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

Gryphon Scientific
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signature science LLC®

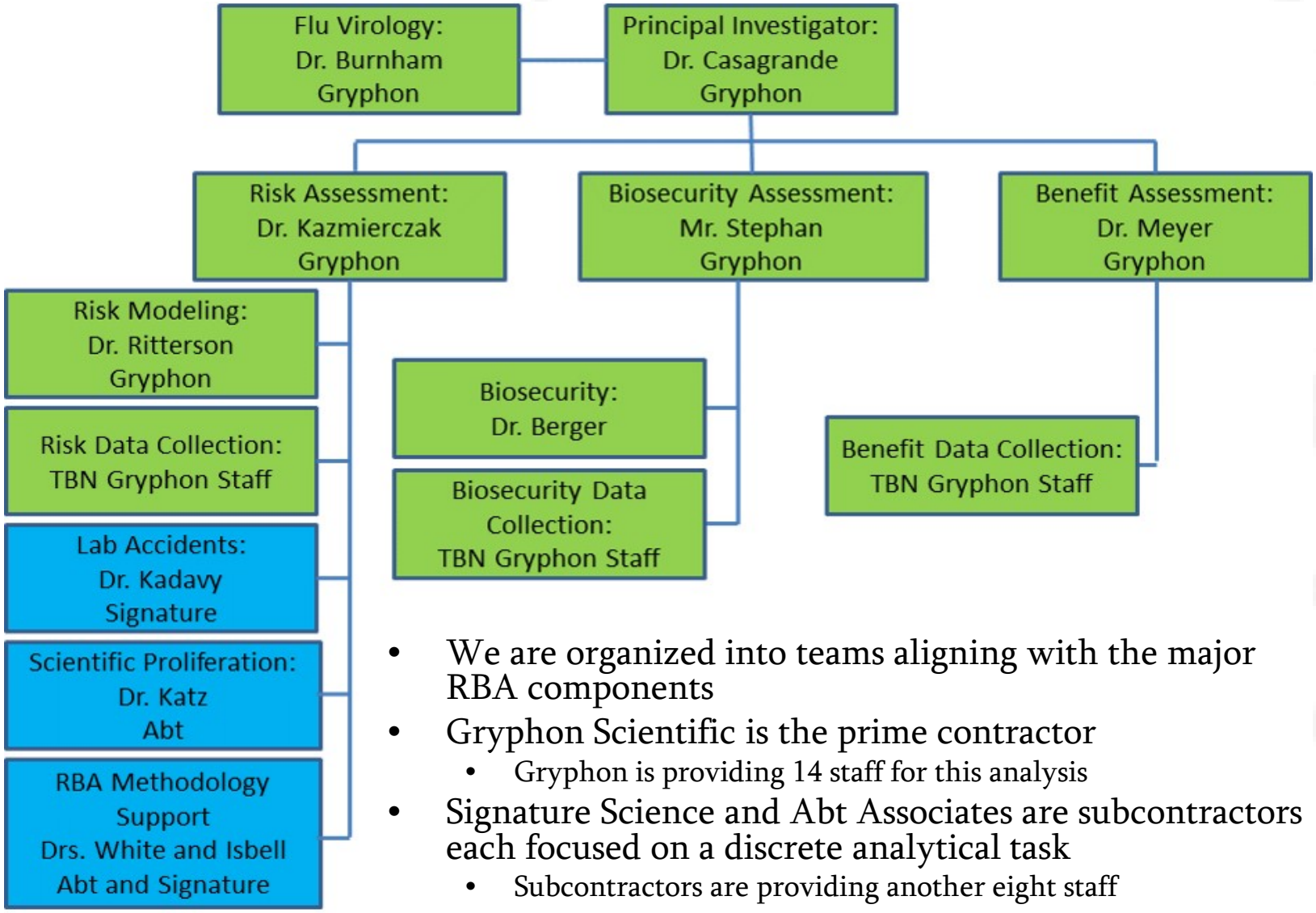
Agenda

- Overview of RBA approach
- Introduction to the RBA team
- Experience with RBAs
- Discussion of RBA approach
  - Assessing risk of accidents and disasters
  - Assessing biosecurity risks
  - Assessing benefits

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
  - Risk analysis of accidents and natural disasters
    - Requires sophisticated, quantitative modeling of the probability and consequences of various events that could lead to an outbreak
  - Biosecurity risk analysis
    - Requires analysis of data from intelligence and law enforcement as well as an assessment of security measures
  - Benefit assessment
    - Requires an understanding of the gaps in scientific knowledge, public health and medicine that GoF experiments could address
    - Requires an understanding of scientific and non-scientific barriers to the realization of these benefits
- Time horizon
  - To ground our work in real science, we will consider a five year time horizon
    - All risks will be considered in this timeframe
    - We will consider the follow-on benefits of research conducted in the five year time-frame even if they are further away
  - New modes of scientific inquiry could obviate GoF research or could open up new opportunities for its application

RBA Team Overview



- We are organized into teams aligning with the major RBA components
- Gryphon Scientific is the prime contractor
  - Gryphon is providing 14 staff for this analysis
- Signature Science and Abt Associates are subcontractors each focused on a discrete analytical task
  - Subcontractors are providing another eight staff

