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Risk and Benefit Analysis (RBA) of Gain of Function Research

Summary

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Overall Approach to the RBA

- The purpose of this eight-month study was to provide data on the risks and benefits associated with research on modified strains of influenza viruses and the coronaviruses
- The RBA is divided into three major tasks, each of which requires a distinct data collection and analysis approach
  - Quantitative Biosafety Risk Assessment
  - Semi-quantitative Biosecurity Risk Assessment
  - Benefit Assessment
- This assessment was comparative
  - To determine the CHANGE in risk from research on GoF pathogens compared to research on wild type pathogens
  - To identify the benefits to science, public health and medicine afforded by GoF research COMPARED TO alternative research and innovations

A Note on Interpreting Our Results

- In this study, we try to analyze GoF phenotypes individually
  - For example, we isolate the effect of strains with increased transmissibility independent of other phenotypes
  - However, many phenotypes are linked:
    - For example, a component of transmissibility of influenza in human populations is the protection afforded by exposure to similar strains in the past—therefore ability to overcome residual immunity and transmissibility are linked
  - Be aware that risks and benefits may be similarly linked
- Translating empirical studies in animals or in cells to epidemiological predictions for human populations is impossible
  - For example, increases in transmissibility in ferrets in isolators are impossible to link to a specific increase in R0 for human cities
    - It is unknown if enhanced transmissibility already observed in ferrets puts strains into a dangerous category or if they must be made even more transmissible to drive risk, however, we can make educated guesses
  - Only one component of R0 is due to the biology of the virus
  - Humans may change behavior depending on the nature of the outbreak

Overall Approach to the RBA

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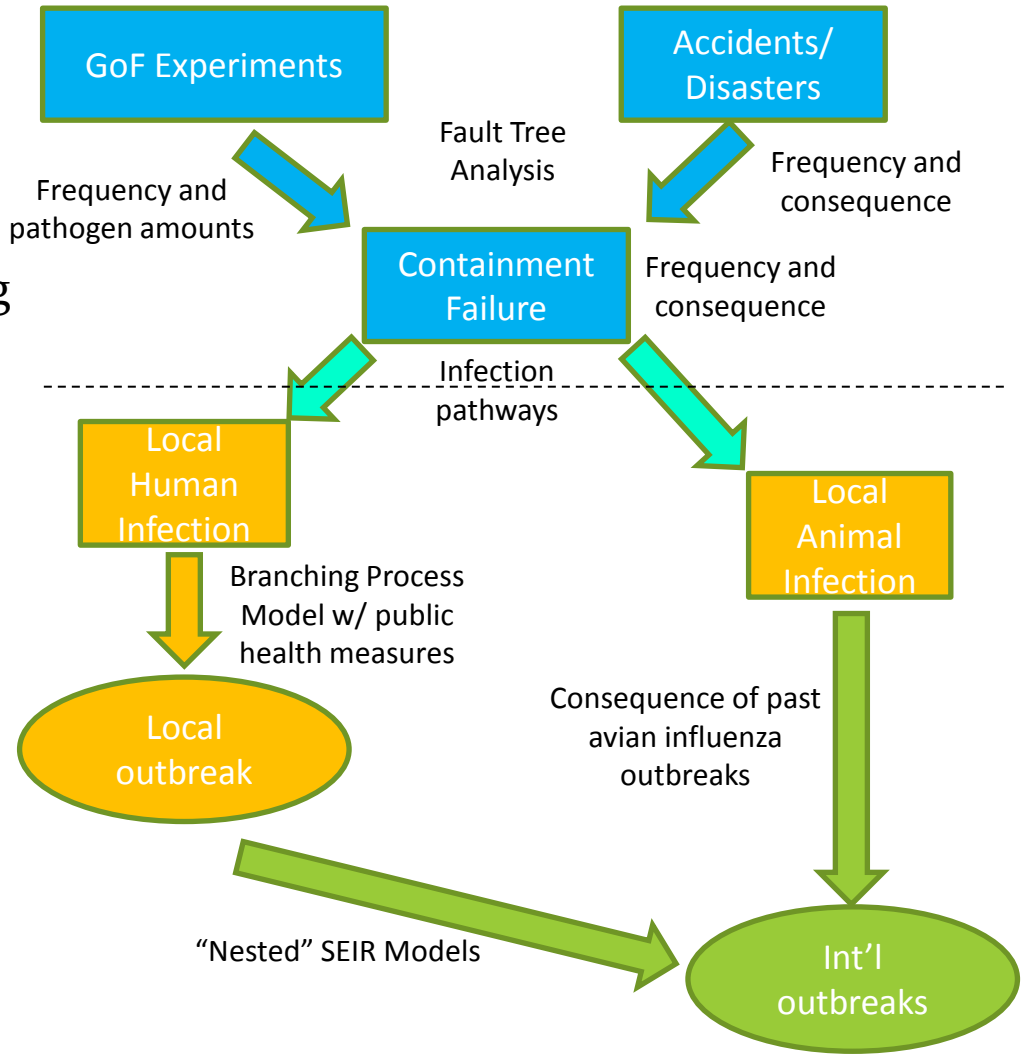
  - Benefit Assessment

Interplay of Components of Biosafety RA

- We model biosafety risk in three components:
  - Probability of an infection occurring outside of containment
  - Probability of an outbreak escaping local control
  - Consequences of a local outbreaks and global pandemics
- Risk is the product of:
  - the probability that an infection occurs
  - the probability an outbreak escapes local control
  - the consequences of a global outbreak

