100 years of Influenza Pandemic and the prospects for new influenza vaccines

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Influenza Deaths in Rio de Janeiro 1918-1919 by month

Deaths in Rio de Janeiro by Age Range

Data taken from the Medical Research Council Report to Government. 1920
Influenza Deaths in London 1918 per week

Data taken from the Medical Research Council Report to Government. 1920
The ongoing impact of influenza

England and Wales Excess Winter Mortality 1951 to 2017

Annual Excess Mortality 1951 to 2017, England and Wales

EURO MoMo project 2014 to 2018
Influenza viruses evolve


Sequences from EpiFlu database of GISAID
Virological surveillance of influenza viruses

- Seasonal Influenza
- Zoonotic Influenza
- Pandemic Influenza

GISRS Laboratories have to ask the questions:
Are there new viruses detected that pose an increased risk
- Of causing an influenza epidemic?
- Of causing a zoonotic infection?
- Of causing an influenza pandemic?
The GISRS network

144 National Influenza Centres in 114 member states
6 Collaborating Centres: 5 Human Influenza & 1 influenza ecology
12 H5N1 Reference Labs
Vaccination is the best intervention to reduce the risk of influenza

Current vaccines are made in:
EGGS – inactivated and LAIV
Cell culture – inactivated antigen
Recombinant technology – Protein Sciences (Sanofi Pasteur) baculovirus expressed HA

Antigen needs to be similar to the current HA
Influenza vaccine changes to strains 1970 to 2018

Vaccine has three or four components and is usually produced in hens' eggs.
Need to match the antigenicity of the vaccine with that of the virus.

Antigenicity cannot be predicted from sequence data with confidence.

Human sera are difficult to work with since people have seen many influenza viruses.

Use serum from an animal model: the ferret.
Haemagglutination Inhibition Assay- a rapid surrogate for neutralisation

\[
\text{Haemagglutinin protein} + \text{Red blood cells} \rightarrow \text{Haemagglutination} \rightarrow \text{Appearance in well}
\]

\[
\text{Influenza} + \text{Red blood cells} \rightarrow \text{Normal RBC settling} \rightarrow \text{Appearance in well}
\]
<table>
<thead>
<tr>
<th>Viruses</th>
<th>Collection Date</th>
<th>Passage History</th>
<th>A/Wis 67/05</th>
<th>A/Trieste 25c/07</th>
<th>A/Bris 10/07</th>
<th>A/Urs 16/07</th>
<th>A/Fm 9/08</th>
<th>A/HK 1952/09</th>
<th>A/HK 1958/09</th>
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<td>2560</td>
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</table>
Antigenic cartography illustrates the HI data – (from Prof. Derek Smith and Dr Colin Russell, Univ. Cambridge)
Virus Plaque Neutralisation assays

Titration of antisera

A/Panama/2007/99
A/Fujian/411/02
A/Wellington/1/04
A/Uruguay/716/07
A/Trieste/25C/07

Plaque reduction assay
Influenza Vaccines are generally propagated in hens’ eggs

Traditional egg-propagated inactivated vaccines:

• Isolated in hens’ eggs,

• Characterised genetically and antigenically,

• Reassorted with high yield donor (e.g. A/PR/8/34) to produce **Candidate Vaccine Virus (CVV)** by a small number of labs.

• **CVV** examined antigenically and genetically

• Passed to companies for vaccine production in hens’ eggs
Live Attenuated Influenza vaccines

LAIV:

- Isolated in hens’ eggs
- Characterised genetically and antigenically,
- Generated through reverse genetics (AZ-MedImmune) to generate a cs/ts CVV.
- CVV examined antigenically and genetically
- Production proceeds
Egg-adapted changes associated with antigenic change in the virus

Robertson et al. Virology 1987: Egg adaptive changes in H1N1 viruses
Katz et al. Virology 1987: Egg adaptive changes in H3N2 viruses
Cell culture-propagated influenza vaccine viruses

