for Disease Control and Prevention*

[4] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:79

[5] Wang W, Winters P (2004) Statistically significant efficiency testing of HEPA filters. *Journal of the IEST* 47**:** 101-106

[6] Kowalski W *et al* (1999) Filtration of airborne microorganisms: modeling and prediction. *ASHRAE TRANS* 105**:** 4-17

[7] Kumar A Evaluation of Mass Emission Rates Down Stream of HEPA Filters as a Function of Source Terms and Selected Failure Modes. *Waste Management* 4

[8] Abraham G *et al* (1998) HEPA filter replacement experience in a biological laboratory. *Journal of the American Biological Safety Association* 3**:** 134-142

1.3.1.2 HEPA Filtration Failure Rates

The USSRA reports the probability of HEPA filter degradation and failure as two separate probabilities based on historical analysis.[9] However, in the present report, because the reduction factor for a failed filter (i.e. the failed filter efficiency) includes both the possibility of degradation and total failure, a single failure probability was used instead. Here, the difference in probability between a slight filter failure and a total filter failure was incorporated into the probability distribution of the *reduction factor* applied to failed filters and not to the direct probability that a filter fails. In the *Australian Animal Health Laboratory (*AAHL) report identified as most comprehensive by the USSRA[10], the authors report on 511 filter installations over thirteen years, resulting in 6643 replacement opportunities, in which 98 filters were replaced for reasons other than blockage. This report modeled these data by a binomial distribution with 6643 trials and 98 "successes," and computed the failure rate as a triangular distribution using the limits of a 95% two-sided binomial confidence interval on the expected filter failure rate, 1.2E-2 and 1.8E-2, with a mode equal to the measured failure rate of 1.5E-2.

If a filter fails in a biosafety cabinet or exhaust stack, an alarm sounds alerting workers of failure. As a result, experiments will not be performed with failed filters unless the alarm fails to function or is otherwise ignored by the workers. This report assumes that workers silence or ignore alarms at rates much higher than alarms mechanically fail, and thus the alarm failure rate was set to the probability of a rules error.

1.3.1.3 HEPA Fan Failure Rates

In addition to the filter failing, the fans creating the directional airflow in the BSC and room may also fail. Because redundant exhaust fans are not a strict BSL3 requirement, they were presumed to be absent.[11] In a book reviewing HVAC fan failure rates in the nuclear power industry, the failure rate across approximately 19,000 fans in commercial plants in the U.S. is "less than 0.015%/year (<1.5E-4).[12] A second report investigating fan failures for fusion applications reports fan failure rates for failures to start of 5E-3/day and failures to run of 3E-5/hr.[13] It was presumed that failures of fans to start in a containment lab would immediately be noticed and work would not begin; thus only the failure to run rate was considered. Additionally, it was presumed that containment lab fans run continuously, at all times, every day of the year. Given a failure rate of 3E-5/hr., the probability that the fan does not fail is 9.9997E-1, and the probability the fan does not fail at any hour during the year is the probability it does not fail raised of the number of hours per year (8670), or 7.69E-1. Given that probability of not failing during a year, the annual probability of failure is 1-7.69E-1 or 2.3E-1. The values from the two sources were used as the minimum and maximum of a log uniform distribution from 1.5E-4 to 2.3E-1.

1.3.1.4 N95 and PAPR Efficiency

Interviews with researchers and biosafety experts revealed that all workers performing experiments with the viruses examined in BL3 conditions wore either an N95 respirator or a personal air-purifying

[9] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:142-148

[10] Abraham G *et al* (1998) HEPA filter replacement experience in a biological laboratory. *Journal of the American Biological Safety Association* 3**:** 134-142

[11] Wilson D, Chosewood L (2009) Biosafety in microbiological and biomedical laboratories (BMBL). 5. *Centers for Disease Control and Prevention*

[12] Ghosh D, Campbell R (2004) HVAC Equipment Aging and Reliability Issues at Commercial Nuclear Power Plants. In *28th Nuclear Air Cleaning Conference*.

[13] Cadwallader LC (1999) Ventilation Systems Operating Experience Review for Fusion Applications. *INEEL Report, INEEL/EXT-99-01318*

respirator (PAPR). The choice of N95 or PAPR and the type of PAPR varied between institution and, occasionally, the individual. For this report, the efficiency of respiratory protection was modeled using the entire range of efficiencies given for all types of PAPR and N95. The USSRA examined several sources reporting N95 efficiency and undertook a statistical assessment of available data to yield a median efficiency of 5.0E-3, with 95% CI limits of 2.0E-4 to 1.3E-2.[14] Because workers at the NBAF indicated that they are not likely to wear PAPRs, the USSRA does not consider them.

The Occupational Safety and Health Administration (OSHA) reports several assigned protection factors (APFs) for various PAPR types.[15] The assigned protection factor (APF) is determined experimentally by measuring the face piece seal and exhalation valve leakage and indicates the relative difference in concentrations of substances outside and inside the face piece that can be maintained by the respirator.[16] The efficiency of the PAPR is the inverse of the APF. The APFs reported by OSHA are listed in the table below.

Table S1. Assigned Protection Factors for Various PAPR types

Type of PAPR	Assigned Protection Factor	Filtration Efficiency
Half mask	50	2.0E-2
Full face piece	1000	1.0E-3
Helmet	25	4.0E-2
Hood	1000	1.0E-3
Loose-fitting face piece	25	4.0E-2

Because the limited number of interviews with researchers was not a statistically significant sample size, the probability of wearing a PAPR versus an N95 respirator could not be assigned. A limited survey of BSL3 labs in the U.S. reported that workers in non-select agent labs use N95 respirators and PAPRs with approximately equal frequency, and workers in select agent labs use PAPRs approximately three-quarters of the time.[17] However, as these data were not broken out by pathogen type, it is not possible to determine whether workers with coronaviruses and influenza prefer one type or the other. As a result, the efficiency of respiratory protection was combined into a single log uniform probability distribution ranging from the highest efficiency (the USSRA 95% CI limit for N95s) of 2.0E-4 to the lowest (the reported helmet PAPR APF) of 4.0E-2.

1.3.1.5 N95 and PAPR Failure Rates

Under BL2 laboratory conditions, N95 and/or PAPRs are not required, and thus it was presumed that workers did not wear them.[18]

[14] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:100

[15] OSHA. (2009). Assigned Protection Factors for the Revised Respiratory Protection Standard. https://www.osha.gov/Publications/3352-APF-respirators.pdf. Last Update 2009. Accessed December 2015.

[16] Special Operations Unit of the Phoenix Fire Department. Respirators http://www.chemicalspill.org/ChemicalsWorkPlace/respirators.html. Last Update 1998. Accessed December 2015.

[17] Richards SL *et al* (2014) BSL-3 laboratory practices in the United States: comparison of select agent and non-select agent facilities. *Biosecurity and bioterrorism : biodefense strategy, practice, and science* 12**:** 1-7

[18] Wilson D, Chosewood L (2009) Biosafety in microbiological and biomedical laboratories (BMBL). 5. *Centers for Disease Control and Prevention*

Under BL3 conditions, the mechanical failure rates of PAPRs and filters were presumed to be significantly lower than the human error rate in choosing or remembering to wear respiratory protection and properly donning it. As a result, the failure to wear respiratory protection was assigned the rules error probability. Failing respirators were assigned the knowledge error probability because the most common failure modes of an N95 or PAPR are self-announcing, such as an easier breathing effort if an N95 is improperly sealed or the disappearance of the powered blower if a battery fails in a PAPR, and identification of these failures will likely increase as workers gain experience. Because a detailed protocol for donning respirators would likely be present in each laboratory, the knowledge error minimum probability was modified to the error rate when following a protocol of greater than ten steps of 3.0E-3. Additionally, because the most common type of error presumed to occur was a failure to follow the protocol correctly, the distribution was converted to a log triangular distribution with the minimum equal to the mode.

1.3.2 Fomite Generation and Reduction

In addition to the aerosols generated by the centrifuge, some material is expected to escape the tube and be subsequently cleaned up by the worker, transferring a portion to the outer surface of the worker's gloves. Here, the pathways considered for infection only consider handshakes and touches of the face by the hands leading to mucosal exposure; as a result, contamination of the worker's shoes and body are not considered. As a conservative assumption, the entirety of the spill may transfer to the glove, of which 1mL remains on the glove surface versus drips on the floor or back into the centrifuge.

Based on interviews and reports of standard procedures, the worker is modeled as decontaminating his or her gloves with ethanol immediately after finishing the cleanup procedure, prior to removing the gloves. Due to this being a single-step standard procedure, failure was modeled as a rules error.

Several sources investigated the effectiveness of ethanol at decontaminating hands and hard surfaces.[19,20,21,22,23] For this report, only sources modeling hand decontamination were used, as it was presumed that hand rubbing, etc., could significantly affect the efficiency of decontamination, and such a process would be most similar to a person wearing gloves. Of the sources investigated, only the work by Bellamy and colleagues[24] tested 70% ethanol, the composition of the solution customarily sprayed on gloves by workers. Based on the similarity to the scenario modeled, the data from that source were used to create the reduction factor distribution for glove decontamination. Decontamination was modeled with a log triangular distribution, using a minimum and maximum equal to the minimum and maximum in the source of 1E-4.3 and 1E-1.3, respectively. The mode was set to the geometric mean of all values in the source, 1E-2.9. Similar work by Sattar and colleagues[25] tested a gel containing 60% ethanol; however, the

[19] Bellamy K *et al* (1993) A test for the assessment of 'hygienic' hand disinfection using rotavirus. *The Journal of hospital infection* 24**:** 201-210

[20] Sattar SA *et al* (2000) Activity of an alcohol-based hand gel against human adeno-, rhino-, and rotaviruses using the fingerpad method. *Infection control and hospital epidemiology* 21**:** 516-519

[21] Geller C *et al* (2012) Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses* 4**:** 3044-3068

[22] Rutala WA *et al* (2006) Efficacy of hospital germicides against adenovirus 8, a common cause of epidemic keratoconjunctivitis in health care facilities. *Antimicrobial agents and chemotherapy* 50**:** 1419-1424

[23] Sattar S *et al* (1989) Chemical disinfection of non-porous inanimate surfaces experimentally contaminated with four human pathogenic viruses. *Epidemiology and infection* 102**:** 493-505

[24] Bellamy K *et al* (1993) A test for the assessment of 'hygienic' hand disinfection using rotavirus. *The Journal of hospital infection* 24**:** 201-210

[25] Sattar SA *et al* (2000) Activity of an alcohol-based hand gel against human adeno-, rhino-, and rotaviruses using the fingerpad method. *Infection control and hospital epidemiology* 21**:** 516-519

range of efficiencies reported in that work were a subset of range reported by Bellamy, and so were indirectly incorporated into the distribution used.

1.3.2.1 Glove Failure and Contamination During Removal

Based on interviews with researchers and biosafety experts, workers performing experiments with the pathogens investigated here were presumed to routinely wear double gloves; because the failure rate of gloves was substantially higher than human error in not wearing them, it was presumed that workers always wore gloves. The USSRA examined several sources of glove failure,[26] reporting an overall failure rate of 7.67%, and a range, when ignoring sources with fewer than 20 samples, of 2.3% to 31.6%. Because no data were available on whether the second glove failure rate was independent of the first, a range encompassing both possibilities was used. Glove failure was modeled with a log triangular distribution, with the minimum of the distribution set to the minimum glove failure rate squared of 5.3E-4, modeling gloves failing completely independently, with the maximum set to the single glove failure rate of 3.2E-1, modeling gloves failing simultaneously in every instance. The mode was set to the USSRA overall failure rate squared of 5.9E-3, presuming that gloves are more likely to fail independently than simultaneously.

When gloves fail, some material on the outside of the glove may penetrate the tear and contaminate the hands. In principle, only the outer glove could fail, with the inner glove stopping further penetration of any material that leaks through the outer set. However, in this analysis, the probability that gloves fail is the probability that both gloves fail *simultaneously*, and single glove failures are not considered. As a result, in this model, the amount of material that penetrates double gloves after a failure is equal to that of single gloves, and the additional protection afforded by the second set of gloves is realized in the reduced probability of failure and not the reduction factor. Work by Broyles and colleagues reported a range of transfer fractions of virus from the outside to the inside of exam gloves if a tear or puncture occurs, dependent on glove type.[27] Because no data were available on the preferences of researchers for particular glove types, the amount of material transferred should gloves fail incorporated the entire range reported in the source, 5.9E-3 to 3E-1. In addition, it was reasoned that should both gloves fail and be contaminated, only a small fraction of the contaminated surface of a glove would overlap with the failure point; however, no data were available to quantify the extent of overlap. In the absence of data, the glove failure transfer efficiency range was multiplied by five percent, resulting in a final reduction factor distribution for failed gloves from 3.0E-4 to 1.6E-2, distributed log uniformly.

