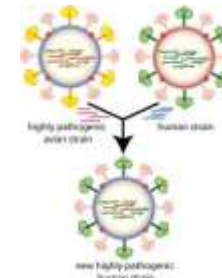
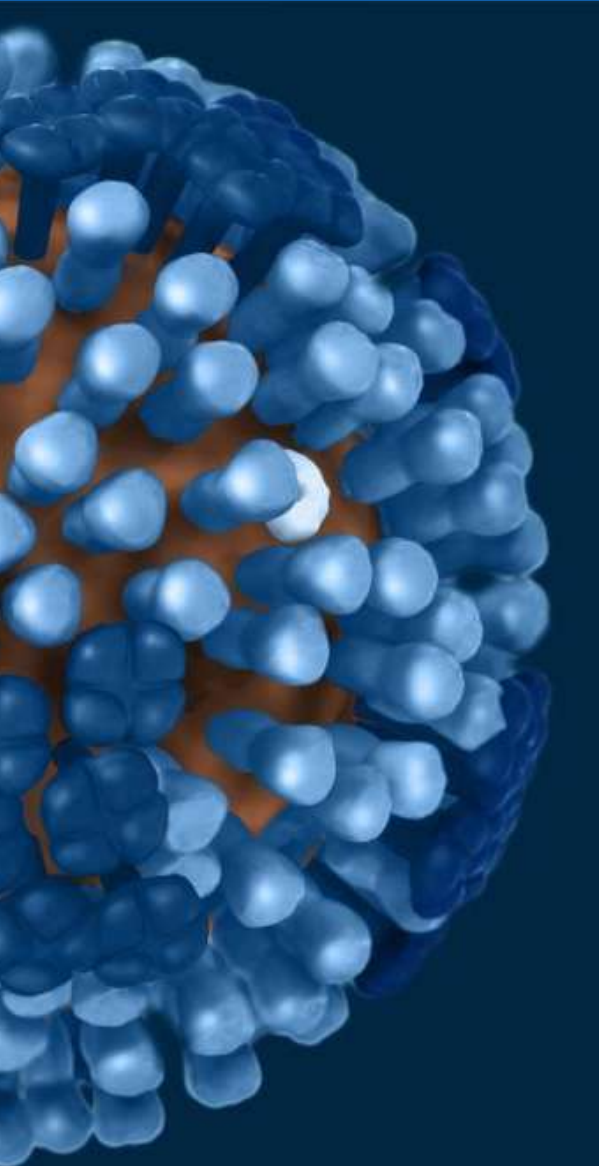


Our Greatest Challenges in Influenza Detection, Prediction and Prevention

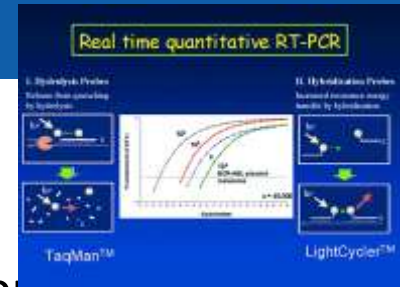
Nancy J. Cox, Ph.D. (retired) Influenza Division Affiliate
Centers for Disease Control and Prevention
Options IX for the Control of Influenza
August 24-28, 2016



Disclaimer: The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Talk Overview: From a Personal and Public Health Perspective

- Advances in Detection
 - Real time RT-PCR for surveillance and diagnosis
 - Expansion of WHO's Global Influenza Surveillance and Response System (GISRS)
 - Capacity building within GISRS
 - Implementation of NGS sequencing in PH surveillance labs
- Advances and Challenges in Prediction
 - Periodic problems associated with vaccine 'mismatch'
 - Computational modeling for vaccine virus selection
- Advances and Challenges in Prevention
 - New vaccines licensed and policies established
 - New vaccine policies implemented
 - Moderate vaccine effectiveness
 - Excess global vaccine production capacity
 - Quest for improved human vaccines and a 'universal' influenza vaccine



Impact of Pandemic Influenza

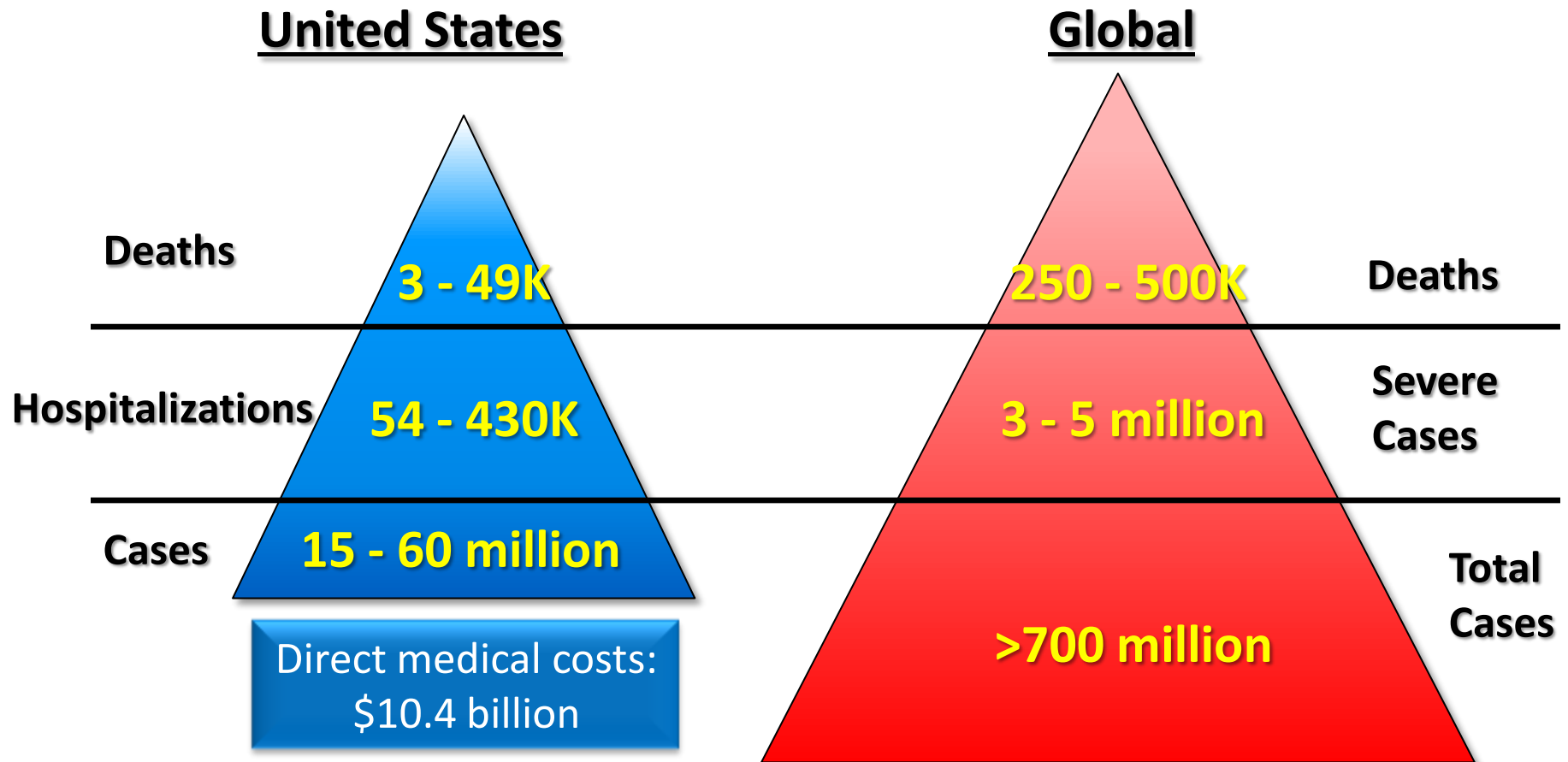
- **1918-19 Spanish Flu Pandemic (H1N1)**
 - ~ 650,000 deaths in the US
 - ~ 35 to 100 million deaths worldwide
- **1957-58 Asian Flu Pandemic (H2N2)**
 - ~70,000 deaths in the US
 - ~ 2 M global deaths
- **1968-69 Hong Kong Flu Pandemic (H3N2)**
 - ~34,000 deaths in the US
 - ~ 1 M global deaths
- **2009 H1N1 Pandemic**
 - ~12,000 deaths in the US
 - ~280,000 global R&C deaths



1968 Hong Kong flu



Estimated Annual Burden of Seasonal Influenza



~ 700,000 U.S. deaths, 1976-2003*; ~ 900,000 U.S. deaths, 1976-2016**

*Thompson W, Weintraub, E, et.al. 2009. Influenza and Other Respiratory Viruses: 3, 37-49

** Extrapolation based on above reference

CDC's Influenza Surveillance Lab in 1976

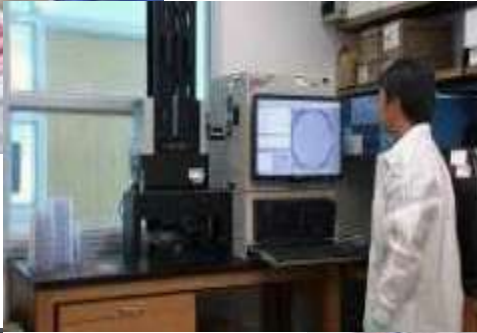


Antigenic Characterization



Receiving Department

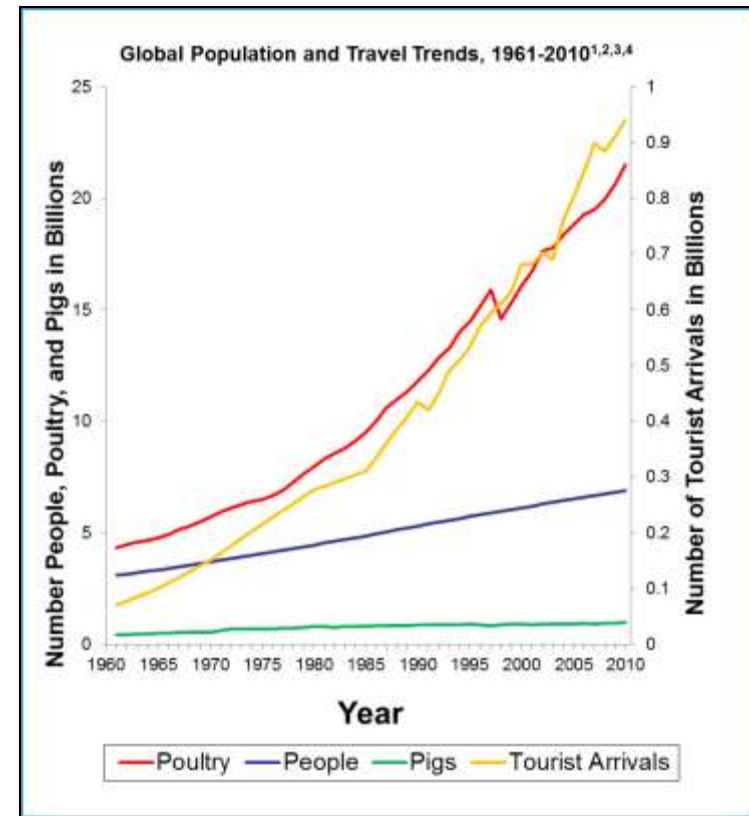
CDC's Influenza Surveillance Laboratory in 2016



