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Considerations in Risk Assessment for Dangerous Pathogens

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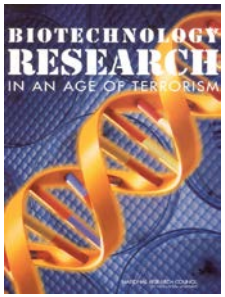
Agenda

- Today, I will describe some of the lessons learned after conducting one of the most ambitious biosafety risk assessments performed
- Background on the Gain of Function (GoF) Risk/Benefit Assessment (RBA)
- Key findings from GoF RBA —focus on avian influenza
  - Knowledge gaps
- Gaps in our biosafety knowledge and their relation to risk assessment
- Toward supporting the guidance for Potential Pandemic Pathogen Care and Oversight (P3CO)

Background on Gain-of-function Research on Respiratory viruses

Key Milestones

2003



FAS

2012

LETTER

Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets

Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets

US Mission

2014

CNN

U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses

Deliberative Process

Gryphon Scientific's Role

RISK AND BENEFIT ASSESSMENT

Purpose

Provide data on the risks and benefits associated with research on modified strains of influenza viruses and the coronaviruses

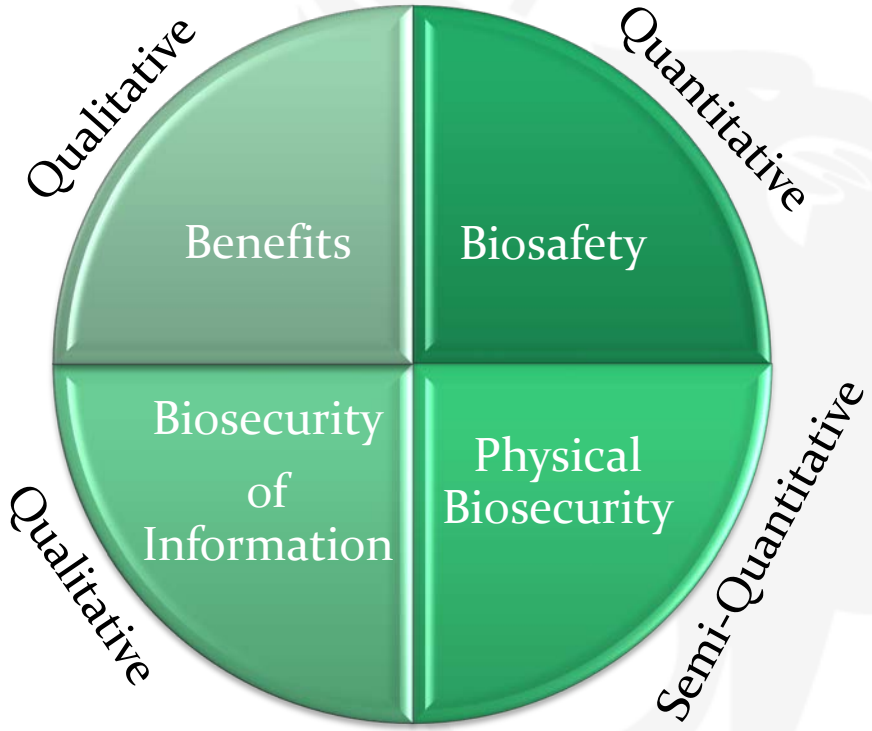
Comparative assessment of:

- The degree to which risks associated with research involving GoF pathogens *change* compared to research with wild-type pathogens.

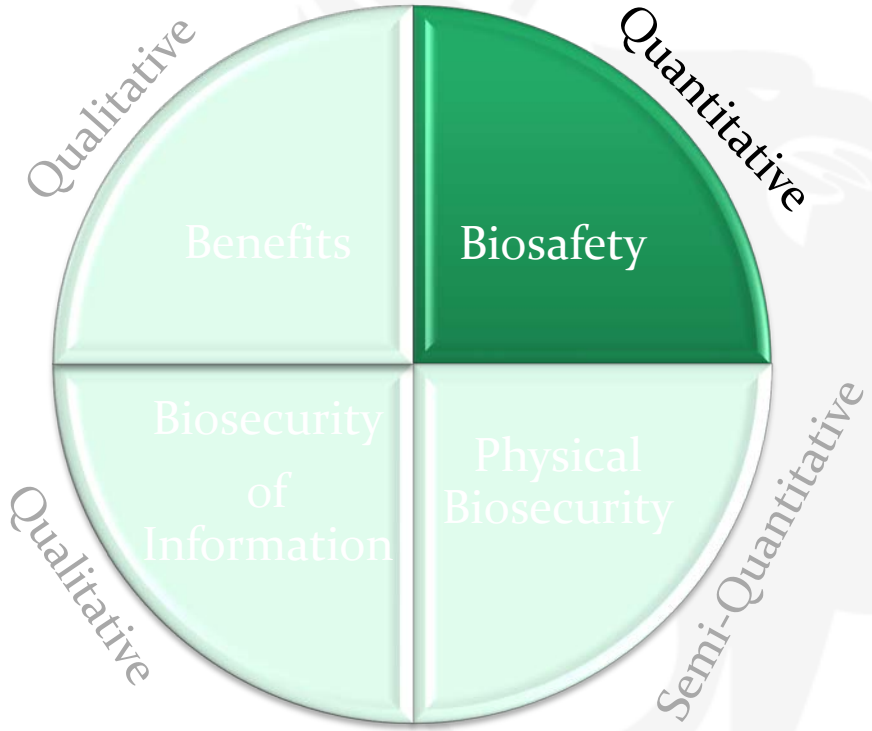
- The *unique* benefits to science, public health, and medicine afforded by GoF research compared to alternative research.

