Influenza 2005: The Laboratory's Role in Pandemic Preparedness & Response

Pete A. Shult, Ph.D.
Director,
Communicable Disease Division
& Emergency Laboratory Response
shult@mail.slh.wisc.edu

Carol Kirk
Laboratory Network Coordinator
cjk@mail.slh.wisc.edu

Wisconsin State Laboratory of Hygiene

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Agenda

- Overview of Influenza Antigenic Characteristics
- Overview of Laboratory Diagnostic Methods
- Surveillance for New Strains of Influenza Viruses
- Current Pandemic Concerns
- Pandemic Preparedness Activities
- The Laboratory's Role in Pandemic Preparedness & Response

Influenza: Resources

- **CDC home page for influenza**
  http://www.cdc.gov/flu
  http://www.cdc.gov/flu/weekly/fluactivity.htm
- U.S. web site for pandemic flu & U.S. Pandemic Flu Plan and Preparedness Planning
  http://pandemicflu.gov/
- W.H.O. home page for influenza (including avian influenza)
  http://www.who.int/csr/disease/influenza/en/

Influenza: Resources

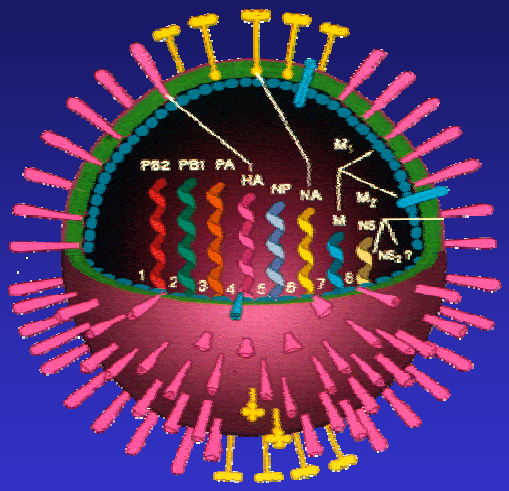
- Promed (Program for Monitoring Emerging Diseases, International Society for Infectious)
  http://www.promedmail.org
- U.S. Food & Drug Administration (FDA)
  - "Cautions in Using Rapid Flu Tests"
    http://www.fda.gov/cdrh/oivd/tips/rapidflu.html
- Review of Performance Characteristics of Rapid Tests:
  Uyeki TM. *Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza.* Pediatr Infect Dis J 2003; 22:164-77.

Influenza: Safety

- *Public Health Guidance for Community-Level Preparedness and Response to Severe Acute respiratory Syndrome (SARS)*,Version 2.3; July 20 2004
  http://www.cdc.gov/ncidod/sars/guidance
- *Biosafety in Microbiological and Biomedical Laboratories (BMBL), 4th ed*
  http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm

Overview of Influenza Antigenic Characteristics

Influenza – The Virus



Family: Orthomyxoviridae

Genera: 3 Influenzavirus Types

- **A & B** & C
- Type B influenza viruses only infect humans.
- Type A influenza viruses infect humans & birds & other mammals.

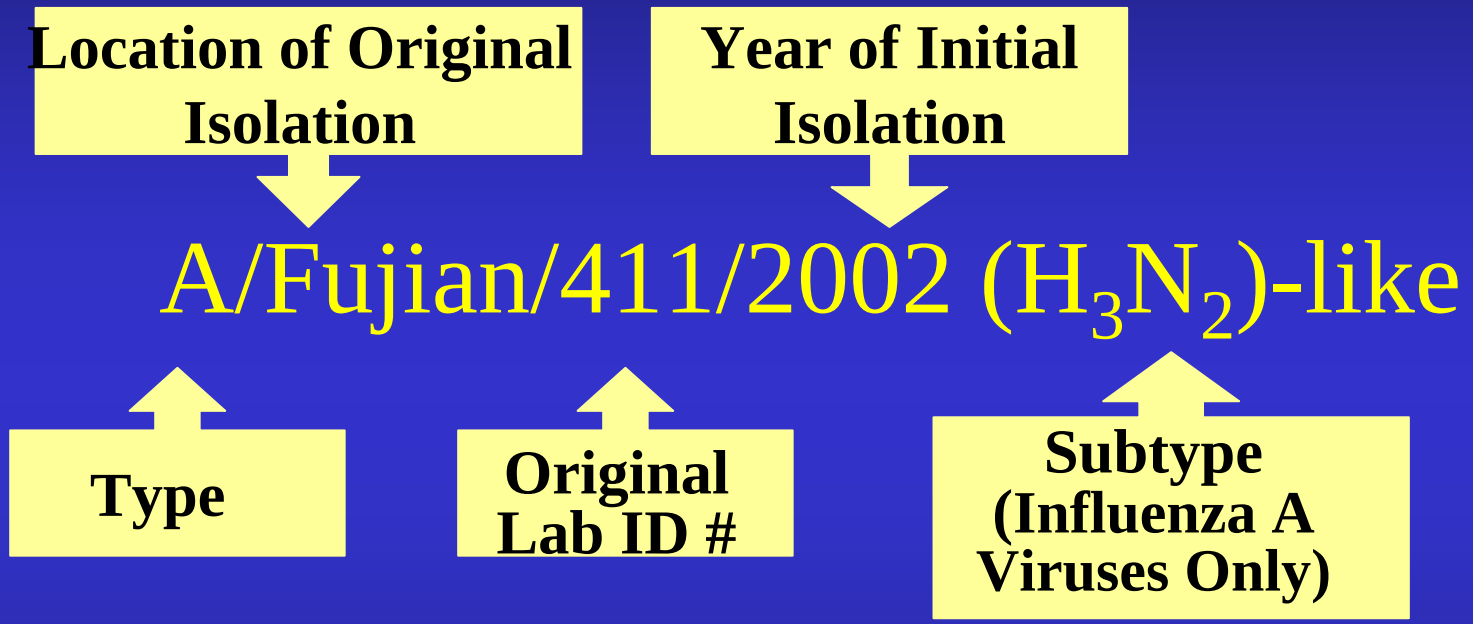
Influenza A Subtypes:

