Session I
Results of the Risk and Benefit Assessments of Gain-of-Function Studies

Moderators:
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Risk and Benefit Assessments of Gain-of-Function Studies

Purpose of the risk and benefit assessments (RBA)

To provide an independent, evidence-based analysis of the potential risks and potential benefits associated with certain GOF studies

NSABB's goal with the RBA

- Understand the different risks associated with research involving certain pathogens and certain GOF experiments
- Identify and distinguish GOF studies that raise significant concerns from those that do not
- Identify and evaluate the potential benefits of GOF studies
- Compare the potential benefits derived from GOF studies to those that may be achieved through alternative approaches

Timeline

- May 2015: NSABB Framework to guide RBA approved
- June 2015: Gryphon Scientific presented its work plan to NSABB working group
- July – November: NSABB working group received periodic updates on RBA progress and some preliminary work products
- November 2015: RBA results were presented to NSABB working group

Session I – Results of the Risk and Benefit Assessments of Gain-of-Function Studies

<u>Presenter:</u>

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Principal Investigator, commissioned Risk and Benefit Analysis of GOF Research

<u>Discussion Panelists:</u>

- Thomas Inglesby, M.D., UPMC Center for Health Security
- Stephen Eubank, Ph.D., Virginia Tech
- Ron Fouchier, Ph.D., Erasmus Medical Center
- Daniel Jernigan, M.D., M.P.H., Centers for Disease Control and Prevention
- Kanta Subbarao, M.B., B.S., M.P.H., National Institutes of Health
- David Relman, M.D., Stanford University

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Risk and Benefit Assessments – Discussion

Questions for Discussion

- What are the strengths and limitations of the risk and benefit assessments?
- Which GOF studies are of greatest concern, if any? Which are of less concern?
- Are the assumptions, approaches, and findings about risks and benefits associated with GOF studies comprehensive and sound?
- Are there specific risks or benefits that are over- or understated in the risk and benefit assessments?

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

Summary

Gryphon Scientific
Rocco Casagrande, PhD, Principal Investigator
NSABB Meeting January 7, 2016

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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

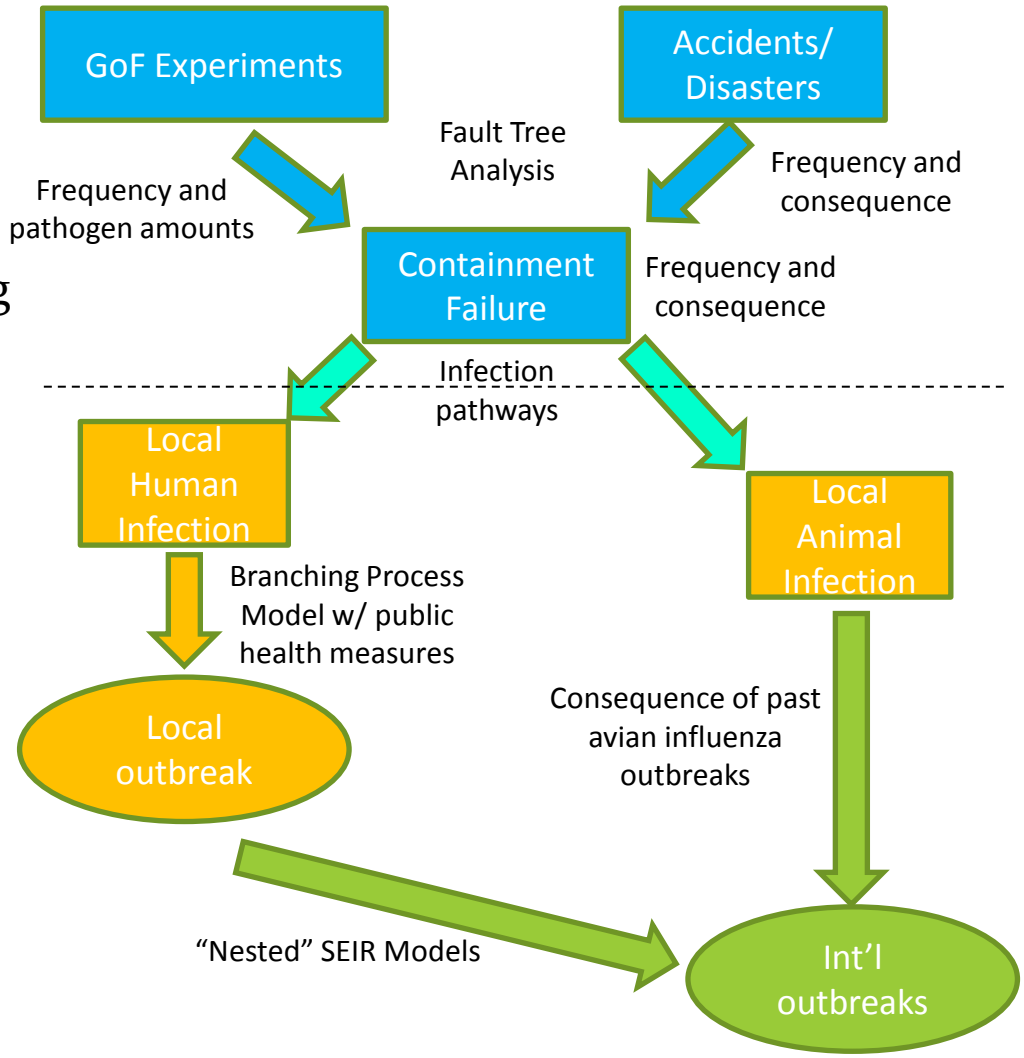
- In this study, we try to analyze GoF phenotypes individually
  - For example, we isolate the effect of strains with increased transmissibility independent of other phenotypes
  - However, many phenotypes are linked:
    - For example, a component of transmissibility of influenza in human populations 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

- 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

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

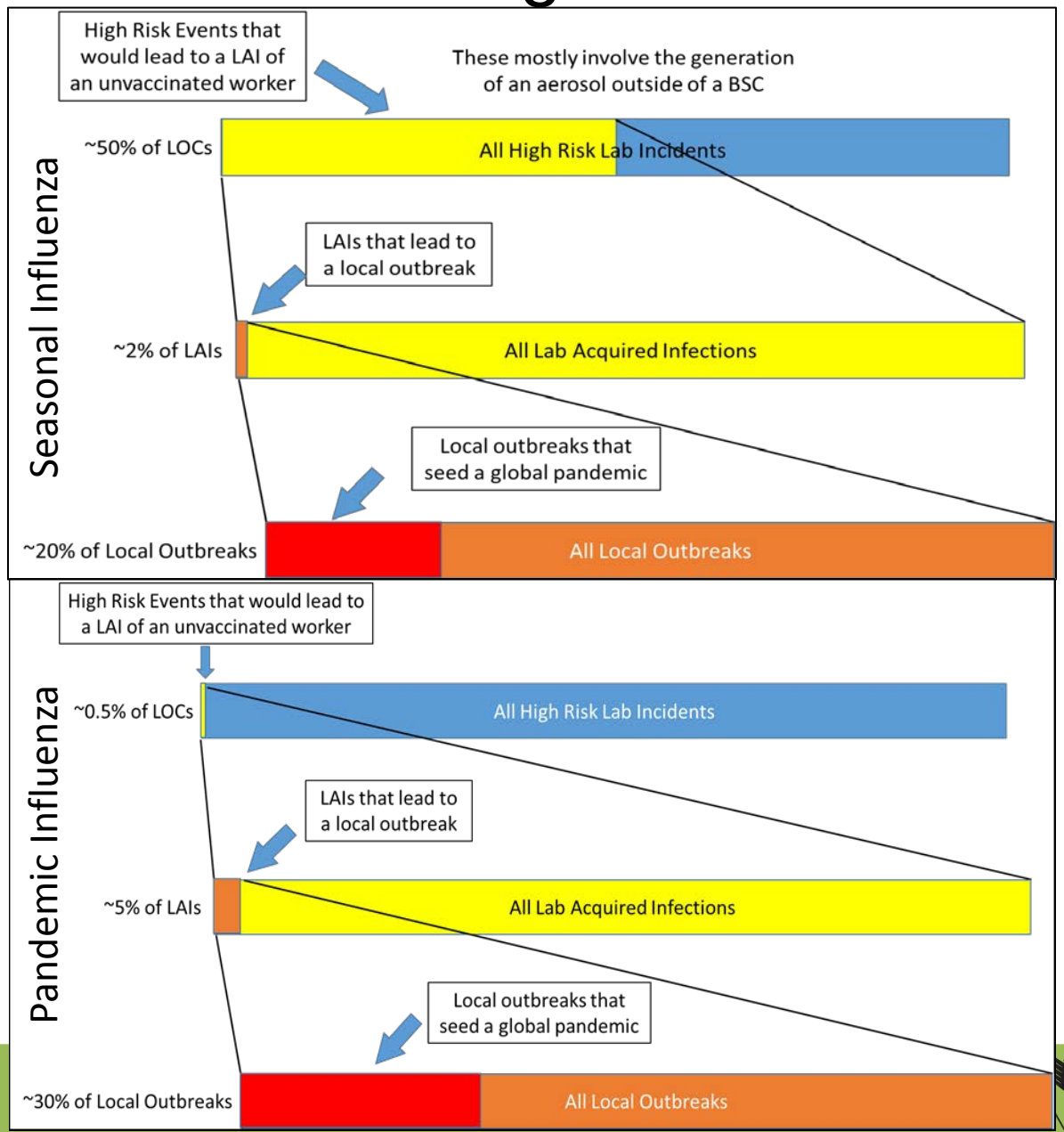


Using Interviews to Inform the Risk Assessment

- 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

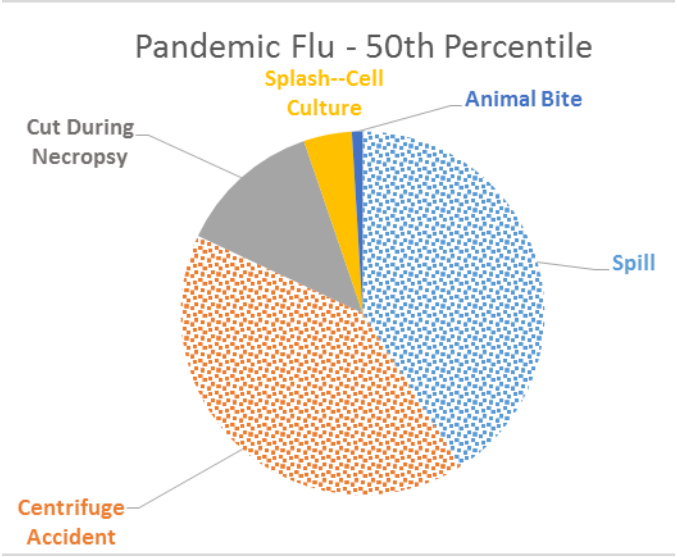


Table 6.2. Relative probability of a laboratory acquired infection for the various pathogens considered in this study as compared to work with seasonal influenza.