Experience with RBAs

- Signature Science and Gryphon together completed the Site Specific Risk Assessments for the National Bio and Agro-defense Facility (NBAF)
- Gryphon supported the development of the federal guidance to the industry that makes custom, synthetic nucleic acids
- Gryphon developed a systematic RBA to evaluate the contents of the Strategic National Stockpile (SNS)
- Gryphon developed a systematic RBA to evaluate triage priorities after a nuclear attack

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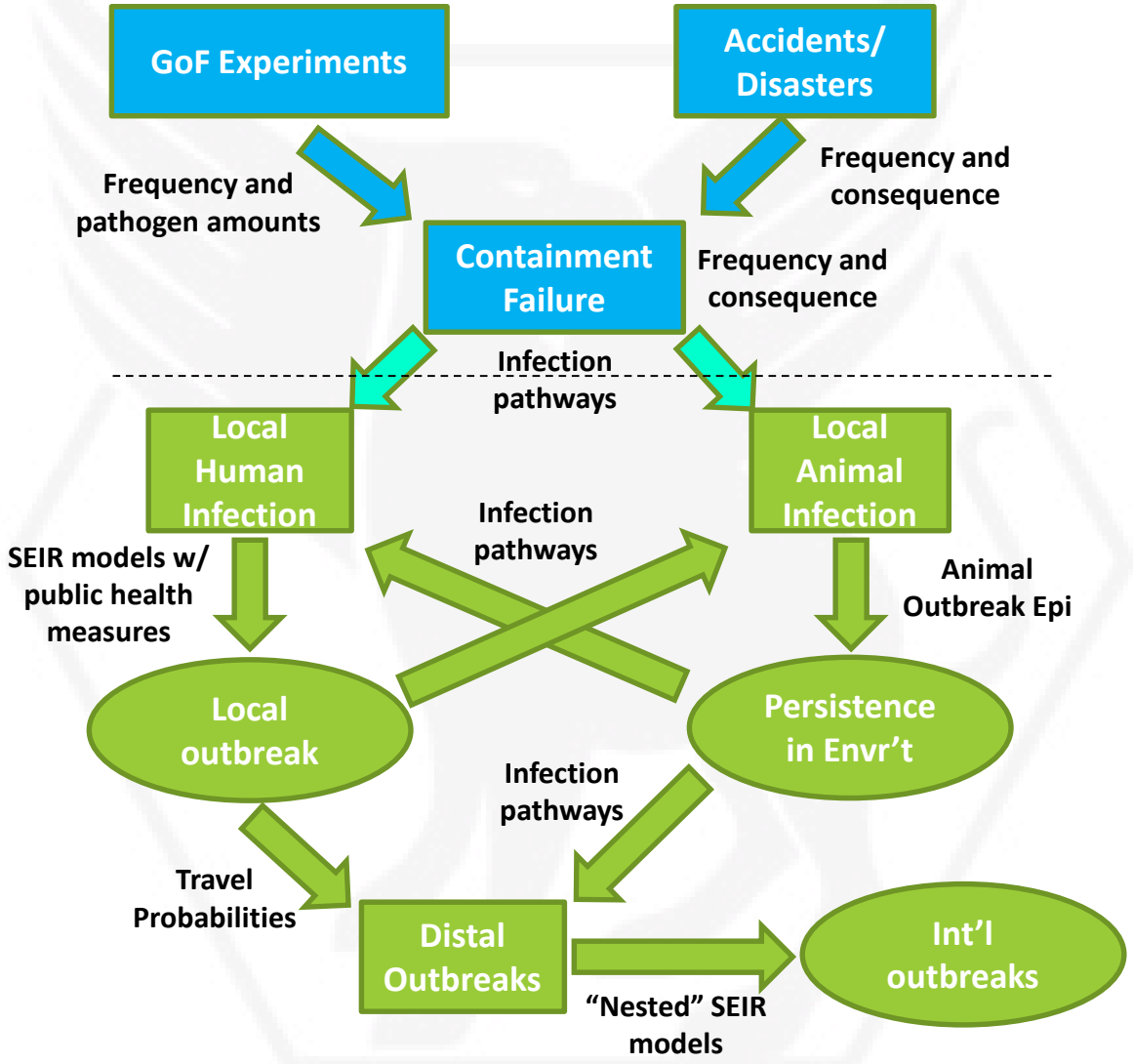
Risk Assessment of Accidents and Natural Disasters

Approach:

- We will examine many pathways to an infection outside of the laboratory
- We will estimate the probability that outbreaks occur due to accidents and natural disasters
- We will estimate the consequences of a resulting outbreak in the human population surrounding the laboratory and internationally