1.3.2.2 Hand Contamination When Removing Gloves

In addition to gloves failing and leading to hand contamination, workers may also inadvertently contaminate the skin while removing contaminated gloves. Because workers wear double gloves, each layer of gloves was modeled as a separate attempt to remove gloves without contaminating the layer beneath. Workers that fail to remove the first set of gloves are likely to contaminate only the inner layer of gloves and may still remove the inner set properly. Even if the worker fails to remove the outer layer properly, not all of the material that was on the outer glove will contaminate the inner glove. Should the failure be repeated, the same is also true for the fraction of material that reaches the hands.

[26] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:104

[27] Broyles JM *et al* (2002) PCR-based method for detecting viral penetration of medical exam gloves. *Journal of clinical microbiology* 40**:** 2725-2728

In work by Olsen and colleagues,[28] five of 105 events where gloves did not leak resulted in hand contamination, resulting in a probability of removal failure of 4.8E-2. In this source, workers only wore a single pair of gloves. Based on the source data and the modification of double gloving, a log triangular distribution was built with a minimum value equal to the source value squared, to incorporate the second set of gloves, and then divided by two, to compensate for potential overestimation of the failure rate by the source. The maximum value was set equal to the source rate, to incorporate the possibility that double gloving did not reduce the failure rate. The mode was equal to the source rate squared, based on the reasoning that each glove layer likely provides independent protection.

The same source provided a range of concentrations of virus on gloves and contaminated hands should workers fail to remove gloves properly. The entire range of these ratios of concentrations were used to build a distribution of the fraction of material that contaminates the hands. The resulting distribution was log triangular, using a minimum equal to the minimum fraction in the source squared, to incorporate double gloves, a maximum equal to the maximum fraction to model double gloving having no reduction, and a mode equal to the geometric mean fraction squared. This resulted in a reduction factor distribution from 1E-10 to 9.5E-3 with a mode of 3.7E-7.

Recent work by Tomas and colleagues[29] also investigated worker failures to remove gloves without contamination. This work was considered, but not incorporated into the analysis for two reasons. First, in Tomas et al., workers primarily focused on avoiding contamination, whereas in the work by Olsen and colleagues, workers focused on routine clinical procedures. Because the scenario modeled here is glove contamination during containment work where workers are focused on the experiments at hand, the situation in Olsen et al. is more similar to the one modeled. Second, in the work by Tomas et al., workers' gloves were intentionally contaminated, and workers were instructed to rub the lotion into their gloves, contaminating all surfaces of the glove, a scenario unlikely to arise during regular practice.

In theory, gloves could both tear and leak and be improperly removed, contaminating the hands by two modes simultaneously. However, because the fraction that contaminates the hands when a glove fails is significantly higher than that of a failure to remove gloves, glove failures would dominate risk, and thus contamination of hands by gloves is only modeled as happening by one mode per event opportunity.

1.3.2.3 Hand Washing

Prior to leaving the laboratory, standard laboratory procedure requires workers to wash their hands[30] In addition, workers should avoid touching their faces prior to washing hands to avoid cross-contamination of the face with any infectious material on the hands. Because of the standard requirements, the failure to wash hands and failure to avoid touching the face were both assigned the rules error probability. Face touches after the worker leaves the laboratory (i.e. after washing hands) are incorporated into the fomite fate model and are not covered in the fault tree analysis.

If a worker does touch their face prior to hand washing, some amount of the material on the hands is transferred to the face, using a triangular distribution from 0 to 1 with a mode of 0, based on an analysis of several sources examining transference of material from the fingers to other sources.[31] If the worker does wash their hands, some of the infectious material is removed from the hands, based on a gamma

[28] Olsen RJ *et al* (1993) Examination gloves as barriers to hand contamination in clinical practice. *Jama* 270**:** 350-353

[29] Tomas ME *et al* (2015) Contamination of Health Care Personnel During Removal of Personal Protective Equipment. *JAMA internal medicine*

[30] Wilson D, Chosewood L (2009) Biosafety in microbiological and biomedical laboratories (BMBL). 5. *Centers for Disease Control and Prevention*

[31] See Supplemental Information section on the details of the fomite model.

distribution with parameters $\alpha = 2.35748$ and $\beta = 0.042933$, based on an analysis of several sources of hand washing efficiency.[32]

Table S2. Material Available for Release and Opportunity Rate for Centrifugation Event		
Type of Exposure	**Opportunity Rate**	**Material Available for Release**
Aerosols	125-1250 times per year per lab, uniformly distributed	1-10mL volume of material, log uniformly distributed * 1e2-1e8 IU/mL, log uniformly distributed
Fomites	125-1250 times per year per lab, uniformly distributed	1mL volume of material, log uniformly distributed * 1e2-1e8 IU/mL, log uniformly distributed

Table S3. Probabilities and Reduction Factors for Release During Centrifugation Events			
Node Name	**Probability of Failure**	**Reduction Factor if Success**	**Reduction Factor if Failure**
Liquid contained by tube	Knowledge Error: 5E-3 to 1E-1, log uniformly distributed	0 (No exposure occurs)	2E-9 to 5.9E-6,[33] log uniformly distributed
Aerosol tight cup used	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No reduction)	1 (No reduction)
Seal in place	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No reduction)	1 (No reduction)
Seal work	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No reduction)	1 (No reduction)
Cup opened in BSC	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No reduction)	1 (No reduction)
BSC work	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[34] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[35]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
Directional airflow present	BL2: 1 BL3: 0	1 (No effect)	1 (No effect)
Directional airflow work	2.25E-8 to 2.3E-1, log uniformly distributed for fan failure[36,37] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	1 (No effect)	1 (No effect)
Suite HEPA present	0	1 (No effect)	-

[32] Ibid.
[33] Bennett A, Parks S (2006) Microbial aerosol generation during laboratory accidents and subsequent risk assessment. *Journal of applied microbiology* 100**:** 658-663
[34] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility
[35] Ibid.
[36] Ghosh D, Campbell R (2004) HVAC Equipment Aging and Reliability Issues at Commercial Nuclear Power Plants. In *28th Nuclear Air Cleaning Conference*.
[37] Cadwallader LC (1999) Ventilation Systems Operating Experience Review for Fusion Applications. *INEEL Report, INEEL/EXT-99-01318*

Primary HEPA work	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[38] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[39]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
Double binding HEPA present	1	-	1 (No effect)
Secondary HEPA work if primary HEPA pass	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[40] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[41]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
Secondary HEPA work if primary HEPA fail	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[42]	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[43]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
N95/PAPR worn	BL2: 1[44] BL3: Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	1 (No effect)
N95/PAPR work	Knowledge & Protocol Error: 3E-3 to 1E-1, log triangularly distributed with 3E-3 mode	2E-4 to 4E-2, log uniformly distributed[45,46]	1 (No reduction)
Gloves decontaminated	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1E-4.3 to 1E-1.3, log triangularly distributed with a mode of 1E-2.9[47]	1 (No reduction)
Gloves work	5.3E-4 to 3.2E-1, log triangularly distributed with a mode of 5.9E-3[48]	1 (No effect)	3E-4 to 1.6E-2, log uniformly distributed[49]
PPE removal/decontamination work	1.1E-3 to 4.8E-2, log triangularly distributed with a mode of 2.3E-3[50]	0 (No exposure occurs)	1E-10 to 9.5E-3, log triangularly distributed with a mode of 3.7E-7[51]

[38] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility
[39] Ibid.
[40] Ibid.
[41] Ibid.
[42] Ibid.
[43] Ibid.
[44] Wilson D, Chosewood L (2009) Biosafety in microbiological and biomedical laboratories (BMBL). 5. *Centers for Disease Control and Prevention*
[45] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:100
[46] OSHA. (2009). Assigned Protection Factors for the Revised Respiratory Protection Standard. https://www.osha.gov/Publications/3352-APF-respirators.pdf. Last Update 2009. Accessed December 2015.
[47] Bellamy K *et al* (1993) A test for the assessment of 'hygienic' hand disinfection using rotavirus. *The Journal of hospital infection* 24**:** 201-210
[48] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:104
[49] Ibid.
[50] Olsen RJ *et al* (1993) Examination gloves as barriers to hand contamination in clinical practice. *Jama* 270**:** 350-353
[51] Ibid.

Face touched before washing hands	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	0 to 1, triangularly distributed with a mode of 0[52]
Washing hands work	Rules Error: 5E-4 to 5E-2, log uniformly distributed	Gamma distribution, $\alpha = 2.3548$, $\beta = 0.042933$[53]	1 (No reduction)

1.4 Splash Event Tree

In this scenario, a worker is performing an experiment with cell culture, or is performing a necropsy on an animal, in both cases within a biosafety cabinet (BSC), and infectious material splashes onto the worker's glove. For cell culture experiments, splashes are presumed to occur when the worker slips with a pipette or other instrument, while for animal experiments splashes are presumed to occur as a routine part of necropsies. Splashes are presumed to land on only one hand. Due to the volume splashed and the containment provided by the BSC, aerosol exposures are not considered in this tree.

For animal experiments, the opportunity frequency is set to 50-5000 animals per year, per laboratory, multiplied by 5-25%. These ranges were based on interviews with researchers regarding the number of animals used per year and the fraction of those that were necropsied as well as a presumption that one splash occurs during every necropsy. The frequency for cell culture experiments is set as 13-400 hours per year, per researcher, with a mode of 127 hours. This information was determined from interviews with researchers and containment lab managers regarding annual number of hours spent in containment per year and the portion of that time spent with cells (50%). The event initiation frequency for cell culture experiments was set to the opportunity rate multiplied by an assumed range of 1-10 opportunities to splash per hour in the BSC, multiplied by the skill error rate on the presumption that a motor skills error triggered the splash.

1.4.1 Concentration of Virus in Animal Tissues

The material available for release is determined by multiplying the material volume by infectious concentration. Considering no animal model for MERS exists and the mouse-adapted strain of SARS cannot transmit, coronaviruses were considered a negligible risk for event trees when the MAR came from animal tissues, such as necropsy splashes. For influenza-infected animals, a literature review revealed a wide range of concentrations of virus in various tissues.[54,55,56,57,58,59,60] Generally, titers of human-adapted viruses were higher than avian viruses, except for the Guangdong-derived H5N1 viruses

[52] See Supplemental Information Section on Fomite Model Parameters
[53] See Supplemental Information Section on Fomite Model Parameters
[54] Price GE *et al* (2009) Vaccination focusing immunity on conserved antigens protects mice and ferrets against virulent H1N1 and H5N1 influenza A viruses. *Vaccine* 27**:** 6512-6521
[55] Mendel DB *et al* (1998) Oral administration of a prodrug of the influenza virus neuraminidase inhibitor GS 4071 protects mice and ferrets against influenza infection. *Antimicrob Agents Chemother* 42**:** 640-646
[56] Smee DF *et al* (2008) Treatment of influenza A (H1N1) virus infections in mice and ferrets with cyanovirin-N. *Antiviral Res* 80**:** 266-271
[57] Fan J *et al* (2004) Preclinical study of influenza virus A M2 peptide conjugate vaccines in mice, ferrets, and rhesus monkeys. *Vaccine* 22**:** 2993-3003
[58] Xu L *et al* (2013) The mouse and ferret models for studying the novel avian-origin human influenza A (H7N9) virus. *Virol J* 10**:** 253
[59] Gillim-Ross L *et al* (2008) Avian influenza h6 viruses productively infect and cause illness in mice and ferrets. *J Virol* 82**:** 10854-10863
[60] Kim YI *et al* (2014) Pathobiological features of a novel, highly pathogenic avian influenza A(H5N8) virus. *Emerg Microbes Infect* 3**:** e75

which had titers equal to or higher than human-adapted viruses. Several sources reported values at or below the limit of detection, possibly as low as zero. Some sources reported titers in concentration per gram of tissue and others in per milliliter of tissue. To facilitate combining data, one milliliter of tissue was presumed to weigh approximately one gram.