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)

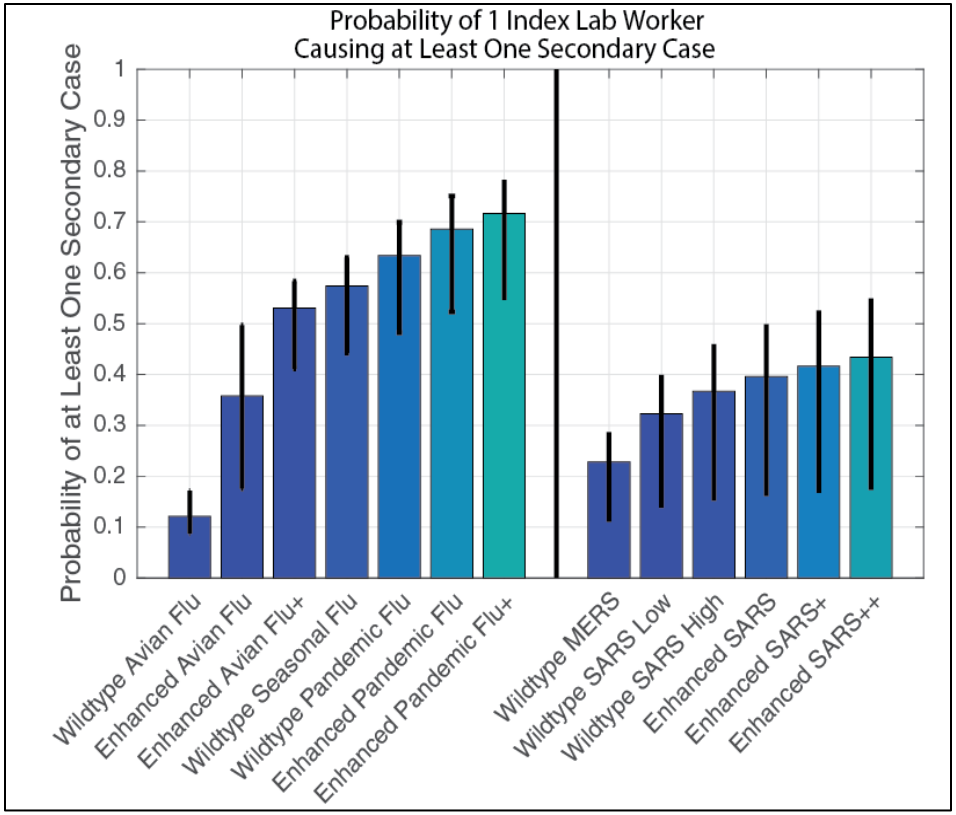
These data are generated by comparing the sums of the frequency of infection from all loss of containment pathways for each pathogen. In this case, we use the term laboratory acquired infection to include an infection of wild birds to capture the comparative risk of working with avian influenza viruses. 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

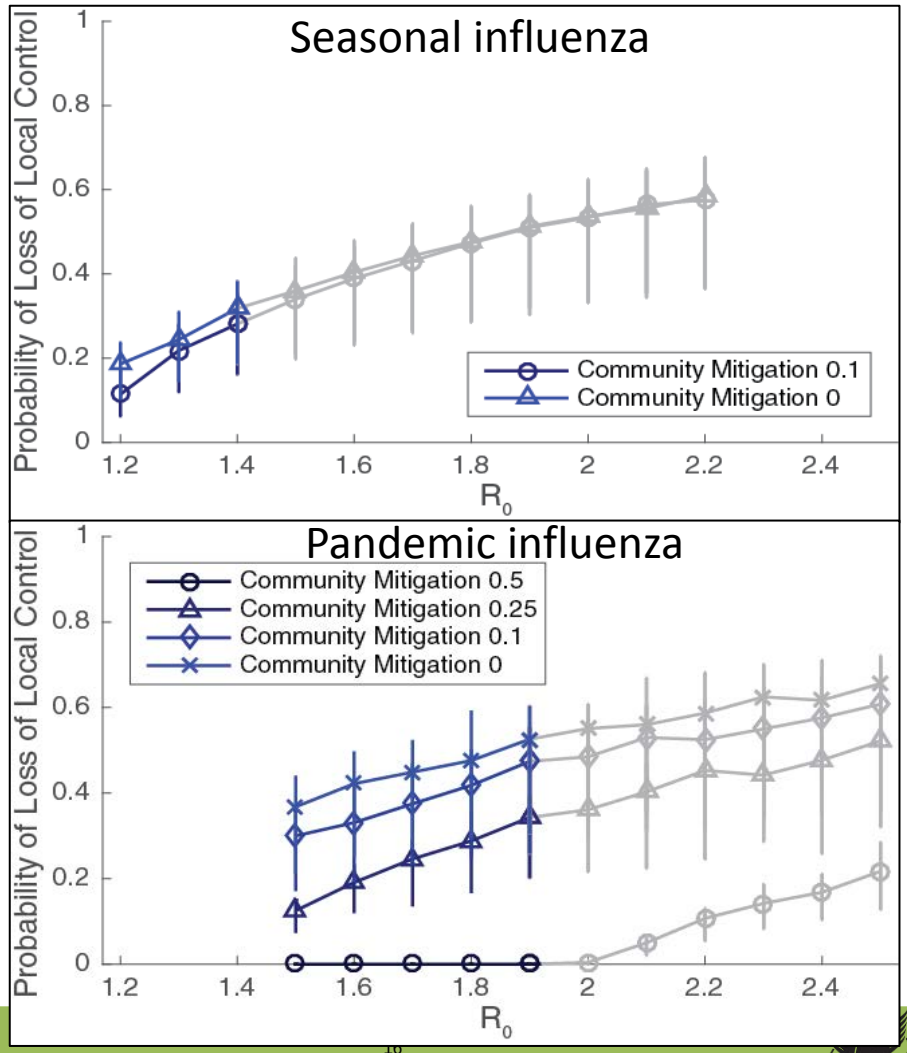
- Except for very low values of R0, most influenza cases in the community will lead to at least one secondary infection
- For the coronaviruses, due to their low K, most infections in the community do not lead to a secondary case even if the worker mingles with the population
- R0 has a modest influence 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

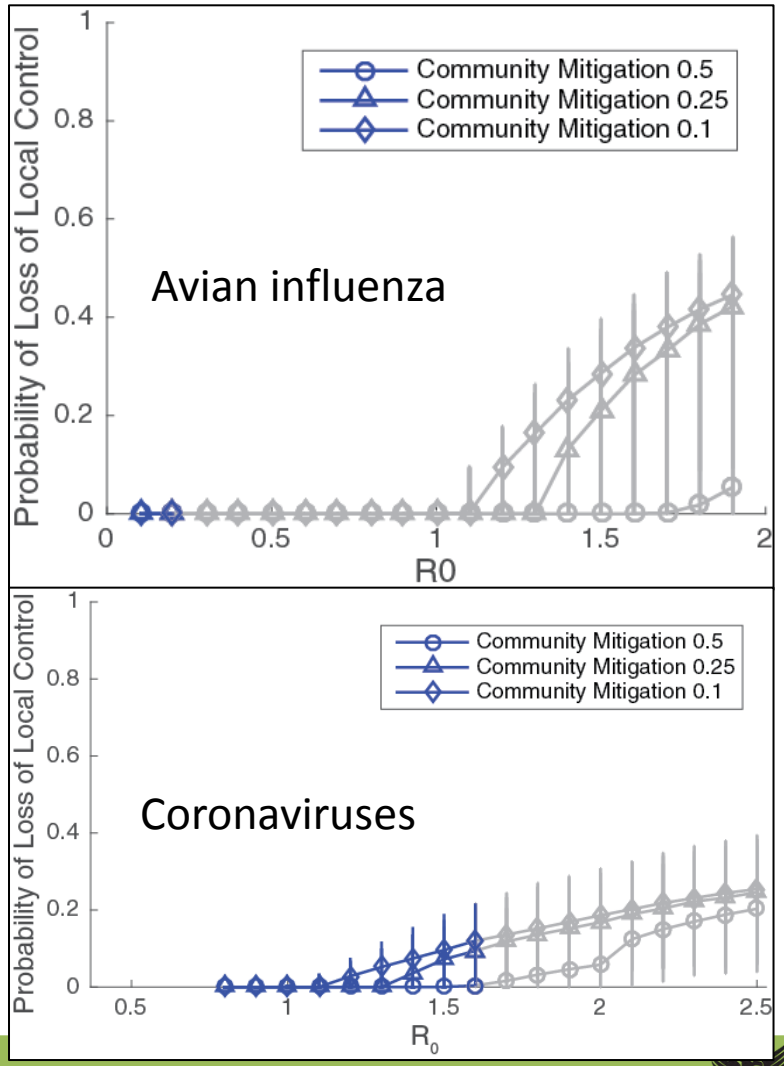
Influence of Transmissibility on an Outbreak Escaping Local Control

- 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



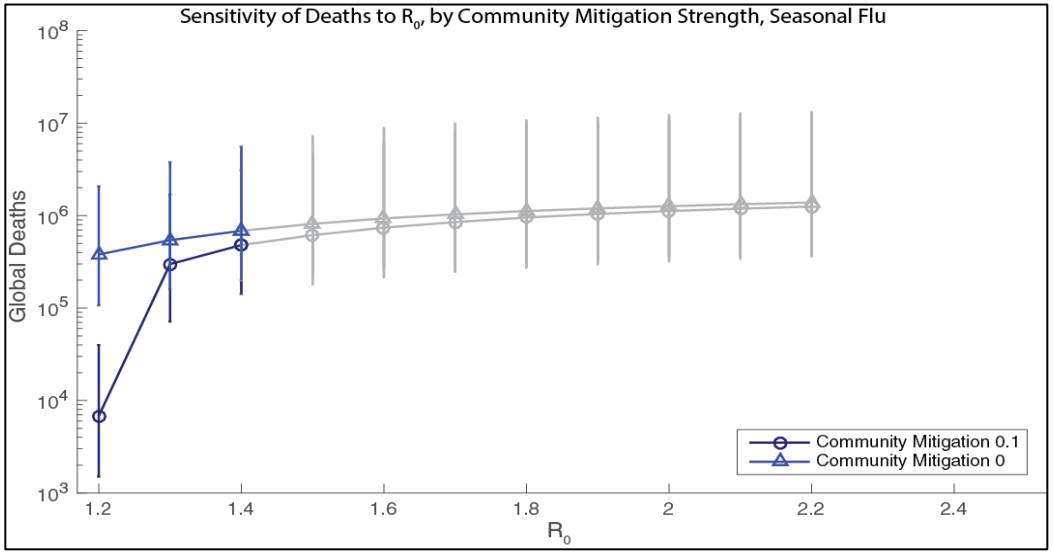
Influence of Transmissibility on an Outbreak Escaping Local Control

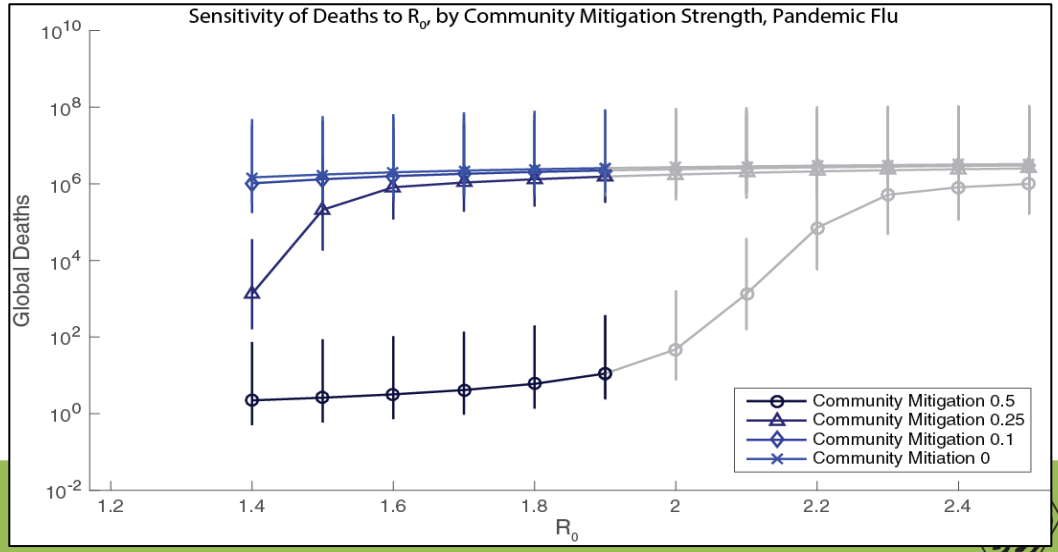
- Increasing R0 beyond one for avian influenza vastly increases the probability that the outbreak would escape, unless community mitigation is robust
- Increasing R0 of the coronaviruses linearly increases the probability that an outbreak escapes



