Improving influenza vaccine virus selection

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8th Meeting with International Partners on Prospects for Influenza Vaccine Technology Transfer
17 – 18 March 2015 • Sao Paulo

Influenza – a virus problem

- Constantly evolving
  - Multiple species
  - Multiple directions

- Rapid spreading
  - without administrative boundaries

- Surveillance & control measures:
  - Timely
  - Continuous
  - Global

Courtesy of Drs. K. Gopal Murti and Robert Webster
St Jude Children’s Research Hospital of Memphis, Tennessee, USA.
Influenza Vaccine Composition

- **1973** - First formal recommendation on influenza vaccine composition issued.

- **17-18 Feb 1986** - First documented WHO annual consultation on composition of influenza vaccines and meeting with influenza vaccine manufacturers in Geneva.

- **Since 1998** – WHO biannual recommendations on composition of influenza vaccines for northern and southern hemispheres.

GISRS – the foundation

- Birth of GISN 1952
  - 2 WHOCCs
    - 59 NICs/42 countries

- 1962
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    - 59 NICs/42 countries

- 1984
  - 3 WHOCCs
    - 108 NICs/76 countries

- 2004
  - 5 WHOCCs
    - 112 NICs/93 countries

- 2008
  - 5 WHOCCs
    - 121 NICs/93 countries

- 2012
  - 6 WHOCCs
    - 136 NICs/106 countries

- Mar 2015
  - 6 WHOCCs
    - 142 NICs/112 countries

- Virus monitoring and risk assessment
- Laboratory diagnostics
- Vaccine support
- Capacity building
- Communication, networking and ad-hoc tasks
GISRS – the mechanism

A recent example: response to pandemic A(H1N1) 2009 (efficiency)

- Confirmed *the* pandemic virus in laboratory – the trigger of all subsequent response
  - (0 day) Gene sequences for diagnostics available on 25 April
  - (+ 3 days) First diagnostic protocol available on 28 April
  - (+ 7 days) First RT-PCR kit sent on 2 May
  - (+ 31 days) Recommended pandemic vaccine virus on 26 May
  - (+ 32 days) First available candidate vaccine reassortant virus on 27 May

Process of influenza vaccine virus selection and development
Data serving vaccine virus selection

Comparative titres by haemagglutination inhibition assays

Sequence data
- mainly HA & NA
- Some others e.g. M

Antiviral drug resistance
- Oseltamivir
- Zanamivir
- Other compounds

Other information
- Growth in eggs & cells

Also used:
- Epi data, Plaque reduction, Virus neuts, Structural data, VE

Human vaccine serology

Vaccine virus selection

Revised from Ian Barr slide

Improving vaccine virus selection

- Opportunities for improvement emerged: awareness, demands, technologies
  - Since 2003 H5N1 re-emergence
  - Since 2009 H1N1 Pandemic

- Global platform provided by WHO
  - 1st Consultation Jun 2010
  - 2nd Consultation Dec 2011
  - 3rd Consultation Apr 2014: 128 participants from 51 countries
  - 4th under planning in 2015

- All consultations
  - Participation by all key players worldwide
Areas under continuous review

- Global surveillance
- Characterization of antigenicity and antibody response
- Technologies and tools
- Manufacturing and regulatory perspectives

Global surveillance

- GISRS surveillance
  - Global/regional approaches
    - Country & population coverage (51%; 91%)
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    - Quality (EQAP) and logistics (SFP)
  - Virus detection and characterization
    - >1.9 million specimens tested by GISRS in 2014
    - Timely information sharing
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    - Virus detection and characterization
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    - Timely information sharing
    - Regional capacity building
  - Individual country approaches – country specific

- PIP Framework – virus sharing and benefit sharing framework
  - Strengthening GISRS pandemic preparedness and response

Global surveillance

- Epidemiologic and disease surveillance
  - ILI and SARI surveillance in countries
  - WHO influenza surveillance standards published in Jan 2014
  - National surveillance system building and linking to policy making

- Efforts from WHO CCs
  - Increasing egg isolates: H3N2 (0.8% 2011, 11% 2013, 18% 2014)
  - Addressing emerging issues e.g. egg vs. cell isolates; low HA titers of some H3N2 viruses