Due to significant variation between strains and no available data on the frequency of experimentation with any particular strain, the entire range, excluding one apparent outlier for H1N1 (of 6.3E8) [61], was incorporated into a log uniform distribution from 1E0-1.6E8 IU/mL. The minimum value of one was incorporated to include the full range of possibilities from sources reporting titers at the detection limit and the possibility that an animal was inoculated with a strain that did not cause infection.

1.4.2 Concentration of Virus in Plates, Flasks, and Tubes

Based on interviews with researchers regarding the maximum expected titers of virus, as well as the typical concentrations used in cell culture experiments, the infectious concentration of cell culture experiments was set to a log triangular distribution from 1E2 to 1E8 IU/mL, with a mode of 1E4. Although viral stocks are expected to be at high concentrations, most cell culture experiments do not involve use of the stock at the original concentration; instead, the stock is diluted to a working concentration many folds less than the original, and that dilute stock is used for the rest of experiments. As no sources presented data on splash volume, an educated assumption was made of 1µL-1mL. In addition, as no data were available regarding the fraction of splashes that land on the a worker's glove versus on the work surface of the BSC, as a conservative assumption, all splashes generated in the BSC are presumed to land on the glove.

Like the centrifuge tree, workers should decontaminate gloves with sprayed ethanol prior to removing them. Unlike the centrifuge tree, however, here workers may fail to notice the splashed material on their gloves, and thus fail to decontaminate. No data were available on the likelihood a worker would perceive splashed materials on gloves, so educated estimates of probabilities were made. For small splashes less than or equal to 100µL, workers may fail to notice the splash based on a uniform probability distribution from 5E-1 to 9.5E-1; for large splashes greater than 100µL, it was presumed that the splash volume on the glove would be so large that it would be obvious and thus workers always notice them.

All other reduction factors and probabilities are the same as the corresponding nodes described in the centrifuge event tree.

Table S4. Material Available for Release and Opportunity Rate for Splash Event

Type of Experiment	Opportunity Rate	Material Available for Release
Animal	50-5000 animals per year per lab, log uniformly distributed * 5-25% of animals necropsied, uniformly distributed	1µL-1mL volume of material, log uniformly distributed * 0 to 1.6E8 IU/mL, log uniformly distributed
Cell culture	13-400 hours in the BSC per year, triangularly distributed with a mode of 127 hours * 1-10 opportunities for splashes per hour in hood per researcher, uniformly distributed *	1µL-1mL volume of material, log uniformly distributed * 1E2 to 1E8 IU/mL, log triangular distributed with a mode of 1E4 IU/mL

[61] Price GE *et al* (2009) Vaccination focusing immunity on conserved antigens protects mice and ferrets against virulent H1N1 and H5N1 influenza A viruses. *Vaccine* 27**:** 6512-6521

	skill error probability of splashing given the opportunity: 5E-5 to 5E-3, log uniformly distributed	

Table S5. Probabilities and Reduction Factors for Release During Centrifugation Events

Node Name	Probability of Failure	Reduction Factor if Success	Reduction Factor if Failure
Splash noticed when volume > 100 µL	0	1 (No effect)	-
Splash noticed when volume ≤ 100 µL	5E-1 to 9.5E-1, uniformly distributed	1 (No effect)	1 (No effect)
Gloves decontaminated	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1E-4.3 to 1E-1.3, log triangularly distributed with a mode of 1E-2.9[62]	1 (No reduction)
Gloves work	5.3E-4 to 3.2E-1, log triangularly distributed with a mode of 5.9E-3[63]	1 (No effect)	3E-4 to 1.6E-2, log uniformly distributed[64]
PPE removal/decontamination work	1.1E-3 to 4.8E-2, log triangularly distributed with a mode of 2.3E-3[65]	0 (No exposure occurs)	1E-10 to 9.5E-3, log triangularly distributed with a mode of 3.7E-7[66]
Face touched before washing hands	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	0 to 1, triangularly distributed with a mode of 0[67]
Washing hands work	Rules Error: 5E-4 to 5E-2, log uniformly distributed	Gamma distribution, α = 2.3548, β = 0.042933[68]	1 (No reduction)

1.5 Spill Event Tree

A spill scenario ensues when a worker spills virus-containing material either inside or outside of the biosafety cabinet (BSC). In comparison to the splash tree, where small droplet volumes are considered, here workers drop or otherwise upset plates, flasks, tubes, and other containers of infectious material. Aerosols and fomite exposures are possible, and both are considered in a manner similar to the centrifuge accident, with similar probabilities and reduction factors. Like the centrifuge, the fault tree is run separately for BL2 and BL3 conditions.

[62] Bellamy K *et al* (1993) A test for the assessment of 'hygienic' hand disinfection using rotavirus. *The Journal of hospital infection* 24**:** 201-210

[63] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:104

[64] Ibid.

[65] Olsen RJ *et al* (1993) Examination gloves as barriers to hand contamination in clinical practice. *Jama* 270**:** 350-353

[66] Ibid.

[67] See Supplemental Information Section on Fomite Model Parameters

[68] See Supplemental Information Section on Fomite Model Parameters

The opportunity rate was set to the same opportunity rate as splashes, for the same reasons. Unlike splashes, spills may also occur outside of the BSC. Because no data were available on either the historical location of containment lab spills or the percent of time spent at the BSC versus using equipment or transporting material, it was presumed that workers performing cell culture experiments work at the hood the majority of the time in containment, with 90% of spills occurring inside the BSC and 10% occurring outside.

The material available for release is determined by multiplying the volume of material within the container, the percent that spills out, the concentration of infectious material, and aerosolized. For spills inside of the hood, the volume ranges from 1-15mL, based on the presumption that a tube containing stock or dilute virus was tipped over, whereas outside of the hood 1-100mL could be spilled, on the presumption that several microtiter plates or flasks could be carried and dropped at once. The volumes were drawn from a log uniform distribution across these ranges, based on the reasoning that each individual experiment would likely use a different volume, and all volumes were equally likely.

A sealed flask or tube that does not break when dropped may spill no material, whereas a microtiter plate that lands upside down will likely spill nearly 100% of the liquid within it. Between these two extreme outcomes lie many possible events resulting in some fraction of material spilling out. Considering all of these possibilities and the higher likelihood that a worker would transport a sealed container than an unsealed one, making smaller fractions of material spilling more likely than large ones, the fraction of material spilled was set to a log uniform distribution from 0-100% (i.e. 0-10% spilling is as likely as 10-100% spilling). Similar to the reasoning for splashes, the concentration of infection material was set to a log uniform distribution from 1E2 to 1E8 IU/mL. No mode was used because while splashes occur inside a BSC and were modeled as splashes of dilute virus stocks during experiment setup, here workers may drop plates or flasks at any point during an experimental course, preventing an estimation of the most likely concentration.

The fraction of material aerosolized when the spill occurs was based on the same data source and distribution used for the centrifuge tree, 2.9E-9 to 5.9E-6, using a log uniform distribution. [69] Although that source contains spill-like accidents, the centrifuge accidents cover a comparable though slightly broader range of aerosolized fractions at both the low and high end and were used instead as a conservative assumption.

All other reduction factors and probabilities were the same as the corresponding nodes described in the centrifuge event tree.

Table S6. Material Available for Release and Opportunity Rate for Splash Event

Location	Probability of Location	Opportunity Rate	Material Available for Release
Inside hood	9E-1	1-10 ops per hour in hood, uniformly distributed * 13-400 hours per year, triangularly distributed with a mode of 127 hours * Skill Error: 5E-5 to 5E-3 per person per year, log uniformly distributed	1-15mL volume of material, log uniformly distributed * 0-100% spills, log uniformly distributed *1e2 to 1e8 IU/mL, log uniformly distributed * 2.9E-9 to 5.9E-6 fraction

[69] Bennett A, Parks S (2006) Microbial aerosol generation during laboratory accidents and subsequent risk assessment. *Journal of applied microbiology* 100**:** 658-663

			aerosolized, log uniformly distributed
Outside hood	1E-1	1-10 ops per hour in hood, uniformly distributed * 13-400 hours per year, triangularly distributed with a mode of 127 hours * Skill Error: 5E-5 to 5E-3 per person per year, log uniformly distributed	1-100mL volume of material, log uniformly distributed * 0-100% spills, log uniformly distributed *1e2 to 1e8 IU/mL, log uniformly distributed * 2.9E-9 to 5.9E-6 fraction aerosolized, log uniformly distributed

Table S7. Probabilities and Reduction Factors for Release From Spill Event

Node Name	Probability of Failure	Reduction Factor if Success	Reduction Factor if Failure
BSC work	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[70] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[71]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
Directional airflow present	BL2: 1 BL3: 0	1 (No effect)	1 (No effect)
Directional airflow work	2.25E-8 to 2.3E-1, log uniformly distributed for fan failure[72,73] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	1 (No effect)	1 (No effect)
Suite HEPA present	0	1 (No effect)	-
Primary HEPA work	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[75]	3E-4 to 1, log triangularly distributed with a mode of 3E-4

[70] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility

[71] Ibid.

[72] Ghosh D, Campbell R (2004) HVAC Equipment Aging and Reliability Issues at Commercial Nuclear Power Plants. In *28th Nuclear Air Cleaning Conference*.

[73] Cadwallader LC (1999) Ventilation Systems Operating Experience Review for Fusion Applications. *INEEL Report, INEEL/EXT-99-01318*

[75] Ibid.

	for degraded filter[74] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm		
Double binding HEPA present	1	-	1 (No effect)
Secondary HEPA work if primary HEPA pass	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[76] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[77]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
Secondary HEPA work if primary HEPA fail	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[78]	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[79]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
N95/PAPR worn	BL2: 1[80] BL3: Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	1 (No effect)
N95/PAPR work	Knowledge & Protocol Error: 3E-3 to 1E-1, log triangularly distributed with 3E-3 mode	2E-4 to 4E-2, log uniformly distributed[81,82]	1 (No reduction)
Gloves decontaminated	Rules Error: 5E-4 to 5E-2, log	1E-4.3 to 1E-1.3, log triangularly	1 (No reduction)

[74] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility

[76] Ibid.

[77] Ibid.

[78] Ibid.

[79] Ibid.

[80] Wilson D, Chosewood L (2009) Biosafety in microbiological and biomedical laboratories (BMBL). 5. *Centers for Disease Control and Prevention*

[81] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:100

[82] OSHA. (2009). Assigned Protection Factors for the Revised Respiratory Protection Standard. https://www.osha.gov/Publications/3352-APF-respirators.pdf. Last Update 2009. Accessed December 2015.

	uniformly distributed	distributed with a mode of 1E-2.9[83]	
Gloves work	5.3E-4 to 3.2E-1, log triangularly distributed with a mode of 5.9E-3[84]	1 (No effect)	3E-4 to 1.6E-2, log uniformly distributed[85]
PPE removal/decontamination work	1.1E-3 to 4.8E-2, log triangularly distributed with a mode of 2.3E-3[86]	0 (No exposure occurs)	1E-10 to 9.5E-3, log triangularly distributed with a mode of 3.7E-7[87]
Face touched before washing hands	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	0 to 1, triangularly distributed with a mode of 0[88]
Washing hands work	Rules Error: 5E-4 to 5E-2, log uniformly distributed	Gamma distribution, α = 2.3548, β = 0.042933[89]	1 (no reduction)

1.6 Slip During Necropsy Event Tree

In this scenario, a worker is performing a necropsy and slips with the sharp instrument, breaking the protective gloves and exposing the worker's hands to virus-containing material. As no sources reported subcutaneous pathways as a source of infection for flu, SARS, or MERS, the exposure route considered was hand contamination leading to fomites. No primary data gave the frequency of sharp object slips that resulted in hand cuts versus, for example, damage to the animal necropsied or working surface; as a conservative assumption all slips were presumed to break the gloves and expose the hand.

The event opportunity frequency was set to 50-5000 animals per year, per laboratory, multiplied by 5-25%, based on interviews with researchers regarding the number of animals used per year and the fraction of those that were necropsied. Per opportunity, the frequency with which events were initiated was set to the skill error probability, on the reasoning that cutting oneself with the sharp tool involved a motor skills mistake.

The material available for release was set to 1-100µL, based on a reasoned estimate of the amount of material that could remain on a blade, multiplied by 1-1.6e8 IU/mL, based on literature sources of the concentration of virus in infected animals as described in the splash tree.

