Gain-of-function studies of influenza viruses

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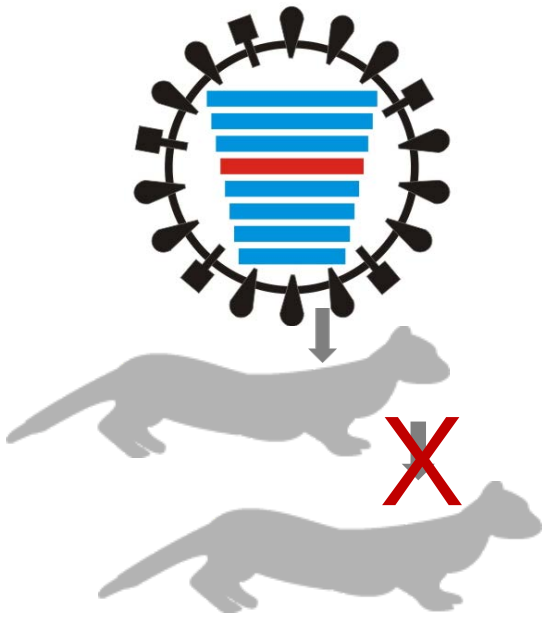
My background

- Identified molecular signatures in highly pathogenic avian influenza viruses now used by the USDA and OIE to guide policy decisions when avian influenza outbreaks occur.

- Established reverse genetics technology for influenza viruses, which has been used to generate live attenuated and H5N1 inactivated vaccine viruses.

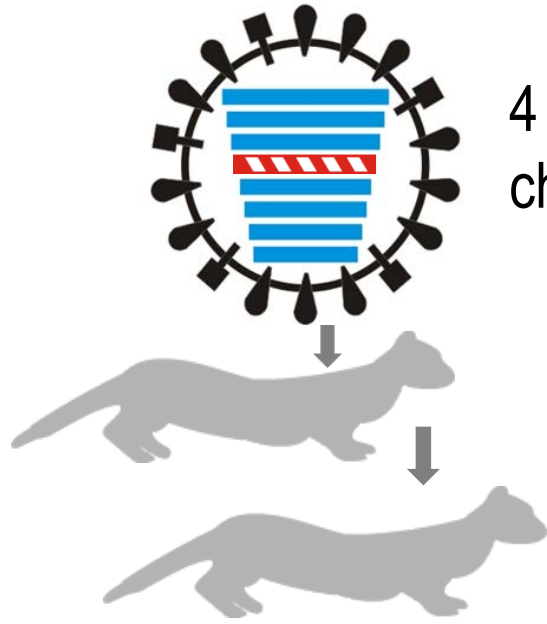
The goal of my research is to improve global health.

Ferret droplet transmission studies of H5N1 influenza viruses



No transmission

Imai et al., 2012, Nature



Transmission

4 amino acid changes

- We demonstrated H5N1 viruses can acquire the ability to transmit via respiratory droplets in mammals.
- This information contributes to the risk assessment of emerging viruses and pandemic vaccine policy decisions.

Biosafety and Biosecurity – prior to transmission experiments

- Since H5N1 viruses are select agents, experiments with these viruses were already highly regulated before we initiated the transmission studies.

- The H5N1 transmission studies were peer-reviewed and conducted with Institutional Biosafety Committee (IBC) approval by experienced scientists under appropriate containment.

Biosafety/Biosecurity

BSL3

- Controlled access through double doors
- Decontamination of all waste
- Protective laboratory clothing
- Negative airflow into laboratory and exhaust air not recirculated

BSL3-Agriculture:

- Entry/exit through a shower/change room
- Double-door autoclaves
- Double HEPA-filtered supply and exhaust air
- Gas decontamination ports
- Air tight dampers on all ductwork & double-gasketed watertight & airtight seals
- Effluent decontamination
- Pressure decay testing of the structure
- Use of disposable coveralls and powered air-purifying respirators

BSL3-Agriculture : ferret transmission studies

BSL4

BSL3-Ag

BSL4

BSL3-Agriculture:

- Staff wear disposable coveralls and powered air-purifying respirators

BSL4:

- Full-body, air-supplied positive-pressure personnel suit
- Exit through chemical shower

Redundancies and back-ups

Extensive redundancies are in place. For example:

- Two air handlers
- Two compressors
- Two filters everywhere filters are needed
- Two effluent sterilization tanks
- Two power feeds to the building

Back-up resources:

- Emergency generator in case of a power failure
- Two-way communication system in case of telephone failure

Biosafety/Biosecurity

Facility

- My research group is housed in a dedicated stand-alone structure - no other groups are present in our building.
- Security measures include monitoring inside and outside the building and securing agents behind two physical barriers.
- Campus police patrol the area.
- Only approved staff can enter the facility.

