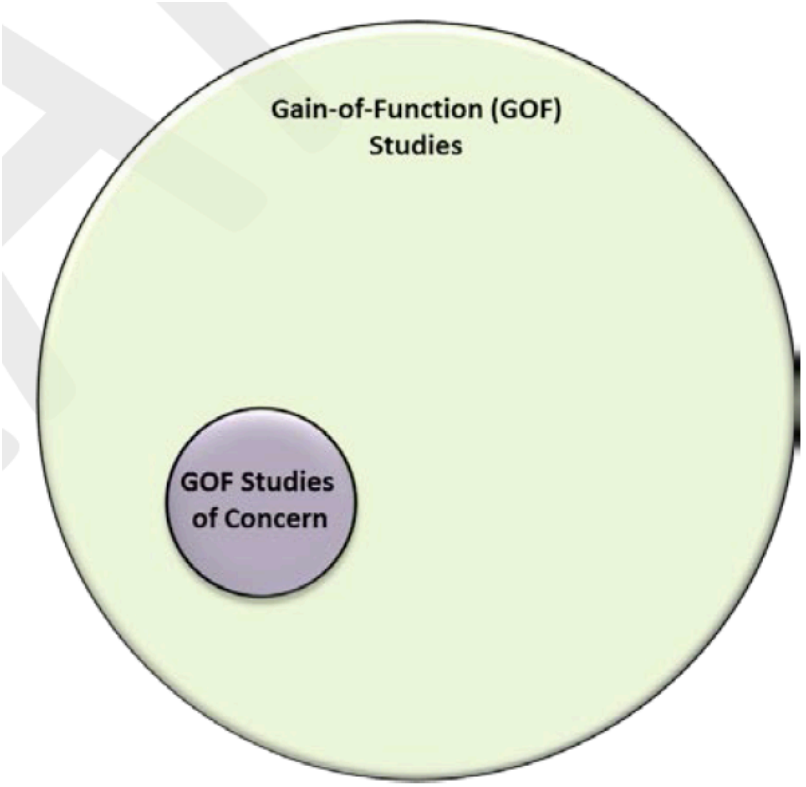
# Points

1. NSABB draft's GOF of concern focus is appropriate
2. RBA significantly underestimates risks of GOF of concern
3. GOF of concern risk estimates in Gryphon RBA are nonetheless so high that the experiments should not be performed
4. Gryphon benefit assessment shows major COI and overstates benefits
5. NSABB draft wrongly states that current processes are adequate for regulating GOF of concern
6. US should not perform or fund GOF of concern; other experiments should follow regular processes

# Appropriate focus on GOF of concern




Draft NSABB response
Fig. 4

- Reasonably anticipated to produce a pathogen that is highly transmissible and highly virulent in humans
- I would not emphasize escaping countermeasures, because these are uncertain and, in most cases, not globally available (e.g., vaccines)

# Gryphon RBA underestimates absolute risk for GOF of concern

- Escape scenarios systematically assume the LAI happens in a high-containment lab – contrary to repeated experience
  - CDC anthrax, Ebola, influenza 2014; DoD anthrax 2015; etc.
- Absolute risk assessment assumes LAI probabilities 10-1000-fold lower than recent data show from BSL3
- Probability of escaping local control is inexplicably low, inconsistent with prior estimates, including by Lloyds-Smith model
  - For coronaviruses because they misread the literature on R0 (3 not 1.5)
  - For influenza viruses, partly because of unsubstantiated assumption of effective community mitigation
- Repeatedly suggests that work with 1918 H1N1 is an acceptable baseline level of risk without justification
  - And uses wrong CFR for 1918, making that arbitrary baseline even higher