All other reduction factors and probabilities were the same as the corresponding nodes described in the centrifuge event tree.

Table S8. Material Available for Release and Opportunity Rate for Slip During Necropsy Events

[83] Bellamy K *et al* (1993) A test for the assessment of 'hygienic' hand disinfection using rotavirus. *The Journal of hospital infection* 24**:** 201-210

[84] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility

[85] Ibid.

[86] Olsen RJ *et al* (1993) Examination gloves as barriers to hand contamination in clinical practice. *Jama* 270**:** 350-353

[87] Ibid.

[88] See Supplemental Information Section on Fomite Model Parameters

[89] See Supplemental Information Section on Fomite Model Parameters

Opportunity Rate	Material Available for Release
50-5000 animals per lab per year, log uniformly distributed * 5-25% of animals necropsied, uniformly distributed	1-100µL volume of material, log uniformly distributed * 0-1.6e8 IU/mL[90] log uniformly distributed

Table S9. Probabilities and Reduction Factors for Slip During Necropsy Events

Node Name	Probability of Failure	Reduction Factor if Success	Reduction Factor if Failure
Slip with sharp object occurs	Skill Error: 5E-5 to 5E-3, log uniformly distributed	0 (No exposure occurs)	1 (No reduction)
Hands washed before touching face	Rules Error: 5E-4 to 5E-2, log uniformly distributed	No virus is transferred from the hands to the face	0 to 1, triangularly distributed with a mode of 0 for the amount removed from the hands.[91] All material removed from the hands is transferred to the face
Worker washes hands	Rules Error: 5E-4 to 5E-2, log uniformly distributed	Gamma distribution[92], α=2.3548, β=0.042933	1 (No reduction)

1.7 Animal Bite Event Tree

In this scenario, a worker is handling an infected animal and the animal bites the worker, potentially exposing them to virus-containing material. Based on interviews and discussions with animal workers, mice bites were excluded from the fault tree, as mouse bites are unlikely to break the skin. In comparison, ferrets are more prone to biting and are much more likely to break the skin should the worker not be wearing the required leather gauntlet. Because no sources indicated that intramuscular or subcutaneous exposure was a route of infection for the pathogens considered in this report, only hand contamination leading to fomites and self-inoculation is considered.

Based on available data regarding animal bite frequencies reported in the literature for similar fields,[93,94] event initiation was computed as a yearly rate per worker instead of based on a fraction of event opportunities. The reported rate of 8.5 animal bites per 100 technicians in university settings[95] was believed to be most representative of containment lab research of the available data sources. The other two reported rates of 38.1 per 100 technicians in research settings and 6.6 per 100 in veterinary settings served as the minimum and maximum estimates, respectively, resulting in a triangular distribution from 6.6E-2 to 3.8E-1 with a mode of 8.5E-2 per person, per year.

[90] See Supplemental Information Section on Fomite Model Parameters
[91] See Supplemental Information Section on Fomite Model Parameters
[92] See Supplemental Information Section on Fomite Model Parameters
[93] Nordgren LD *et al* (2014) Evaluation of risk and protective factors for work-related bite injuries to veterinary technicians certified in Minnesota. *Journal of the American Veterinary Medical Association* 245**:** 434-440
[94] Nienhaus A *et al* (2005) Work-related accidents and occupational diseases in veterinarians and their staff. *International archives of occupational and environmental health* 78**:** 230-238
[95] Nordgren LD *et al* (2014) Evaluation of risk and protective factors for work-related bite injuries to veterinary technicians certified in Minnesota. *Journal of the American Veterinary Medical Association* 245**:** 434-440

No data were available regarding the salivary volume transferred to the surface of the worker's skin during an animal bite, so primary data were gathered. Ten human volunteers each bit down on the surface of a glove and then the change in mass of the glove was measured, using a presumptive salivary density of 1g/mL. The experiment was repeated three times per volunteer, and, in each case, the total change in mass was below the 30µg limit of detection of the balance used. Because no data were available relating human salivary volume to ferret volume, as a conservative assumption, the maximum ferret bite volume was set to the maximum bounds of the human bite volume of 30µL.

Few sources directly measured the concentration of virus in mouse and ferret saliva. Instead, salivary concentrations were computed via conversion from titers in other tissues.[96] Due to significant variation between sources and viruses, but without enough samples to be statistically significant, the full range of possible values from the minimum to the maximum reported by any source was used, resulting in a uniform distribution from 1E0.3 to 1E5.9 IU/mL.

Interviews with researchers revealed that workers regularly wear leather gauntlets when handling awake and alert ferrets due to the propensity of bites. Because of the requirement to wear the leather glove, failure to wear it was assigned the rules error probability. It was reasoned that a ferret would be unable to bite through the leather; however, after a ferret bites the outer leather glove, a worker may still fail to remove the leather glove without contaminating the latex gloves worn beneath and eventually his or her bare hands, leading to a potential fomite exposure. It was presumed that leather glove removal failures occur at the same frequency with the same contaminant fraction transferred as latex glove removal failures, as described in the centrifuge tree.

All other reduction factors and probabilities were equal to the corresponding nodes described in the centrifuge tree.

Table S10. Material Available for Release and Opportunity Rate for Animal Bite

Opportunity Rate	Material Available for Release
6.6E-2 to 3.8E-1 per person per year, triangularly distributed with a mode of 8.5E-2[97,98]	0-30 µL volume of material, uniformly distributed * 1e0.3 to 1e5.9 IU/mL, log uniformly distributed

Table S11. Probabilities and Reduction Factors for Release From Animal Bite

Node Name	Probability of Failure	Reduction Factor if Success	Reduction Factor if Failure
Leather glove worn	Rules Error: 5E-4 to 5E-2, log uniformly distributed	0 (No exposure occurs)	1 (No effect)

[96] For full details, see the Supplemental Information section on calculating salivary titers

[97] Nordgren LD *et al* (2014) Evaluation of risk and protective factors for work-related bite injuries to veterinary technicians certified in Minnesota. *Journal of the American Veterinary Medical Association* 245**:** 434-440

[98] Nienhaus A *et al* (2005) Work-related accidents and occupational diseases in veterinarians and their staff. *International archives of occupational and environmental health* 78**:** 230-238

PPE removal/decontamination of leather glove work	2.4E-2 to 9.5E-2, triangularly distributed with a mode of 4.8E-2[99]	0 (No exposure occurs)	1.0E-5 to 9.5E-3, log triangularly distributed with a mode of 6.1E-4[100]
PPE removal/decontamination of latex glove work	1.1E-3 to 4.8E-2, log triangularly distributed with a mode of 2.3E-3[101]	0 (No exposure occurs)	1E-10 to 9.5E-3, log triangularly distributed with a mode of 3.7E-7[102]
Face touched before washing hands	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	0 to 1, triangularly distributed with a mode of 0[103]
Washing hands work	Rules Error: 5E-4 to 5E-2, log uniformly distributed	Gamma distribution, α = 2.3548, β = 0.042933[104]	1 (No reduction)

1.8 Shipping Event Tree

In this scenario, infectious samples are shipped to a lab, and exposure happens when the package is incorrectly opened out of containment, or the packaging material fails prior to final delivery, resulting in potential exposure by shipping company employees, administrative and other non-research staff at the delivery location, and by research personnel. Note that interviews with researchers revealed that gain of function strains are not shipped, and are instead generated via reverse genetics. Thus, this tree only applies to work with wild type strains and contributes to a small *reduction in risk* for the gain of function experiment. In this fault tree, both aerosol and fomite exposures are possible. Aerosol exposures are only possible for packages damaged in transit, as significant aerosolization of the material would be unlikely to occur except in circumstances that would destroy the packaging. Fomite exposure is possible during shipping and after delivery.

For packaging failure scenarios, fomite exposures are modeled as occurring when a worker carries a box with a wet spot where the infectious material has absorbed, leading to hand contamination, or where the worker attempts to clean up a spill of the contents of the shipment. As a conservative assumption, it is presumed that workers do not wear proper PPE and thus contaminate their hands while attempting to clean up the spill.

In contrast, exposures from packages opened in an improper location are indirect due to potential splash events while opening the inner tubes, either because a tube is dropped or material was present on the lid or lip of the tube when it was opened. For these events, the magnitude of the potential fomite exposure is modeled via initiation of a splash event, using the splash event fault tree. The frequency and reduction factors are modeled within that tree using the MAR values from the initiating shipping events.

[99] Olsen RJ *et al* (1993) Examination gloves as barriers to hand contamination in clinical practice. *Jama* 270**:** 350-353
[100] Ibid.
[101] Ibid.
[102] Ibid.
[103] See Supplemental Information Section on Fomite Model Parameters
[104] See Supplemental Information Section on Fomite Model Parameters

This tree is run separately for select agents and non-select agents. Select agents have heightened labeling and transport requirements that make identifying them as a package for containment more likely.

Based on interviews with researchers at sites that receive viral strains from outside locations, the opportunity frequency is 5-50 packages per year, per laboratory, for both select and non-select agents. Because gain of function strains are not shipped, the shipments modeled here are regular shipments of surveillance samples gathered in the field. Each shipment is presumed to contain between 10-100 tubes; based on interviews with researchers, each tube is modeled as containing a sample volume of 1mL, resulting in a final shipment volume of 10-100mLs, distributed uniformly. The concentration of material within the tubes is modeled a log uniform distribution from 1E6 to 1E8 IU/mL, based on the reasoning that the samples come from actively infected animals and people and are likely to be at high concentrations.

1.8.1 Packaging and Packaging Failures

The requirements for packaging infectious material are prescribed and detailed in several regulations.[105, ,106 ,107] Typically, three layers of packaging are required: a primary containment vessel, often a screw cap microcentrifuge tube; a layer of absorbent material with a volume large enough to absorb the entirety of the infectious material should the primary container fail; a secondary container; and a tertiary container, typically a standard shipping cardboard box.

Because of the set regulations and requirements for packaging, failure to package a shipment correctly was assigned the rules error probability, modified to a log triangular distribution. The mode was set equal to the failure to follow a protocol of greater than ten steps, believed to be the most likely type of error made.

The USSRA interviewed subject matter experts to estimate the rate and frequency at which packages fail in transit. They use different values depending on whether the package was correctly packed, with a higher probability of failure if the package was packed improperly.[108] Those values were similarly applied here with modifications. In the USSRA, the fault tree is initiated after a package is jostled or dropped, and thus the probability of jostling or dropping is incorporated into the event frequency. Here, because this fault tree also models the possibility that a properly shipped package is not dropped but is instead opened in incorrect containment, the event tree is initiated with a package being shipped. Resultantly, the probability that primary and secondary containers fail was set equal to the USSRA probability of a package being dropped or jostled of two percent, multiplied by the probability that a package breaks if dropped or jostled or 1E-6 (1E-3 for each of the primary and secondary containers), resulting in an overall probability of 2E-8. The probability that a tertiary container fails was set equal to the USSRA probability without the additional multiplication, since nodes involving tertiary containers failing always succeed

[105] Pipeline and Hazardous Materials Safety Administration. (2011) Code of Federal Regulations Title 49 Class 6, Division 6.2—Definitions and Exceptions. In Department of Transportation (ed.), *173.134* U.S. Government Publishing Office, Washington, D.C., pp. 536-4543.

[106] Pipeline and Hazardous Materials Safety Administration. (2011) Code of Federal Regulations Title 49 Category A Infectious Substances. In Department of Transportation (ed.), *173.196*. U.S. Government Publishing Office, Washington, D.C., pp. 571-572.

[107] Pipeline and Hazardous Materials Safety Administration. (2011) Code of Federal Regulations Title 49 Category B Infectious Substances. In Department of Transportation (ed.), *173.199*. U.S. Government Publishing Office, Washington, D.C., pp. 575-577.

[108] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:140

those involving primary/secondary failing and thus the probability of dropping or jostling would have already been incorporated.

As a conservative assumption, the rate at which primary and secondary containers fail if a shipment is improperly packaged and then dropped or jostled were each increased 100 fold compared to the USSRA to a value of 1E-1. Resultantly, the probability that both containers fail is equal to that value squared (once for each container) multiplied by 2E-2 (the probability of being dropped or jostled), or a final probability of 2E-4.