Outcome of Risk Assessment

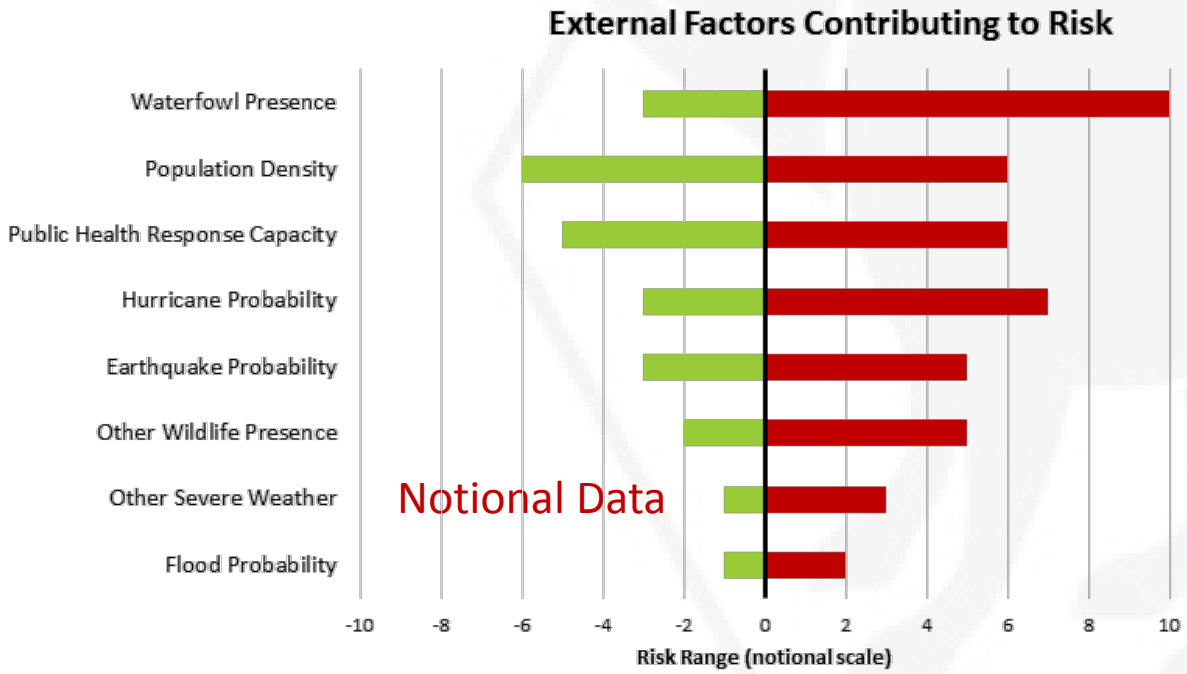
- To support decision-making, the RBA must support the answering of "what if" questions:
  - How would risk change if the number of sites performing this work were to increase?
  - How would risk change if the work were performed with different containment measures?
  - How would the risk change if transmissibility/pathogenicity/ countermeasure resistance were increased?
- The answers to these questions can help clarify the conditions under which this work could proceed safely (if any)

Addressing Scientific Unknowns

- This effort attempts to assess the risk of experiments that have not been performed yet, in places that do not yet perform the work
- To accomplish this goal, we will explore how the changes in key parameters that describe the pathogens, containment features and laboratory locations all affect risk
  - Phenotypic description of pathogens explicitly focuses risk assessment on the characteristics of pathogens that will drive risk
    - Specific pathogens will be characterized as exemplars to anchor the parametric analysis in real-world science
    - Enables the comparison of risk from GoF-research to that already accepted for research on unmodified pathogens
  - Parametric description of containment features avoids semantic arguments over what constitutes various biosafety levels

Sensitivity Analysis is Used to Identify Risk Drivers

- We will determine how various features of containment, response, and the pathogen affect risk
- These findings will help define how to best limit risk
  - In the notional "tornado plots" below, we show how varying a parameter value from a baseline would move risk (less risk is in green, greater is in red)