Influence of Transmissibility on Consequences of a Global Pandemic

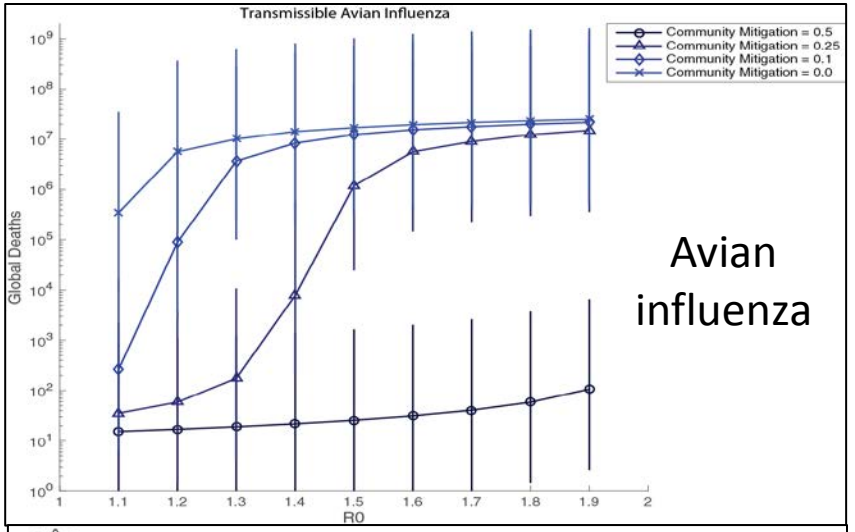
- For *seasonal* strains, if community mitigation cannot be sustained during a global pandemic, increasing R0 increases global consequences.
- For *pandemic* strains, increasing R0 beyond that of any wild type strain minimally affects deaths unless community mitigation can be sustained

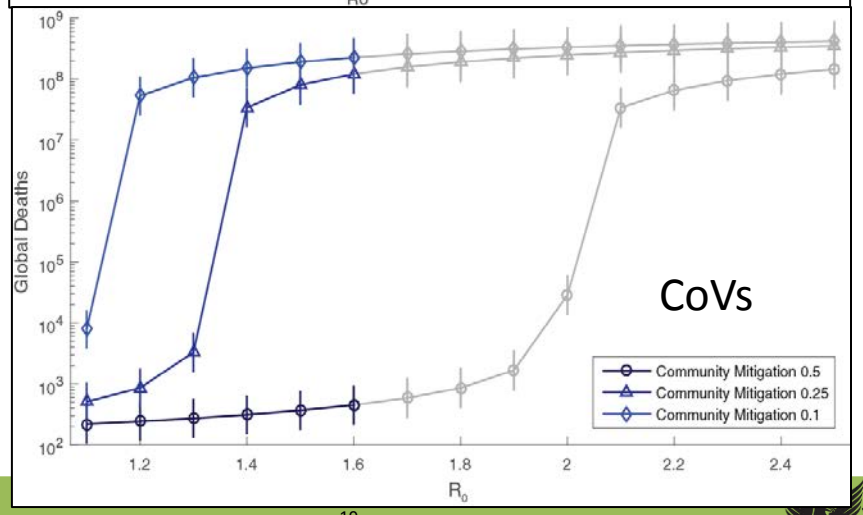




Influence of Transmissibility on Consequences of a Global Pandemic

- 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

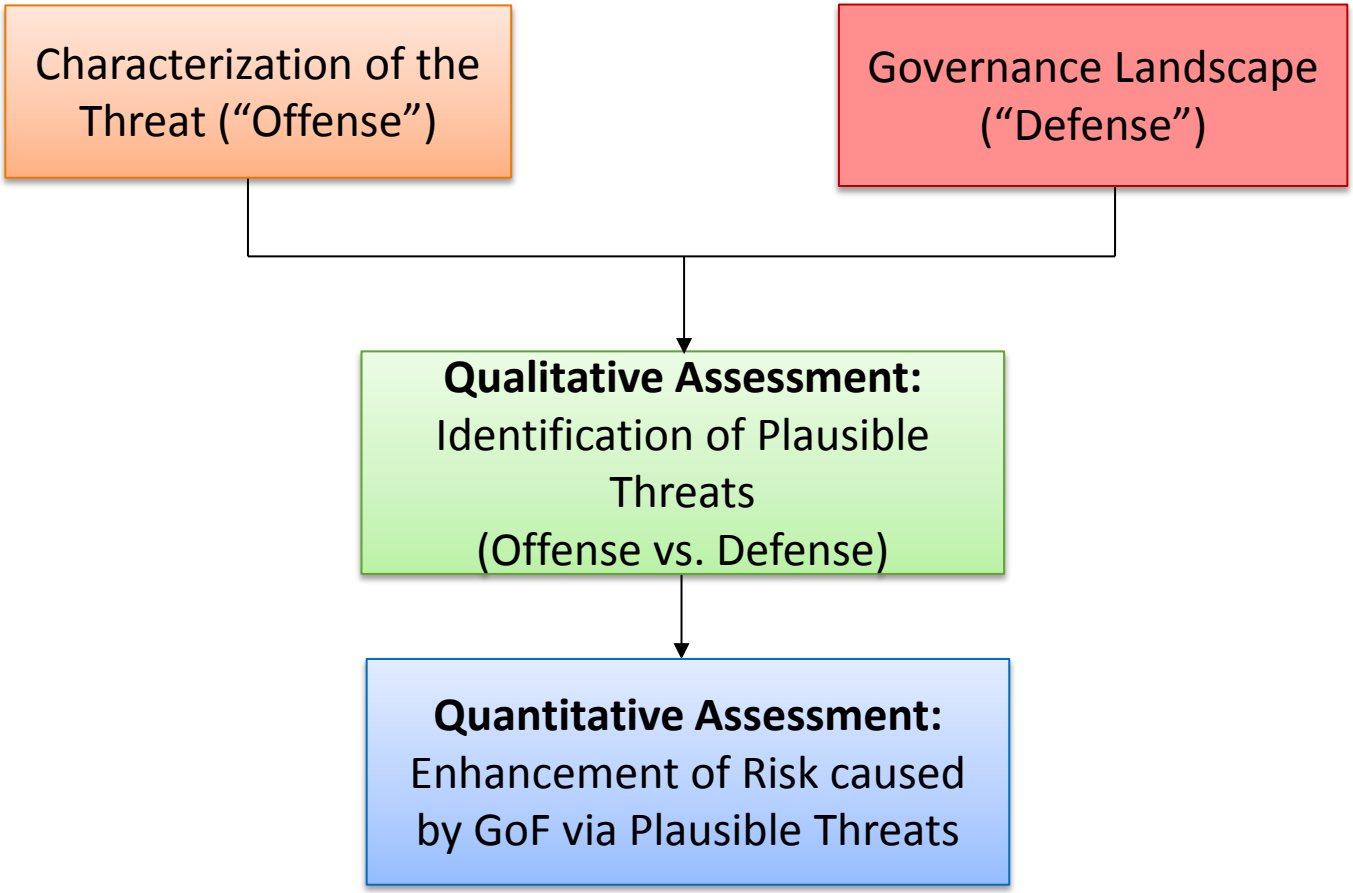
- The RBA can be divided into three major tasks, each of which requires a distinct data collection and analysis approach
  - Quantitative Biosafety Risk Assessment
  - Semi-quantitative Biosecurity Risk Assessment
  - Benefit Assessment

Biosecurity Risk Assessment

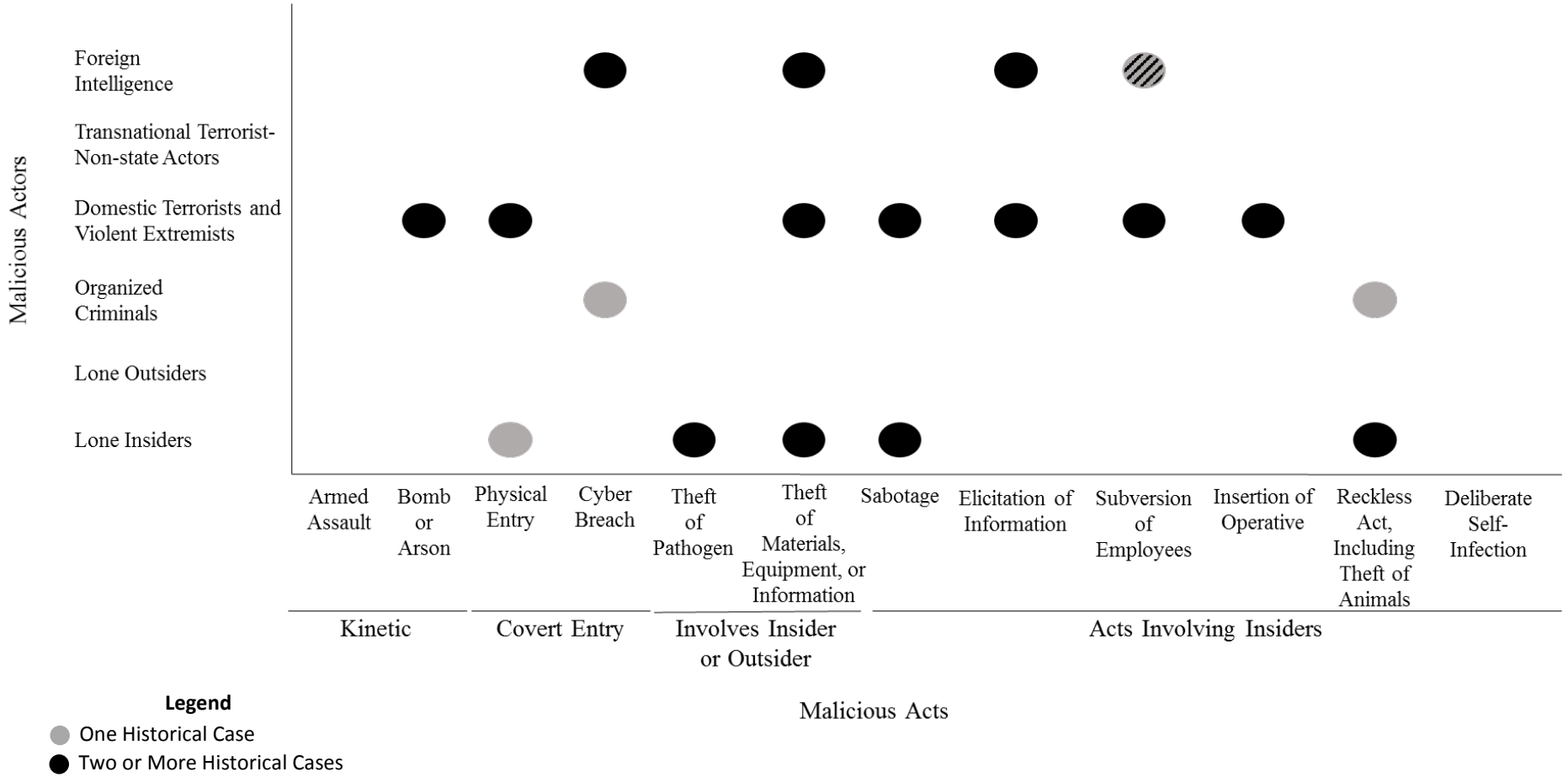
- The biosecurity risk assessment has two components
  - A semi-quantitative analysis of the risk posed by hostile acts occurring at laboratory that performs GoF research
  - An analysis of the risk posed by the misuse of the information generated by GoF research

