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# “Gain of Function” and Influenza A Virus

The two have been intertwined for decades.

By Dr. Robert Malone
Global Research, May 22, 2024
Who is Robert Malone 21 May 2024

Region: USA
Theme: Science and Medicine



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*“Those that fail to learn from history are doomed to repeat it.” – Winston Churchill*

## What Is Gain of Function Research (GOF)?

There is no clear consensus regarding what constitutes GOF research. In the current political climate where the role of US Government (NIH/NIAID, DoD/DTRA, USAID and by implication CIA) in funding of what is clearly GOF research seeking to increase human infectivity of bat Coronaviruses has created an opportunity for stakeholders to sow confusion and ambiguity concerning what actually constitutes GOF research. Much of the resulting obfuscation has involved technical parsing of the definition of GOF in ways which conveniently support the interests of key stakeholders such as Dr. Peter Daszak and his EcoHealth Alliance organization, as well as Dr. Anthony Fauci and his famous denial and attack on the credibility of Senator Rand Paul during congressional testimony.

On October 17, 2014, the Obama White House issued a statement titled “U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses” which included a brief statement incorporating a useful general definition.

> Gain-of-function studies, or research that improves the ability of a pathogen to cause disease, help define the fundamental nature of human-pathogen interactions, thereby

> enabling assessment of the pandemic potential of emerging infectious agents, informing public health and preparedness efforts, and furthering medical countermeasure development. Gain-of-function studies may entail biosafety and biosecurity risks; therefore, the risks and benefits of gain-of-function research must be evaluated, both in the context of recent U.S. biosafety incidents and to keep pace with new technological developments, in order to determine which types of studies should go forward and under what conditions.

Dr. Yoshihiro Kawaoka, from the University of Wisconsin-Madison is a leading influenza GOF researcher who identified and published research demonstrating that four point mutations in the H5N1 hemagglutinin protein (analogous to SARS-CoV-2 Spike protein) which will convert productive and transmissible H5N1 from being restricted to birds to being able to infect and efficiently transmit between mammals (and potentially humans). In the 2015 workshop summary cited above, further details and discussions relating to the nature of GOF research are summarized in "Section 3: Gain-of-Function Research: Background and Alternatives". In this section, Dr. Kawaoka described and classified types of GoF research depending on the outcome of the experiments.

> The first category, which he called "gain of function research of concern," includes the generation of viruses with properties that do not exist in nature. The now famous example he gave is the production of H5N1 influenza A viruses that are airborne-transmissible among ferrets, compared to the non-airborne transmissible wild type. The second category deals with the generation of viruses that may be more pathogenic and/or transmissible than the wild type viruses but are still comparable to or less problematic than those existing in nature. Kawaoka argued that the majority of strains studied have low pathogenicity, but mutations found in natural isolates will improve their replication in mammalian cells. Finally, the third category, which is somewhere in between the two first categories, includes the generation of highly pathogenic and/or transmissible viruses in animal models that nevertheless do not appear to be a major public health concern. An example cited the high-growth A/PR/8/34 influenza strain found to have increased pathogenicity in mice but not in humans.
>
> Routine virological methods involve experiments that aim to produce a gain of a desired function, such as higher yields for vaccine strains, but often also lead to loss of function, such as loss of the ability for a virus to replicate well, as a consequence. In other words, any selection process involving an alteration of genotypes and their resulting phenotypes is considered a type of Gain-of-Function (GoF) research, even if U.S. HHS policies and definitions are intended to apply to only a small subset of such work.
>
> One leading virologist, Dr. Subbarao emphasizes that such experiments in virology are fundamental to understanding the biology, ecology, and pathogenesis of viruses. He introduced the key questions that virologists ask at all stages of research on the emergence or re-emergence of a virus and specifically adapted these general questions to three viruses of interest (see below). To answer these questions, virologists use gain- and loss-of-function experiments to understand the genetic makeup of viruses and the specifics of virus-host interaction. For instance, as we all know based on the work performed at the Wuhan Institute of Virology, researchers now have advanced molecular technologies, such as reverse genetics, which allow them to produce de novo recombinant viruses from cloned cDNA, and deep sequencing that are critical for studying how viruses escape the host immune system and antiviral controls. Researchers also use targeted host or viral genome modification using small interfering

