Update on influenza monitoring and vaccine development

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Outline

- Why do surveillance
- Types of influenza surveillance
- Influenza vaccines
- Role of surveillance in vaccine strain selection
- Challenges
Global burden of seasonal influenza

- **Annual attack rate estimates**
  - 5-10% in adults
  - 20-30% in children
  - 3-5 million severe illnesses
  - 291,243-645,832 influenza-associated respiratory deaths

- **Prevention and control**
  - Vaccination
  - Antiviral drugs

- **Two main types**
  - **Influenza A**
    - 2 subtypes: A(H1N1), A(H3N2)
  - **Influenza B**
    - 2 lineages: B/Yamagata, B/Victoria

Iuliano et al. Lancet. 2018
Changes to the viruses result in lifetime susceptibility

- **Antibodies in blood and airways**
  - Prevent infection (neutralize) & virus spread
  - Antigens ~ Virus envelope proteins recognised by antibodies

- **Antigenic drift**
  - Mutations within envelope genes that decrease antibody binding
  - Why we keep getting reinfected

- **Antigenic shift**
  - Acquisition of a non-human virus envelope gene segments
  - No/little population immunity ➔ pandemic potential
Influenza Surveillance Objectives and Outcomes

- Detect events with pandemic potential early (novel influenza viruses and other respiratory pathogens)
- Prepare for and respond to seasonal influenza
- Monitoring influenza activity for trends and patterns
- Provides data:
  - burden of influenza disease
  - variation of influenza severity between seasons
  - relationships between severity & virus types/subtypes 2009 pandemic
  - vaccine effectiveness
Surveillance components

- Outpatient consultations
  - ILI: Influenza-like illness (sentinel = ASPREN)
- Patients admitted to hospitals
  - SARI: Severe Acute Respiratory Infection (Sentinel = FLUCAN)
- Laboratory diagnostics
  - Viral confirmation & characterization (Sentinel = VICSPIN/ASPREN)
- Population data
- Event-based surveillance
  - Severe pneumonias surveillance
  - For detection of new, severe variants
    - e.g. SARS, H5N1, MERS, H7N9
Confirmed influenza notifications, Australia

- 2018: 15.5%
- 2017: 5.28%
- 2015: 0.03%
- 2014: 0.11%
- H1N1: 52.6%
- H3N2: 26.4%
- B Yam: 5.28%

~2009 level
Objectives of Influenza Virological Surveillance

- 3 primary virological goals:
  - monitor changes in viral antigenicity
  - guide selection of virus strains for annual vaccine
  - provide virus samples for vaccine production

- Vaccines are considered to be the best available means available for controlling influenza epidemics
136 National Influenza Centres in 106 countries

4 WHO Collaborating Centres (CC) for Influenza (human)

1 WHO CC for the Surveillance, Epidemiology and Control of Influenza

1 WHO CC for Studies on the Ecology of Influenza in Animals

4 Essential Regulatory Laboratories (FDA, TGA, NIBSC, NIID)

12 H5 Reference Laboratories

Data not available
Not applicable
Sample submitted to GISRS

- Unsubtypable samples
- Samples from patients who are:
  - Vaccinated
  - Geo/demographic range
  - Involved in an outbreak
  - Receiving antivirals
  - Pregnant
  - Severe / ICU / died

- Sentinel surveillance established in hospitals and outpatient clinics can provide samples representative of circulating viruses and can capture key groups of interest
Influenza vaccines

Targets of antibody mediated protection should be accessible to antibody Envelope proteins
Haemagglutinin (HA) + Neuraminidase (NA)

Influenza vaccine = 15+ microgram HA and variable amounts of NA
Influenza Vaccine Formulations

- **Inactivated split virus**
  - Flublok
  - Recombinant HA protein
  - 1-2%
  - 10-15%

- **Live weakened virus**
  - Flucelvax
  - intranasal
  - healthy 2-49 Y
  - 85-90%
## Vaccine virus composition

