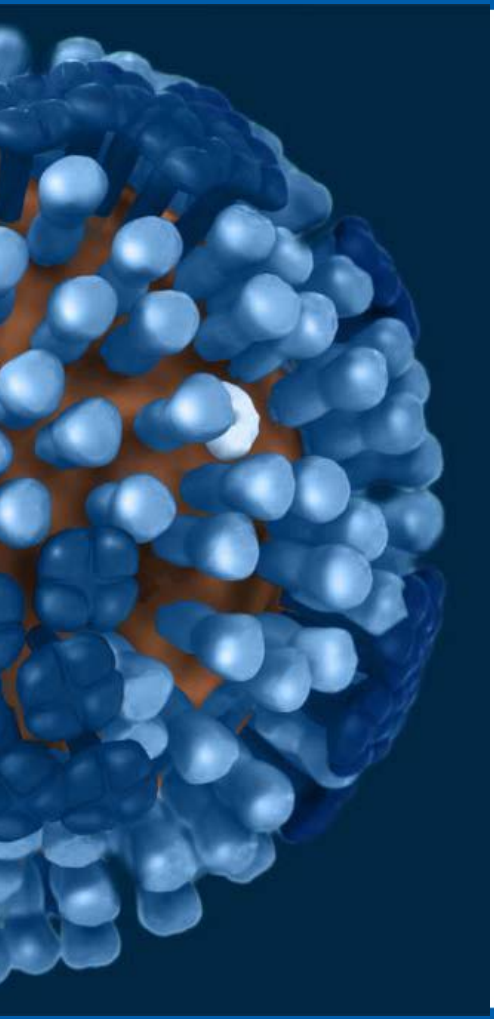

Results of the Risk and Benefit Assessments of Gain-of-Function Studies

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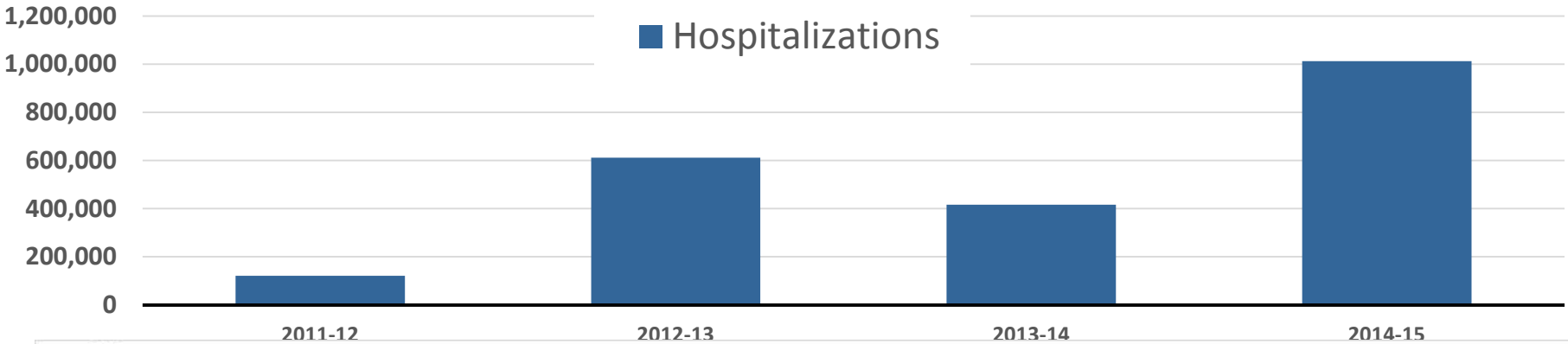
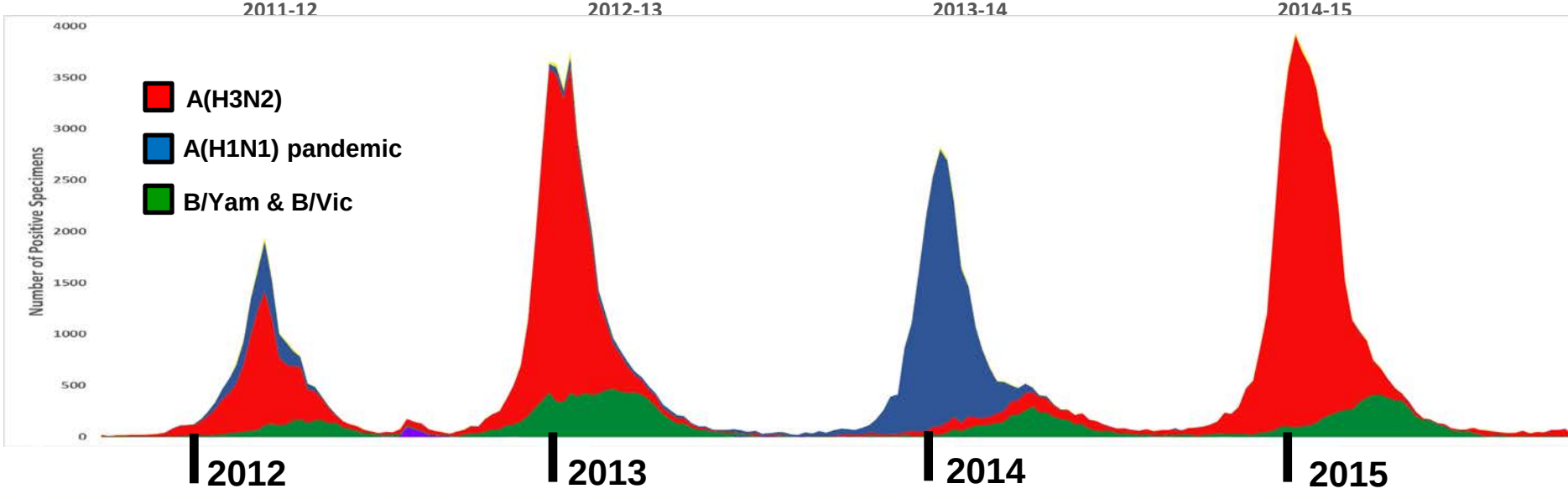
January 7, 2016