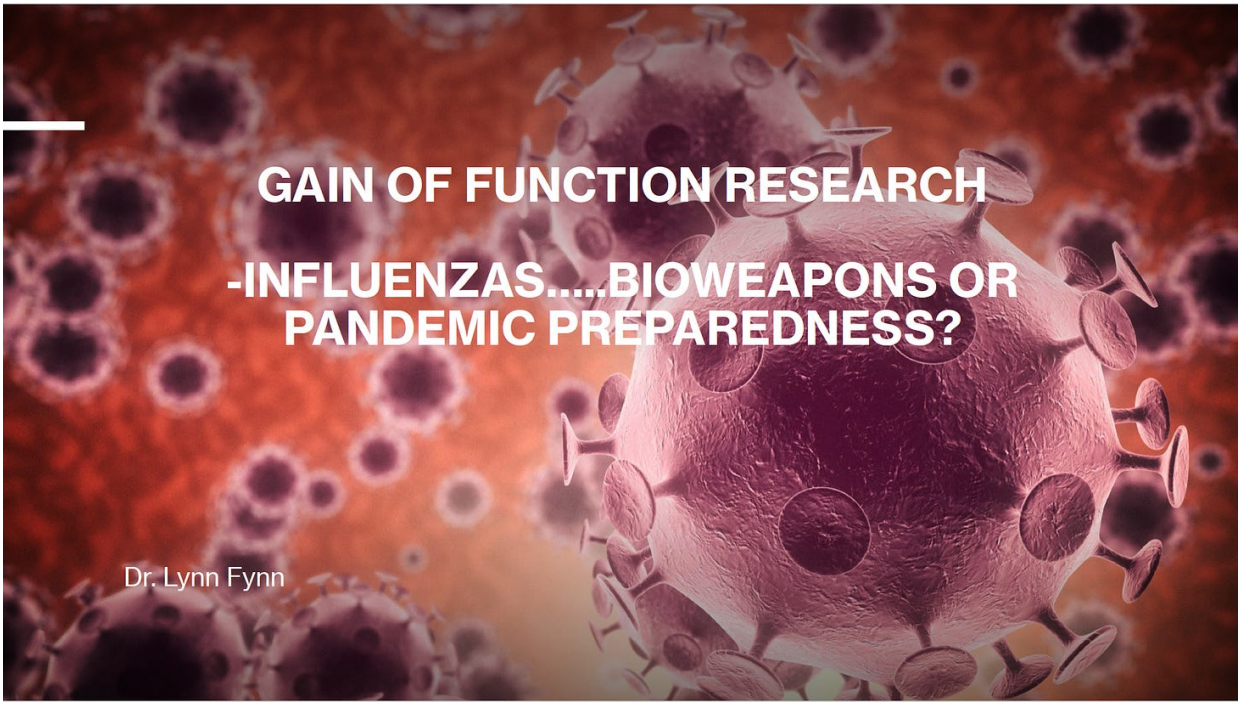
RNA or the bacterial CRISPR-associated protein-9 nuclease as an editing tool.