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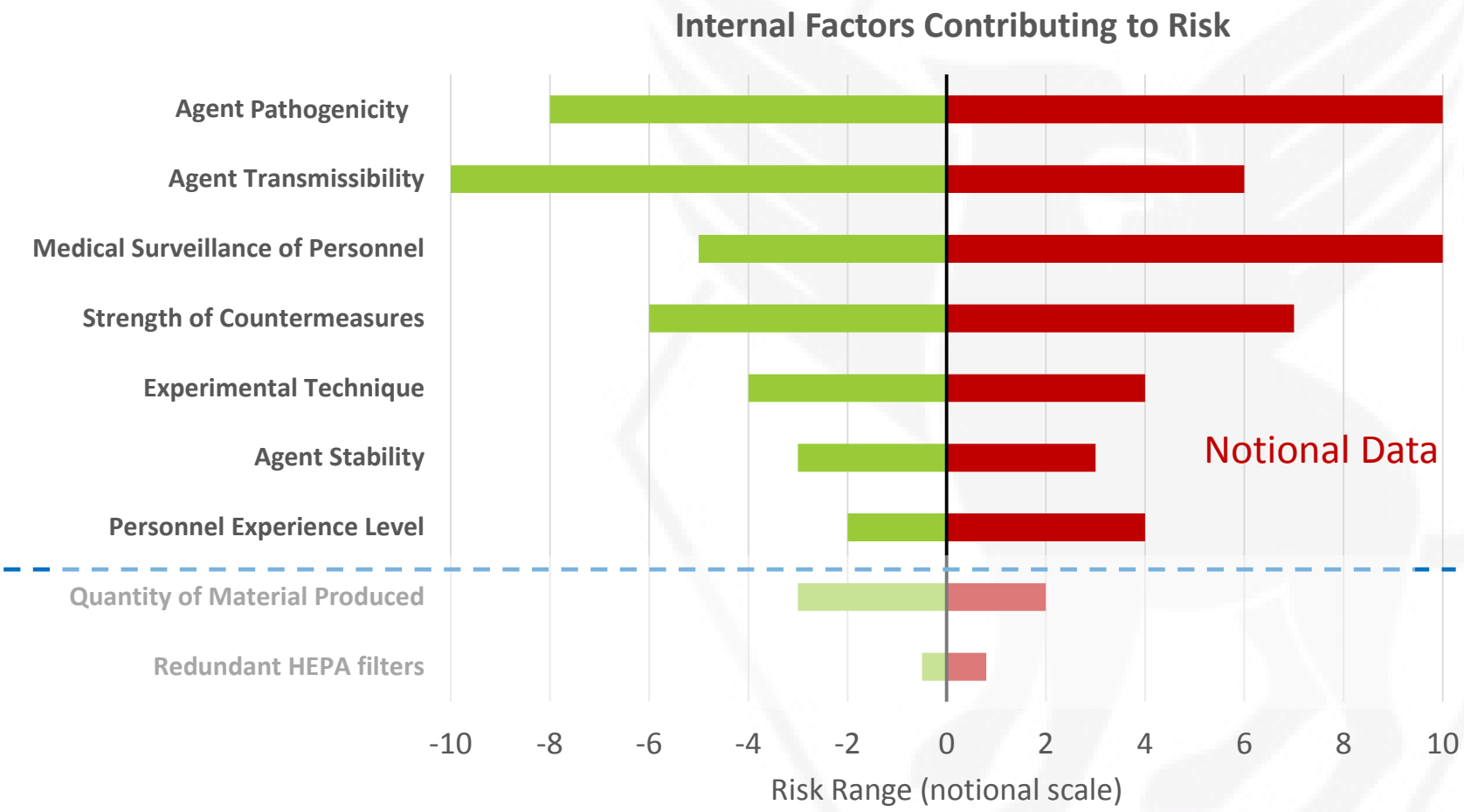