In a nutshell: Assess the risk/benefits of experiments that have yet to be proposed, on pathogens that do not yet exist in places yet to be identified, across the research enterprise

Multi-Pronged Approach

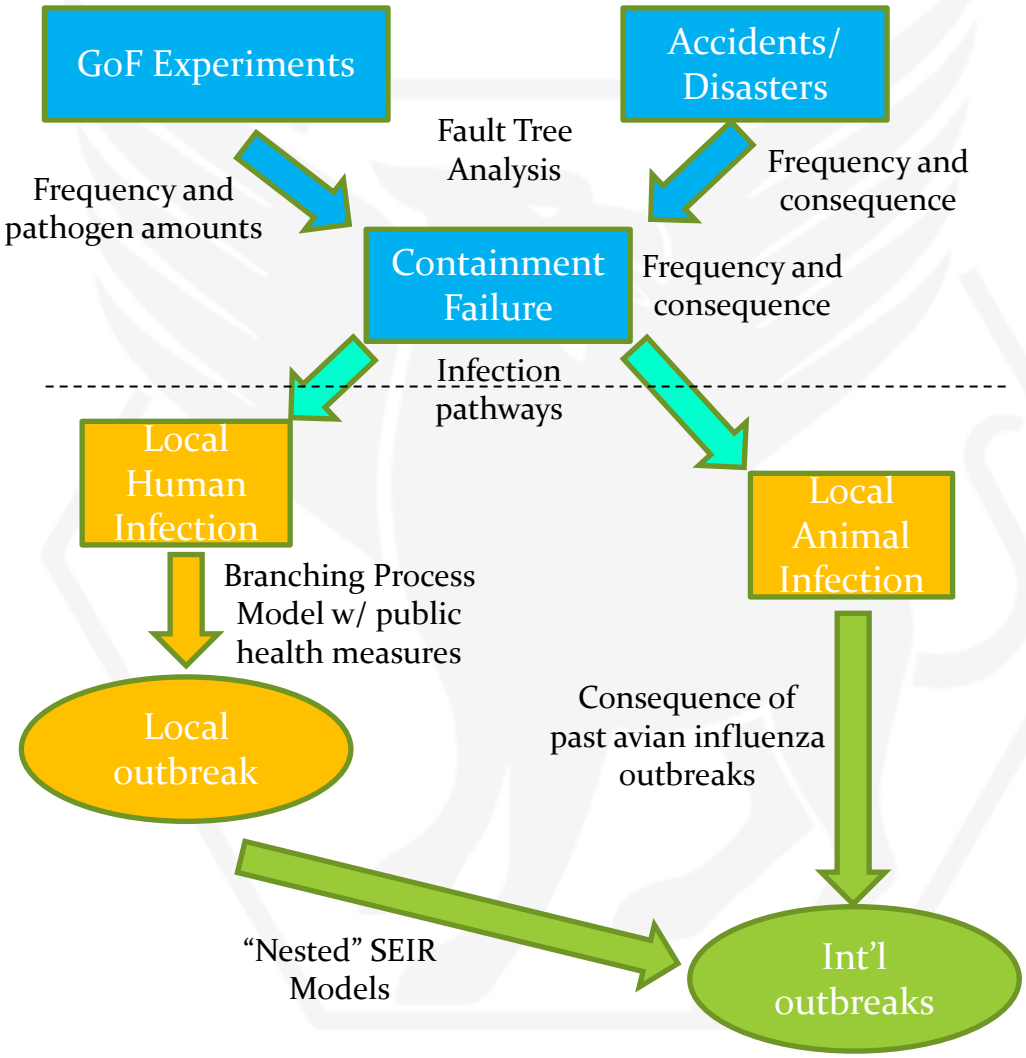


Biosafety


Qualitative
Quantitative
Benefits
Biosafety
Biosecurity of Information
Physical Biosecurity
Qualitative
Semi-Quantitative