Emerging Influenza Threats

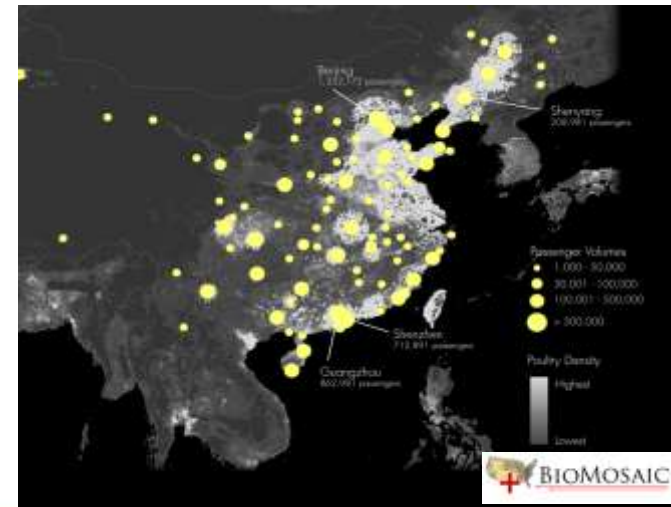
Novel Influenza Viruses with Pandemic Potential

- Global conditions favor emergence of novel influenza threats – the world is increasingly:
 - Crowded
 - Connected
 - Converging
- Novel influenza virus infections are increasing and increasingly detected with better detection methods
 - H5N1, 854 cases/450 deaths in 12 years
 - H7N9, 826 cases/306 deaths in 4 years
- A flu pandemic could spread quickly and kill millions around the world



Cases of H7N9 Infection Highlight Factors Leading to Emergence of Novel Influenza

- Increasingly Crowded
 - In the affected region, around 575 million people - 45% of China, 8% of World¹
- Increasingly Connected
 - 40 Million passengers through Shanghai Airport yearly
 - Connections globally within incubation period
- Increasingly Converging
 - In the 50 km around the 60 early cases of H7N9, there were an estimated²:
 - 131 M people
 - 241M domestic chickens
 - 47M domestic ducks



1. National Bureau of Statistics - China Statistical Database , 2011 (<http://219.235.129.58/welcome.do>)

2. Butler D. Mapping the H7N9 avian flu outbreaks. www.nature.com

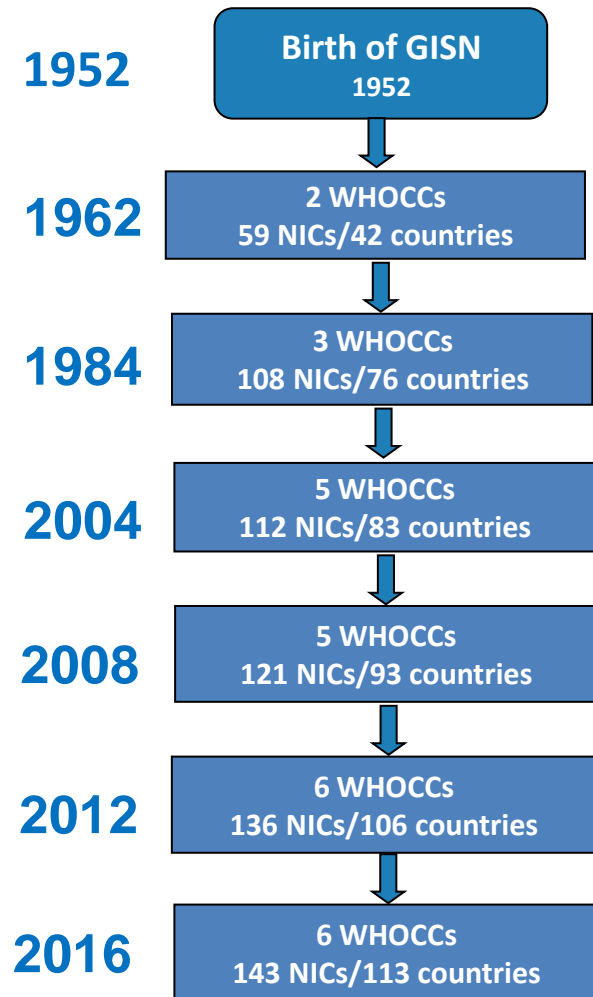
Formation of the WHO's Global Influenza Surveillance Network



- 1947/8 - WHO established as health agency of the United Nations after 3 years of discussion post-World War II
- From WHO's inception, influenza surveillance viewed as important
- 1947/8 – 'World Influenza Centre' established in London with Sir Christopher Andrews as first director
- 1948 to 1952 - National Influenza Centers (NIC) nominated by MoHs leading to formation of WHO's Global Influenza Surveillance Network
 - First NIC designated in the Netherlands
 - Now Global Influenza Surveillance and Response System (GISRS)
- WHO Collaborating Centers for human influenza established Atlanta in 1956, Melbourne in 1992, Tokyo in 1993, and Beijing in 2011; CC in Memphis for animal influenza, 1975
- Four essential regulatory laboratories also contribute to vaccine strain selection



Growth of the Global Influenza Surveillance and Response System (GISRS)



- Virus monitoring and risk assessment
 - Laboratory diagnostics
 - Vaccine virus selection
 - Capacity building
 - Communication and networking
 - Regular interactions with industry
-
- **Serves as a model international surveillance system with strong ethos of collaboration and cooperation**

H5N1 Events Leading to the Pandemic Influenza Preparedness Framework

- For many years low and middle income countries provided information and virus samples to the WHO's Global Influenza Program
- Pharmaceutical companies in developed countries obtained free access to influenza virus samples and made profits from vaccines and other products used in high income countries
- Developing countries with H5N1 cases could not afford to purchase H5 vaccines and antivirals
- Trust in the WHO's GIP was 'broken' for Indonesia and some other affected countries that asserted that reform was needed wrt virus and benefit sharing (i.e., access to vaccines)
- In short, Indonesia and other LMIC had greatest H5N1 disease burden but could not afford to purchase pandemic vaccines made from viruses they shared

Dispute Over H5N1 Virus Sharing – 2011

Pandemic Influenza Preparedness Framework

- In early 2007 Indonesia refused to share H5N1 viruses from human cases with WHO's global influenza network and claimed sovereignty over its H5N1 viruses based on the Convention for Biological Diversity (CBD)*
 - CBD is an international treaty meant to protect indigenous/traditional resources in LMIC (e.g., traditional medicinal plants, etc. often exploited by others)
- Indonesia asserted that the International Health Regulations of 2005, a legally binding international law, did not require sharing of biological samples; document is ambiguous
- This became an 'existential' crisis for WHO's Global Influenza Surveillance Network. How much was it valued internationally and would it survive?

*Fidler DP. Negotiating equitable access to influenza vaccines: global health diplomacy and the controversies surrounding avian influenza H5N1 and pandemic influenza H1N1. *PLoS Med.* 2010;7(5):e1000247

The PIP Framework Negotiated from 2007-2011

- Why did it take 4 years and millions of dollars to negotiate?
 - The identified problems were complex; equity, fairness, transparency
 - Countries had divergent interests; developed countries value intellectual property rights while LMIC valued equity in health
 - Took time to find a way to put virus sharing and benefit sharing on an equal footing
- The PIP framework is a landmark in global governance for public health*
- Governs sharing of influenza viruses with human pandemic potential and the benefits accruing from them
- Goal is to improve pandemic preparedness through WHO's GISRS by sharing viruses and capacity building and by enhancing equitable access to benefits including vaccines in LMIC

*Fidler DP. Negotiating equitable access to influenza vaccines: global health diplomacy and the controversies surrounding avian influenza H5N1 and pandemic influenza H1N1. *PLoS Med.* 2010;7(5):e1000247

Benefits Sharing

- Benefit-sharing system in PIP-FW
 - Requires industry must pay for “half” of GISRS’s annual operating costs (\$28 M/yr); 70% of contributions distributed to LMIC for improving pandemic and seasonal preparedness and 30% set aside for buying vaccines etc. during a pandemic
 - Industry has access to viruses with pandemic potential under SMTA 2 in exchange for providing funding and pledging pandemic vaccine in advance
 - So far a success due to cooperation of GISRS labs, industry and Industry
 - Only possible because of annual influenza vaccine industry and so model not directly applicable to other emerging infectious diseases
 - Unique solution to health inequities
 - PIP Framework is undergoing a 5 year review
 - Still TBD how influenza genetic sequence data will be treated under the PIP Framework

GISRS Capacity Building Efforts by CDC, 2004-2013

- Cooperative Agreements with 39 governments to strengthen global influenza surveillance by providing:
 - Funding for equipment, lab reagents and personnel
 - Hands-on training and technical follow-up
 - Participatory, standardized assessments with targeted technical recommendations
- Most important development areas:
 - Achieving status as National Influenza Center
 - Improving laboratory testing for influenza
 - Increasing sentinel surveillance for ILI
 - Reporting weekly data to WHO's FluNet
 - Sharing specimens with WHO Collaborating Centers for vaccine virus selection

Increase in WHO National Influenza Centers

23 countries working toward National Influenza Center status; 13 have achieved designation (4 new in 2013)

- | | | |
|------------------------|------------------|--------------------------------------|
| • Afghanistan | • Kyrgyzstan | • Philippines |
| • Angola | • Laos | • Rwanda |
| • Armenia | • Madagascar | • South Africa |
| • Bangladesh | • Maldives | • Sri Lanka |
| • Bhutan | • Mali | • Tanzania |
| • Brazil | • Mexico | • Thailand |
| • Cambodia | • Moldova | • Tunisia |
| • China | • Mongolia | • Uganda |
| • Côte d'Ivoire | • Morocco | • Ukraine |
| • DRC | • Mozambique | • United Republic of Tanzania |
| • Egypt | • Nepal | • Viet Nam |
| • Ethiopia | • Nigeria | • Zambia** |
| • Georgia | • Pakistan | |
| • India | • Paraguay | |
| • Indonesia | | |

