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

Progress Update

Gryphon Scientific
Rocco Casagrande, PhD, Principal Investigator
Corey Meyer, PhD
Kavita M. Berger, PhD
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signature science LLC®

Abt ASSOCIATES

Agenda

- Overview of RBA approach
- Alignment of RBA approach with NSABB framework
- Progress report: biosafety risk assessment
- Progress report: biosecurity risk assessment
- Progress report: benefit assessment
- Discussion

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
- These major tasks are supplemented with additional analyses

Alignment of RBA Approach to Framework

- The RBA approach aligns to the NSABB Framework, except:
  - The BA should address beneficial outcomes of GoF research and how probable they are
    - The BA is largely qualitative so "probabilities" won't be given. Instead we will describe barriers to the realization of the benefits to understand their relative likelihood
  - The RBA should focus on the US but account for international research
    - Our RBA is focused on the US, and:
      - The RA can accommodate the loss of containment features that may be absent overseas
      - We interviewed foreign SMEs to understand their perspective on benefits
      - We analyze the potential globalization of benefits
      - We are not considering how US policy on GoF affects the rest of the world
  - Consider the risks to agriculture and the benefits to animal health
    - We are assessing only human health risks and outcomes that affect public health
    - Insufficient information is available to accurately assess risk of novel strains to poultry and swine
    - However, because wild-type avian strains are already highly contagious and deadly, the *increased* risk of GoF strains to poultry is probably minimal
  - Consider economic risks and intellectual property risks
    - We are assessing only human health risks
    - Insufficient information is available to accurately assess the risk of novel, avian strains, which may drive economic harm

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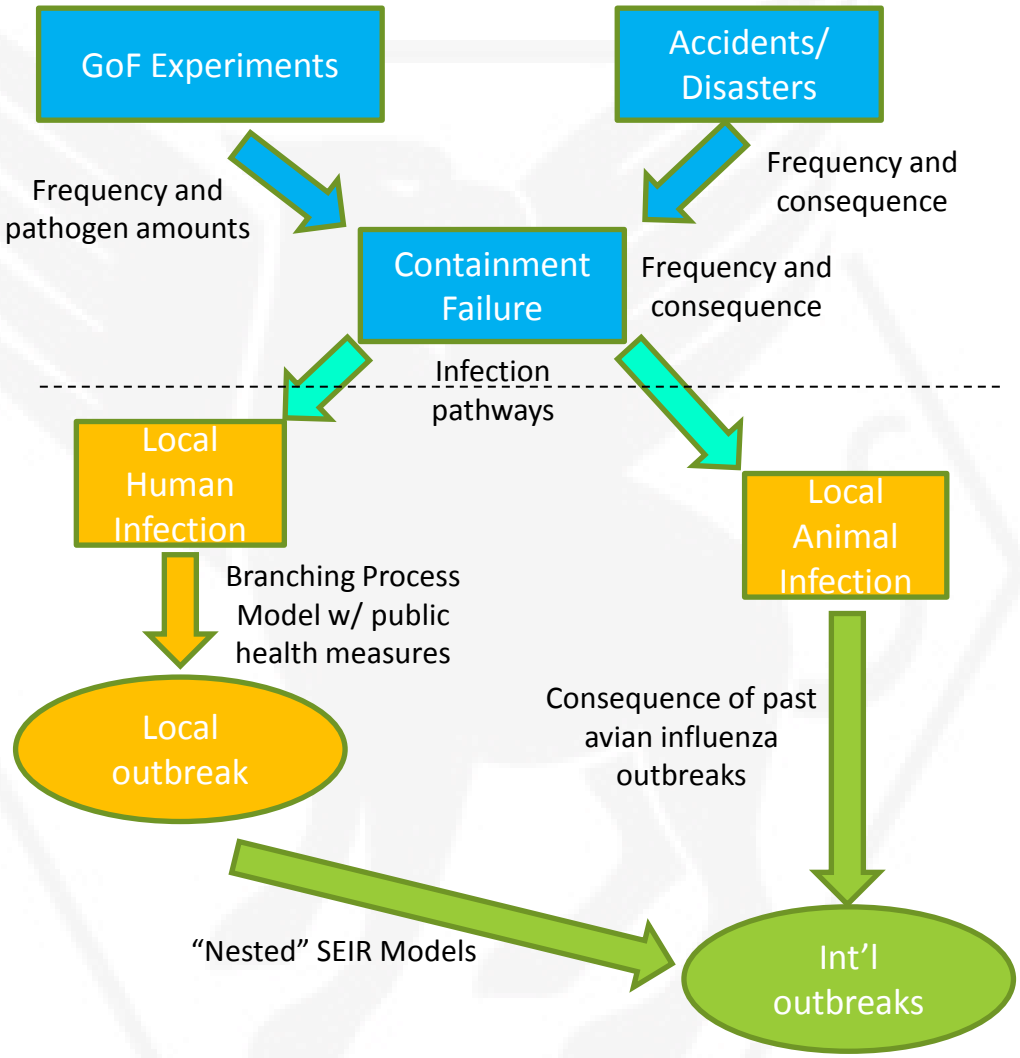
Interplay of Components of Biosafety RA

- We model biosafety risk in three components:
  - Probability of an infection occurring outside of containment
  - Probability of an outbreak escaping local control
  - Risk of an outbreak causing a global pandemic
    - Including estimates of the severity and extent of the outbreaks
- Our current biosafety RA has a simple consideration of the consequences of avian influenza outbreaks due to lack of data