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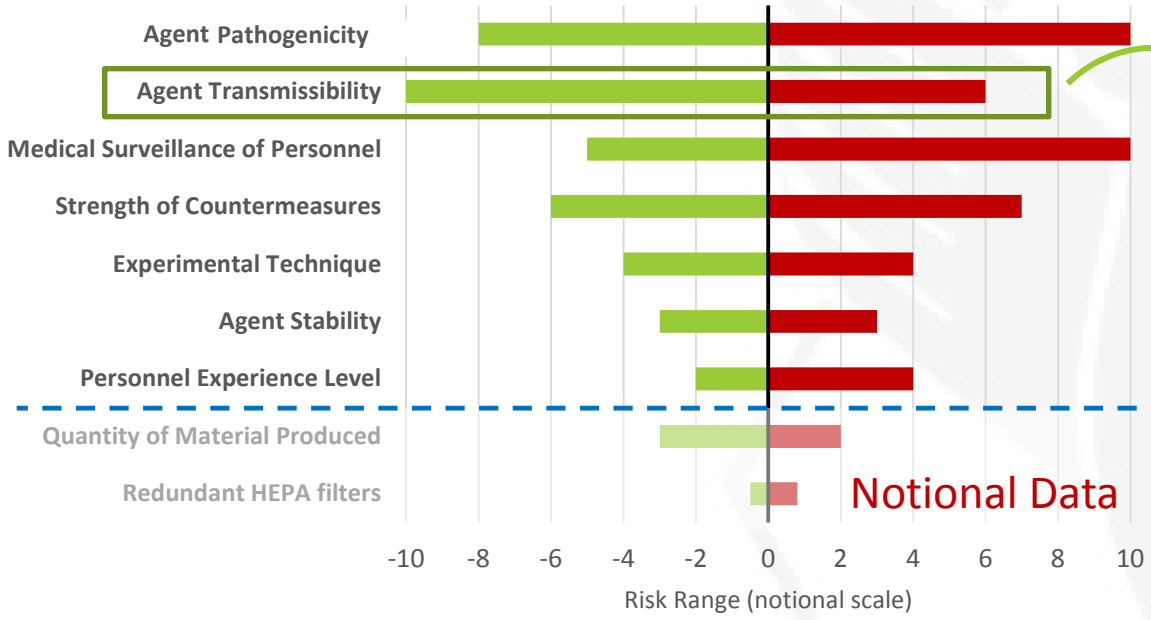
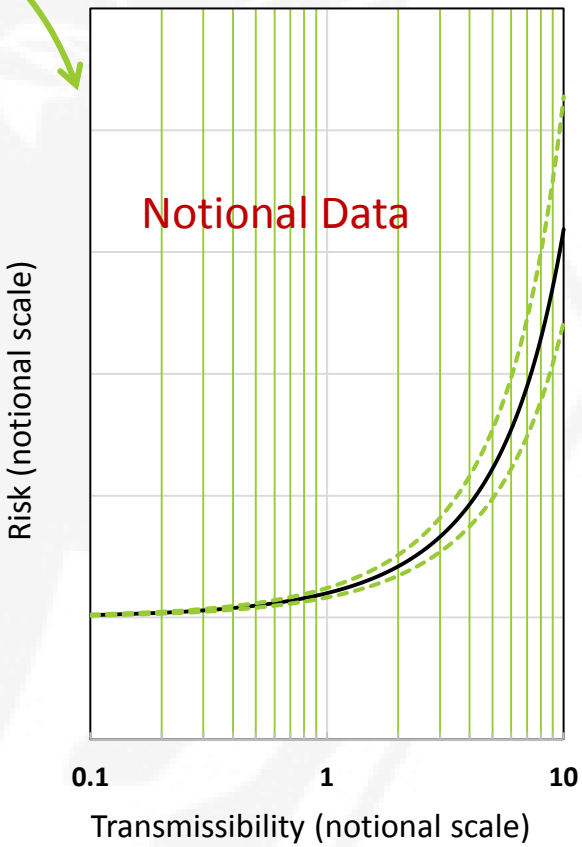
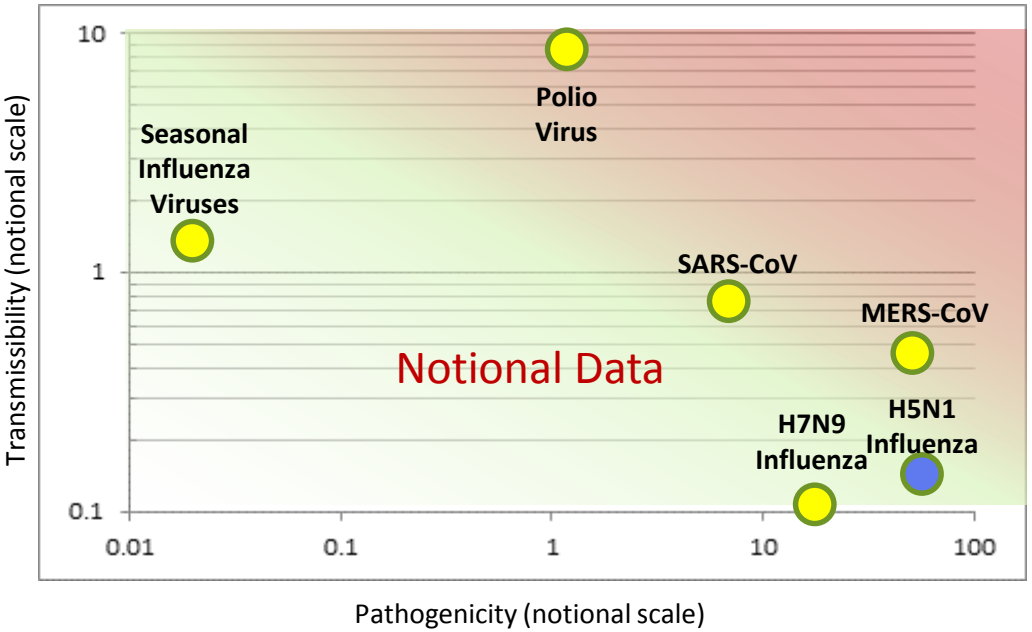
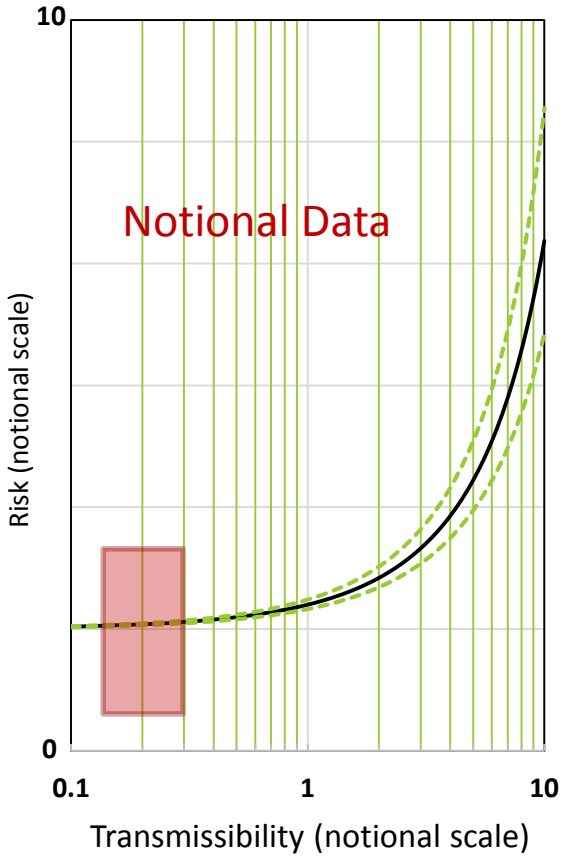




- Once a parameter is found to be an important driver of risk, we can explore how changes in its value affects risk to inform decision-making