- Collaboration with vet sector: GISRS-OFFLU collaboration

- Collaboration with vaccine manufacturers
  - Provision of sera from vaccinees
  - Egg isolation and hgr development CRADA
  - Use of isolates from qualified cell lines
## Global surveillance

- **Specific issues on vaccine composition in tropics and sub-tropics**
  - WHO recommendations so far for NH and SH
  - Complexity in tropics and sub-tropics
  - Strengthened surveillance providing needed data for policy
    - Seasonality
    - Virological patterns
    - VE
  - Efforts globally
    - Countries
    - WHO
    - BMGF, GAVI and others

## Global surveillance

- **Challenges, among many, main …**
  - Timeliness, representativeness/quality of viruses and information sharing
  - Timing of WHO vaccine composition recommendations
    - Just at/right after peak
Areas under continuous review

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- Manufacturing and regulatory perspectives

Antigenicity and antibody response

HA-focused

- HAI, surrogate for virus neutralization - widely used
  - Currently vaccine virus selection process largely based on HAI
- Challenges and efforts in WHO CCs
  - Differential reactivities of cell- vs. egg- derived viruses
  - Complications of binding of NA to RBC
- Limited progress
  - Synthetic bead - based
  - Non-bead technologies based on recombinant proteins
- No viable alternative to HAI emerged
**Antigenicity and antibody response**

**NA-focused**

- NA and NA antibodies contributing to immunity
- Regulatory requirement
  - No precise determination and standardization
- Continuous efforts on better understanding of patterns of antigenic drift of NA and its impact on vaccine virus selection

**Antigenicity and antibody response**

**Antibody-focused**

- “Antibody landscape” approach
  - “antigenic mapping” → understandings of quality and breadth of
    - Antibody response to HA (and NA)
    - Influence of prior immunity on vaccination responses
  - “Back-boost” effect
  - With advances in prediction of virus evolution, potential for selecting “optimum vaccine virus”
Areas under continuous review

- Global surveillance
- Characterization of antigenicity and antibody response
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- Manufacturing and regulatory perspectives

Technologies and tools

- Opportunities and challenges: high-throughput methodologies
  - Whole genome beyond HA and NA
  - Outbreak investigation, Risk Assessment
  - Need to understand and use comprehensive datasets
  - Require expertise and resources

- Application of synthetic genomics technology
  - H7N9 vaccine virus development

- Application of RG
  - Candidate vaccine viruses
  - Reconstruct viruses e.g. ancestral H5N1
Technologies and tools

- Mathematical modeling
  - Integrating antigenic and genetic data → factors determining antigenic drift
  - “Viral fitness” concept → predict the evolution of HA sequence clades
  - Retrospective results encouraging
- System genetics and systems biology concept, potential to
  - Identify specific host-susceptibility genes
  - Identify diagnostic and prognostic markers
  - Understand pathogenic and virulence mechanisms
  - Evaluate vaccine performance and response: molecular correlates of immune responsiveness and immunogenicity
- “Big data” – a concept
  - 3Vs
  - Future depends on many advances

Areas under continuous review

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Manufacturing and regulatory perspectives

- Influenza vaccine cycle \(\rightarrow\) extremely tight timeframe
  - Manufacturing one component “at risk” before WHO recommendation
  - Efficient communication between GISRS (CCs and ERLs) and manufacturers

- Optimizing “backbone” \(\rightarrow\) hgr development and yield
  - Efforts from US

- Increasing regulatory demands on new vaccine types
  - Quadrivalent, cell-based, adjuvanted vaccines, recombinant protein ....

Summary

- Prediction challenging
  - Limited understanding on biological mechanism of virus evolution
  - In general tools so far are retrospective, hypothetical and experimental

- Measures on the correlation of antigenicity and vaccine effectiveness at clinical endpoint
  - Measures on effectiveness yet to be established

- Better vaccine technology – to shorten the production period
  - Allow for "later" timing for vaccine virus selection

- Better vaccines needed
  - Broad-spectrum of protection
  - "Universal" vaccines
  - Taking into consideration of current zoonotic influenza situation

- WHO commitment and partnership
Gracias

Thank you

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