Biosafety/Biosecurity

Staff

- All staff in the facility have received clearance from the FBI.
- All BSL3-approved personnel undergo extensive training.

Pathogens

- Controlled by the CDC and USDA
- Virus inventory is checked monthly.
- Transfer/shipment is controlled (DoC, CDC, IATA)

Administrative Oversight

- All experiments are approved by the IBC.
- The UW-Madison Biosecurity Task Force, which comprises experts in biosafety, facilities, compliance, security, law, communications, and health, reviews the research program.
- The CDC and USDA inspect us; approval granted every 3 years; in reality, site visit every year including unannounced visits.

New regulations – after moratorium on H5N1 transmission studies

March 29, 2012

United States Government Policy for **Oversight** of Life Sciences **Dual Use Research of Concern**

February 21, 2013

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules amendments
- additional enhancements for research on mammalian-transmissible H5N1 viruses

February 21, 2013

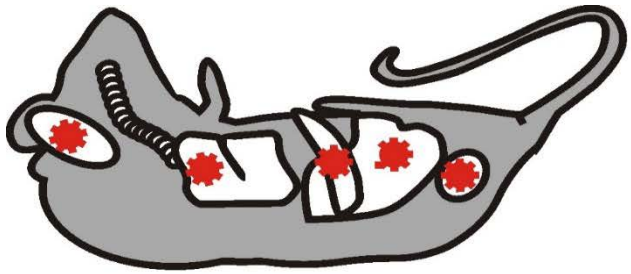
Framework for Guiding **Funding Decisions** about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza **H5N1 Viruses** that are **Transmissible** among Mammals by Respiratory Droplets

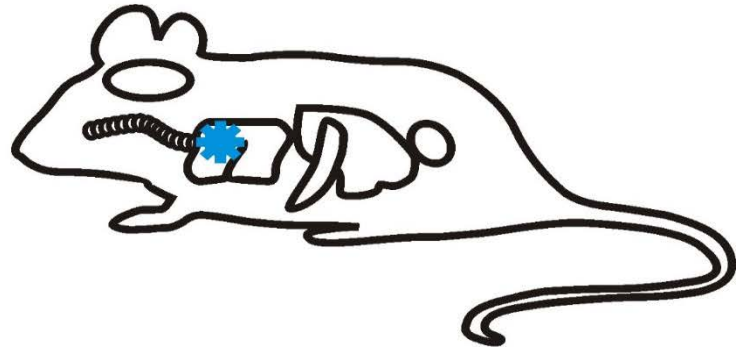
September 24, 2014 (Effective date: September 24, 2015)

United States Government **Policy** for **Institutional Oversight** of Life Sciences **Dual Use Research of Concern**

H5N1 transmission studies are highly regulated.

Why do we need to work on highly pathogenic H5N1 viruses?





Highly pathogenic avian influenza viruses differ from other influenza viruses in that the former viruses:

- Replicate substantially faster than other viruses
- Can grow in organs other than respiratory tissues

➡ The results obtained with low pathogenic viruses may not apply to highly pathogenic influenza viruses and can be misleading

The consequences of halting gain-of-function experiments

Current status of H5N1 transmission studies:

HHS approved H5N1 transmission experiments to:

- Characterize hemagglutinin (HA) stability mutations
- Evaluate specific mutations in other H5N1 viruses
- Determine the contributions of viral genes other than HA