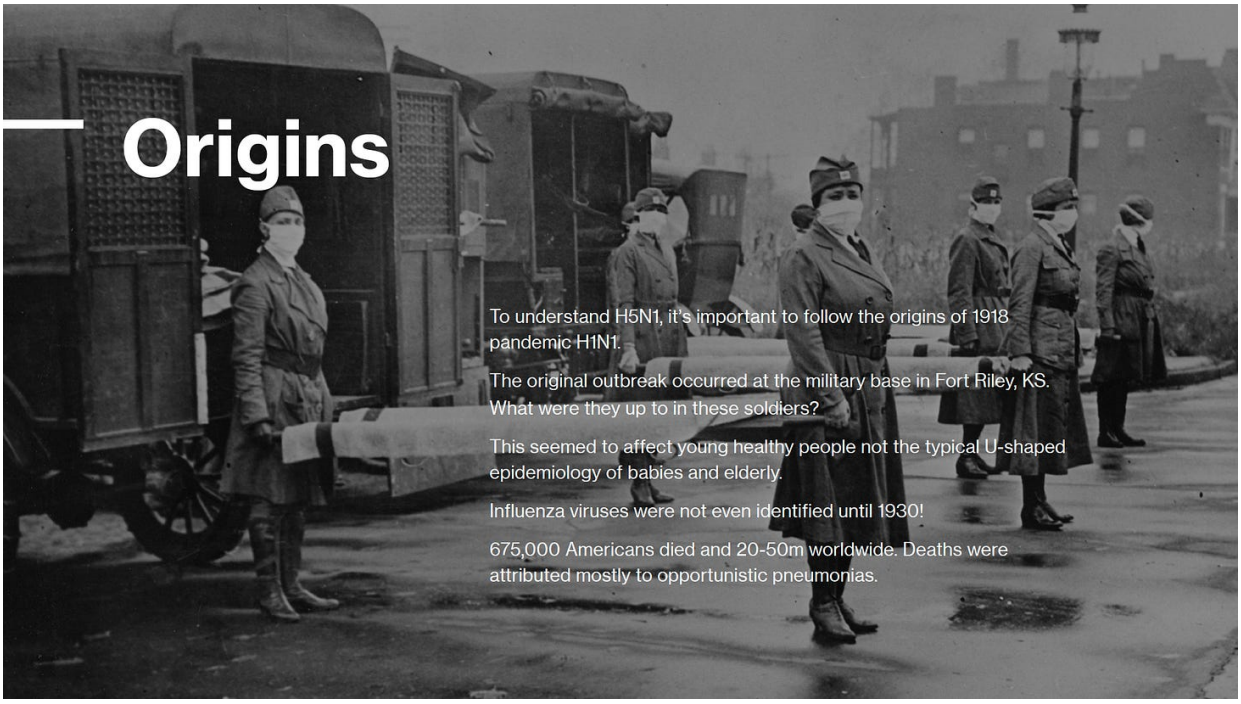
General Virology Questions and Questions Specific to Influenza, SARS, and MERS Research

- Why/how does the virus infect and kill mammals?
- What are the critical host range and virulence determinants of MERS-CoV?
- Why are some influenza strains more virulent than others?
- Do antiviral drugs work, and how does the virus become resistant?
- Can we identify antiviral drugs that are safe and effective for MERS-/SARS-CoV?
- What drives the evolution of influenza antigenic change and antiviral resistance?
- Do current or novel vaccines or monoclonal antibodies provide protection, and can the virus escape?
- Can we develop a SARS-/MERS-CoV candidate vaccine that is safe, immunogenic, and efficacious?
- Can monoclonal antibodies be used safely for prevention and treatment?
- Are there some influenza viral targets that will not allow escape from the immune system?
- How does the virus spread within animals or between animals?
- Why do some influenza strains spread efficiently while others do not?
- Could the virus cause a pandemic?
- What is the likelihood of (re)emergence?
- Will SARS or a SARS-like CoV re-emerge from bats or other animal hosts?

## A Brief History of Gain of Function Research on Influenza A Viruses

During a recent seminar and presentation at the 5/4/24 Rancho Mirage Summit, Dr. Lynn Fynn, MD (a pseudonym) presented a slide deck which briefly summarized the history of GOF research on Influenza A viruses, beginning with the H1N1 influenza virus associated with the infamous 1918 “Spanish Flu” pandemic (which was as much about bacterial pneumonia as it was about H1N1), and carrying through to the present situation with H5N1. She has kindly provided a copy of the deck and permission to republish on this substack.





# Origins

To understand H5N1, it's important to follow the origins of 1918 pandemic H1N1.

The original outbreak occurred at the military base in Fort Riley, KS. What were they up to in these soldiers?

This seemed to affect young healthy people not the typical U-shaped epidemiology of babies and elderly.

Influenza viruses were not even identified until 1930!

675,000 Americans died and 20-50m worldwide. Deaths were attributed mostly to opportunistic pneumonias.

