Right tools, Right application, Right answer

Maria Zambon
Public Health England
Tools for Assessment of Disease Burden

Surveillance

Clinical

Virological

Deaths

Hospitalised cases

Community cases seen by medical services

Community cases not seen by medical services
Changes in Diagnostic tools & capability

From: Immune-fluorescence

To: Real-time PCR

- Influenza B positive
- Influenza A positive
- Negative control

To Rapid near-patient tests (clinical)
The Decreasing Cost of Genotype Information
Improving Information for Interventions

HI (and neutralisation) data

Table 3. Antigenic analysis of influenza A(H3N2) viruses (Quinua/Pig RSC with 2mM Oseltamivir) 2012-01-11

<table>
<thead>
<tr>
<th>Virus</th>
<th>Genotype Group</th>
<th>HA 50%</th>
<th>HA 70%</th>
<th>HA 90%</th>
<th>NA 50%</th>
<th>NA 70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Florida/1/2002</td>
<td>1</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>A/Hong Kong/156/2005</td>
<td>2</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>A/New Jersey/1/2009</td>
<td>1</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>A/California/07/2009</td>
<td>2</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>A/Victoria/361/2009</td>
<td>3</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

Sequence analysis

Antigenic cartography

Structural/functional significance of mutations
Introduction of New technologies

Top of the pyramid

Case studies
Winter 2003-2004: emergence antigenic variant
A/Fujian/411/2002-like viruses

Poor vaccine match

Unusual high number of influenza fatalities in children:
Sept-Dec 2003 in the UK

No pre-existing risk factors

None vaccinated

Bacterial coinfection only in 3/17 (18%) cases

WGS of all fatal cases & matched controls (1:3)

Findings

• Fatal Cases distributed along all genetic lineages

• Several additional changes in internal genes & reassortment events noted

• No genetic changes associated with fatal outcome

• Host-related susceptibility → naïve unvaccinated children undergoing first influenza infection
Fatal cases, A(H1N1) pandemic 2009 viruses

WGS comparison of viruses isolated from fatal and ‘control’ mild cases from first, second and third wave of pandemics in the UK

No genetic differences between viruses from fatal and mild cases

Third wave viruses: Several signature changes

Ongoing adaptation to host? Enhanced fitness? New virulence factors?
Key findings

• WGS fatal vs. non-fatal ….no specific genetic changes associated with a fatal outcome,
  (HA- D222G → not enough evidence)
• Variation observed in replication kinetics between viral strains in different waves
• Variation observed within and between waves

Clinical outcome of infection determined by host-related factors…. 
Influenza clinical and public health challenges

**Clinical**
- Mortality statistics
- Critical care use
- Hospital admissions/discharges
- Spotter practice (cases per 100,000)
- Schools absence
- Sickness absence
- Telephone advice
- Pharmacy sales
- Community studies (ad hoc)

**Virological**
- Virus recovery from fatal cases
- Antiviral susceptibility
- Virus sampling serious illness
- Diagnosis of illness
- Spotter practice (weekly samples % positive)
- Diagnosis of illness
- Antiviral susceptibility
- Outbreak investigation
- Seroepidemiology
- Sampling from telephone calls

**Surveillance**
- Community cases seen by medical services
- Community cases not seen by medical services
Influenza virus detections in the region

European early warning based on convergence of technologies
Overall activity Influenza A 2014/15
Developing the information
Test-negative design for estimating influenza VE

Sentinel ILI patients

Swabbed patients

Test-positive

Test-negative

Unvaccinated
Vaccinated

Patient data:
- vaccination history
- age
- gender
- comorbidities

VE = (1 - OR_{adj}) \times 100\%

Rapid Communications

Low effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 mid-season results

R G Pebody (Richard.Pebody@phe.gov.uk)\textsuperscript{1}, F Warburton\textsuperscript{1}, J Ellis\textsuperscript{1}, N Andrews\textsuperscript{1}, C Thompson\textsuperscript{2}, B von Wissmann\textsuperscript{3}, H K Green\textsuperscript{4}, S Cottrell\textsuperscript{4}, J Johnston\textsuperscript{5}, S de Lusignan\textsuperscript{6}, C Moore\textsuperscript{7}, R Gunson\textsuperscript{8}, C Robertson\textsuperscript{9,10}, J McMenamin\textsuperscript{3}, M Zambon\textsuperscript{2}

1. Public Health England Centre of Infectious Disease Surveillance and Control, London, United Kingdom
2. Public Health England Operations Directorate, Microbiology Services, Colindale, London, United Kingdom
3. Health Protection Scotland, Glasgow, United Kingdom
4. Public Health Wales, Cardiff, United Kingdom
5. Public Health Agency Northern Ireland, Belfast, United Kingdom
6. Royal College of General Practitioners Research and Surveillance Centre, United Kingdom
7. Public Health Wales Molecular Diagnostics Unit, Cardiff, United Kingdom
8. West of Scotland Specialist Virology Centre, Glasgow, United Kingdom
9. University of Strathclyde, Glasgow, United Kingdom
10. International Prevention Research Institute, Lyon, France

Citation style for this article:

Article submitted on 30 January 2015 / published on 05 February 2015
**The Daily Telegraph**

Flu jab given to millions is useless

Number of deaths this winter will be the worst for 15 years as vaccination has no effect on most common strain of the virus.