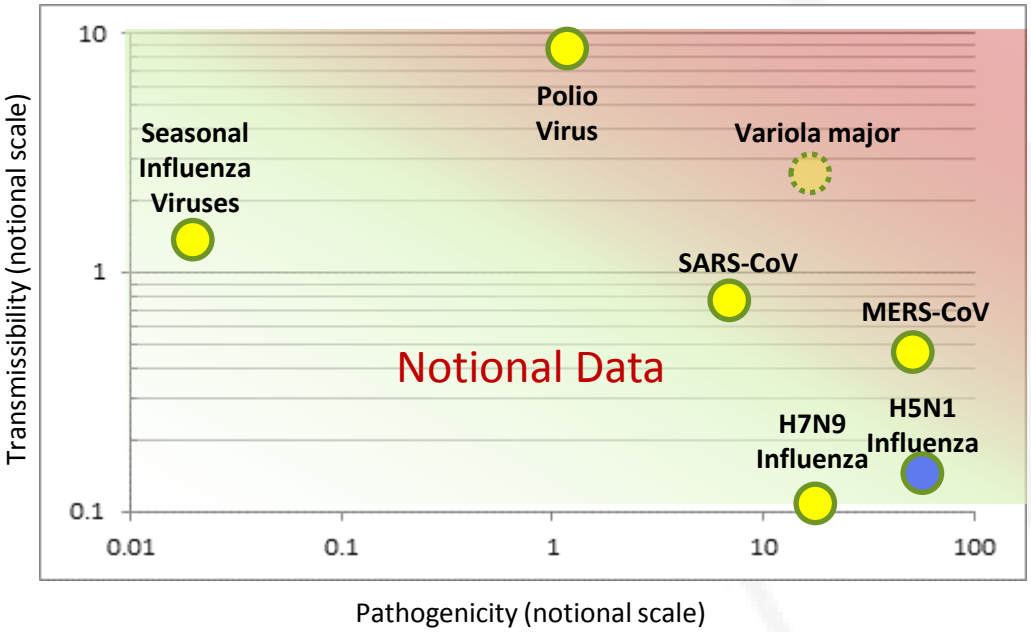


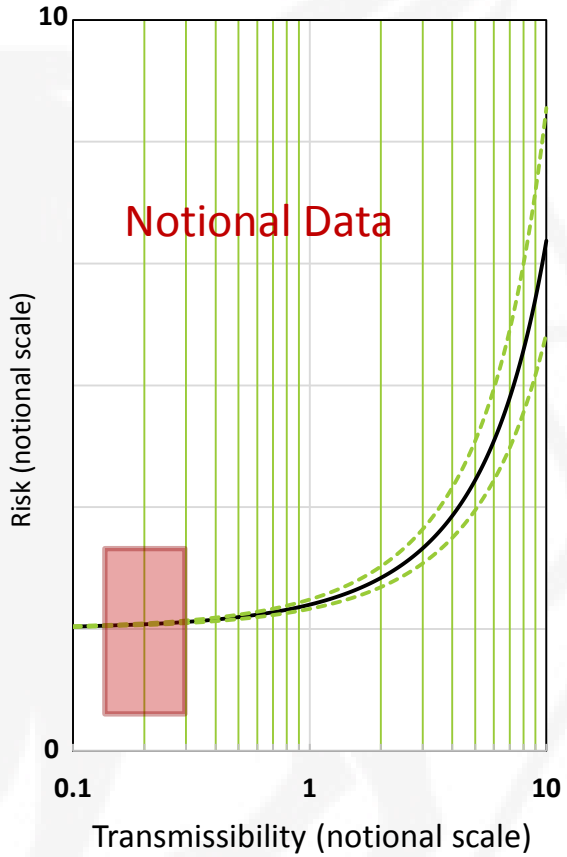
Format of Results

- The results of our overall biosafety RA will be a list of the GoF outcomes and research conditions that are expected to significantly increase risk of an outbreak, for a completely notional example:
  - *Experiments that create strains of human-transmissible influenza virus that can overcome protective vaccination would significantly increase risk of an outbreak because an incident is more likely to cause an infection outside of the laboratory and the resulting outbreak is expected to lead to three-fold more cases and deaths than wild-type strains.*
  - All five phenotypes mentioned in the Framework will be explicitly addressed in this manner and as broken out below

- This result can be further divided out by RBA component:
  - The estimate of the probability of an incident would lead to an infection outside of the lab
    - *Experiments that increase the viral titer of SARS-CoV in vitro are expected to significantly increase the risk of an outbreak because of the increased probability that an infection outside the laboratory would occur and that a death of a laboratory worker would occur. This risk is driven by events that create aerosols.*
  - The estimate of the probability that an infection outside of the lab would spread beyond the local area
    - *Experiments that increase the contagiousness of SARS-CoV are expected to significantly increase the risk that an outbreak would spread beyond the immediate area of the laboratory.*
  - The estimate of the risk of resulting global outbreaks
    - *Experiments that increase anti-viral resistance of seasonal influenza viruses are expected to significantly increase the risk from outbreaks by increasing the median number of cases by half and deaths by two-fold compared to wild type pathogens. (median deaths increase from 40,000 to 80,000)*

Format of results





- The effect of altering a phenotype on risk will be discussed for each pathogen of concern
  - In this notional example, risk increases significantly only if H5N1 transmissibility can surpass that of seasonal flu, an extremely unlikely outcome
  - A finding like this would suggest that experiments that increase transmissibility of H5N1 have minimal effect on risk
- For each pathogen, we will also consider the three components of risk separately: an infection occurring, escape from local control and global spread

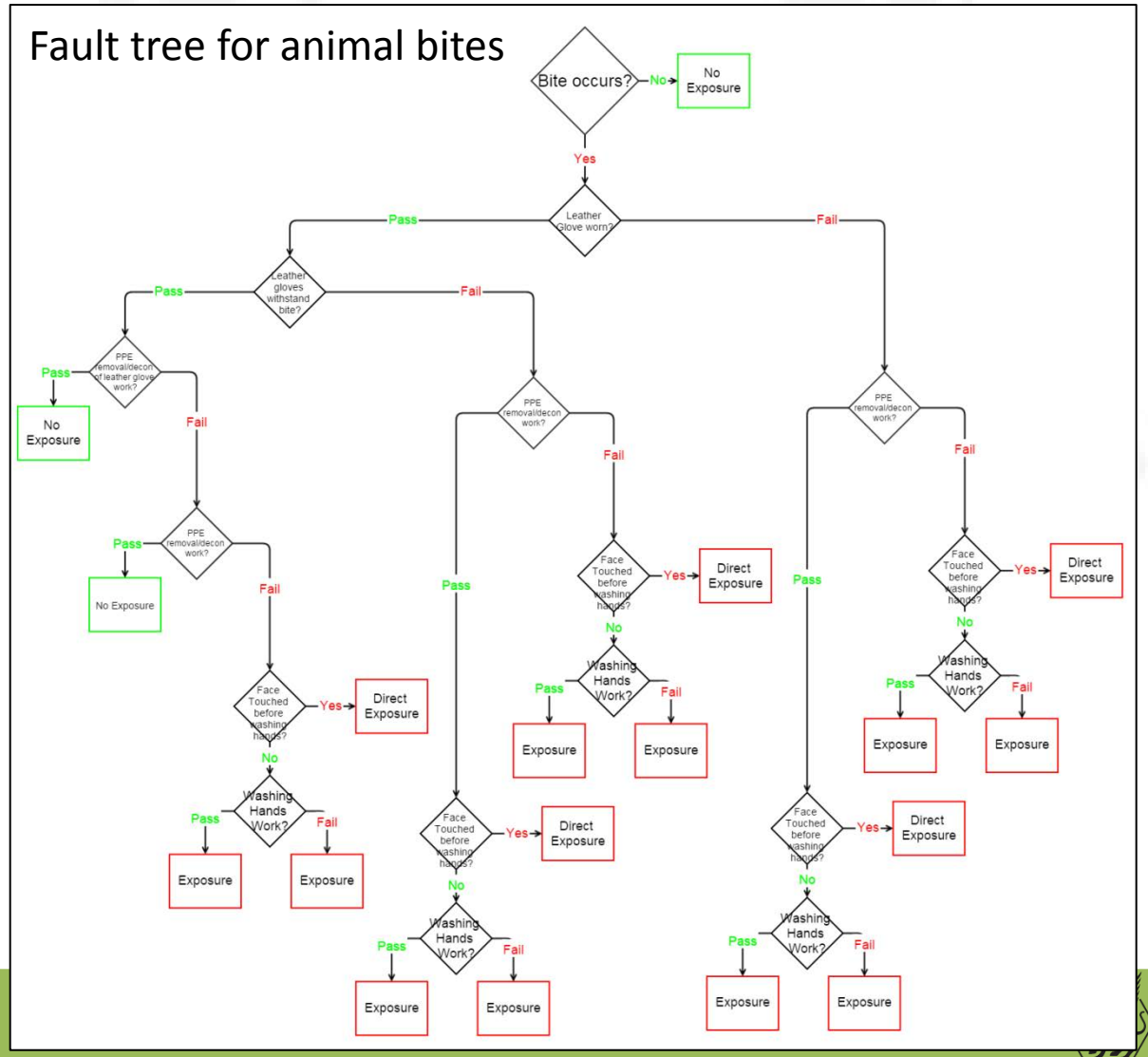
Identify Riskiest Accidents to Study in Detail

- We have completed our analysis of accident/incident reports and previous laboratory RAs to identify the most common or riskiest events that could lead to a loss of containment
  - We supplemented this list with incidents particular to GoF research or of current concern

- Animals:
  - Bites/scratches
  - Escape from containment
  - Aerosol generation
- Waste
  - Carcass
  - Other solid waste
  - Liquid waste
- Improper inactivation for use outside containment
- Centrifuge
  - Spill
  - Aerosol
- Natural disaster
  - Flood
  - Earthquake
- Needlestick/laceration
- Shipping
  - Improper receiving
  - Breakage
- Spills/splashes
  - Aerosol generation
  - Fomites
- Containment failures

