Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Viruses Clinical Issues and Gaps

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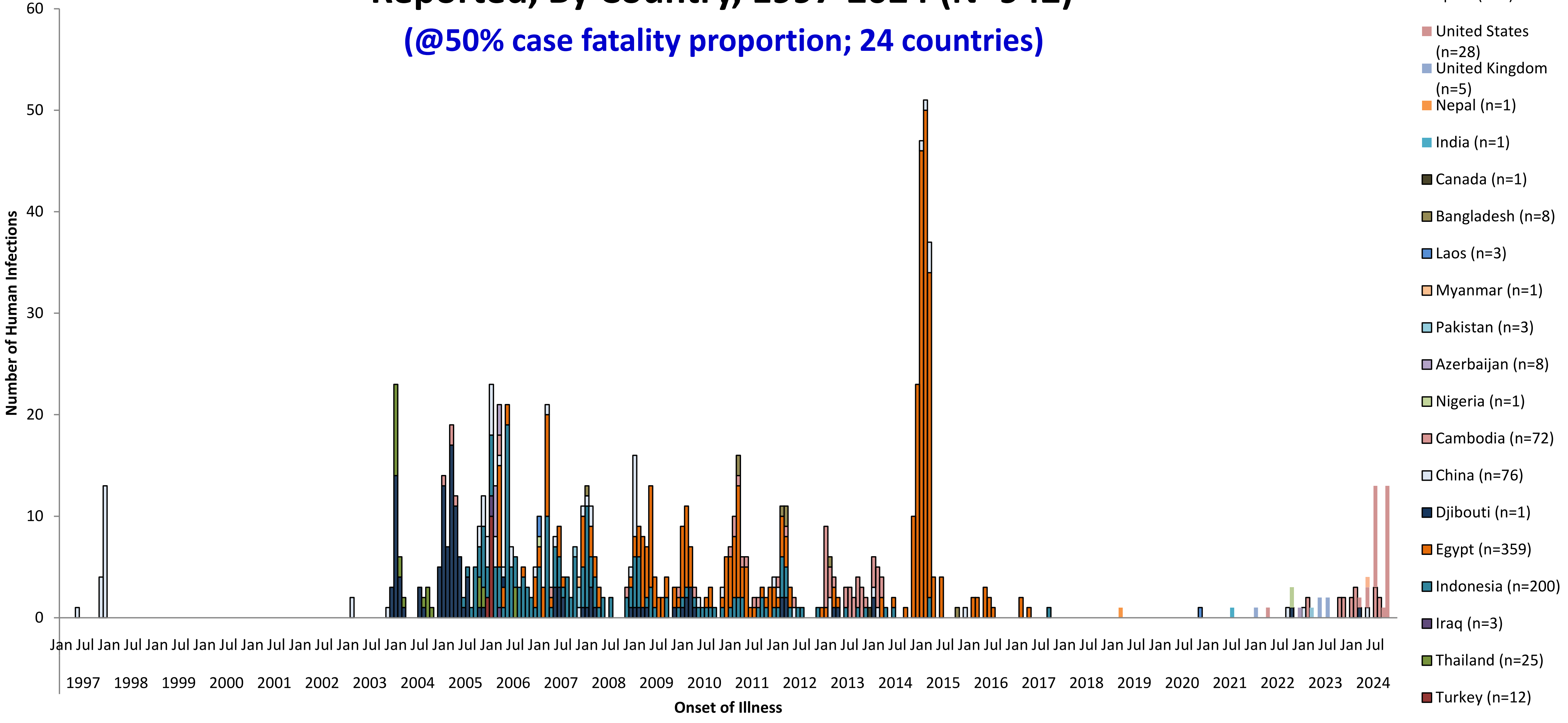
Epidemic Curve of Human Cases of A(H5N1) by Illness Onset Date or Date Reported, By Country, 1997-2024 (N=942)*

(@50% case fatality proportion; 24 countries)



*As of October 22, 2024

U.S. Cases, 2022-2024* (H5N1 clade 2.3.4.4b viruses)

- 28 Human cases (27 in 2024) (no secondary transmission identified)
  - Oseltamivir treatment given/offered; Oseltamivir PEP for close contacts
  - Associated with poultry exposures: 10
    - April 2022: 1 case reported “fatigue” while depopulating poultry
    - July 2024: 9 cases of conjunctivitis in poultry workers depopulating poultry (one state)
  - Associated with dairy cattle exposures: 17 (contact transmission)
    - 332 H5N1+ dairy cattle farms in 14 states (March-October 2024)
    - March - October 2024: 17 cases in dairy farm workers (4 states)
    - Mild illness (16 with conjunctivitis, 1 with respiratory illness)
  - Unknown source: 1
    - August 2024: 1 case in a person with no exposures to animals or sick persons
    - Moderate non-respiratory illness in a person with chronic medical conditions (hospitalized)
    - Hospitalized for 3 days, received Oseltamivir treatment; recovered


Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.

Uyeki NEJM 2024

**As of October 22, 2024; Morse NEJM 2024; Uyeki NEJM 2024; Drehoff MMWR 2024*

Severe/Critical Illness (H5N1 clade 2.3.4.4b viruses)

- **Ecuador (2022)**
  - **9-year-old girl hospitalized with pneumonia, respiratory failure, septic shock. History of exposure to backyard poultry that died (rural area)**
    - **Received Oseltamivir treatment during hospitalization, survived; no secondary transmission**
- **Chile (2023)**
  - **Middle-aged man hospitalized with pneumonia, respiratory failure (lived in coastal area with die-offs of seabirds and marine mammals)**
    - **Received Oseltamivir treatment during hospitalization, survived, no secondary transmission**
- **China (2022-2024)**
  - **1 case of mild illness, 2 cases of critical illness, 1 death**

Bruno J Travel Med 2023; Castillo J Travel Med 2023

Cambodia Cases (2023-2024) (H5N1 clade 2.3.2.1c viruses)

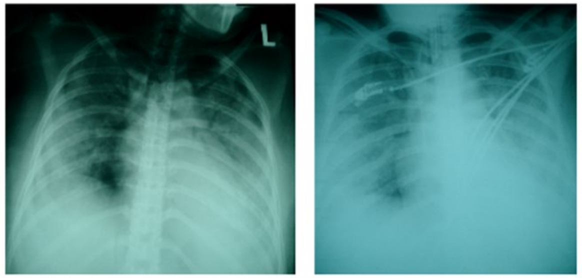
- **16 cases in rural villagers exposed to sick/dead backyard poultry**
  - **Some clinically mild cases (children, adults)**
  - **10 severe/critical illness cases, 6 deaths**
    - **Oseltamivir treatment started after H5N1 was diagnosed in hospital**
    - **Oseltamivir post-exposure prophylaxis given to close contacts (household members)**

As of October 20, 2024

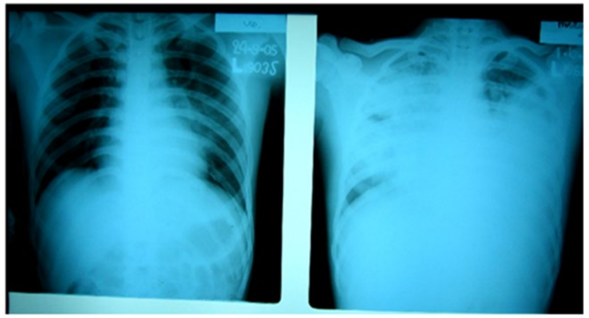
Complications of H5N1 Virus Infection

- **Pneumonia is the most common complication**
  - **Progression to respiratory failure, ARDS**
    - **Community-acquired bacterial co-infection is rare**

- **<u>Other severe complications</u>**
  - **Acute kidney injury**
  - **Cardiac failure**
  - **Sepsis, shock, DIC, multi-organ failure (respiratory and renal failure)**
  - **Atypical complications**
    - **Encephalitis** with diarrhea and pneumonia; encephalitis with obstructive hydrocephalus; meningoencephalitis with pneumonia
    - **Reye syndrome** with salicylate exposure
    - **Spontaneous miscarriage** in a pregnant woman
    - **Vertical transmission** (mother-to-fetus)



37-yo woman, illness day #7 Admission CXR | Illness day #10; died day #11



21-yo male, illness day #5 Admission CXR | Illness day #12; survived (not ventilated)

