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

Gaps and Future Considerations

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Agenda

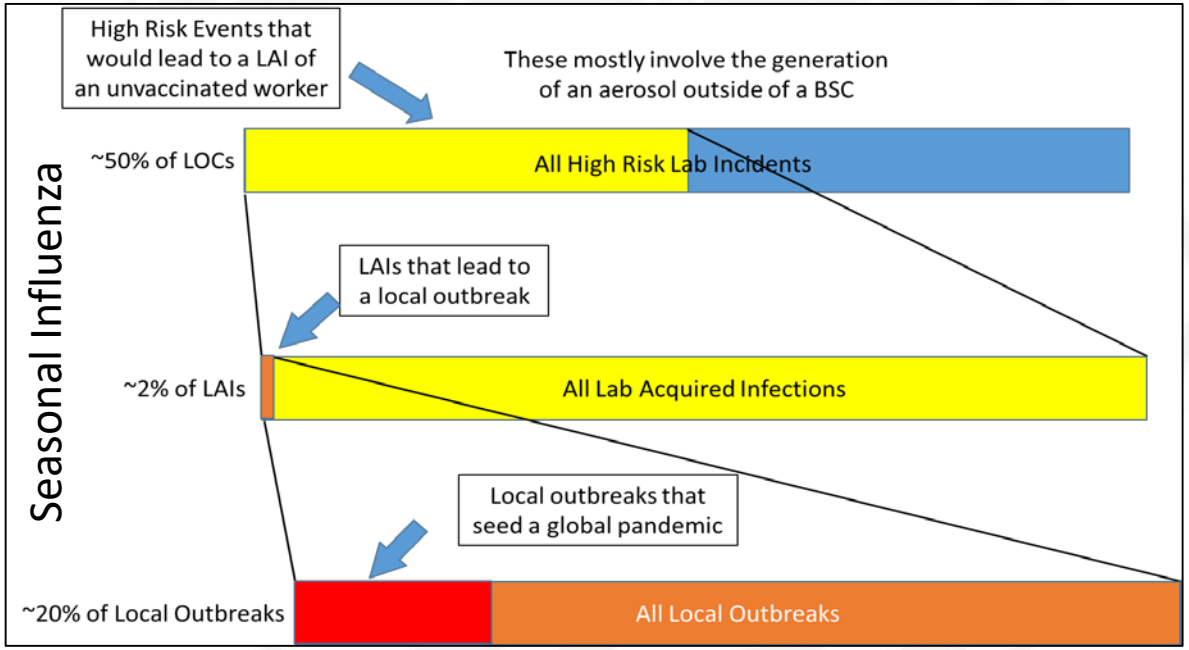
- A brief overview of the RBA study
- Lessons learned and data gaps
- Applying the RBA to specific experiments
- Discussion of using the 1918 H1N1pdm strain as a comparator

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

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

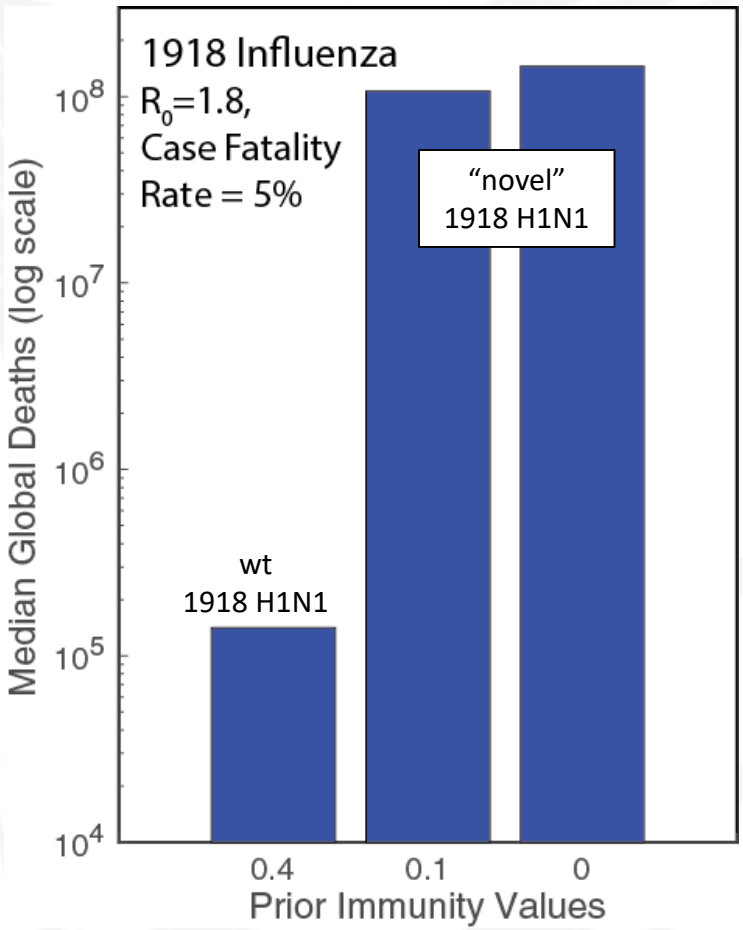
GoF Phenotype	Seasonal Influenza Viruses	Pandemic Influenza Viruses	Avian Influenza Viruses	Coronaviruses
Enhanced transmissibility	Increases probability of an outbreak and the consequences of an outbreak	Increases probability of an outbreak and the consequences of an outbreak	Increases probability of 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

Highlighted in yellow are changes from the draft RBA, due to cross protection afforded by infection with recently circulating strains vs older pandemic strains

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.