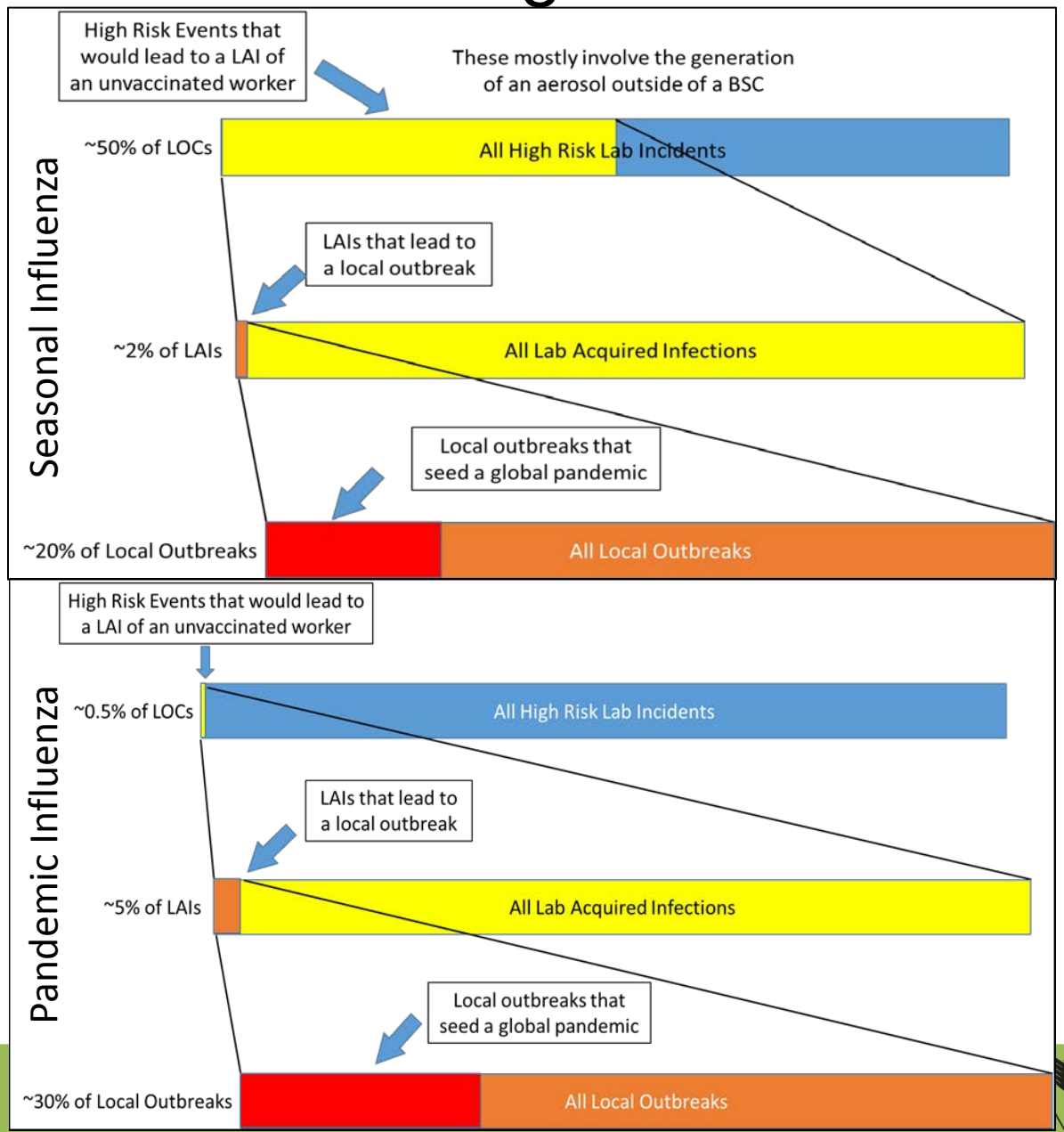


Using Interviews to Inform the Risk Assessment

- The risk assessment was informed by the scientific literature
- Information gaps were supplemented by interviews with laboratorians, laboratory safety professionals and public health practitioners
- These interviews were undertaken to describe specific containment features, frequencies of experiments, quantities of reagents and pathogens used and response protocols
  - Used to build distributions in the Monte Carlo analysis
  - E.g. How are samples deactivated prior to sequencing?
  - E.g. How often are ferret experiments performed and how many animals are infected?
- Only researchers were interviewed for this because only personnel performing this work know these needed details

Summary—Factors Influencing Accident Risk

- Only a small minority of laboratory accidents with the most contagious influenza viruses cause a local outbreak, and only a minority of those lead to a global pandemic



Summary—Biosafety Risk Comparison

GoF Phenotype	Seasonal Influenza Viruses	Pandemic Influenza Viruses	Avian Influenza Viruses	Coronaviruses
Enhanced transmissibility	Increases probability of an outbreak and the consequences of an outbreak		Increases probability of an outbreak and the consequences of an outbreak	Increases probability of a global outbreak and consequences of a global outbreak
Enhanced pathogenicity	Increases consequences	Increases consequences		
Adaptation to mammals	N/A	N/A	Decreases probability of an outbreak	N/A
Evasion of induced immunity	Increased consequences in high income countries only			N/A
Evasion of natural/residual immunity	Increases probability of an outbreak and the consequences of an outbreak		N/A	N/A
Antiviral resistance	Increased consequences in high income countries only	Increased consequences in high income countries only		N/A
Enhanced growth in culture/eggs		Increased chance of a LAI		Increased chance of a LAI

The darker the shade of gray, the more a GoF phenotype increases risk of human illnesses and deaths. Marked in white are GoF phenotypes that are not relevant (N/A) to risk or reduce risk.

Biosafety Risk Conclusions

- A modified strain of influenza virus that is as transmissible as a pandemic strain AND causes a disease with a case fatality rate of 5% or more would pose more risk of a global pandemic than any wild type strain heretofore identified
  - No experiments likely to be conducted under the rubric of GoF research will drive risk more than this combination of phenotypes
  - All other combinations of traits would lead to a pathogen that has a less total global risk than the wild type 1918 pandemic influenza strain
- Increasing the transmissibility of the coronaviruses, while increasing risk compared to wild type strains of those viruses, creates pathogens that pose no more risk of a global pandemic than the 1918 influenza strain

Biosafety Risk Conclusions

- For seasonal influenza viruses
  - Risk inheres in work only with strains that have not circulated recently
  - An unresolved question is if a laboratory associated epidemic would supplant or supplement the annual toll of seasonal influenza
  - Increasing the low case fatality rate of a seasonal influenza virus can obviously increase risk significantly
  - Increasing transmissibility (or evading residual immunity) can increase the probability and consequences of a local outbreak and global pandemic
  - Antiviral resistance increases the consequences of an outbreak only in economically developed countries with a significant stockpile of antivirals
- Manipulating GoF seasonal influenza strains at BSL3 may compensate for the increase in risk posed by modified strains by decreasing the risk of a laboratory acquired infection
  - Mostly by an extra system of respiratory protection

Biosafety Risk Conclusions

- For pandemic influenza viruses (1918, 1957 and 1968 flu strains)
  - The only trait that significantly increases risk is antiviral resistance, and in this case, consequences increase in only the economically developed countries who have a significant cache of antivirals
- For avian influenza viruses
  - Wild type strains are insufficiently transmissible amongst people to cause a global outbreak driven by spread between humans
  - Therefore, increasing transmissibility can significantly increase risk
  - No other manipulation increases risk
- For the coronaviruses
  - Wild type strains are insufficiently transmissible and sufficiently susceptible to public health control measures such that a global pandemic has a minimal chance of occurring
  - Increasing transmissibility can significantly increase risk of a global pandemic
    - Need a modest increase for SARS-CoV or a significant increase for MERS-CoV

Biosafety Risk Conclusions

- Some of the manipulations that could theoretically increase risk may not be achievable or desirable
  - A strain that can overcome protective vaccination increases risk only if it can evade vaccine protection via immune modulation, not antigenic change
    - A strain with novel antigenic properties could be targeted by a vaccine developed to fight the outbreak
  - The scientific value of increasing the transmissibility of influenza virus beyond that of the most transmissible strains is questionable and perhaps infeasible
  - Strains that could grow to 1E9 or 1E10 pfu/ml would increase the risk of a laboratory accident but:
    - There is little need to produce a strain that grows beyond 1E8 pfu/ml
    - This is an "end point" titer and therefore most often materials with this titer are not manipulated
    - This phenotype may not be achievable
  - There is no model of transmission for the coronaviruses, so manipulation of this trait is not currently achievable

Drilldown—Causes of LAIs

- The Fault Tree Models of laboratory accidents predict that the only GoF phenotype that significantly increases the chance of a dangerous laboratory infection is enhanced growth to a titer higher than wild type viruses can achieve
  - Albeit, as just mentioned, research along these lines is of questionable value
- The release pathways that contribute to risk differ for each pathogen

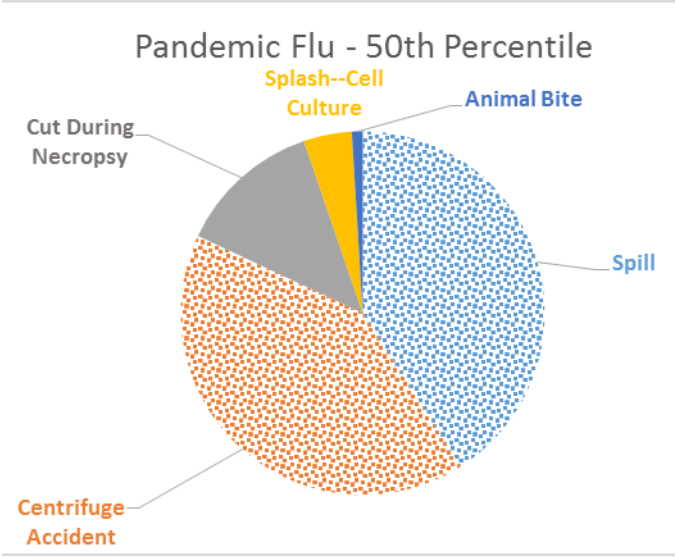


Table 6.2. Relative probability of a laboratory acquired infection for the various pathogens considered in this study as compared to work with seasonal influenza.