BIOSECURITY RISK ASSESSMENT OF ACTS TARGETING A LABORATORY

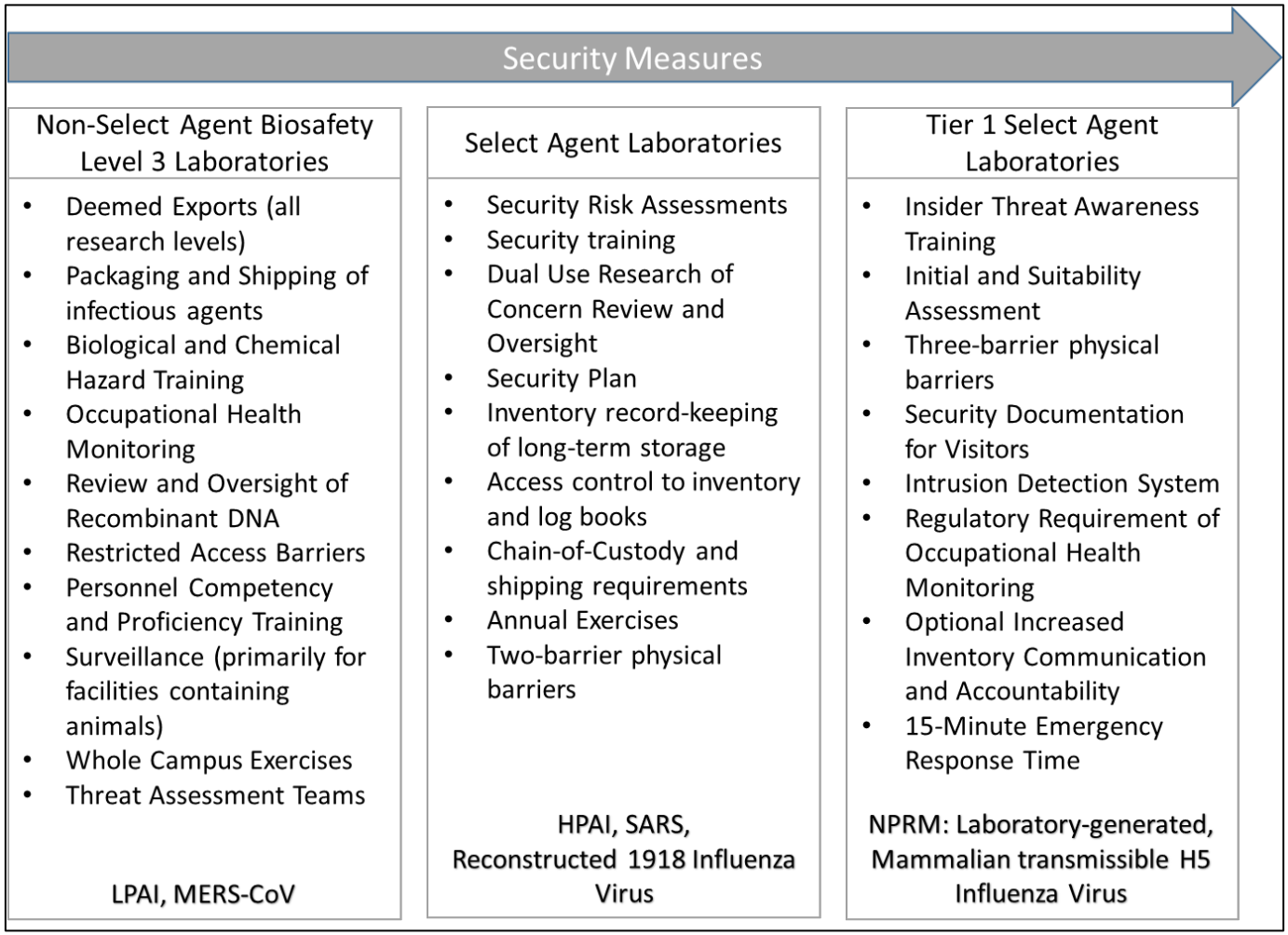
Process for RA for Acts Targeting A Laboratory



Historical Incidents: Malicious Actors and Acts



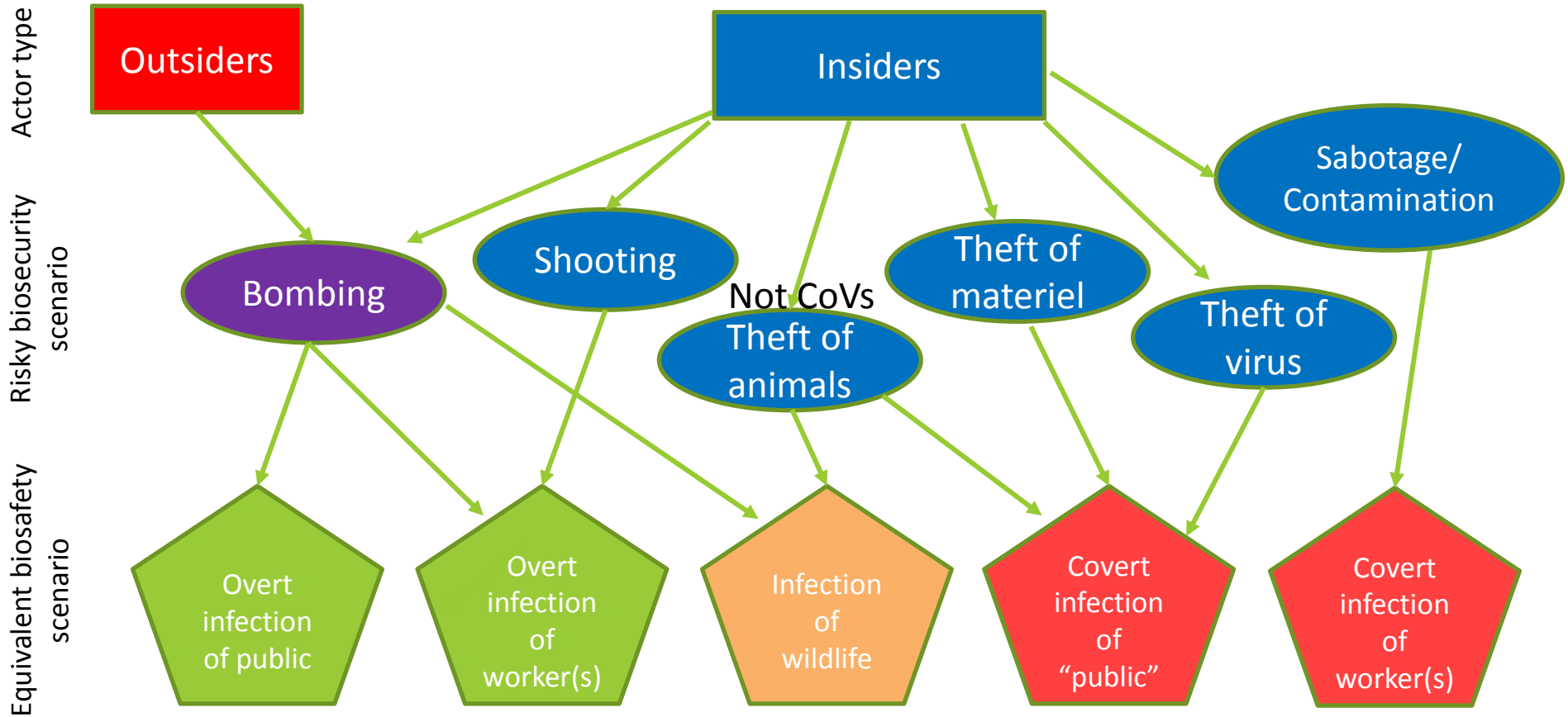
Security Measures at High Containment Laboratories



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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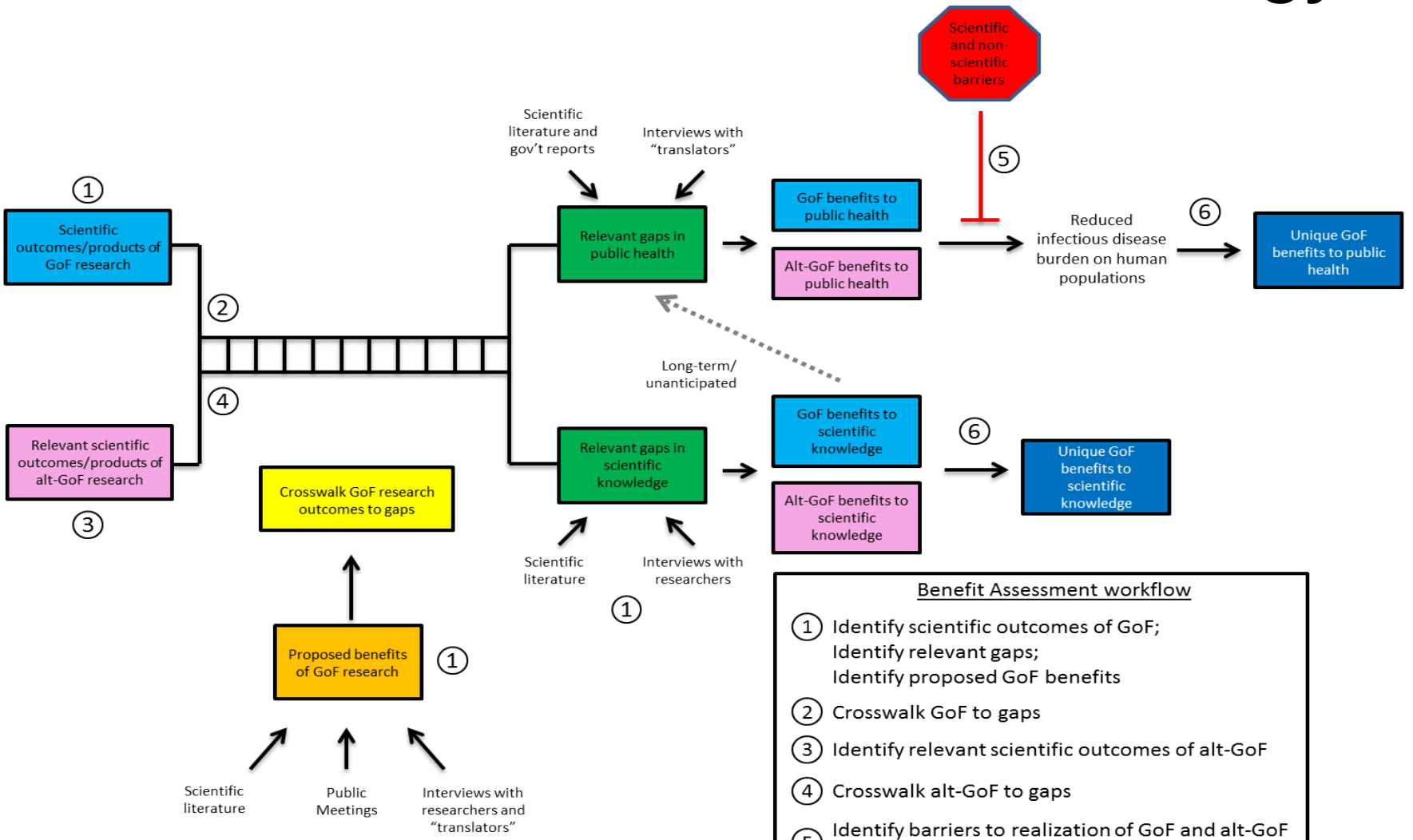
Benefit Assessment Methodology