Human - **H_1N_1, H_3N_2, H_1N_2,** H_2N_2

Birds - H_1 to H_{16}, N_1 to N_9

Bird →Human - H_5N_1, H_9N_2 , H_7N_7, H_7N_2, H_7N_3

Influenza: Nomenclature



Strains: A/California/7/2004 (H_3N_2)-like

(2005-6) A/New Caledonia/20/99 (H_1N_1)-like

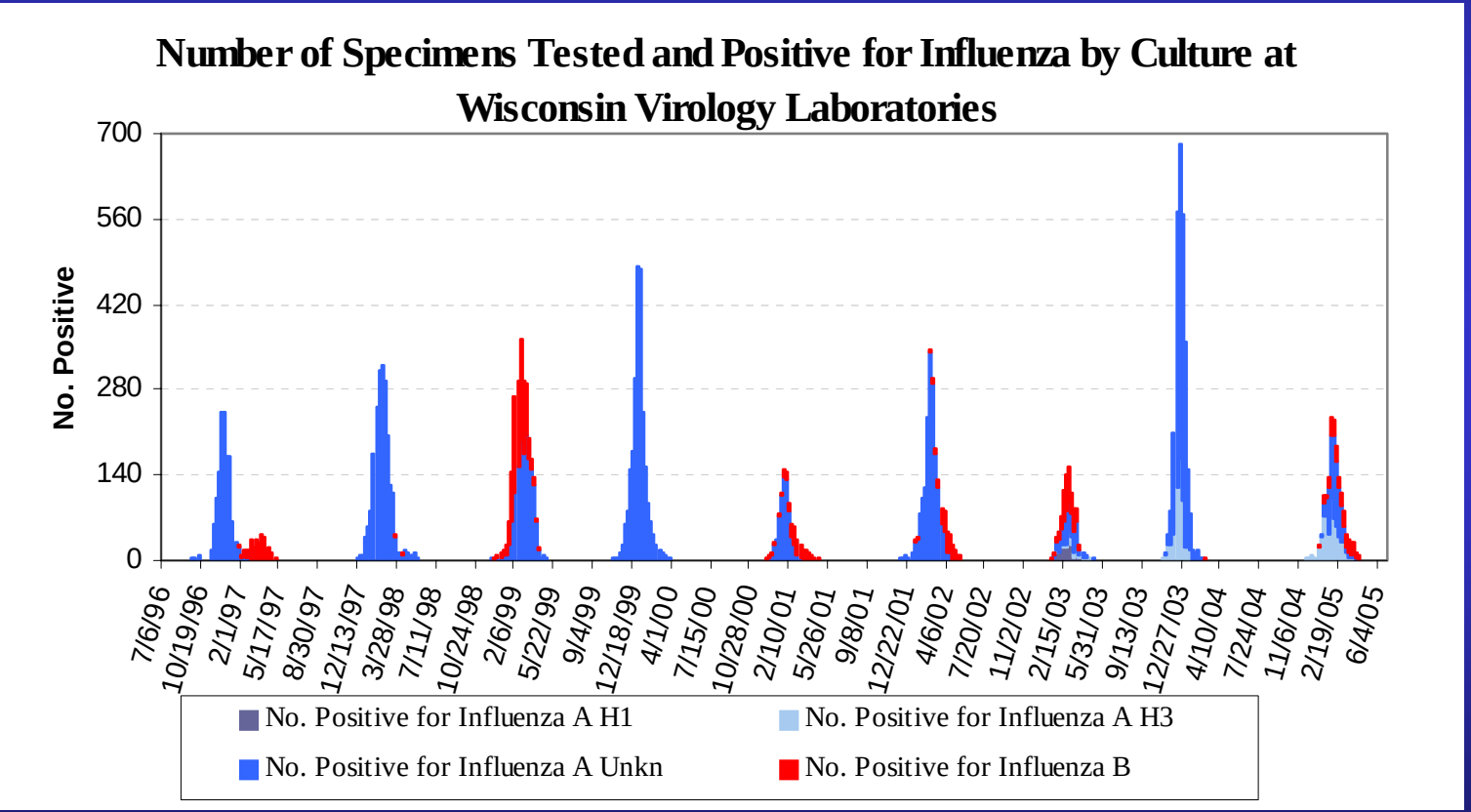
B/Shanghai/361/2002-like

Influenza
Antigenic Change- A Hallmark

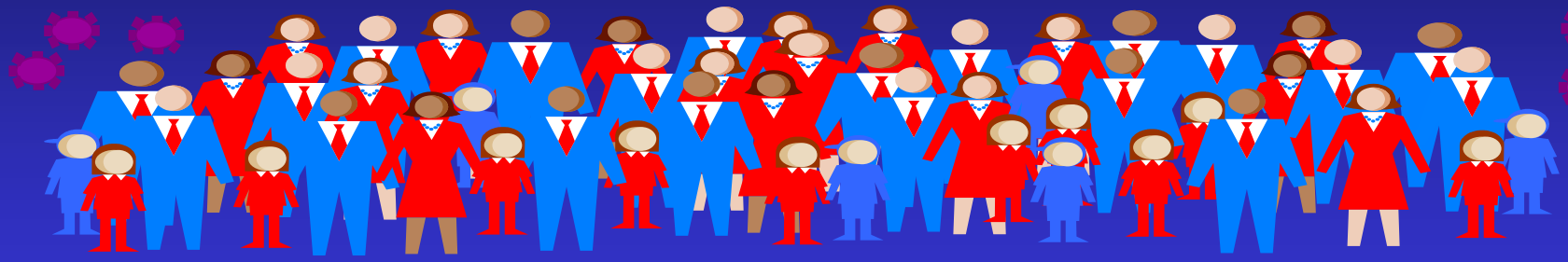
Antigenic Drift

- Process of gradual and continuous change in HA and NA glycoproteins
  - Accumulation of point mutations in the genes during viral replication
- Occurs with both influenza A and B, leading to new *viral strains*
- Allows for repeated infections over a lifetime
- Responsible for annual epidemic

Annual Epidemic (Interpandemic) Influenza, Wisconsin, 1996 - 2005



Influenza
Annual Impact



U.S. population ~290 million

~10%-20% Infected (29-59 million)

~50% Symptomatic (15-30 million)

Seek Care

Treat at Home

Hospitalized> 200,000

Death ~36,000

Influenza
Antigenic Change- A Hallmark

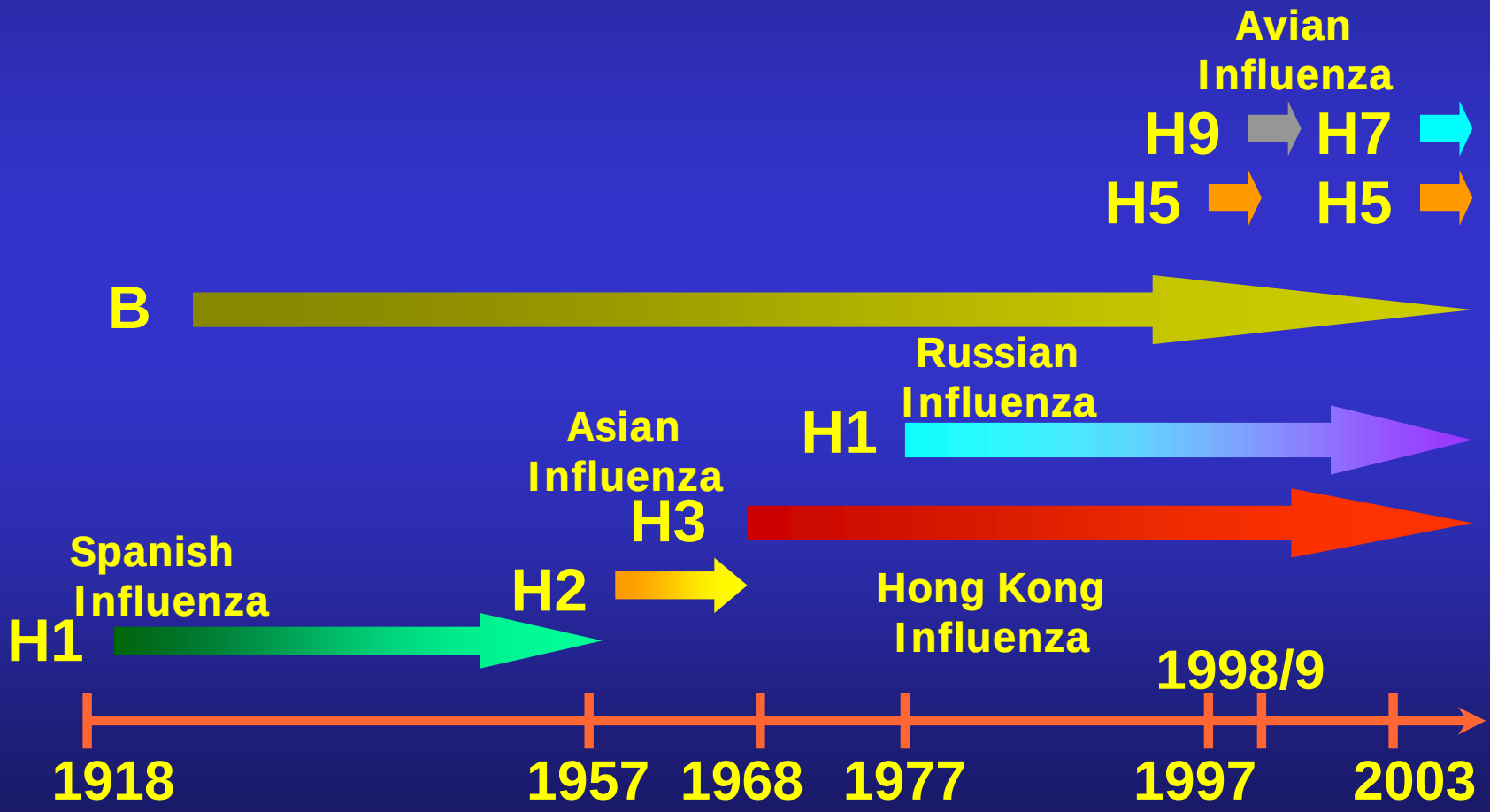
Antigenic Shift

- Process(es) whereby existing surface HA and/or NA proteins are replaced by HA and NA proteins that are *significantly different (novel).*
- Occurs only with influenza A and leads to a new *viral subtype*
- An abrupt change, infrequent and unpredictable
- Can result in a *pandemic influenza*

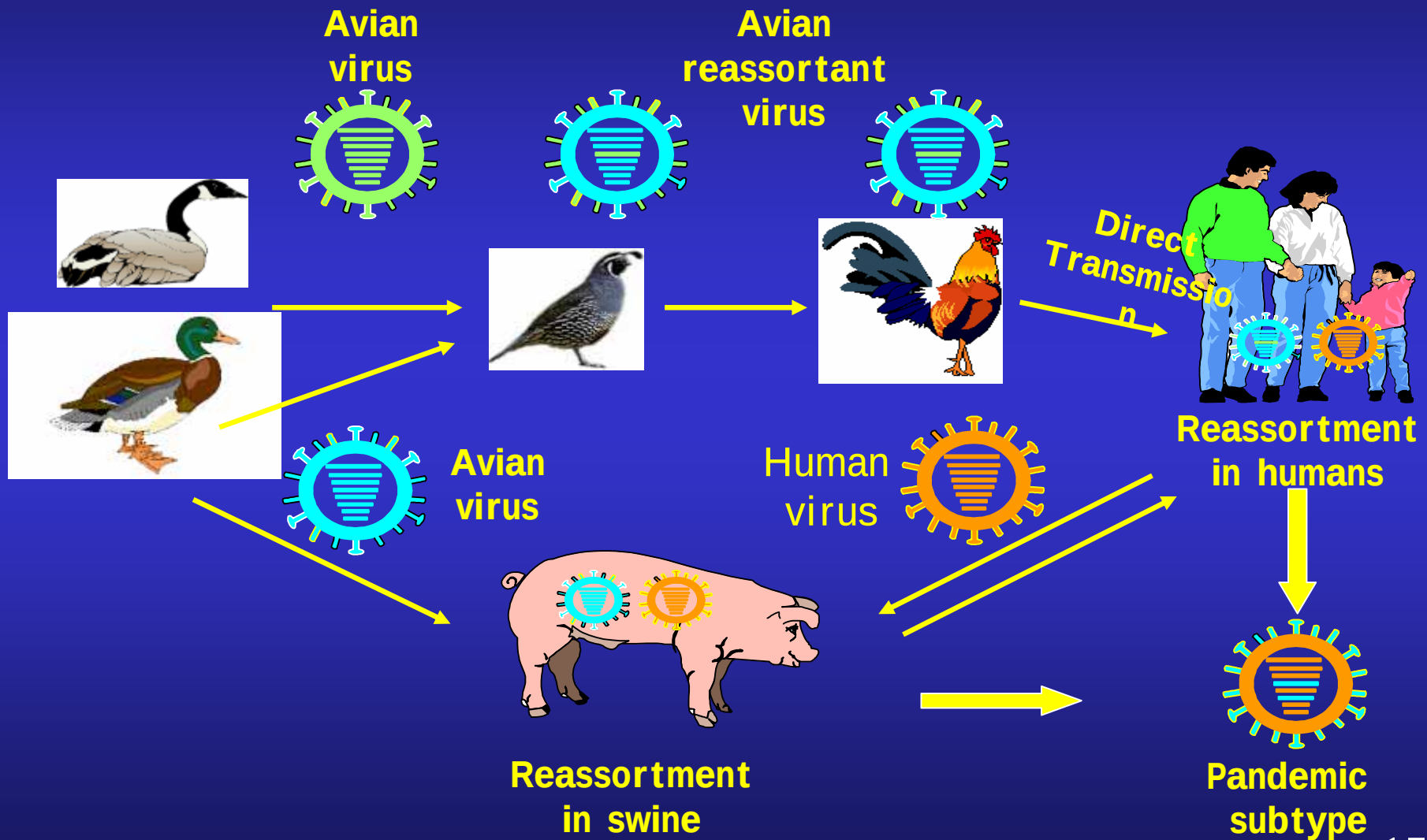
What is Pandemic Influenza?