By Louis倍Bennett, Health Editor

The flu vaccine given to millions of people is useless against the virus that is currently spreading through the UK, new research has shown.

The vaccine is proving to be so ineffective against the current strain of the virus that it will not stop the expected number of deaths from the flu.

The research, published in The Lancet medical journal, found that the vaccine was only 15% effective against the current strain of the virus, compared to one in four in previous years.

The vaccine works by stimulating the immune system to produce antibodies to fight against the virus. But the current strain is so similar to the vaccine strain used to make the vaccine that the body is unable to produce enough antibodies to protect against it.

Flu vaccine 'barely effective' against main viral strain

By Louise Broom

Health Editor

The flu vaccine is proving to be so ineffective against the current strain of the virus that it will not stop the expected number of deaths from the flu.

The research, published in The Lancet medical journal, found that the vaccine was only 15% effective against the current strain of the virus, compared to one in four in previous years.

The vaccine works by stimulating the immune system to produce antibodies to fight against the virus. But the current strain is so similar to the vaccine strain used to make the vaccine that the body is unable to produce enough antibodies to protect against it.

**Daily Mail**

**FLU JAB IS A WASTE OF TIME FOR 97% OF PATIENTS**

Thousands of Scots given jab which only protects 3pc of patients as health chiefs admit they knew about flaw months ago

By Sophie Bartland

Health Correspondent

The flu jab will protect just three per cent of patients, official figures show.

Thousands of Scots are being given a completely useless flu vaccine, health officials have admitted.

The vaccine is only 15 per cent effective against the current strain of the virus, which is spreading rapidly through the UK.

A survey found that just 3 per cent of patients who received the flu jab were protected against the disease.

The vaccine is given free to people over 65 and to those with long-term health conditions, but it is only effective against one strain of the virus.

**Scottish Daily Mail**

**WARNING OVER FLU VACCINES**

Labour backer fear Miliband victory

By Scott McNeice

Scotland Editor

The Labour Party's plans to replace the strikes by rail workers with a new contract have been labelled as a "catastrophic" failure.

A leaked report showed that the party's proposals were so weak that they were "not worth the paper they were written on".

The deal reached with the RMT union was described as a "complete and utter disaster".

The plan to replace the rail strikes with a new contract was agree.
Influenza A(H3N2) Northern Hemisphere – Interim Data

Ambulatory setting

Northern Hemisphere VE against Influenza A(H3N2) - ambulatory setting

Study Group

- ALL AGES
- U.S. Flu VE Net (≥6 m)
- Canada SPSN (>1 y)
- U.K. (>6 m)
- Spain, Navarra (≥6 m)
- Spain, SIISS (≥6 m)
- I-MOVE (>6 m)
- USAFASAM (≥6 m)
- U.S., NHRC

- CHILDREN
- U.S. Flu VE Net (6 m-17 y)
- Spain, SIISS (<15 y)
- I-MOVE (<15 y)
- USAFASAM (6m-17y)
- U.S., NHRC (6-18 y)

- ADULTS
- U.S. Flu VE Net (18-64 y)
- Canada SPSN (20-64 y)
- Spain, SIISS (15-64 y)
- I-MOVE (15-64 y)
- USAFASAM (>18 y)
- U.S., NHRC (19-64 y)

- ELDERLY
- U.S. Flu VE Net (>65 y)
- Spain, SIISS (>65 y)

- TARGET
- Spain, SIISS
- I-MOVE

Adjusted Vaccine Effectiveness

VE [% CI] Test+ (% vax) Test- (% vax)
18% [6.29] 1385 (53) 3238 (57)
-8% [-50.23] 379 (37) 451 (33)
-2% [-56.33] 271 (23) 1025 (17)
2% [-135.56] 124 (15) 116 (13)
55% [25.73] 677 (6) 608 (12)
64% [30.79] 390 (6) 399 (13)
23% [-3.42] 468 (29) 694 (27)
47% [9.69] 140 (17) 278 (31)
14% [-0.31] 571 (43) 1343 (50)
40% [-60.60] 323 (3) 237 (6)
56% [-10.83] 163 (6) 322 (7)
21% [-14.45] 297 (29) 402 (27)
32% [-33.65] 100 (16) 190 (26)
18% [-2.33] 594 (52) 1405 (55)
2% [-49.36] 213 (33) 283 (30)
64% [24.83] 316 (5) 329 (11)
70% [33.87] 204 (4) 442 (10)
23% [-21.51] 171 (27) 292 (28)
45% [-77.83] 35 (14) 77 (31)
29% [-16.57] 220 (81) 400 (66)
76% [-18.95] 38 (34) 42 (50)
67% [27.83] 101 (25) 112 (42)
66% [31.85] 60 (16) 173 (36)
Influenza A(H3N2) Northern Hemisphere