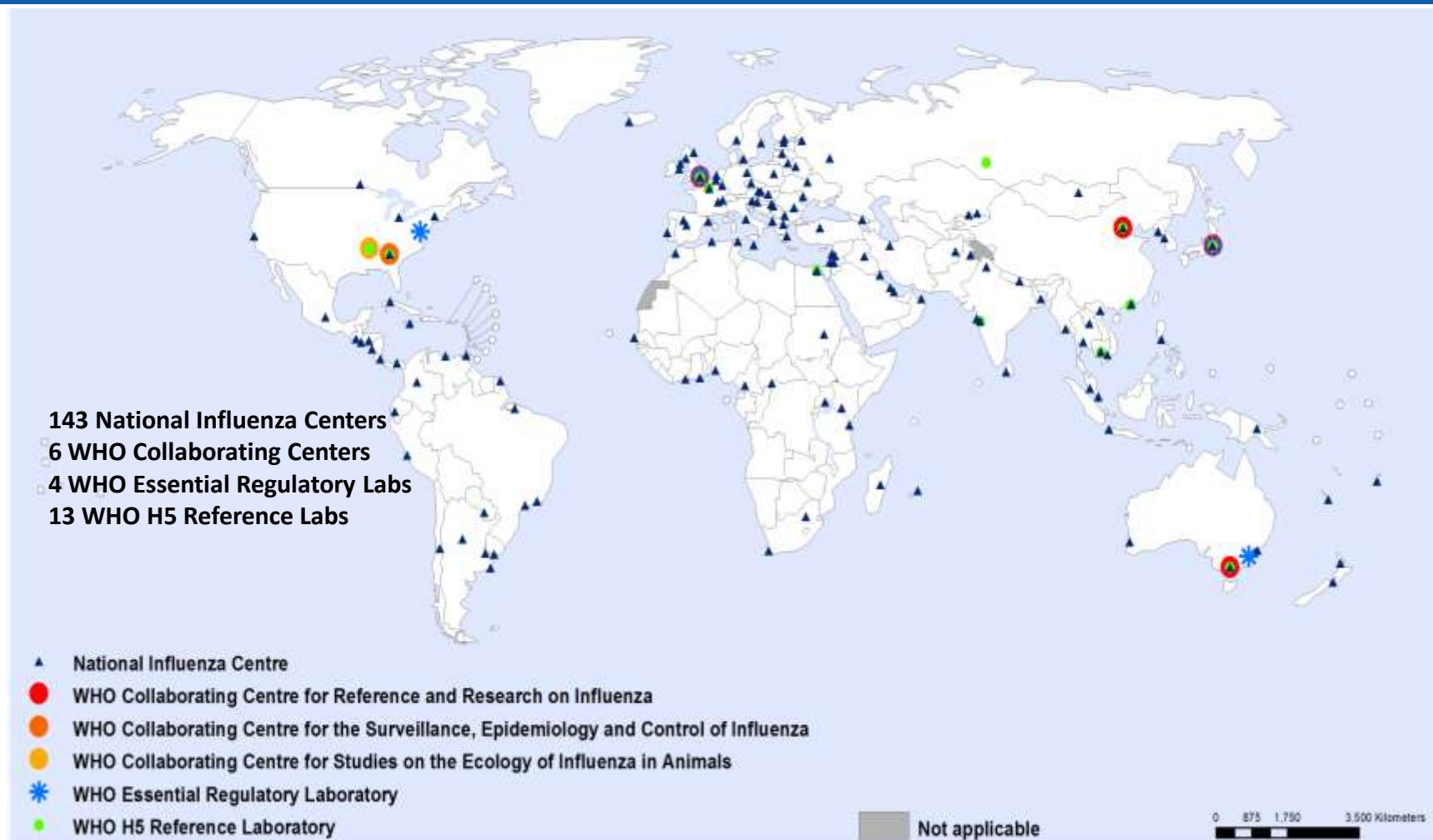
Prior NIC
Became a NIC
Became a
WHOCC
Working towards
Status



Capacity Building and Collaboration with China

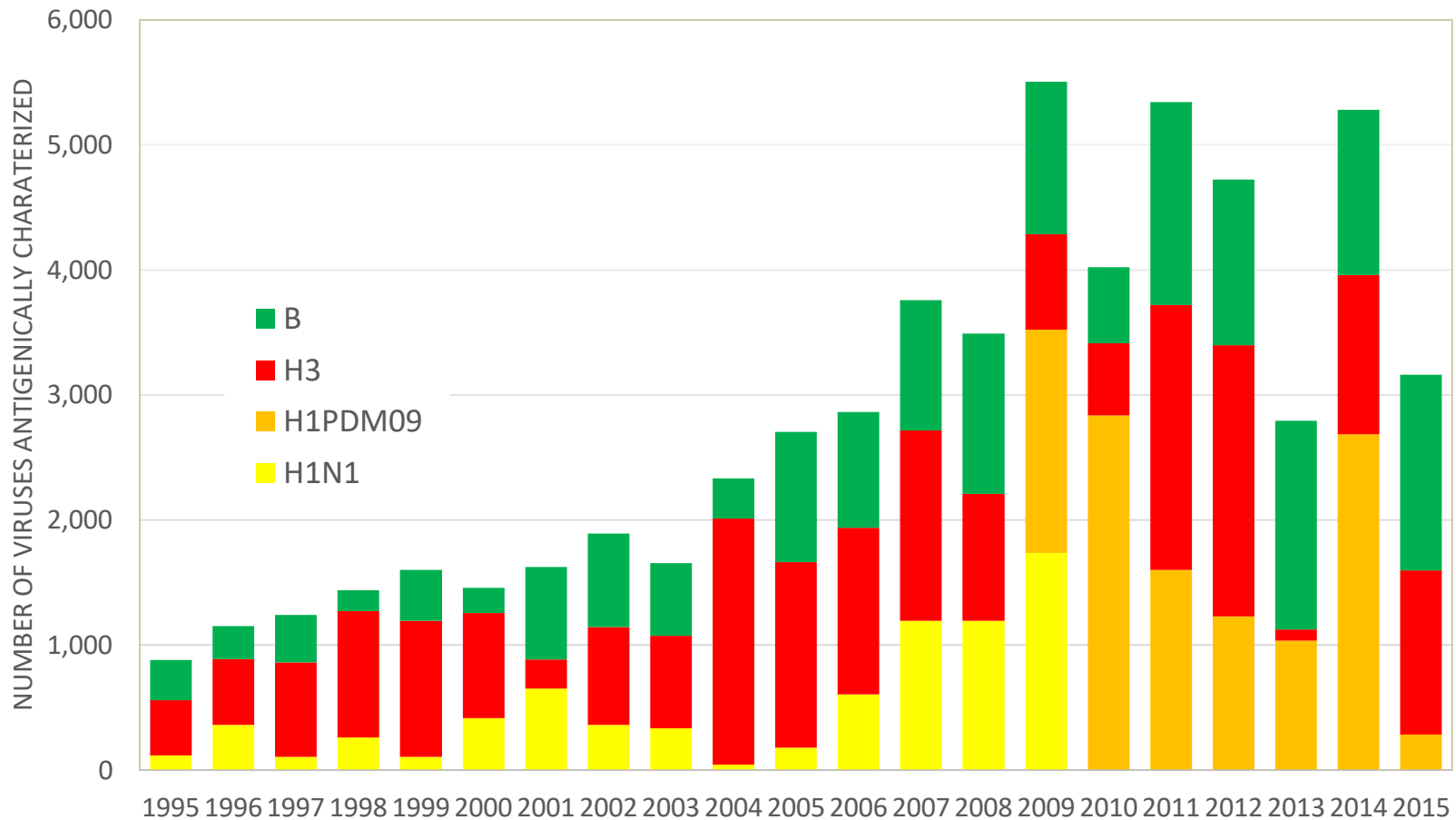
- 1988 – CDC's influenza program began collaboration with the Chinese National Influenza Center (CNIC)
 - Financial and technical support and training for virologic surveillance provided through the Chinese Academy of Preventive Medicine
- CDC established a Cooperative Agreement with Chinese National Influenza Center (NIC) for epidemiology and lab capacity development in 2005
- CNIC became a WHO Collaborating Center in 2011 with continuing close ties with CDC
- Rapid reporting of human infections by seasonal and novel influenza viruses, especially for H7N9 and other zoonotic influenza infections
 - South China postulated as the epi-center for emergence of pandemics
 - New antigenic variants of seasonal influenza often emerge first in SE Asia

Expansion of GISRS



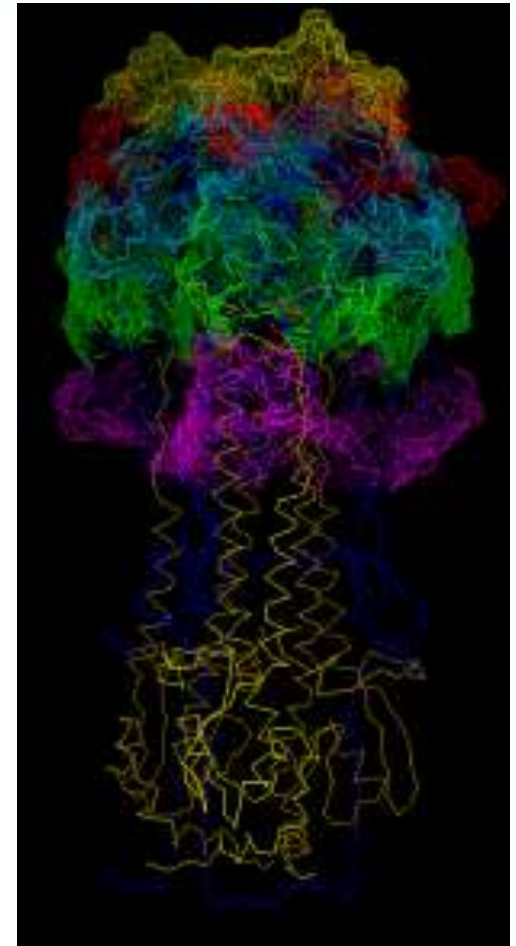
> 2,000,000 specimens/yr tested in GISRS
> 20,000 viruses/yr shared with WHO CCs
~ 10,000 viruses/yr characterized by CCs

Influenza Viruses Antigenically Characterized by CDC, 1995-2015



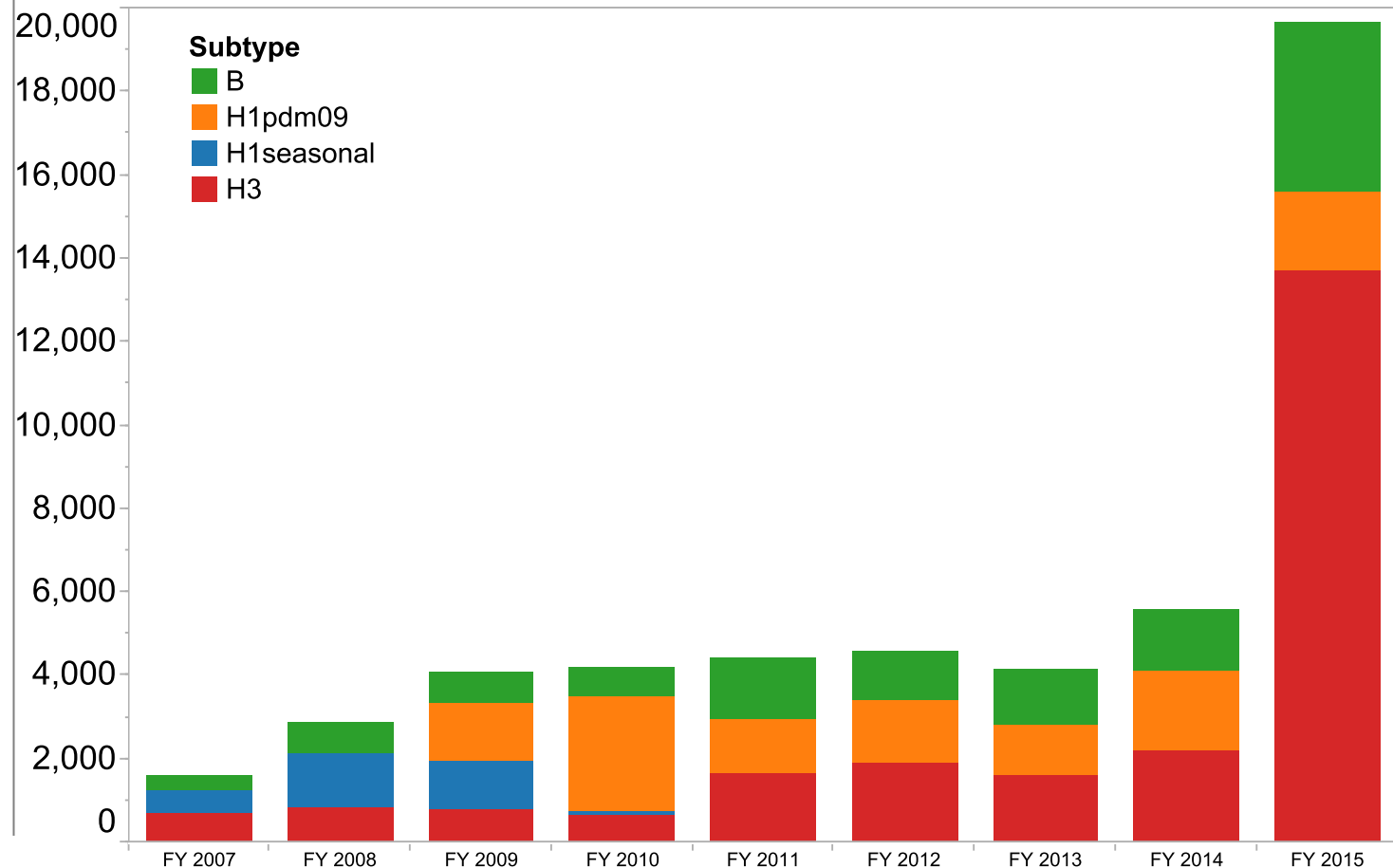
Molecular Epidemiology of Influenza Viruses To Support Vaccine Virus Selection, 1986