T Uyeki, CDC September 2005

Uyeki Clin Infect Dis 2009

Pathogenesis of Severe Disease

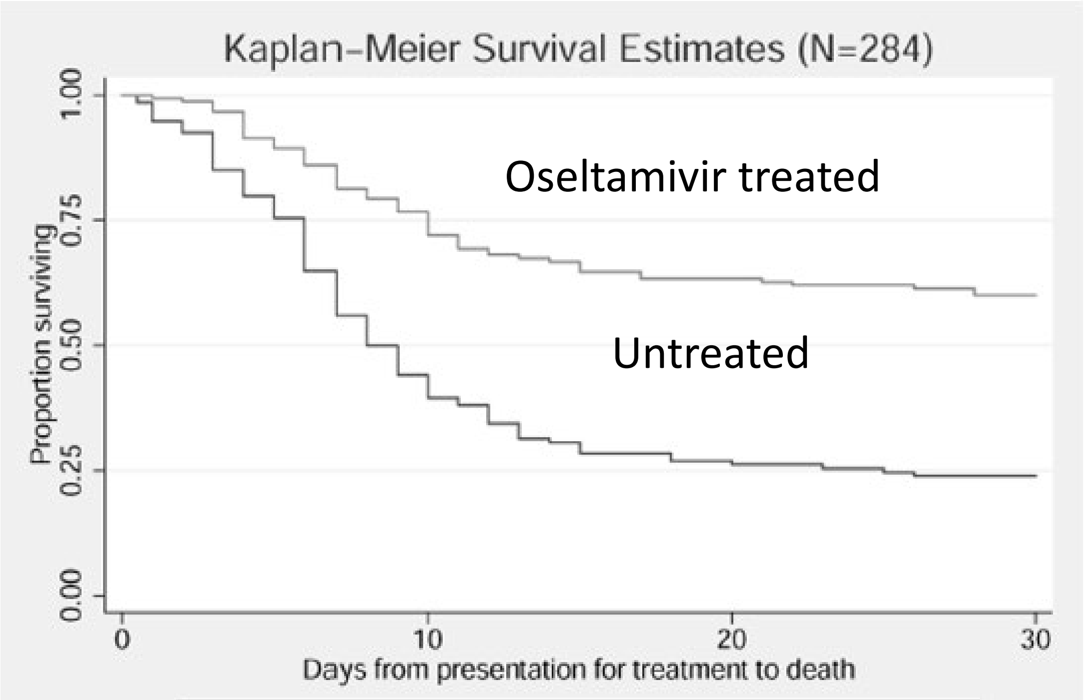
H5N1 virus infection of the respiratory tract (lower respiratory tract) → high viral levels → triggers a dysregulated host inflammatory response

- **Proinflammatory cytokines and chemokines can cause diffuse alveolar damage/acute lung injury, and multi-organ tissue injury**
- **Extrapulmonary viral dissemination can occur from viremia**
  - **H5N1 virus isolated from blood/serum/plasma, rectal swab/feces, CSF**

de Jong Nature Medicine 2006; WHO NEJM 2008

Clinical Management: Antiviral Treatment for H5N1

- **No RCTs of antivirals for H5N1 patients**
- **Limited observational data**
  - **Oseltamivir treatment versus no treatment and starting treatment early after symptom onset is associated with lower mortality**



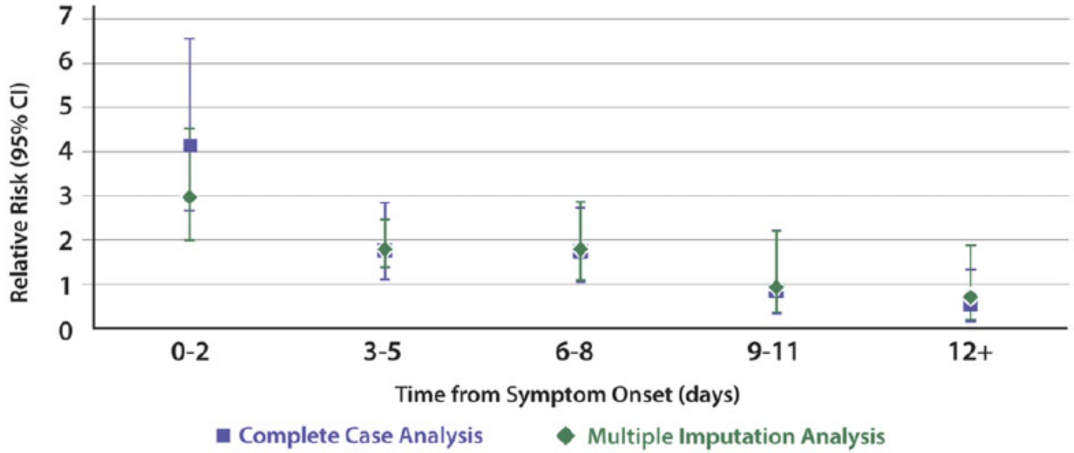


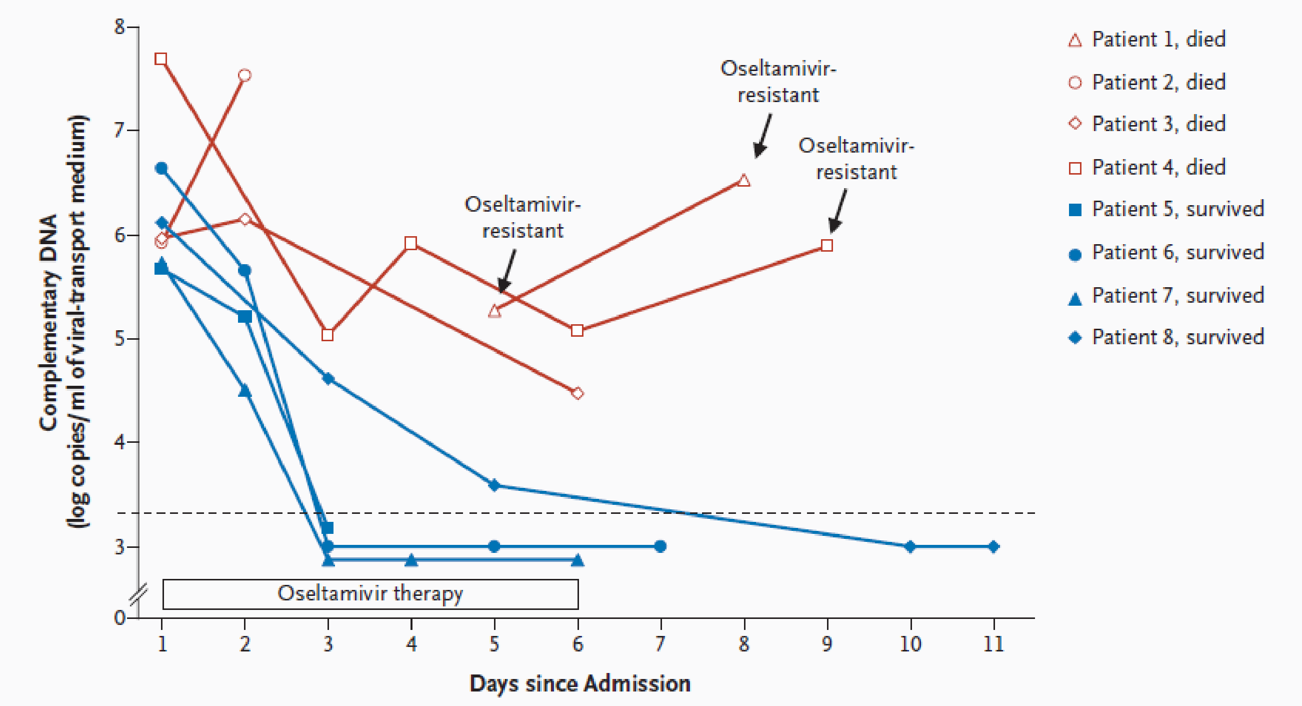
Figure 1. Comparison of relative risk of survival by timing of oseltamivir initiation between complete case and multiple imputation analysis. Squares, complete case analysis; diamonds, multiple imputation analysis. CI, confidence interval.

Adisamito J Infect Dis 2010; Adisamito J Infect Dis 2011; Kandun Lancet 2008; Liem Clin Infect Dis 2009; Yu PLoS ONE 2008

Clinical Management: Antiviral Treatment

- **H5N1 viruses infecting patients in 2024 are susceptible to Oseltamivir**
- **Start Oseltamivir treatment empirically <u>as soon as possible for suspected H5N1 virus infection</u> (based on history of exposures)**
  - **Oseltamivir standard dosing: twice daily x 5 days (*no data for Baloxavir*)**

- **<u>Lower respiratory tract disease</u>:**
  - **Optimal Oseltamivir dosing/duration unknown; longer treatment for severe disease, prolonged shedding**
  - **Emergence of oseltamivir resistance reported during or after treatment**



de Jong NEJM 2005

Clinical Management: Research Gaps

- What is the duration of H5N1 viral shedding?
- Optimal Antiviral post-exposure prophylaxis strategies?
- Optimal Antiviral treatment?
  - Optimal dosing and duration; benefit of combination treatment?
  - Role of immunotherapy?
- Optimal Adjunctive therapy
  - Clinical benefit of low-dose/moderate-dose corticosteroids?
  - Clinical benefit of other immunomodulators (e.g., IL-6 receptor blockers, JAK inhibitors)?
- Optimal Supportive care
  - Optimal advanced organ support; who can benefit most from ECMO?
- Prognostic biomarkers?