1.8.1.1 Aerosol Exposure Follow Packaging Failures

If one or more layers of the packaging fail during shipping, aerosol exposures are either possible or prevented depending on the specific layers that fail and the whether the shipment was packaged correctly. If the primary and secondary containers remain intact, no exposure is possible. Similarly, should the primary and secondary containers fail but the tertiary container remains intact, any aerosol generated will be contained within the tertiary container, preventing exposure. In addition, if the primary and secondary containers fail but the shipment is packaged properly, the absorbent material will contain any generated aerosol, again preventing exposure. Only if the all three layers fail and no absorbent material is present can aerosol escape and generate a possible exposure.

Because no primary data were available regarding the fraction of material aerosolized following a package being dropped or otherwise broken, data from laboratory accidents were used as a proxy.[109] Because it was not clear which laboratory accidents were analogous to package drops, the aerosolized fractions of all accidents involving liquid material were used to build a distribution, resulting in a range from 2E-9 to 1.1E-5. The scenario involving the dropping of a bottle was believed to be the most similar event to a package being dropped, and thus it was used as the mode of the distribution, resulting in a final distribution that was log triangular from 2E-9 to 1.1E-5 with a mode of 5.7E-7.

As in the laboratory aerosolization scenarios, such as spill or centrifuge, as a conservative assumption the nearest shipment facility worker to the dropped package was modeled as breathing in the entirety of the aerosol generated.

1.8.1.2 Fomite Exposure Following Packaging Failures

Like aerosols, if one or more layers of the packaging fail during shipping, fomite exposures are either possible or prevented depending on the specific layers that fail and whether the shipment was packaged correctly. Also, like aerosols, should the primary and secondary containers remain intact, no exposure is possible. Should they fail, however, some fraction of the material contained within the tubes is likely to escape. No primary data were available regarding the fraction of material spilled if a tube breaks during a drop; as an educated assumption drops were modeled as spilling from 10% to all of the material, with a mode of 90%, resulting in a triangular distribution from 1E-1 to 1E0, with a mode of 9E-1.

If the primary and secondary containers fail and material spills, some of the liquid material may be retained by the absorbent material if the shipment was packaged correctly, and some material may absorb into the cardboard of the tertiary container should it remain intact. If the shipment was packaged correctly and the tertiary container remained intact, it was presumed the absorbent material contained the vast majority of the material, and the remaining volume was too small to penetrate the cardboard and wet the

[109] Bennett A, Parks S (2006) Microbial aerosol generation during laboratory accidents and subsequent risk assessment. *Journal of applied microbiology* 100**:** 658-663

outside of the box, preventing exposure. Should the tertiary container remain intact but the absorbent material be absent, the tertiary container was modeled as absorbing most of the material, with some leaking through the box and transferring to the shipping worker's hands. No data were available regarding the fraction of material that would be absorbed by the box; to ensure coverage of all possible outcomes, the resulting distribution ranged from none to all of the material being absorbed by the box, or a reduction factor from 0 to 1. Due to the small volume of the samples shipped, most of the infectious material should be absorbed by the box, resulting in a mode of 1E-1 (i.e. 90% is absorbed), resulting in a final distribution that was triangular from 0 to 1 with a model of 1E-1.

Similarly, should the tertiary container fail but the absorbent material be present, the absorbent material may absorb all of the infectious material on the inner layers. If the outer layers touched by the shipping worker during cleanup remain dry, exposure is prevented. If the contaminated material wets the outer layers of the absorbent material and transfers to the worker's hands, exposure occurs. It was believed that, in most cases, the absorbent material would work as designed and capture most of the liquid, resulting in the same distribution used above: one that was triangular from 0 to 1 with a mode of 1E-1.

Finally, should both the tertiary container fail and the absorbent material be absent, the box may again absorb all or none of the material. However, in this circumstance, it is likely that the infectious material would be largely separated from the tertiary container during failure, resulting in only a small fraction of the material being absorbed. This resulted in a reduction factor distribution that was again triangular from 0 to 1, but with a mode of 9E-1.

1.8.2 Package Opening Outside Containment

If a package containing infectious material is delivered intact, exposure is still possible if the infectious material is opened outside of a containment space and without proper PPE in place. Here, because the package did not experience a violent agitation and the primary container remains sealed, aerosol exposure is not possible. Instead, the modeled events are fomites that end up on staff or researcher hands when the primary tubes are opened outside of containment, due to small amounts of material being present on the lip or lid of the tube when opened, or dropping the tube while open.

Interviews with researchers revealed that shipments of surveillance samples were sent frozen in order to preserve the virus within. Because the exposure scenario modeled here is exposure to liquid upon opening the tubes, if a shipment is sent frozen, when the first person to open the package does so, all material inside will be solid, and thus no material could transfer from the tube to the hand. Because shipments are generally set frozen, failure to do so was assigned the rules error probability.

1.8.2.1 Receipt by a Trained Individual

Interviews with researchers regarding package deliveries also revealed significant differences from site to site regarding the handling of packages when delivered. At some sites, packages are delivered directly to the laboratory, with select agent packages being delivered directly to the hands of a specified individual. However, some sites used central receiving docks that accepted packages and then redelivered them to the internal destination. Some sites had no designated package delivery location, and instead stated that all packages may be delivered to a reception area or other various individuals, depending on who was available when the delivery arrived, after which packages would be forwarded to the destination site within the building.

In this model, persons trained or otherwise experienced in handling packages containing infectious material are presumed to be less likely to open them before reaching the final destination, whereas

untrained individuals are more likely to open them prior to forwarding them. Laboratory workers and central receiving workers were considered trained, and all other persons were considered untrained.

For non-select agents, at sites where anyone could receive any package, the probability of an untrained individual receiving the package was set to 50%. As an extreme case, this person was modeled as never attempting to forward the package, and thus the overall probability the package was opened outside of containment was 50%, and this was used as the maximum of the distribution. Sites where only laboratory workers receive packages would only result in an untrained person receiving the package if an error were committed, modeled as a rules error, and the minimum likelihood of a rules error, 5E-4, served as the minimum of the probability distribution. The most common circumstance during delivery was believed to be receipt by an untrained person who would immediately attempt to forward the package to the proper location and would only fail to do so if he or she misread a label. Accordingly, the mode of the distribution was set to the probability an untrained person receives the package of 50%, multiplied by the probability of misreading a label of 3E-3. When these circumstances were combined, it resulted in a log triangular distribution from 5E-4 to 5E-1, with a mode of 1.5E-3.

For select agents, due to the additional labeling requirements and special delivery regulations, the failure scenario modeled was misreading a label by the delivery person resulting in attempted delivery to the wrong individual followed by subsequent failure to forward the package by that individual due to another misreading of the label. As a result, the failure of a select agent to be delivered to a trained individual was set to the fixed misreading probability squared, or 9E-6.

1.8.2.2 Proper Package Labeling

Due to the regulations describing in the detail the way packages must be labeled with the appropriate hazard warnings on the proper containers, failing to label the package correctly was modeled as a rules error, 5E-4 to 5E-2. Because a detailed set of packaging rules would likely be available, the mode was set equal to the probability of failing to follow a protocol of greater than 10 steps, resulting in a log triangular distribution with a mode of 3E-3. These probabilities were then conditionally modified on the proper packaging status of the shipment. If the person had correctly packaged the shipment, it was reasoned that the same person would be less likely to err in labeling, so the minimum and mode were each halved. On the other hand, had the person failed to package correctly, it was reasoned the person would be more likely to fail to err in labeling, and the maximum and mode were each doubled.

1.8.2.3 Redirection to the Laboratory

Once a package had been received by an untrained individual, that individual should attempt to redirect the package to the final destination within the laboratory, but may fail to do so. Because individuals are generally inclined not to open mail not addressed to them, failure to redirect a package was assigned the rules error probability. Should a package fail to be redirected, it was assumed to be opened by the intermediate receiver, causing a potential exposure.

1.8.2.4 Opening in Containment

Should a package make it to the laboratory, it must still be opened in containment in order to prevent exposure. If the package's label is correct with the contents properly marked and the appropriate hazard stickers present, the standard requirement is to open the package under containment. All laboratory worker should be aware of this procedure, and thus failure to do so was assigned the rules error probability. On the other hand, if the package is not properly labeled, workers must intuit that the package should be opened in containment; years of experience with packages and their contents would increase

the probability that this was intuited. As a result, the opening in containment of a mislabeled package was assigned the knowledge error probability.

1.8.2.5 Fomite Exposure Following Improper Opening

Should a package be opened outside of containment, a splash event was initiated at the same probability as splashes with cell culture, and, as none of nodes prior to this point in the shipping tree had a reduction factor, using the entire MAR from the initiation of the shipping tree.

Owing to the many cascading errors that would have to occur in order for all three layers of a package containing infectious material to be opened outside of containment, this scenario was never reached in any of the Monte Carlo simulations, and all potential exposures were to shipping workers due to failed packaging.

Table S12. Material Available for Release and Opportunity Rate for Shipping Event

Opportunity Rate	Material Available for Release
5-50 per year per lab, uniformly distributed	10-100mL volume per shipment, uniformly distributed * 1e6 to 1e8 IU/mL, log uniformly distributed

Table S13. Probabilities and Reduction Factors for Release From Shipping Event

Node Name	Probability of Failure	Reduction Factor if Success	Reduction Factor if Failure
Packaged correctly	Rules & Protocol Error: 5E-4 to 5E-2, log triangularly distributed with mode of 3E-3	1 (No effect)	1 (No effect)
Primary/secondary container work if packaged correctly pass	2E-8[110]	0 (No exposure)	Aerosol: 0 (No exposure) Fomite: 1E-1 to 1, triangularly distributed with a mode of 9E-1
Primary/secondary container work if packaged correctly fail	2E-4[111]	0 (No exposure)	Aerosol: 2E-9 to 1.1E-5, log triangularly distributed with a mode of 5.7E-7[112] Fomite: 1E-1 to 1, triangularly distributed with a mode of 9E-1
Tertiary work if packaged correctly pass	1E-3[113]	0 (No exposure)	Aerosol: 1 (No effect) Fomite: 0 to 1, triangularly distributed with a mode of 1E-1
Tertiary work if packaged correctly fail	1E-3[114]	Aerosol: 0 (No exposure) Fomite: 0 to 1,	Aerosol: 1 (No effect) Fomite: 0 to 1, triangularly distributed with a mode of 9E-1

[110] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility

[111] Ibid.

[112] Bennett A, Parks S (2006) Microbial aerosol generation during laboratory accidents and subsequent risk assessment. *Journal of applied microbiology* 100**:** 658-663

[113] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility

[114] Ibid.

		triangularly distributed with a mode of 1E-1	
Shipment sent frozen	Rules Based Error: 5E-4 to 1E-1, log triangularly distributed with a mode of 6E-3	1 (No effect)	1 (No effect)
Received by trained individual, for select agent	9E-6	1 (No effect)	1 (No effect)
Received by trained individual, for non-select agent	Rules Based Error: 5E-4 to 5E-1, log triangularly distributed with a mode of 1.5E-3	1 (No effect)	1 (No effect)
Labeled correctly if packaged correctly pass	Rules & Protocol Based Error: 2.5E-4 to 5E-2, log triangularly distributed with a mode of 1.5E-3	1 (No effect)	1 (No effect)
Labeled correctly if packaged correctly fail	Rules & Protocol Based Error: 5E-4 to 1E-1, log triangularly distributed with a mode of 6E-3	1 (No effect)	1 (No effect)
Redirected to laboratory	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	1 (No effect)
Opened in containment if labeled correctly pass	Rules Error: 5E-4 to 5E-2, log uniformly distributed	0 (No exposure)	1 (No effect)
Opened in containment if labeled correctly fail	Knowledge Error: 5E-3 to 1E-1, log uniformly distributed	0 (No exposure)	1 (No effect)

1.9 Solid Waste Event Tree

This scenario models the fate of solid waste, in the form of an animal carcass or animal bedding, in the decontamination process. Because the fate model of the uncontaminated waste only considers seagulls becoming infected by directly consuming the waste at a municipal waste dump, the fault tree model does not consider cell culture or other types of solid waste, as they were presumed to be inedible and thus unappealing to birds. In addition, because no data were available on the amount of material a bird would

have to consume to become infected, as a conservative assumption, any still-contaminated material was considered enough to cause infection and the concentration of virus was not tracked. Because no data were available on the decontamination state of the viruses under investigation here should a suboptimal cycle of the autoclave run, solid waste are modeled as either decontaminated or not. The fault tree is run under four conditions: each combination of material (carcass or bedding) and biosafety (BL2 or BL3) conditions.