Creating Realistic Bounds for Analysis





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

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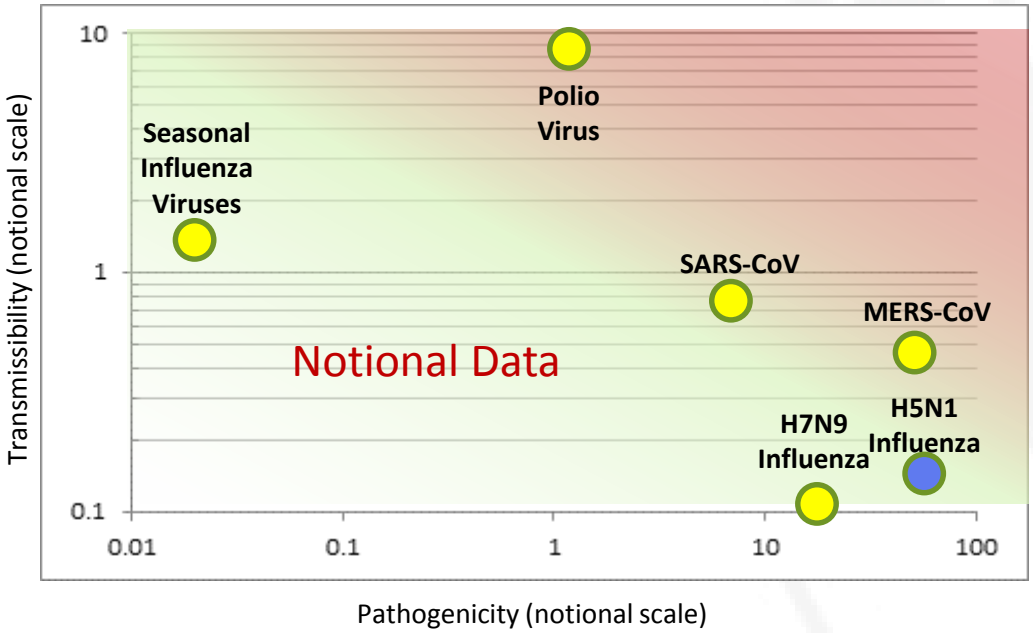