# GOF of concern is unacceptably risky even with optimistic numbers from Gryphon RBA

Pr(LAI with modified HPAI in BSL3 per labs  year) = 3/2000 x 0.1 = 0.015%

Pr(outbreak that escapes local control|LAI) = 0.4%

Pr(outbreak that escapes local control)/BSL3 labs/year = $6 \times 10^5$

Attack rate | pandemic = 25%

CFR = 5%

Population = $7 \times 10^9$

Expected fatalities | pandemic = 9 x 10

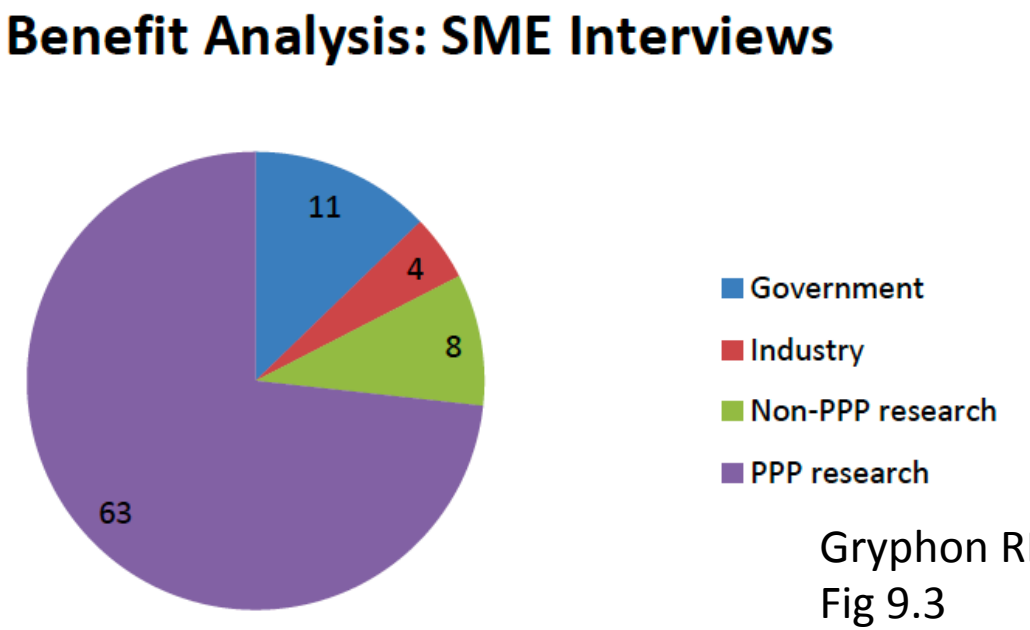
Risk = 54 expected fatalities per lab-year. No IRB would permit a year's worth of research with 54 expected fatalities.

Lynn Klotz. Sources Table 6.2, Fig. 6.59,

# Exaggerated benefit claims

- 14 site visits to speak to GOF/PPP lab PIs, students, postdocs

- >80% of sources were researchers or funders for PPP studies




Gryphon RBA
Fig 9.3

# Benefits: General observations

- Almost all GOF of concern benefits will be limited largely to rich countries (BA pp. 438, 442, 444). GOF of concern unjustly imposes risks on whole populations who would be denied the potential benefits.
- Contrary to assertions in BA, nearly all benefits claimed for GOF of concern are not unique to GOF but can be achieved by alternatives. Given that alternative approaches are risk free (for pandemic risk), it would be imprudent and unethical to use GOF approaches instead of alternatives.

# Example: PPP studies unncecessary and possibly misleading for prepandemic risk assessment

| Mutation claimed to be significant based on GOF by Davis or Schultz-Cherry *mBio* 2014 | Prior studies not involving PPP creation that identified these mutations | Counterexamples |
|---|---|---|
| H5 H7N9 HA Q222L HA | Chutinimitkul 2010<br>Jongkon 2009<br>Yamada 2006 Liu 2009<br>Stevens 2006 Russell 2006<br>Tharakaraman 2013 | CONTEXT DEPENDENCE: Changes do not quantitatively shift receptor binding in related H5 strains (Tharakaraman 2013) |
| H5N1 HA S133A S135N S123P S155N | Yamada 2006<br>Yang 2007 | |
| H7N9 HA T156A Q222L | Stevens 2008 Wang 2011 Gao 2013 NEJM | |
| PB2 E627K D701N | Subbarao 1993<br>De Jong 2011 | MISLEADING INFERENCE: Both absent in 2009pdm. Would have led to its misclassification as low risk |

# Existing processes inadequate

- Prior to funding pause, HHS framework inadequate
  - Risk and benefit assessment completely non-quantitative and largely credulously accepting of investigator's claims (Wisconsin IBC)
  - HHS Department-level review done privately, no public input or scrutiny
  - HHS-funded GOF (Richard et al. Nature) on H7N9 was published in same issue as HHS H7N9 Framework: Behind the curve
- Even during pause, SARS GOF paper published without explanation of how it was permitted
- Clear COI placing funders and performers of GOF work, and those supported by its indirect costs, as reviewers of global risk
- No resources provided for IBCs or others to assess GOF risk, benefit