- Results from a ***novel subtype*** of influenza A virus to which the overall population possess no immunity
- Occurrence in multiple or widespread geographic areas worldwide; locally explosive epidemics
- Associated with unusually high rates of morbidity and mortality
- Extremely rapid global spread
- Multiple waves of disease

Timeline of Emergence of Influenza Viruses in Humans



Generation of Pandemic Influenza Subtypes
Current Models



Overview of Laboratory Diagnostic Methods

Laboratory Diagnosis of Influenza

Test Method	Time to Results	Comments
Culture	1-10 days	**Still gold standard(?), requires expertise, provides virus for studies**
Molecular (RT-PCR)	2-4 hours	**Becoming gold standard(?), requires expertise & expensive equipment**
Antigen Detection (IF)	2-4 hours	**Requires reading expertise & IF microscope**
Serology	>2 weeks	**Retrospective, requires paired sera**
Antigen Detection (Rapid EIA-like)	**15-30 minutes**	**Widely available, requires little expertise**

Laboratory Diagnosis of Influenza
Rapid EIA-Like Tests

Test	CLIA Status	Antigen Detected
Clearview Flu A/B	Non-Waived	A & B
Directigen Flu A	Non-waived	A
Directigen Flu A & B	Non-waived	A & B
Directigen EZ Flu A + B	Non-waived	A & B
Flu OIA	Non-waived	A / B
Flu OIA A/B	Non-waived	A & B
NOW Flu A and NOW Flu B	Waived/Non-waived	A & B
BinaxNOW Influenza A & B	Waived	A & B

Laboratory Diagnosis of Influenza
Rapid EIA-Like Tests (continued)

Test	CLIA Status	Antigen Detected
QuickVue Influenza	Waived	A / B
QuickVue Influenza A + B	Waived	A & B
SAS Influenza A and Influenza B	Non-Waived	A & B
Xpect Flu A & B	Non-waived	A & B
ZstatFlu	Waived	A / B

Rapid Influenza Tests

Advantages

- Rapid turn-around time
- “Stat” testing possible
- Rapid outbreak identification
- Cost-effective (?)
- Wide-spread testing possible
- Less expertise required
- Optimize antibiotic and antiviral usage

Concerns

- Performance Characteristics:
  - Poor PVP early & late season
  - Poor test sensitivity→Impact on PVN
- Biosafety issues
- Supplies of test kits
- Loss of isolates for further characterization
- Loss of surveillance data

Rapid Tests: Optimizing Use

- Educate clinicians on predictive values & limitations of test results
- Confirm early, late and out-of-season positives
- Confirm peak-season negatives, if applicable
- Recognize the value of negative results.
- Use prevalence indicators to decide:
  - When to test
  - When to qualify result
  - When to confirm results

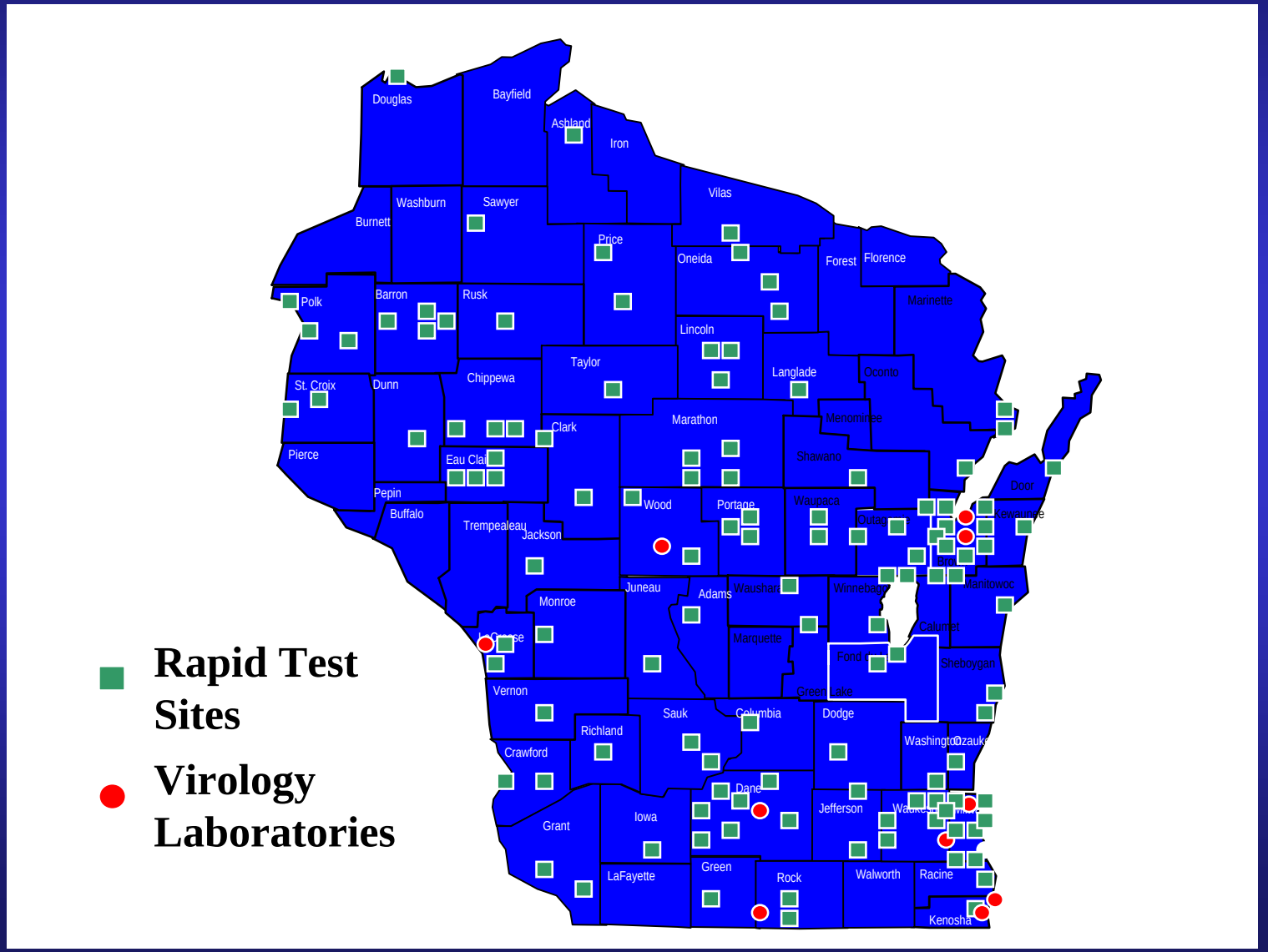
Rapid Tests: Biosafety Concerns in an Age of Emerging Diseases

Reasons for Concern: SARS, avian influenza, influenza A (H2N2)