# Virus Hunters

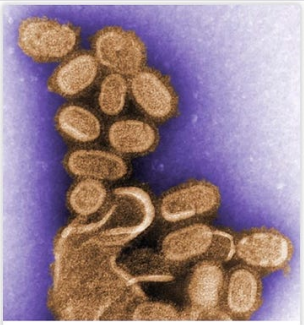
- 1951 Johan Hultin's (U of Iowa) first attempt to recover lung tissue from bodies in permafrost in Brevig Mission, Alaska, and grow viral contents in chicken eggs was unsuccessful (mouth pipetting).
- 1997 published work of partial sequencing performed on sample from a 1918 soldier at Ft. Jackson by Taubenberger who extracted RNA identifying 9 fragments
- 1997 Exumed body of large Inuit woman (Lucy) below more than 7 ft of ice preserved for 75 years.
- Shipped preserved lungs to AFIP
- 2005 entire genome was completed

**Scientists Describe How 1918 Influenza Virus Sample Was Exhumed In Alaska**

*Date:* July 4, 2007

*Source:* NIH/National Institute of Allergy and Infectious Diseases

*Summary:* In an article in the journal Antiviral Therapy, scientists at NIAID narrate the story of how scientists discovered samples of the 1918 strain in fixed autopsy tissues and in the body of a woman buried in the Alaskan permafrost. The article places this discovery in the context of decades of research into the cause of pandemic influenza, and the authors detail the strange convergence of events that allowed them to recover and sequence the virus in the first place.



## Influenza gain-of-function experiments: their role in vaccine virus recommendation and pandemic preparedness.

In 2003, scientists discussed the potential of recreating 1918 H1N1, even though it was already 6 years in the process of genomic reverse engineering. It was fully reconstructed and replicated by 2005 by Dr. Trumpey (CDC) using GOF techniques in human kidney cells.

## Raising the ghost of 1918: Could flu be the ultimate bioweapon?

*September 1, 2003*

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**Raising the ghost of 1918: Could flu be the ultimate bioweapon?**

***Skeptics doubt terror factor, but pandemic planning praised***

In an age of exploding genetic engineering, could the Spanish influenza strain of 1918 — the unholy grail of infectious diseases — be resurrected as the ultimate bioweapon?

"It would not be easy; but with advances in this technology, it gets easier every day," warns **Mohammed Madjid**, MD, lead author of a provocative new paper about the possibilities of using the flu virus as a weapon of bioterrorism.

- By 2005, The did just that. The CDC and NIAID reconstructed and replicated the pandemic virus and studied it **with** the Avian Flu virus circulating in Asia, H5N1.
- This was the first attempt to justify such risky practices with deadly pathogens.

## Scientists recreate 1918 flu virus, see parallels with H5N1

*Robert Roos, October 5, 2005*

*Topics: Avian Influenza (Bird Flu), Biosecurity Issues, Influenza, General, Pandemic Influenza*

SHARE

Oct 5, 2005 (CIDRAP News) – Scientists today reported findings that may help explain what made the 1918 pandemic influenza virus so deadly and that reveal similarities between that virus and the H5N1 avian influenza virus now circulating in Asia.

Scientists at the Centers for Disease Control and Prevention (CDC) reconstructed the virus and tested it in laboratory animals, which quickly died. The CDC says the work, to be reported in *Science*, will enhance preparedness for the next flu pandemic, a potential benefit believed to justify the risk of recreating the virus and publishing the information.

Yoshihiro Kawaoka (left) and Ron Fouchier (right) in 2012, after their work with H5N1 bird flu virus sparked a global controversy over research that can potentially make pathogens more dangerous to humans. MARTIN ENSERINK/*SCIENCE*

Science

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**Scientists Brace for Media Storm Around Controversial Flu Studies**

23 NOV 2011 · BY MARTIN ENSERINK

UNIVERSITY OF MINNESOTA

CIDRAP

**Fouchier study reveals changes enabling airborne spread of H5N1**

*Robert Roos, June 21, 2012*

*Topics: Avian Influenza (Bird Flu) , Biosecurity Issues , Bioterrorism , Dual-Use Research , Pandemic Influenza*