Summary—Biosafety Risk Comparison

- Example: 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



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
  - Mostly by an extra system of respiratory protection
- 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
    - Also, some contend that SARS-CoV is already so transmissible that further manipulation would not affect risk

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

Information Risk--Conclusions

- 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
- Information risk could easily be generated by research on other transmissible pathogens

Benefit Analysis Conclusions

- For influenza viruses, the following research has critical benefits:
  - Studies that enhance viral growth from low titer
  - Studies that lead to evasion of residual or induced immunity
  - Studies that enhance virulence
  - Studies that enhance transmissibility
  - Studies that lead to evasion of therapeutics in use and in development
- For coronaviruses, the following research has critical benefits:
  - Studies that alter host tropism
  - Studies that enhance virulence
  - Studies that lead to evasion of therapeutics in development

Lessons learned and gaps

- Several lessons were learned during the execution of the RBA, but these stand out
  - Artificiality of distinctions between pandemic and seasonal influenza strains
  - Lack of data on human reliability in life science laboratories
  - Difficulty posed by having no risk benchmark for work with wild type pathogens
  - Difficulty posed by restriction of RBA to influenza and coronaviruses

Artificial Distinctions Between Seasonal and Pandemic Influenza Strains

- Public health and policy stakeholders compartmentalize pandemic and seasonal influenza strains, often due to the disparity in risk immediately after emergence
- However, long after emergence, pandemic strains often contribute to the population of seasonal strains in the following years
  - Today's seasonal H1N1 strains are descendants of 1918 H1N1pdm
- Risk from a laboratory accident or a biosecurity incident with an older pandemic strain must be understood in the context of a non-naïve population
  - Transmissibility is much lower than when it emerged, some portion of the population is protected
- There is no bright line between seasonal strains and old pandemic strains so risk is best understood as a single continuum
- Future safety/security RBAs should not artificially separate out pandemic from seasonal strains
  - Not true for RBAs that examine risk of emergence

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
- To address this shortcoming, primary research on human factors in life sciences laboratories must be conducted
- 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 the worst pandemic strain (now 1957 H2N2 pdm)
- Does it make sense to suspend funding of research that creates new risky strains while continuing funding research on 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)?
- 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

Restriction of the RBA to influenza viruses and coronaviruses

- The information risk section of the RBA identified that manipulations of pathogens other than the influenza and coronaviruses could pose similar levels of pandemic risk
- The remainder of our study examined just one component of potential pandemic risks, the full suite of which should be considered together as part of a comprehensive RBA
- This comprehensive RBA should provide a set of benchmarks:
  - Highest tolerable risk of working with pathogens that currently exist vs ones that are extinct/could evolve
  - Highest tolerable risk working at any particular containment level (BSL4, BSL3, BSL3E)

RBAs Applied to Specific Experiments

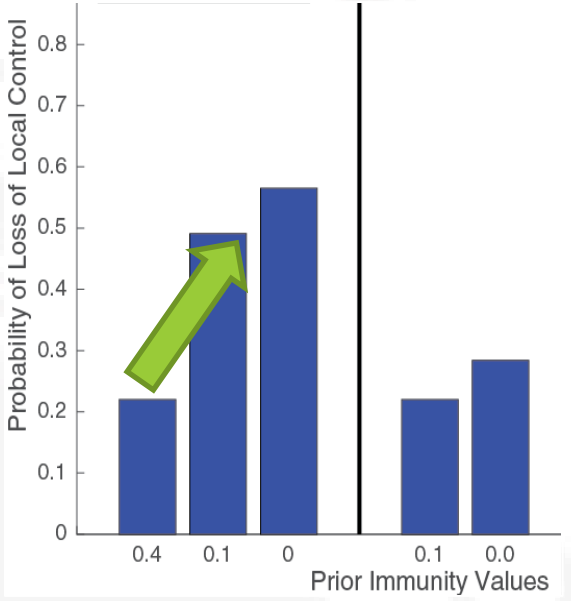
- Moving forward, decision-makers may be asked to evaluate the risk and benefits posed by specific experiments, either in grant proposals or in institutional reviews
- Our RBA was designed to be used as a flexible reference document that could be used to assess risk of any experiment relevant to GoF studies
- A simple understanding of the change in risk can be obtained in five steps
  - Identify the strain worked on and describe its properties relevant to pandemic risk (R0, case fatality rate, MCM resistance)
  - Understand how the proposed experiment COULD alter any of these properties
  - Examine how the proposed change COULD affect probability of an outbreak escaping local control (RBA section 6.6)
  - Examine how the proposed change COULD affect consequences of a global outbreak (RBA section 6.7)
  - Multiply these two increases together to obtain a perspective on change in risk