Clinical Management: Research Gaps

- **H5N1 (global research)**
  - **Standardized clinical data collection for cases (observational studies)**
  - **Serial clinical specimen collection and testing**
  - **Integrated analyses of epidemiologic/clinical/laboratory data**
- **Seasonal Influenza (need sustained funding commitment)**
  - **Need to optimize early diagnosis and early initiation of antiviral treatment**
  - **Need to develop national clinical research infrastructure capacity to improve clinical management of seasonal influenza patients (before the next pandemic)**
    - **Clinical trials of interventions (therapeutics, supportive care strategies) for patients with severe seasonal influenza**
      - **Platforms: adaptive clinical trials; prospective observational studies**
      - **Can also be an integrated clinical research platform for respiratory virus infections of public health importance (e.g., RSV, SARS-CoV-2, influenza viruses)**

H5N1 Avian Influenza Research Priorities

clinical care, preparedness and response

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EMORY UNIVERSITY

The Hope Clinic

Emory Vaccine Center

EMORY UNIVERSITY SCHOOL OF MEDICINE

“Covid was not influenza and H5N1 is not COVID”

Identification

Testing is critical and needs to be rapid accurate and accessible for case identification

- Need for testing in healthcare facilities rather than public health labs (the recent FDA ruling on LDTs is an additional impediment to getting this done)
- Testing must quickly be deployed to hospitals and clinics
- Point of care testing can enable rapid treatment

Research priorities include:

- Who to screen and test, and how extensively, should this be dependent on epidemiology and individual risk factors?
- What is the best test to use in clinical testing?
- Can rapid testing impact clinical care?

Isolation

Isolation precautions are designed to achieve containment, as that is the phase of the outbreak we are in. PPE shortages could occur if we have a larger outbreak

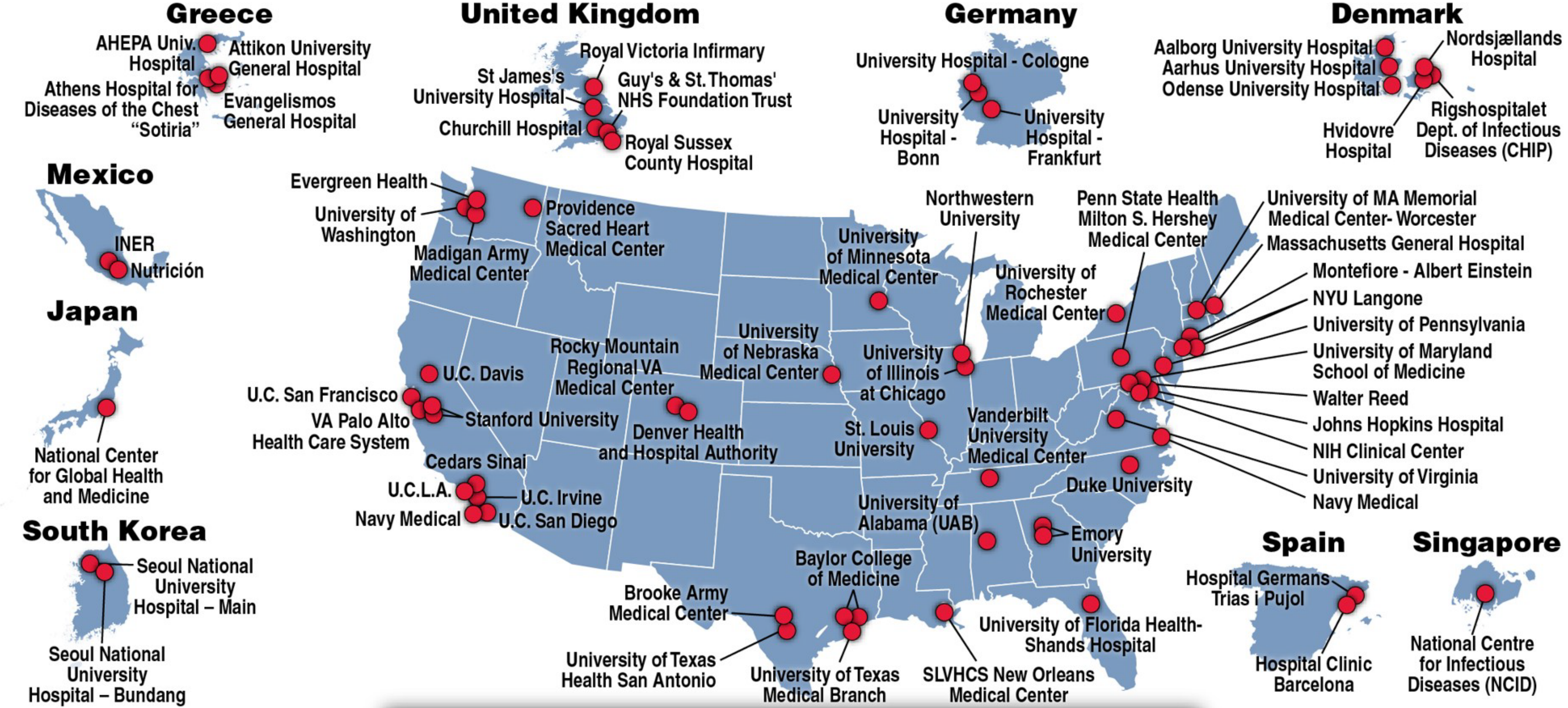
Research priorities include:

We need a better understanding of how PPE functions in a variety of settings	We need to really understand airborne transmission of influenza better and to really understand what constitutes aerosol generation procedures in health care and probably in the milking parlor as well	High temperatures outside of healthcare have made compliant use of some PPE especially face masks challenging, what is the right PPE that people will use and be comfortable and protected

Clinical management

- **Its hard to change clinical practice.**
- Antivirals need to be started soon after symptom onset which means distribution and supply chain are critical.
- Oseltamivir is recommended for both treatment and PEP. Shortages could occur if we have a larger outbreak. We don’t know the optimal dose.
- Our existing antivirals are effective but only moderately so.
- Steroids do not improve outcomes for seasonal flu but the were important in COVID.
- Children were left out of clinical research for Covid-19, which was not catastrophic because the burden on children was not as great.
- There will be a need to develop clinical guidelines.
- **Research questions include:**
  - Novel ways to dispense testing and antivirals such as telemedicine and alternate delivery modes such as the use of drones.
  - We will need an effective rapid clinical trial response as we did for CoVPN to evaluate newer agents (antivirals and monoclonals) as well as combination therapy.
  - Role of steroids and other therapies targeting the host response
  - Be sure to include children and pregnant women in clinical trials

NIAID Adaptive Randomized, Controlled Treatment Trial for COVID-19



1,062 enrollees at trial close, 4/19/2020

AS Fauci/NIAID

Vaccination

Lessons learned from covid can be reused to scale up vaccination if that becomes necessary

Prototype H5N1 vaccines exist, however, egg-based production cannot provide enough vaccine in a timely fashion

Research priorities include:

- Need data on effective vaccines that can be produced quickly – cell-culture based, recombinant and hopefully mRNA.

- Need production capacity for these vaccines

- Need to understand the neutralizing effect of the currently available vaccines against the circulating virus

- We need better vaccines

Communication

Communications should make clear that recommendations and policies can and will change.

Research priorities include:

We need effective research, evaluation and communication around non-pharmaceutical interventions	Communication is key, but to improve, we need to deploy real time research on communication strategies, effective ways to combat misinformation and to understand what channels work, particularly for marginalized communities

Equity, equity, equity....

There were tragedies and successes in reaching at risk communities during COVID. We can use that experience to do better.

Mass General Brigham

Reality, Barriers, and Gaps: Infection Prevention and Control for Novel Influenza