Develop Fault Trees for Accidents

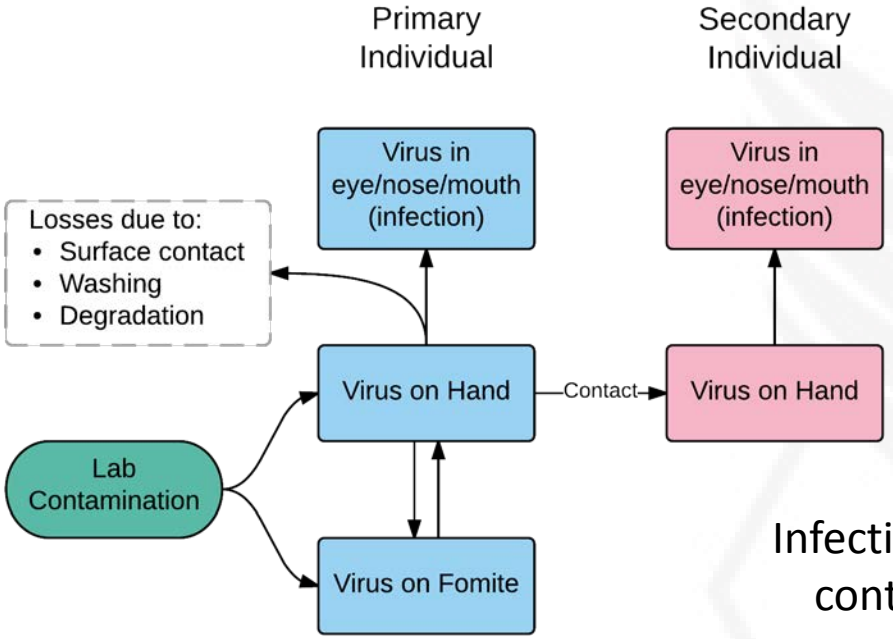
- Monte-Carlo simulations through these trees produces a probability distribution of contamination/ exposure events
- Each of these events is underpinned by an analysis of human reliability, which contributes significantly to the risk of lab accidents



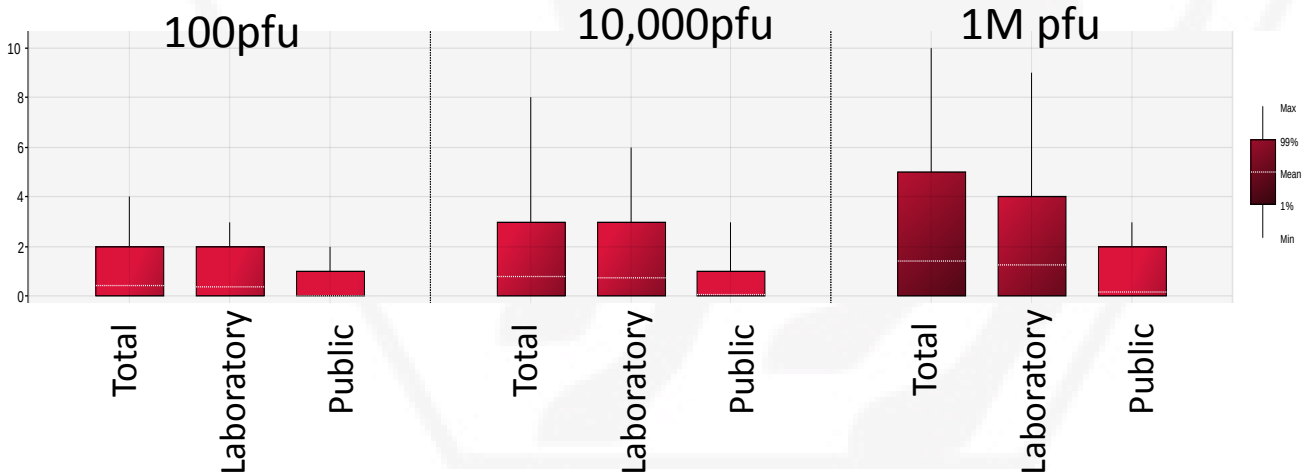
Predicting Outbreak Initiation from Laboratory Accidents

- Infection of laboratory worker
  - Probability that the accident is covert so that an infection is not noticed and probability that infection control protocols are violated
- Contamination of a laboratory worker
  - We developed a model to predict probability of a contaminated worker infecting self via hand-to-face contact or outside individuals via hand-to-hand contact
- Release of an infectious aerosol
  - Using the Hazard Prediction and Analysis Capability—a Sci-Puff based aerosol hazard modeling tool to predict downwind infection in humans and birds
- Animal escapes
  - Probability of an animal escaping a laboratory is miniscule
    - Must bolt through several self-closing doors without anyone noticing
  - Risk inheres in escaping some containment features, infecting/contaminating laboratory workers and creating aerosols (modeled above)

Model of Contamination of Lab Workers



Infections assuming contamination leaves containment on the hand of a worker



Modeling Human Health Consequences of Outbreaks of Avian Influenza

- The initially proposed model had more components modeling interaction of wild and domestic birds
  - Too many unknowns prevent the accurate prediction of spread of a virus with new properties within birds and to humans
- Current approach:
  - If the strain is contagious amongst people—model just the human outbreak
    - This will dominate human infection risk (more people contact people than birds)
  - If strain is transmissible amongst birds only and a bird is infected outside the lab (which we model quantitatively), then:
    - Presume that an ongoing outbreak is initiated
      - No modeling of loss of control
    - Presume that between 0 and 1,000 human cases occur
      - Historical range of all avian influenza outbreaks—we presume equal likelihood of all results in this range
    - Presume that between 0-500 human deaths occur
      - Historical range of all avian influenza outbreaks—we presume an equal likelihood of a case fatality rate between 0% and 50%

Modeling Loss of Local Control of Outbreaks

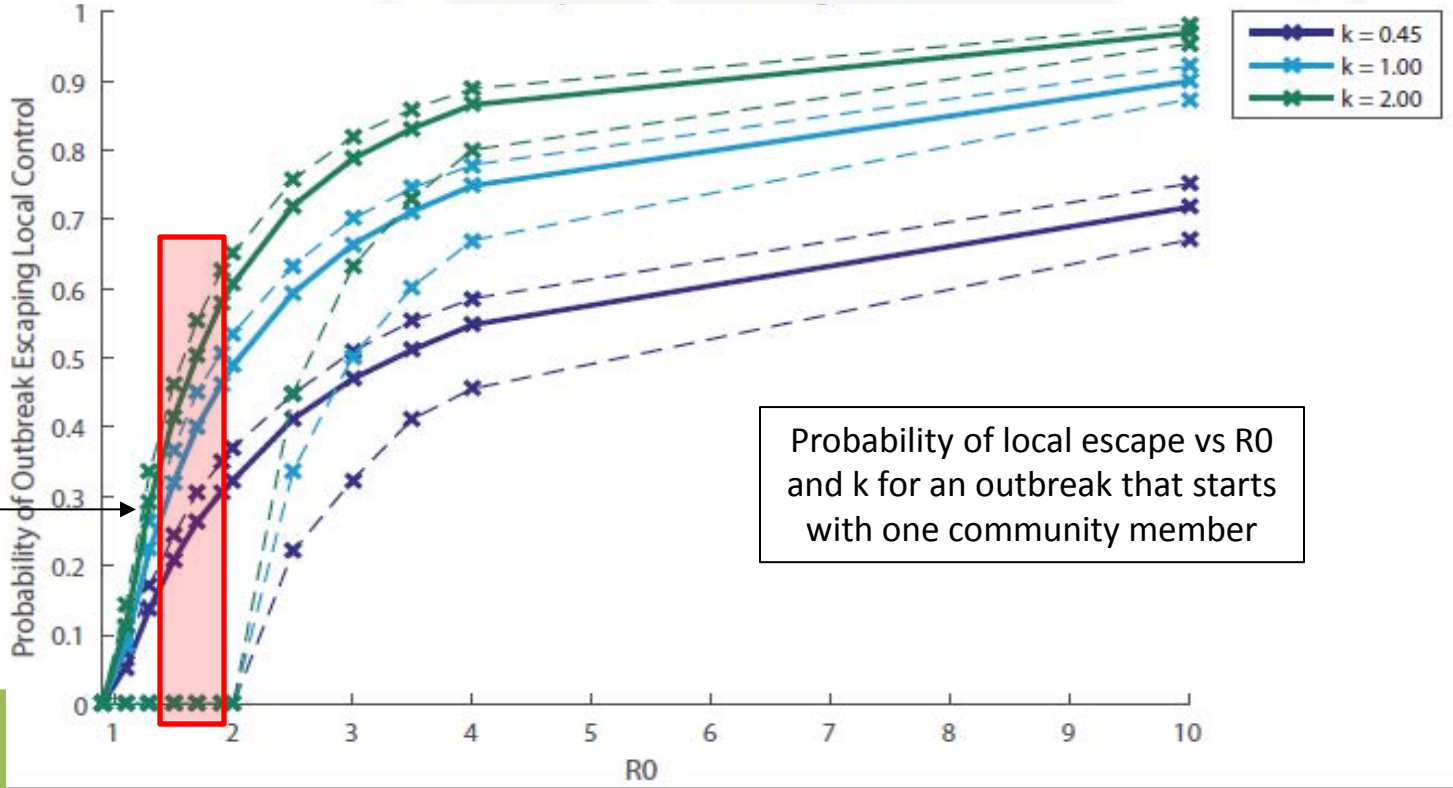
- We use a branching process model, developed by, and in consultation with, Dr. James Lloyd-Smith (UCLA), a recognized world expert in stochastic epidemic modeling.*
- Branching process models are stochastic, where each case creates a number of new cases based on a probability distribution with parameters R_0 and k:
  - R_0 is the average number of new cases each case generates
  - k reflects the variation in infectiousness between individuals
    - Low k means high variation, high k means low variation.
      - Low k is appropriate for MERS/SARS: most people create no secondary cases, some create a very large number
      - Higher k is appropriate for flu: many people infect one or two others, some zero, some a large number
- Branching process models capture one crucial feature of new outbreaks:
  - Many new outbreaks extinguish at a low number of cases
- Our model tracks laboratory workers and community members separately, so that we can subject each to different control measures
- Our model considers various control measures that could be implemented early in an outbreak