- ❑ Antibody combining sites A and B are critical for antigenic variation
- ❑ The number of glycosylation sites has continued to increase over time
- ❑ Most surface accessible residues of HA have changed during circulation of H3 and H1
- ❑ Different topologies observed for HA genes of types A, B and C viruses



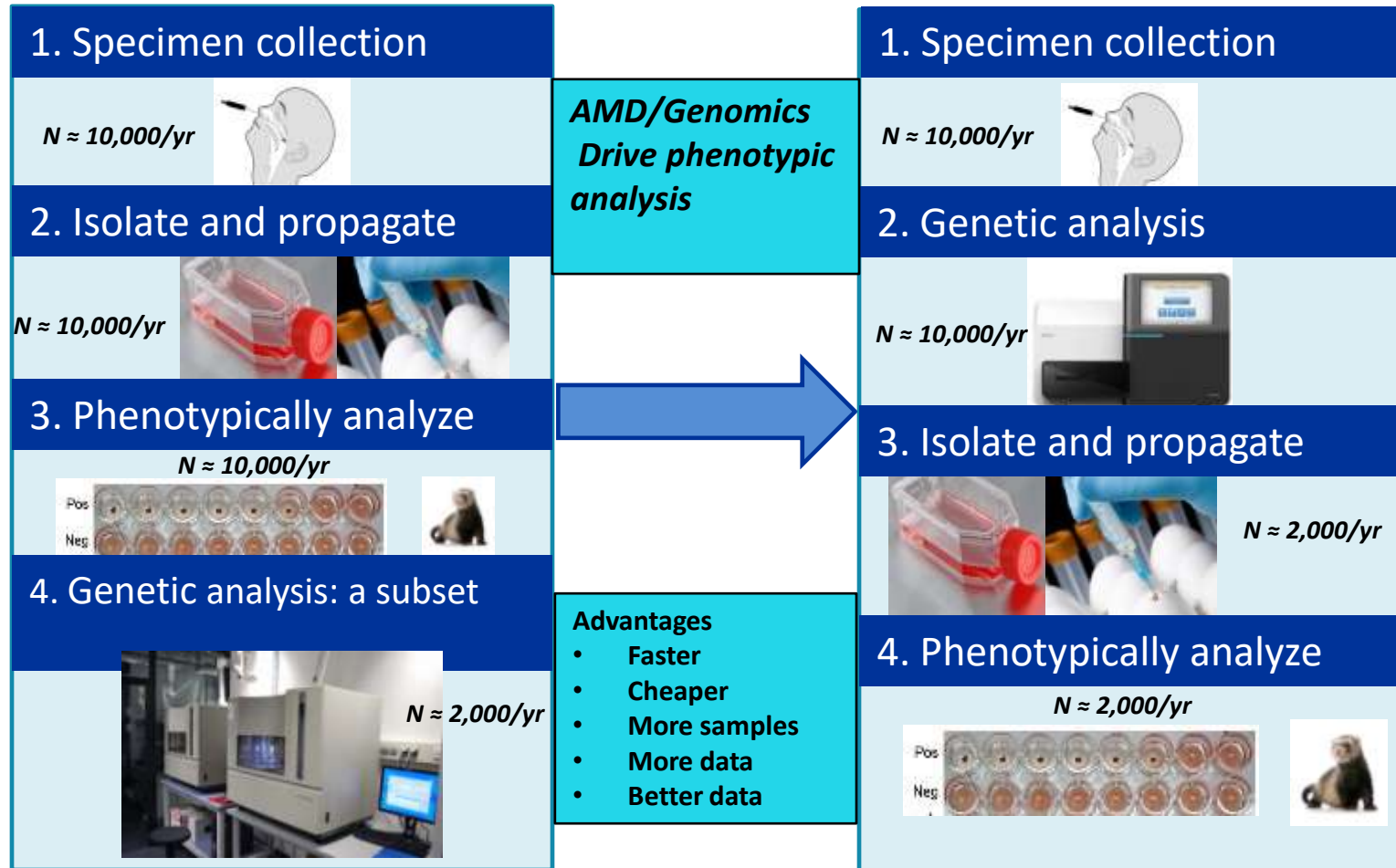
Improving Detection: Increase Sequencing

Number of Gene Segments Sequenced per Season, CDC

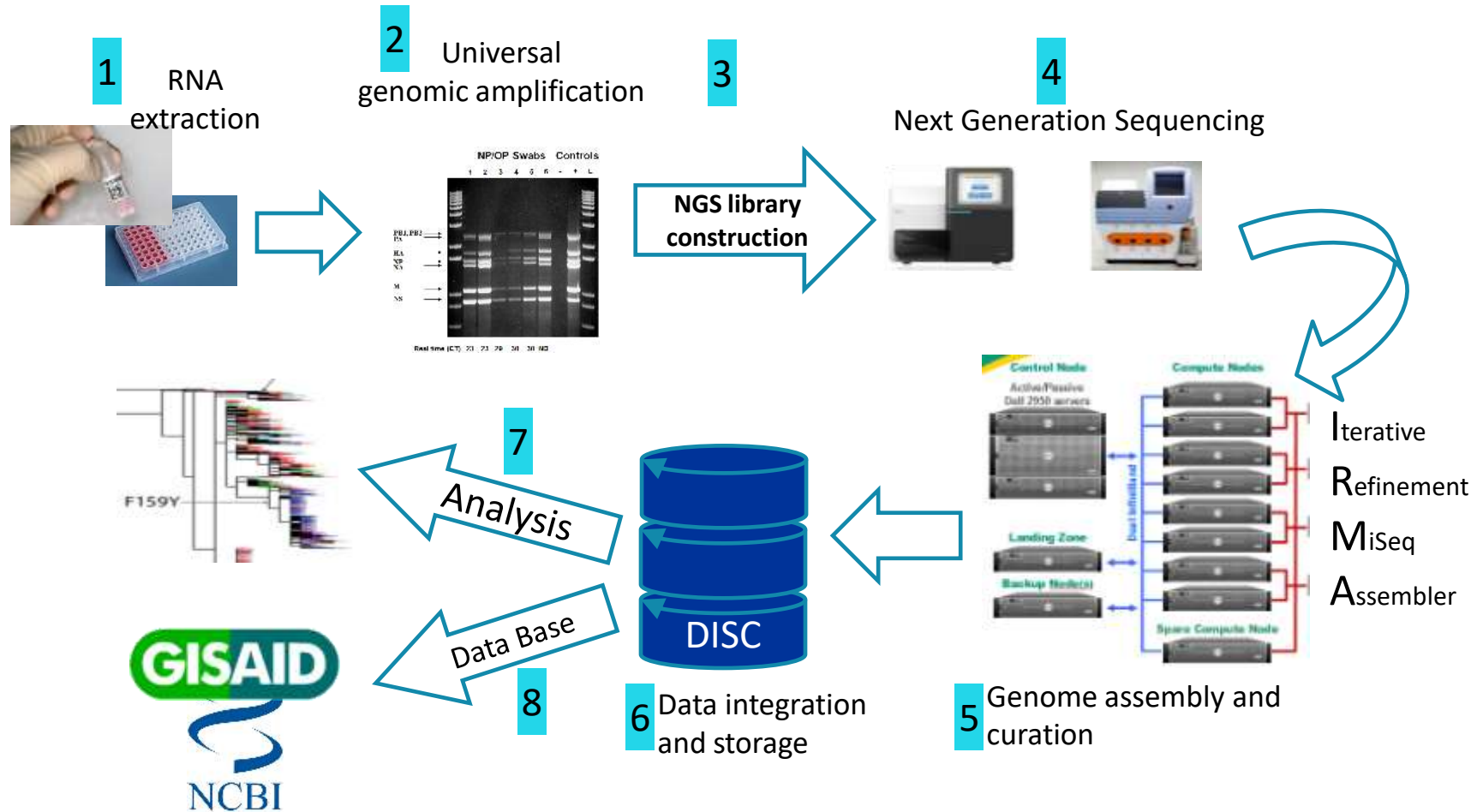


**2016 Season - Goal influenza positive specimens will undergo full genome sequencing
(forecast > 50,000 segments)**

Transforming the Virologic Surveillance Paradigm:

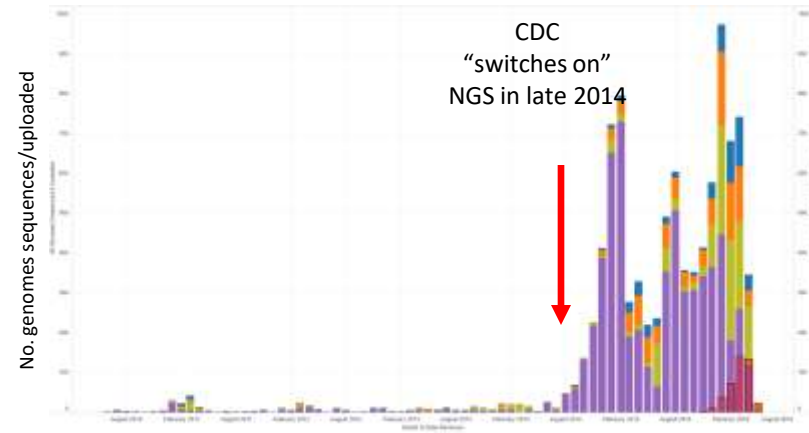
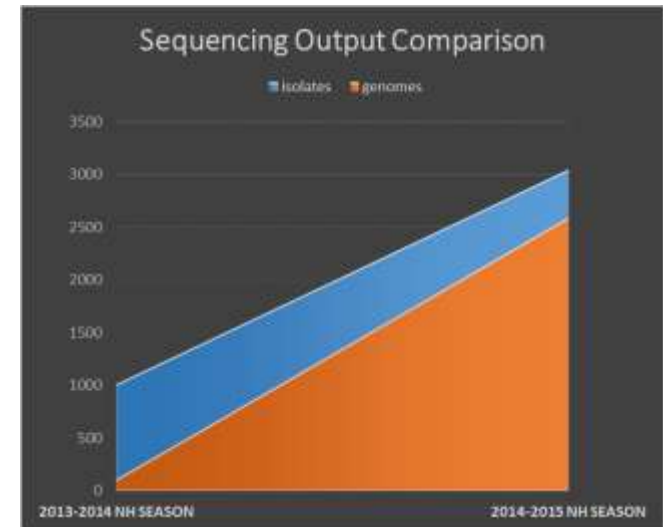


CDC Influenza Virus NGS Pipeline



Increasing Volume of GSD for Seasonal and Zoonotic Influenza Viruses: CDC example