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

NSABB meeting

January 7, 2016

Scope of RBA too broad

- Assessment included “gain of function” experiments outside area of greatest concern
- Substantial discussion on manipulation of seasonal strains: not discussed as major concern in last few yrs
- Using GOF techniques to increase vaccine virus yield: this is logical and beneficial as these techniques attenuate strains while enhancing growth
- Expanded scope leads to understated risks and overstated benefits

Would narrow focus of process to proposed creation of novel strains that are highly virulent and highly transmissible

On potential consequences of accident

- Consequences of accident/misuse much more explicit than USG reports
  - "An accident that starts a pandemic with 1918-like influenza strain could cause 80 million deaths."
  - "Creation of strains that are human transmissible would greatly increase the risk that such an outbreak could occur, which could cause millions of illnesses. "

- Don't agree: implications that 1918 level pandemic be considered upper bound, or that PPP induced epidemic < 1918 be considered less alarming

- Global pandemic induced by PPP accident or misuse with a case fatality anywhere above a normal flu season would be shocking global event that would kill many and deeply damage science

Would not use 1918 influenza as threshold of acceptable risk. Without extraordinary, unique benefit, experiments where accidents could start pandemics that lead to thousands or millions of deaths should not be performed

On biosecurity risks

- Disagree that biosecurity assessment should be so focused on risks in US--this is global issue, not a US one.
- Don’t think it is possible to predict future misuse of biology or pandemic pathogens by studying past events.
- Notable conclusion in report: biosecurity risks pose as much threat as biosafety
- **Focus on what the biosecurity risks would be internationally (not only in US) if the norm were set that this work should be approved and funded**
- **Other recommendations as per EMBO paper with D Relman**

On laboratory accidents

- "Data are lacking on how often humans will make mistakes of a variety of kinds in a biological laboratory (epistemic uncertainty)…Lab workers are humans and some humans are more prone than others to errors due to carelessness, unfamiliarity with protocols, distraction or stress." (p 124)

- "Increasing transmissibility of coronaviruses could significantly increase the chance of a global pandemic due to a lab accident." (p 3)

- *Also says that even if coronaviruses modified to be as transmissible as influenza, the susceptibility to control measures would still contain a majority of outbreaks.* But if virus spreads as efficiently as flu, it's not susceptible to control measures

- SARS contained only after months of intense effort, infecting thousands, killing hundreds. Crashed Asian economy. Big cities look like ghost towns. **Even if coronavirus transmission only minimally increased, should be very concerned**

- **Given absence of rigorous reporting of human errors in life sciences, danger in pursuing experimental work where consequences of accidents could be pandemics**

On ‘control’ of PPP induced epidemics

- Report implies that human behavior will reduce risk of transmission during a PPP outbreak(p 9) –
  - But in the case of influenza, there is no evidence that human behavior (e.g. social distancing, p 131) could change the course of a pandemic

- Report cites the reproductive number of SARS to be 1.4, but more authoritative sources calculate it at 3

- **Planning should assume that human behavior will not substantially change course of pandemic flu**
- **Human behavior could affect outcome of coronavirus spread, but not if it were made as transmissible as flu**

On information risks

- Don't agree: "Little information risk remains from GOF research…."or that "methods to produce these strains have already been published and so no information risk remains."

- More PPP work is being proposed which will carry new immediate risks and information risks.

- Possibility of new approaches to create novel pathways to PPP strains, perhaps more efficient techniques

- Interest in creating PPP strains with major flu strains across spectrum

New PPP research will carry new information risks

International repercussions

- The RBA focuses on risks in the US. If this funding pause is lifted now, other governments will see this as a green light to fund this work elsewhere.
- Based on past case studies, RBA says this kind of work may proliferate to as many as 70 labs in the next 10-15 years(p 4)
- No international consensus effort going on now that would seek a different outcome.

USG needs to make these decisions with international research community and global impact in mind

Benefit Assessment

- Majority interviewed were proponents of this research, or came from institutions supporting it
- Benefit claims in RBA are made as if fact (as opposed to opinions)
- Should be public forum with companies who make relevant vaccines. Do they need PPP work in critical path for making new vaccines? Almost none have commented publicly, some have said opposite
- RBA implies that PPP research might have identified molecular markers in the 2009 H1N1 strain that would have accelerated vaccine production and saved hundreds of thousands of cases(p 328). No evidence this is true.
- Agree with comments submitted by Plotkin and by Lipsitch

Benefits claims overstated and need external validation. Should be public forums with vaccine companies and impartial surveillance experts

Other notable elements

- RBA statement: "Other pathogens that lie outside the framework could be manipulated to cause a global outbreak" (p 8)
  - Of note - in earlier NSABB meeting, one research scientist prepared a slide justifying creation of making Ebola airborne transmissible

- RBA: Other traits of influenza or coronaviruses not covered by the Framework (e.g. environmental stability or other mechanisms of transmission) could increase the possibility of global pandemic

- RBA judges risk in 5 yr time horizons, but benefits w/out time constraints

- **Other risks will emerge that USG will need to deal with outside framework**
- **Judge risks and benefits without time constraints -- once a risk is created, it will endure**

NSABB Draft Working Paper

Agree:

- Finding 3 – Current oversight insufficient for all GOF studies of concern
- Finding 4- Some research should not be conducted at all on ethical or PH grounds if potential risks not justified by benefits
- Finding 5 – Subset of GOF studies have potential to generate high, potentially unknown risks

- Rx 1: Studies of greatest concerns generate highly transmissible, highly virulent virus (highly transmissible **by definition will be resistant to PH controls** so would NOT add that as separate criterion).

NSABB Draft Working Paper

Don't agree:

- …That existing oversight mechanisms for this work are robust or sufficient;

Funding criteria listed in NSABB document useful but insufficient:

- Benefits should be > than Risks – who determines that?
- Proposed research is ethically justifiable – who decides that?

Doesn't make sense for USG funding to be only vehicle discussed for control of experiments. USG should decide whether to fund **or approve**

Overall recommendation to USG

- Benefits of PPP are not so crucial and singular that they are worth the high risks. Potential number of people affected globally by an accident or deliberate use is more extreme than most dangers that humans could willingly choose to take

- Would not fund or allow PPP research (aka “GOF research of concern”) unless highly compelling case for benefits validated that merit such extraordinary risks (including vaccine companies)

- Seek international consensus on how to proceed

My significant sources of bias

- NIH funded, not directly affected by the result
- Advocate the relevance of math modeling
- Prior statements on NEIDL Risk Assessment
- Concerned about opportunities and mechanisms for public engagement in science policy-making
- Parallels with nuclear weapons and physics

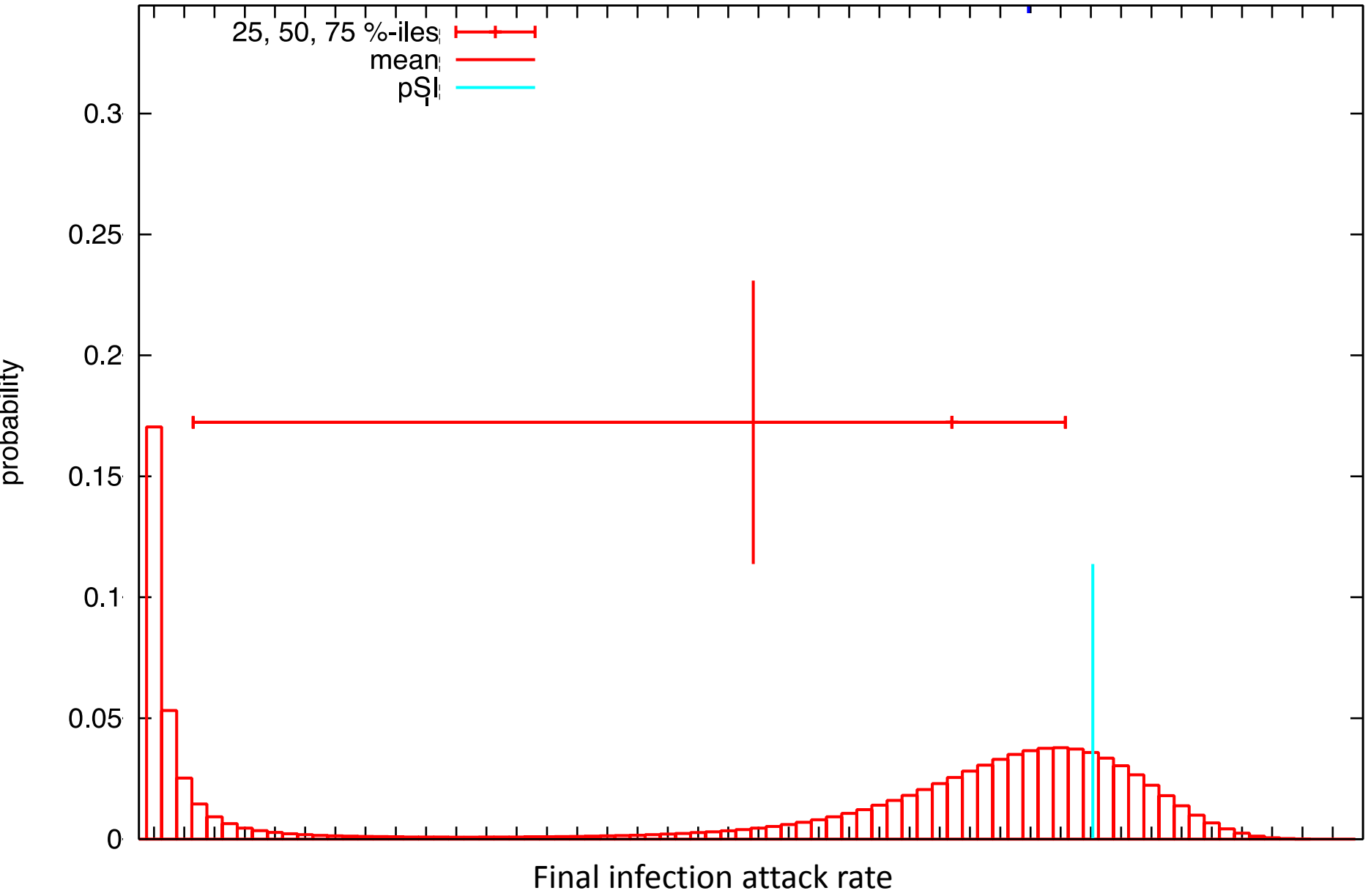
Beware implicit assumptions about unimodality, independence, and linearity

In general:

- mean is a poor representation of a bimodal distribution
- (mean value of product) ≠ (product of mean values)
- small changes in assumptions may produce large changes in outcomes