*J. O. Lloyd-Smith, S. J. Schreiber, P. E. Kopp & W. M. Getz. Superspreading and the effect of individual variation on disease emergence. *Nature* 438: 355-359 (2005)

Modeling Loss of Local Control

- For influenza, an outbreak begins to have a significant probability of escaping local control as transmissibility approaches that of wild-type seasonal or pandemic strains
  - Small increases in transmissibility of seasonal or pandemic strains could increase probability of escape
    - Significant in the context of modified avian strains
  - Also modifies overall risk picture: not all outbreaks outside the lab become widespread even for contagious strains

Likely range of R0 of wild type seasonal and pandemic flu



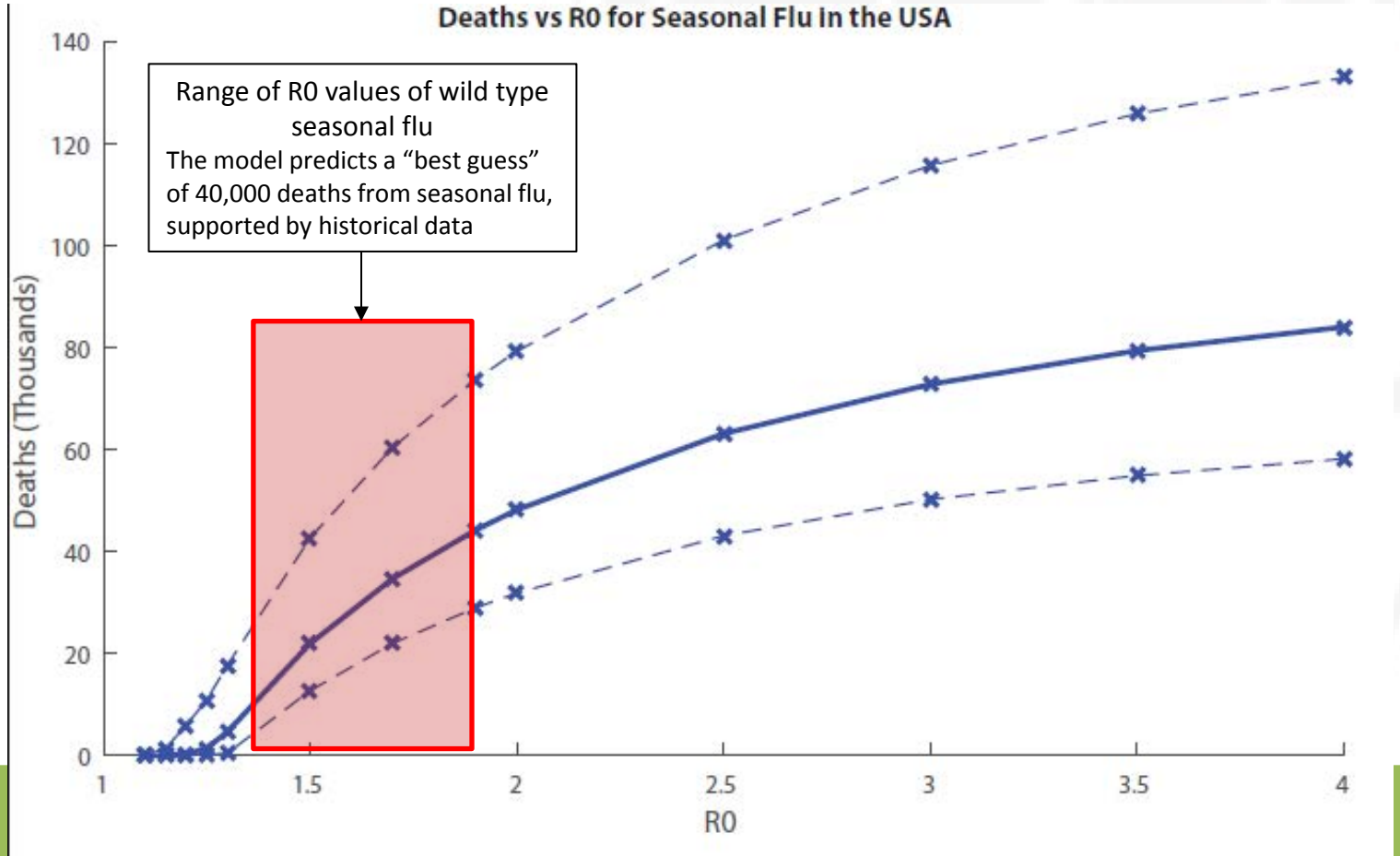
Probability of local escape vs R0 and k for an outbreak that starts with one community member

Modeling Global Spread

- To estimate the extent and severity of outbreaks that escape local control, we will be using the HHS-BARDA Interactive Influenza Model (IIM)
  - Used by BARDA and the CDC to explore how various response options can mitigate influenza outbreaks
- IIM is an SEIR model that considers the contribution of special populations (children and the elderly) to disease spread and consequences
- This model was developed for the US; we will run the model on several global regions to estimate global consequences of disease
  - We include regional data on age distribution, household size, classroom size, total population, vaccination rates, etc.