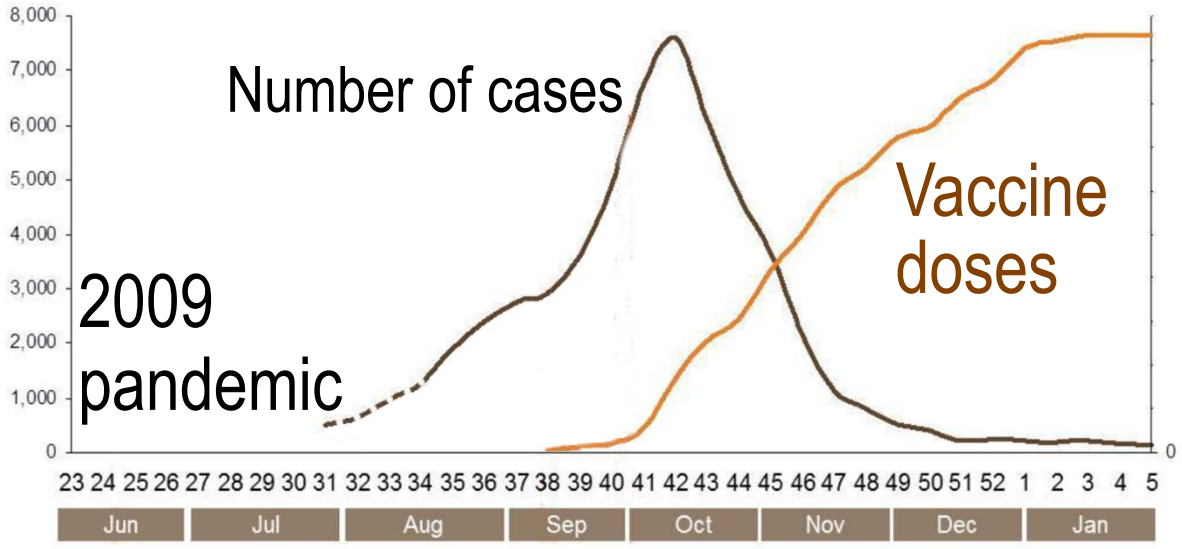
These additional studies are key to understanding the transmission of H5N1 viruses, but have been voluntarily paused.

A gain of function experiment:

Generation of a virus that grows well in cells and eggs for vaccine production

Due to poor growth of vaccine strains,

we occasionally suffer from a lack of sufficient doses of vaccine (e.g., 2009 pandemic).



The New York Times

WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY SCIEN

RESEARCH FITNESS

Nation Is Facing Vaccine Shortage

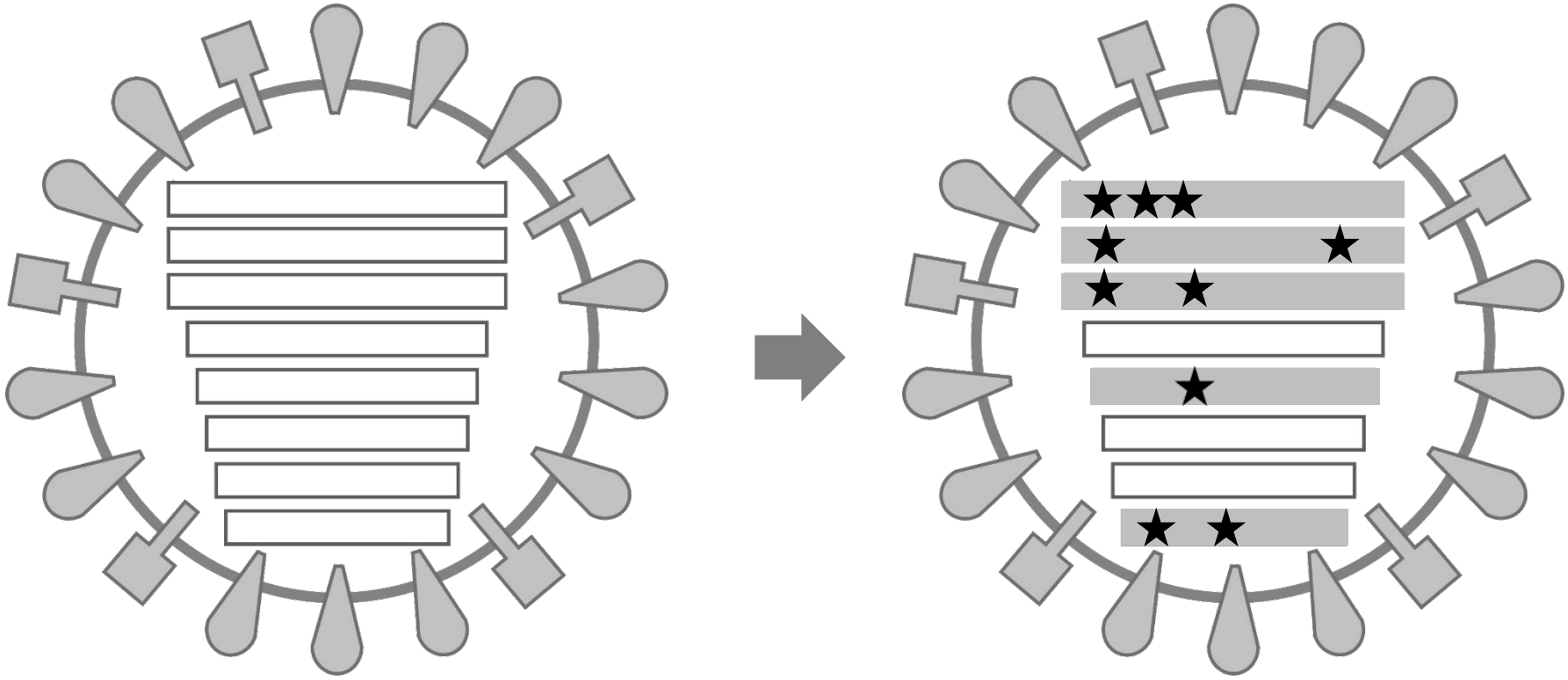
By DONALD G. McNEIL Jr.
Published: November 4, 2009