E.g. risk = consequence *probability of occurrence

Distribution of final attack rates is strongly nonlinear

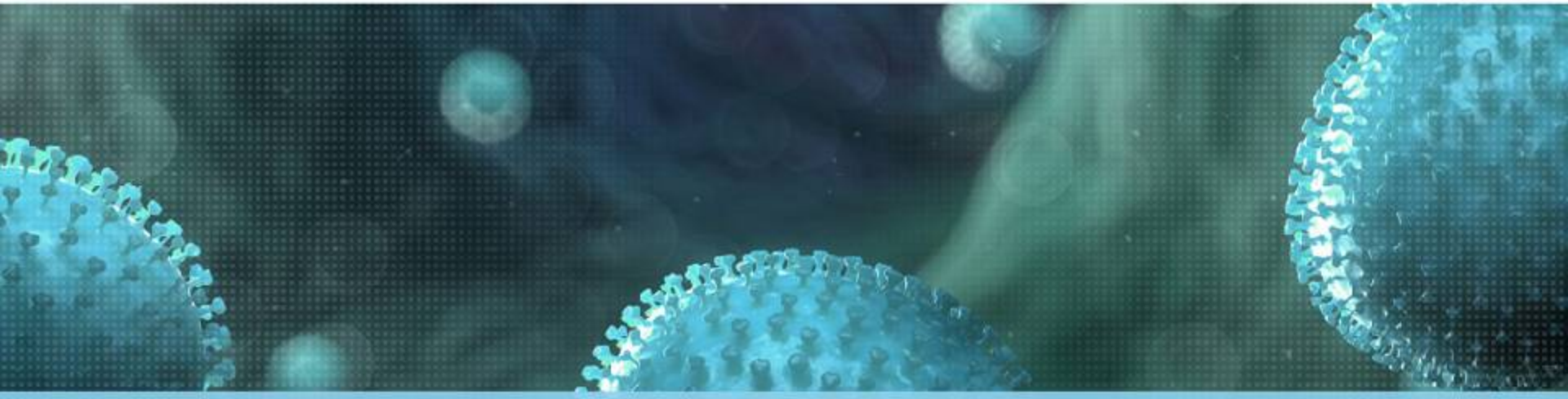


Erasmus MC

NSABB meeting, January 7 & 8, 2016

Viroscience lab

WHERE SKILLS MEET TO STUDY & PROTECT



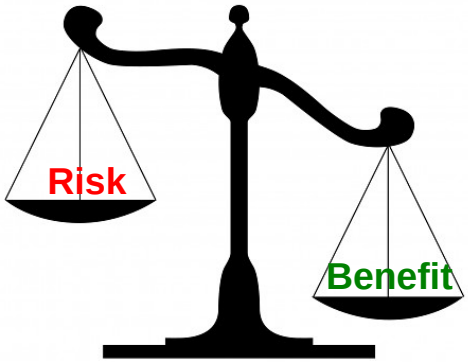
Reflections on Gryphon Scientific's Risk and Benefit Analysis and NSABB WG's Draft Working Paper

Ron A.M. Fouchier, PhD
Professor Molecular Virology

Strengths and limitations of the RBA
- Gryphon Scientific Final Report Dec 2015 -

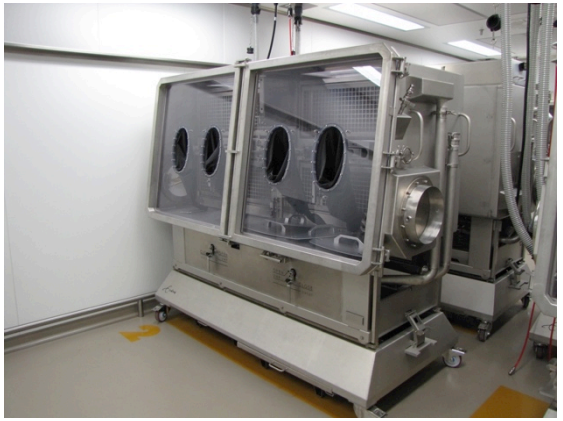
Strength: broad scope of benefit analysis (but excluding long-term benefits and blue-sky research) :
- Identifies "stringent limitations" of alt-GOF experiments as stand-alone tool
- Identifies situations where GOF experiments "provide unique benefits"
- Identifies instances where GOF "moderately contributes to overall risk"

Limitation: biosafety risk assessment
- Risk relative to "wildtype pathogen" (for which no major outbreaks occurred)
- Estimate of "absolute risk" is still "hypothetical"; no LAIs have been recorded
- Biosafety risk assessment (explicitly) ignores biosafety enhancements



Risks: not quantified/quantifiable
Benefits: not quantified/quantifiable
Weighing: impossible/subjective

Biosafety 2.0 in agreement with Asilomar 1975
- Pathogen-specific enhancements -

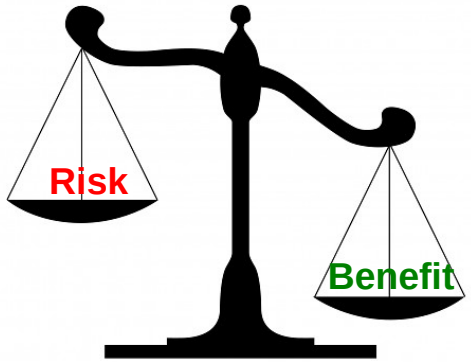


Preventing the LAI
- Class III units (monitored, validated)
- Extra layer of PPE
- Extensive training (incl incident response)
- Personnel work in pairs
- Vaccine use when possible
- Antiviral treatment upon any incident

> 140-fold risk reduction (very conservative)

Preventing onward transmission from LAI
- Reduce virus shedding (vaccine, drugs)
- Quarantine of personnel

> 20,000-fold risk reduction



Overall reduction of risk from very low to negligible

> 6 orders of magnitude risk reduction

A DEPARTMENT OF Erasmus MC

Fouchier RA, Studies on influenza virus transmission between ferrets: the public health risks revisited. MBio. 2015 Jan 23;6(1). pii: e02560-14.

Which GOF studies are of greatest concern?

- None (to date), relative to nature -

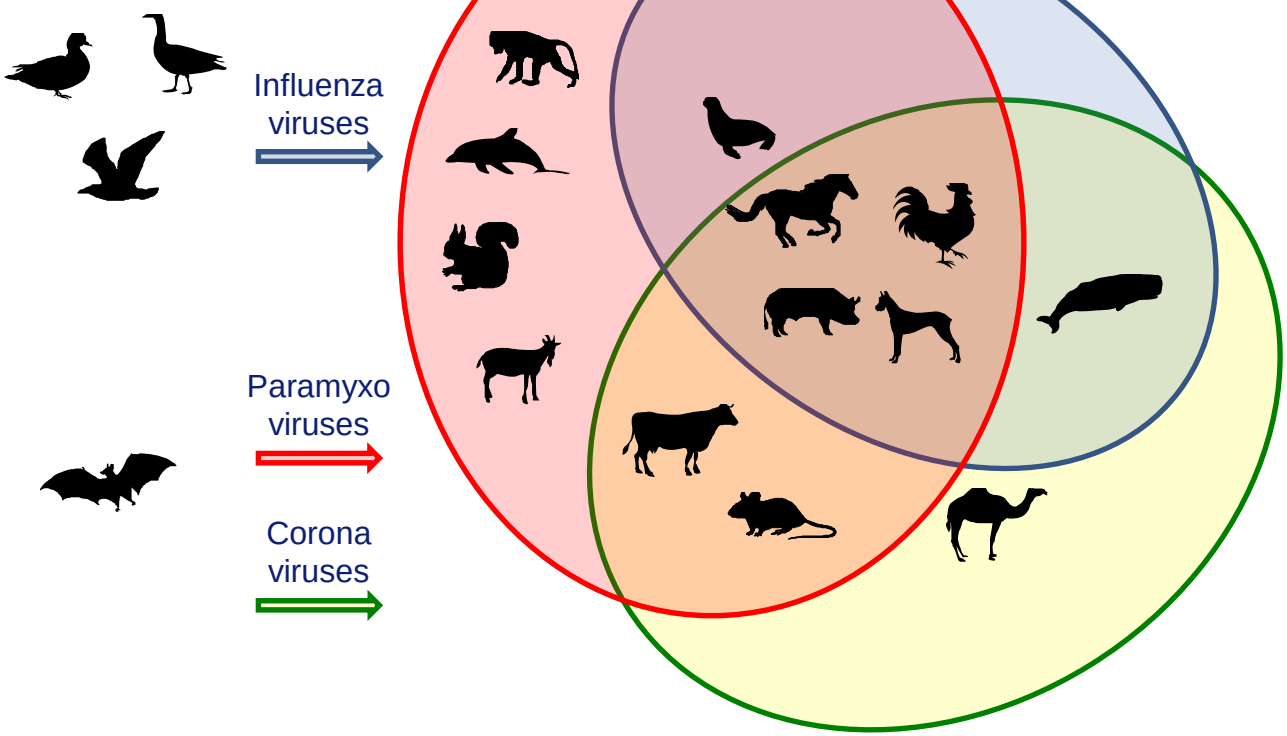


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Image: Herfst & Fouchier, Eurosurveillance 2014

Working paper NSABB WG
- Deliberative draft, December 2015 -

Thoughtful document, comprehensive and sound
Articulates limitations of RBA (lack of quantitation of risks and benefits)

Key Finding 1: There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF studies—GOF studies of concern—entail risks that are potentially significant enough to warrant additional oversight.

Key Finding 4. There are life sciences research studies that should not be conducted on ethical or public health grounds if the potential risks associated with the study are not justified by the potential benefits. Decisions about whether GOF studies of concern should be permitted will entail an assessment of the potential risks and anticipated benefits associated with the individual experiment in question. The scientific merit of a study is a central consideration during the review of proposed studies but other considerations and values are also important.

Recommendation 1. Research proposals involving GOF studies of concern entail the greatest risks and should be reviewed carefully for biosafety and biosecurity implications, as well as potential benefits, prior to determining whether they are acceptable for funding. If funded, such projects should be subject to ongoing oversight at the Federal and institutional levels.

Recommendation 3. The risk-benefit profile for GOF studies of concern may change over time and should be re-evaluated periodically to ensure that the risks associated with such research is adequately managed and the benefits are being realized.

Assumptions:
i) Risks are not negligible;
ii) Risks can be quantified;
iii) Benefits can be quantified;
iv) Risks & benefits can be weighed (objectively?)

Working paper NSABB WG
- Deliberative draft, December 2015 -

Proposed Conceptual Approach for Funding Potential GOF Studies of Concern

1. Identify proposals anticipated to involve GOF studies of concern, as described by the following attributes:

i. The pathogen generated is highly transmissible in a relevant mammalian model

ii. The pathogen generated is significantly virulent in a relevant mammalian model, and

iii. The pathogen generated is likely resistant to control measures or more capable of being spread among human populations than currently circulating strains of the pathogen.

2. Review proposal to determine whether they meet the following criteria:

i. The research proposal has been evaluated by a peer-review process and determined to be scientifically meritorious and has been assessed to be likely to exert a sustained, powerful influence on the research field(s) involved.

ii. An assessment of the overall potential risks and benefits associated with the project determines that the potential risks compared to the potential benefits are justified.

iii. There are no feasible, equally efficacious alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach.

iv. The investigator and institution proposing the research have the demonstrated capacity to carry it out safely and securely.

v. The research information is anticipated to be broadly and legally shared in order to realize its potential benefits to global health.

vi. The research will be supported through funding mechanisms that include appropriate oversight of: a) all aspects of the research including its conduct, b) the sharing of data and materials, and c) the communication of the research.

vii. The proposed research is ethically justifiable.

Proposals not meeting these criteria should not be funded.