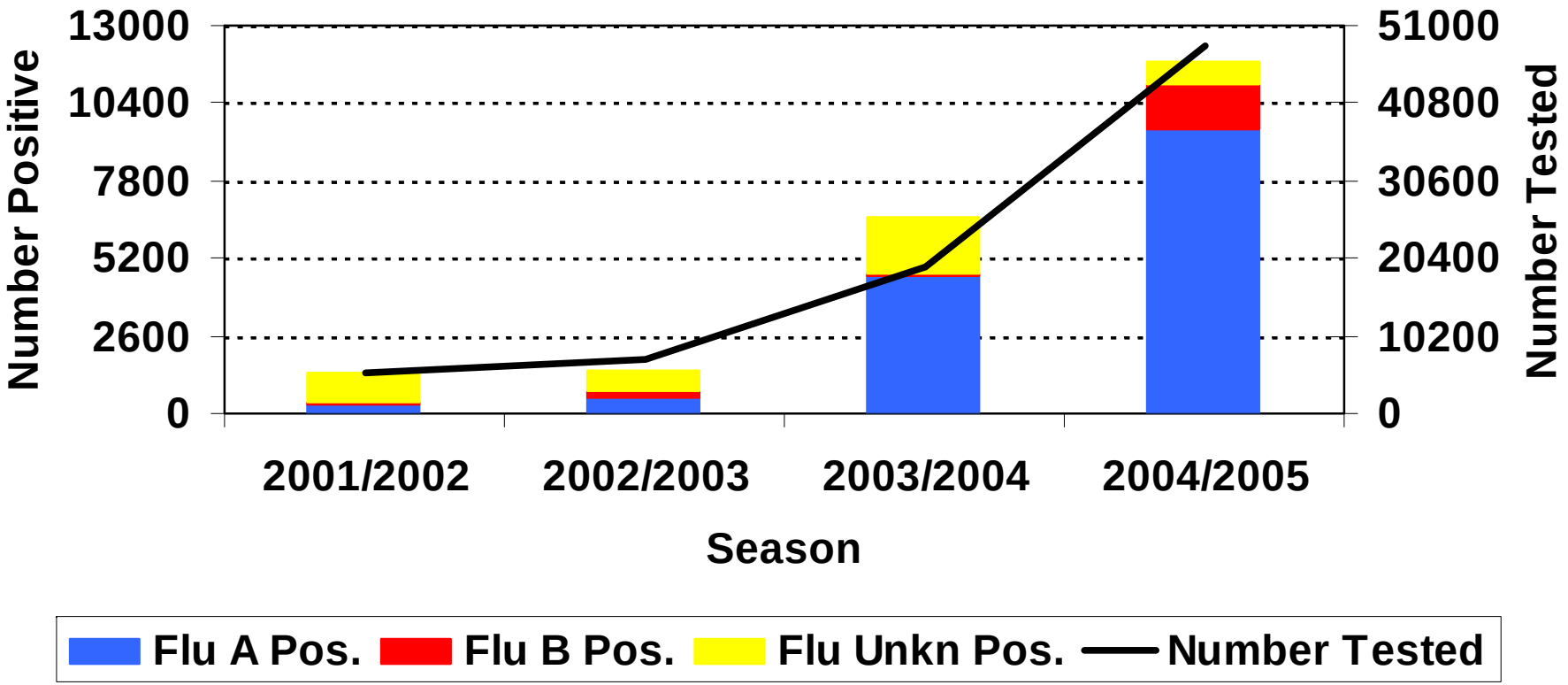
Addressing the Concerns:

- Enhance communication with ID Drs., Infection Control
  - Need patient travel history
- Perform risk assessment
- Consider strategies to enhance biosafety
  - Use BSC, additional PPE, isolated testing area
- Need for a new model for biosafety in the laboratory?
  - Universal ("Standard") precautions for blood in the 80's
  - Enhanced precautions for suspect EIDs in the 2000's?

Wisconsin Influenza Rapid Testing Sites Identified in 2004-2005



Rapid Influenza Testing Reported by Wisconsin Test Sites



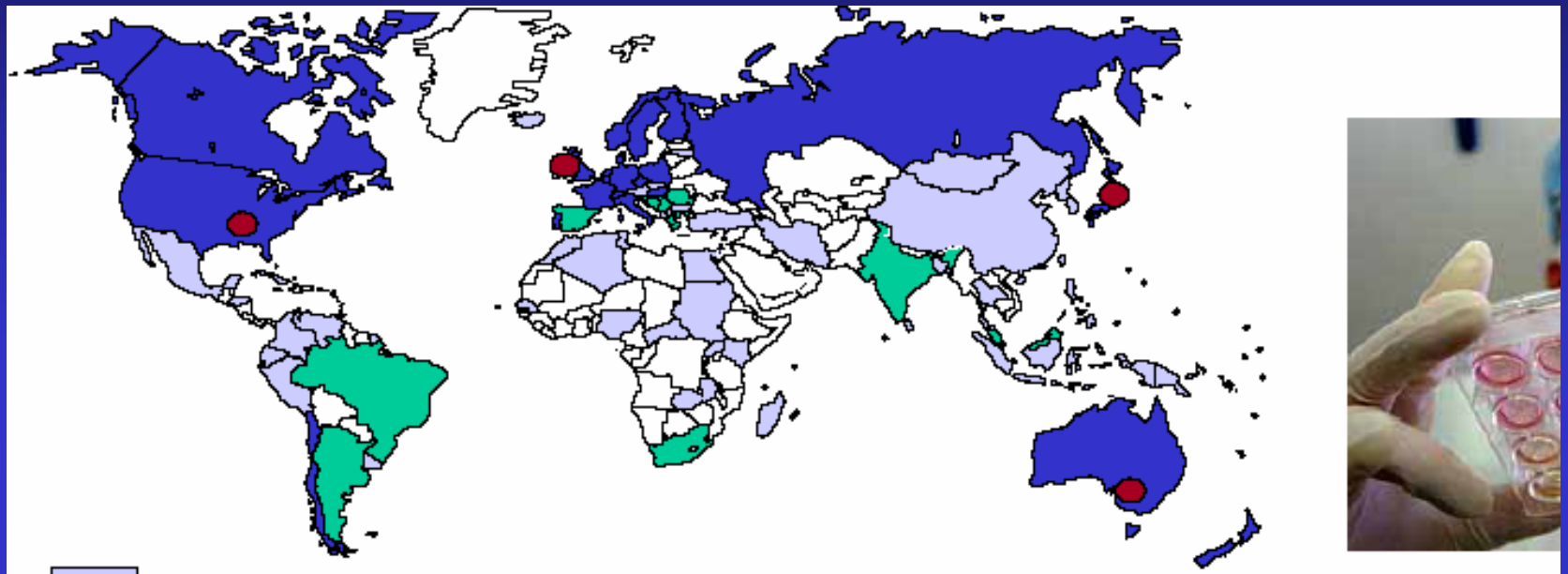
Surveillance for New Strains of Influenza Viruses

Objectives of Influenza Surveillance

- Determine when influenza viruses are circulating*
- Determine where influenza viruses are circulating*
- Determine how much influenza activity is occurring (intensity and impact)
- Identify the types & strains of circulating influenza viruses*
- Detect unusual events
  - Infection by unusual viruses*
  - Unusual syndromes caused by influenza viruses
  - Unusually large/severe outbreaks of influenza
  - Increased mortality
- Optimize use of vaccines & antivirals*

*Laboratory contributions

WHO Global Surveillance System for Human Influenza



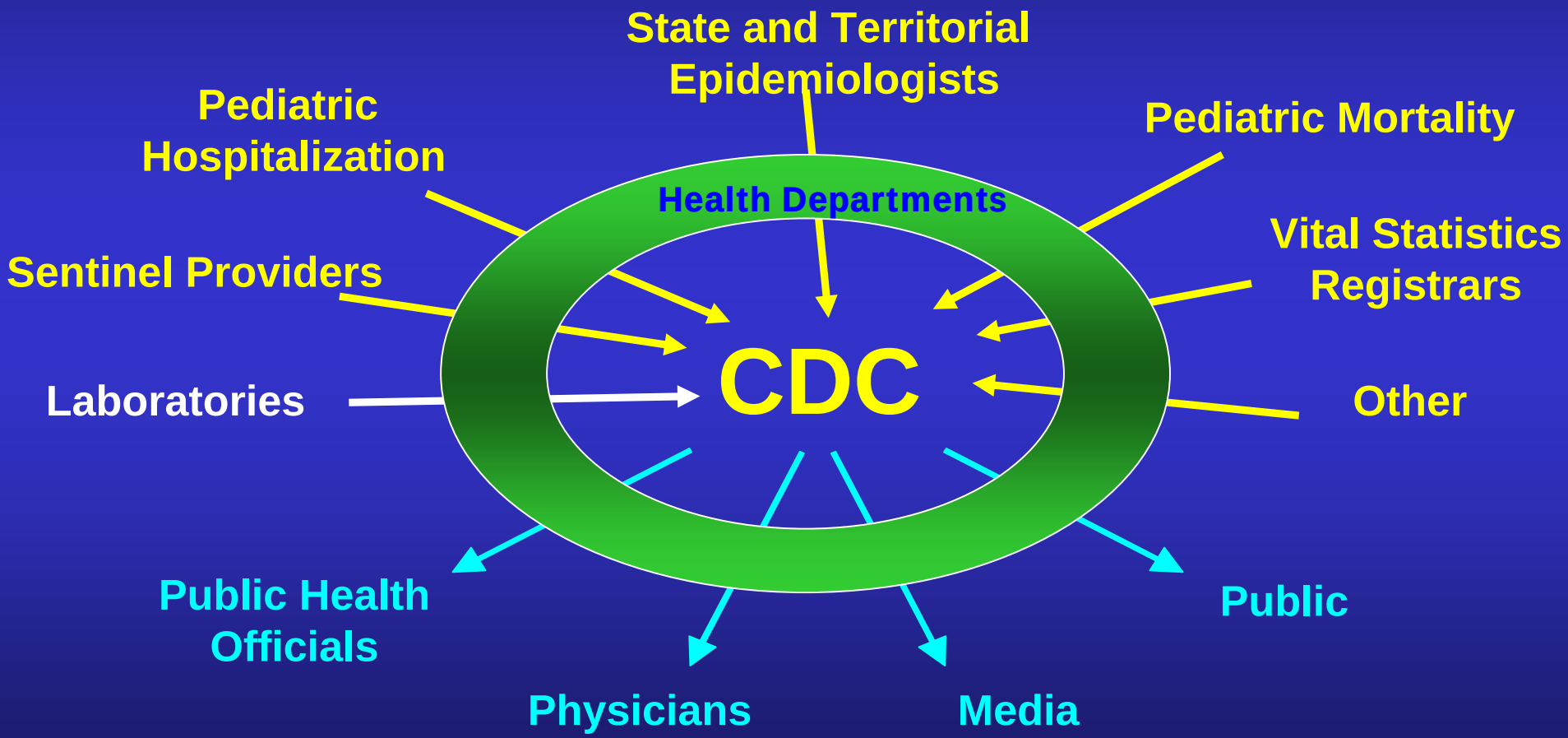
Annual output

- ~ 175,000-220,000k samples;
- 15,00-40,000 isolates;
- 2,000- 10 000 viruses characterized