<table>
<thead>
<tr>
<th></th>
<th>2018/19 NH</th>
<th>2019 SH</th>
<th>2019/20 NH</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>A/Michigan/45/2015</td>
<td>A/Michigan/45/2015</td>
<td>A/Brisbane/02/2018</td>
</tr>
<tr>
<td>H3N2</td>
<td>A/Singapore/INFIMH-00019/2017</td>
<td>A/Switzerland/8060/2017</td>
<td>pending</td>
</tr>
<tr>
<td>B/Yam</td>
<td>B/Phuket/3073/2013</td>
<td>B/Phuket/3073/2013</td>
<td>B/Phuket/3073/2013</td>
</tr>
<tr>
<td>B/Vic</td>
<td>B/Colorado/06/2017</td>
<td>B/Colorado/06/2017</td>
<td>B/Colorado/06/2017</td>
</tr>
</tbody>
</table>

Composition is updated twice per year
February: northern hemisphere
September: southern hemisphere
Various information is used to select influenza vaccine viruses

Antibody titres assays
Do antibodies raised against existing vaccine viruses recognize circulating strains?

Sequence data
- HA & NA genes
Does a new genetic group predominate?

Antiviral drug resistance
- Oseltamivir
Do we need to prevent spread?

Will the viruses grow to high titre in eggs/qualified cells?

Also used
- Epidemiological data
- Vaccine effectiveness
- Human Serology – are viruses recognized by sera from vaccinees

Candidate vaccine viruses (CVV’s)
Generating egg derived influenza vaccine candidates

Clinical samples, e.g. nasal swab

Amniotic Egg Isolation

3 days

Virus quantification by HA assay

<table>
<thead>
<tr>
<th>Components</th>
<th>Interaction</th>
<th>Microtiter Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs</td>
<td></td>
<td>No Reaction</td>
</tr>
<tr>
<td>Virus</td>
<td>+ RBCs</td>
<td>Hemagglutination</td>
</tr>
</tbody>
</table>

Repeat passage up to 3x

Potential vaccine strains are reassorted with egg-adapted strains to promote high growth

Reassortant (HA+NA WT, internal genes from PR8)

Large scale production

Sterility

Ferret antisera (some)

HI assay

Sequencing

Characterisation by WHO Collaborating Centres
Identifying vaccine breakthroughs

- Comparison of viruses obtained from patients known to be vaccinated
- Current H3N2 viruses show no clustering with respect to vaccination
Challenges
Limitations of current influenza vaccines

- Antigenic drift
  - limits the duration of protection and necessitates annual reformulation
  - impacts effectiveness when vaccine and epidemic strains are antigenically mismatched

43% effectiveness in adults >65 Y, so in 2018 Aust. Govt. introduced
- *Fluzone High-Dose* = 60 µg of each HA, Trivalent,
- *Fluad* = 15 µg of each HA + MF59C adjuvant

*Flublok* containing 45 µg of each as recombinant protein has similarly increased efficacy in > 65 Y
Viruses change when grown in eggs, so vaccination can induce antibodies that don’t recognize circulating viruses.

Skowronski D. PLoS ONE 2014
Egg-acquired adaptations alter antigenicity and reduce effectiveness

- A(H3N2) and B/Victoria viruses most severely affected
Challenges with current A/H3N2 influenza viruses

- Concern that HI assays may not be optimal for resolving antigenic change among recent A/H3N2 viruses
  - Poor A/H3N2 VE in 2017 ≠ antigenic mismatch (if cell grown)
  - Molecular data shows significant genetic heterogeneity
    - Genetic drift ≠ antigenic drift (particularly when assessing human sera)
  - Other assays are not high-throughput

[Diagram showing HI assay with host cell, RBC attachment inhibited, and RBC agglutinated]
Are immune responses biased towards past/egg-grown virus antigens, and does this limit immunity against future viruses?

- Influenza vaccines work best when they are boosting pre-existing antibodies (naturally acquired)
- Repeated annual vaccination may focus the immune response too much
  - In some years this can limit the protection afforded by the vaccine

Antibodies recognize various epitopes

Antibodies focused on limited epitopes

virus HA protein

in the vaccine
Possible solutions

- Screen for/prevent antigenic change in eggs
- Cell-grown (Flucelvax) or recombinant HA vaccines
- Increase the breadth of the immune response
  - Include other antigens, optimize NA content, adjuvants, select more distinct viruses
- A new “universal” vaccines – US NIH priority
Summary

- Influenza surveillance is necessary to understand the burden of influenza, to keep track with virus changes and identify novel viruses
- Virological surveillance is crucial for updating vaccine viruses but
- Recent challenges in identifying optimal vaccine candidates underscores the need for better vaccines and for better understanding of how to update human immunity
- Significant investment in new vaccines and research
Acknowledgements

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