Even though the regular flu season has yet to start, th
facing a severe shortage of seasonal flu vaccine as wel
vaccine.

Enlarge This Image

Federal officials and i
experts have said the
unavoidable, given th

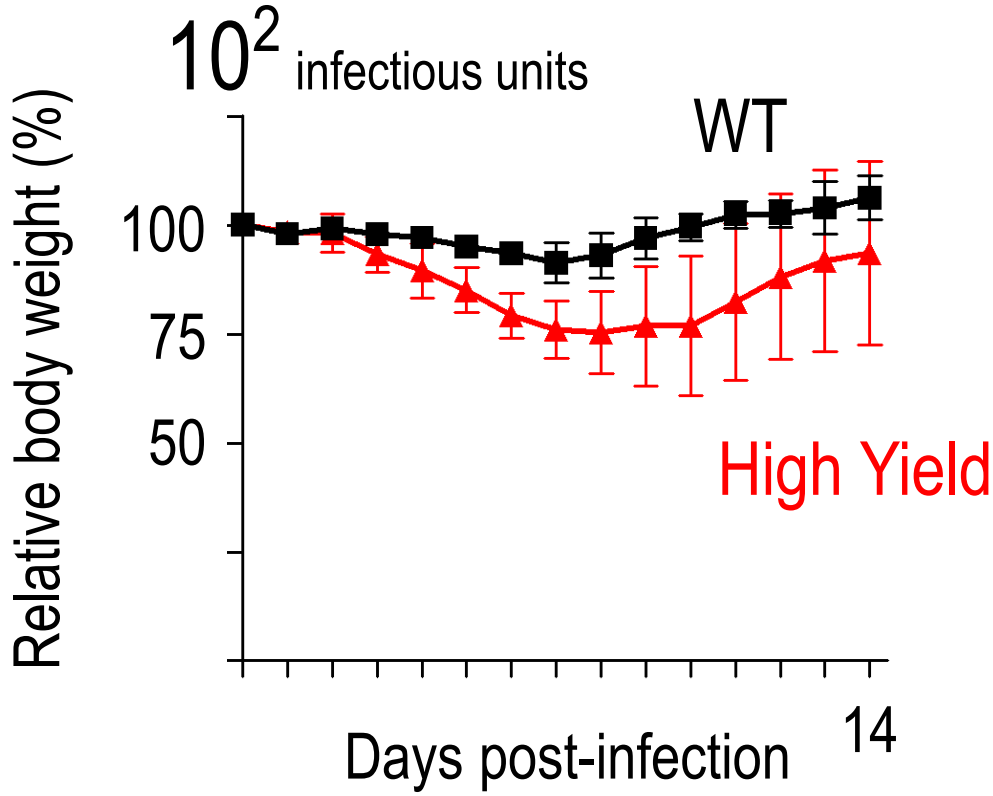
Generation of a high yield virus



Wild type

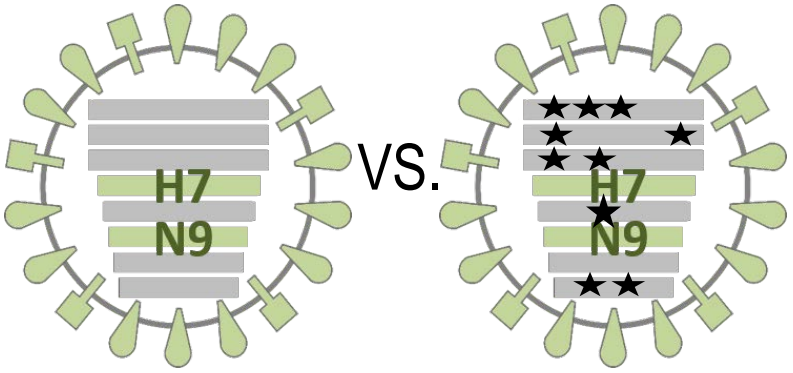
High Yield

Pathogenicity in mice



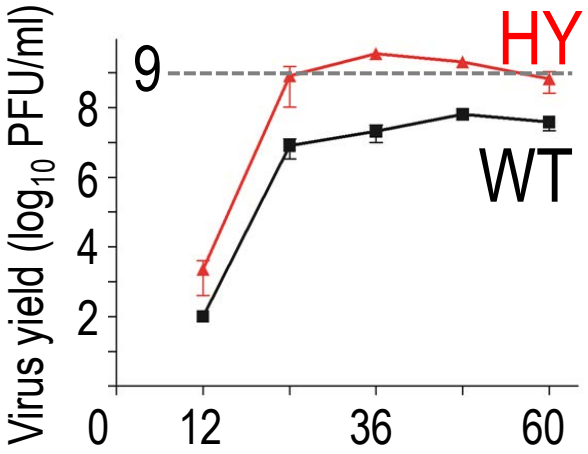
The high-yield virus is slightly more pathogenic than the wild-type virus in mice.

High-yield virus with HA & NA from A/Anhui/1/2013 (H7N9)