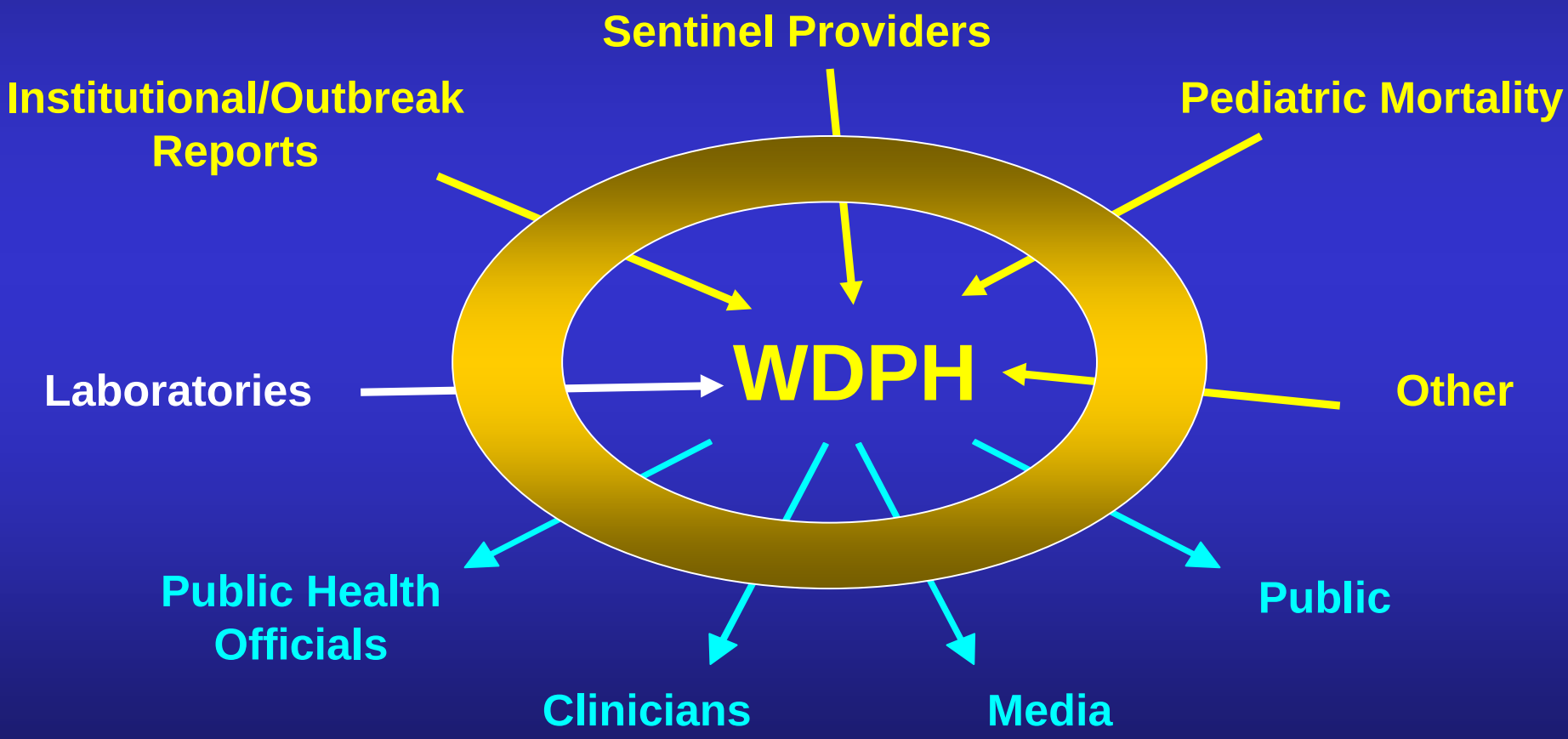
Source: Status of Human Health Preparedness & Response, Meeting on Avian & Human Pandemic Influenza, WHO, Nov 7-9, 2005

U.S. Influenza Surveillance

Weekly Updates at **http://www.cdc.gov/flu/weekly.htm**

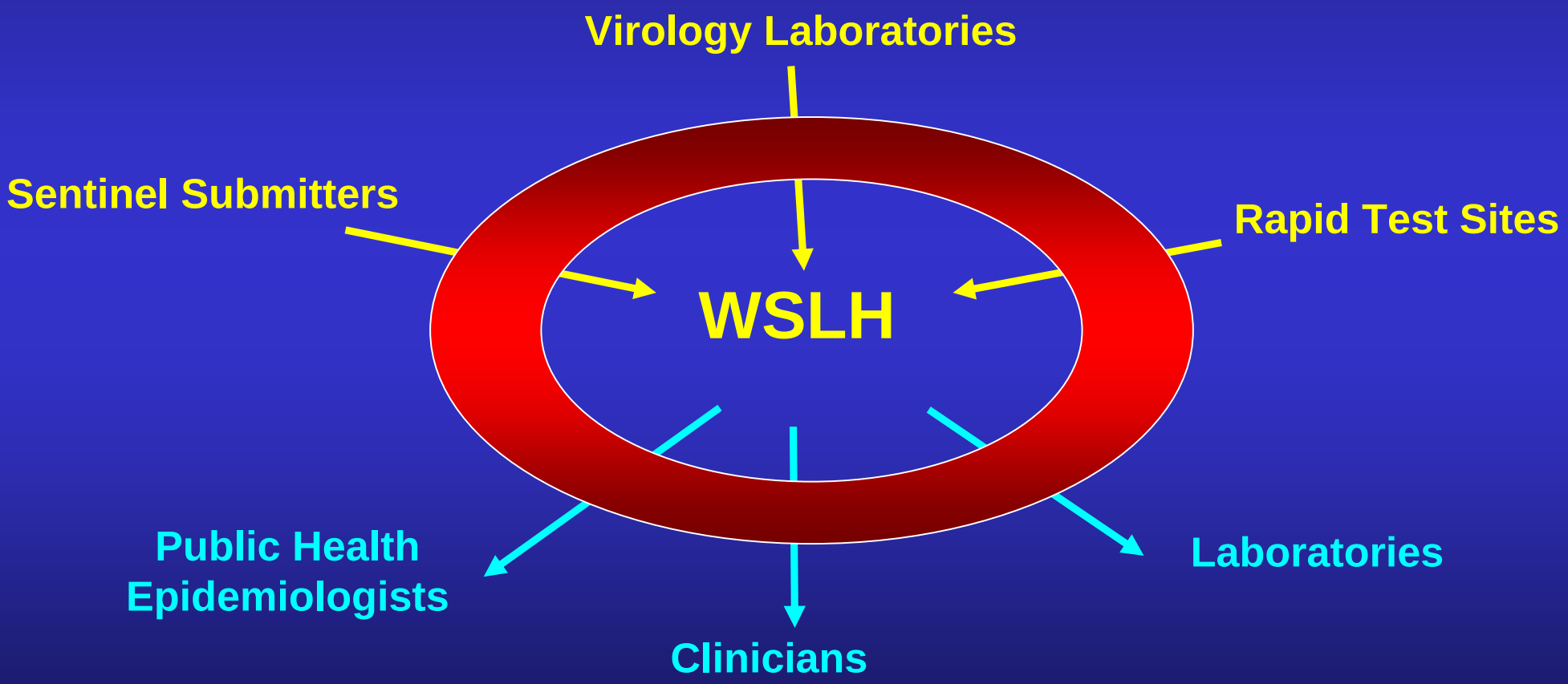


Influenza Surveillance in Wisconsin



WDPH = Wisconsin Division of Public Health

Statewide Laboratory-Based Influenza Surveillance in Wisconsin



WSLH = Wisconsin State Laboratory of Hygiene

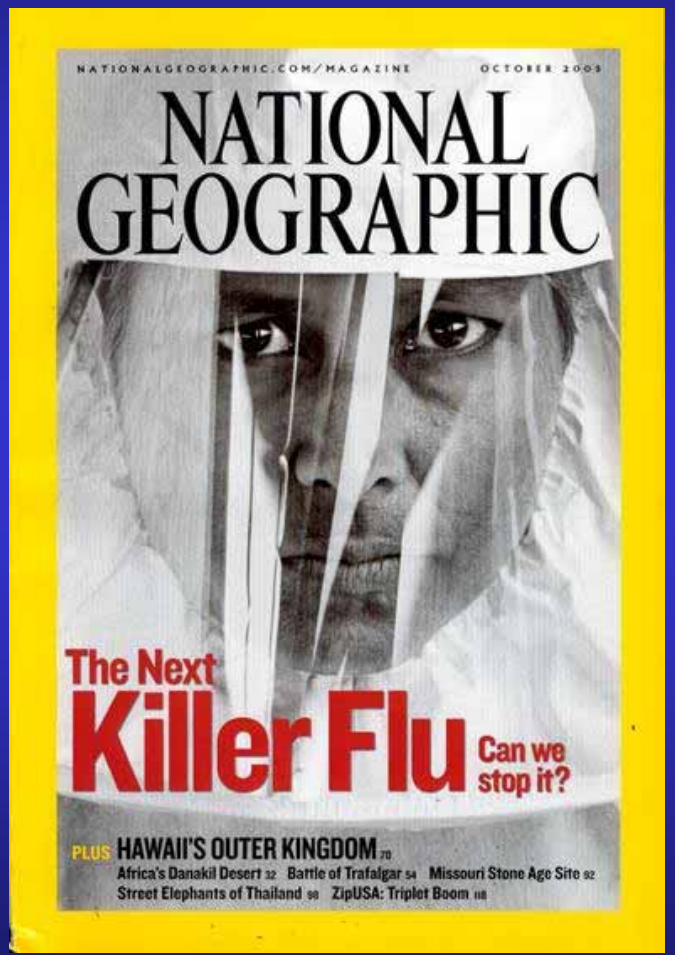
Elements of Laboratory-Based Surveillance