Modeling Global Spread

- We can predict consequences (and extent) of an outbreak
- Increasing R0 of seasonal strains does not lead to significantly more deaths
  - Conversely, a poorly contagious strain that approaches the R0 of seasonal flu would greatly increase consequences



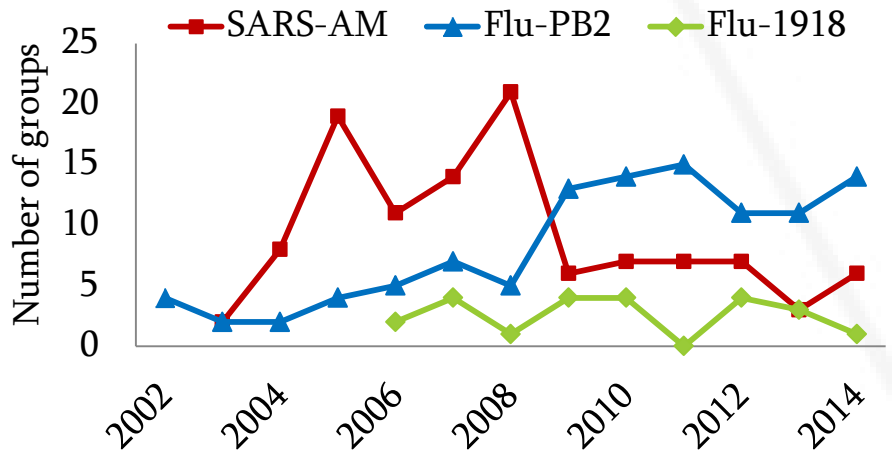
Considering Research Proliferation

- Purpose: to characterize the potential proliferation of GoF research; helps inform risk assessment
- Method:
  - Determine interest and capability to perform GoF through analysis of containment space, funding and key informant interviews
  - Examine three case studies of similar research and its proliferation
- Results:
  - About 40 groups in the US are likely able and have similar enough interest to undertake GoF research based on an analysis of publications in the field
  - Median funding for these 40 groups is $1.5M/yr from government sources
  - Roughly 300 BSL-3 and less than 10 BSL-4 labs exist in the US

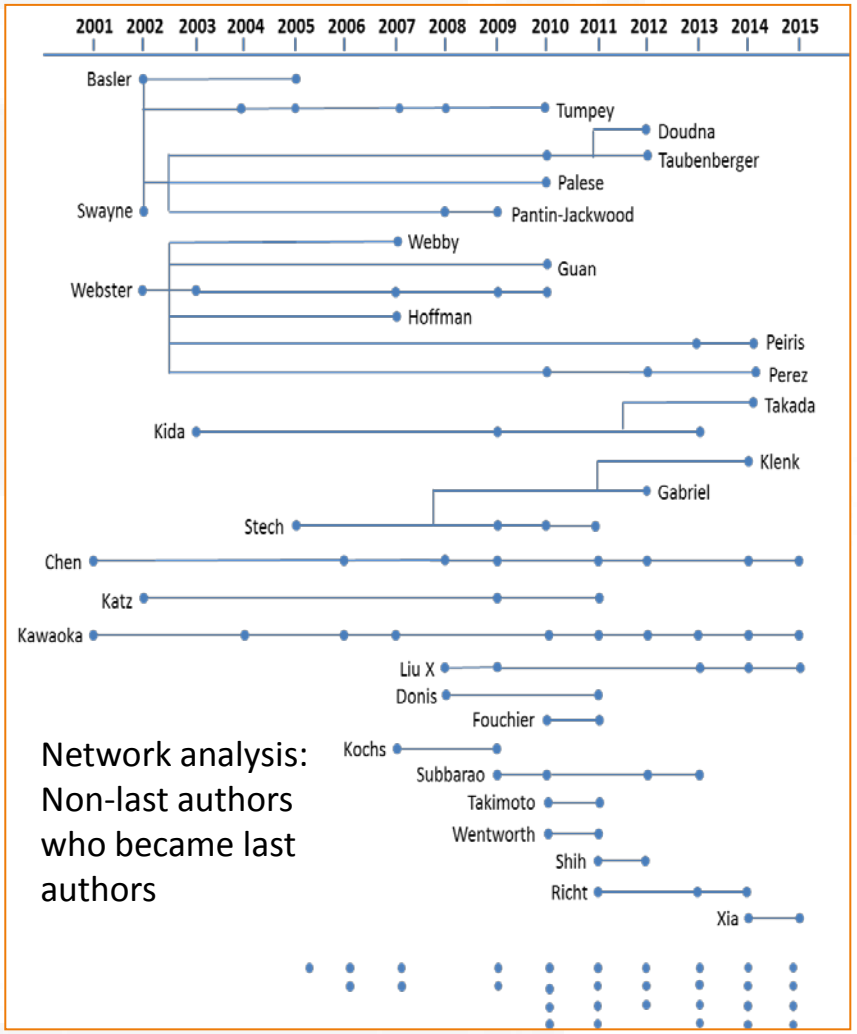
Considering Research Proliferation

- Case studies:
  - Of the three cases we examined, some barely proliferated, others grew (and contracted)
  - Maximum proliferation of 30 or so US groups and 70 world-wide
  - A little less than 1/3 of labs undertaking the work can be linked via personnel to the labs performing the work in the first three years

Discovery propagation



Relationship of Last Authors in Flu-PB2 Case Study



Network analysis: Non-last authors who became last authors

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Security Risk Assessment

- Open source evaluation of malicious actor threats
  - Identify historical incidents described in open source literature
  - Extrapolate malicious actor motivation and capability from open source information
  - Determine possible malicious actor, malicious act, consequence combinations
- Evaluation of governance of security and overlapping safety/security measures
  - Identify legal requirements
  - Review implementation of security measures
- Develop security scenarios to be modeled by evaluating plausible actor, act, consequence combinations based on possible threat combinations and governance of security measures
- Future: Model the potential for actor/act/consequence combinations to result in a pandemic.