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

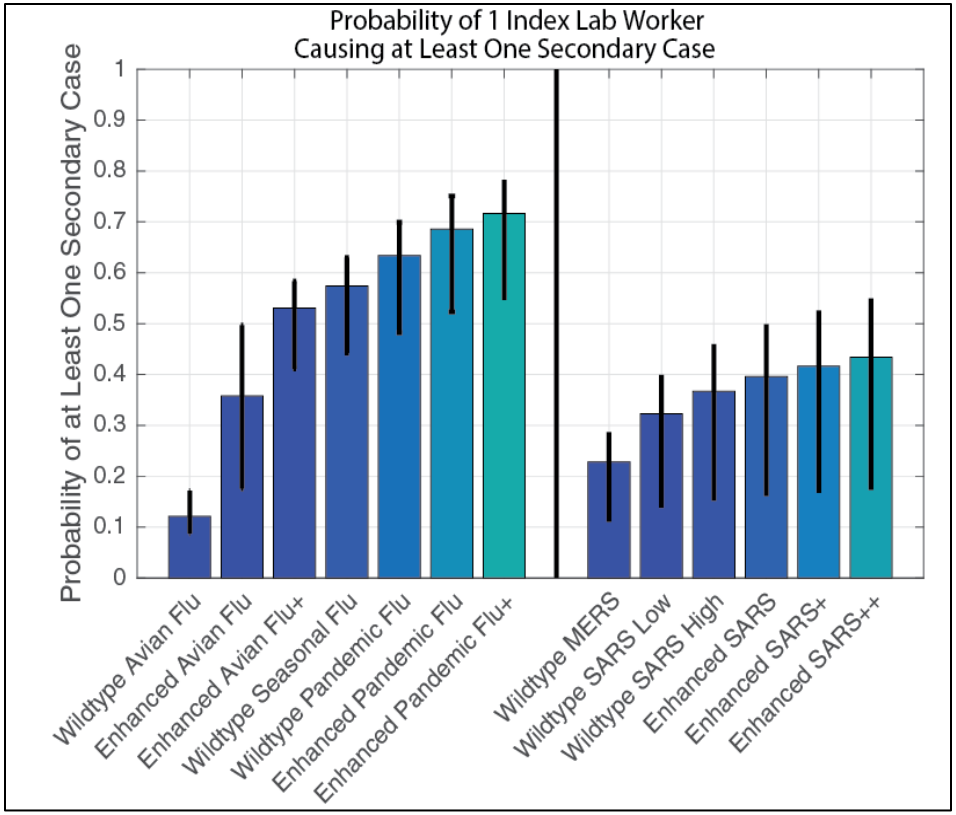
These data are generated by comparing the sums of the frequency of infection from all loss of containment pathways for each pathogen. In this case, we use the term laboratory acquired infection to include an infection of wild birds to capture the comparative risk of working with avian influenza viruses.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

Because transmissibility is critical to the risk posed by several strains, the next few slides focus on HOW transmissibility influences risk

DRILLDOWN--TRANSMISSIBILITY

Influence of Transmissibility on a Local Outbreak Occurring

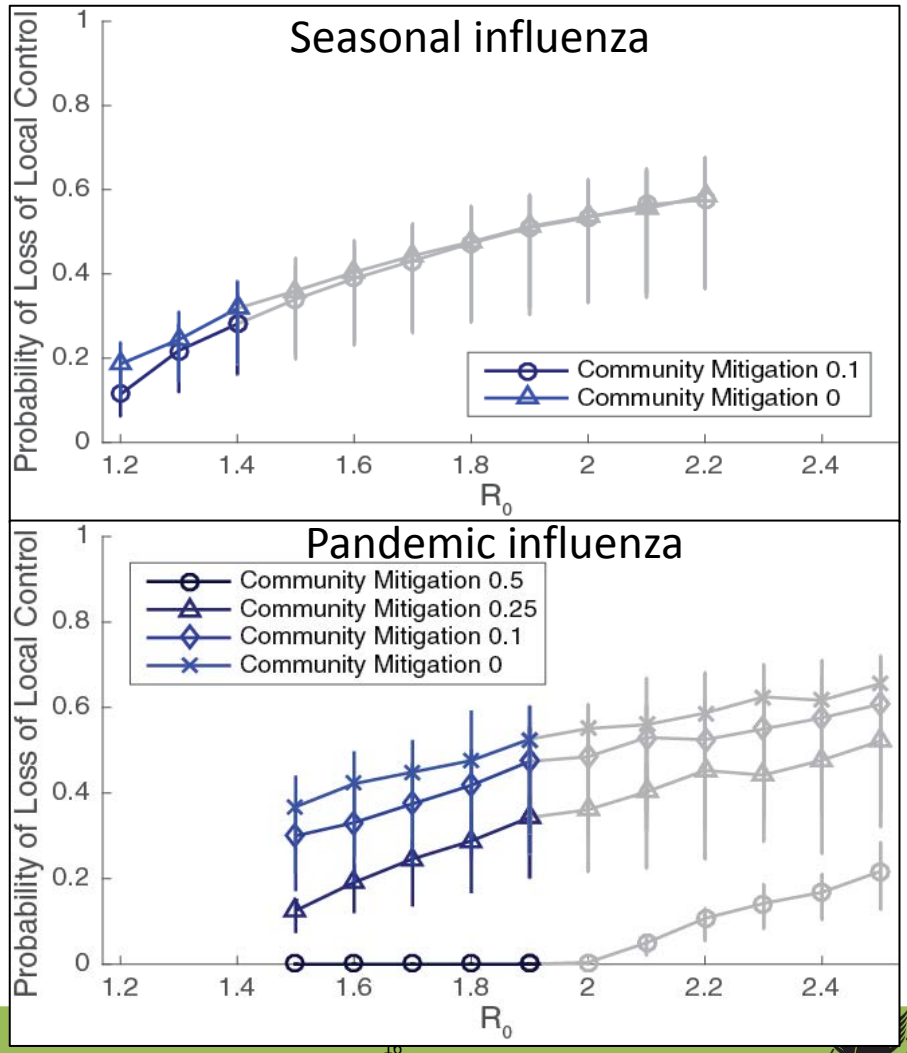
- Except for very low values of R0, most influenza cases in the community will lead to at least one secondary infection
- For the coronaviruses, due to their low K, most infections in the community do not lead to a secondary case even if the worker mingles with the population
- R0 has a modest influence on the probability that a local outbreak occurs as long as R0 is above one and K is high