- Selected patient samples and viral isolates for testing at State Laboratory
- Weekly reports of number & types of specimens tested and test results
- Communication/information about unusual occurrences, current status of influenza activity
- Education for clinicians and test sites of implications of prevalence, use and interpretation of tests

Recommendations to Enhance Laboratory-Based Surveillance

- Develop algorithms for use of PCR for surveillance by state public health laboratories
- Incorporate rapid test sites as key partners
- Incorporate molecular sites in influenza surveillance
  - Provide public health testing protocols
  - Provide clinical testing data
  - Refer samples for test verification, confirmatory testing & subytping and repositories
- Expand influenza surveillance to year-round

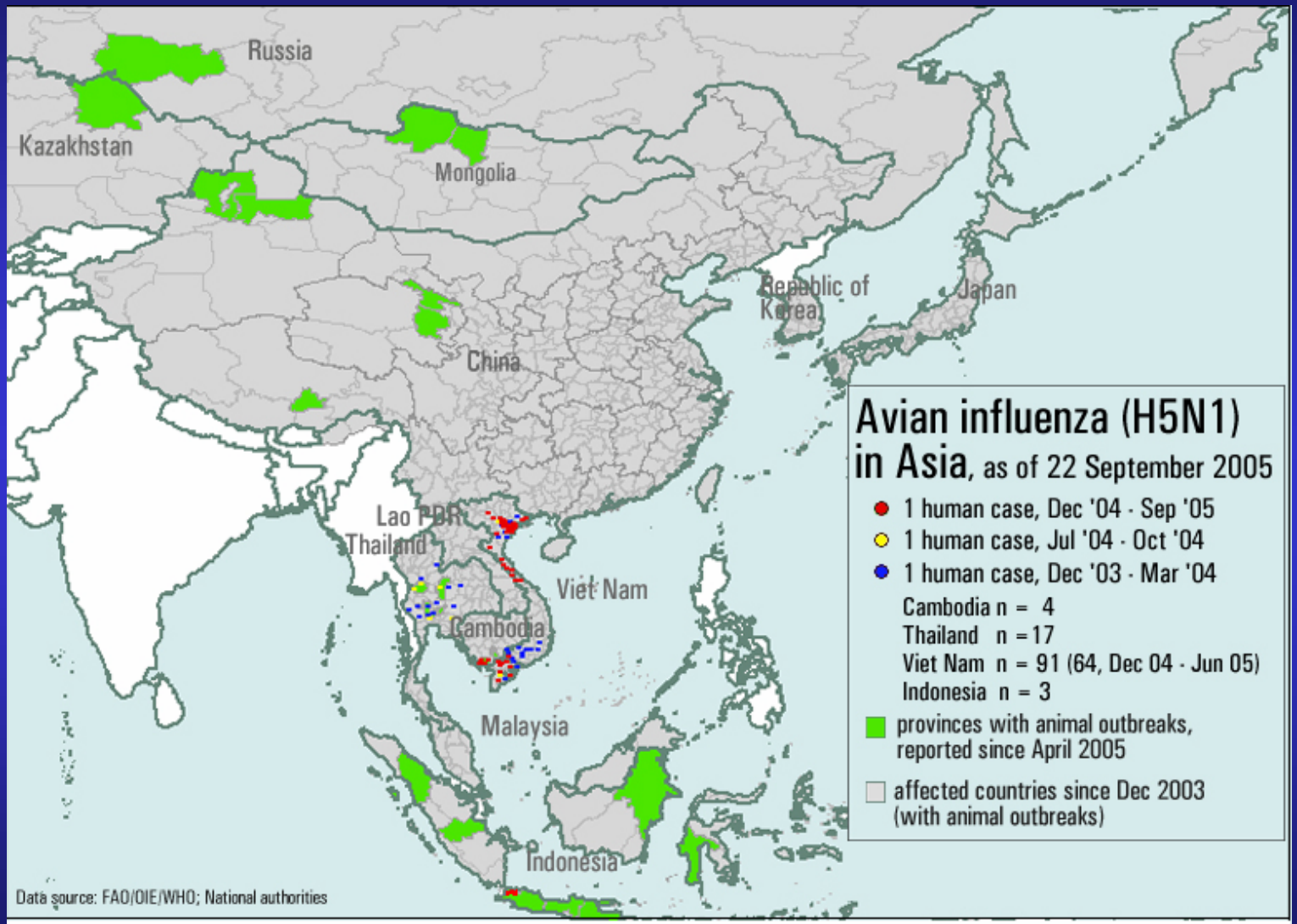
Current Pandemic Concerns



Direct Interspecies Transmission of Avian Viruses to Humans Exposed to Infected Poultry

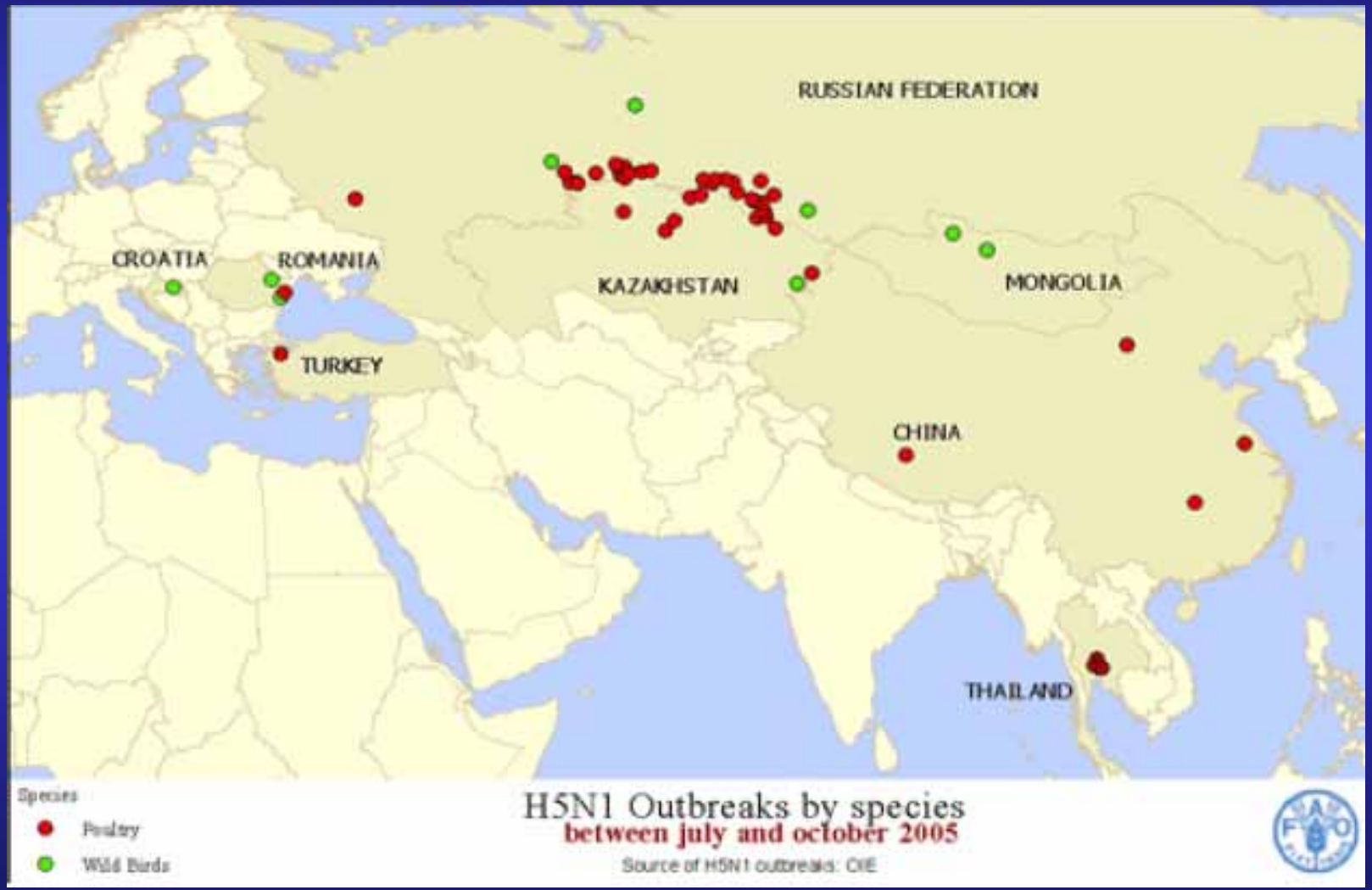
- 1997: 18 cases of respiratory illness caused by HP avian H5N1; 6 deaths – Hong Kong
- 1998/9: 7 cases of respiratory illness caused by H9N2; no deaths – China, HK
- 2003: 2 additional HP H5N1 cases; 1 death – China, HK
- 2003: >80 cases of infection by HP H7N7 avian viruses; 1death – The Netherlands
- 2004: 2 cases of infection by HP H7N3; no deaths – British Columbia
- 2004-2005: Additional cases of H5N1 in Southeast Asia

2004-2005: H5N1 in Southeast Asia



Disclaimer: The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or its authorities of its frontiers or boundaries.