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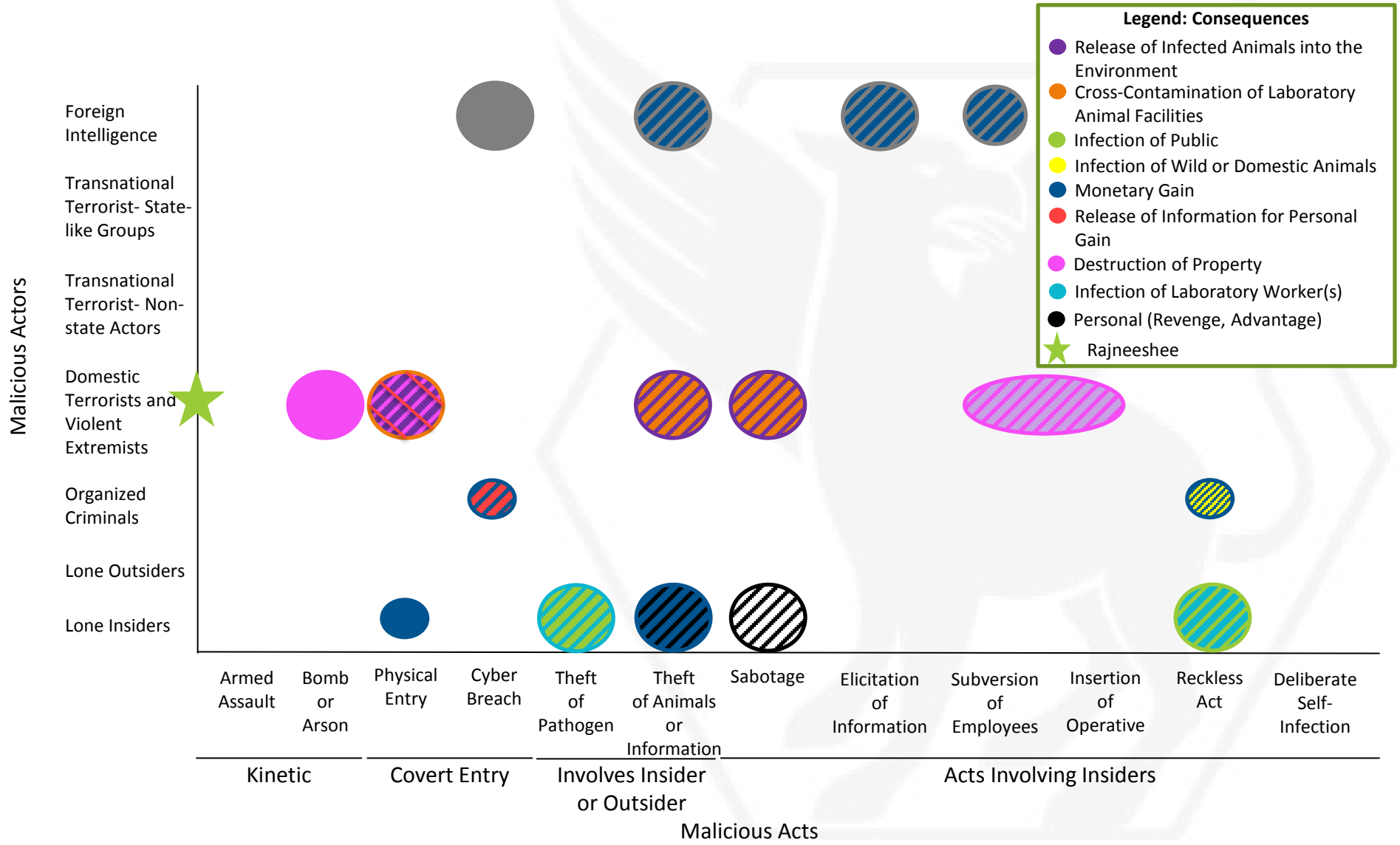
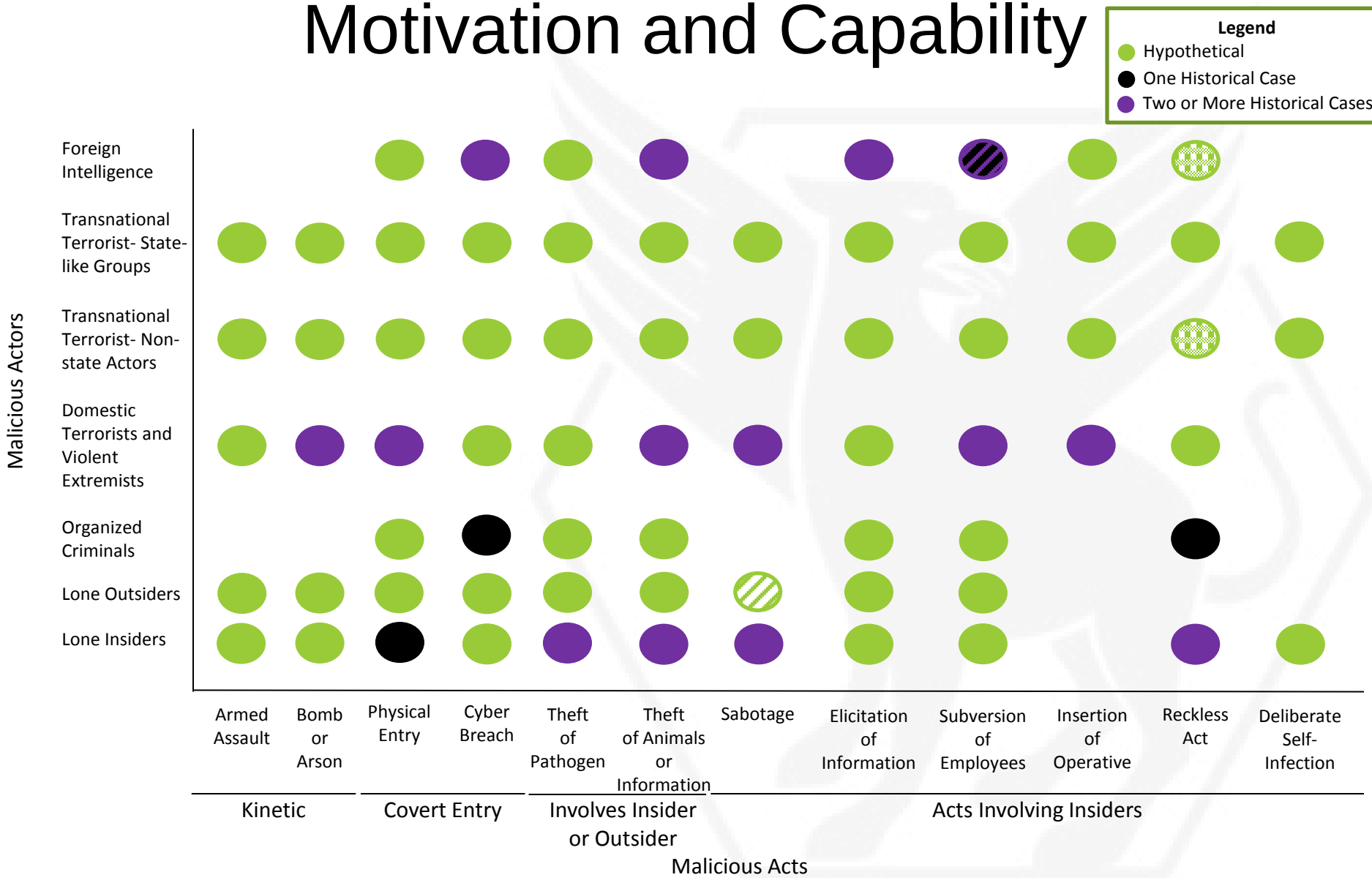
Historical Incidents involving Laboratories in the United States