- Large gains in genetic information
 - ~2,000% increase in whole genomes
 - ~200% increase in isolates sequenced
- Complete genomes were generated for H1N1, H3N2, H5Nx, H7N9, and Influenza B viruses
- Genetic data regularly uploaded to GISAID; US seasonal virus data also goes to GenBank
 - Three US public health contract labs now doing NGS of seasonal US viruses



CDC Fostering Influenza Virus Sequencing and Analysis Capacity

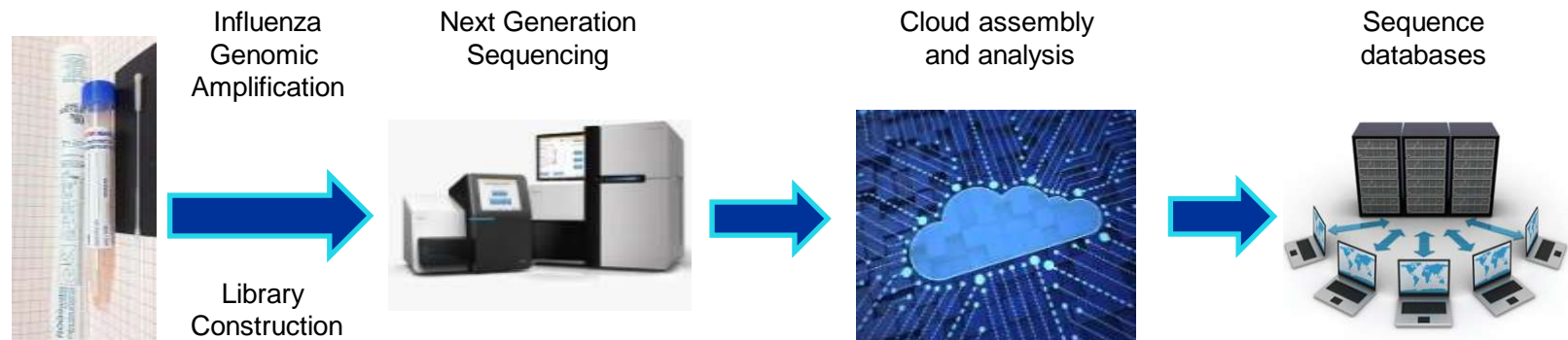
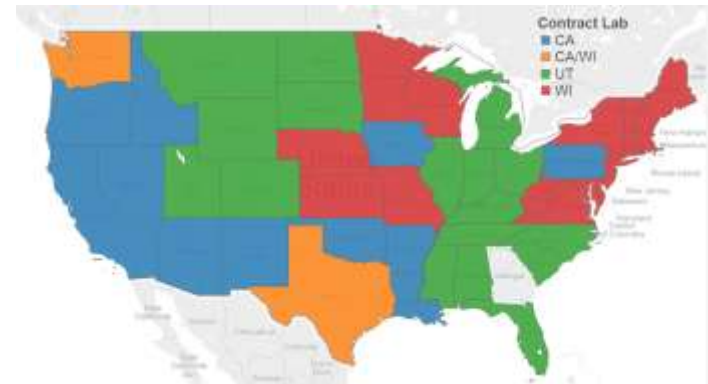
Robust next generation sequencing scheme

- Wisconsin, California and Utah implemented

Future directions

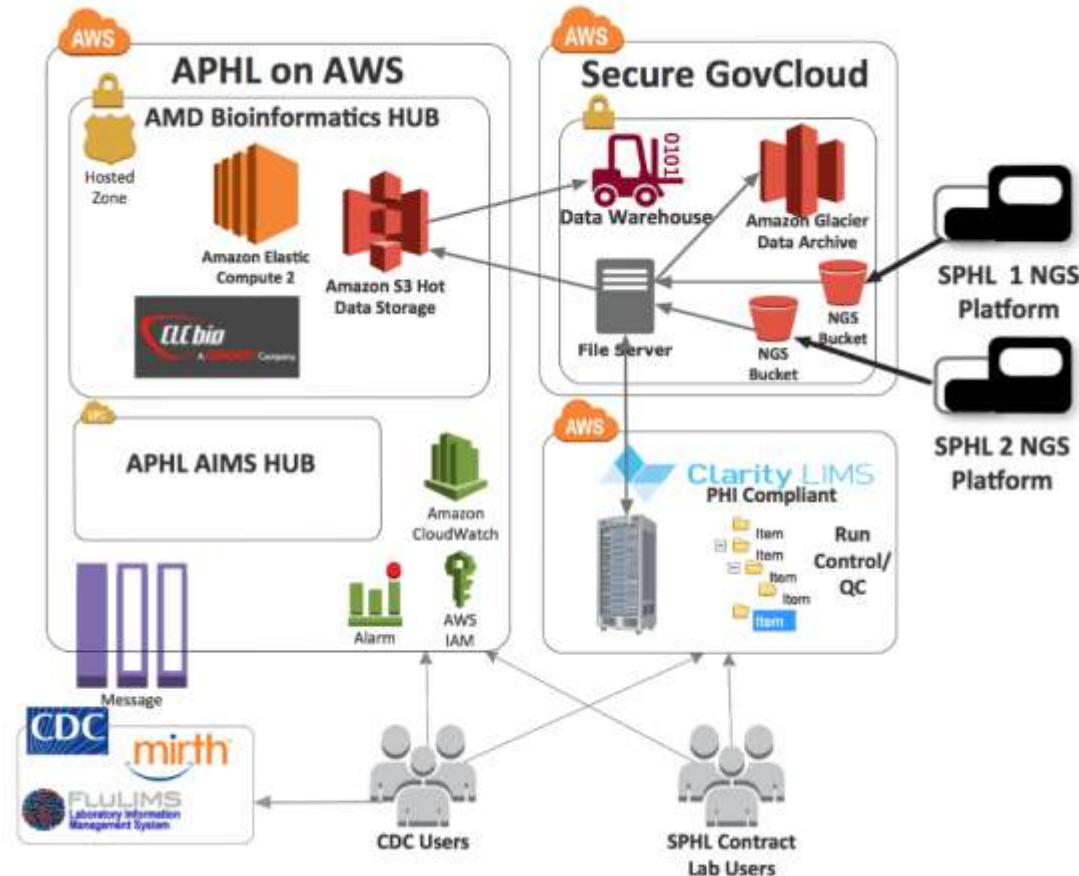
- State and local PH departments
- WHO Collaborating Centers
- National Influenza Centers

2015 Influenza Division Contract Labs



Developing Critical Cloud Based Analytics for Future Influenza NGS Expansion

- Cloud based analytic NGS
 - Important for implementing at and PHL and NICs
- Collaborating with APHL
 - Analytic resource to assemble, analyze and store NGS data



The Future of Influenza Detection

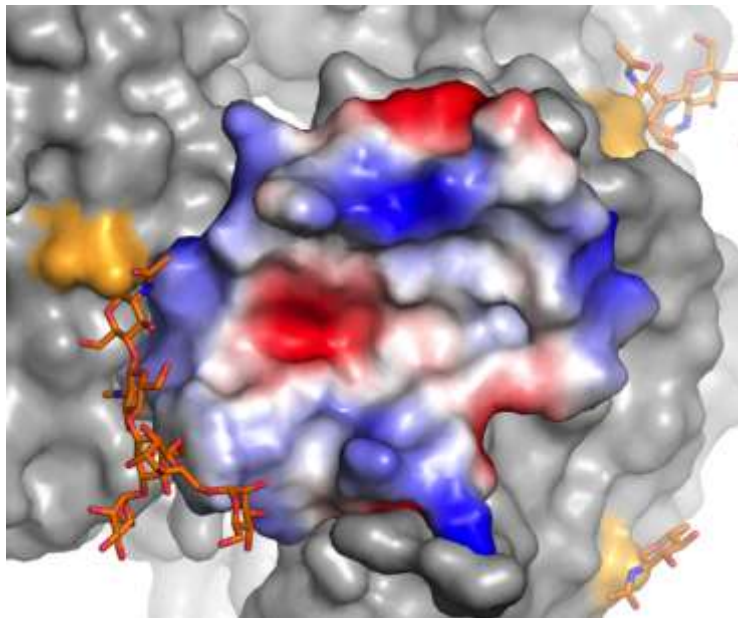
- Next Generation Sequencing
 - Influenza detection is on solid footing with RT-PCR and NGS
 - NGS is saves time if sequencing conducted locally on clinical specimens and data transmitted to cloud for storage and analysis
 - NGS is cost saving for equivalent data compared to Sanger sequencing
 - But requires substantial investment in bioinformatics
 - Human resources and high-speed computing resources required to analyze huge influx of GSD
 - Challenging for many resource challenged PH laboratories
- NGS and sequence first is appropriate for high income countries
 - Transitioning NGS to low and middle income countries will take time and significant additional resources
- Remaining need for cheaper and more accurate POC tests for use in clinical and institutional settings
 - Greater sensitivity and ability to differentiate viruses

Remaining Challenges For Vaccine Virus Selection

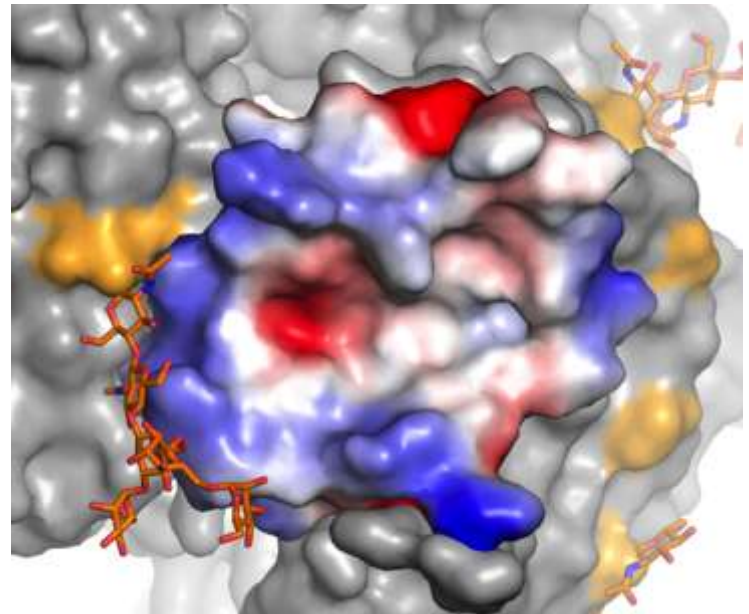
- Timeliness of data for vaccine virus selection
 - Delays from respiratory specimen collection to receipt of viruses at WHO Collaborating Centers
- Rapid data comparison and data visualization
 - Large quantities of NGS, antigenic, epidemiologic and serological data require new methods of analysis and visualization
- Growing H3N2 viruses in eggs to develop a candidate vaccine virus antigenically-like circulating viruses is problematic
 - Most doses of vaccine still produced in eggs (86% of vaccine doses are inactivated egg-based vaccines)
 - **The decades long efforts to replace egg-based influenza vaccine production has had only modest success but efforts need to continue so we can take eggs out of the equation!**
 - Current H3 viruses are highly mammalian-adapted after almost 50 years of circulation in human and have to adapt to grow in an avian environment in order to be propagated in eggs and these adaptations often confer changes in antigenicity
 - Vaccine effectiveness of the H3N2 vaccine component may be compromised

H3 Receptor Binding Pocket, 1968 - Today

Hong Kong/1/1968



Victoria/361/2011



- RBS has changed in overall shape and charge
 - Maintains α 2-6 receptor specificity
 - Reduced receptor avidity
 - Egg adaptation necessary for vaccine virus growth in eggs and this often alters antigenicity

Data Analysis for Vaccine Virus Selection



- Epidemiology

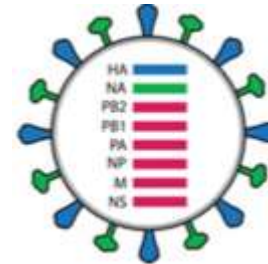


- Antigenic characterization, HI MN

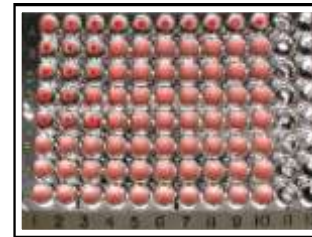


- Gene sequencing

- Sanger
- NGS



- Human Serology

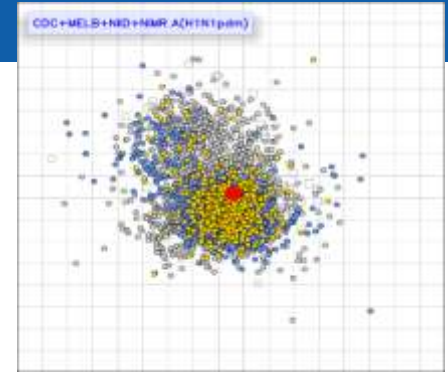


Advances and Challenges in Prediction: Should Vaccine Viruses Be Updated?