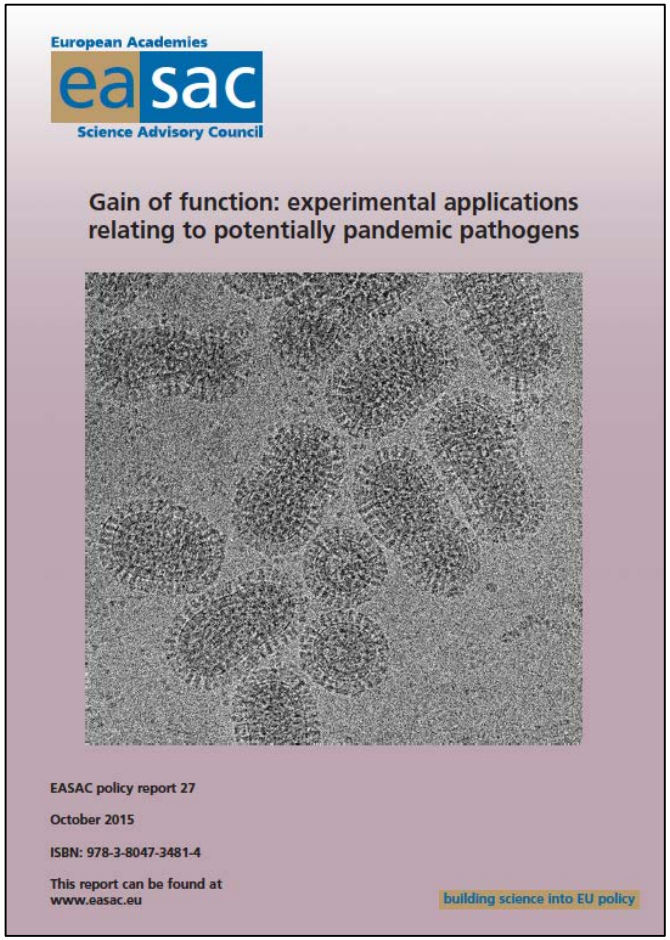
3. Fund, do not fund, or fund with required additional risk mitigation measures or stipulations.

4. Conduct the research in accordance with applicable oversight policies and employ any additional risk mitigation strategies that were identified at the time of funding or that are deemed necessary during the course of the research.

i. Research should be reviewed regularly at the institutional level

ii. Research should be reviewed regularly by the Federal funding agency

An EU perspective
- Laws, rules, regulations, codes are in place -



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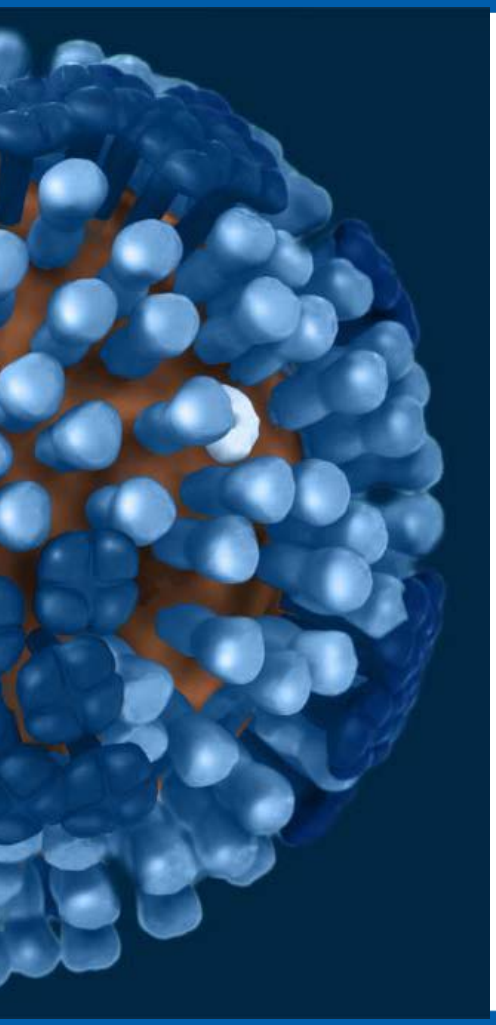
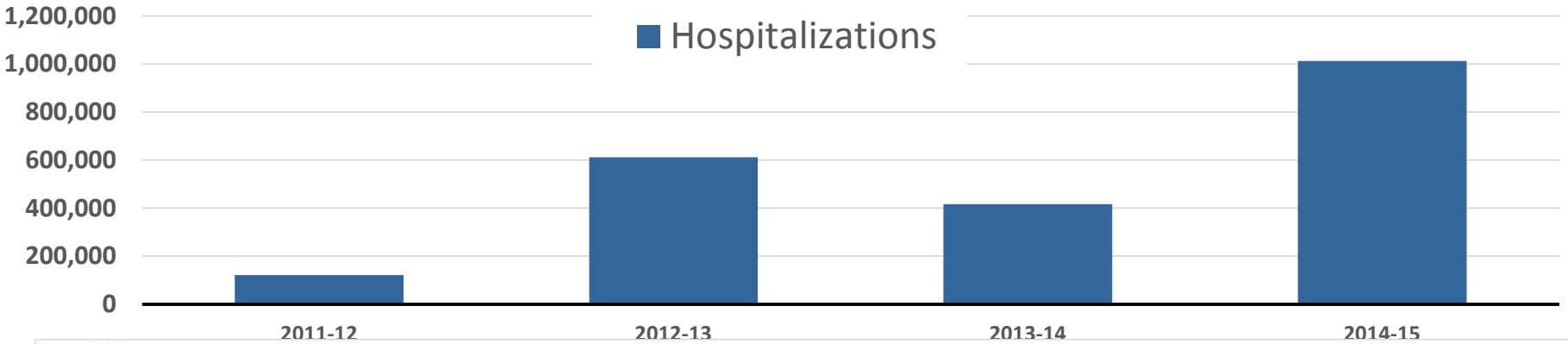
http://www.easac.eu/home/reports-and-statements/detail-view/article/easac-report-1.html
Fears R, Ter Meulen V. Elife 2015 Dec 30. pii: e13035 & J Virol 2015 Dec 23. pii: JVI.03045-15

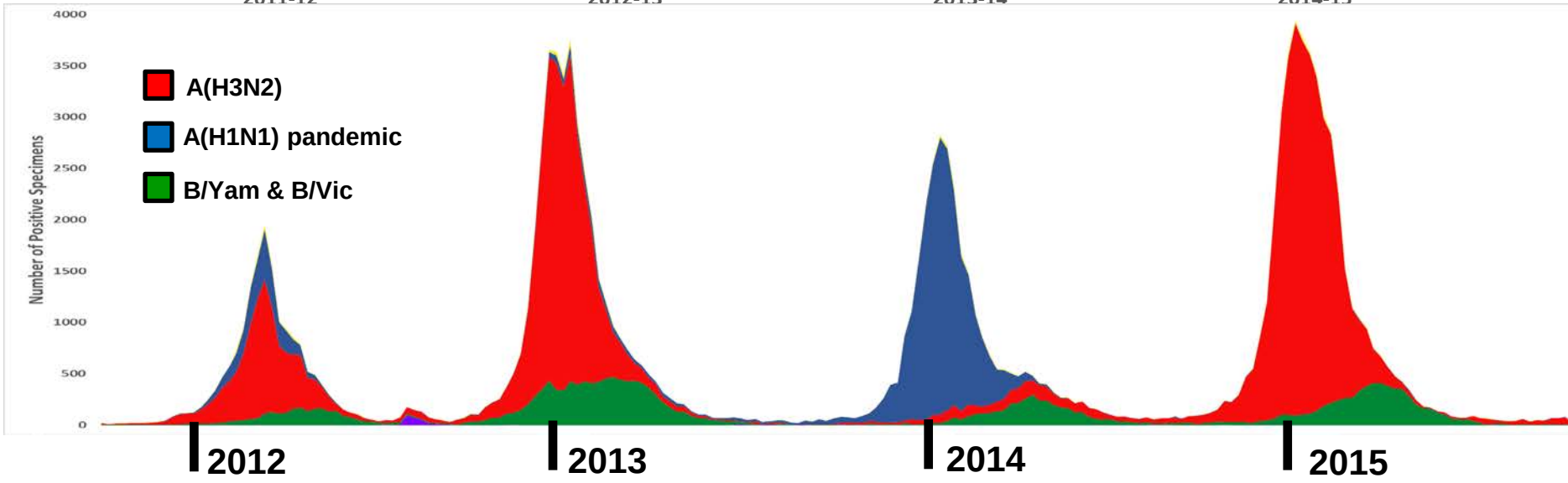


Results of the Risk and Benefit Assessments of Gain-of-Function Studies

Daniel B. Jernigan, MD, MPH
Director, Influenza Division
Centers for Disease Control and Prevention
January 7, 2016

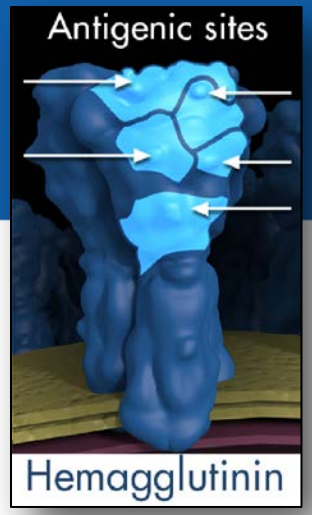
Burden of Seasonal Influenza



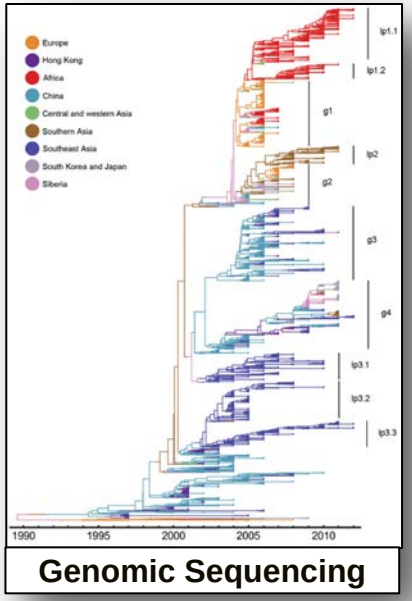


Reed et al, Estimating Influenza Disease Burden. PLoS One. 2015 Mar 4;10(3):e0118369. (Data for 2011-13)
Reed et al, Unpublished CDC data for 2013-15.
CDC. US Influenza Virologic Surveillance. www.cdc.gov/flu/weekly/overview.htm

New Challenges Require New Solutions



- H3N2 virus characterization and vaccine development is increasingly difficult
  - Drift occurs regularly and rapidly
  - H3N2 changes antigenicity in egg- and cell-propagation
  - Unable to use traditional assays
  - Poor growth in eggs
- Current efforts to address the challenges
  - Increasing global surveillance
  - Increased use of genomic sequencing
  - Developed new phenotypic assays
  - Developing higher yield egg-propagated and cell-propagated vaccine candidates



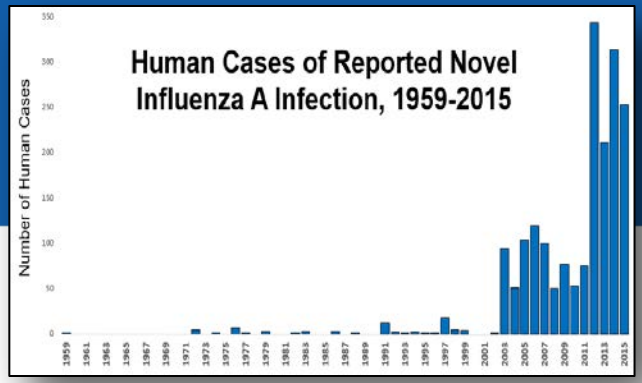
Genomic Sequencing

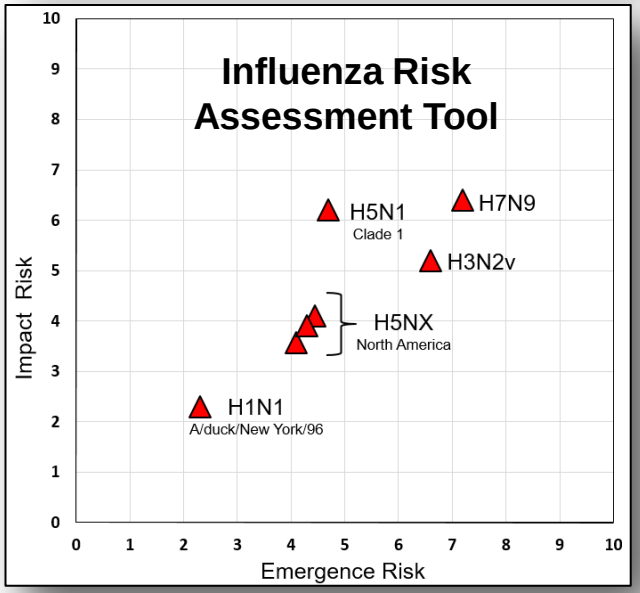
Public Health Benefits from GOF for Seasonal Influenza