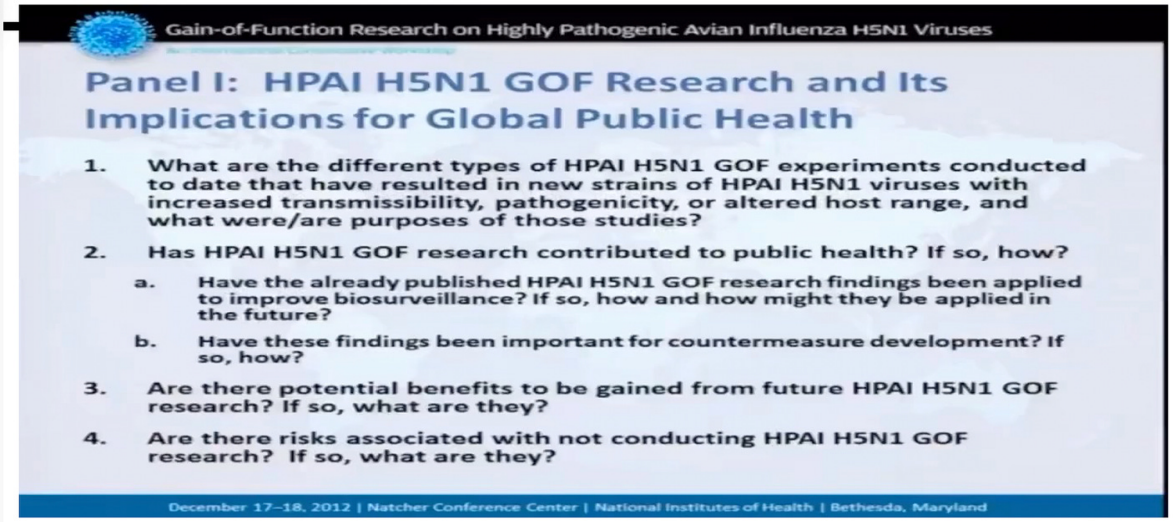
Science

**ROTTERDAM, THE NETHERLANDS**—Locked up in the bowels of the medical faculty building here and accessible to only a handful of scientists lies a man-made flu virus that could change world history if it were ever set free.

The virus is an H5N1 avian influenza strain that has been genetically altered and is now easily transmissible between ferrets, the animals that most closely mimic the human response to flu. Scientists believe it's likely that the pathogen, if it emerged in nature or were released, would trigger an influenza pandemic, quite possibly with many millions of deaths.

In a 17th floor office in the same building, virologist Ron Fouchier of Erasmus Medical Center calmly explains why his team created what he says is "probably one of the most dangerous viruses you can make"—and why he wants to publish a paper describing how they did it. Fouchier is also bracing for a media storm. After he talked to *Science*Insider yesterday, he had an appointment with an institutional press officer to chart a communication strategy.

Though there is still no record of human-to-human transmission of H5N1 bird flu. It's not for lack of trying. 2012



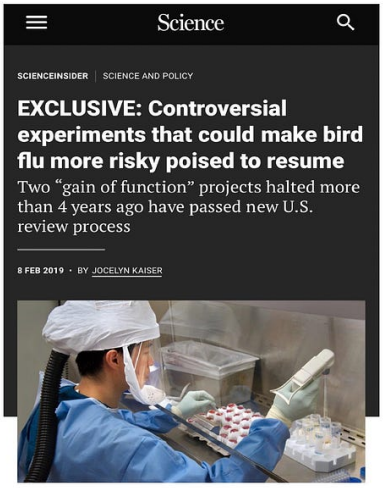

This is a video clip from the above meeting, in which Dr. Robin Robinson (then serving as the Director, HHS/ASPR/BARDA) was asked about benefits obtained from H5N1 GOF research. Notable is that his answer focused on vaccine development. The subsequently developed and currently FDA authorized H5N1 vaccine does not incorporate any sequence information derived from GOF research. I am aware of no evidence that this or any other FDA authorized vaccine, antibody or drug development benefitted from H5N1 GOF research.