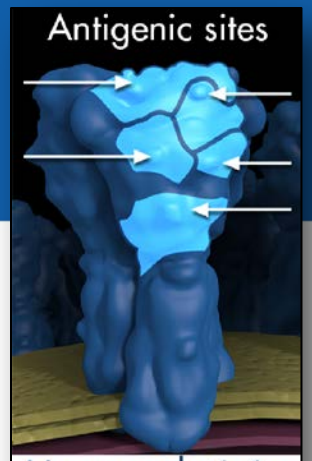
Burden of Seasonal Influenza





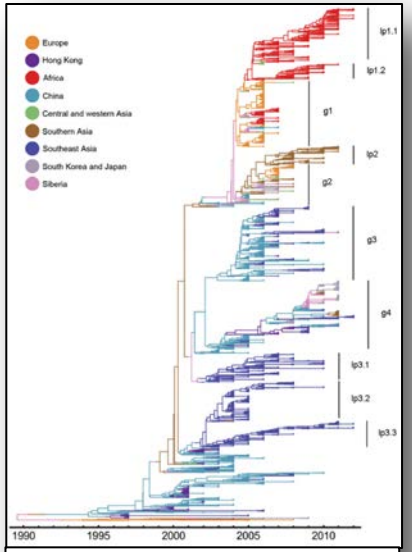
Reed et al, Estimating Influenza Disease Burden. PLoS One. 2015 Mar 4;10(3):e0118369. (Data for 2011-13)
Reed et al, Unpublished CDC data for 2013-15.
CDC. US Influenza Virologic Surveillance. www.cdc.gov/flu/weekly/overview.htm

New Challenges Require New Solutions



Hemagglutinin

- H3N2 virus characterization and vaccine development is increasingly difficult
  - Drift occurs regularly and rapidly
  - H3N2 changes antigenicity in egg- and cell-propagation
  - Unable to use traditional assays
  - Poor growth in eggs
- Current efforts to address the challenges
  - Increasing global surveillance
  - Increased use of genomic sequencing
  - Developed new phenotypic assays
  - Developing higher yield egg-propagated and cell-propagated vaccine candidates