- Viruses isolated in Qualified cell lines
- Vaccine Production on Qualified Cell lines
- Inactivated Vaccine Viruses
- Antigenic and Genetic Analysis undertaken
- Approved in USA
- Field Effectiveness data likely to be available in 2018
Recombinant Haemagglutinin

- Produced by Protein Sciences from a baculovirus HA licenced in USA (became part of Sanofi-Pasteur in 2017)
- Not clear that the criteria are for assessing the antigenic properties of the vaccine.
Recent H3N2 evolution has resulted in greater barriers to egg-adaptation — the alteration in receptor binding
The Test Negative Design measures the effectiveness of vaccines in the ‘general population’.

- **Sentinel ILI patients**
  - Unvaccinated
  - Vaccinated

- **Swabbed patients**
  - Patient data: vaccination history, age, comorbidities, sex, etc.

- **Test-positive**
  - 16 infected:
    - 6 vaccinated
    - 9 not vaccinated

- **Test-negative**
  - 27 uninfected:
    - 7 vaccinated
    - 20 not vaccinated

\[ VE = (1 - OR_{adj}) \times 100\% \]
Vaccine Effectiveness and Egg Adaptation

Skowronski et al. PLOS One 2014
Postulated that low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses.

<table>
<thead>
<tr>
<th>Vaccine Effectiveness in Canada 2012-2013</th>
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<tbody>
<tr>
<td>H1N1 effectiveness</td>
<td>80% (40-93%)</td>
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<tr>
<td>H3N2 effectiveness</td>
<td>53% (28-69%)</td>
</tr>
<tr>
<td>Influenza B effectiveness</td>
<td>70% (40-85%)</td>
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</table>

But the Flu B vaccine effectiveness was pretty good
<table>
<thead>
<tr>
<th>Vaccine effectiveness UK 2016-2017</th>
<th>Vaccine type/age group</th>
<th>Effectiveness</th>
<th>Confidence Interval</th>
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<td>24.9</td>
<td>(-296.1 to 85.8)</td>
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<td>2–17 (LAIV4)</td>
<td>57.0</td>
<td>(7.7 to 80.0)</td>
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<td>18–64</td>
<td>36.6</td>
<td>(10.4 to 55.1)</td>
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<td>≥ 65</td>
<td>-68.4</td>
<td>(-248.9 to 18.7)</td>
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<td>B</td>
<td>2–17 (LAIV4)</td>
<td>78.6</td>
<td>(-86.0 to 97.5)</td>
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<td>18–64</td>
<td>52.1</td>
<td>(-20.0 to 80.9)</td>
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<td>≥ 65</td>
<td>17.2</td>
<td>(-249.7 to 80.4)</td>
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Pebody et al. Euro Surveill. 2017;22(44)

2016-2017
H3N2 vaccine
- Very poorly effective in over 65s
- Moderate in 18 to 65 age group
- LAIV Good in children

<table>
<thead>
<tr>
<th>Vaccine effectiveness UK 2015-2016</th>
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<th>Effectiveness</th>
<th>Confidence Interval</th>
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<td>(13.3–100)</td>
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<td>18–44</td>
<td>59.8</td>
<td>(35.8–74.8)</td>
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<td>(1.0–70.4)</td>
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<td>(15.1–85.6)</td>
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<td>-20.2</td>
<td>(–259.1 to 59.8)</td>
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Pebody et al. Euro Surveill. 2017;22(44)

2015-2016
H1N1 vaccine
- IIV generally good
- LAIV less good in children than the IIV
The timelines for vaccine production are challenging
Influenza Seasonal Vaccine Manufacturing Model
It’s all very tightly time-limited

Dec Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov

- Manufacture Strain 1
- Manufacture Strain 2
- Manufacture Strain 3
- Strain Balancing
- Strain Balancing
- Strain Balancing
- Produce Working Seed
- Produce Reassortant
- Produce & Standardize Potency Reagents
- Annual License Approval
- Formulate Bulk Trivalent Vaccine Fill & Package
- Distribute Vaccine