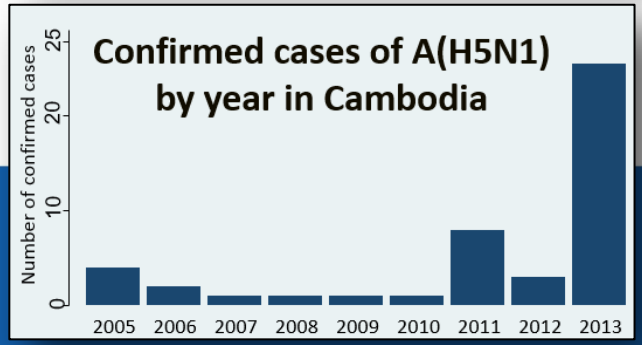
- Enhancing Virus Production
  - Production of sufficient and effective vaccines
  - Optimizing growth in eggs and cells
  - Shortening vaccine development and production timelines
- Revealing pathways for evasion of immunity
  - Predicting antigenic phenotype from genotype
  - Timeliness of antigenic surveillance and characterization
  - Predicting antigenic drift and potential for better vaccine match
- Revealing pathways for evasion of therapeutics
  - Timeliness of antiviral resistance surveillance using sequencing
  - Treatment guidelines for emerging antiviral resistance

Emerging Influenza Viruses with Pandemic Potential

- WHO GISRS supports surveillance and testing for seasonal and novel influenza viruses
- Increasing numbers of infections and global expansion of viruses requires ongoing vigilance
- Regular risk assessments are made utilizing data (some from GOF studies) to inform:
  - Novel/pre-pandemic vaccine development
  - Development of “Readiness Toolkits”
- Availability of a “Genetic Changes Inventory” informed by GOF studies has been critical:
  - Investigation of H5N1 cases of concern in Cambodia
  - Rapid H7N9 assessment
  - Evaluation of rapid rise in H5N1 cases in Egypt
  - Assessment of H5NX (H5N2, H5N8, H5N1) emergence in North America







Public Health Benefits from GOF for Novel and Pandemic Influenza

- Enhancing infectivity, transmissibility, or virulence in mammals
  - Surveillance of animal influenza viruses of concern
  - Computational models for predicting phenotypes
  - Rapid pandemic risk assessment to prioritize vaccine development and countermeasure efforts
- Investigating Reassortment Potential
  - Informs surveillance data, notably with rapid and expanded use of whole genome sequencing

Questions on the Application of the Risk and Benefit Analysis Approach

- Risk for Seasonal studies appear incorrect in RBA – A Miscategorization?
  - Categories for “Seasonal, Avian, and Pandemic” for RBA do not appropriately account for differences in population immunity or differences in intrinsic characteristics of the viruses.
    - Currently circulating “Seasonal” ≠ historic non-circulating “Seasonal”
  - Use of 1918 H1N1 Pandemic as the standard for all pandemics should be reconsidered
- Theoretical risks of a lab accident appear to have greater weight than the very real impact of currently circulating seasonal influenza
- Clarification is needed on the use of the three criteria for GOF of concern (transmissible, virulent, and evasive)
- Implementation of the RBA should be flexible for use in emergencies
- Application of the RBA in practice is not clear

Session I: Results of the Risk-Benefit Assessment for Gain-of-Function Studies

Kanta Subbarao,

Laboratory of Infectious Diseases,
NIAID, NIH

Comments

- Gryphon did a very good job summarizing the research landscape, the knowledge gaps and the approaches (GOF and alt-GOF).
- Important points to remember (these were mentioned in the RBA):
  - While presence of a known molecular marker of virulence or transmissibility often predicts these phenotypes, absence of known molecular markers does not mean that the virus will not be virulent or transmissible.
  - It is difficult to know how well transmissibility of influenza viruses in ferrets or guinea pigs translates to transmissibility in humans.
- A focus on highly pathogenic avian influenza viruses is understandable because of the ongoing H5 epizootic with associated sporadic severe illness in humans but we should not forget that the last 4 influenza pandemics were not derived from HPAI.

I do not have the expertise to assess the methods used for the RBA but here are a few items that I found surprising:

- All comparisons, including consequences of coronavirus GOF research were made to the 1918 pandemic.
- The section on pandemic viruses included 1918 and 2009 H1N1 viruses. Population immunity against both is high – this section should only focus on human H2N2 viruses.
- Table 6.7, p 118: Conducting CoV research at BSL2 instead of BSL3 only increased the probability of a laboratory acquired infection by 2-fold- the preceding paragraph states that for all except avian influenza, this is primarily caused by the addition of respiratory protection.
- Fig 6.23 p 122 vs. p 109 and 116: On p 109 and 116, the RBA states that although additional respiratory protection is worn in BSL3 labs working with coronaviruses, most infections are caused by aerosol exposure. However, on p 122 (Figure 6.23) the greatest increase in probability that a LAI would lead to an individual mingling in the community came from failure to wash hands (50-fold) and failure to double glove (4-fold), not respirator use/efficiency/reliability.

- Limitations:
  - Information risk doesn't deal with new information
  - Need clarification: Page 133: …even dramatic increases in transmissibility do not relate to dramatic increases in chance that an outbreak will extinguish….is this correct as written?

GOF of concern?

- Nature and science are always evolving and scientists studying pathogens at the animal-human interface are generally addressing public health concerns posed by newly emerged pathogens. Technologies and biosafety practices in laboratories are also modified over time.
- Concerns about laboratory accidents and biosecurity threats must be balanced against public health needs.
- The fact that some experiments are of greater concern than others does not mean that they should not be studied in a laboratory or that they cannot be studied safely in a laboratory. A vast majority of experiments can be undertaken under greater oversight.

GOF of greater concern?

- Any highly virulent, highly transmissible virus associated with a high case fatality rate that is resistant to MCM.

Examples of GOF of less concern?

- Currently circulating seasonal influenza viruses
- Adaptation of CoV to mammals to develop animal models
- Improving the growth of a virus
- Mapping escape mutations against antibodies or drugs that are developed as MCM
- Reassortants or spike swaps on attenuated or host-range restricted backbones

- Overstated:
  - Laboratory manipulation of seasonal influenza viruses
  - Page 326: too much time spent on a rapid phenotypic assay for mammalian adaptation and transmissibility that doesn't yet exist.
  - Pages 353-354: the human population does not have widespread immunity to the 1918 virus. After the 2009 H1N1 pandemic, we do.
- Understated:
  - The risk of not conducting research that is needed to address public health concerns

What has not been addressed?

- The beneficial and detrimental effects the voluntary moratorium followed by the deliberative pause have had on influenza and coronavirus research in the US.
- Are influenza and coronaviruses stand-ins for all pathogens of high consequence? How and when will this debate extend to other aspects of microbiology? Antibiotic resistance?
- Can we balance the need for research on pathogens of high consequence that address important public health needs with biosafety and biosecurity concerns? Yes, we can minimize and mitigate risk and proceed with caution and oversight.

Comments, NSABB Meeting, Session I

David A. Relman, Stanford University
January 7, 2016

Summary, Highlights

- Working Paper Findings: lack resolve, fail to address a clear need in the face of 'difficulty' (i.e., to describe studies that should not be funded)
- Attributes 'of concern': transmissibility 'trumps' countermeasure resistance
- Safety and security assessments are based on faulty and dangerous logic, unjustified assertions; risks are underestimated

Findings are too tentative (and hence, unhelpful)

"Key Finding 1: There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF studies--GOF studies of concern--entail risks that are potentially significant enough to warrant additional oversight" (lines 81-83)

Comment:

- Why "potentially"? ...Define a subset that does warrant additional oversight

Findings are too tentative (and in this case, says nothing)

"Key Finding 4: There are life sciences research studies that should not be conducted on ethical or public health grounds if the potential risks associated with the study are not justified by the potential benefits" (lines 90-92)

Comment:

- Re-states the starting premise!
- What are those studies?? (Why then the RBA?)

NSABB fails to address a clear need, abdicates responsibility

"There may be GOF studies that should not be funded on ethical grounds, but it is difficult to identify or describe such studies, particularly based on general or hypothetical descriptions." (lines 1159-60)

Comment:

- "Guiding principle 9": "NSABB will consider whether there are certain studies that should not be conducted under any circumstances, and if so, articulate the critical characteristics of such studies" (lines 320-1)
- Yes or no? (This is actually not so difficult!)
- If yes, the studies need to be identified now (will not get easier!)

Attributes of concern?

"the working group identified the attributes of GOF studies of concern, which are studies that could generate a pathogen that is: highly transmissible, highly virulent, and resistant to public health control measures" (Recommendation 1, lines 110-112)

Comment:

- Public health measures, despite being effective in theory, often cannot control highly transmissible pathogens! (Note: influenza A(H1N1)pdm09 virus)
- High transmissibility renders control measure resistance irrelevant (acknowledged in RBA 8.4.4.3)
- Any 2 of these phenotypes are sufficient for concern

Findings are unsupported

"Key Finding 2: The U.S. government has effective policy frameworks in place for managing risks associated with life sciences research"

Comment:

- Effectiveness has not been demonstrated
- On the contrary, framework may be flawed:
  - players, institutions affected by conflicts of interest
  - process non-transparent (acknowledged…line 891)
  - local oversight = haphazard, inconsistent, non-standardized, unfunded

RBA: poorly justified assumptions, flawed, dangerous logic (security)

"interestingly, risks associated with information from future GOF studies with influenza, SARS and MERS appear small...because most of the information of interest is already published, or non-GOF information relating to pathogens that are more attractive agents of harm is already available" (lines 472-4)

Comment:

- Not true! Optimized phenotypes have not been described (e.g., further enhancements in mammalian adaptation, transmissibility; combinations)
- Presumes to know motivations and goals of all mal-actors in all circumstances, assumes others will act as we would = grossly irresponsible guesswork!

RBA: poorly justified assumptions and flawed logic (safety and security)

"If currently mandated biosecurity systems are effective, outsiders have little chance of causing harm on their own." (lines 471-472)

Comment:

- Do we really think they are always effective?? And if not...?

"...risk associated with the wild-type 1918 strain is already so great it is difficult to increase risk substantially" (lines 457-458)

Comment:

- On what basis is this asserted?? (none)
- Why use 1918 strain as comparator?

RBA: poorly justified assumptions and flawed logic (safety and security)

Comment:

- Analysis of laboratory safety assumes that all work takes place in U.S. or in high-containment labs = Not true
- Fails to recognize that freely-available information allows re-creation of strains 'of concern' in very different laboratory settings, with lesser degrees of physical security and safety
- Safety and security risks are greater than asserted (assumed) in RBA

Confusion about biosecurity?

"Key Finding 5: The biosafety and biosecurity issues associated with GOF studies are similar to those issues associated with all high containment research..."

Comment:

- Meaning unclear, possibly confused
- 'High containment' is not necessarily relevant
- Information-associated risks can occur in other settings

RBA: poorly justified assumptions, assertions (benefits)

"Most GOF studies provide benefits in the form of new scientific knowledge, and many of these benefits are unique" (lines 475-6)

Comment:

- Scientific knowledge, per se (alone), does not justify large risks
- Uniqueness is over-stated, and/or specific attributable benefits (attributable to unique knowledge) minimal (and not justified)
- In fact, benefits are less 'unique' than risks!