- Have new antigenic variants been detected? **YES**
 - Hemagglutination-inhibition assays and neutralization assays using post-infection ferret antisera
- Do the antigenic variants have accompanying molecular changes in the HA that are associated with the observed antigenic changes? **YES**
 - Sequencing HA genes to look for “signature” amino acid changes
 - Look at nature and position of the HA aa changes
 - NA also analyzed in detail
- If yes above, are the new antigenic variants associated with localized outbreaks epidemics ? **YES**
 - **Trend analysis** - monitor influenza activity around the world for spread of new variant. Is frequency of variant detection increasing.
- Are current vaccines able to induce high levels of antibody to new variant viruses? **NO**
 - Panels of serum from vaccinated children, adults and older adults to determine if antibody levels are significantly lower to variant viruses than to vaccine virus itself
- Are there suitable egg-propagated high growth reassortants available for vaccine production? **YES**
 - It takes many attempts to produce an H3N2 candidate vaccine virus with suitable antigenic properties due to difficulties in egg isolation
- What are interim vaccine effectiveness studies telling us? Are there signals of suboptimal VE that might be attributed to laboratory finding above?

Challenges For Influenza Prediction

- Assay Standardization across GISRS laboratories
- Data integration visualization across CCs
- Data analysis
- Series of 4 WHO Consultations on Improving Vaccine Virus Selection
 - Latest meeting November 2015 focused more on collaboration with predictive modelers and making predictions with data available for Vaccine Consultation Meetings
- ‘Modelling Influenza Conference’ held at Princeton University, July 2016
 - Brought together modelers and WHO Collaborating Center staff
 - To broaden and strengthen understanding of different influenza predictive models
 - Determine how to assess and harness potential contributions of computational modeling to vaccine virus selection
 - Considerable promise for the future, but..... **“It’s tough to make predictions, especially about the future.” Yogi Berra, renown baseball player, coach and philosopher (1926- 2015)**



Challenges in Influenza Virus 'Prediction'

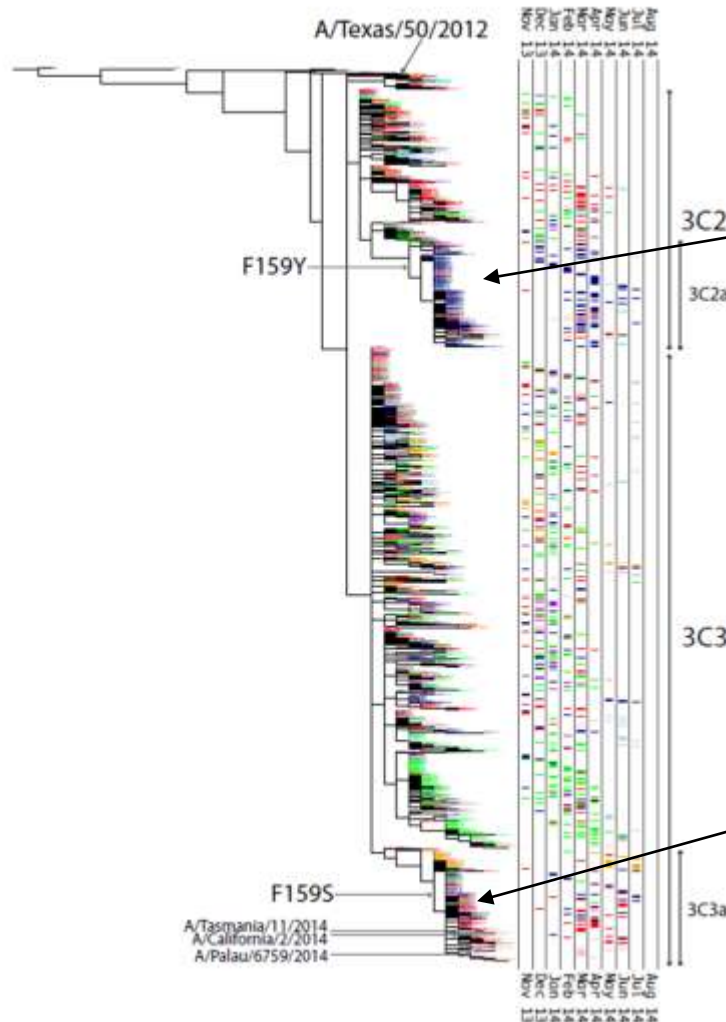
- We know many HA positions where key amino acid changes confer changes in antigenicity
- We understand that antigenic evolution is punctuated and determined by a limited number of amino acid changes in key sites
- Inferring antigenic phenotype from genetic data remains a fundamental challenge and emphasizes the continuing need for virus isolation and characterization as the foundation to infer antigenicity
- We focus on emerging trends but challenge remains in predicting if trends will continue for the next 6-9 months
- Example: Two emerging antigenic/genetic groups, (e.g., clades 3C.3a and 3C.2a of A/H3N2 viruses in spring and summer of 2014) and both spreading globally
- Other things being equal, which emerging group do you choose for inclusion in the vaccine?

The H3N2 Influenza Vaccine Virus Conundrum

Data confirmed expansion of Groups 3C.2a, 3C.3 and 3C.3a

Greatly enhanced the data available for Southern Hemisphere Vaccine Consultation Meeting

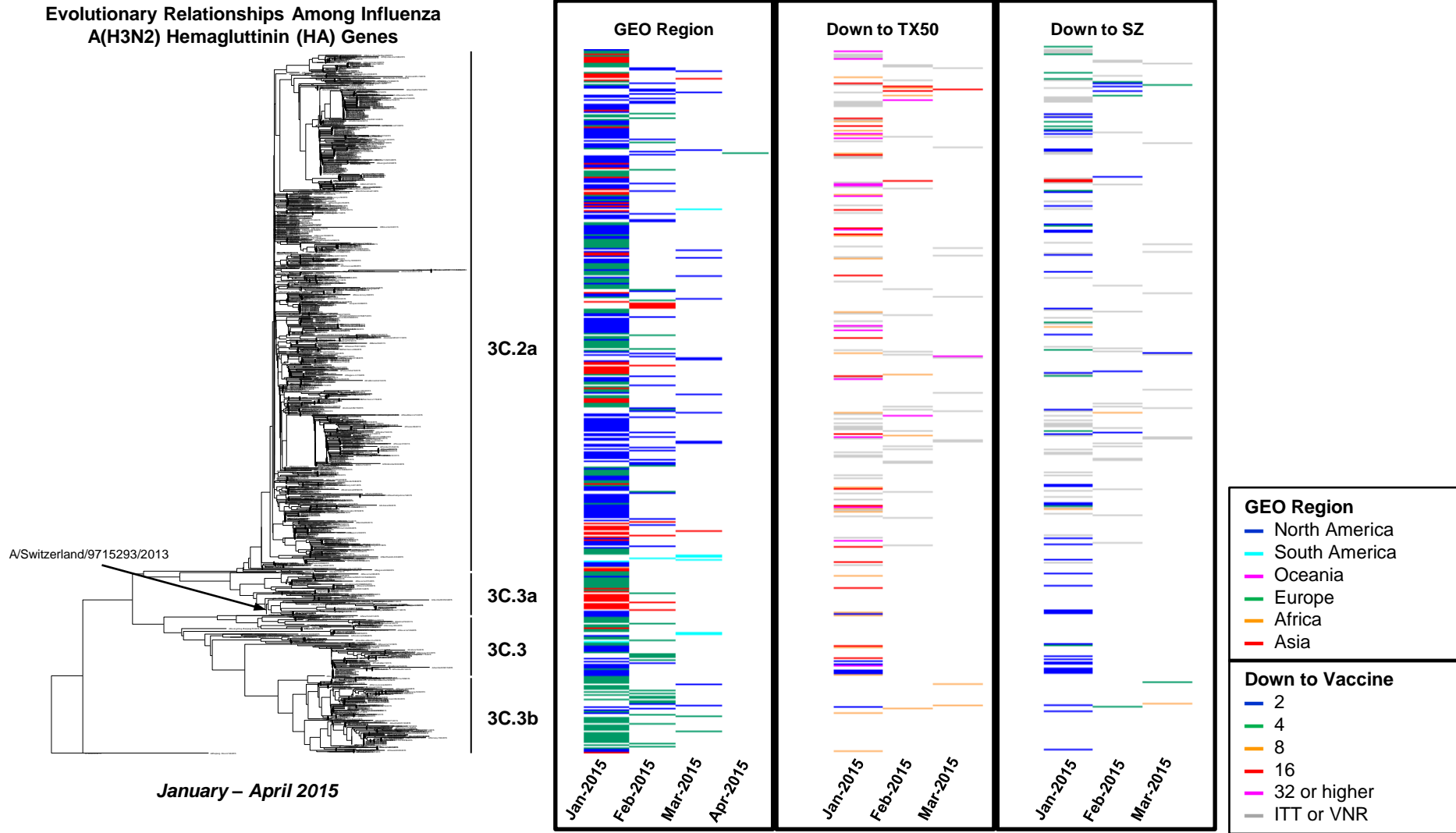
H3N2 vaccine component was changed to A/Switzerland/9715293/2013 a 3C.3a virus