Slide from Tony Colegate, Formerly with Novartis and IFPMA
Influenza Vaccines are generally propagated in hens’ eggs

- Live virus is handled in plants
- In a pandemic. Safety testing is needed to ensure that the new CVV is safe to handle
- Production will follow the established timelines
- 5 months to widespread and full availability
Live Attenuated Influenza vaccines during a pandemic

**LAIV:**
- RG virus produced in hens’ eggs
- Good production capacity
- As fast as standard vaccines
- Ferret Safety testing still required
Recombinant Haemagglutinin Influenza vaccines during a pandemic

• In principle: there is likely to be some increase in speed to first dose

• The production is small at present, can it be scaled up for a pandemic?
Other ideas

Plant-based vaccines (e.g. Medicago)
HA (and NA) antigens could be used for making ‘virus-like particles’

Recombinant DNA technology – so potentially rapid to first dose
But set-up and scalability not obvious
Chasing Seasonal Influenza — The Need for a Universal Influenza Vaccine

Catharine I. Paules, M.D., Sheena G. Sullivan, M.P.H., Ph.D., Kanta Subbarao, M.B., B.S., M.P.H., and Anthony S. Fauci, M.D.

As clinicians in the United States prepare for the start of another influenza season, experts have been watching the Southern Hemisphere winter for hints of what might be in store for us in the North. Reports from Australia have caused mounting concern, with record-high numbers of laboratory-confirmed influenza notifications and outbreaks and higher-than-average
World-first trial for universal flu vaccine

The world's first widespread human testing of a flu vaccine which researchers hope will...
The Oxford University Jenner Institute

500 people given Inactivated Vaccine
500 people given Inactivated Influenza Vaccine with Modified Vaccinia Ankara expressing the influenza NP and M polypeptides
and monitored for improved protection

Is the fluMVA a good adjuvant or is there something ‘special’ about it?
Use egg-propagated virus from immunise with the stalk region of the HA or with standard viruses from subtypes previously not seen in succession with the aim of generating the cross-reactive stalk antibodies.
Express the stalk alone parts of HA1c and HA2

Express a chimeric HA to focus the immune response on the conserved region

Will the protection to the conserved region be as protective as to the whole HA?

Will the antigen give yields sufficient for production?

Safety testing of a new product?
The scheme:
chimeric H9, then boost with cH5 then with cH6

Or
chimeric H1, boost with cH5 then cH6
An alternative route to attenuation

Live attenuated viruses with no NS1 protein (Vivaldi Biosciences Austria)
  • Vero cell production
  • delNS1 promotes a better immune response

Will protection be broad?
When will this vaccine be a ‘product’?
How scalable will production be?
When will safety testing be needed?
mRNA based vaccines

Presented yesterday at VI Seminario Annual by Dr Mike Watson, Moderna Therapeutics, USA

High potential for a rapid response to a pandemic or a new seasonal virus

Questions:
 Scalability – can 50 mil, 100 mil, 500 mil, 5 billion doses be made in a few weeks?

Grat potential for a rapid response, but needs to be shown.
To be able to plan for a pandemic there must be:

- The ability to respond quickly
- Have production that can meet the demands when a pandemic arises

If there are ‘universal vaccines’ they must

- Give robust protection against seasonal viruses
- Be part of a programme for ‘universal’ vaccination of the population
- Be able to be increased in production when a pandemic arises since it seems unlikely that there will be universal coverage
Other ideas?

The problem is probably not a lack of great ideas, but the economics of vaccination for flu.

Q. “Why do we not have better flu vaccines?”
A. “Because the current ones are so cheap!”
Thanks are due to
WHO National Influenza Centres
WHO Collaborating Centres
WHO HQ and
WHO Regional Offices
ECDC