Click here to watch the video

The H5N1 influenza virus research was temporarily ceased in January 2012 due to the risks involved with disseminating experimental results that could be used for nefarious purposes. All research on H5N1 transmission was halted after laboratories at the University of Wisconsin and the Dutch Eramus Medical Center in Rotterdam, Netherlands created mutant forms that could be transmitted directly among ferrets. This was concerning because viruses that are easily transmissible between ferrets are often airborne transmissible between humans. Experts argued that the benefits of this kind of H5N1 research on human health and vaccine were overhyped and not worth the risk of an accidental release that would expose the public to these mutant strains.

2012 MORATORIUM

Bioterrorism, biosafety, and regulatory issues have also been brought to light since the initiation of the year-long voluntary moratorium. Many scientists fear that the scientific details on creating a potentially dangerous virus could be used for bioterrorism. Researchers claim that the experiments have the potential to lead to public health benefits but have also exposed regulation gaps on dual-use research. The public health benefits include: influenza surveillance that catches infectious strains early, better drugs, and improved vaccines. Yoshihiro Kawaoka of the University of Wisconsin and Ron Fouchier of Erasmus University in the Netherlands, both leading H5N1 researchers, argued the fears were overblown and surpassed by the potential public health preparedness their studies may lead to.[v]



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**EXCLUSIVE: Controversial experiments that could make bird flu more risky poised to resume**

Two "gain of function" projects halted more than 4 years ago have passed new U.S. review process

8 FEB 2019 · BY JOCELYN KAISER

A worker at a Centers for Disease Control and Prevention laboratory harvests avian flu viruses for sharing with other laboratories in 2013. JAMES GATHANY/CDC

A controversial scientist who carried out provocative research on making influenza viruses more infectious has completed his most dangerous experiment to date by deliberately creating a pandemic strain of flu that can evade the human immune system.

Yoshihiro Kawaoka of the University of Wisconsin-Madison has genetically manipulated the 2009 strain of pandemic flu in order for it to "escape" the control of the immune system's neutralising antibodies, effectively making the human population defenceless against its reemergence.

By 2014, Y. Kawaoka started risky GOF on the deadly pathogen in a BSL3 lab which was met with considerable pushback.

- Yoshi Kawaoka completed GOF with H7N9 and H5N1 in which there is little to non-existent immunity.

| Characteristic | H7N9 | H5N1 |
|---|---|---|
| Pathogenicity | Low pathogenicity (LPAI) | Highly pathogenic (HPAI) |
| Total number of cases* | 660 [3] | 827 [3] |
| First case detected in humans | 2013 [3] | 1997 [3] |
| Case-fatality rate* | 39% [1] | 53·2% [3] |
| Incubation period | Median 2–7 days, range 1–10 days [5, 6] | 2–4 days (up to 8 days) [4] |
| Epidemiological risk factors | Older adults; more common in males; comorbidities: COPD, diabetes, hypertension, obesity, chronic lung and heart disease [25] | Younger adults; more common in females [12] |
| Average age of infected individuals | 54–63 years of age; cases in children, teenagers and young adults are rare [25] | 20–30 years of age [12] |
| Host tropism | Humans, chickens, pigeons, ducks, geese [10, 11] | Humans, wild migratory birds (LPAI), ducks, geese, chickens (HPAI) [7, 8] |
| Human tissue tropism | Epithelial and endothelial cells of multiple organ systems, particularly human bronchus and lung epithelial cells [10, 11] | Epithelial and endothelial cells of multiple organ systems, particularly human bronchus and lung epithelial cells [7, 8] |
| Geography of human cases | Mainland China, Imported cases in Canada, Taiwan, Malaysia, and Hong Kong [3] | Azerbaijan, Bangladesh, Cambodia, Canada, China, Djibouti, Egypt, Indonesia, Iraq, Lao People's Democratic Republic, Myanmar, Nigeria, Pakistan, Thailand, Turkey, and Vietnam [3] |
| Vaccine status | No vaccines yet; Eight candidate vaccine viruses [27] | US FDA approved vaccine in 2013 [28] |
| Treatments | Neuraminidase (NA) inhibitors [12] | Neuraminidase inhibitors [12] |
| Antiviral resistance | Most isolates sensitive to NA inhibitors (oseltamivir, zanamivir); resistance to adamantanes (amantadine and rimantadine) [12] | Most isolates sensitive to NA inhibitors (oseltamivir, zanamivir); resistance to zanamivir reported in some wild-type strains; resistance to adamantanes (amantadine and rimantadine) [12, 13] |
| Reproductive number $R_0$ | 0·08–0·39 [18, 19] | 0·1–0·4 [21] |
| Reservoir and exposure risks | Wild birds, domestic birds (poultry), poultry markets, wet markets [14] | Wild birds, domestic birds (poultry) [7, 15] |
| Human to human transmission | Low to moderate transmissibility; some family clusters reported; no sustained transmission [12, 18, 19] | Low transmissibility; limited human-to-human transmission has been reported [12, 21] |
| Population immunity | Low or non-existent [22–24] | Low or non-existent [22, 24] |