Expansion of 3C.2a in US and Bangladesh

Global expansion of 3C.3a

Another Example of High Level Trend Analysis



Rainbow Phylogenetic Tree and Heat Maps Developed by Yunho Jang

The Future of Prediction – Progress but a Long Way to Go

nextflu

Real-time tracking of seasonal influenza virus evolution in humans

Virus: A/H3N2

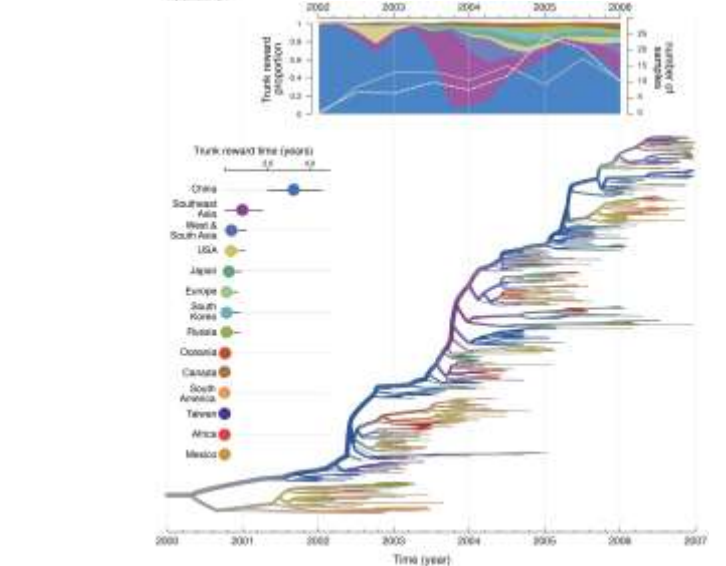
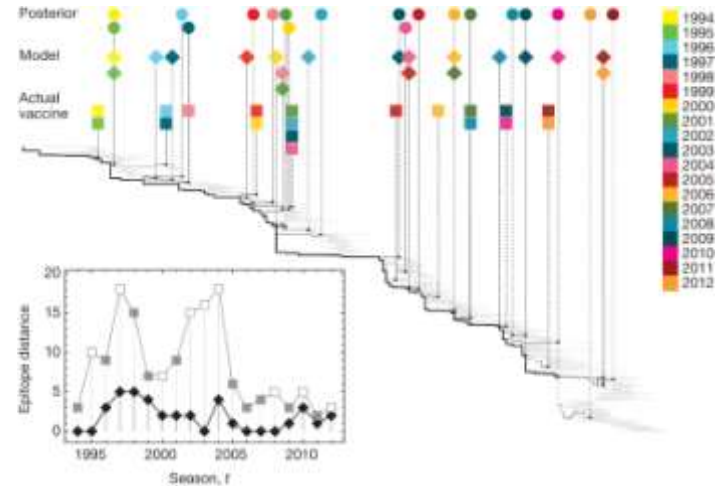
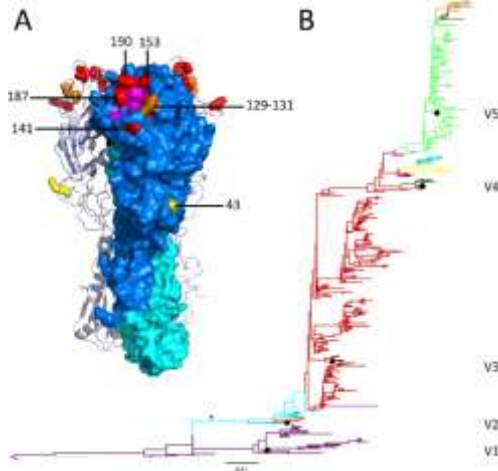
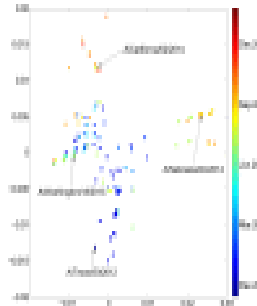
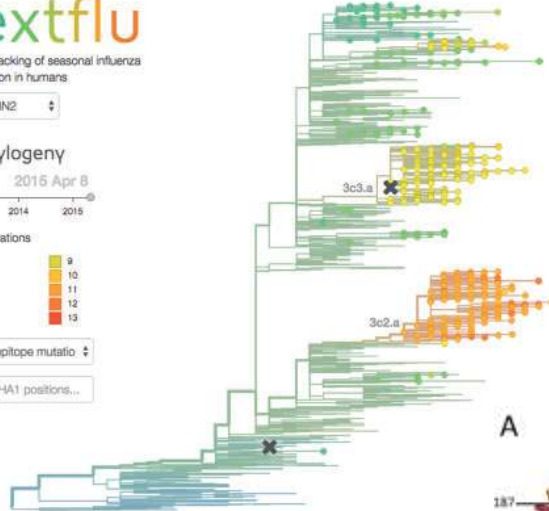
HA phylogeny

2015 Apr 8

Epitope mutations



Or: HA1 positions...



Neher, RA and Bedford T. 2015. *Bioinformatics* 3, 3546-3548

Łuksza M & Lässig M. 2014. *Nature* 000, 1-5 doi:10.1038/nature13087

Li and Deem M. 2016. *Protein Engineering, Design & Selection*, vol. 29 no. 8, pp. 309–316

Advances in Prevention

- New vaccines licensed
- New 2012 WHO vaccination policy with emphasis on vaccinating pregnant women, young children and health care workers
 - Increased coverage in some populations
- WHO's Global Action Plan for Influenza Vaccines*
- Increase in vaccine uptake in the Americas (USA and Latin American Countries)**
- Annual estimates of PCR laboratory-confirmed vaccine effectiveness estimates in multiple countries

* Partridge J and Kieny MP. 2013. Vaccine 31. 728-31

**Ropero-Alvarez AM, Omeriri N, et al. 2016. Human Vaccines and Immunotherapy 12, 2206-2014

Multiple Licensed Influenza Vaccine Presentations, U.S. Season

- Fluarix QIV
- FluLaval QIV
- Fluzone QIV
- Afluria TIV
- **Fluad MF-59**
- Fluarix TIV
- FluLaval TIV
- Fluvirin TIV
- Fluzone ID TIV
- **Flucelvax CC TIV**
- Fluzone High Dose TIV
- **FluBlock Recomb TIV**
- **FluMist QIV***
- Single and multi-dose vials

Different vaccines have different age indications

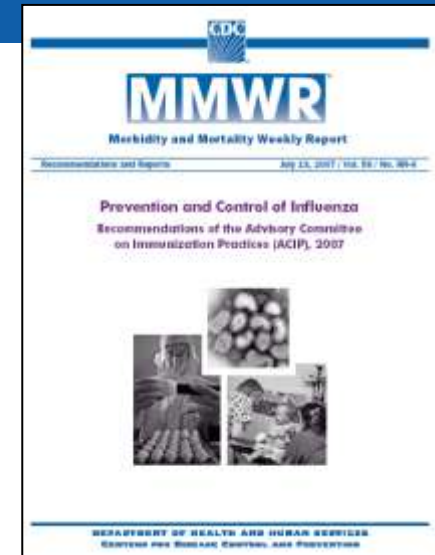
ACIP recommends influenza vaccine for everyone ≥ 6 m of age

Vaccine effectiveness estimates = 45-60% for well matched and lower VE for 'mismatched' years

***Not recommended by the Advisory Committee on Immunization Practices for use in 2016-17 influenza season due to low VE in children over several seasons. Rec will be reconsidered with new data.**

Influenza Vaccination Recommendations Over Time

Before 2000:	Persons aged 65 or older Persons with high-risk chronic medical conditions Pregnant women in the 2 nd /3 rd trimester Household contacts of the above Health care workers
2000:	Adults 50 and older
2004:	Children aged 6—23 months Household contact of children aged 0--23 months Women who will be pregnant during influenza season
2006:	Children aged 6—59 months Household contacts of children aged 23-59 months
2008:	All children aged 6 months—18 years
2010:	All persons > 6 months in the US



Global Influenza Vaccine Manufacturing Capacity Has Increased; Demand Stagnated

- WHO's Global Action Plan for Influenza Vaccines - a comprehensive strategy to reduce the global shortage of influenza vaccines for seasonal epidemics and pandemic influenza in all countries of the world
- Vaccine manufacturing capacity increased to ~ 1,069 M doses for the Northern Hemisphere 2011-12 season
 - But only 534 M doses (~ 50%) were actually produced due to lower demand
- ~ 352 M doses could be manufactured for 2011 season in the Southern Hemisphere
 - 86 M doses (~ 24%) actually produced due to lower demand
- How long will increased mfg. capacity be maintained, particularly as WHO's Global Action Plan sunsets this year?

Improvements in Vaccine Uptake: Experience in The Region of the Americas

- Over half of global doses distributed in the Region of the Americas
- Significant increases in Latin America and the Caribbean (LAC) countries
 - 40/45 (89%) of countries have seasonal flu vaccination policies
 - 30/45 (67%) of countries purchase through the PAHO/WHO Revolving Fund
 - Strong PAHO leadership and strong national commitment to regionally agreed vaccine policies
 - Horizontal learning among LAC countries for establishing flu immunization programs
 - Based on new seasonality data, several countries in tropical areas changed to SH vaccine formulation and altered timing of vaccine administration
- *Palache A, Oriol-Mathieu V, Abelin A, Music T. 2014. Vaccine 32, 6369-76. WM
- , ** Palache A, Oriol-Mathieu V et al. 2015. Vaccine 33, 5598-5605.

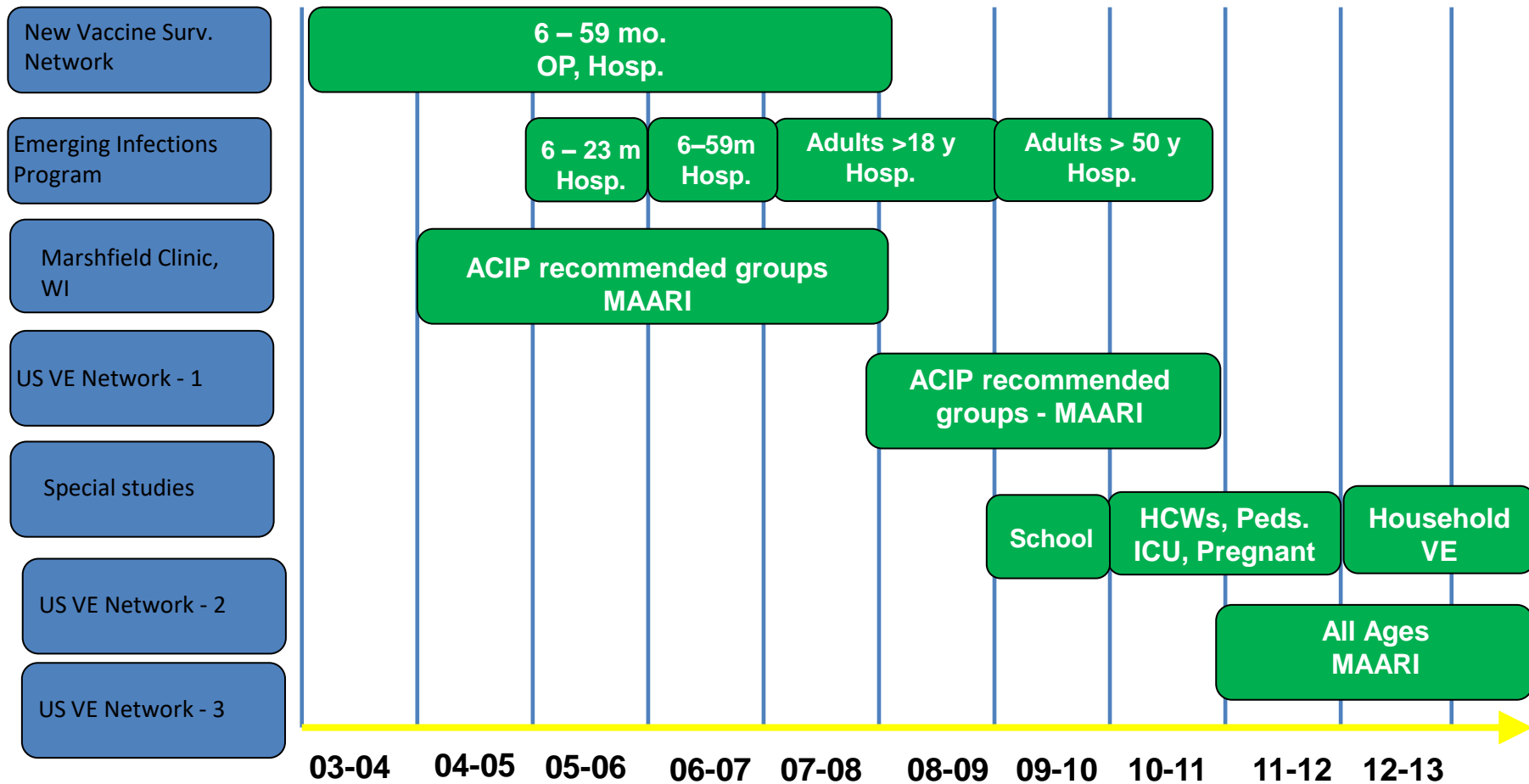
Global Challenges in Vaccine Uptake

- Only 4% of the global supply of flu vaccine distributed in African, Southeast Asia and Eastern Mediterranean Regions which account for half of world's population*
- Distribution in European Region decreased by 32% between 2008 and 2013, with 72% of countries having lower rates of distribution**
- 74 countries in tropical and subtropical countries have no national seasonal influenza vaccination policy in place (~ 60% of world's population)
 - Other health priorities
 - Lack of burden of disease data

*Palache A, Oriol-Mathieu V, Abelin A, Music T. 2014. Vaccine 32, 6369-76. WM

, ** Palache A, Oriol-Mathieu V et al. 2015. Vaccine 33, 5598-5605.