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23 October 2024

Roadmap

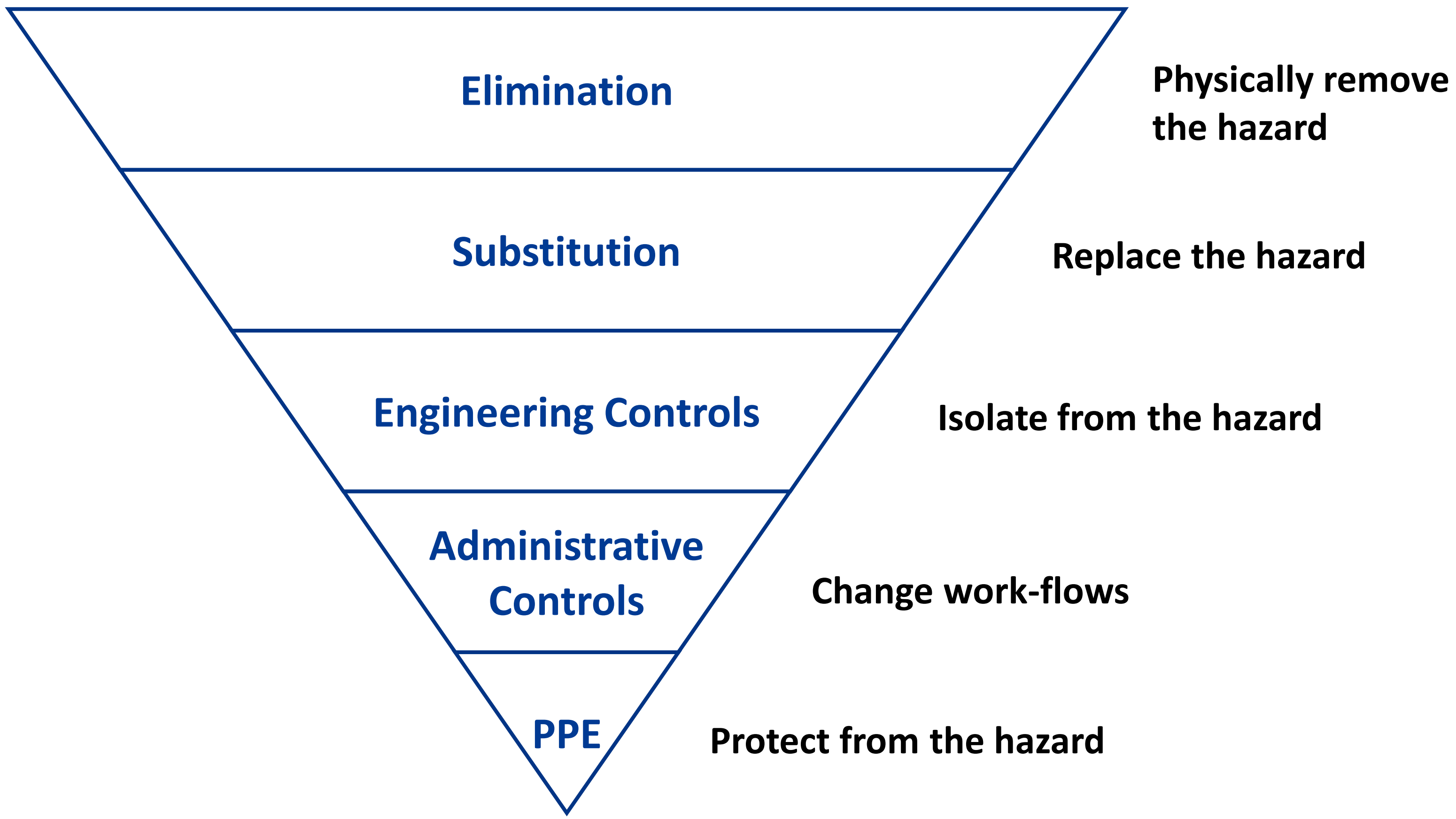
- Background on IPC approaches and impact
- Current state reality and barriers
- Research gaps

Acronyms:
IPC: Infection Prevention and Control
HCP: healthcare personnel
PPE: Personal Protective Equipment
AIIR: Airborne Infection Isolation Room (“Negative Pressure” room)

Background on IPC and a Framework for Hazard Reduction

- Infection Prevention and Control (IPC) uses evidence-based strategies to reduce the risk of transmission of infection in healthcare settings

- For an emerging infection, we will need to apply principles and available evidence related to modes of transmission, severity of illness, availability of medical countermeasures, and other factors to approach to management of patients, healthcare personnel (HCP), and visitors



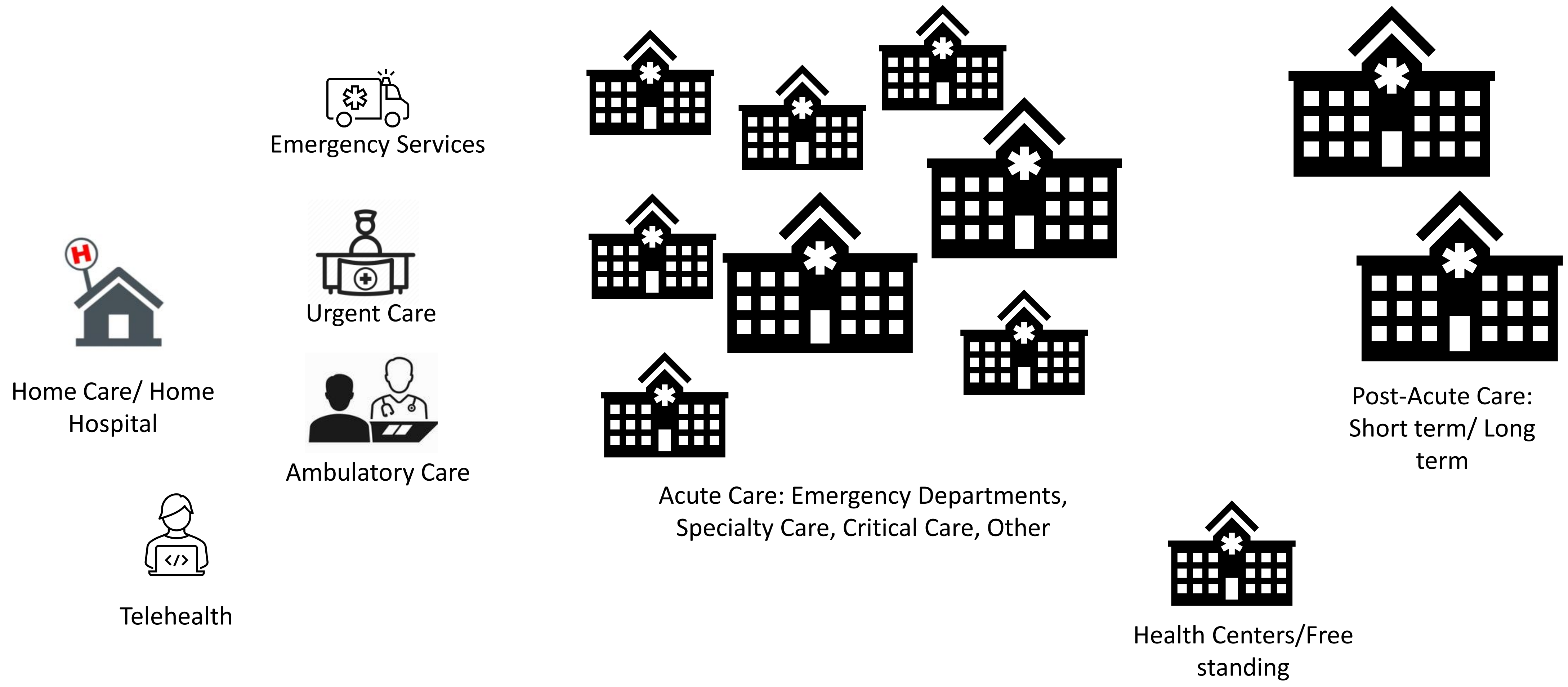
https://www.cdc.gov/niosh/topics/hierarchy/default.html

When an infection emerges/re-emerges

- Early in the emergence of a pathogen with potential for human impact and person-to-person spread, HCP will be unfamiliar with risk factors, presentation, as well as testing strategies, isolation, PPE, clinical evaluation and management, and de-isolation
  - New information will need to be assimilated by a healthcare workforce that is experiencing unprecedented burn out
  - Minimizing cognitive burden is essential to patient and HCP safety
  - Testing availability will be key to inform IPC

- IPC choices and strategies will have major impacts on quality of care and healthcare facility operations
  - Bed capacity and patient throughput
  - Supply chain (lab, PPE, cleaning and disinfection products…)
  - Workforce capacity and resiliency
  - Data/surveillance integrity
  - Collateral impact on healthcare associated infections, patient safety

IPC Needs Span **All** Healthcare Settings | Patients and Healthcare Personnel **Move** Between Settings



We need IPC on-ramps ***and*** off-ramps…

- Our IPC approaches to emerging infections need to be implemented, and de-implemented when appropriate
- Periodic reassessment of risk : benefit of approaches is necessary
- De-implementation can be bumpy
  - Ex: universal masking in healthcare settings

Shenoy ES, Babcock HM, Brust KB, Calderwood MS, Doron S, Malani AN, Wright SB, Branch-Elliman W. Universal Masking in Health Care Settings: A Pandemic Strategy Whose Time Has Come and Gone, For Now. Ann Intern Med. 2023 Jun;176(6):859-861. doi: 10.7326/M23-0793. Epub 2023 Apr 18. PMID: 37068281; PMCID: PMC10111407.

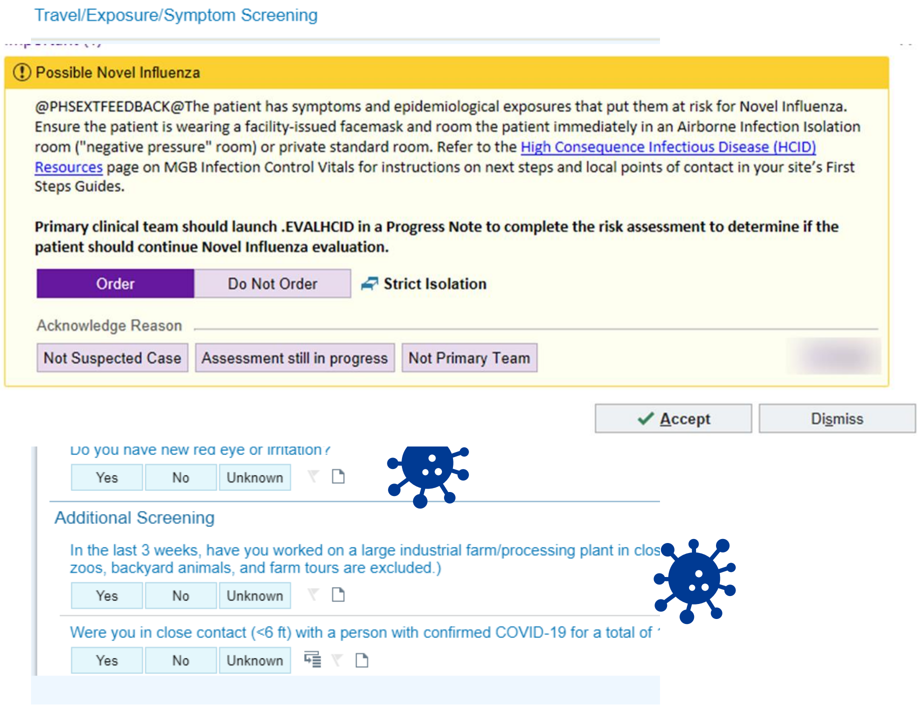
Current State Reality and Barriers

Current State (1): How will HCP **identify** patients at risk for novel influenza in order to **isolate** and evaluate?