Possible Threats Based on Actor Motivation and Capability

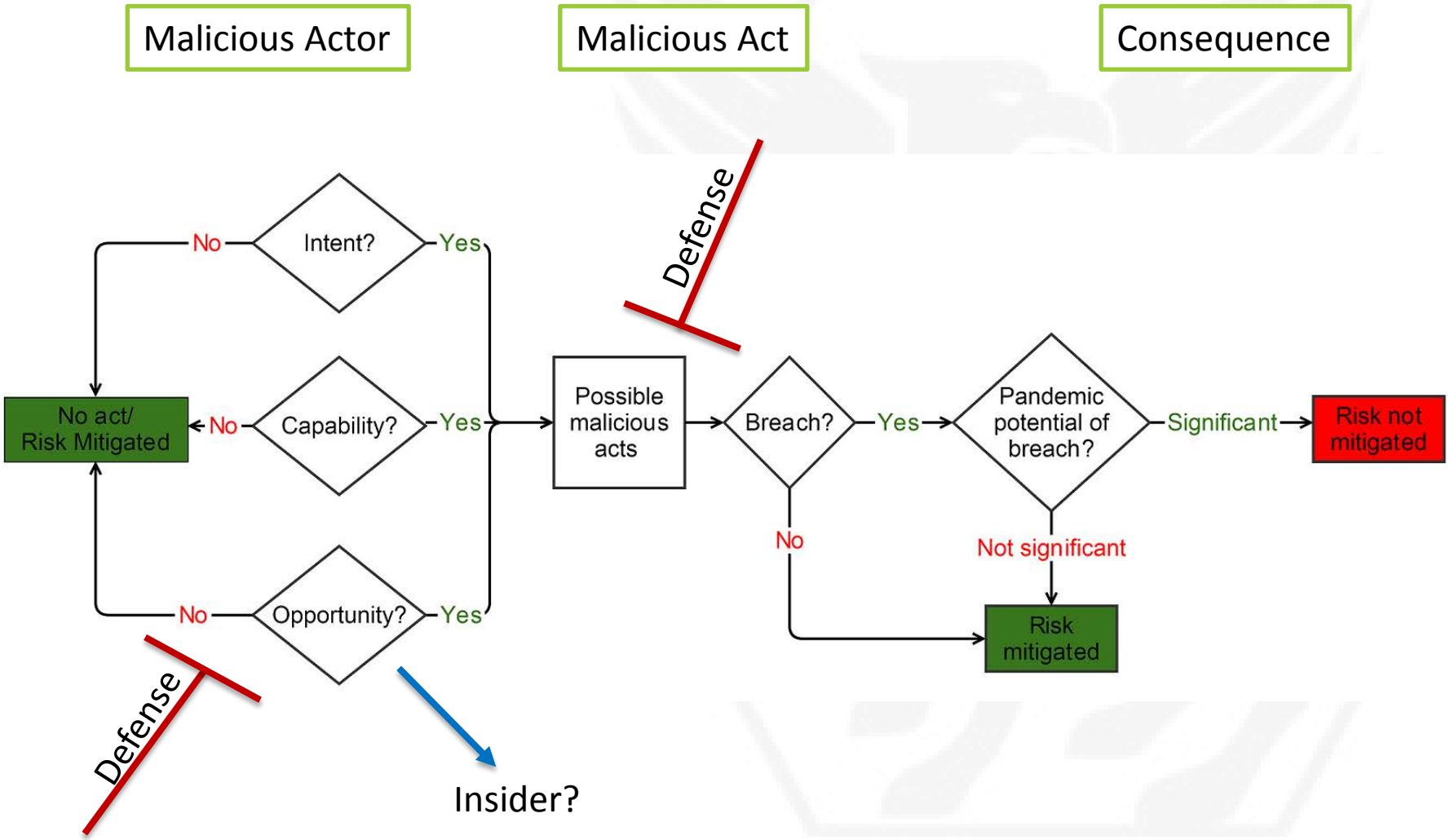


Governance and Implementation

Security Measures

Non-Select Agent High-Containment Laboratories	Select Agent Laboratories	Tier 1 Select Agent Laboratories
• Deemed Exports (all research levels) • Packaging and Shipping of infectious agents • Biological and Chemical Hazard Training • Occupational Health Monitoring • Review and Oversight of Recombinant DNA • Restricted Access Barriers • Personnel Competency and Proficiency Training • Surveillance (primarily for facilities containing animals) • Whole Campus Exercises • Threat Assessment Teams **LPAI, MERS-CoV**	• Security Risk Assessments • Security training • Dual Use Research of Concern Review and Oversight • Security Plan • Inventory record-keeping of long-term storage • Access control to inventory and log books • Chain-of-Custody and shipping requirements • Annual Exercises • Two-barrier physical barriers **HPAI, SARS, Reconstructed 1918 Influenza Virus**	• Insider Threat Awareness Training • Initial and Suitability Assessment • Three-barrier physical barriers • Security Documentation for Visitors • Intrusion Detection System • Regulatory Requirement of Occupational Health Monitoring • Optional Increased Inventory Communication and Accountability • 15-Minute Emergency Response Time **NPRM: Laboratory-generated, Mammalian transmissible H5 Influenza Virus**

Process for Developing Security Scenarios



Information Biosecurity Risk

- We have determined which GoF phenotypes would provide a unique advantage to a hostile actor
- We have assessed the published literature to determine which of this information already exists in the literature
- We are currently comparing the information that has yet to be published with the motivations and capabilities of adversaries

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Benefit Assessment– Goal and Principles

- Background: the benefits of scientific research derive from applications of new scientific information/products to gaps in scientific knowledge and public health

- Goal: identify the **unique** benefits of GoF research
  - GoF research outputs that can uniquely, more effectively, or more rapidly address gaps in scientific knowledge and public health than alternative approaches

- Key considerations
  - The BA must enable evaluation of individual approaches within each GoF phenotype
    - Individual approaches to generate the same phenotype may be associated with different risks and benefits
    - Enables exploration of different boundary lines between GoF research of concern and GoF research of lesser concern
  - The BA must be structured to enable comparison of the risks and benefits associated with each GoF approach
    - Risks derive from the experimental manipulation and virus used, whereas benefits derive from the outcomes/products of the experiment
    - The risk analysis is quantitative, while the benefit analysis is largely qualitative

Characterizing the "landscape" of GoF and alt-GoF research

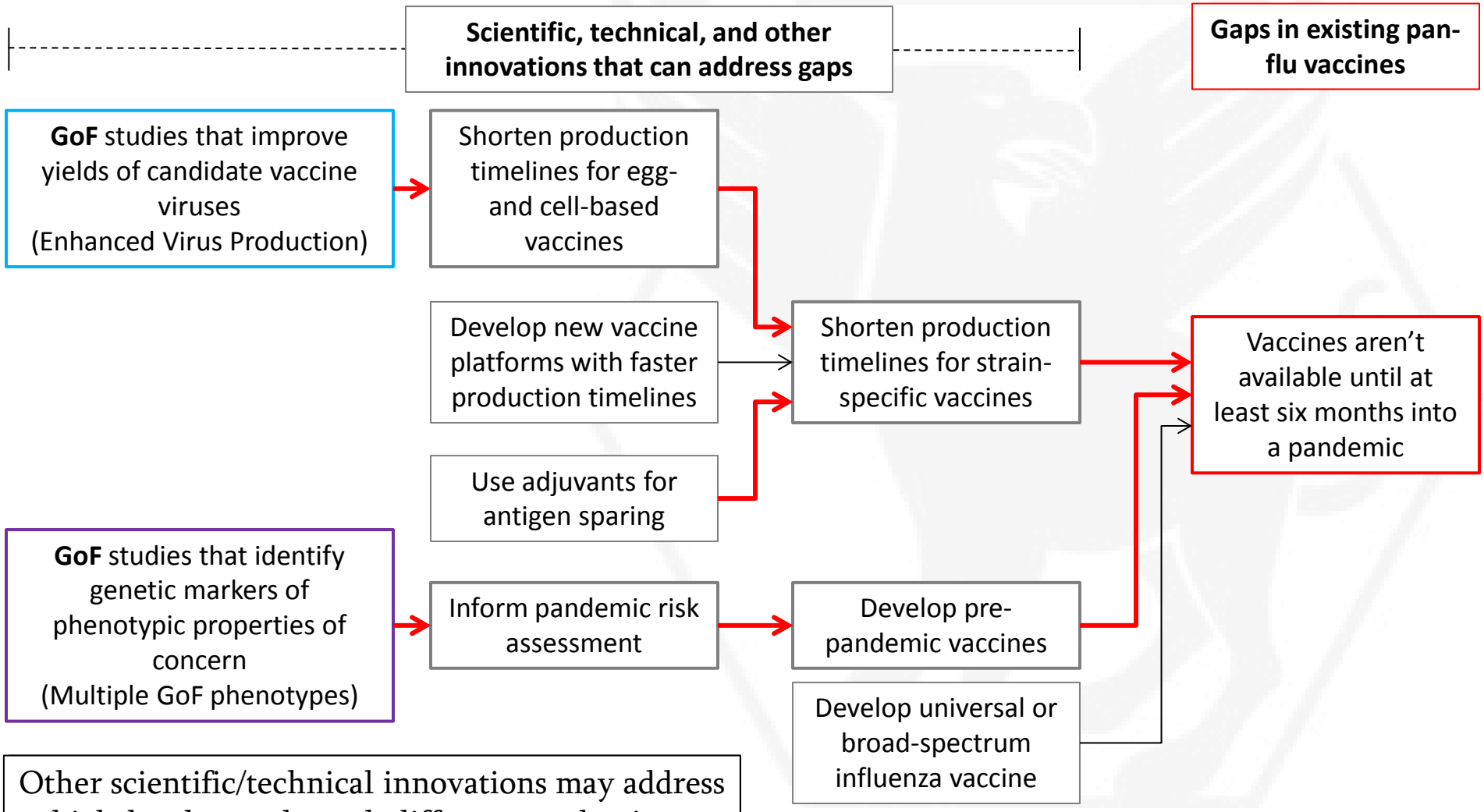
"Landscape" tables provide a foundation for comparing the risks and benefits associated with GoF research relative to alternative approaches.

