# Biosafety and Bioethics

## Special Challenges of Gain-of – Function Experiments and Potential Pandemic Pathogens

Marc Lipsitch, D.Phil.

Eagleson Lecture, ABSA

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HARVARD
SCHOOL OF PUBLIC HEALTH

Center *for*
Communicable
Disease Dynamics

Models of Infectious
Disease Agent Study

*Funded by the National Institutes of Health*

*"And it was so typically brilliant of you to have invited an epidemiologist."*

Views my own!

Models of Infectious Disease Agent Study
MIDAS

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# HPAI GOF will add to scientific information

- We will learn some AA residues that are important, in specific genetic backgrounds, to transmission among ferrets, a model host.
- We will add to our catalog of examples of how, with a specific genetic background, individual mutations may have pleiotropic effects on phenotype
- Science is unpredictable; we may learn more than this

# The first hi-path influenza GOF experiment: recreating 1918 H1N1

## Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus

Terrence M. Tumpey,[1*] Christopher F. Basler,[2] Patricia V. Aguilar,[2] Hui Zeng,[1] Alicia Solórzano,[2] David E. Swayne,[4] Nancy J. Cox,[1] Jacqueline M. Katz,[1] Jeffery K. Taubenberger,[3] Peter Palese,[2] Adolfo García-Sastre[2]

Note added in proof: This research was done by staff taking antiviral prophylaxis and using stringent biosafety precautions (15) to protect the researchers, the environment, and the public. The fundamental purpose of this work was to provide information critical to protect public health and to develop measures effective against future influenza pandemics.

Since published in 2005, no new classes of antivirals or vaccines based on this work; No decisions in the H1N1 2009 pandemic, to my knowledge, were usefully informed by this work

# Summary

- Interesting science alone is not justification for doing an experiment that produces risk to human health and life, especially on a large scale for uninformed, unconsenting persons; human health benefit should be a likely outcome.
- The claimed benefits of HPAI GOF are overstated
- The risks are significant
- The risks outweigh the likely benefits

# Most science that could produce interesting results is not done, and some is prohibited

- Grants not funded
  - Benefits too small
  - Approach is not best way to get the knowledge
- IRB prohibits
  - Risk to subjects too great
- IACUC prohibits
  - Harm to animals too great
- Biosafety prohibits
  - Risk to investigators, facility too great. Smallpox, others

# Hence the question

- Are the prospective benefits of HPAI GOF large enough to justify the risk of an accidental (or deliberate) pandemic?
- Since risks are to life and health of humans, the benefits should be measured on the same scale

# Research ethics: Helsinki Declaration

Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

Risk-benefit analysis

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

Benefit outweighs risk

In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal.

Informed consent required

# Interacademy Panel Declaration on Biosecurity

Scientists have an obligation to do no harm. They should always take into consideration the reasonably foreseeable consequences of their own activities.

# HPAI GOF is nearly unique in its combination of properties

| Study | High Virulence | Pandemic potential | Exists in Nature | BSL |
|---|---|---|---|---|
| Characterize natural hemorrhagic fever viruses | + | - | + | 4 |
| Characterize H5, H7 HPAI | + | - | + | 3 |
| Smallpox-any | + | + | - | Two labs |
| GOF on HPAI | + | + | - | 3+ |

# Risk of a pandemic is to humanity, not investigator or individual subjects

| Pandemic | Estimated Incidence | Global deaths if 1% CFR in 2013 | If 60% CFR |
|---|---|---|---|
| 1918 | 29% | 21 million | 1.2 billion |
| 1957 | 24% | 17 million | 1.0 billion |
| 1968 | 38% | 27 million | 1.6 billion |
| 2009 | 24% | 17 million | 1.0 billion |

Van Kerkhove et al. IORV 2013 (2009 est.) USG Community Mitigation Guidance 2007 (others)

*Availability of stockpiled vaccines and seed strains might reduce these numbers, if effective against the strain that is released*

# Laboratory escapes happen, even in BSL3

- Pirbright FMDV 2007 leading to large outbreak
- SARS 2004 Beijing: six further infections
- 1977 H1N1?