- Current novel influenza exposure risks are specific and geographic
  - How should screening for risks be incorporated into healthcare facility triage, keeping in mind current workforce challenges, resiliency, likelihood of changing case definitions?

- If wider distribution of human cases and then human-human/community spread, specific exposure risks become less helpful in assessment, and triage will be based mostly on symptoms

- Changing definitions and protocols will overwhelm HCP and make triage less efficient



Current State (2): Where will patients be **evaluated** and what **PPE** will be used?

Seasonal Influenza

- **Patient Placement**
  - Standard patient room
  - Cohorting with confirmed type (Flu A with Flu A)
- **HCP PPE**
  - Mask
  - +/- eye protection
- **Patient PPE**
  - Mask outside room

SARS-CoV-2

- **Patient Placement**
  - Standard patient room
  - Cohorting permitted once confirmed infection
- **HCP PPE**
  - N95
  - Eye protection
  - Gowns and gloves- CDC recs; some jurisdictions have stopped
- **Patient PPE**
  - Mask outside room

Novel Influenza

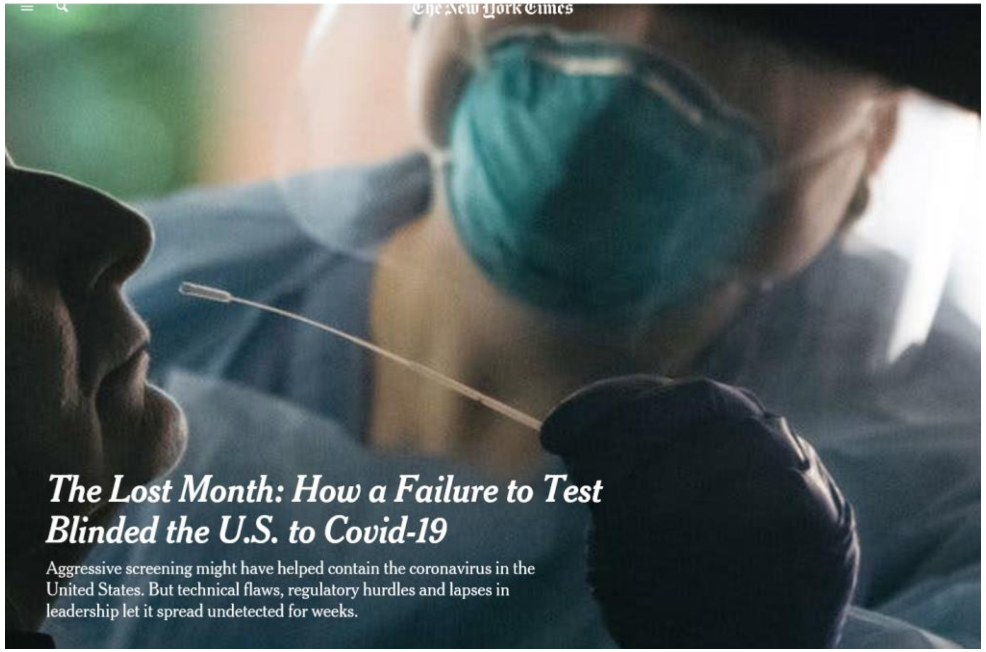
- **Patient Placement**
  - AIIR
  - No Cohorting
- **HCP PPE**
  - N95 respirator
  - Eye protection
  - Gowns
  - Gloves
- **Patient PPE**
  - Mask outside room

Current State (3): How will patients be **tested** so we can determine isolation, de-isolation, treatment, and more?

- **Laborious process** for *both* HCP and public health colleagues
  - Request approval for testing (hours)
  - Collect specimens (hours)
  - Fill out paper forms (why?)
  - Ship specimens (hours)
  - Await result (days)
  - Results interface delays

- Patient **remains isolated** during that time, treatment delayed, other impacts

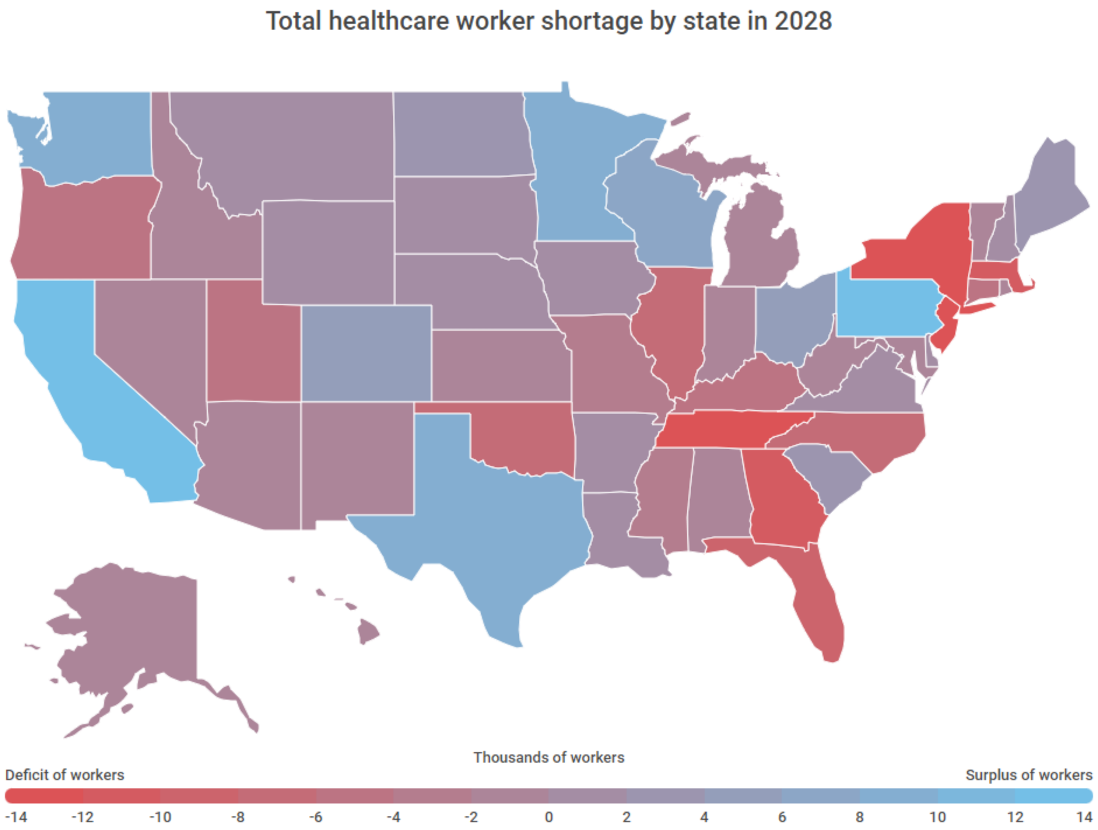
- This will be a major bottleneck that we can anticipate, now, and it **won't just last a month**.



Current State (4): How will HCP with exposure, symptoms, infection be **managed**?

- Public health requirements
  - monitoring potentially exposed
  - restriction from work for unprotected exposure
  - Testing, prophylaxis and treatment

- Impact on workforce staffing, healthcare capacity to deliver care and HCP well-being can be anticipated, now



[Interim Guidance for Infection Control Within Healthcare Settings When Caring for Confirmed Cases, Probable Cases, and Cases Under Investigation for Infection with Novel Influenza A Viruses Associated with Severe Disease | Bird Flu | CDC]; [https://www.advisory.com/daily-briefing/2024/09/09/workforce-shortage]

Research Gaps

Questions we need answers to

- IPC Fundamentals
  - Transmission
  - PPE
  - Engineering controls

- Data and Informatics
  - Data collection, maintenance, and release
  - Informatics solutions to support patient evaluation

- Workforce Resiliency, Communication, and De-implementation
  - Supporting workforce resiliency
  - Communicating change and maintaining trust
  - Metrics guiding de-implementation

IPC Research Needs (1): IPC Fundamentals

Transmission

- What is the **major mode** of transmission?
- What are the **incubation**, **infectious**, and **exposure** periods?
- How does **type** of exposure impact risk of infection?