R0: 0.1 → 2.5 R0: 0.4 → 2.5

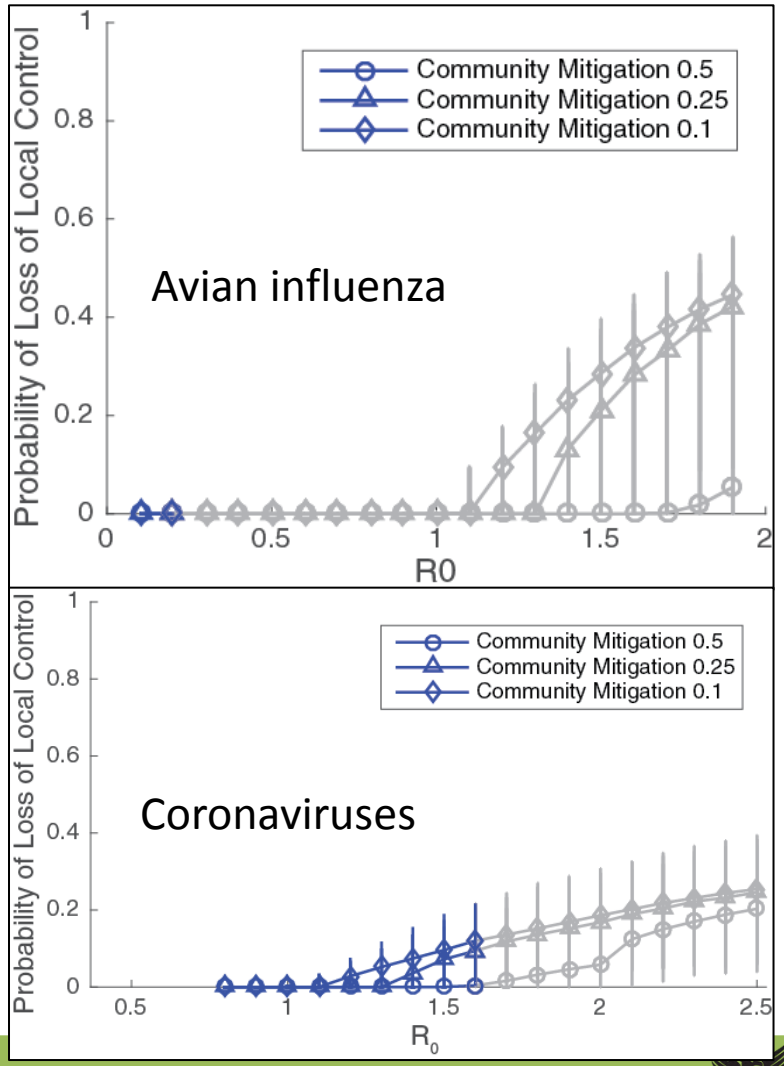
Influence of Transmissibility on an Outbreak Escaping Local Control

- Increasing R0 beyond that of the most transmissible seasonal strains can nearly double the chance that an outbreak of seasonal influenza escapes local control
- Increasing R0 beyond that of the most transmissible pandemic strains has a modest effect on the probability that an outbreak escapes unless community mitigation (social distancing) is strong



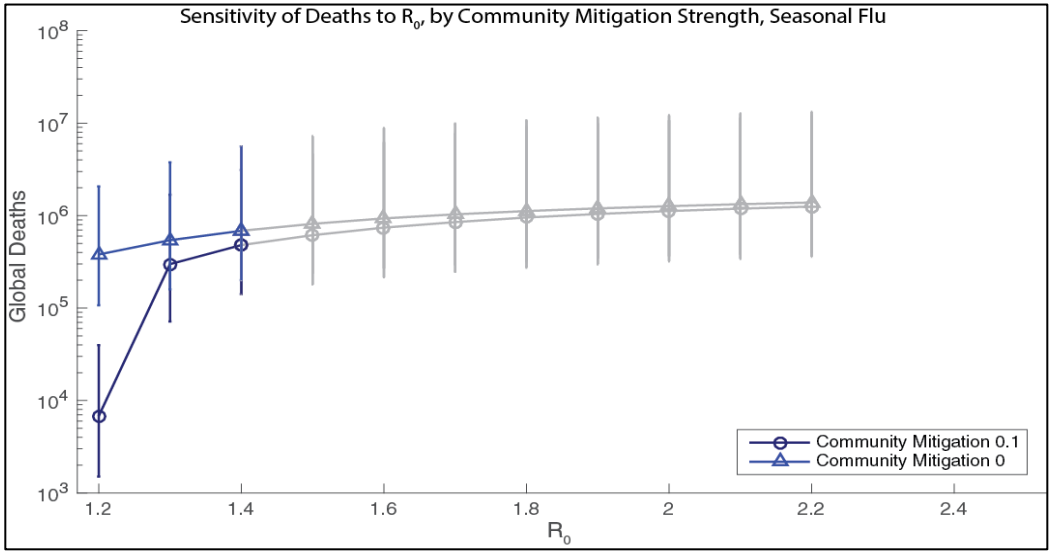
Influence of Transmissibility on an Outbreak Escaping Local Control

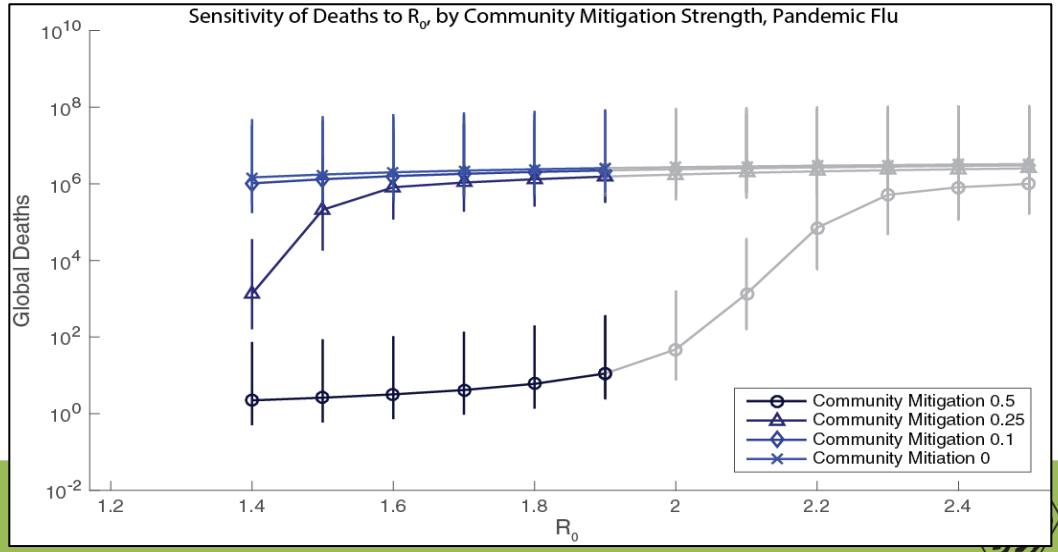
- Increasing R0 beyond one for avian influenza vastly increases the probability that the outbreak would escape, unless community mitigation is robust
- Increasing R0 of the coronaviruses linearly increases the probability that an outbreak escapes



Influence of Transmissibility on Consequences of a Global Pandemic

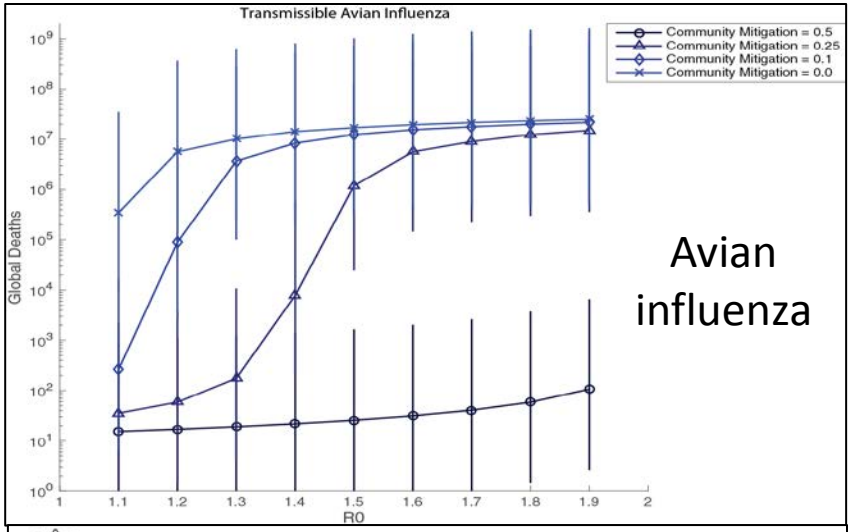
- For *seasonal* strains, if community mitigation cannot be sustained during a global pandemic, increasing R0 increases global consequences.
- For *pandemic* strains, increasing R0 beyond that of any wild type strain minimally affects deaths unless community mitigation can be sustained