July-October, 2005: H5N1 in Birds



Source: Food and Agriculture Organization, World Health Organization

Human H5N1 Cases Reported to WHO Through November 17, 2005

Country	H5N1 Cases	Deaths	Case Fatality
Cambodia	4	4	100%
Thailand	21	13	62%
Indonesia	11	7	64%
Vietnam	92	42	46%
China	2	1	50%
Total	**130**	**67**	**52%**

Avian (H5N1) Influenza
Situation Update – November 18, 2005

- Expansion of geographic and host range via wild birds
- Continuing large outbreaks in domestic fowl
- In human isolates so far, all genes of avian origin
- Viral resistance to adamantanes; sensitive to oseltamivir
- Continued evolution of pathogenicity & antigenicity
- **No evidence of sustained human-to-human transmission!**

AVIAN INFLUENZA (H_5N_1)

The Recipe For a Human Pandemic

- Emergence of a novel subtype of influenza
  - An immunologically naïve population
- Replication in humans → disease
- Efficient human-to-human transmission

An Influenza Pandemic Will be Unlike A Bioterrorism Event or A Natural Disaster

- **Inevitable yet unpredictable**
  vs. imminent, overdue???
- ***Widespread, not focused like a bioterrorism event***
  - ***Will be a <u>global</u> event***
  - ***Will affect entire national infrastructure rapidly***
- Effect will be relatively prolonged, weeks to months, occurring in waves
- May have unique age predilection

PANDEMIC INFLUENZA
Risk Communication

Walking the fine line between

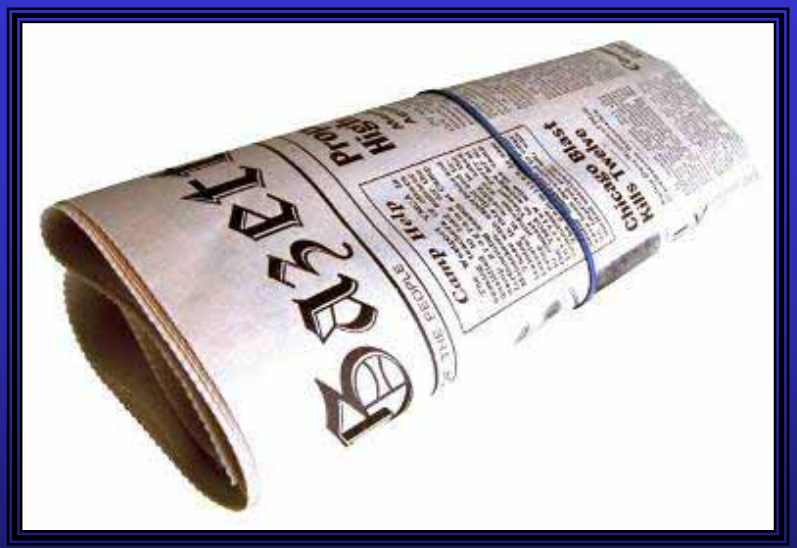
“*appropriately sounding the alarm*”

and “*causing panic*”

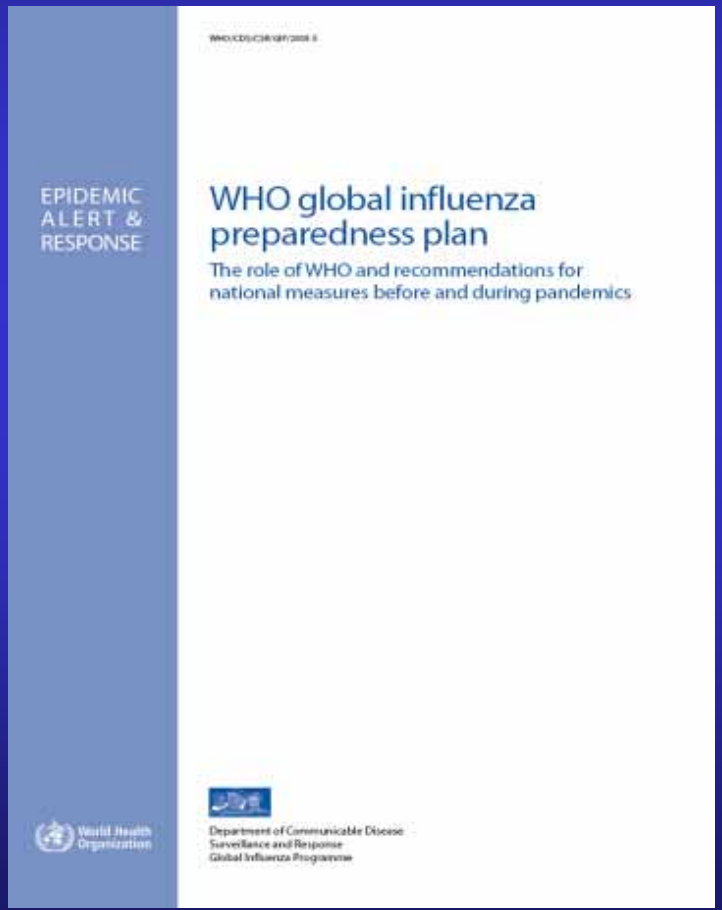
The Arrival of Avian Flu in the U.S.???

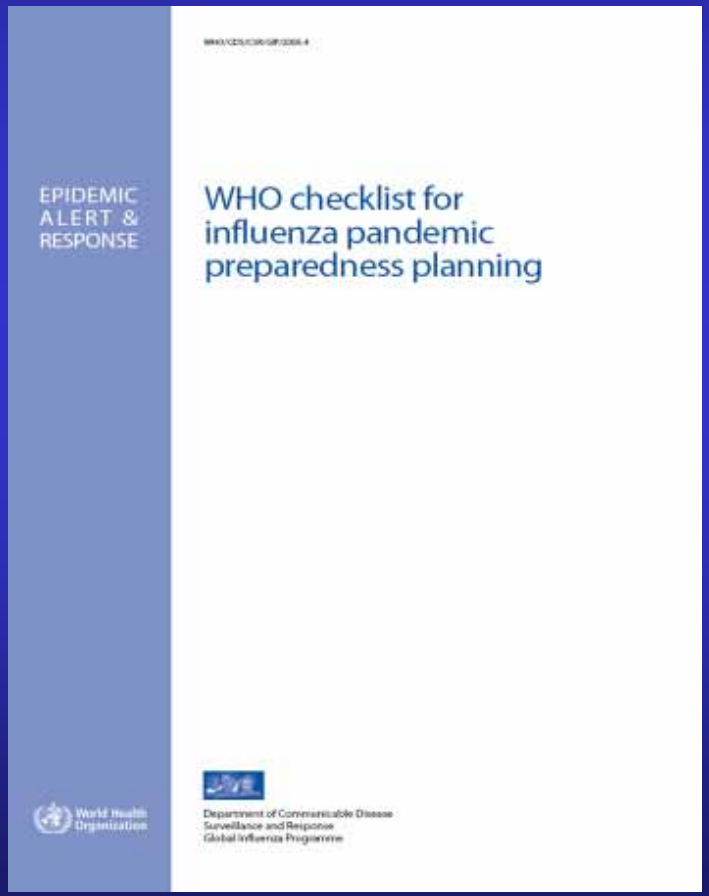
Article from Orlando Sun Times,

"Beloved Duck at Theme Park
Succumbs to Mystery Flu"



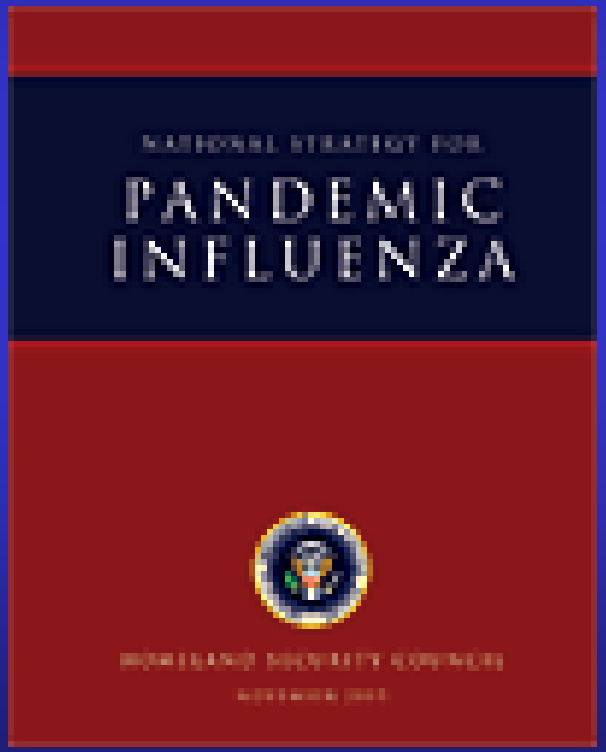
Pandemic Preparedness Activities: An International Priority