PPE

- Should **masks or respirators** be utilized to prevent infection?
- Does transmission and infection occur through **contact**?
- If there is relevant **supply chain disruption**, what are optimal strategies to ensure continuity of operations and patient care? (not specific to H5N1)

Engineering Controls

- Are **AIIRs indicated** for all patients, specific patients, specific procedures, or not at all?
- Are there **other engineering controls** that should be implemented to reduce risk of infection?

IPC Research Needs (2): Data and Informatics

Data Collection, Maintenance, and Release

- How can we reduce surveillance, reporting, and other data flow **burdens** on healthcare facilities and HCP while **optimizing** use of data to inform policy at facility, state, and national level?

Clinical Decision Support

- How can we leverage electronic decision support to **reduce cognitive burden** on clinicians and support up to date evaluations (including isolation, PPE, testing, de-isolation)?

Healthcare Workforce Decision Support

- How can we deploy workforce decision support to assist with **communicating** changing public health guidance?

IPC Research Needs (3): Workforce Resiliency, Communication, and De-implementation

Workforce Resiliency

- How can the healthcare workforce be educated and supported to **respond effectively** to emerging infections?

Communication

- How can changes in policy and recommendation be **communicated in a transparent, accessible manner**?

De-implementation

- What **metrics** will be used to guide **de-implementation** of interventions?

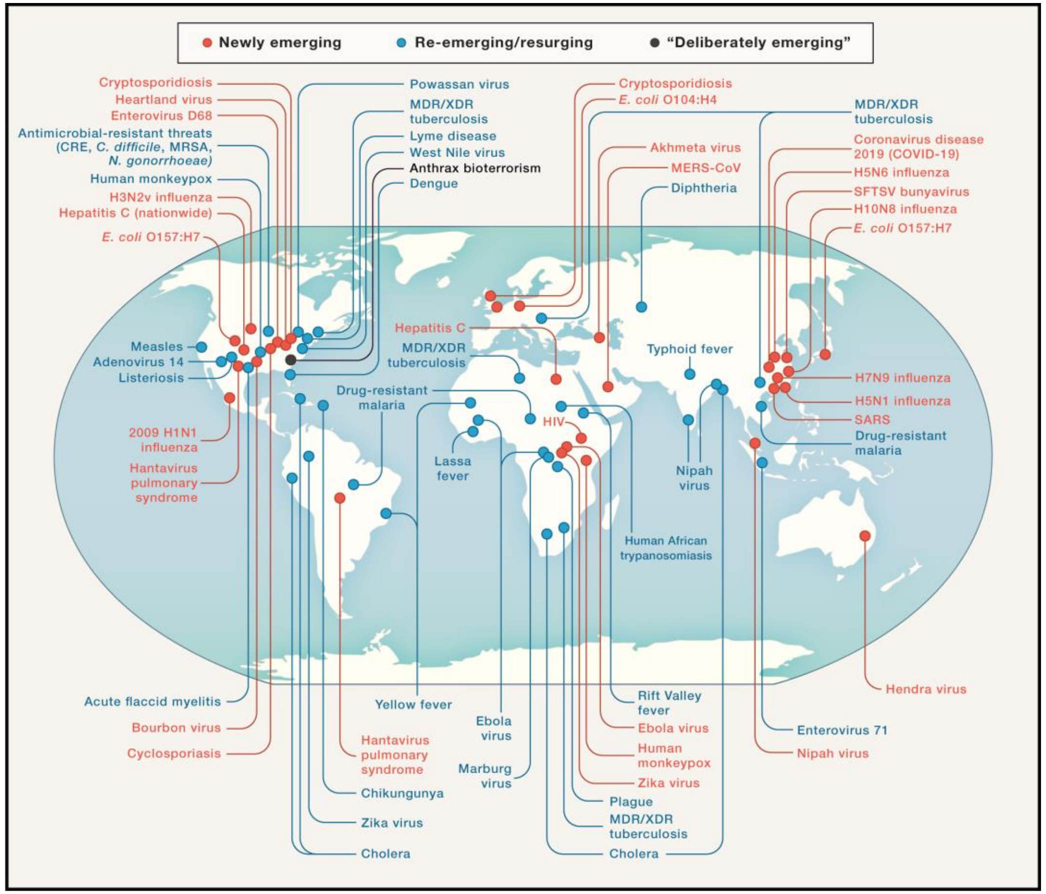
Here and *Now*

1. Prioritize **testing** availability in healthcare settings

2. Establish protocols for conducting **real world studies** on transmission, use of PPE, engineering controls

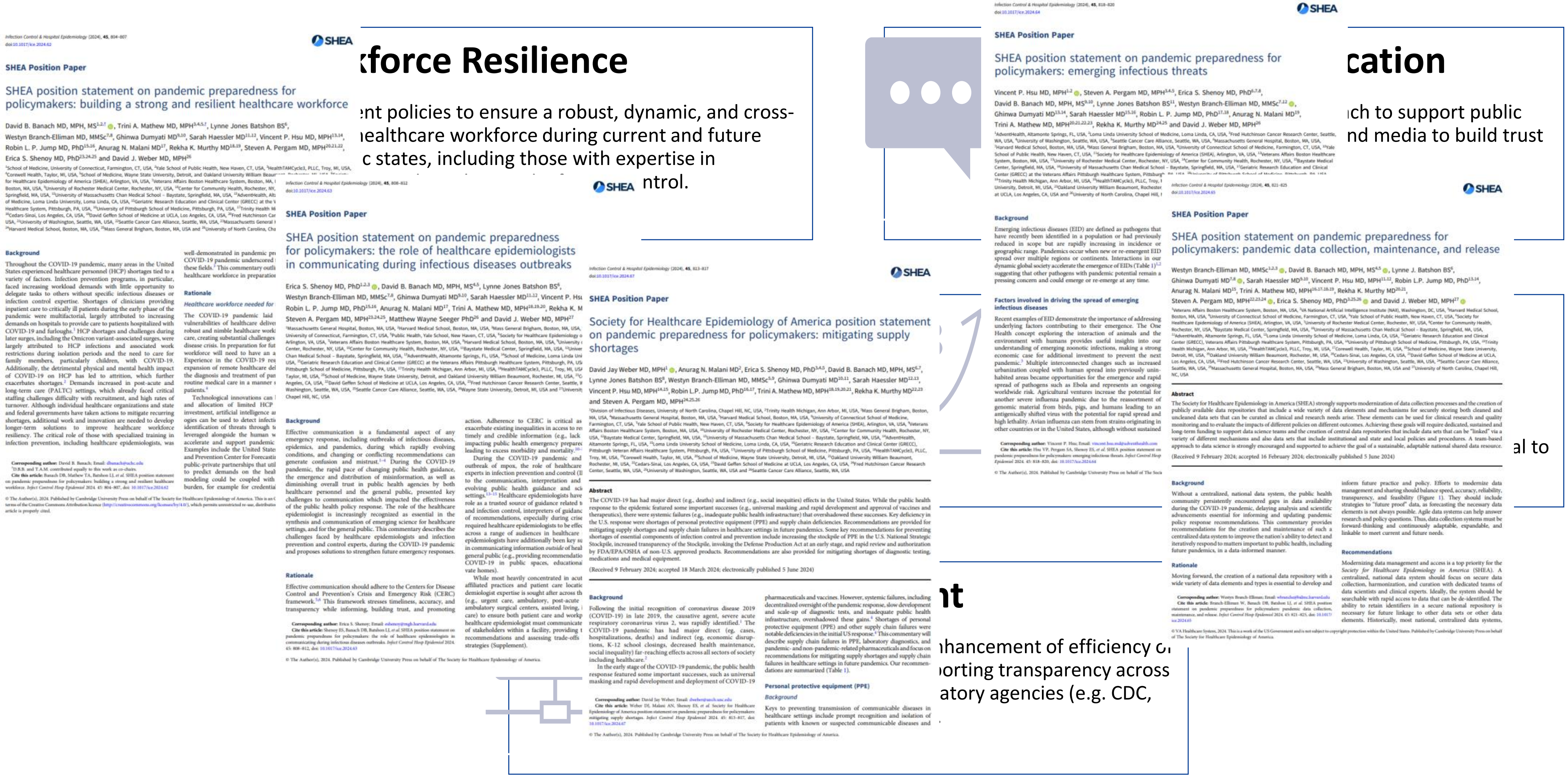
3. Invest in **data infrastructure and ways to leverage informatics** to guide patient evaluation and workforce decision making

4. Incorporate workforce **resiliency**, **communication** from IPC experts, **de-implementation** into planning



Morens DM, Fauci AS. Emerging Pandemic Diseases: How We Got to COVID-19. Cell. 2020 Sep 3;182(5):1077-1092. doi: 10.1016/j.cell.2020.08.021. Epub 2020 Aug 15.
Erratum in: Cell. 2020 Oct 29;183(3):837. doi: 10.1016/j.cell.2020.10.022. PMID: 32846157; PMCID: PMC7428724.

Resources



SHEA position statements on pandemic preparedness for policymakers. Infect Control Hosp Epidemiol. 2024 Jul.