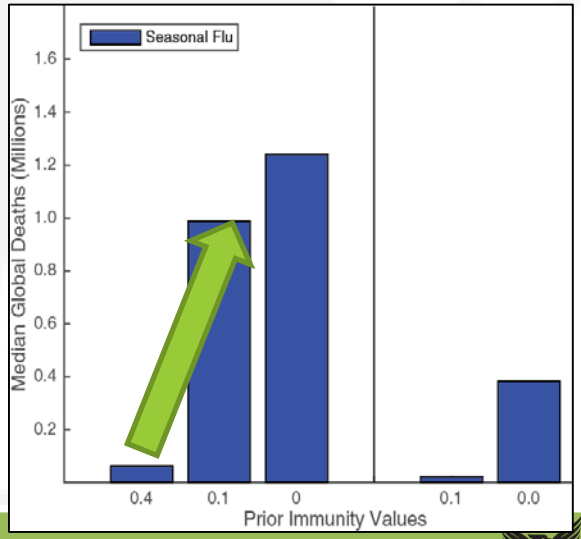
RBAs Applied to Specific Experiments

- Example 1: What is the risk of posed by experiments that include virulence factors from 1918 H1N1 influenza in a 2009 H1N1 strain
  - Section 6.6 states that virulence does not increase the probability that an outbreak escapes local control
  - Section 6.7 states that global consequences scale linearly with case fatality rate
    - The difference in the case fatality rates of these strains is several orders of magnitude, suggesting that consequences could increase by several orders of magnitude from an accident with this strain compared to a wild-type 2009 H1N1 strain
    - Since probability is unchanged and consequences increase, the risk of this type of experiment increases by several orders of magnitude

RBAs Applied to Specific Experiments

- Example 2: What is the risk posed by experiments that aim to create antigenically distinct strains of a recently circulating seasonal influenza strain
  - Section 6.6 shows that antigenically distinct strains have a 2-3x increase in risk of escape.
  - Section 6.7 shows that antigenically distinct strains may inflict 10x more global deaths.
  - Therefore, risk increases by roughly 20-30x
    - Recall that it is unknown if any illnesses caused by an accident with seasonal influenza virus would supplement or supplant seasonal infections





RBAs Applied to Specific Experiments

- However, the meaning of this risk increase is difficult to interpret in the absence of standards for risk tolerance
  - Is a 100x increase in risk from a low level sufficient to not fund the research?
  - Is 10x? Does it matter if work is going on down the hall on wild type pathogens with greater levels of risk?
  - This information is sufficient to state that more controls and measures should be taken to control infection risk from this modified pathogen than the wild-type pathogen
- Also, bench researchers may not be familiar enough with the epidemiological properties of pathogens to properly characterize their strains
  - Guides or tools are needed to easily obtain parameter values for wild type strains and, perhaps, to aid with the calculations

Use of 1918 H1N1 pdm as a Comparator

- In the summaries of our RBA, we discuss risk of GoF strains relative to the risk posed by the 1918 H1N1pdm strain
  - The full text enables a comparison of the risk of any manipulation against any benchmark
- The revised document will have more comparators in the summaries
  - Also, 1918 H1N1pdm will not be the highest risk of all because of the pre-existing immunity in the population due to the circulation of 2009 H1N1pdm
- This comparator was chosen because at the time there was limited discussion of a funding moratorium for work on wild type versions of 1918 H1N1pdm, so we decided it was a reasonable benchmark for "maximum allowable risk"

Use of 1918 H1N1 pdm as a Comparator

- A new comparator: 1957 H2N2 pdm
  - R0 likely 1.7 (low residual immunity against H2 strains)
    - Compared to ~1.2 for 1918 H1N1 pdm nowadays
  - Case fatality rate of 0.35%
    - Compared to up to 5% for 1918 H1N1pdm
  - Other parameters likely similar
- Therefore, if H2N2 is the comparator:
  - Increases in transmissibility don't increase risk much
  - Increasing case fatality rate can increase risk by a factor of 10 or more
  - Other parameters don't influence risk

Use of 1918 H1N1 pdm as a Comparator

- The use of any other strain as a comparator is arbitrary
  - Why does it matter if the strain poses more risk/less than MERS-CoV or 1968 H3N2pdm?
- As stated before, relative increases in risk (or absolute risk estimates) are useful to help determine if additional safety/security measures are needed, but not if risks are worth the benefit overall
- The only sensible comparators are benchmarks for the riskiest allowable research for existing/novel pathogens at particular containment levels
  - These benchmarks should be set regardless of the pathogen studied or the particular manipulation undertaken

Thank you

- The full risk assessment (and its final version), with all supporting materials, can be found at: http://www.gryphonscientific.com/gain-of-function/