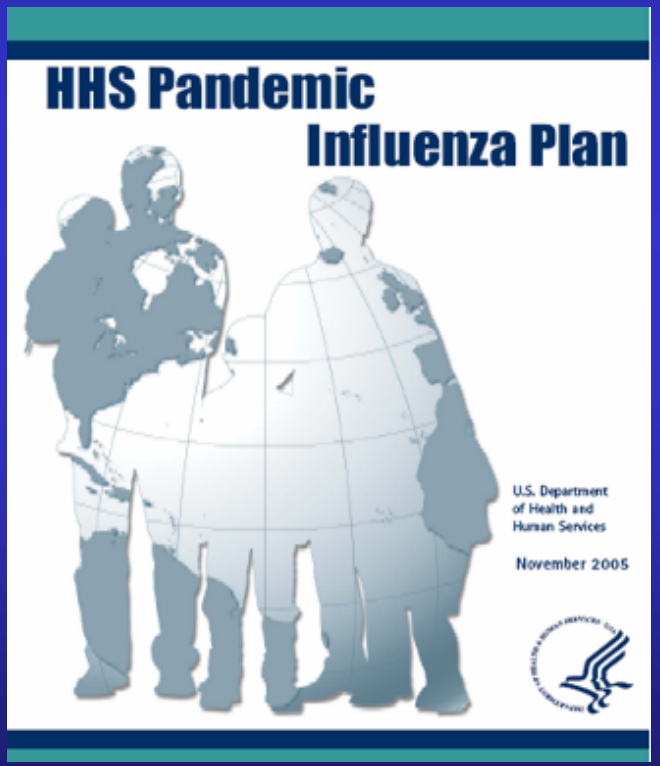


Pandemic Preparedness Activities: A National Priority

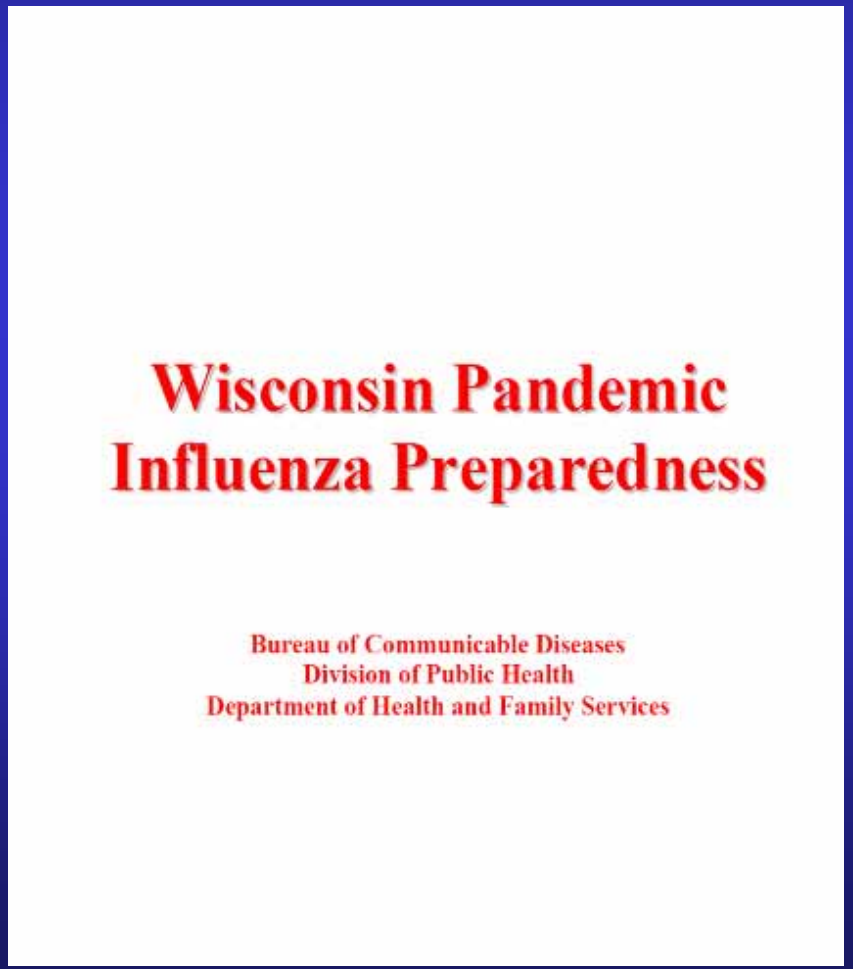
National Strategy for Pandemic Influenza



National Pandemic Influenza Plan



Pandemic Preparedness Activities: A State Priority



W.H.O. Framework for Pandemic Planning

Interpandemic period	
Phase 1	No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low.
Phase 2	No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.
Pandemic alert period	
Phase 3	Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact.
Phase 4	Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.
Phase 5	Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).

W.H.O. Framework for Pandemic Planning (continued)

Pandemic period	
Phase 6	Pandemic phase: increased and sustained transmission in general population.
Postpandemic period Return to interpandemic period.	

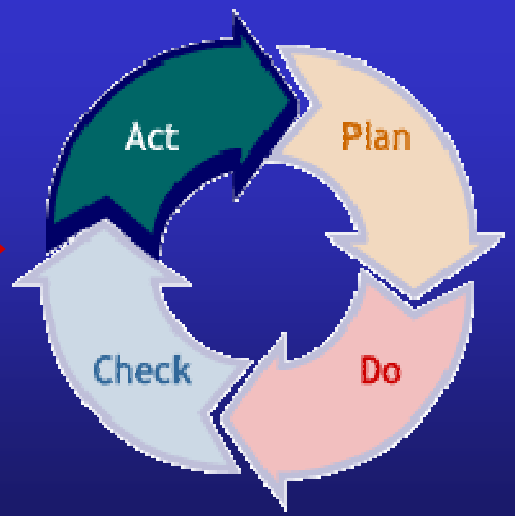
The Laboratory's Role in Pandemic Preparedness & Response

Pandemic Influenza Preparedness & Response

Interpandemic Period → Pandemic Alert Period → Pandemic Period → Postpandemic Period

Planning → Implementation

Preparedness → Response



Interpandemic/Pandemic Alert Influenza: *Laboratory Responsibilities*

- Perform diagnostic testing
- Support surveillance activities
  - Seasonal influenza
  - Novel influenza subtypes
- Participate in pandemic planning and exercises
- Develop/review pandemic response plans and checklists
- Educate clinicians and laboratorians

Pandemic Influenza Period: *The Laboratory's Responsibilities*

Clinical Laboratories

- Perform diagnostic testing for influenza (stat)
- Maintain other diagnostic services
- Support surveillance activities
- Continue clinician education
- Other?

Public Health Laboratories

- Maintain surveillance activities
- Conduct special studies with CDC
- Maintain reference testing for influenza
- Maintain emergency response for other outbreaks (e.g., foodborne)
- Continue education of clinicians & laboratorians
- Share data/information in "real-time"
- Maintain other diagnostic services?
- Other?

Pandemic Influenza Period: *The Impact on the Laboratory*

- Staff shortages
- Supply shortages
- **Very high** demand for diagnostic testing
- Continued need for routine (non-pandemic) work
- Disruptions of medical community
- Severe disruptions of community infrastructure
- High visibility likely for laboratory

Pandemic Influenza Period: ***Plan Now!***

Issues & Options

- **Staffing Shortages:**
  - "Continuity of Operations" Plan
  - Cross-train
  - Surge testing laboratories
  - Temporary employment agencies
  - Prioritize testing (influenza AND non-influenza)
  - Identify other staff capabilities
- **Supply Shortages:**
  - Stockpiles
  - Multiple vendors

Pandemic Influenza Period: ***Plan Now!***

Issues & Options

- **Biosafety:**
  - Risk assessment (specimen collection, testing processes)
  - Enhanced biosafety, e.g., PPE, sequestering work, barriers
- **Protocols:**
  - Notification of changes to testing capabilities & schedules
  - Clinical diagnosis vs. testing
  - Specimen management
  - Specimen referral to public health laboratory
  - Employee health
  - Alternate transport options

Pandemic Influenza Period: ***Plan Now!***

Issues & Options

- **Training/Education:**
  - Cross-train staff
  - Accelerated training protocol
  - Clinician training
- **Communications:**
  - Integration of laboratory planning with institutional plans
  - Institutional prioritization
  - Real-time information-sharing from PHLs to sentinel laboratories

Pandemic Influenza Period: ***Plan Now!***

- Develop/Review your “Continuity of Operations” Plan
- Develop checklist(s)
- Exercise
- Support surveillance for earliest detection
- Integrate plans with:
  - institutional plans
  - community plans
  - regional & statewide plans
  - other laboratories’ plans
- Public health laboratories must accept responsibility for leadership in laboratory planning & response

THE LRN FOR BIOTERRORISM

PUBLIC HEALTH EMERGENCIES