CDC's Program to Measure Influenza Vaccine Effectiveness in the U.S.



U.S. Flu VE Network: Methods

- Design: Prospective case-control study
 - Cases: MAARI with RT-PCR confirmed influenza
 - Controls: MAARI but negative for influenza
- Vaccination status: confirmed by medical record or registry (4 sites) and self report (1 site)
- Immunization: defined by receipt of at 1 dose of vaccine 14 or more days before onset of respiratory symptoms (or 2 doses for <9 years)
- Analysis: $VE = (1 - \text{adjusted OR}) \times 100\%$, estimated with logistic regression models
- Similar VE studies are also conducted in Europe (I-MOVE), Canada, Australia & New Zealand; VE network established in Latin America allowing comparisons
- **VE studies are important to monitor vaccine performance in real-world conditions**

Challenges for Performance of Influenza Vaccines

- Vaccine performance - lower than desired VE for both IIV and LAIV
 - VE is ~ 50-70% for antigenically well-matched circulating influenza B and H1N1 viruses, but typically lower for well-matched H3N2 viruses
 - Potential for antigenic mis-match
 - Example: Adjusted VE by type and subtype 2014-15 season was 55% and 63% for influenza B Yam and Vic lineages, respectively, but only 13% for A(H3N2) which was not antigenically well-matched
 - Need to determine vaccine virus components twice a year; don't always change vaccine components
 - Need to administer annually
- New influenza vaccine development
 - Significant scientific and regulatory challenges
 - Cost of new vaccine development estimated ~ \$1B USD

Challenges in Influenza Prevention with Current Influenza Vaccines

- Vaccine targets are rapidly changing seasonal viruses & infrequently emerging pandemic viruses
- HA variant-specific” acquired after infection and vaccination; reduced protection vs. new antigenic variant
- A race against time to detect new influenza variants AND develop and produce vaccines prior to widespread disease
- Production of seasonal and pandemic influenza vaccines is a high-risk, high-stress endeavor for manufacturers. We’ve see a recent consolidation of influenza vaccine manufacturers.



The Future of Influenza Vaccines

- We have ‘next generation influenza gene sequencing’ now we need ‘next generation influenza vaccines’
- In 2012 Mike Osterholm called for a Manhattan-type project* for influenza vaccines but the idea did not gain traction
- Influenza vaccine-specific challenges
 - Variable target antigens and absence of long-lived protective immunity
- Population-specific challenges
 - Immaturity of the immune system in neonates
 - Immune senescence in the elderly
- Human Vaccines Project launched in 2014**

• *Osterholm MT and Kelley NS et al. 2012. Lancet Infectious Diseases 12, 36-44.

• **Koff, WC, Gust ID and Schenkelberg T. Toward a Human Vaccines Project. 2014. Nature Immunology 15, 589-592.

Human Vaccines Project

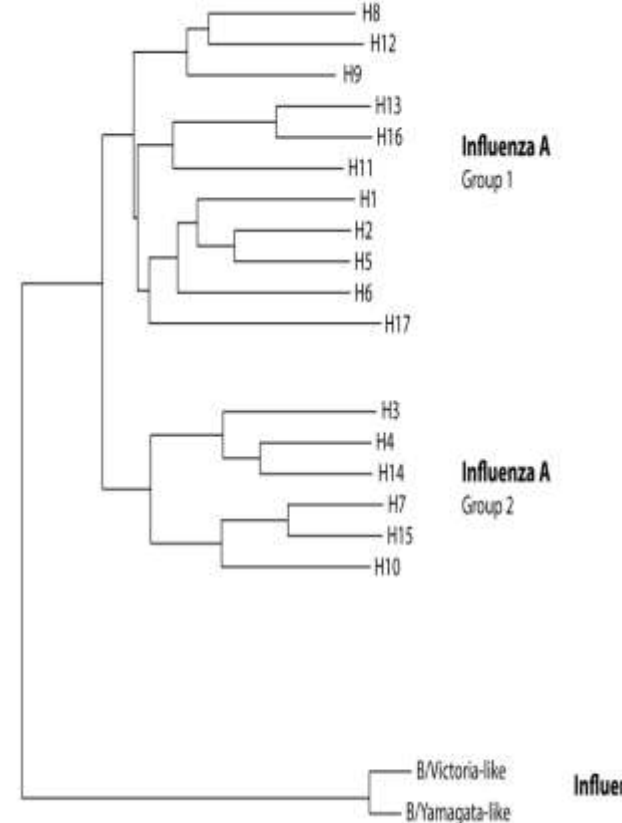
- Vaccines for preventing infectious diseases are one of the greatest achievements of modern medicine but developing vaccines to HIV, HCV and developing universal flu vaccines has proven extremely challenging
- Human Vaccines Project based on concept that next generation vaccines to will generate specific, potent, broad and durable vaccine-induced immune responses to difficult targets will require a different approach than used in the past
- Built on vast transformation in the nature of research in the biological sciences. Start by conducting a comprehensive assessment of human immune responses to licensed and experimental vaccines in rapid, focused and iterative clinical research trials
 - Includes a ‘big-science’ component aimed at determining of all genes and proteins associated with the immune system
 - Includes a target antigen discovery component
 - Contingent on recent developments in gene sequencing, immune monitoring, increased computing power and the data managing systems able to analyze massive amounts of data

Human Vaccines Project

- Business model
 - Focus on 'pre-competitive' space for maximum collaboration and progress
 - Raising funds from multiple sources with expected need of \$1 B over 10 years
- Establish hubs in existing institutions with necessary infrastructure and skill sets
 - First hub at Vanderbilt University School of Medicine
 - Second in San Diego, California (UC San Diego, J Craig Venter Institute, Scripps Research Institute)
- Project goals
 - Improve efficacy of selected licensed vaccines (influenza ?)
 - Expedite AIDS, TB, malaria and cancer vaccine development
 - Emphasis on heterogeneous populations including infants and elderly and developing world populations
 - Emphasis on emerging epidemic/pandemic threats
 - Redefine the requirements for licensure for future vaccines

Universal Influenza Vaccines

- ❑ The Ideal Flu Vaccine
 - A single vaccine or series with lifelong protection against influenza A subtypes and both lineages of influenza B
- ❑ Is it achievable?
- ❑ A practical outcome: A vaccine with protection for several (possibly 3-5) years
 - Reduce need to re-formulate annually
 - Reduce or negate impact of vaccine 'mismatches'
 - Surveillance would remain important
 - Potential to reduce production and administration costs
 - Potential surge capacity for rapid scale up for pandemic vaccine
 - Potential for reducing vaccine shortages
 - Year around production → increase global vaccine supply



Most Important Influenza Challenge/Unmet Need

- Development and licensure of truly “universal” flu vaccine pose enormous scientific and regulatory challenges
- Must do better than nature to protect from influenza disease
 - Individuals over 57 years of age have been exposed to H1N1, H2N2, H3N2 and B viruses over a lifetime but death and hospitalization are highest in older age groups
- Incremental advances in breadth and durability of protection are desirable in the interim
- Combinations of approaches and partners including government funding may be required
- One of the most important and greatest scientific challenges in the field of influenza



Incremental Advances toward Better Prevention

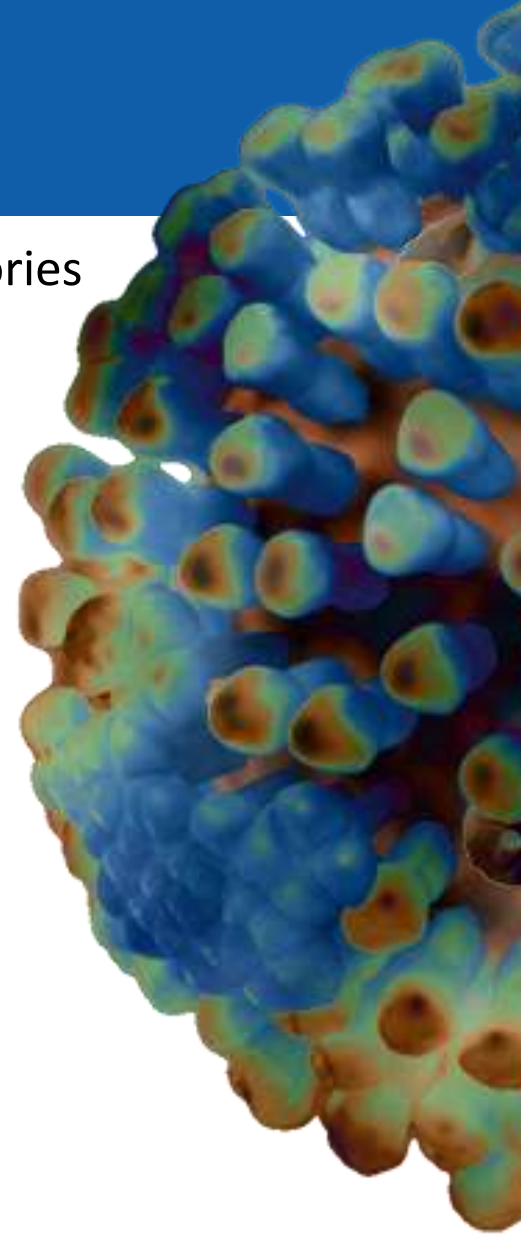
- Are we doing the best we can with current influenza vaccines?
- Broader use of adjuvanted vaccines for older adults/other populations?
- Are we using the best dose of each antigen for all types/subtypes?
Current 15 ug dose based on decades old H1N1 trials
- Can we enhance CMI and mucosal response through LAIV prime followed by IIV boost?
- Are there other prime boost strategies that would improve VE?
- Can we inducing better CMI through vectored vaccines or recombinant protein/peptide vaccines
- Will enhancing antibody response to NA improve vaccine effectiveness?

Many Other Challenges

- Better understanding of influenza pathogenesis and new tools for treatment of severe influenza illness
 - New antivirals
 - Monoclonal antibodies
- Animal/human interface
 - Continuing need to strengthen influenza surveillance in animals, especially pigs and poultry
 - Continuing need to strengthen veterinary services in LMIC
- Vaccines for low and middle income countries
 - Need vaccine for children < 6 months of age
 - Concern that a universal vaccine will be too expensive for many LMIC

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Thank You!

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