# Accidental infections are more frequent than true escapes in BSL3/4

- SARS Taiwan 2003
- Ebola Novosibirsk 2004
- SARS-contaminated WNV Singapore 2003
- Marburg Novosibirsk 1988
- At least 13 Lab-acquired infections in USA BSL3 2002-8

U.S. Department of Homeland Security, National Bio and Agro-Defense Facility, Final Environmental Impact Statement, Appendix B (2007); www.dhs.gov/xlibrary/assets/nbaf_feis_appendix_b.pdf

# Lab accidents happen, even in BSL3

- NIAID high-containment labs: 1 lab worker infection, 12 exposures, per 600,000 worker-hours.

Expected Exposures and infections over 10 years

| Labs | ½ - time techs/lab | Exposures | Infections |
|---|---|---|---|
| 1 | 1 | 1/5 | 1/60 |
| 20 | 5 | 20 | 1.7 |
| 100 | 3 | 60 | 5.1 |

U.S. Department of Homeland Security, National Bio and Agro-Defense Facility, Final Environmental Impact Statement, Appendix B (2007); www.dhs.gov/xlibrary/assets/nbaf_feis_appendix_b.pdf

# Another estimate based on CDC data

4 lab-associated infections (LAI) from BSL3 in less than 2044 lab-years

**Monitoring Select Agent Theft, Loss and Release Reports in the United States—2004-2010**

Richard D. Henkel*, Thomas Miller, and Robbin S. Weyant

Centers for Disease Control and Prevention, Atlanta, Georgia

0.2% probability of a LAI/ BSL3 lab / year
=> 18% chance of an LAI over 10 labs for 10 years under US standards

L. Klotz 2013 http://armscontrolcenter.org/The_Human_Fatality_Burden_of_Gain_of_Function_Flu_Research_v8-29-13.pdf

# Will a single LAI lead to a pandemic?

Calculations from epidemic theory suggest probability depends strongly on $R_0$ of GOF strain. For $R_0$=1.5-1.8, reasonable values in range 5% to 60% (overdispersed branching process)

Vaccination and prophylaxis may help. Neither is perfectly effective, especially vaccines.

J Lloyd-Smith et al. *Nature* 2005
M Lipsitch et al. *Science* 2003

# BSL-4 around the globe


Federation of American Scientists
https://www.google.com/fusiontables/DataSource?snapid=S567513UnBn

# Global variation in lab standards

Similarly, regulations and guidance have not always kept pace with developments. In some countries, rules exist but are poorly understood and enforced, and many countries lack national guidelines and regulations altogether. Many felt that while these topics are predominantly national issues, international discussions could facilitate progress.

US National Academy of Sciences report 2012

# Could reduce risks by doing studies in LPAI

- Proponents claim: Because genetic context is crucial, and we can't extrapolate from LPAI to HPAI
  - Proponents contradict this by arguing we can extrapolate from H5 to H7, and that they have urged policy decisions such as closing poultry markets in China, on the basis of the H7 strains having some of the GOF mutations
  - Any GOF experiments will be done in a genetic background different from the strain that causes a future pandemic. Natural HPAI strains are heterogeneous and constantly evolving
  - Given that we all agree genetic context is important ANY GOF experiment will be done in the "wrong" strain. So why not use LPAI strains, at least in the first several years of experiments, to establish common principles?

