Human Influenza Vaccine Antigen Selection

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Outline

Background on the viruses we are fighting and the inherent challenges they pose to developing vaccines

What are the key questions addressed for vaccine antigen composition and the types of data needed

Examples of how these questions are addressed
Influenza A and B Viruses

- Influenza A/B viruses of humans
  - Influenza A(H3N2)
  - Influenza A(H1N1)pdm09
  - Influenza B/Victoria
  - Influenza B/Yamagata
    - Not detected since March 2020

- Important surface proteins
  - Hemagglutinin – Vaccines induce antibodies to block its function
  - Neuraminidase – Antibodies and antiviral drugs inhibit this protein

- Genome: 8 segments negative sense RNA
  - Enables reassortment and high error rate
Influenza Viruses Survive On The Edge of Catastrophe

• Influenza viruses are constantly changing
  • Requires continuous comprehensive virus surveillance
  • Necessitates frequent updates to the vaccine
• Replication of influenza viruses is error-prone
  • Disadvantage for the virus
    • Close to the threshold of extinction (e.g., many defective viruses)
  • Advantages for the virus
    • Increased adaptability, variants are rapidly selected upon any type of evolutionary pressure (e.g., antiviral drugs, new host, immune)
    • Evolutionary benefit for evading host immunity
• Influenza survives as a population of viruses, not as a single virus
Why Existing as Population of Variants is Important

Example of Co-circulation Dynamics H3 HA Gene Variants

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
Selecting Four Vaccine Antigens
Six Months in Advance is Complicated

Analyzing Complex Biological System

What’s that, you need an accurate prediction 6 months from now and how to stop it! 😊

Fitness landscape

Original image compliments of E. Neuhaus

Host genetics, immunity, .....
Key Questions Addressed As Part of Influenza Virus Vaccine Antigen Recommendations

Goal is to identify antigen(s) that elicit immunity to protect against diverging viruses that will likely co-circulate in the future

• Are/were there significant epidemics and where were they?
• What are the genetic subclades (variants) that have emerged in our population?
• Are the new emerging variants spreading geographically?
• Are emerging variant viruses antigenically distinct from prior or contemporary viruses?
• What is the proportion of the new group(s) and what group(s) is/are likely to predominate?
• Do current vaccines induce antibodies in humans that protect against co-circulating viruses and/or emerging variants?
  • For each of the 4 groups (type/subtype/lineage)?
• Is the current vaccine antigen likely to provide the best protection, or is a new prototype needed?
Data Used to Address Key Questions

• Epidemiologic and clinical data
  • Where are recent epidemics occurring, are they unusual in magnitude or disease?

• Virus surveillance (*GISRS: 70 years in the making*)
  • GISRS labs test 50-150 thousand samples per week year-round and identify influenza positive specimens
    • Four virus groups: A(H1N1)pdm09, A(H3N2), B/Victoria, B/Yamagata, enabled by training, diagnostic kits (e.g., Dx rtRT-PCR, EQAP)
    • Regularly share representative specimens to WHO-CCs

• Genomic characterization of viruses (*Influenza changes rapidly and multiple subclades of interest continually emerge*)
  • Primary focus are HA and NA genes, conduct genome constellation analysis and identify reassortants, patterns of parallel/convergent evolution

• Antigenic characterization of representative emerging viruses
  • Level of antigenic drift from progenitors and/or vaccine references
    • Naïve animal models used to determine level of antigenic variation (“drift”) understand immune response triggered by the proteins on the surface of influenza virus to determine if they would be neutralized by the current vaccine, or have the potential to be a new vaccine virus,
    • Emerging antigenically distinct variants are selected early as new reference viruses for serological analysis and as candidate vaccines (two-way characterization)

• Data integration and comparison among WHO-CCs (*shared data methods, reagents, and viruses*)
  • Influenza epidemiology, surveillance, phylogenetics, phylogeography, and antigenic data integration
  • Antigenic chartography, fitness forecasting

• Post vaccination human serology studies
  • Comparative analysis of cocirculating antigenic variants to identify those that pose the greatest risk of immune escape

• Vaccine effectiveness studies (*global consortium*)
  • VE lower than expected, decreasing and/or show clade/subclade specific VE differences identified (*data on the previous selections and their continued utility*)