Based on interviews with researchers, the opportunity frequency for animal carcasses was set to once per week to once per day, or 50-250 opportunities per year, per laboratory, uniformly distributed. As for bedding, interviews with researchers revealed that animal bedding is most commonly changed every other day, or twice per week at a minimum. Given that many facilities run animal experiments continuously, and that a facility could have multiple animal experiments running simultaneously, the opportunity frequency for animal bedding was set from twice per week to every day, or 100-250 times per year, per laboratory, uniformly distributed.

In a BL3 facility, all material must be autoclaved out, and many BL3 labs have a pass-through autoclave at the boundary of the containment and non-containment space. Given the unlikeliness of a worker taking infectious material out on his/her person, the autoclave was presumed to be run for all waste in the BL3. In contrast, although infectious materials from a BL2 lab are required to be autoclaved, often the autoclaves are located distant to the containment space, and regular trash cans are present within the containment space. As a result, a worker could either forget to dispose of the infectious material in the autoclave bag and/or forget to autoclave material, sending it with regular trash. Because of the requirements to autoclave, failing to autoclave BL2 material was assigned the rules error probability.

Interviews with researchers revealed that a biological indicator (BI) is not typically run with most types of waste. Instead, BIs are only used when an autoclave is brought back into service after maintenance or at a regular interval to verify autoclave function, typically quarterly or monthly. One exception to this is animal bedding. In order to prevent failures to decontaminate cages due to steam inability to penetrate tightly stacked cages, BIs are required for each bedding decontamination run. In the fault tree, failure to use a BI with carcasses is set to one minus the rate of success, with the success rate set to 4/(yearly frequency of autoclave runs) to 12/(yearly frequency of autoclave runs), distributed uniformly, to model quarterly to monthly use. For animal bedding, due to the requirements, failure to use a BI was set to the rules error rate. Properly interpreting the BI involves following a standard protocol included with the BI kit. As a result, the failure to interpret the BI correctly was set to a log triangular distribution bounded by the rules error probability, with a mode of failure to follow a protocol of greater than ten steps of 3E-3, given that a protocol failure is expected to be the most common error resulting in failure.

Interviews with researchers also revealed that secondary incinerators are used at all sites for animal carcasses. Some sites use incinerators for all wastes, while others use them only for carcasses. Based on these interviews, the fraction of sites that use incinerators for all wastes was estimated to be 9% to 25%, with the corresponding failure to use an incinerator of 7.5E-1 to 9.1E-1. Note that sites that only use an autoclave meet all decontamination requirements; the use of a secondary decontamination method is neither a requirement nor a recommendation.

Table S14. Material Available for Release and Opportunity Rate for Solid Waste Event

Opportunity Rate for Animal Carcass	Opportunity Rate for Animal Bedding
5-250 per year per lab, uniformly distributed	100-250 per year per lab, uniformly distributed

Table S15. Probabilities and Reduction Factors for Release From Solid Waste Event			
Node Name	**Probability of Failure**	**Reduction Factor if Success**	**Reduction Factor if Failure**
Waste sent for decontamination	BL2: Rules Error: 5E-4 to 5E-2, log uniformly distributed BL3: 0	BL2: 1 (No effect) BL3: 1 (No effect)	BL2: 1 (No effect) BL3: -
Autoclave run properly	Rules Error: 5E-4 to 5E-2, log uniformly distributed	0 (No exposure occurs)	1 (No effect)
BI used	Carcass: (1-4/frequency) to (1-12/frequency) for quarterly or monthly use, uniformly distributed Bedding: Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	1 (No effect)
BI interpreted correctly	Rules & Protocol Error: 5E-4 to 5E-2, log triangularly distributed with mode of 3E-3	0 (No exposure occurs)	1 (No effect)
Incinerator used	Carcass: Rules Error: 5E-4 to 5E-2, log uniformly distributed Bedding: 7.5E-1 to 9.1E-1, uniformly distributed	0 (No exposure occurs)	1 (No effect)

1.10 Animal Respiration Event Tree

In this scenario, a worker inadvertently omits an animal isolation cage, or omits or otherwise improperly installs an air filter on an isolation cage, resulting in worker exposure to virus respired by an infected animal. This scenario focused exclusively on ferrets infected with influenza, as mice infected with influenza cannot transmit the virus and no transmissible animal model exists for coronaviruses. The opportunity frequency is the estimated number of ferrets used in a laboratory per year derived from interviews with researchers, 66-1600, distributed uniformly. If an event occurs, the animal respires virus into the room for a period of time between 0-48 hours, which is the maximum time until the animal is placed in a new cage with a new filter during the next bedding change.

Based on literature reporting the maximum exhalation rate of ferrets[115] and human sneeze rates,[116] the infectious material available for release is determined to be between 0 to 6.8e2 IU/hour with a mode of 22.2 IU/hour. From the ferret-exhalation source, ferret viral exhalation rates from the three human-transmissible viruses PN99, SI06 and MX09, and excluding the non-transmissible H5N1 viruses, were combined into an overall distribution. Several ferrets exhaled no detectible virus, resulting in a minimum of 1 IU. One ferret, infected with MX09, exhaled a total of approximately 700 IU in the five-minute stimulated sneeze period (source Figure 5C, right panel). Per the source, ferrets sneezed approximately

[115] Gustin KM *et al* (2013) Comparison of the levels of infectious virus in respirable aerosols exhaled by ferrets infected with influenza viruses exhibiting diverse transmissibility phenotypes. *Journal of virology* 87**:** 7864-7873

[116] Bischoff WE *et al* (2006) "Gesundheit!" sneezing, common colds, allergies, and Staphylococcus aureus dispersion. *The Journal of infectious diseases* 194**:** 1119-1126

30-100 times in that five-minute period. If, as a conservative assumption, the maximally exhaling ferret sneezed the minimum 30 times, sneezes conservatively emit 2.3E1 IU/sneeze.

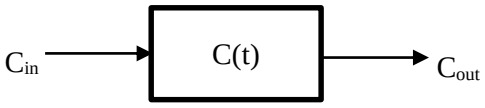
This per sneeze emission amount was combined with a sneeze rate to compute the typical and maximum emission rates. Because no data were available regarding typical unstimulated ferret sneeze rates, human sneeze rates were used as a proxy for ferrets. In a study examining human sneeze rates, unstimulated humans sneezed four times in a total of 176, 20-minute observation periods, or four times in 3520 minutes. Modeling the sneeze rate with a binomial distribution with 3520 trials and four "successes" results in a conservative, 95% CI baseline sneeze rate of 2.9E-3 sneezes per minute. The source reveals no single maximum number of sneezes, but reports volunteers sneezed 5.4±4.4 times after histamine exposure prior to rhinovirus exposure (the maximum rate reported in the source). The +1 SD rate of 9.8 sneezes per 20-minute observation period, or 4.9E-1 sneezes per minute was used as a proxy for the maximum sneezing rate. Using the 2.3E1 IU/sneeze emission calculated above results in 22.2 IU/hr. emission for ferrets sneezing at the baseline human sneeze rate and 6.8E2 IU/hr. for ferrets sneezing at the maximum human histamine-stimulated rate. The baseline sneeze rate was used as the most likely scenario for an infected ferret, and the maximum sneeze rate was used as the maximum emission rate, modeling a ferret experiencing several sneezing fits per hour. As a result, these numbers were combined with the minimum emission rate of 1 IU, modeling ferrets that do not sneeze, to result in a log triangular distribution from 1-6.8E2 IU/hr. with a mode of 22.2 IU/hr.

Because isolation cages and cage HEPA filters are required for the types of experiments modeled here, the failure to use them properly was assigned the rules error rate. All other failure rates were the same as those for the aerosol component of the centrifuge fault tree, described above.

1.10.1 Conversion of Event Outcomes to Infection Probability

The output of this fault tree is the number of hours per year that a worker may be exposed to infectious animal respiration and the average infectious units (IU) per hour originating from the infected animal and filtered by worker PPE. Unlike the output of many of the other trees, this IU exposure is not directly convertible into an infection probability because it does not take into account room volume or air exchange in the lab. Compared to other aerosol sources, such as that modeled in the centrifuge and spill trees, the worker is not modeled as breathing in all of the virus as in the scenario modeled here. The aerosol is generated at a low level over a significant period of time, allowing the steady state condition to be reached. In addition, the worker may not encounter the aerosol until a significant period after it is first generated, while in the centrifuge and spill scenarios, the worker experiences the aerosol the moment it first appears. This also makes the steady state condition modeled here more appropriate.

To account for both air volume and air exchange, a one box stock-and-flow model was constructed to calculate the steady-state concentration of IUs in the lab air. This model had a constant inflow of the animal respiration value divided by the volume of the room (400 ft^3)[117] and a constant outflow of 12 air volume exchanges per hour, based on the routine standards in animal care facilities.[118] The change in the room concentration is the simple difference between the inflow and outflow.



[117] Based on a conservative minimum room area of 50 ft^2 from the distribution of room sizes in the animal escape tree, and a conservative ceiling height of 8 ft.

[118] National Research Council (U.S.). Committee for the Update of the Guide for the Care and Use of Laboratory Animals. *et al* (2011) *Guide for the care and use of laboratory animals*, 8th edn. Washington, D.C.: National Academies Press.

$$C_{in} = \frac{E}{V}\left[\frac{IU}{hr - ft^3}\right]$$

$$C_{out}(t) = C(t) * \lambda\left[\frac{IU}{hr - ft^3}\right]$$

$$\Delta C(t) = C_{in} - C_{out}(t)\left[\frac{IU}{hr - ft^3}\right]$$

$$C(\infty) = \frac{E}{V * \lambda}\left[\frac{IU}{ft^3}\right]$$

Where:

C(t) = IU concentration in the room at time t

C_{in} = In flow of IUs into the room – this is constant based on the exhalation of the animal and worker PPE

E = Exposure to worker in IU, undiluted by room or exchange

V = Room volume = 400 ft^3

C_{out} (t) = Out flow of IUs into the room – this is a fraction of the current concentration in the room

λ = Number of time room air volume is exchanged per hour = 12 hr^{-1}

ΔC(t) = Change in the room concentration at time t

C(∞) = The steady state concentration of IUs in the room

Once the steady state concentration in the room was calculated, it was multiplied by the volume of air a worker breathes during each hour based on a typical breathing rate of 20 liters per minute.[119] This final value, in IU, was used to calculate the infection risk from exposure to the aerosol generated by an animal respiration event. Since animals infected with the two corona viruses (MERS/SARS) are not infectious to humans, the infection hazard from these two viruses was presumed negligible.

Table S16. Material Available for Release and Opportunity Rate for Animal Respiration Event

Opportunity Rate	Material Available for Release
66-1600 ferrets per lab per year, uniformly distributed * 0-48 hours per experiment, uniformly distributed	0 to 6.8e2 IU/hour, log triangularly distributed with a mode of 22.2 IU/hour[120,121]

Table S17. Probabilities and Reduction Factors for Release From Animal Respiration Event

Node Name	Probability of Failure	Reduction Factor if Success	Reduction Factor if Failure
Animal in primary containment cage	Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	1 (No effect)
Cage filter work	Rules Error: 5E-4 to 5E-2, log uniformly distributed	2E-6 to 3E-4, log triangularly	1 (No reduction)

[119] Standards for Protection Against Radiation. 10 C.F.R. § 20, Appendix B

[120] Gustin KM *et al* (2013) Comparison of the levels of infectious virus in respirable aerosols exhaled by ferrets infected with influenza viruses exhibiting diverse transmissibility phenotypes. *Journal of virology* 87**:** 7864-7873

[121] Bischoff WE *et al* (2006) "Gesundheit!" sneezing, common colds, allergies, and Staphylococcus aureus dispersion. *The Journal of infectious diseases* 194**:** 1119-1126

		distributed with a mode of 3E-5[122]	
Directional airflow present	BL2: 1 BL3: 0	1 (No effect)	1 (No effect)
Directional airflow work	2.25E-8 to 2.3E-1, log uniformly distributed for fan failure[123,124] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	1 (No effect)	1 (No effect)
Suite HEPA present	0	1 (No effect)	-
Primary HEPA work	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[125] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[126]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
Double binding HEPA present	1	-	1 (No effect)
Secondary HEPA work if primary HEPA pass	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[127] * Rules Error: 5E-4 to 5E-2, log uniformly distributed for ignoring the alarm	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[128]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
Secondary HEPA work if primary HEPA fail	1.2E-2 to 1.8E-2, triangularly distributed with a mode of 1.5E-2 for degraded filter[129]	2E-6 to 3E-4, log triangularly distributed with a mode of 3E-5[130]	3E-4 to 1, log triangularly distributed with a mode of 3E-4
N95/PAPR worn	BL2: 1[131] BL3: Rules Error: 5E-4 to 5E-2, log uniformly distributed	1 (No effect)	1 (No effect)
N95/PAPR work	Knowledge & Protocol Error: 3E-3 to 1E-1, log triangularly distributed with 3E-3 mode	2E-4 to 4E-2, log uniformly distributed[132,133]	1 (No reduction)

1.11 Animal Escape Event Tree

This scenario models an animal potentially escaping its primary cage, the containment room, and the antechamber immediately outside of the containment room. A worker inadvertently forgetting to re-latch

[122] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility

[123] Ghosh D, Campbell R (2004) HVAC Equipment Aging and Reliability Issues at Commercial Nuclear Power Plants. In *28th Nuclear Air Cleaning Conference*.