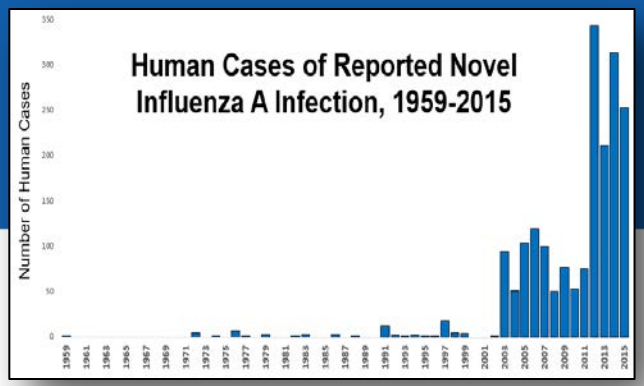
Genomic Sequencing

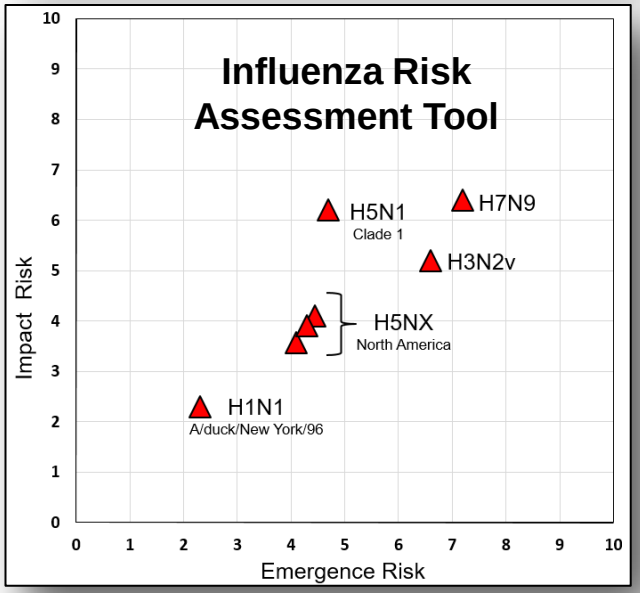
Public Health Benefits from GOF for Seasonal Influenza

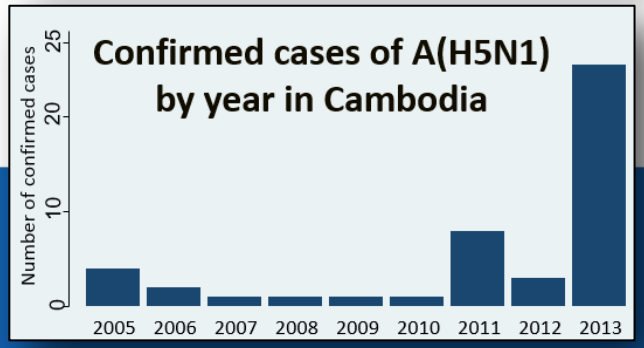
- Enhancing Virus Production
  - Production of sufficient and effective vaccines
  - Optimizing growth in eggs and cells
  - Shortening vaccine development and production timelines
- Revealing pathways for evasion of immunity
  - Predicting antigenic phenotype from genotype
  - Timeliness of antigenic surveillance and characterization
  - Predicting antigenic drift and potential for better vaccine match
- Revealing pathways for evasion of therapeutics
  - Timeliness of antiviral resistance surveillance using sequencing
  - Treatment guidelines for emerging antiviral resistance

Emerging Influenza Viruses with Pandemic Potential

- WHO GISRS supports surveillance and testing for seasonal and novel influenza viruses
- Increasing numbers of infections and global expansion of viruses requires ongoing vigilance
- Regular risk assessments are made utilizing data (some from GOF studies) to inform:
  - Novel/pre-pandemic vaccine development
  - Development of “Readiness Toolkits”
- Availability of a “Genetic Changes Inventory” informed by GOF studies has been critical:
  - Investigation of H5N1 cases of concern in Cambodia
  - Rapid H7N9 assessment
  - Evaluation of rapid rise in H5N1 cases in Egypt
  - Assessment of H5NX (H5N2, H5N8, H5N1) emergence in North America







Public Health Benefits from GOF for Novel and Pandemic Influenza

- Enhancing infectivity, transmissibility, or virulence in mammals
  - Surveillance of animal influenza viruses of concern
  - Computational models for predicting phenotypes
  - Rapid pandemic risk assessment to prioritize vaccine development and countermeasure efforts
- Investigating Reassortment Potential
  - Informs surveillance data, notably with rapid and expanded use of whole genome sequencing

Questions on the Application of the Risk and Benefit Analysis Approach

- Risk for Seasonal studies appear incorrect in RBA – A Miscategorization?
  - Categories for “Seasonal, Avian, and Pandemic” for RBA do not appropriately account for differences in population immunity or differences in intrinsic characteristics of the viruses.
    - Currently circulating “Seasonal” ≠ historic non-circulating “Seasonal”
  - Use of 1918 H1N1 Pandemic as the standard for all pandemics should be reconsidered
- Theoretical risks of a lab accident appear to have greater weight than the very real impact of currently circulating seasonal influenza
- Clarification is needed on the use of the three criteria for GOF of concern (transmissible, virulent, and evasive)
- Implementation of the RBA should be flexible for use in emergencies
- Application of the RBA in practice is not clear