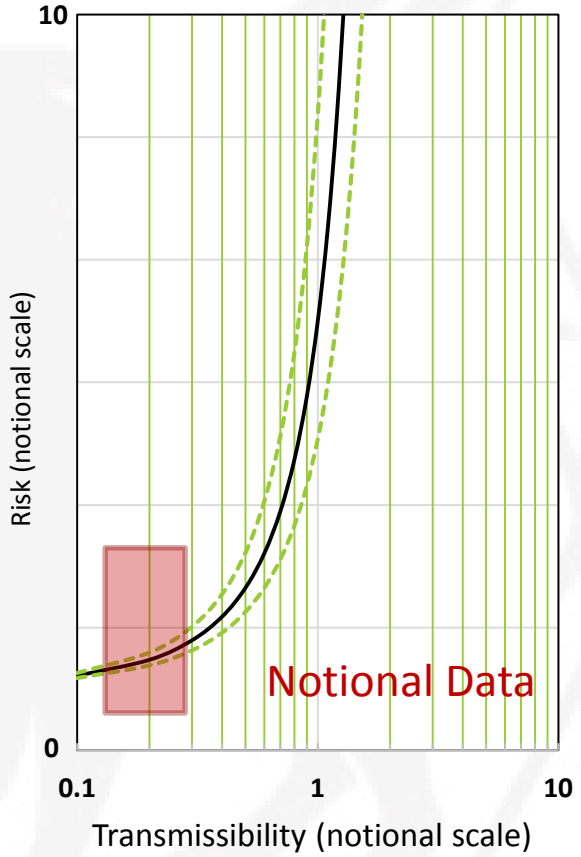

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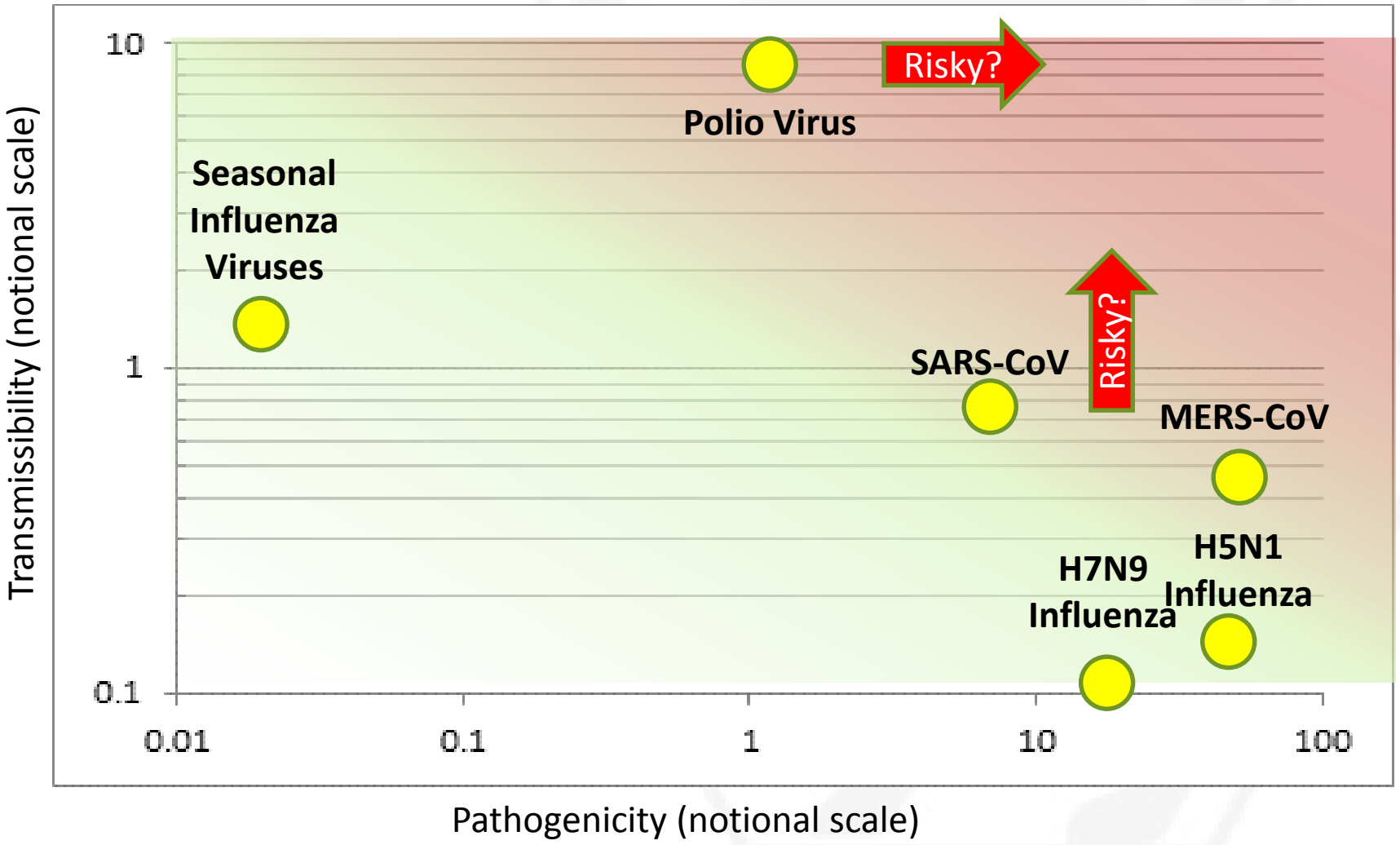
Understanding Risk Drivers



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Biosecurity Risk Assessment

- The biosecurity risk assessment has two main components:
  - A semi-quantitative assessment of the risks of intentional acts against the laboratory, causing infections outside the laboratory
  - An assessment of the potential for misuse of the information generated by GoF research

Semi-quantitative biosecurity risk assessment

- We will identify the types of actions that hostile actors could attempt against GoF laboratories and estimate their probability of success given known capabilities of the offense and defense

		Malicious Acts						Containment Loss Pathway							
		Armed Assault	Kinetic Attack	Covert Entry	Subversion of Employee	Insertion of Operative	Reckless Act	Covert Sabotage	Overt Destruction	Release of Infected Animals	Outside of Continment	Infection of Lab Animals	Loss of Containment	Infection of Lab Worker	Infection of Public	Infection of Outside Animal
Malicious Actor	Foreign Intelligence	NO	NO	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
	Transnational Terrorists	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES
	Domestic Terrorists	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES
	Criminals	NO	NO	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
	"Distressed" Individuals	YES	NO	YES	NO	NO	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES
Containment Loss Pathway	Covert Sabotage	NO	NO	YES	YES	YES	NO									
	Overt Destruction	YES	YES	NO	NO	NO	YES									
	Release of Infected Lab Animals	YES	YES	YES	YES	YES	YES									
	Infection of Lab Animals Outside of Continment	NO	NO	YES	YES	YES	YES									
	Loss of Containment	NO	YES	YES	YES	YES	YES									
	Infection of Lab Worker	NO	NO	YES	YES	YES	YES									
	Infection of Public	YES	YES	YES	YES	YES	YES									
	Infection of Outside Animal	YES	YES	YES	YES	YES	YES									

Lab-based release

Non-lab-based release

Either lab- or non-lab-based releas

Notional Data

Semi-quantitative biosecurity risk assessment

- Given the consequences should the action be successful, hostile acts could be compared in terms of frequency to natural and accidental events
  - E.g. "risk of theft by a criminal/terrorist is equivalent to risk of accidents if an attempted theft occurs once every 100 years"
- Will focus decision-makers on biosecurity aspects that compare in importance to biosafety concerns
- This method focuses on data in hand in the law enforcement/ intelligence community
  - State and sub-state and criminal capabilities and motivations
  - Hostile actor knowledge/interest in specific pathogens and sources
- Typically, this method relies on classified data

Information Biosecurity Risk

- The risk of misuse of the information generated by GoF research will be comparative
  - What can various actors accomplish with biological agents that already exist or are already described in the literature?
  - What additional capabilities are afforded by GoF research compared to other ongoing research topics and existing studies?
  - Intelligence and law enforcement data will be used to determine:
    - If these unique capabilities are desired by various groups
    - If the publishing of "more" (albeit not-uniquely risky) pathways to dangerous pathogens drives risk of misuse
- If unique capabilities afforded by GoF research are desirable, we will characterize the resources and skill needed to replicate it
  - Using intelligence and law enforcement data, determine:
    - If these are within the reach of various actors
    - If the required tacit knowledge to develop these pathogens influences which actors can acquire them