[124] Cadwallader LC (1999) Ventilation Systems Operating Experience Review for Fusion Applications. *INEEL Report, INEEL/EXT-99-01318*

[125] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility

[126] Ibid.

[127] Ibid.

[128] Ibid.

[129] Ibid.

[130] Ibid.

[131] Wilson D, Chosewood L (2009) Biosafety in microbiological and biomedical laboratories (BMBL). 5. *Centers for Disease Control and Prevention*

[132] Department of Homeland Security Science and Technology Directorate (2012) *Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment* Vol. I, The National Bio and Agro-defense Facility 1:100

[133] OSHA. (2009). Assigned Protection Factors for the Revised Respiratory Protection Standard. https://www.osha.gov/Publications/3352-APF-respirators.pdf. Last Update 2009. Accessed December 2015.

the cage after performing an animal procedure precipitates the event. Ferrets are the only animal considered in this scenario. Mice were not considered as the cages typically used in relevant work fit tightly into racks, leaving no room for the lid to be open while the cage is racked. Additionally, interviews with researchers revealed that, even if there was room to remove the lid, a mouse would not be strong enough to lift it. An animal escape has no direct consequences; instead, if an animal escapes it initiates an animal respiration event using the animal respiration event tree. Additionally, the animal may initiate an animal bite event when the worker attempts to recover the animal. Both of these events are modeled via subsets of the corresponding event trees, using the material available for release numbers in those trees. These two outcomes may lead to either aerosol exposure or hand contamination.

The opportunity frequency was set to twice per week to every work day, or 100-250 times per year, based on interviews with researchers and the rate at which animals are weighed and cage bedding changed, and accounting for the possibility that multiple animal experiments may be running concurrently. In this model, workers had the potential to leave up to one cage unlatched, as the probability of committing multiple errors and leaving multiple cages open was a low enough probability as to be an insignificant contributor to risk.

Cages are required to be latched when animal procedures are not in progress. Failure to latch the cage was assigned the rules error probability with one modification: many ferret cages have two sets of latches, one on the inner cage and one on the outer one, and both would have to be unlatched for a ferret to escape. To incorporate that, the minimum probability of a worker failing to latch the cage was modified to the minimum rules error rate squared, resulting in an overall log uniform distribution from 2.5E-7 to 5E-2.

A review of the literature and interviews with researchers revealed that the period of time during which an animal is infectious varies from one to seven days, with the exact duration varying significant from strain to strain and animal to animal. As a result, the maximum time since inoculation the animal allowed to escape was set to seven days. Note that uninfected animals may escape and perhaps injure workers via bites, but cannot cause infections.

1.11.1 Animal Lethargy

Infected animals may be lethargic due to the ongoing infection and these animals may lack the will or energy to escape the cage. Additional sources and interviews revealed that the time from inoculation to the day the animal becomes lethargic varies considerably from strain to strain, and so was modeled as a uniform distribution from one to seven days. It was assumed that all cages were equally likely to be left unlatched, and that the state of the contained animal did not influence the probability that the worker forgot to latch the cage. Considering that, the number of days elapsed since inoculation in which the animal could escape was modeled as a second uniform distribution from one to seven days. In order for the animal to escape, the cage must be unlatched on a day prior to the animal becoming lethargic. It was conservatively assumed that if both events coincide, the cage is left unlatched at an hour prior to onset of lethargy. Given both events are described by uniform distributions from one to seven days, the probability the day drawn in the first draw is equal to or less than the day drawn in the second is 5.7E-1, and this was used as the fixed value the animal is lethargic on the day the cage is unlatched.

1.11.2 Animal Desire to Escape

Animals were presumed to desire to escape given the possibility, so the probability the animal fails to remain in the cage should it not be lethargic was fixed at unity.

Once an animal has escaped a cage, it may choose to remain the room with a familiar environment, a known source of food and water, and a social group, or it may choose to continue exploring if given the opportunity to dart through a door opened by a worker. Because no data were available assessing the escape probability of a laboratory animal, data from the rate at which minks choose to stay or leave farms when released by animal activists was used as a proxy.[134,135,136,137,138] A minimum fraction of 1.2E-2 and a maximum fraction of 9.8E-1 of the animals reportedly left the farm, with a mean of 1.6E-1. These numbers were combined into a triangular distribution using the source mean as the distribution mode.

An animal that desires to leave the room must do so during the small window of time that the door is open, as it was presumed that an animal that does not escape during the first time a worker enters the room would be noticed and caught by that worker. It was reasoned that animals would only be able to move quickly enough to escape through the open door if they were within one foot from the sweep of the door. Ferrets further from the door would either be noticed immediately by personnel or not have time to escape before the door closes. Using a typical door width of three feet gives a total possible escape zone of six square feet. Because no data were available on the typical size of an animal containment room, a reasoned estimate of 50 and 150 square feet was used, with any size in between equally likely. It was presumed that an animal desiring to escape would be equally likely to be anywhere in the room at the moment the door was open, resulting in the probability the animal was in the escape zone of 6/50 to 6/150, distributed uniformly.

It was presumed that antechambers could be larger, up to 500 feet, modifying the probability the animal was within the escape zone. However, the desire of animals to escape and probabilities of being noticed by workers were modeled as the same as in the containment rooms.

Finally, an animal in the escape zone that attempts to escape must also remain unnoticed by the worker. Because no data were available to estimate the probability that a worker in a research lab would notice an animal attempted to escape, an informed estimate that an animal would fail to be noticed between one in 1000 and one in ten attempts, leading to a failure probability distribution of 1E-3 to 1E-1, distributed log uniformly.

1.11.3 Conversion of Event Outcomes to Infection Probability

As mentioned above, the outcome of animal escape events are potential animal respiration and animal bite events. For the animal respiration component, the animal was assumed to be loose for ten hours. As cages are usually checked at the beginning and end of the work day, ten hours represents a conservative maximum for the duration an animal could be loose before the escape would be noticed, and, as a

[134] Nuovo blitz degli animalisti Liberati 1.400 visoni da pelliccia. *Gazzetta di Mantova*, January 18, 2012, http://gazzettadimantova.gelocal.it/mantova/cronaca/2012/01/18/news/nuvo-blitz-degli-animalisti-liberati-1-400-visoni-da-pelliccia-1.3080658. Last Update 2012. Accessed December 2015.

[135] Minkfarm drabbad av utsläppta djur. Småland, October 10, 2010, http://sverigesradio.se/sida/artikel.aspx?programid=105&artikel=4086537. Last Update 2010. Accessed December 2015.

[136] Carbery G. Investigation under way after 5,000 mink freed from farm. *The Irish Times*. September 29, 2010. http://www.irishtimes.com/news/investigation-under-way-after-5-000-mink-freed-from-farm-1.656730. Last Update 2010. Accessed December 2015.

[137] Thousands of mink freed in B.C. in apparent act of `eco-terrorism' *Vancouver Province*, August 27, 2008. http://www.canada.com/reginaleaderpost/news/story.html?id=7d4845f1-4bc7-4162-bb57-4919aff76869. Last Update 2009. Accessed December 2015.

[138] Skrinjar J. Mink released from Pa. farm; 400 die. *Farm and Dairy*, June 14, 2007, http://www.farmanddairy.com/news/mink-released-from-pa-farm-400-die/478.html. Last Update 2007. Accessed December 2015.

conservative assumption, the workers are presumed to be exposed to the respiration of the animal for the entirety of the event. Considering the animals modeled here were ferrets typically used for human transmissibility studies on zoonotic influenzas, animals in the main containment chamber were assumed to be respiring in a BL3 environment while those that escaped to the antechamber were assumed to be respiring in a BL2 environment.

Due to the propensity for ferrets to bite and the likely heightened fear of a ferret, it was conservatively presumed that the animals would always attempt to bite the worker upon recapture. This was modeled by taking the animal bite tree outcomes, weighted by probability of occurring, and multiplying them by the probability of infection for each of those outcomes.

The final infection risk from animal escape events is the one minus the joint probability that the worker is not infected by either the animal respiration or the animal bite. Animal escape events thus incorporate risk from aerosol exposure and fomite exposure on the hands or face. Since animals infected with the two corona viruses (MERS/SARS) are not infectious to humans, the infection hazard from these two viruses was set to zero.

Table S18. Opportunity Rate for Animal Escape

Opportunity Rate
100-250 times per year per lab, uniformly distributed

Table S19. Probabilities and Reduction Factors for Release During Animal Escape

Node Name	Probability of Failure	Reduction Factor if Success	Reduction Factor if Failure
Cage latched	Rules Based Error: 2.5E-7 to 5E-2, log uniformly distributed	1 (No effect)	1 (No effect)
Animal lethargic	5.7E-1, fixed	1 (No effect)	1 (No effect)
Animal remains in cage	1	1 (No effect)	1 (No effect)
Animal noticed by personnel	1E-3 to 1E-1, log uniformly distributed	1 (No effect)	1 (No effect)
Animal remains in room	6/50-150, uniformly distributed for potential of escape * 1.2E-2 to 9.8E-1, triangularly distributed with a mode of	1 (No effect)	1 (No effect)

	1.6E-1 for desire to escape[139,140,141,142,143]		
Animal remains in antechamber	6/50-500, uniformly distributed for potential of escape * 1.2E-2 to 9.8E-1, triangularly distributed with a mode of 1.6E-1 for desire to escape[144,145,146,147,148]	1 (No effect)	1 (No effect)

1.12 Worker Response to Incident Event Tree

This event tree models the actions a worker or several workers may take after experiencing an exposure. The incidents are divided into two types modeled separately. First, high-risk and overt events occur when the likelihood of exposure is high and the event is self-announcing (e.g. spills), resulting in an immediate response. Secondly, low-risk or covert events occur when either the likelihood of exposure is low or the exposure may be unnoticed, pushing a response off until one or more workers become symptomatic. The output is the number of workers that were successfully isolated or avoided infection and the number of workers that mingled with the community, potentially causing secondary cases. Based on interviews with researchers, overt and high-risk exposures are modeled as required to be reported, while covert or low-risk exposures may not be. Additionally, and based on the same interviews, workers are required to report any illness symptoms, regardless of the circumstance.

In the fault tree analysis, each worker has the opportunity to report the exposure immediately as it happens for overt or high-risk exposures. If any worker reports the exposure, all potentially exposed workers are treated and isolated from the general population. The probability each worker fails to report

[139] Nuovo blitz degli animalisti Liberati 1.400 visoni da pelliccia. *Gazzetta di Mantova*, January 18, 2012. http://gazzettadimantova.gelocal.it/mantova/cronaca/2012/01/18/news/nuvo-blitz-degli-animalisti-liberati-1-400-visoni-da-pelliccia-1.3080658. Last Update 2012. Accessed December 2015.

[140] Minkfarm drabbad av utsläppta djur. Småland, October 10, 2010, http://sverigesradio.se/sida/artikel.aspx?programid=105&artikel=4086537. Last Update 2010. Accessed December 2015.

[141] Carbery G. Investigation under way after 5,000 mink freed from farm. *The Irish Times*. September 29, 2010. http://www.irishtimes.com/news/investigation-under-way-after-5-000-mink-freed-from-farm-1.656730. Last Update 2010. Accessed December 2015.

[142] Thousands of mink freed in B.C. in apparent act of `eco-terrorism' *Vancouver Province*, August 27, 2008. http://www.canada.com/reginaleaderpost/news/story.html?id=7d4845f1-4bc7-4162-bb57-4919aff76869. Last Update 2009. Accessed December 2015.