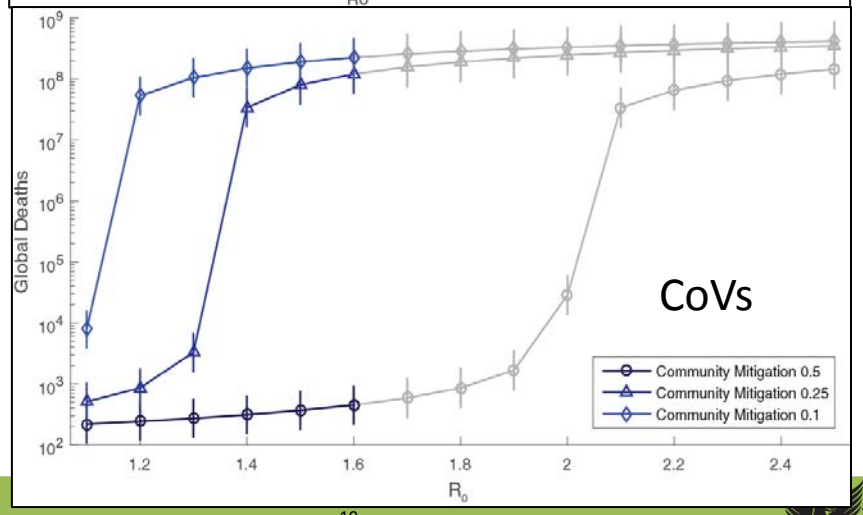




Influence of Transmissibility on Consequences of a Global Pandemic

- For transmissible avian influenza strains and coronaviruses, relatively low values of R0 can maximize global consequences assuming community mitigation cannot be maintained.
  - Unless community mitigation is robust, wild type SARS-CoV is sufficiently transmissible to maximize global deaths assuming it escapes local control and continually seeds international outbreaks
- If community mitigation can be sustained at a significant level, much greater transmissibility is needed for the consequences to be maximized





Using the RBA to Estimate Risk of Alternates to GoF

- A myriad of alternates to GoF were investigated in this study, the risk of some were vanishingly small
  - In silico approaches pose no safety risk (an information risk only)
  - Biochemical studies with viral components pose a chemical risk hazard only (if any)
- Many alternate approaches involve the use of wild type strains
  - This is one reason that the risk assessment uses wild type strains as the baseline
- Other alternate approaches involve the use of attenuated strains
  - These strains can be described by a wide range of parameter values
  - The risk assessment provides risk information for various parameters values, including those that are minimally pathogenic or transmissible
- Some alternate approaches involve the avoidance of animal infections
  - The contribution of animal experiments to risk is explicitly shown in the RBA
- Some alternate approaches involve the use of strains that are engineered to be safe
  - We did not explicitly calculate the risk of infection from these strains
    - The risk is expected to be small because even though a "repaired" particle may be present in a viral culture of 1E8 particles, these rare mutants are unlikely to be in the small inoculum that reaches an individual in an accident

Overall Approach to the RBA

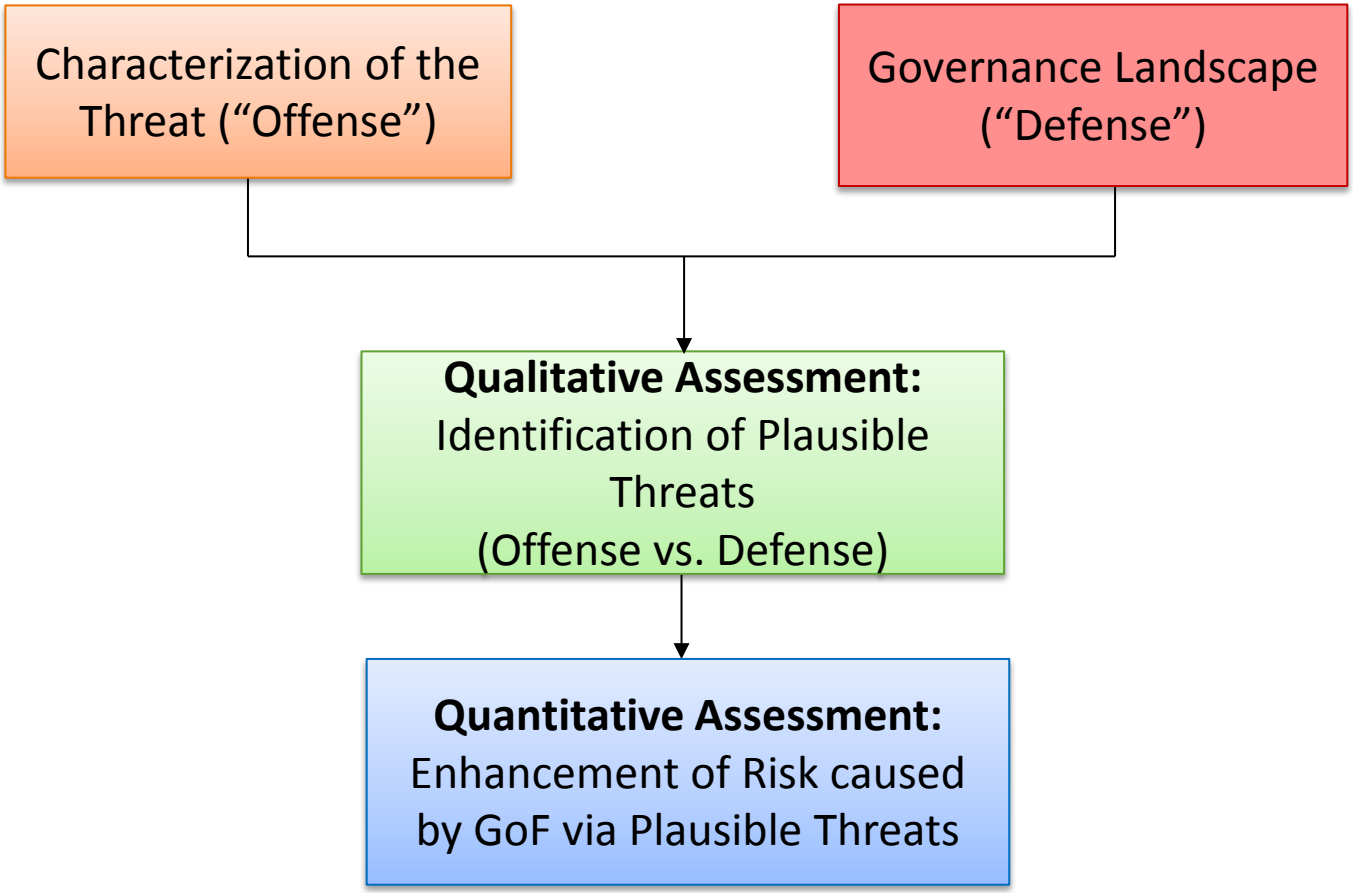
- The RBA can be divided into three major tasks, each of which requires a distinct data collection and analysis approach
  - Quantitative Biosafety Risk Assessment
  - Semi-quantitative Biosecurity Risk Assessment
  - Benefit Assessment