# Risks: summary

- Large-scale research program just in one country at BSL3 over 10 years presents a significant risk of one or more laboratory-associated infections
- Global spread of research increases risk due to variation in lab safety standards.
- Flu case may be infectious before symptomatic; nontrivial risk of further infections
- Pandemic with 1% CFR could kill ~20m globally.
- Could reduce risks by learning general principles from LPAI

# Purported Public Health Benefits of HPAI GOF

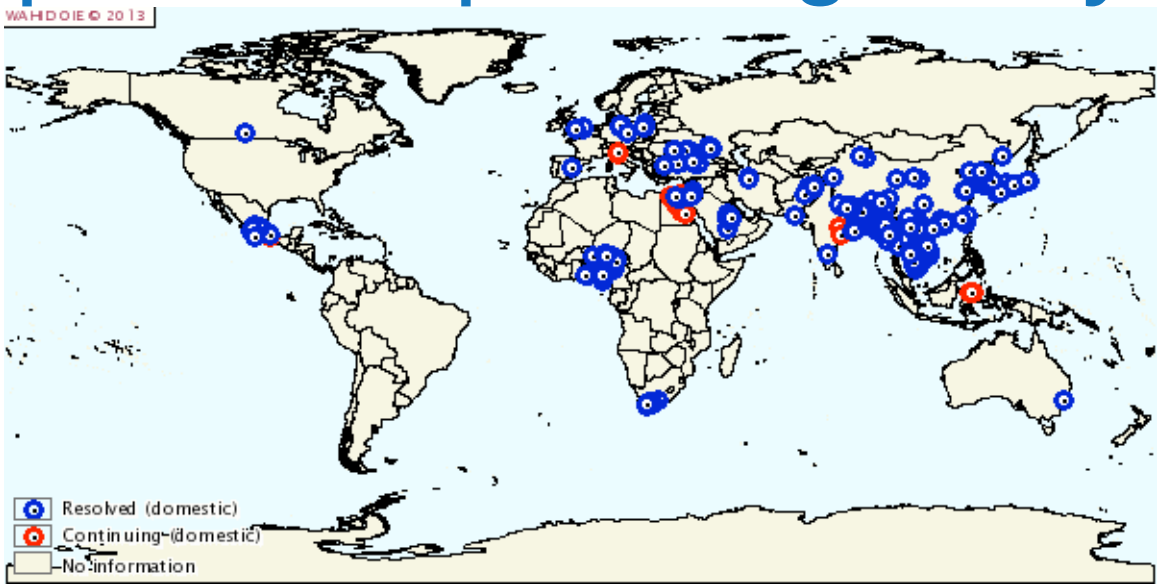
- Better-informed surveillance
- Vaccine design

# Benefits depend on the ability to interpret individual mutations to predict phenotype

- This is repeatedly shown to be false
  - H275Y NA resistance can be either crippling or fitness-enhancing in H1N1, depending on the genetic background
  - E627K PB2 mutation can be either crucial for virulence and transmissibility, or not
  - GOF mutations found to date do not confer human binding on HA in Egyptian H5N1 strains

Kiso et al., *Lancet* 2004; Herlocher et al., *JID* 2004; Kramarz et al, *Euro Surveill*. 2009 Bloom et al. *Science* 2010. Tharakamaran et al. *Cell* 2013

# Avian flu surveillance is inadequate, sequencing delayed




| Database | Global H5 Sequences/ month since 2008 | % older than 3 months | % older than 1 year |
|---|---|---|---|
| Genbank | 22 | 92% | 75% |
| GISAID | 31 | 92% | 69% |

# We don’t need GOF for vaccine design

- We have vaccines against at least 34 species or strains of pathogen that work well, without a detailed molecular understanding of transmission of any of them
- The problem with existing flu vaccines is not that they do not include “transmission factors” (if such exist) but that they have limited immunogenicity, efficacy and duration
- US already has H5N1 vaccines stockpiled (at least 20m doses). What decision would GOF results change concerning this stockpile?
- Former chief of Merck Vaccines Adel Mahmoud says the use of GOF for vaccine shows “complete lack of understanding of how vaccines are made.” (*Independent* August 7, 2013)
- Inactivated vaccines target HA; how could mutations on other segments be incorporated?