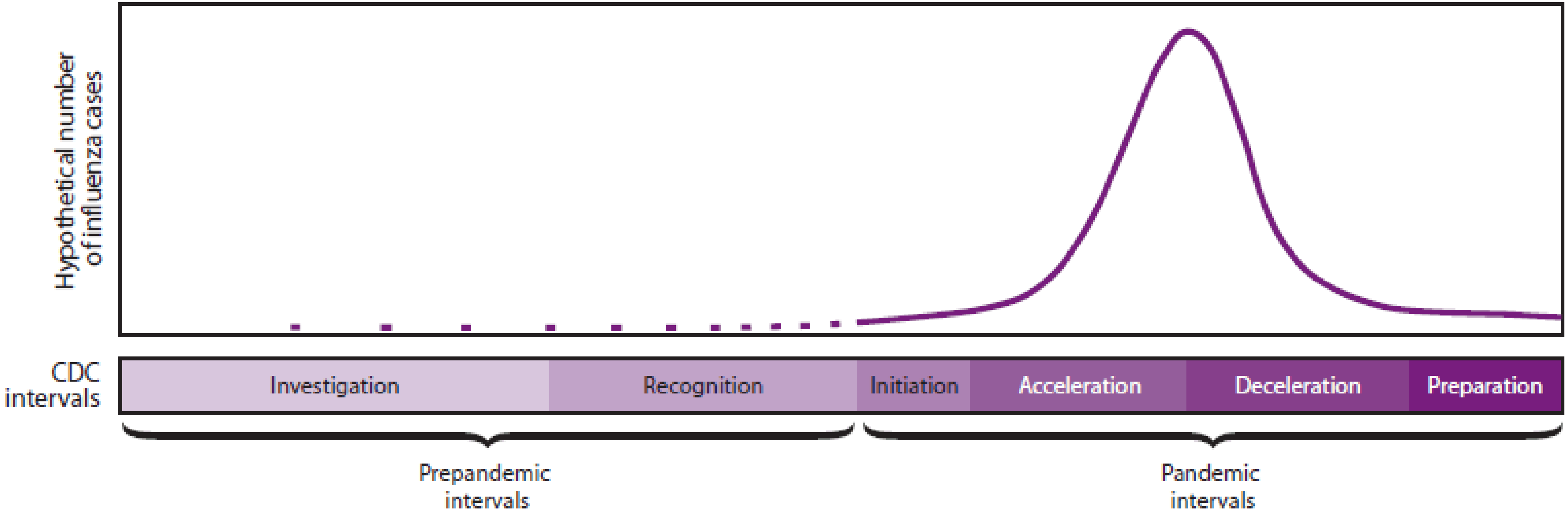
Thank you

Mass General Brigham

Potential Research Priorities to Inform Readiness and Response to Highly Pathogenic Avian Influenza A (H5N1)

Clinical Care, Preparedness and Response

Preparedness and response framework for novel influenza A virus pandemics: CDC intervals



Influenza A (H5) subtyping by PCR available in 90 public health laboratories

Existing Influenza A assays will detect the circulating H5N1 virus

CDC has 16 licensing agreements with 14 companies to use their basic assay design

CDC awarded IDIQ contract to 5 laboratories to support surge testing with specific workorders in place for Influenza A (H5)

USG is working with manufacturers to develop Influenza A(H5) specific tests (lab based and POC)

FDA has granted enforcement discretion for laboratory developed tests (LDTs) for Highly Pathogenic Avian Influenza (HPAI)

CDC is working with pharmacy networks on a pilot program to provide free testing of symptomatic persons in California and one other state

Develop high throughput Influenza A (H5) assays on random access platforms

Explore alternatives to RT-PCR to improve sensitivity in specimens with low virus copies

Assess performance of existing point of care tests with this virus and develop H5 specific POC tests with that technology

Assess pandemic intervals and develop evidence-based triggers for expanding diagnostic capacity

Identify approaches to improve access to testing in public health laboratories and at CDC including cost analysis for implementation

Assess performance of antigen tests with conjunctival swabs and assure material is available for test verification

Leveraging Networks for H5N1 Research Preparedness

Lauren M. Sauer
Director
Special Pathogens Research Network

National Emerging Special Pathogens Training and Education Center

Big Picture

Where are we?

Research Response Challenges

NETEC

- New animal population and limited access to farms/animals and personnel for sampling
- Work environment
- PPE challenges
  - Temperature
  - Education/Training
  - Uptake
- Wild/farmed animal interface
- Workforce overlap
- Upcoming respiratory virus season
- Farm/Fair Season

2 attractions pulled from Iowa State Fair due to avian influenza concerns

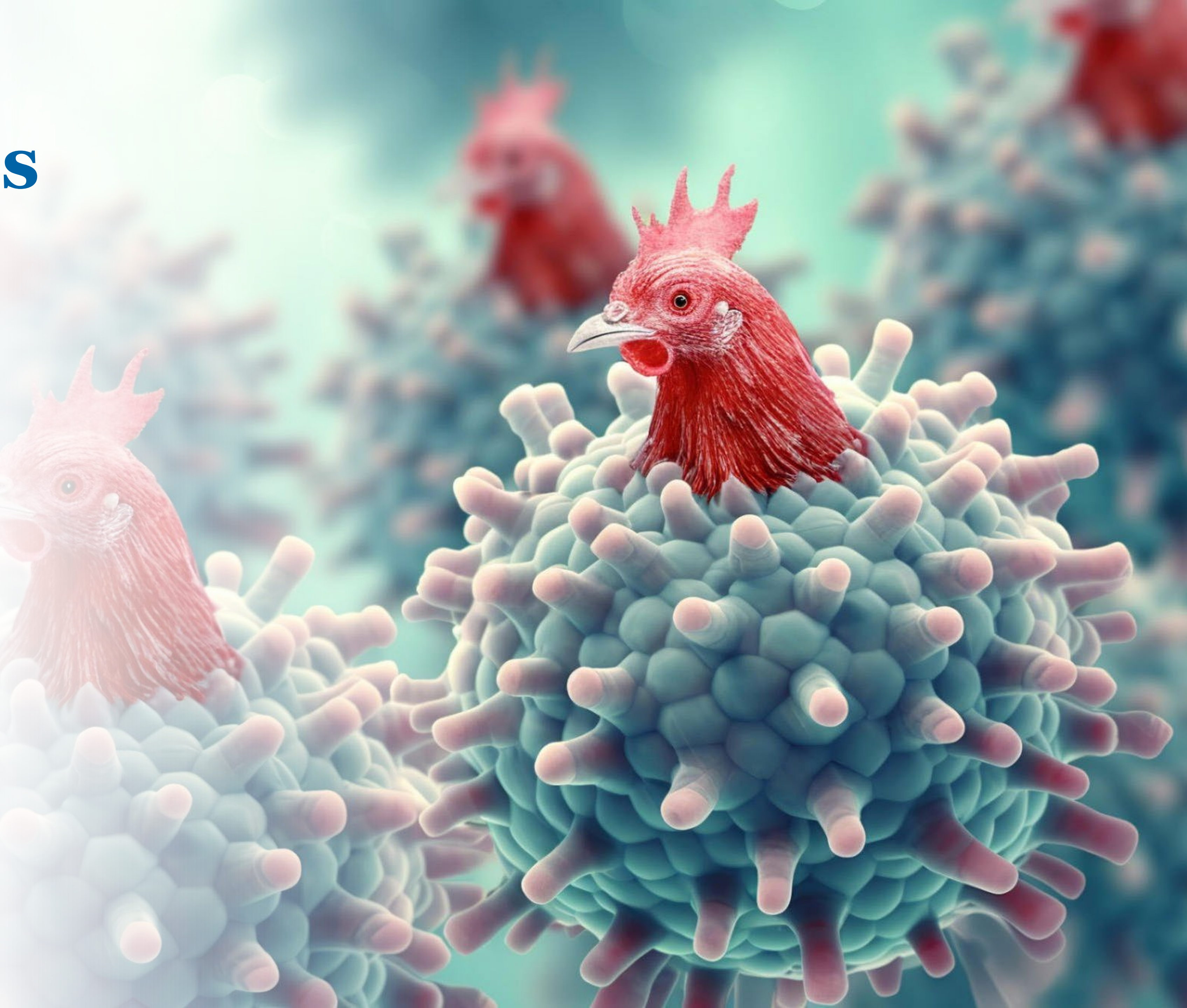
Story by Griffin Wright • 1h • 2 min read