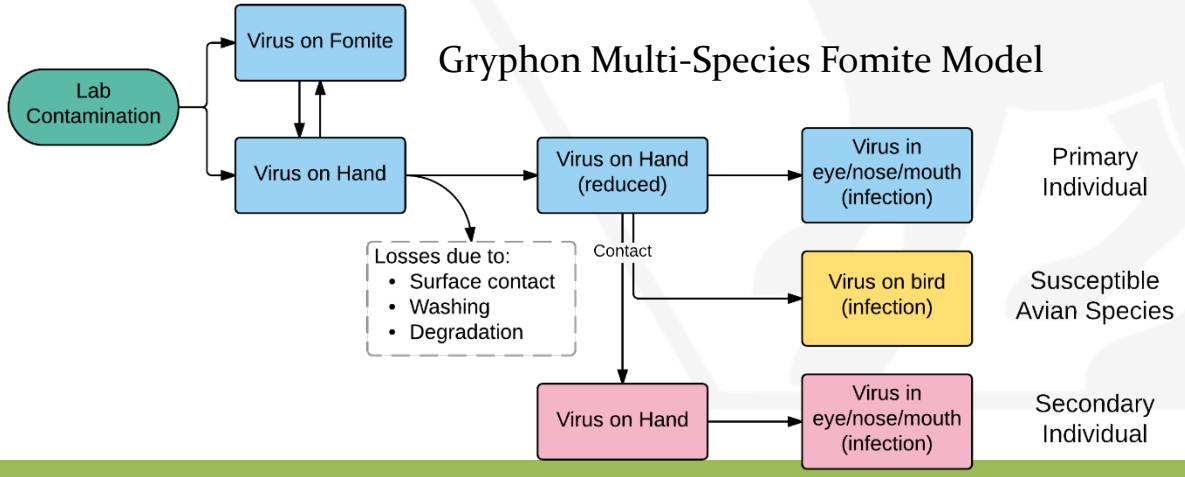
Methodology: Quantitative Biosafety RA

- Modeling Components:
  - Probability of an infection occurring outside of containment
  - Probability of an outbreak escaping local control
  - Consequences of a global pandemic
- Risk is the product of:
  - the probability that an infection occurs
  - the probability an outbreak escapes local control
  - the consequences of a global outbreak



Modeling Infection Probability of Wild Birds

- If a loss of containment event happens, wild birds could be infected via several pathways:
  - Contact with poorly sterilized infectious waste at a landfill
  - Inhaling an infectious aerosol released from the laboratory
    - Using data on wild bird populations and minute tidal volume and aerosol transport modeling
  - Contact with a laboratory worker with contamination on his/her hands
  - Contact with contaminated water released from a laboratory



Why was the consequence estimate of avian-restricted flu outbreaks abstract?

- Predicting behavior of novel bird-restricted strains is difficult
  - Difference of pathogenicity for 2015 H5N2 vs 2003 H5N1 or 2015 H7N9 vs 2003 H7N9
    - Is the difference due to behavioral changes or biology of the strain?
    - No relationship between severity of signs in birds and severity of symptoms in humans
  - Differences in the degree to which these outbreaks spread
    - Some restricted to just a few flocks others went international
- In short, epistemic uncertainty was irreducible
  - More research is needed on the biology and life cycle of avian flu to adequately understand risk of novel subtypes

Biosafety Risks of GoF Phenotypes

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 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	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.