<table>
<thead>
<tr>
<th>Study Site</th>
<th>H3N2-positive cases</th>
<th>Genetically-characterized H3N2 viruses</th>
<th>Group 3C.2a n (%)</th>
<th>Group 3C.3a n (%)</th>
<th>Group 3C.3 n (%)</th>
<th>Group 3C.3b n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Flu VE Net</td>
<td>1385</td>
<td>764</td>
<td>624 (82%)</td>
<td>25 (4%)</td>
<td>26 (3%)</td>
<td>89 (11%)</td>
</tr>
<tr>
<td>Canada, SPSN</td>
<td>379</td>
<td>226</td>
<td>205 (91%)</td>
<td>0</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>271</td>
<td>44</td>
<td>35 (80%)</td>
<td>0</td>
<td>9 (20%)</td>
<td></td>
</tr>
<tr>
<td>Spain, SISS</td>
<td>677</td>
<td>97</td>
<td>53 (55%)</td>
<td>9 (9%)</td>
<td></td>
<td>35 (36%)</td>
</tr>
<tr>
<td>Europe, I-MOVE</td>
<td>390</td>
<td>27</td>
<td>14 (52%)</td>
<td>3 (11%)</td>
<td></td>
<td>10 (37%)</td>
</tr>
</tbody>
</table>
Influenza clinical and public health challenges

### CLINICAL
- Mortality statistics
- Critical care use
- Hospital admissions/discharges
- Spotter practice (cases per 100,000)
- Schools absence
- Sickness absence
- Telephone advice
- Pharmacy sales
- Community studies (ad hoc)

### VIROLOGICAL
- Virus recovery from fatal cases
- Antiviral susceptibility
- Virus sampling serious illness
- Diagnosis of illness
- Spotter practice (weekly samples % positive)
- Diagnosis of illness
- Antiviral susceptibility
- Outbreak investigation
- Seroepidemiology
- Sampling from telephone calls

### SURVEILLANCE
- COMMUNITY CASES NOT SEEN BY MEDICAL SERVICES
- COMMUNITY CASES SEEN BY MEDICAL SERVICES
- HOSPITALISED CASES
- DEATHS
Free home flu test kits for Flusurvey participants

Scientists from Flusurvey and i-sense call for public to help monitor spread of UK flu more accurately than ever before

People taking part in this year's Flusurvey, the UK's biggest crowd-sourced study of influenza will for the first time be offered a swab to confirm if their symptoms are caused by a flu virus or not as part of a new collaboration with i-sense. Data from social media and internet searches will also be combined with Flusurvey, allowing flu trends to be monitored across the UK more accurately and earlier than ever before.
Self-sampling for community respiratory illness: a new tool for national virological surveillance

A J Elliot (Alex.Elliot@phe.gov.uk)¹, A Bermingham², A Charlett², A Lackenby², J Ellis², C Sadler², P Sebastianpillai², C Powers², D Foord³, E Povey³, B Evans², H Durnall⁴, D M Fleming⁴, D Brown², G E Smith⁴, M Zambon²

1. Public Health England, Birmingham, United Kingdom
3. National Health Service Direct, Milton Keynes, United Kingdom
4. Royal College of General Practitioners Research and Surveillance Centre, Birmingham, United Kingdom

Citation style for this article:

Article submitted on 03 September 2013 / published on 12 March 2015
The soft palate is an important site of adaptation for transmissible influenza viruses

Seema S. Lakdawala†, Akila Jayaraman², Rebecca A. Halpin³, Elaine W. Lamirande³, Angela R. Shih¹, Timothy B. Stockwell³, Xudong Lin³, Ari Simenauer³, Christopher T. Hanson¹, Leatrice Vogel¹, Myeisha Paskel¹, Mahnaz Minai⁴, Ian Moore⁴, Marlene Orandle⁴†, Suman R. Das³, David E. Wentworth³†, Ram Sasisekharan² & Kanta Subbarao¹
• Switching technologies, improve prediction, increase information strain diversity. WGS/NGS…unbiased information
• Technology is ahead of Knowledge (Virus & patient)
• STRATIFIED MEDICINE…Consider the host…link to clinical outcome
• Population Susceptibility….better methods for prediction of susceptibility
• Study of vaccine failures will help improve vaccine design

Automated analysis of known drug resistance mutations
Pay attention to the sample. Rubbish in = rubbish out.
Implications & Issues

Moving to an unbiased approach to analysis

Data analysis is bottleneck:

We have more data than we know what to do with

Powerful epidemiological analysis: new insights and hypothesis generation

Data storage and release issues