# Unlikely we would change stockpiles following GOF results

- What if we found that GOF mutants were poorly neutralized by the existing vaccines in the stockpile. Would we
  - replace the stockpile with GOF-based vaccine? This would be a highly speculative action: assuming that this vaccine would be more similar to the actual pandemic strain. There is no evidence for this assumption.
  - US Stockpile of new strain would cost ~$20-30m in startup and $200m to complete the stockpile.
- GOF has no particular applicability to finding a universal flu vaccine, the most promising option for pandemic (and seasonal) preparedness.
  - If it did, then the GOF experiments should be done in a low-path strain.

# Benefits are overstated

- Vaccine design doesn't need GOF; more promising approaches exist
- Bird surveillance is too limited, sequencing too slow to change policy based on GOF information.
- Public health benefits depend on ferret model's predictive value, which is unproven
- Benefits also depend on assumption that individual mutations are predictive; repeatedly for flu, that has turned out to be false.

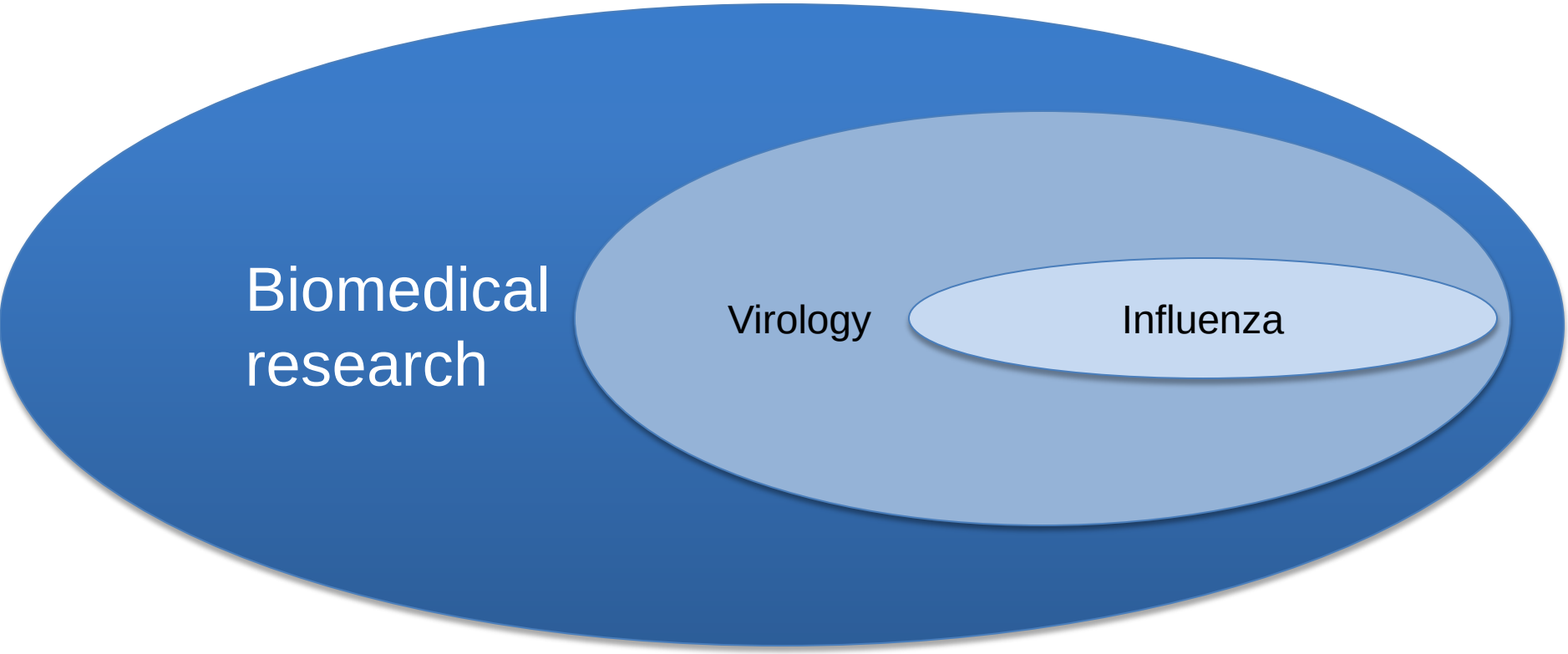
# Conclusions (I)