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Covered by P3CO

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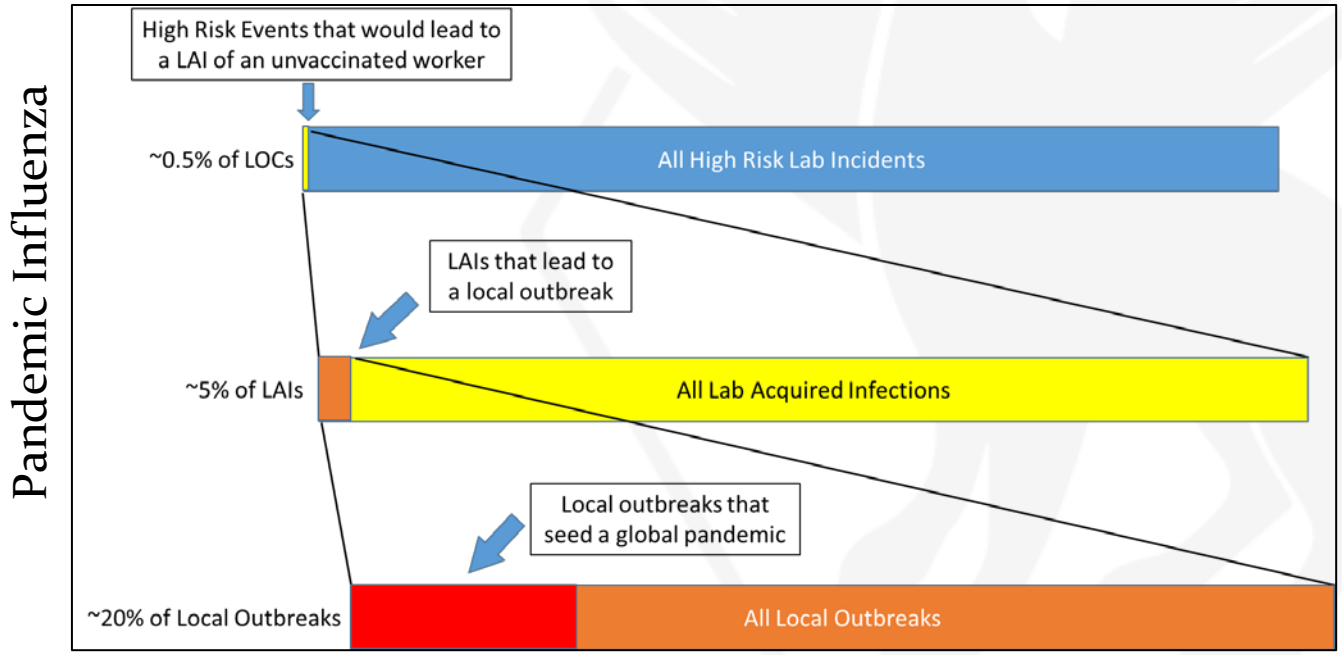
Factors Influencing Accidental Risk

- Small minority of laboratory accidents with the pandemic influenza viruses cause a local outbreak, and only a minority of those lead to a global pandemic
  - A mammalian-adapted, mammalian-transmissible avian influenza strain would (at worst) resemble a pandemic strain



Causes of Laboratory Acquired Infections

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

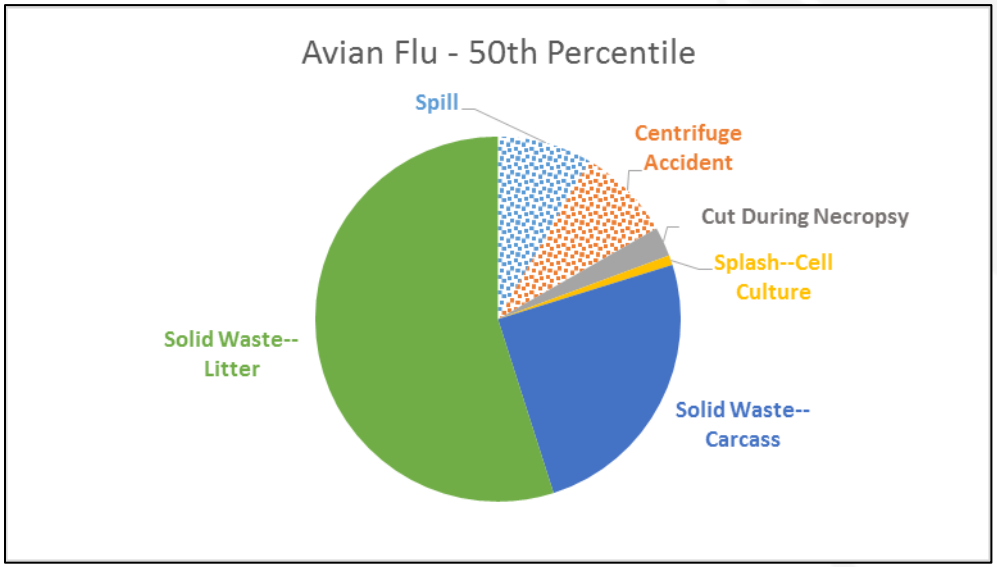
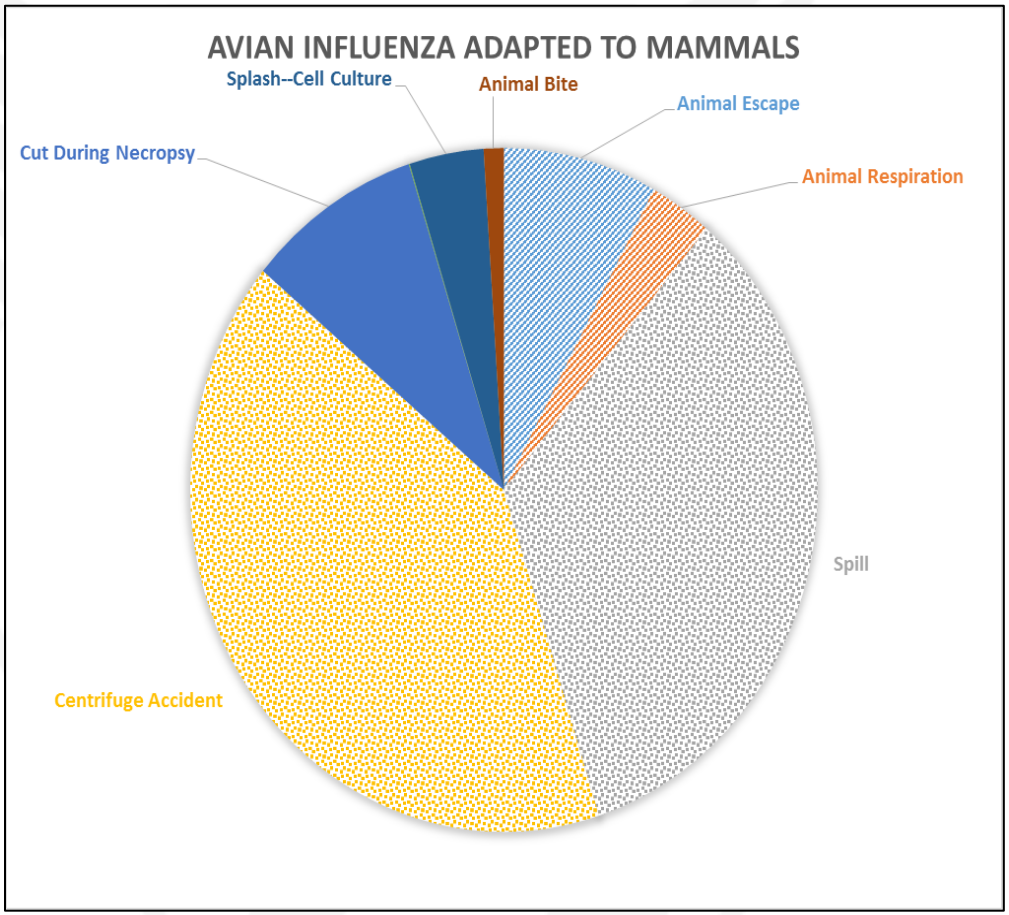