[143] Skrinjar J. Mink released from Pa. farm; 400 die. *Farm and Dairy*, June 14, 2007, http://www.farmanddairy.com/news/mink-released-from-pa-farm-400-die/478.html. Last Update 2007. Accessed December 2015.

[144] Nuovo blitz degli animalisti Liberati 1.400 visoni da pelliccia. *Gazzetta di Mantova*, January 18, 2012. http://gazzettadimantova.gelocal.it/mantova/cronaca/2012/01/18/news/nuvo-blitz-degli-animalisti-liberati-1-400-visoni-da-pelliccia-1.3080658. Last Update 2012. Accessed December 2015.

[145] Minkfarm drabbad av utsläppta djur. Småland, October 10, 2010, http://sverigesradio.se/sida/artikel.aspx?programid=105&artikel=4086537. Last Update 2010. Accessed December 2015.

[146] Carbery G. Investigation under way after 5,000 mink freed from farm. *The Irish Times*. September 29, 2010. http://www.irishtimes.com/news/investigation-under-way-after-5-000-mink-freed-from-farm-1.656730. Last Update 2010. Accessed December 2015.

[147] Thousands of mink freed in B.C. in apparent act of `eco-terrorism' *Vancouver Province*, August 27, 2008. http://www.canada.com/reginaleaderpost/news/story.html?id=7d4845f1-4bc7-4162-bb57-4919aff76869. Last Update 2009. Accessed December 2015.

[148] Skrinjar J. Mink released from Pa. farm; 400 die. *Farm and Dairy*, June 14, 2007, http://www.farmanddairy.com/news/mink-released-from-pa-farm-400-die/478.html. Last Update 2007. Accessed December 2015.

the exposure was assigned to the rules error rate, and the joint probability *all* workers fail to report is the probability of failure of a single worker raised to the power of the number of exposed workers. If no worker reports, workers are not isolated until at least one worker shows symptoms, at which point workers are offered a second opportunity to report the illness, and, if any do, any exposed workers are isolated. The failure of any or all workers failing to report once symptoms have appeared was assigned the same probability as failing to report the initial exposure, for the same reasons. Workers not isolated until after symptoms appear have a possibility that they were contagious before they were isolated, causing a secondary case in the community.

In comparison, low-risk or covert exposures are not reported immediately or are not immediately acted upon. These exposures only become reportable once one or more workers shows symptoms, after which the exposure follows the same tree as an originally unreported high-risk exposure.

For influenza, one source deliberately infected several people with influenza on the same day, then tracked the severity of illness afterward. This source reported both the fraction of people showing particular symptoms on the first day after exposure, as well as the fraction of people shedding on that day. A maximum of approximately 70% of people were shedding virus on the first day after exposure. In the same period, approximately 35% of people had the diagnosable symptom of nasal patency, the symptom with the highest prevalence. As the total number of people showing any symptom was not reported, any individual who had one or more symptoms was presumed to show nasal patency, and thus approximately 35% of the exposed individuals had symptoms on day one. By assuming everyone who was showing symptoms was shedding virus, the fraction of people not showing symptoms but shedding on day one was calculated as 70-35% = 35%, or half of the 70% who shed. This 50% was assigned as the maximum probability that a person with an active influenza infection would be contagious. This study is incomplete, however, and does not provide data sufficient to provide a direct estimate. A study that captures individuals, the days they shed, the amounts they shed, and the severity of the symptoms, on a per individual basis, would provide a significant contribution to the epidemiology of flu infections and provide better estimates of the numbers in this fault tree.

Three other studies[149,150,151] reported the fraction of seasonal influenza infections that remain asymptomatic, with a mean of 13%. A single study[152] reported 9.4% of 2009 H1N1 pandemic infections were asymptomatic. The fraction asymptomatic for each strain were averaged to 11%, and this value used in combination with the 50% value computed above to result in a final distribution of the probability of contagiousness prior to symptoms of 1.1E-1 to 5E-1, uniformly distributed.

For coronaviruses, two studies[153,154] provided estimates of 0% and 13% for the asymptomatic infection rate of SARS. No studies were found to report rates of asymptomatic infection in MERS. These two values for SARS served as the boundaries of a uniform probability distribution, and the same values were used for MERS.

[149] Lau LL *et al* (2010) Viral shedding and clinical illness in naturally acquired influenza virus infections. *Journal of Infectious Diseases* 201**:** 1509-1516

[150] Loeb M *et al* (2012) Longitudinal study of influenza molecular viral shedding in Hutterite communities. *Journal of Infectious Diseases* 206**:** 1078-1084

[151] Suess T *et al* (2012) Comparison of shedding characteristics of seasonal influenza virus (sub) types and influenza A (H1N1) pdm09; Germany, 2007–2011. *PloS one* 7**:** e51653

[152] Papenburg J *et al* (2010) Household transmission of the 2009 pandemic A/H1N1 influenza virus: elevated laboratory-confirmed secondary attack rates and evidence of asymptomatic infections. *Clinical Infectious Diseases* 51**:** 1033-1041

[153] Le Vu S *et al* (2006) Absence of infection in asymptomatic contacts of index SARS case in France. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 11**:** 40-41

[154] Wilder-Smith A *et al* (2005) Asymptomatic SARS coronavirus infection among healthcare workers, Singapore. *Emerging infectious diseases* 11**:** 1142-1145

Once a worker reports an exposure, regardless of type, he or she and all other potentially exposed workers are expected to be isolated from the community. Given the large number of people involved in coordinating the institution response, the probability that all individuals simultaneously commit an error and forget to isolate workers was considered negligible. However, any specific individual may break isolation and mingle with the community. Due to the isolation protocol being a requirement, the failure of any individual to obey the isolation protocol was assigned the rules error probability.

For influenza exposures, workers are expected to be vaccinated if a vaccine is available. As the vaccine is much more likely to be ineffective than a worker is likely to fail to be vaccinated, the probability that a worker becomes infected despite a vaccine being available is dominated by the vaccine efficacy. For the fault tree analysis, the vaccines workers received were modeled as having an efficacy distribution similar to that of the seasonal vaccine. During the last ten flu seasons, CDC estimates the influenza vaccine efficacy ranged from 1E-1 to 6E-1, with a mean of 4.4E-1[155], resulting in a failure probability distribution of 4E-1 to 9E-1 with a mean of 5.6E-1. These data were combined with the possibility that no vaccine existed for the strain the worker was using (i.e. a failure probability of 1.0), resulting in a triangular distribution from 4E-1 to 1E0, and, as it was presumed that a vaccine being available would be the most common circumstance, with a mode of 5.6E-1.

Additionally, interviews with researchers revealed that, for influenza, antivirals would be given prophylactically as soon as the exposure were reported. Given the number of people likely to be aware of the exposure incident, giving no antivirals would require several consecutive errors by many parties, and thus it was presumed that the probability of no antivirals being given was negligible. Because no sources were available describing the reduction in transmissibility of an influenza infection under antiviral treatment, the prophylactic efficiency of antivirals at preventing infection was used as a proxy, with the presumption that an infection prevented entirely by the antivirals was never contagious. Across all types of influenza and available neuraminidase inhibitors, sources reported between a 0 and 80% efficacy at preventing infection when given prophylactically.[156,157,158,159,160,161,162,163,164] When no source documenting prophylactic effectiveness in humans was available, antivirals were presumed to be ineffective.

[155] Centers for Disease Control and Prevention. Seasonal Influenza Vaccine Effectiveness, 2005-2015. http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm. Last Update June 24, 2015. Accessed Aug 11, 2015.

[156] Welliver R *et al* (2001) Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 285**:** 748-754

[157] Hayden FG *et al* (1999) Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *The New England journal of medicine* 341**:** 1336-1343

[158] Calfee DP *et al* (1999) Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 43**:** 1616-1620

[159] Monto AS *et al* (1999) Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 282**:** 31-35

[160] Monto AS *et al* (2002) Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *The Journal of infectious diseases* 186**:** 1582-1588

[161] Barroso L *et al* (2005) Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. *Antiviral therapy* 10**:** 901-910

[162] Odaira F *et al* (2009) Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May-June 2009. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 14

[163] Govorkova EA *et al* (2007) Efficacy of oseltamivir therapy in ferrets inoculated with different clades of H5N1 influenza virus. *Antimicrob Agents Chemother* 51**:** 1414-1424

[164] World Health Organization (2014) Avian influenza A(H7N9) virus: Post-exposure antiviral chemoprophylaxis of close contacts of a patient with confirmed H7N9 virus infection and/or high-risk poultry/environmental exposures.

For antivirals given after symptoms appeared, it was assumed that an infection had already begun and the worker was already contagious. The probability that antivirals would be able to stop contagiousness, then, was insignificant compared to the probability the worker would violate quarantine; both antivirals and following of isolation protocol were combined into a single node, where each worker may break isolation with a failure probability equal to a rules error. Mr. T

For coronaviruses, no antivirals or vaccines are available, and so the failure rates of both were set to 1.0.

Table S20. Material Available for Release From Worker Behavior

Material Available for Release
Discrete values of number of workers, from 1 to 5.

Table S21. Probabilities and Reduction Factors for Release From Worker Behavior

Node Name	Probability of Failure	Reduction Factor if Success	Reduction Factor if Failure
Worker(s) vaccinated against agent	Flu: 0.4 to 1, triangularly distributed with a mode of 0.56[165] SARS/MERS: 0	0 (No exposure occurs for worker)	1 (No effect)
Incident is reported as high-risk by at least one worker	Rules Based Error: 5E-4 to 5E-2 raised to the power of the number of workers in MAR, log uniformly distributed	1 (No effect)	1 (No effect)
Worker(s) follow isolation protocol	Rules Error: 5E-4 to 5E-2 for each individual worker, log uniformly distributed	0 (No exposure occurs for worker)	1 (No effect)
Worker(s) infectious before symptoms	Flu: 0.11 to 0.50, uniformly distributed[166] SARS: 0 to 0.13, uniformly distributed[167,168]	1 (No effect)	1 (No effect)
At least one worker reports symptoms when they appear	Rules Based Error: 5E-4 to 5E-2 raised to the power of the number of workers in MAR, log uniformly distributed	1 (No effect)	1 (No effect)

[165] Centers for Disease Control and Prevention. Seasonal Influenza Vaccine Effectiveness, 2005-2015. http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm. Last Update June 24, 2015. Accessed Aug 11, 2015.

[166] Doyle WJ *et al* (1998) Effect of rimantadine treatment on clinical manifestations and otologic complications in adults experimentally infected with influenza A (H1N1) virus. *The Journal of infectious diseases* 177**:** 1260-1265

[167] Wilder-Smith A *et al* (2005) Asymptomatic SARS coronavirus infection among healthcare workers, Singapore. *Emerging infectious diseases* 11**:** 1142-1145

[168] Le Vu S *et al* (2006) Absence of infection in asymptomatic contacts of index SARS case in France. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 11**:** 40-41

Antivirals prevent transmissible infections	0.2 to 1 for each individual worker, uniformly distributed[169,170,171,172,173,174,175,176,177]	0 (No exposure occurs for worker)	1 (No effect)
Worker(s) follow isolation protocol and/or antivirals prevent transmission	Rules Error: 5E-4 to 5E-2 for each individual worker, log uniformly distributed	0 (No exposure occurs for worker)	1 (No effect)

[169] Welliver R *et al* (2001) Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 285**:** 748-754

[170] Hayden FG *et al* (1999) Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *The New England journal of medicine* 341**:** 1336-1343

[171] Calfee DP *et al* (1999) Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 43**:** 1616-1620

[172] Monto AS *et al* (1999) Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 282**:** 31-35

[173] Monto AS *et al* (2002) Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *The Journal of infectious diseases* 186**:** 1582-1588

[174] Barroso L *et al* (2005) Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. *Antiviral therapy* 10**:** 901-910

[175] Odaira F *et al* (2009) Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May-June 2009. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 14

[176] Govorkova EA *et al* (2007) Efficacy of oseltamivir therapy in ferrets inoculated with different clades of H5N1 influenza virus. *Antimicrob Agents Chemother* 51**:** 1414-1424

[177] World Health Organization (2014) Avian influenza A(H7N9) virus: Post-exposure antiviral chemoprophylaxis of close contacts of a patient with confirmed H7N9 virus infection and/or high-risk poultry/environmental exposures.