JULY 11, 2014 | 4 MIN READ

## CDC Botched Handling of Deadly Flu Virus

The third recent mistake in handling of pathogens is a "wake-up call," says Centers for Disease Control head

BY DINA FINE MARON

Health

In March researchers at the U.S. Department of Agriculture received a shipment of what they thought was a relatively harmless strain of animal flu from the U.S. Centers for Disease Control and Prevention. It was, in fact, highly pathogenic H5N1 flu virus. Months later the researchers only began to suspect something was amiss when their experiments yielded results that they didn't expect and couldn't explain. The CDC, it turns out, had sent the deadly samples inadvertently.

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## CDC explains mix-up with deadly H5N1 avian flu

Overworked researcher may have failed to pro… et

15 AU…

**Key Takeaways**

- The Intercept obtained over 5,500 pages of NIH documents, including 18 years of laboratory incident reports, detailing hundreds of accidents.
- In 2013, a University of Wisconsin lab had two accidents, a spill and a needle prick, involving modified strains of H5N1 avian influenza.
- The accidents prompted a stern reaction from NIH, as did a university plan to quarantine all exposed researchers at home. The agency threatened to end the lab's grant unless the quarantine plan was changed.

USA TODAY

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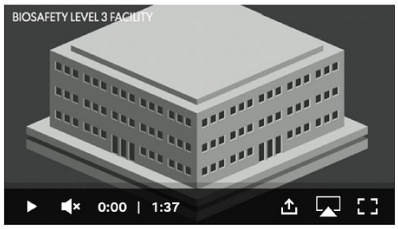
## Lab-created bird flu virus accident shows lax oversight of risky 'gain of function' research

*The story of how the H5N1 viruses came to be created – and the response to a 2019 safety breach – raises uncomfortable questions about the tremendous trust the world is placing in research labs.*




The story of how the H5N1 viruses came to be created – and how the University of Wisconsin and the Kawaoka lab would later respond to the 2019 safety breach during the ferret experiment – raises uncomfortable questions about the tremendous trust the world places in these kinds of labs.