- HPAI GOF will add to science, but not every interesting experiment should be done, as the scientific community acknowledges
- HPAI GOF experiments, if done in many labs in many places present significant risk of LAI, which presents significant risk of causing pandemic
- Pandemic of even attenuated HPAI would be devastating, threatening lives of those who are uninformed, nonconsenting – a special ethical situation

# Conclusions (II)

- Such risks should not be undertaken without high probability of saving lives – given that many lives are put at risk (unlike almost all other science)
- Public health benefits are overstated
  - Inadequate surveillance
  - Vaccine design rationale unclear
  - Ferret model unproven for human transmission
  - Unlikely GOF in ferrets will precisely replicate pandemic emergence
  - General principles can be learned from LPAI or other experiments

# Hi-Path Gain of Function in Context



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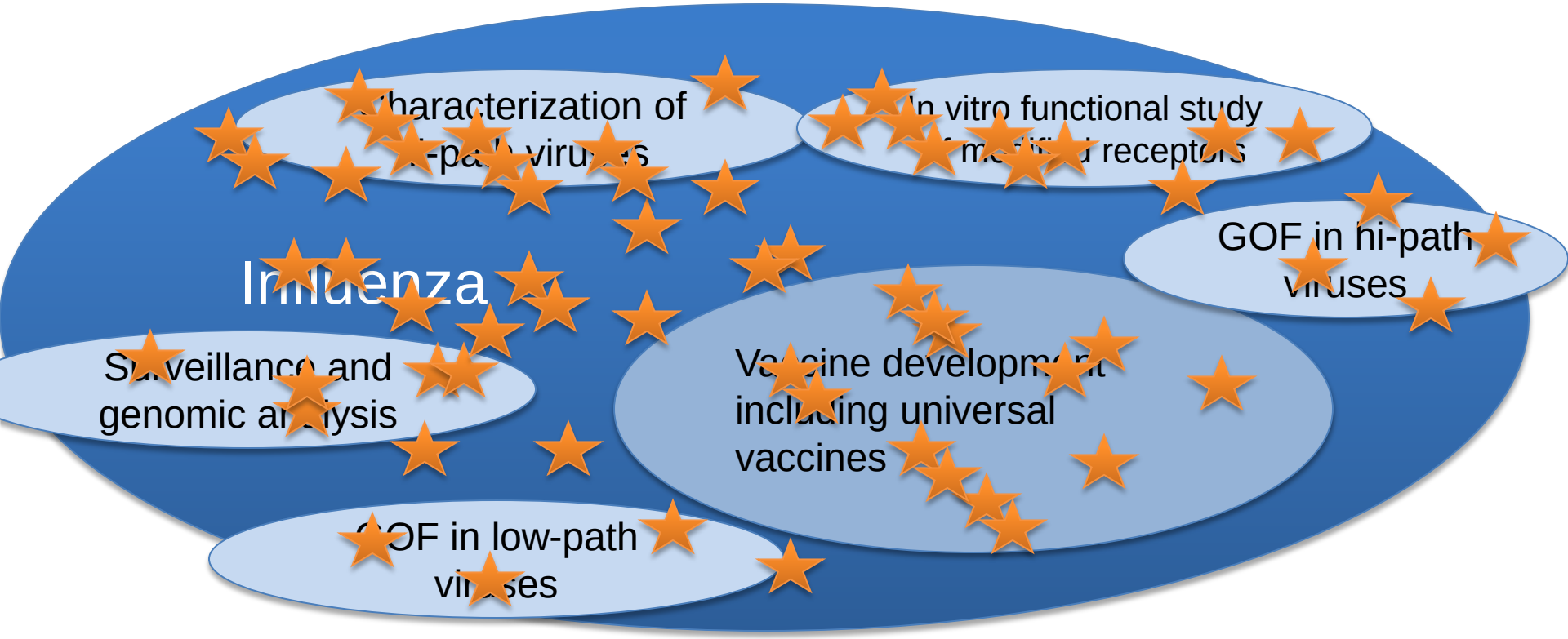
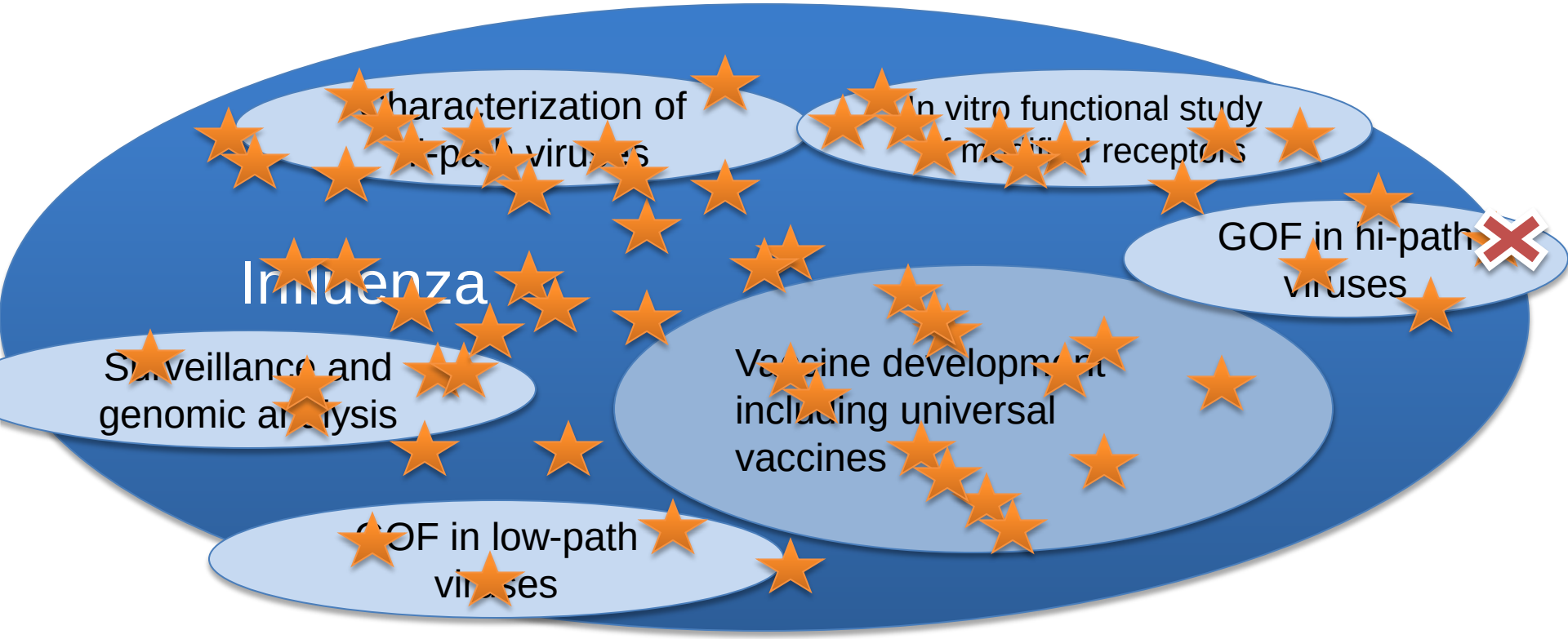