Table 6.5 Increase in the Probability of a Laboratory Acquired Infection Associated with GoF Phenotypes in Avian Influenza	
Phenotype	Increase in Probability of a LAI
Evasion of vaccines	+11%
Antiviral resistance	+8%
Growth to 1E9/ml	+20%
Growth to 1E10/ml	+120%
Adaptation to humans	-30%

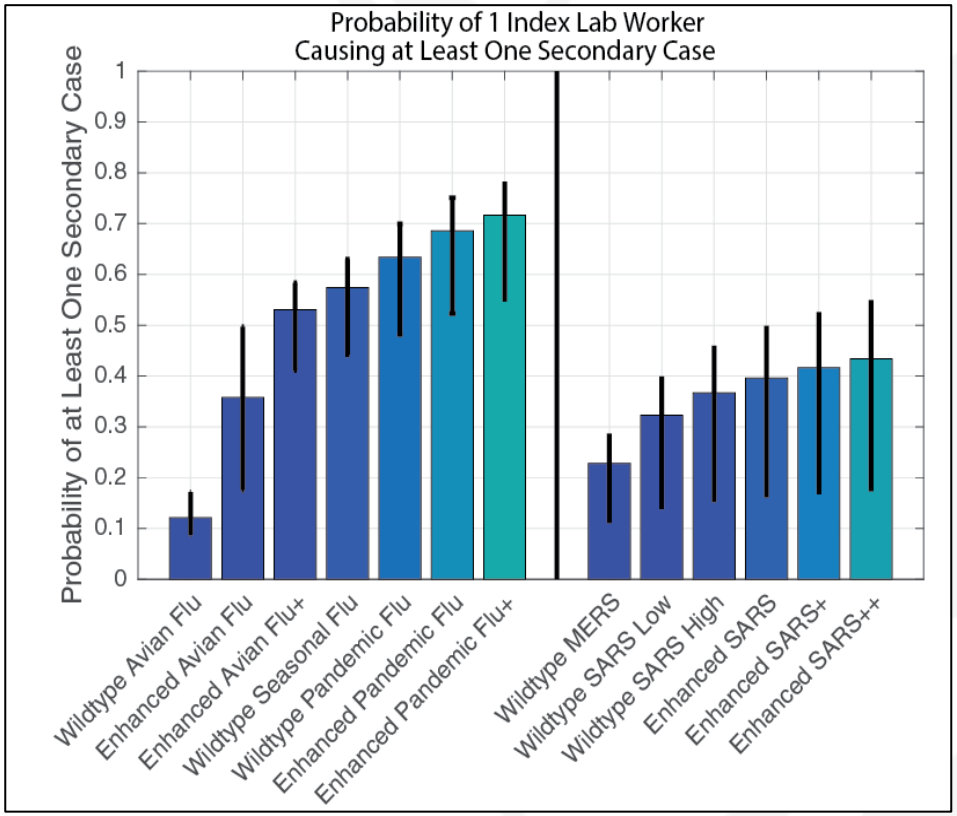
The release pathways that contribute to risk differ for each pathogen.