Biosecurity Risk Assessment

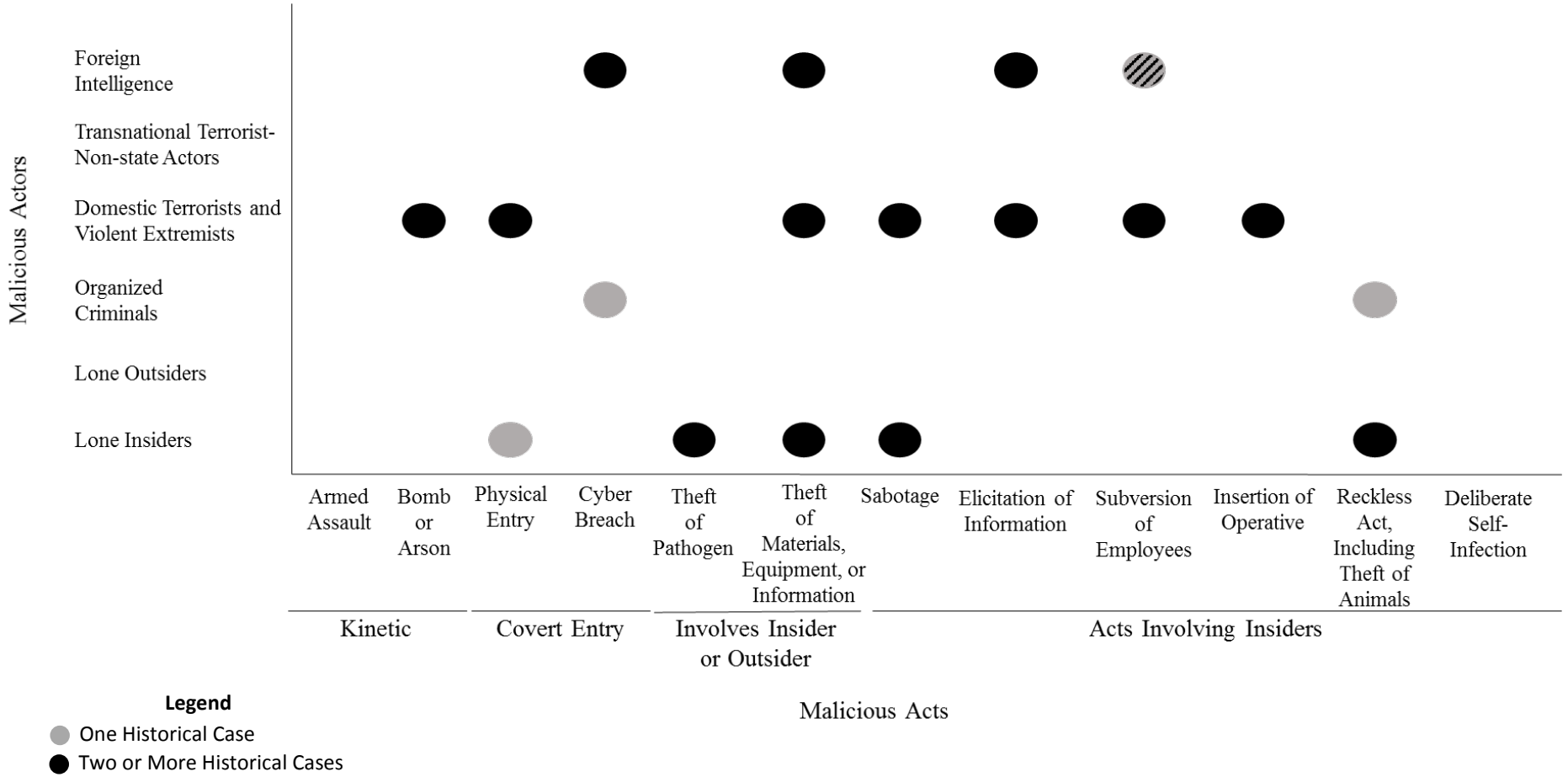
- The biosecurity risk assessment has two components
  - A semi-quantitative analysis of the risk posed by hostile acts occurring at laboratory that performs GoF research
  - An analysis of the risk posed by the misuse of the information generated by GoF research

BIOSECURITY RISK ASSESSMENT OF ACTS TARGETING A LABORATORY

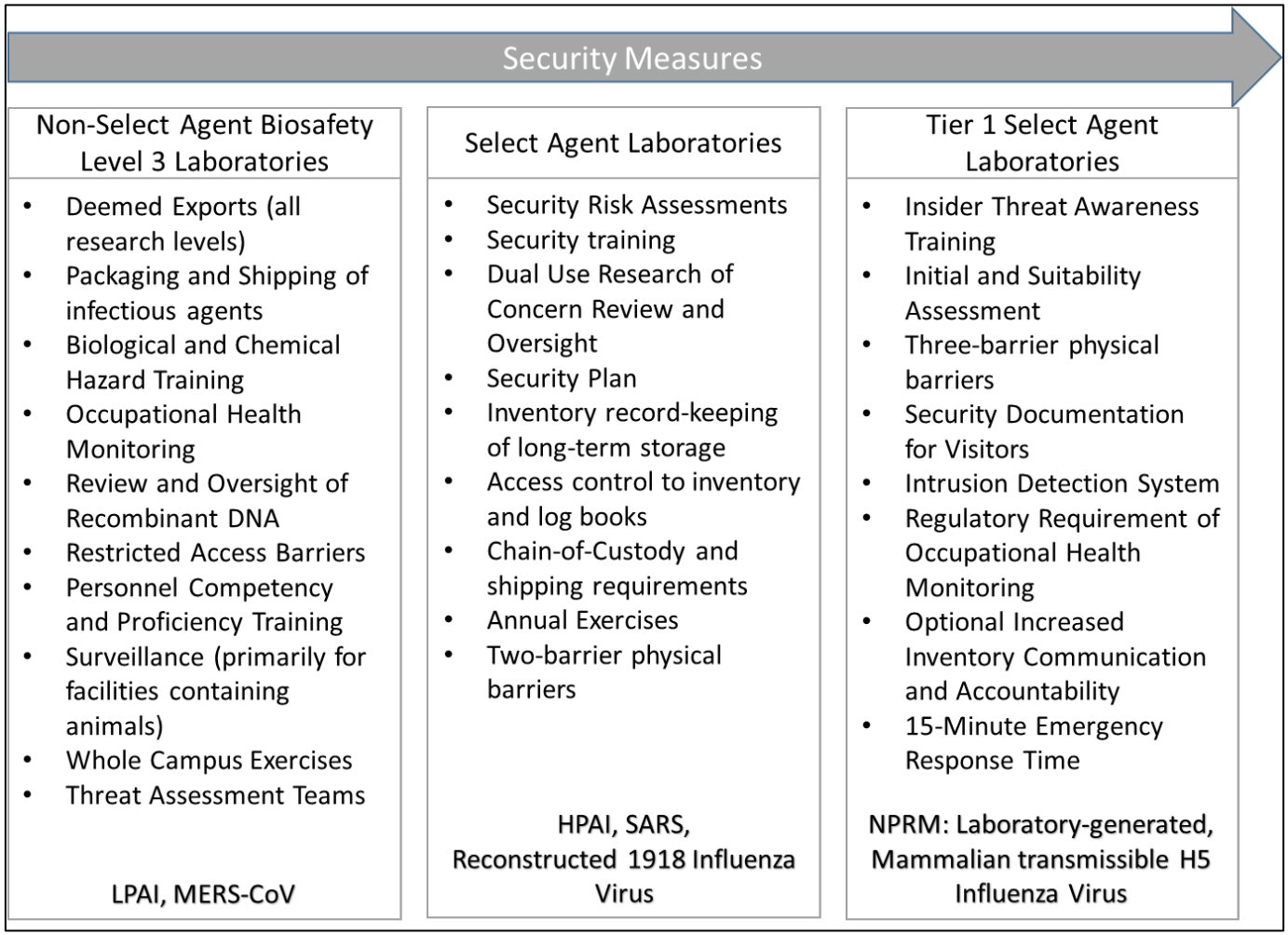
Process for RA for Acts Targeting A Laboratory