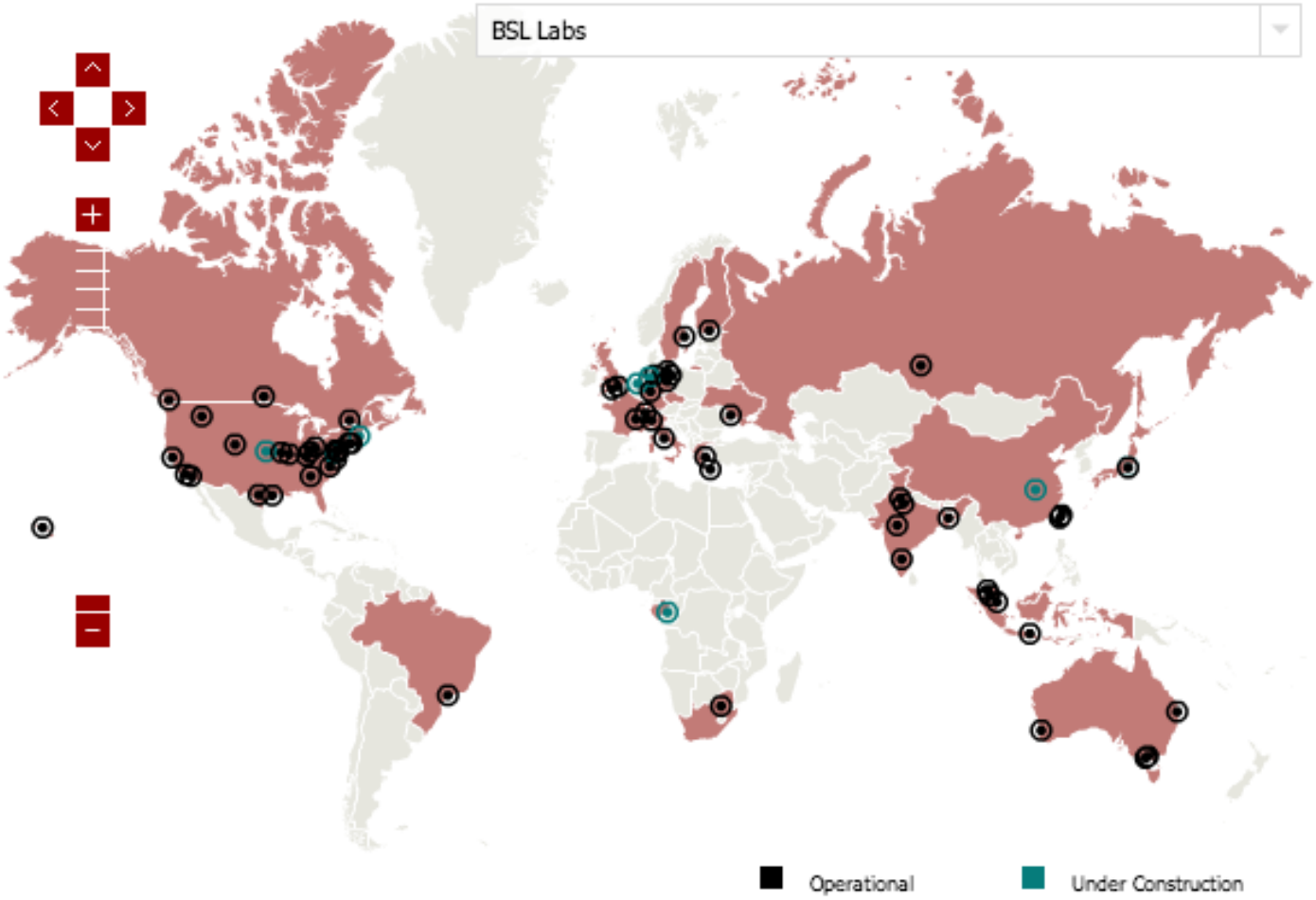
# Hi-Path Gain of Function in Context



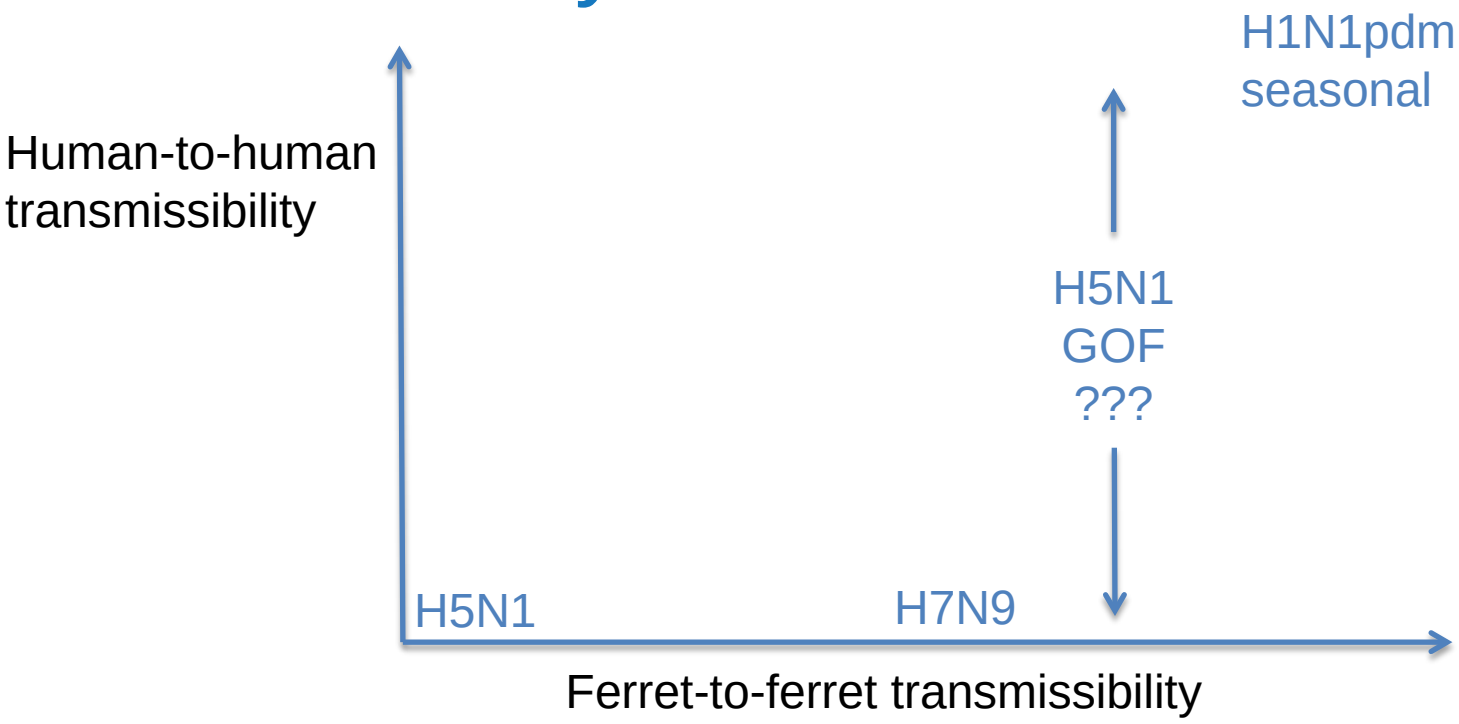
# Thank you for your attention

# BSL3/4 selected (FAS)

This map displays major Biosafety Level 3 and 4 (BSL-3 & 4) facilities around the world.* These high-containment facilities are used to conduct beneficial research on dangerous and emerging pathogens.



# Ferret transmissibility ≠ Human transmissibility




*Unethical to test this relationship experimentally*
*But contrast between H5N1 wt and H7N9 wt suggests it is not predictive*
*Public health benefits HINGE ON reliability of the model*