Causes of Laboratory Acquired Infections

- Risk of an LAI of avian flu DECREASES when strains are adapted to animals because probability of an outbreak in the wild decreases
  - Drops risk of most common LOC pathways



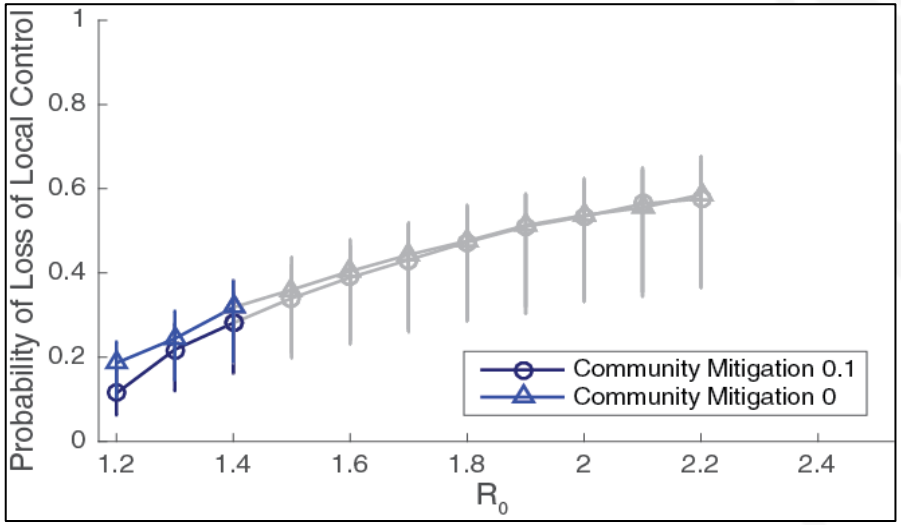
Influence of Transmissibility on An Outbreak Occurring