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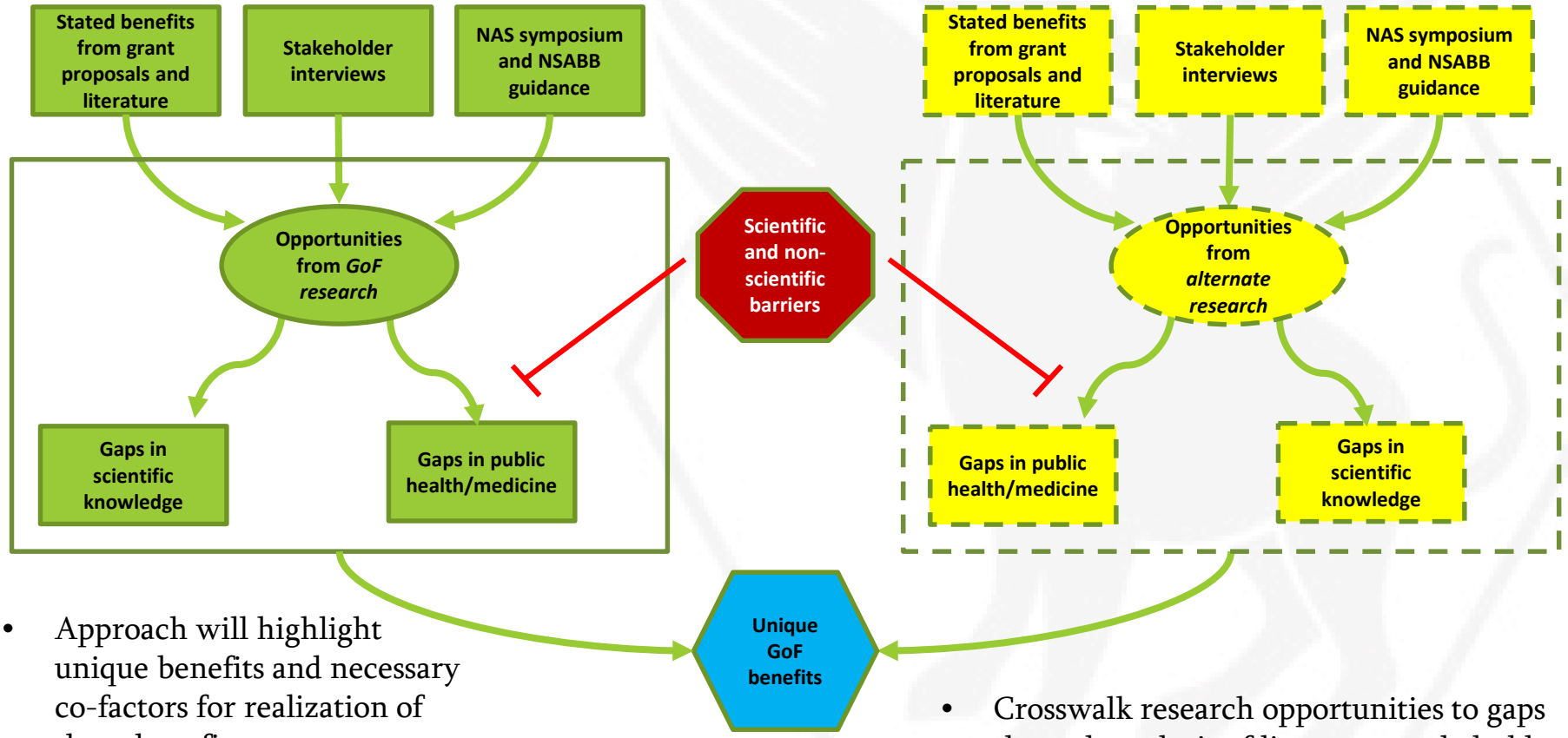
Qualitative Benefit Assessment

- The benefit assessment uses a systematic approach to identifying opportunities, barriers and competing pathways to benefits



- Approach will highlight unique benefits and necessary co-factors for realization of those benefits
  - Proxy for criticality of benefits and probability of realization
- Crosswalk research opportunities to gaps through analysis of literature, stakeholder interviews, and case studies

Evaluation of GoF and Alternate Research Benefits – notional example

Experiment type	Passage of virus in mammals with the intent to generate airborne transmissible strains			
Research Opportunities	Reveals mechanisms of airborne transmissibility	Identifies genetic determinants of airborne transmissibility		
Benefits: Research Application to Gaps	Addresses gaps in scientific knowledge	Informs interpretation of surveillance data	Vaccine development	
			Can remove risky genetic signatures from vaccine strains	Informs selection of pre-pandemic vaccine strains
Barriers		Scope of surveillance is limited - complicates comprehensive evaluation of data	Phenotypic consequences of mutations in other virus backbones are unknown	Scope of surveillance is limited - true prevalence of various strains in nature unknown
Barrier type		Non-scientific	Scientific	Non-scientific

NOTIONAL EXAMPLE

- Will evaluate other GoF experiment types and alternate experiment types similarly

Consider Globalization of Benefits

- We will consider the possibility that benefits will become globalized
- Stakeholders have rightfully stated that because risk is inherently global from a pandemic, the benefits must be considered in the same light
- Qualitative analysis is necessary because the benefits are not realized yet
- We propose to use historical examples of the globalization of other biomedical advances

Questions?