- Links the experimental manipulation, virus strain, and outcomes associated with each GoF approach
- Enables evaluation of the risks and benefits associated with individual approaches

GoF Experiments that Lead to Enhanced Virus Production (and Associated alt-GoF Approaches)			
	Experimental Approach	**Virus Strains used**	**Scientific Outcomes**
GoF	*In vivo* approach: Serial passaging of virus in eggs/cells	• Vaccine backbone strains • CVVs • Wildtype viruses	Identify novel mutations that are *sufficient* to confer greater-than-wildtype levels of growth
GoF	Compare sequences of CVVs with varied growth properties	• CVVs	Identify mutations that are *associated* with naturally high levels of growth
Alt-GoF	Loss of function approach: forward genetic screen to identify mutations that reduce yields	• Vaccine backbone strains • CVVs • Wildtype viruses	Identify mutations that are *necessary* for naturally high levels of growth

- Comparatively analyze how effectively the outcomes of each approach address a critical gap in scientific knowledge about influenza viruses
  - Consider the nature and quality of the scientific information, as well as the resources needed to carry out each approach (different experimental approaches, different strains)

Crosswalk: Identify GoF Benefits to Public Health



Example Summary – Benefits of GoF Studies

GoF

Alt-GoF

Benefits of GoF Studies that Lead to Enhanced Virus Production and Alternative Approaches with Similar Benefits				
Scientific/technical Innovation	**Experimental Approach**	**Scientific Knowledge Benefits**	**Public Health Benefits**	**Barriers to Realization of Public Health Benefits**
Improve yields of candidate vaccine viruses	*Enhance virus production:* Targeted genetic modification of CVVs to introduce mutations associated with high yield	Identify mutations that are necessary and sufficient to confer high yields to CVVs	Shorten egg/cell-based vaccine production timelines	• Possible licensure of modified CVVs
Use adjuvants for dose sparing	N/A	N/A	Shorten egg/cell-based vaccine production timelines	• Only one adjuvanted pandemic vaccine is licensed • Licensure of new vaccines is a lengthy and expensive process
Develop pre-pandemic vaccines	N/A	N/A	• Rapid deployment of vaccine during a pandemic • Shorten production timelines for pandemic vaccines	• Limited resources for stockpiling

- Translation of research and technology may depend on other scientific, technical, regulatory, and societal factors
  - These "barriers" reduce the likelihood and delay the timing of the realization of the benefits
  - Informs evaluation of immediate risks versus future benefits

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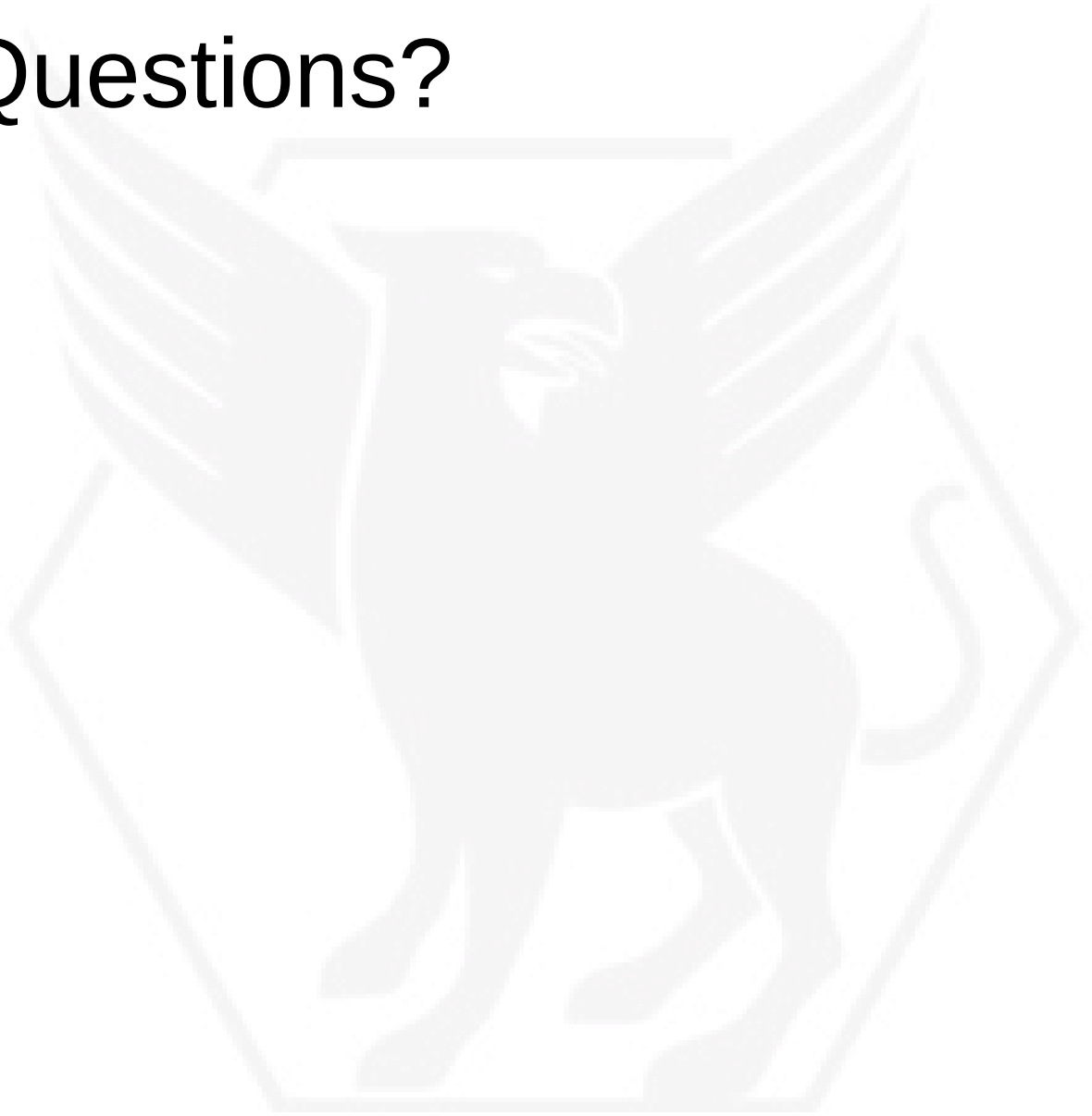
Additional analysis

- We performed a historical analysis of incidents that lead to a loss of public trust in science
  - We have direct data from public surveys and indirect data from testimonies and political actions taken
  - We also examined influence of incidents on:
    - Enrollment in specific STEM fields in universities
    - Employment in STEM jobs
- We have summarized the historical epidemiological and economic data to provide information on the burden of influenza and coronaviruses
- We are assessing if laboratory-generated GoF phenotypes are likely to arise in nature
  - This study is rolled into the benefit assessment because it provides context for the possible benefit
  - Also speaks to the risk of not doing the research

Questions?



Backup Slides

Modeling Human Health Consequences of Outbreaks of Avian Influenza Strains

- Insufficient data is currently available to develop a useful quantitative model of the consequences of a novel strain of non-human-transmissible avian influenza
  - Scant evidence of wild birds causing human infection, no confirmed cases
  - Transmissibility from wild birds to poultry appears to be unpredictable and strain specific
  - Consequences to humans of poultry influenza outbreaks are unpredictable and highly variable:
    - 2015 USA H5N2, like most poultry outbreaks, has caused no known human cases, despite the fact that the H5 gene is descended from same clade as an H5N1 that caused human mortality
    - 2003 Netherlands H7N7 infected up to 250 poultry workers, primary symptom was conjunctivitis only, one fatality
    - 2013-2015 in China H7N9 has infected 677+ people, including 275+ fatalities
  - Size and scope of outbreaks in poultry vary significantly from strain to strain and outbreak to outbreak:
    - 2015 USA H5N2 spread rapidly through 211 flocks across Midwest
    - 2004 USA H5N2 only infected a single flock in Texas
- The environment of the outbreak probably plays a huge role in its spread
- Even if we knew exactly which strain was being manipulated, its consequences would be impossible to predict