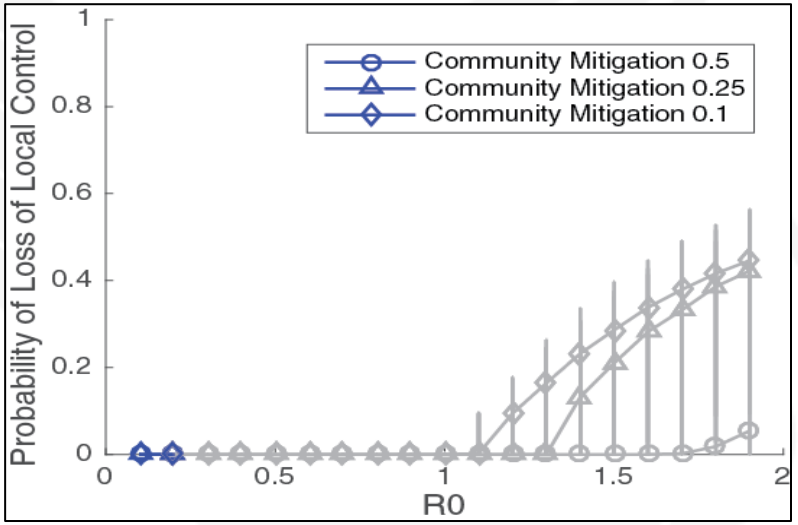
Ro: 0.1 → 2.5 Ro: 0.4 → 2.5

Increasing Transmissibility of Influenza Virus Strains

Seasonal influenza



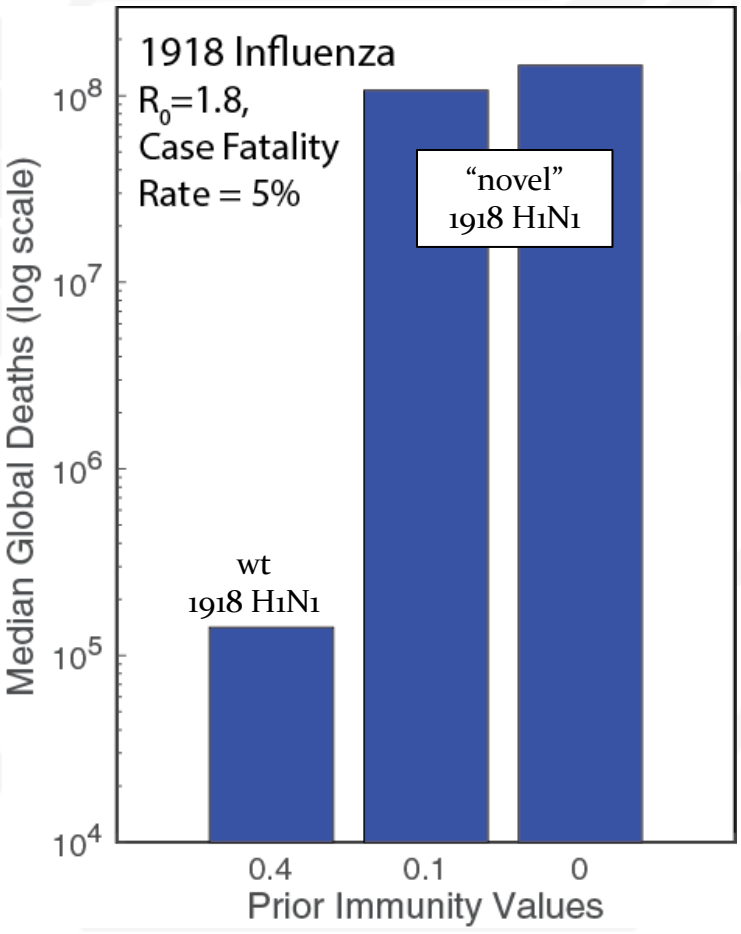
Avian influenza



- Increasing transmissibility of seasonal influenza strains can double the chance of an outbreak if accidentally released
- Increasing transmissibility over 1 ($R_0 \geq 1$) for avian influenza significantly increases the probability that an outbreak escapes

Effects on Evasion of Immunity

- Effect on consequences of cross protection against 1918 H1N1 pdm afforded by exposure to 2009 H1N1 pdm
  - 1957 H2N2 pdm becomes the "riskiest" pandemic strain
    - Causes more than 100x as many global cases while being only 1/10th as deadly
  - Riskiest modified strain is a 1918 H1N1 strain modified to evade residual immunity or to be otherwise more transmissible



Other Biosafety Risk Conclusions

- 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
- 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
  - The scientific value of increasing the transmissibility of influenza virus beyond that of the most transmissible strains (or final titer beyond 1E8) is questionable and perhaps infeasible
  - There is no model of transmission for the coronaviruses, so manipulation of this trait is not currently achievable

Lessons Learned

Risk Drivers Are Difficult To Identify without a Quantitative and Thorough RA

- Without performing this study, we would not have identified:
  - Which accidents drive risk of an LAI and a local outbreak
    - And that the risk drivers are different
  - Means to mitigate risk by:
    - Upgrading equipment
    - Changing human practices/training
    - Subtly altering experimental setup
- Risk drivers were not necessarily those commonly accepted as high risk
  - Riskiest events were often covert and so would not be reported unless an LAI occurred (which is low probability even after the event)
  - Given that LAIs and local outbreaks caused by a laboratory are extremely rare, past experience is not as useful as quantitative studies
    - Somewhat like using personal experience to predict risk of meteor strikes on the earth instead of the geologic record

Lack of Data on Human Reliability Assessment in Life Science Laboratories

- From data in other industries, it is clear that most failures in safety equipment are due to human ignorance, carelessness or neglect
  - Faulty PAPRs are produced much more rarely than sound PAPRs are poorly worn, poorly assembled or poorly maintained
- Moreover, most mechanical failures are accompanied by some signal that a human must ignore, misunderstand or override to create a dangerous situation
- Lastly, unlike in the nuclear, chemical or transportation sectors, in a life sciences laboratory, most potential releases require a human error to initiate
  - The most frequent accidents are slips, spills, centrifuge misuse and cuts
  - Exceptions in the life sciences include natural disasters, aerosol generation experiments and animal containment
    - Though the vast majority of infections from these incidents still require a human error (misuse of PAPRs, poor installation of filters, etc)

Lack of Data on Human Reliability Assessment in Life Science Laboratories

- Despite the importance of human factors in driving the risk of accidents, very little data was found from the life sciences enterprise
  - Data on animal bites in laboratories was found
- Our RBA had to analogize from human reliability data from other industries to activities in the laboratory
- This shortcoming prevented a rigorous assessment of absolute risk
  - The relative risk assessment "cancelled out" much of the uncertainty