# Written comments available at www.cambridgeworkinggroup.org/news

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# EXTRA SLIDES

# LAI are likely to occur outside GOF labs

On Dec. 22, a worker at CDC's biosafety level 4 lab in Atlanta — where scientists wear spacesuit-like, full-body protective gear that filters the air they breathe — accidentally confused some specimens and sent an un-killed sample from an Ebola experiment to a lower-level lab with minimal protections. – *USA TODAY* 2/4/2015

…a culture of non-pathogenic avian influenza was unintentionally cross-contaminated at the CDC influenza laboratory with the highly pathogenic H5N1 strain of influenza and shipped to a BSL-3 select-agent laboratory operated by the United States Department of Agriculture (USDA). – CDC press release, 7/11/14

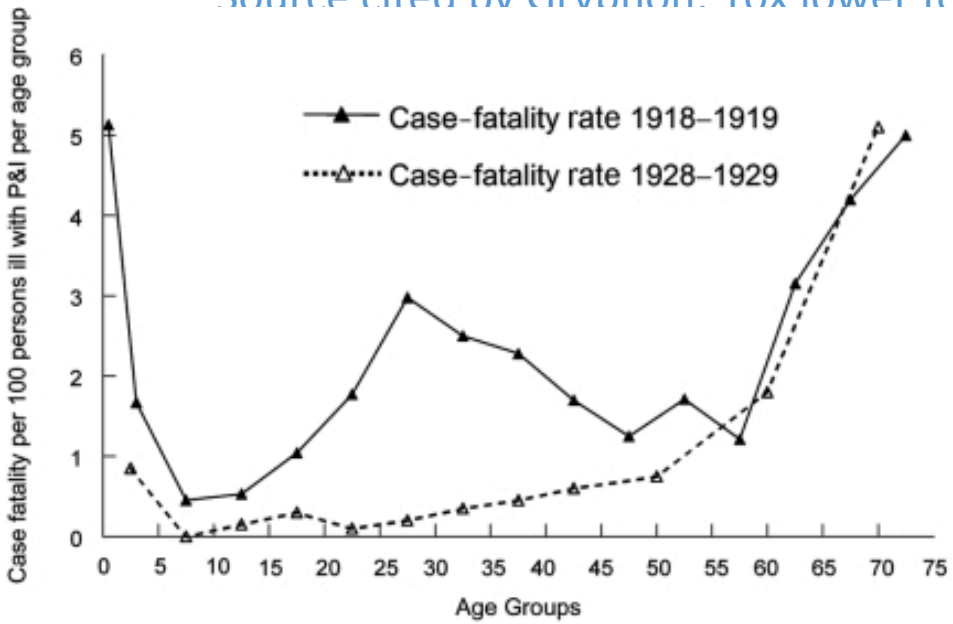
Mr. Work said that live anthrax samples had been sent from Dugway to 86 government and private labs and other facilities in the United States and seven other countries: Australia, Britain, Canada, Germany, Italy, Japan and South Korea. – *NYT* 7/23/15

# Errors in CFR

Gryphon report

| Table S7. Percentage of Pandemic Influenza Infected Individuals who Die, by Pandemic | |
|---|---|
| **Pandemic** | **Percent Mortality of Infected Persons** |
| 1918 Spanish Flu[82] | 10% - 20% |
| 2009 H1N1[83] | 0.00010% - 0.00043% |

Source cited by Gryphon: 10x lower for 1918




2009 systematic review : 10-100 higher: We included 77 estimates of the case fatality risk from 50 published studies, about one-third of which were published within the first 9 months of the pandemic. We identified very substantial heterogeneity in published estimates, ranging from less than 1 to more than 10,000 deaths per 100,000 cases or infections. The choice of case definition in the denominator accounted for substantial heterogeneity, with the higher estimates based on laboratory-confirmed cases (point estimates = 0-13,500 per 100,000 cases) compared with symptomatic cases (point estimates = 0-1,200 per 100,000 cases) or infections (point estimates = 1-10 per 100,000 infections). Risk based on symptomatic cases increased substantially with age. Wong JY, Kelly H, Ip DK, Wu JT, Leung GM, Cowling BJ. Case fatality risk of influenza A (H1N1pdm09): a systematic review. Epidemiology. 2013 Nov;24(6): 830-41. doi: 10.1097/EDE.0b013e3182a67448. Review.