Improving influenza vaccine virus selection and development process

Wenqing Zhang

1st WHO Integrated Meeting on Development and Clinical Trials of Influenza Vaccines
Inducing Broadly Protective and Long-lasting Immune Responses
24 – 26 Jan 2013 • Hong Kong
Context

- Influenza vaccination – the cornerstone
- Vaccine virus selection and development – the heart
- WHO recommendations since 1971
  - 1978, trivalent, a total of 45 changes since then
  - 1998, biannual
  - 2004, H5/H9/zoonotic influenza review incorporated
  - 2009, pandemic H1N1 out-of-season
  - 2012, quadrivalent in addition to trivalent
- Retrospective studies shown WHO recommendations closely matched the viruses circulating during the targeted season
  - Very few exceptions e.g. A/Sydney/5/1997-like virus in 1997 and "Fujian"-like virus in 2003
Context

- **GISRS – Global Influenza Surveillance and Response System**
  - Functioning since 1952
  - 149 labs
  - Vaccine composition recommendation – one of the key products of GISRS

- **WHO coordination**
  - Strengthening GISRS capacity
  - Continuous review of the process
    - Challenges
      - Surveillance gaps
      - Emerging technical difficulties in assays
      - Limited understanding of correlation of antigenic change and immune response
    - Partnerships
      - Global consultations
Review areas

- Global surveillance
- Characterization of antigenicity and antibody response
- Vaccine viruses
- Exploration and new methods
Global surveillance

- GISRS surveillance – the basis of vaccine virus selection and development process

![Graph showing global surveillance data](image-url)
Global surveillance

- Surveillance strengthening
  - ILI and SARI surveillance in countries
  - Collaboration with vet sector e.g. “One health”, GISRS-OFFLU collaboration

- Challenges
  - Sustainability
    - National activities
    - SFP, EQAP, IRR
  - Coverage (geographical, age distribution) and representativeness
  - Impact of using molecular methods – reduced virus isolates
  - Incentives of continuous surveillance
Review areas

- Global surveillance
- Characterization of antigenicity and antibody response
- Vaccine viruses
- Exploration and new methods
Antigenicity and antibody response

HA-focused

- HAI, surrogate for virus neutralization - widely used
  - Currently vaccine virus selection process largely based on HAI

- Challenges and refinements
  - RBCs
    - Receptor-binding evolution → RBCs
    - RBCs surrogates
      - Silica beads coated with natural or synthetic glycon
  - Selection in MDCK passage in 151 NA
    - Contributing to binding to RBCs
    - Adding oseltamivir
Antigenicity and antibody response

HA-focused

- **Challenges**: vagaries of virus evolution
  - Inadequacies of virus isolation and assays

- **Difficulties generally surmounted**
  - Adaptation of existing procedures
  - Implementation of alternative assays
  - Increasing use of extensive sequence data

- **HAI**: standardization difficult, automation unsuitable

- Need for new assays and approaches
Antigenicity and antibody response

NA-focused

- NA and NA antibodies contributing to immunity
  - NA content of vaccines required, but not standardized

- Studies of NA antigenic evolution limited
  - Sequencing
    - Contemporary NA co-selected with HA in vaccine virus
  - Recent developed NAI
    - Antigenic drift discontinuous and discordant of N1 and N2 with HA

- NAI assays
  - Moderate-scale throughput assays
    - TBA
    - ELLA
  - Limits
    - Viruses with heterologous HAs or purified NA reagents
Antigenicity and antibody response

**MN assays**

- More sensitive and measure a broader repertoire of functional antibodies
  - Consistent degree of correlation with HAI
  - More commonly used now

- Under Development
  - Being Simplified → routine use
  - Automation
  - Use MN for H1 and B viruses
  - Use pseudotype viruses: offering advantages for highly pathogenic viruses
Antigenicity and antibody response

Serological studies

- Serological studies by CCs and ERLs, part of the process, valuable
  - Limitations:
    - Limited amount of sera
    - Short timeframe
    - Variation in data
    - Criteria: 50%

- Recent developments
  - Antigenic cartography and antibody landscape - assess impact of pre-vaccination titres
  - GFPDLs - analyse repertoires of epitopes
  - SPR - assess affinity maturation
  - Applications
    - Cross-clade reactivity of H5N1 vaccines; adjuvants
    - Antibody response in different age/risk groups
    - Antibody response by novel vaccine types e.g. recombinant proteins or virus-like particles
Review areas

- Global surveillance
- Characterization of antigenicity and antibody response
- Vaccine viruses
- Exploration and new methods
Vaccine viruses
Reassortant development

- Continuous development of high-growth reassortants
  - Close collaboration among GISRS CCs/ERLs/NICs and reassorting labs
  - Manufactures timely informed

- Lack of H3N2 egg isolates
  - CRADAs
  - “Flu-cell-culture” project

- Use of reverse genetics
  - LAIV and H5N1 vaccine viruses
  - Less successful for H1N1pdm09 vaccine viruses
  - Potential
    - Development of high-growth reassortants
    - More reassortants for evaluation
**Vaccine viruses**

**Vaccine yield**

- **Status**
  - Well establishment – “classical” reassortants
  - Little known – molecular determinants of virus growth and stability of antigen
  - Empirical

- **Recent development**
  - US HHS initiative
    - Alternative donor virus genes other than PR8
    - Molecular determinants – working seeds of serial passages
  - Synthetic production of candidate vaccine viruses
Review areas

- Global surveillance
- Characterization of antigenicity and antibody response
- Vaccine viruses
- Exploration and new methods
**Exploration and new methods**

**Prediction of antigenic drift**

- **In experimental settings**
  - Antibody escape mutants of H1N1pdm09 HA – AA substitutions identified
  - Such variants tending to cluster into a single antigenic group

- **In real world**
  - Such mutants occurring sporadically since 2009
  - Not associated with divergent genetic groups
  - Unknown if harbingers of future antigenic drifts
Exploration and new methods

Computational tools

- **Systems-biological approaches**
  - Analyze virus-host relationships, dynamics of virus infection and replication
  - Recent experimental generation of cell-lines
    - Potential for improved virus isolation and vaccine yield

- **Deep-sequencing platforms**
  - Evaluate virus dynamics not captured by consensus sequencing
    - Interspecies transmission
    - Development of antiviral resistance during therapy
    - Emergence and transmission of antigenic variants

- **Mathematic modeling**
  - Correlate antigenicity and AA sequence changes in HA
  - Correlate AA sequence data and HA structural and physicochemical features
  - Exploratory modeling
Exploration and new methods

Synthetic genomics

- A program co-funded by US NIAID, BADAR and HHS
  - Generate libraries of HA and NA genes
  - Rapid generation of high-yield vaccine viruses
    - 5 days – production of synthetic genes and rescue into backbones
  - IP issues
  - Regulatory considerations
Summary

- Fight against influenza will continue
  - Influenza vaccines – cornerstone
  - Influenza vaccine viruses – heart
  - Global coordinated approaches – key

- The process of vaccine virus selection and development
  - Highly technical, complex and collaborative
  - Successful for decades, responsive and adaptive – facing constant challenges
  - Model of public-private collaboration

- Research, exploration and development
  - A great opportunity to improve the vaccine virus process
  - Need global platform to review, direct and facilitate
Summary

- GISRS - delivering the products since first recommendation 1971
  - Resilient and robust; recognized more than ever
  - Continuous capacity building - new technologies
  - WHO Collaborating Centres: technical leadership
  - WHO Global Influenza Programme (GIP): coordinating body

- WHO
  - Work with GISRS
  - With partners
  - Commitment

- Partnership