Health Topics mentioned in this article

+4 Q&A : Bird Flu +110 Q&A : Flu

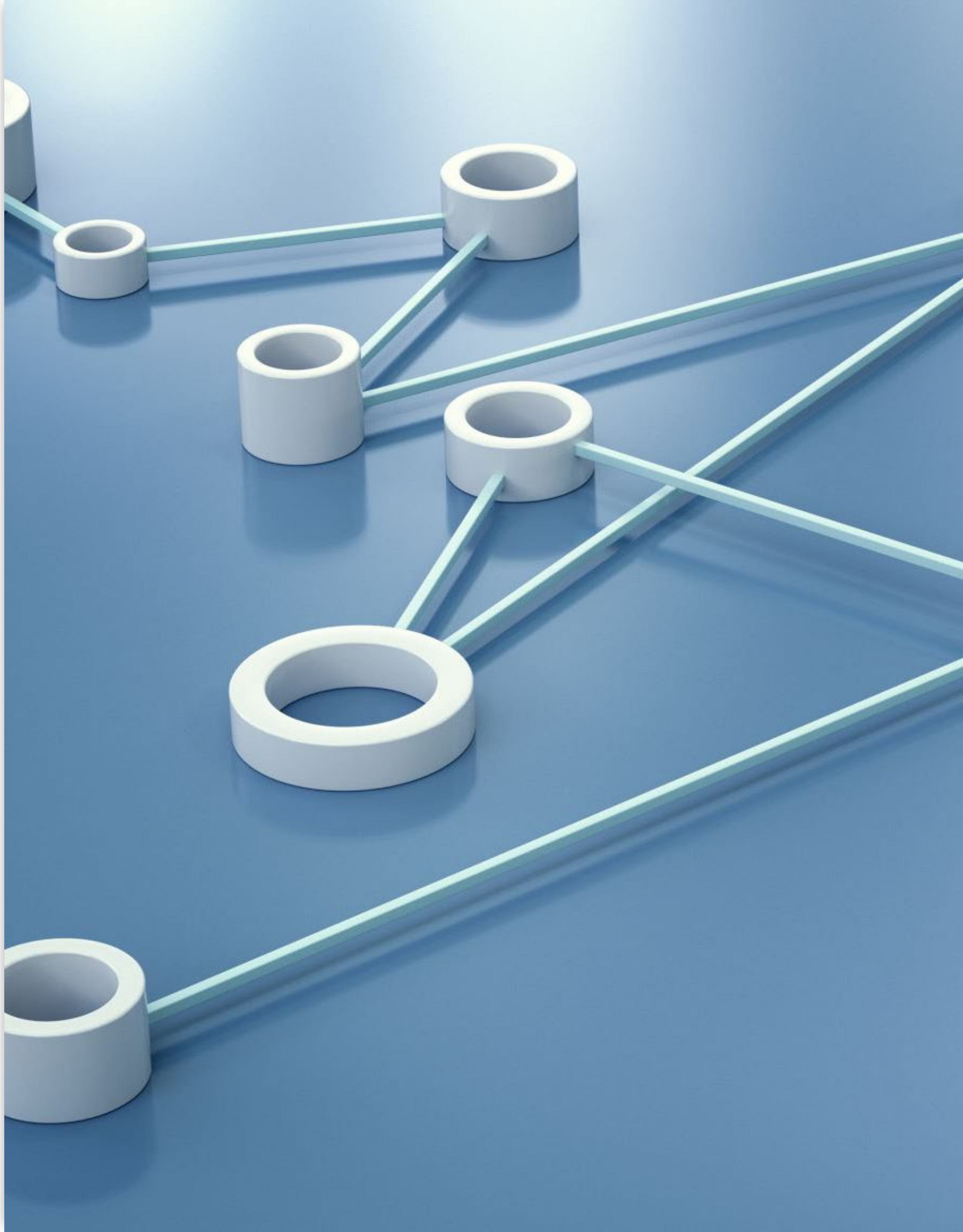
Research Gaps

- Surveillance and Early Detection
  - Wildlife Surveillance
  - Human Surveillance
  - Environmental Monitoring
- Viral Evolution and Genetic Mutations
- Longitudinal Immunologic Studies
- Human Cases and Transmission
  - Spillover
  - H2H Transmission
- Medical Countermeasures
- Community-Based and RCCE Research



How can Research Networks Help?

- Leveraging existing resources and access to participants
- Ensuring study designs are scientifically sound and ethical
- Supporting access to research through existing trusted relationships
- Pivoting resources for rapid implementation
- Creating cross-network connections for research at scale



Clinical Research Network Opportunities

NETEC

- Prepositioning Research Frameworks
  - Establish community-based frameworks that allow for the quick mobilization of essential workers into H5N1 studies.
  - Opportunities for use of pre-approved study protocols and rapid-response teams that can be activated when a case presents
- Co-Designing Studies
  - Involve community leaders and essential workers in the design of H5N1 research studies, ensuring the studies reflect their needs and priorities.
  - Can increase participation rates and improve data collection.
- Decentralized Systems
  - Develop streamlined, community-based enrollment systems that connect research networks with at-risk workers through their employers, local clinics, or community groups
  - Reduces complexity , increases efficiency and access

The Need for Community Engagement

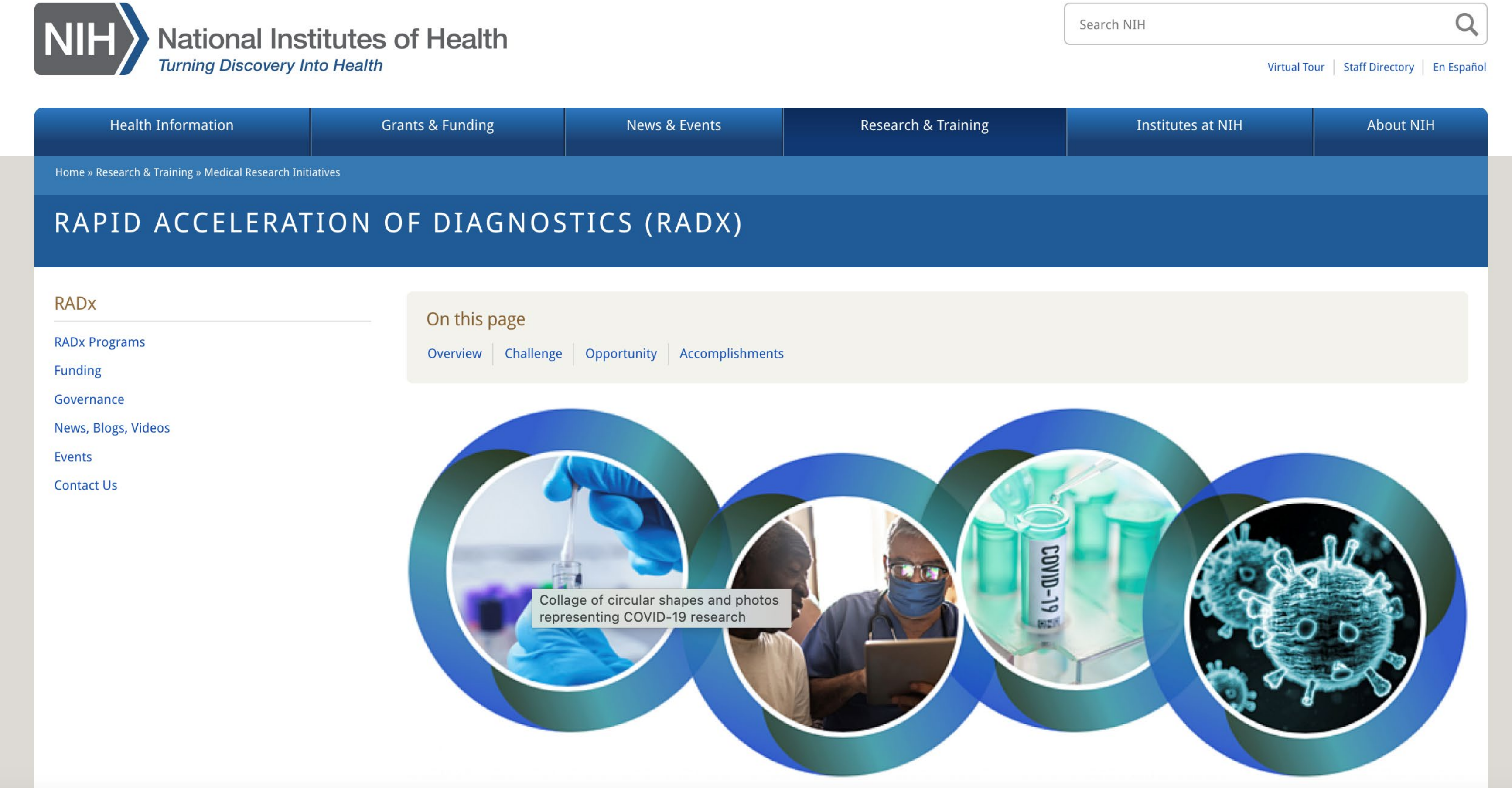
- Use of Local Infrastructure
- Community Health Worker Partnerships
- Co-creation of Research Protocols
- Addressing Misinformation and Building Trust
- Feedback and Reciprocity
- Use of Local Infrastructure

Community Networks as Gateways to Essential Workers

NETEC

- Building Trust
  - Can help bridge the gap between clinical researchers and the population by addressing concerns, misconceptions, and hesitations.
  - Critical in high-risk populations like essential workers, who may be cautious about participating in research.
- Increasing Accessibility
  - Create research participation opportunities and access to research in communities where essential workers live and work
  - Reduce barriers such as transportation, time constraints, and resource access.

Community Network Impact



Thank you!