A call to action

- To address this shortcoming, primary research on human factors in life sciences laboratories must be conducted
  - A no-fault database of accidents and errors in laboratories must be compiled and reporting must be encouraged
  - Best practices amongst high-containment laboratories must be identified, discussed and shared
  - Primary research into the causes and consequences of laboratory accidents must be conducted
  - A simple-to-use RA tool should be developed to enable biosafety professionals to identify heretofore unrecognized contributors to risk for risk mitigation
- Given that the potential consequences of an accident arising from life sciences research eclipses that of accidents in the chemical, nuclear and transportation sectors at least as much investment should be devoted to human factors in a life sciences laboratory

A Lack of a Risk Benchmark

- Our study focused on the CHANGE in risk posed by the manipulation of wild type pathogens
  - We highlight how much risk increases for particular manipulations, although sometimes that increase is from a low level
    - For example, increased virulence/titer in attenuated strains
  - Sometimes pandemic risk increases to a level beyond that posed by any wild type strain
  - Most of the time, pandemic risk increases but to a level less than that posed by the worst pandemic strain (now 1957 H2N2 pdm)
- Does it make sense to have enhanced oversight of research that creates new risky strains but not for wild type pathogens that pose more pandemic risk?
  - Does it matter that the non-manipulated strains were created by nature?
    - Does it matter if these strains no longer exist in nature (SARS-CoV, 1918pdm)?
  - P3CO covers pathogens that are manipulated AND can cause a global pandemic
    - Does this include the mildest, old seasonal flu strain made to be slightly more transmissible?
    - Note: Suggests that an RBA must be performed, which could show the possibility of millions of infections
- In the absence of agreed to risk benchmarks for wild type strains, absolute or relative risk metrics for any manipulated strain cannot be effectively interpreted
  - Much of the disagreement in the debate seems to be generated from a difference of opinion on what the "baseline acceptable risk" should be

Toward supporting the guidance for Potential Pandemic Pathogen Care and Oversight (P3CO)

P3CO guidance

- Covers pathogens with pandemic potential that are enhanced to increase their transmissibility or virulence
  - Covers “highly” transmissible pathogens capable of “uncontrollable” spread
  - Covers pathogens likely to cause “significant” morbidity/mortality in humans
  - Does not cover modifications for growth to high titre, and other potential modifications unrelated to the two traits above
  - Does not cover unmodified pathogens no matter how transmissible/virulent they are
  - Does not cover pathogens that do not affect humans
    - I.e. a modified Rinderpest virus that can overcome protective vaccination

P3CO guidance

- For research involving covered strains, the following principals should apply:
  - The project plan is scientifically sound
  - The new strain is a plausible future human pandemic threat
    - Would strains created by multiple forced passages count?
  - An RBA should be conducted, considering alternate methods to get same scientific answers
    - Only projects that promise unique benefits with reasonable risks should be conducted
    - This was the approach taken in our Gain of Function RBA
  - The work can be conducted safely and securely and respond to incidents
  - The work should be "responsibly" communicated to realize the benefit
  - The work should be funded to allow appropriate ongoing risk management at several levels
  - The project is ethical
- These principals are applied at the institutional and agency levels

Interpreting P3CO guidance

- The guidance regarding what highly transmissible and virulent means confusing and backup source material is contradictory
  - MERS-CoV is considered not highly transmissible but *Y. pestis* is
    - Even though plague requires closer contact for spread than MERS
    - SARS-CoV is not listed as a specific example
  - Specific and quantitative metrics should be established to avoid regulatory confusion
    - However, I think the cautionary principal applies: include the experiment for review if it COULD be considered a PPP
    - If it is a borderline case, then risk is probably low

Operationalizing P3CO guidance

- For risk assessment and mitigation plans, a thorough and quantitative analysis of all possible accident pathways should be conducted for the experiments proposed
  - Driven by reviewable evidence, not just experiential data
  - Use real projections for frequency of experiments, concentration of stocks used and containment systems
  - Consider entire accident pathway as some accidents are more likely to cause an LAI but less likely to create an outbreak
    - Overt needle sticks and animal bites vs glove contamination
  - The event trees and data we provide in the GoF RBA and the supplemental information could probably complete about 75% of this work for you—all on line at our website
- Given irreducible uncertainty, I would suggest assessing risk compared to wild type agents (prior to enhancement)

Operationalizing P3CO guidance

- For benefit assessment and the suitability of alternative research paths to get the same data
  - We suggest using a third party to perform this assessment
    - We found that most PIs had an inflated concept of how their data were actually used and underestimated the value of alternative lines of research
      - No surprising as this is a hallmark of good grantsmanship
  - Data should be collected from public and private sector experts who actually leverage the basic scientific data
  - For influenza and the coronaviruses we have much of these data in our RBA report and the supplemental information on line

Thank you!

- Rocco Casagrande, Ph.D.
- rocco@gryphonscientific.com
- http://www.gryphonscientific.com/gain-of-function/
  - Free to use and download
  - More than 30 files in the supplemental information