# Current headlines H5N1

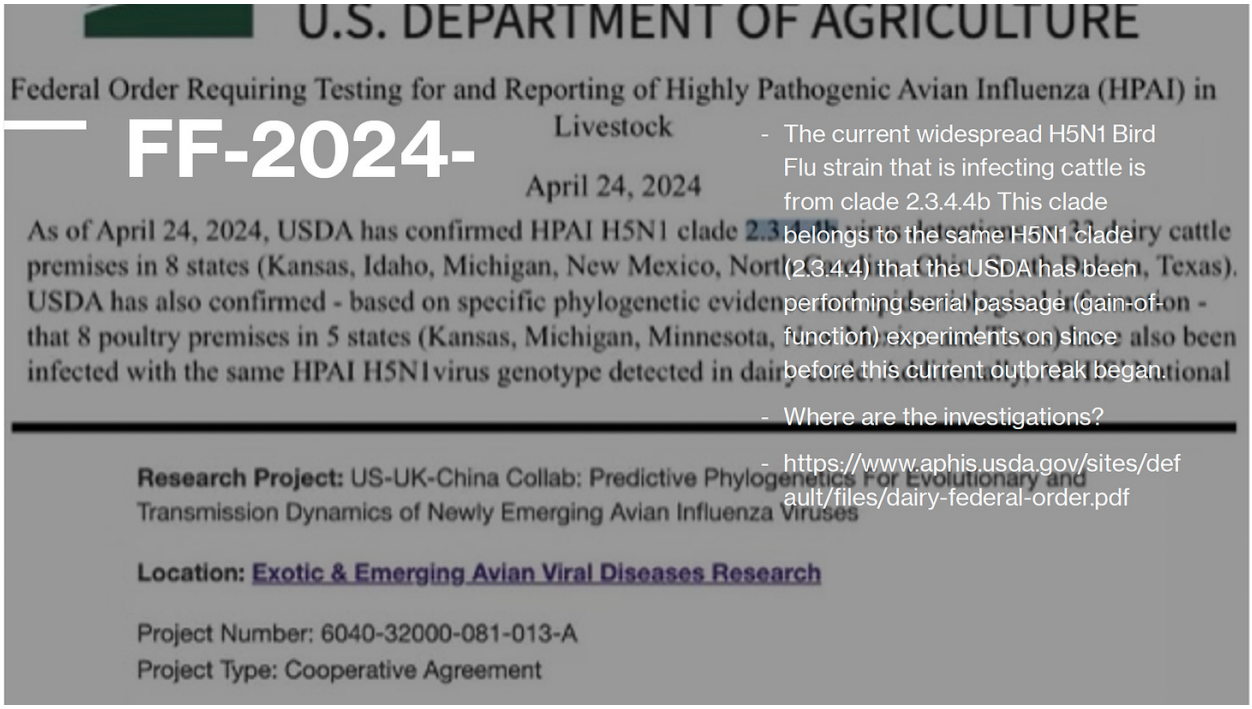
Now that COVID does not elicit as much fear, we are back to the H5N1 scare which has been discussed in headlines for years

Lactoferrin in cow's milk, along with pasteurization, enzymes in saliva and HCl in stomach prevents illness in consumer

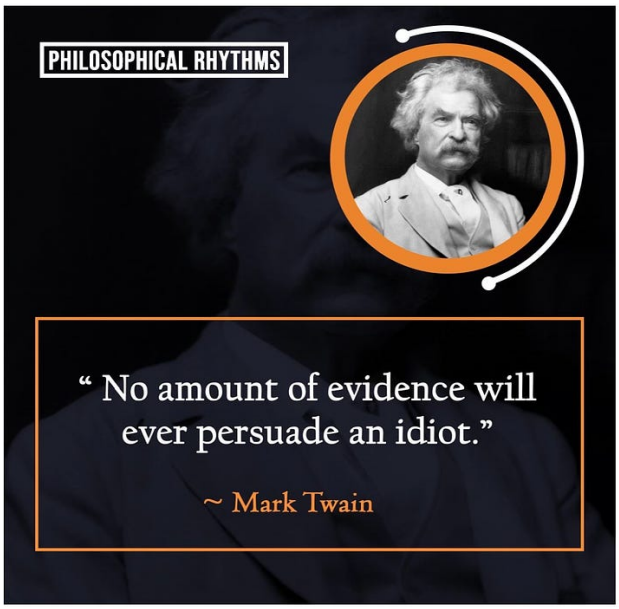
Despite allegedly billions of cases in birds and some cows, less than 900 cases of H5N1 have been recorded in humans, ever!

There has been no credible evidence of human to human transmission, despite earlier GOF serial passage to spread the virus between mammals

If H5N1 became better adapted to humans, which it is not, it would become less virulent.




- The current widespread H5N1 Bird Flu strain that is infecting cattle is from clade 2.3.4.4b This clade belongs to the same H5N1 clade (2.3.4.4) that the USDA has been performing serial passage (gain-of-function) experiments on since before this current outbreak began.
- Where are the investigations?
- https://www.aphis.usda.gov/sites/default/files/dairy-federal-order.pdf

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