Historical Incidents: Malicious Actors and Acts



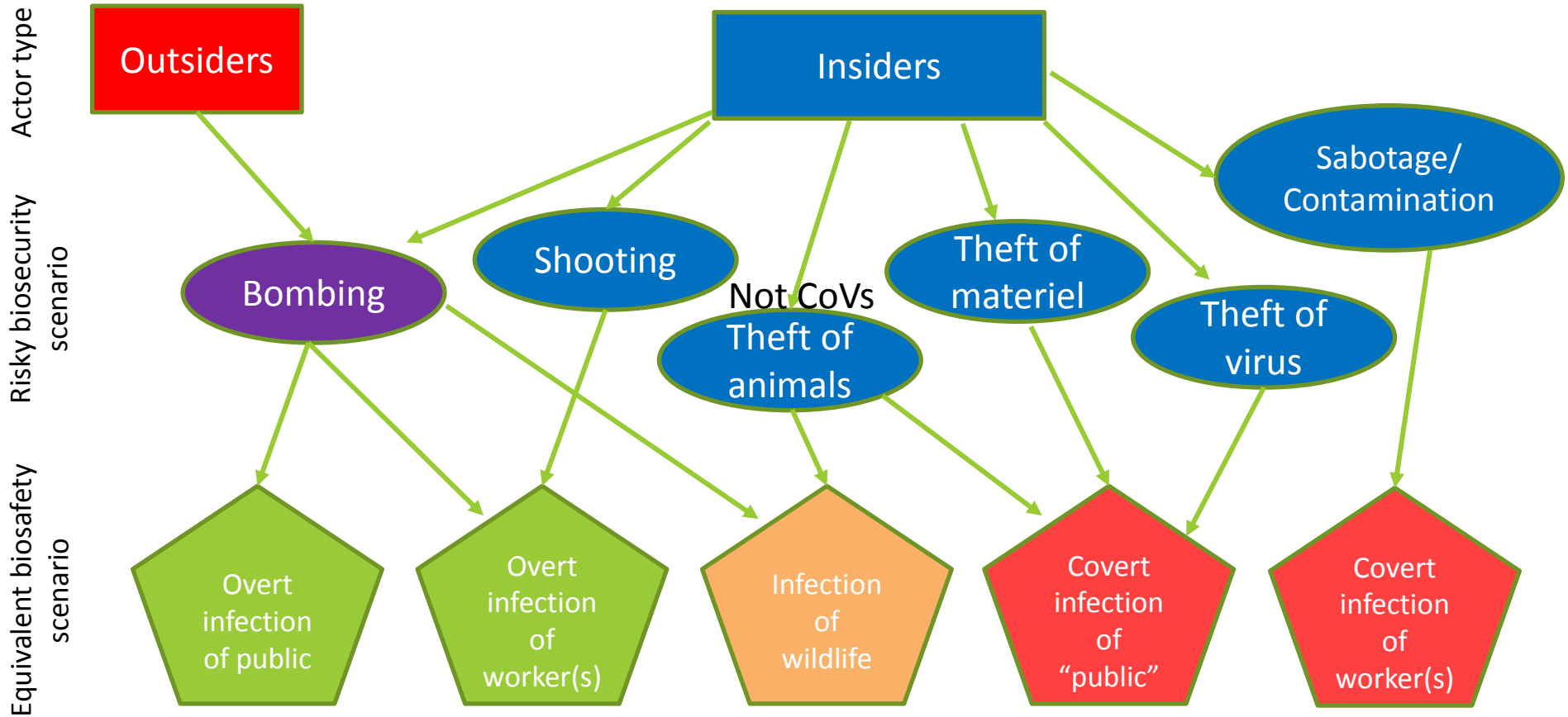
Security Measures at High Containment Laboratories



Plausible Threats Targeting a GoF Laboratory

Incident Class	Actor Type	Incident type
Overt	Insider	Active shooter or physical assault Bomb detonated near or inside high containment space
	Outsider	Bomb detonated at building periphery
Covert Act (Expose Public)	Insider	Removal of GoF virus (frozen stock or experimental sample), infected animals, or contaminated equipment
Covert Act (Expose Laboratory Workers)	Insider	Removal of GoF virus in experimental samples Deliberate contamination of personal protective equipment or laboratory equipment Deliberate compromise of laboratory equipment or personal protective equipment Mixing of experimental samples or animals into lower containment

Alignment of Risky Biosecurity Scenarios to Biosafety Incidents



The risk of these events were modeled for wild type and modified agents

Biosecurity RA of Acts Targeting a Laboratory--Conclusions

- The traits that drive risk are similar when considering biosafety and biosecurity because the pathogens are transmissible
  - That is, how the initial infections were caused is of little consequence once a local outbreak begins
- However, because biosecurity events are predicted to often involve the covert infection of the public, an infection is MUCH more likely to cause a local outbreak
  - Laboratory workers benefit from health surveillance and isolation protocols
- To match the risk posed by biosafety incidents given a historical rate of laboratory acquired infections, a biosecurity event that covertly infects a member of the public must occur only once every 50-200 years
  - These events include theft of an infected animal, contaminated piece of equipment or viral stock
  - Given the frequency with which these events have happened, this analysis suggests that biosecurity be given as much consideration as biosafety

BIOSECURITY RISK ASSESSMENT OF GOF INFORMATION

Methodology

- Purpose: to evaluate the risk that GoF information could be misused to intentionally cause illness or death in the human population
- Determined the potential dual utility of all GoF manipulations compared to wild type pathogens
- Assessed if methods to achieve desired traits has been published already
  - If methods to achieve dual use traits have already been published then the information risk is already realized (none remains)
  - If the methods to achieve dual use traits have not yet been published, then information risk may remain
  - Simplicity of method is considered
- **Information Risk remains only if there is dual utility and the information has yet to be published**
- Determined which actors likely have the capability and motivation to leverage this information

Information Risk—Dual Utility

Dual-Use GoF Phenotype	Seasonal/Pandemic Influenza	Avian Influenza	Coronaviruses
Enhanced transmissibility in mammals			
Enhanced pathogenicity in mammals			
Enhanced transmissibility while maintaining pathogenicity			
Overcoming natural or induced immunity			
Evading diagnostics			
Antiviral resistance			
Enhanced production in cell culture or eggs			

Dark boxes indicate dual-use traits

- The GoF traits with dual-utility are similar to those that pose an increased biosafety risk
  - Enhanced titer is not dual-use because actors can produce a sufficient amount of agent using a strain that grows to 1E8 pfu/ml to inflict enough initial casualties to ensure that the disease sparks a global pandemic

Information Risk—State of the Science

Dual-Use GoF Phenotype	Influenza	Coronaviruses
Enhanced transmissibility in mammals		
Enhanced pathogenicity in mammals	Published methods require skills in molecular biology. No publications exist on creation of influenza strains that lead to chronic illness.	
Enhanced transmissibility while maintaining pathogenicity		
Overcoming natural or induced immunity	Via the creation of antigenically distinct strains only	N/A
Evading diagnostics	Evasion of immunological diagnostics only	Evasion of immunological diagnostics only
Antiviral resistance		N/A
Enhanced production in cell culture or eggs	Published methods require skills in molecular biology.	N/A

Dark boxes indicate unpublished combinations, light grey indicates that publications have some shortcomings to reach dual use potential

- Methods to create strains of influenza with all GoF traits have been published
  - Albeit some methods require skill in molecular biology, or address only some aspects of the possible GoF traits
- Because appropriate model systems do not exist, no publications on CoVs with enhanced pathogenicity or transmissibility in relevant animal models exist