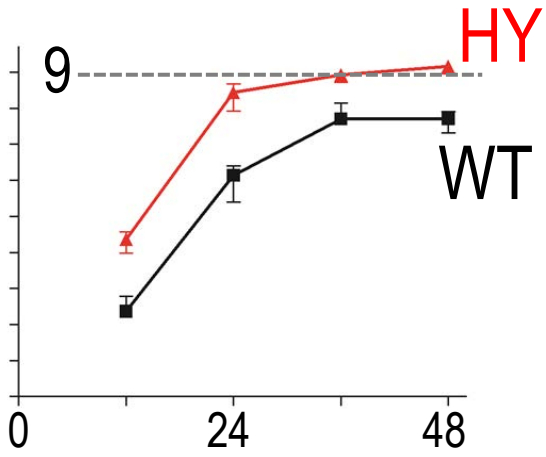


- The high-yield virus replicates >10 fold better than the wild-type virus.
- These viruses will be used as inactivated vaccines – mouse pathogenicity is irrelevant.
- Yet, due to the US government's announcement, this study has been voluntarily paused.

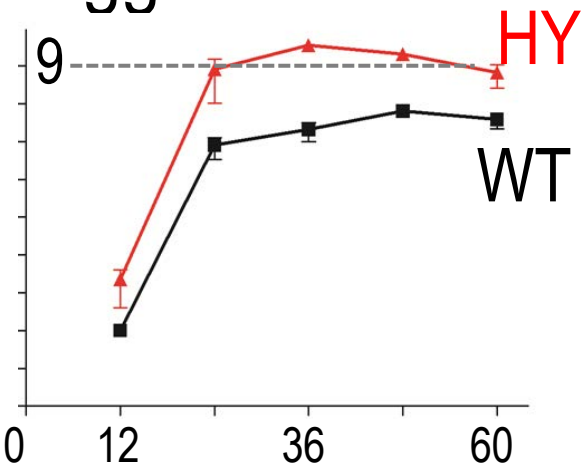
VERO cells



MDCK cells



Eggs



Hours post-infection

Conclusions

- H5N1 transmission studies are already highly regulated.

- Influenza gain-of-function studies are critical to public health and scientific progress.