• Availability and characteristics of new candidate vaccine virus antigens
  • Data generated that illustrates the new antigens induce antibodies that neutralize viruses most likely to co-circulate in upcoming seasons or are cross-protective (progenitors and/or emerging variants)
Global Influenza Surveillance and Response System (GISRS) Critical to Vaccine Antigen Updates

Conducting continuous surveillance

- 147 WHO National Influenza Centers in 123 Member States
  - 50,000-150,000/wk year-round
  - Share representative specimens with WHO-CCs
- 7 WHO Collaborating Centers for Influenza
- 4 Essential Reference Laboratories
- 12 WHO H5 Reference Laboratories

Genotype to phenotype analysis now central to vaccine antigen selection

- Identify emerging lineages early
  - National influenza centers (NICs)
  - Regularly share samples to WHO-CCs and they are sequenced and deposited into databases
  - Some NICs sequence and publish in databases

- Are they disseminating (country/global)
- Are they antigenically distinct
- To what level do they escape antibodies elicited by vaccine antigen?
- Data integration and fitness forecasting

**Phylogenetics of A(H3N2) HA Gene (time tree)**

- HA clade 2a.2 predominate
  - Continue to diversify into genetic subgroups typically encoding D53G, H156S, L157I or D53N, N96S, H156S, I192F
- Small proportion of 1a (yellow) and 1b (green) clades circulating

Source: Nextflu (J. Huddleston, T. Bedford, J. Lee & R. Neher). Based on HA sequences available as of 02/12/2022
Genotype to phenotype analysis now central to vaccine antigen selection

• Identify emerging lineages early
• **Are they disseminating (country/global)**
• Are they antigenically distinct
• To what level do they escape antibodies elicited by vaccine antigen?
  - Naive animal
  - Vaccinated Humans
• Data integration and fitness forecasting
  - How fit is new lineage among other circulating and emerging lineages
  - Identify optimal vaccine antigen
    - Which virus antigens induce protection from emerging group(s) and other co-circulating virus groups

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Source: U.S. CDC
Human Post-vaccination Sera Analysis of A(H3N2) Viruses Illustrates Reactivity with Emerging Threats

**NH 2021-2022 Vaccine (2a.1), Individual Responses (Older pediatric)**

- Vaccination increased titers to HA clade 1a, 1b, 2a.1 and 2a.2 viruses
- Boost immune memory (HK/45 (1b) (back)
- Boost immunity to emerging viruses (forward)
  - Emerging 1a (TGO/771)
  - Multiple emerging 2a.2 variants
    - DAR/06 (D53G, H156S)
    - MD/02 (D53G, H156S, L157I)
    - AK/01 (D53N...I192F)
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### Analysis of Candidate Vaccine Viruses

#### Ferret antisera to:

- **SH 2021 reference viruses**
  - Inhibit clade 1a and 1b
  - Poorly inhibited clade 2a1 and 2a2 viruses

- **NH 2021-22 reference viruses**
  - Inhibited 1a, 1b and 2a1 viruses
  - Reduced inhibition of clade 2a2 viruses

- **2a2 reference viruses**
  - Well inhibited 2a2
  - Reduced inhibition of 2a1
  - Poor inhibition of 1a and 1b viruses

#### Reference Ferret Antiserum

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Summary

• Influenza viruses rapidly evolve and evade immunity generated from prior infection and/or vaccines
  • Many divergent populations are co-circulating
  • Evolve rapidly and escape host immunity
• Major goal is to identify antigen(s) that elicit immunity against diverging viruses that will likely co-circulate in the future
  • Use many data sources to address key questions related to emerging variants
    • Identification, dissemination, antigenic characterization, immune escape and risk
    • Genotype to phenotype approach and integration of that data now central vaccine antigen recommendations
• Many efforts are underway to overcome contemporary vaccine challenges and improve vaccine antigen selection
  • Increased use of Next-Generation sequencing
  • Data integration and fitness forecasting
  • Generation of many CVVs early and down select as vaccine recommendation date approaches
Acknowledgements I

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  - National Influenza Centers (NICs)
  - WHO-Global Influenza Program and regional offices
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  - Association of Public Health Laboratories
  - United States Air Force School of Aerospace Medicine (USAFSAM)
  - Naval Health Research Center (NHRC)

- Data integration and fitness forecasting partners in Europe and US
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  - M. Lässig, M. Łuksza et. al.,
  - T. Bedford, R. Neher et. al.,

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## Acknowledgements II: CDC Influenza Division

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