Information Risk--Conclusions

Dual-Use GoF Phenotype	Seasonal/Pandemic Influenza	Coronaviruses
Enhanced transmissibility in mammals		
Enhanced pathogenicity in mammals	Published methods require skills in molecular biology or were in poor animal models of pathogenicity. No publications exist on creation of influenza strains that lead to chronic illness.	
Enhanced transmissibility while maintaining pathogenicity		
Overcoming natural or induced immunity	Via the creation of antigenically distinct strains only	N/A
Evading diagnostics		The evasion of diagnostics that target the genomic sequence of the virus may pose an information risk.
Antiviral resistance		N/A
Enhanced production in cell culture /eggs		N/A

Dark boxes indicate remaining information risk

- Minimal information risk remains for GoF studies in influenza viruses because dual-use methods have already been published
- Significant information risk remains for GoF studies in the coronaviruses, but these studies are hampered by a lack of model systems

Overall Approach to the RBA

- The RBA can be divided into three major tasks, each of which requires a distinct data collection and analysis approach
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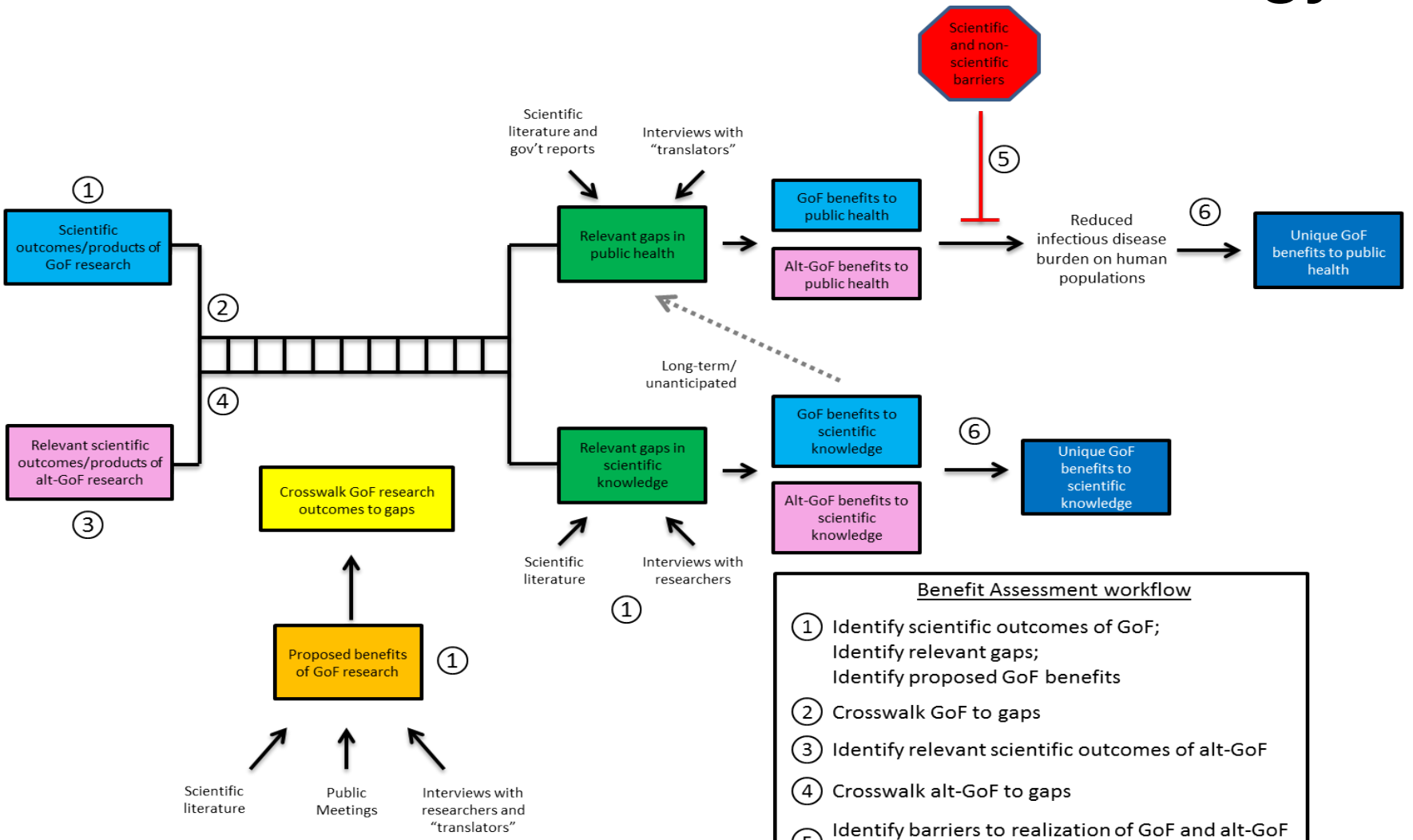
Benefit Assessment Methodology



Benefit Assessment workflow

1. Identify scientific outcomes of GoF;
   Identify relevant gaps;
   Identify proposed GoF benefits
2. Crosswalk GoF to gaps
3. Identify relevant scientific outcomes of alt-GoF
4. Crosswalk alt-GoF to gaps
5. Identify barriers to realization of GoF and alt-GoF benefits
6. Identify unique benefits of GoF research

Using Interviews to Inform the Benefit Assessment

- We reviewed the entire corpus of literature on the GoF debate, identifying all "pro" and "con" arguments
  - We contacted every author with an argument for further explanation
  - We then investigated all arguments to validate/refute them
- To further research benefits, we interviewed the researchers themselves, including SMEs involved in MCM development, surveillance and preparedness
- We understand some authors are not named in our report, however, we believe we have addressed all arguments made and either supported or refuted them

Benefit Analysis Conclusions- Coronaviruses

- GoF approaches that:
  - Alter host tropism and enhance virulence are critical for the development of animal model systems that recapitulate human disease pathogenesis, which are essential for the study of CoV pathogenesis and for advanced MCM development
  - Enhance virulence are critical for safety testing of live attenuated vaccines (albeit from a highly-attenuated state)
  - Enhance virulence inform the development of new therapeutics and vaccines, but alternative approaches may also be used
  - Lead to evasion of therapeutics in development are critical for the development and regulatory approval of new therapeutics
- GoF approaches provide unique benefits to the study of cross-species adaptation and pathogenicity of CoVs, but alternative approaches may also be used

Benefit Analysis Conclusions– Influenza Viruses

- GoF approaches that enhance virus production are uniquely critical for the current ability to produce sufficient and effective vaccines and represent the only strategy for improving vaccine production capabilities in the near-term
  - Improvements will translate to more effective seasonal flu vaccines and faster vaccine availability during a pandemic
- GoF approaches that enhance the infectivity, transmissibility, and virulence of animal flu viruses inform pandemic risk assessments and downstream decision-making about pre-pandemic vaccine development and other preparedness initiatives
  - GoF approaches can guide the selection of viruses for the basis of pre-pandemic vaccines
  - Non-GoF data contributes more, however, GoF data is particularly helpful to inform risk assessments when a virus first emerges

Benefit Analysis Conclusions– Influenza Viruses

- GoF approaches that enhance the infectivity and virulence of flu viruses are used to create animal models for the study of flu pathogenesis and to support MCM development
- GoF approaches that lead to evasion of therapeutics in development are uniquely critical for the development and regulatory approval of new therapeutics
- GoF approaches that lead to evasion of therapeutics inform therapeutic recommendations for seasonal flu and pandemic preparedness initiatives for high-risk animal strains, but other approaches may also be used
- GoF approaches that lead to evasion of existing natural or induced immunity have potential to improve the efficacy of seasonal influenza vaccines