Vaccine Safety Monitoring for pH1N1 2009 pandemic vaccine: lessons learned in British Columbia

2011: Eighth Annual Bi-National Cross Border Workshop
Pacific Northwest Border Health Alliance

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Key milestones in the immunization response:

- June 11\textsuperscript{th}: WHO declares pandemic
- Late July: Type of vaccine
- Late August: Target population and ‘sequencing’
- September:
  - Vaccine volumes: start date and rate
  - Vaccine format and injection equipment
  - Seasonal vaccine recommendations in BC; available early October
- October 21\textsuperscript{st}:
  - Release of adjuvanted vaccine and product monograph / recommendations for use
- Oct 26\textsuperscript{th}:
  - Immunization clinics begin with adjuvanted vaccine
  - Mid November: unadjuvanted vaccine available for pregnancy
Recommended recipients for the pH1N1 vaccine: National ‘sequencing’

1. Those Who Will Benefit Most From Immunization and Those Who Care For Them:
   - Persons with chronic conditions (NACI list) under the age of 65
   - Pregnant women
   - Children 6 months to less than 5 years of age
   - Persons residing in remote and isolated settings or communities
   - Health care workers
   - Household contacts and care providers of:
     - Infants <6 months of age
     - Persons who are immunocompromised
   - Populations otherwise identified as high risk

2. Others Who Will Benefit From Immunization:
   - Children 5 to 18 (inclusive) years of age
   - First responders (police, firefighters)
   - Poultry and Swine Workers
   - Adults 19 to 64 (inclusive) years of age
   - Adults 65 years of age and over
Arepanrix: Adjuvanted pH1N1 vaccine

- Utilized a novel GSK proprietary adjuvant called AS03
- Better immune response with less antigen (3.75 μg vs. 15 μg)
- Thought to provide some cross protection in case the virus changes (“drifts”)
- Faster induction of immune response
- More immunogenic than regular vaccine formulations in the very young and at older ages

Image courtesy of BCCDC
What was in the AS03 adjuvant?

- Squalene
- Alpha-tocopherol (vitamin E)
- Polysorbate 80
- AS03 is approved in 30 countries

Safety profile is based on 39,000 subjects who have received A/H5N1 avian influenza vaccine, trivalent vaccine, or pH1N1 influenza vaccine adjuvanted with AS03.

Image courtesy of BCCDC
Known serious adverse events following seasonal influenza vaccines:

- **Anaphylaxis** (1 per 1 million doses given)
  - Contraindications:
    - History of anaphylactic reaction to a previous dose of influenza vaccine or the following components:
      - Eggs; formaldehyde; sodium deoxycholate; thimerosal

- **Guillain-Barré syndrome (GBS)** (1 per 1 million doses given)
  - Contraindications:
    - History of Guillain-Barré syndrome within 8 weeks of a prior dose of influenza vaccine
### Immune Response to pH1N1 Vaccines (Adults 18-60 years)

<table>
<thead>
<tr>
<th>Anti-HA Antibody</th>
<th>Adjuvanted Vaccine (n=61)</th>
<th>Non-Adjuvanted Vaccine (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroprotection rate</td>
<td>100%</td>
<td>93.9%</td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td>96.7%</td>
<td>84.8%</td>
</tr>
</tbody>
</table>

**Seroprotection rate:** % of individuals with haemagglutininination inhibition (HI) antibody titres $\geq 1:40$ post-vaccination

**Seroconversion rate:** % of seronegative subjects with post-vaccination HI titres $\geq 1:40$ or that were seropositive and had a 4-fold increase in HI titre

Source: Arepanrix™ product monograph, GlaxoSmithKline Inc.
## Common adverse events with H5N1 AS03 vaccine

<table>
<thead>
<tr>
<th>Local Symptoms</th>
<th>Incidence</th>
<th>General Symptoms</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjuvanted Vaccine</td>
<td>Non-adjuvanted Vaccine</td>
<td>Adjuvanted Vaccine</td>
</tr>
<tr>
<td>Pain</td>
<td>90%</td>
<td>38%</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Redness</td>
<td>18%</td>
<td>18%</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Swelling</td>
<td>20%</td>
<td>8%</td>
<td>Fever</td>
</tr>
<tr>
<td>Induration</td>
<td>28%</td>
<td>10%</td>
<td>Headache</td>
</tr>
<tr>
<td>Bruising</td>
<td>16%</td>
<td>8%</td>
<td>Myalgia</td>
</tr>
</tbody>
</table>

*Based on trials with Prepandrix, with subjects 18-60 years of age*

AEFI Surveillance for pH1N1 in Canada

- **Passive surveillance**
  - National AEFI Surveillance
  - Electronic extract
  - BC Centre for Disease Control
  - Entered into iPHIS
  - Regional Health Authority
  - Voluntary reporting
  - Primary care provider or hospital
  - AEFI case

- **Active surveillance**
  - PCIRN
    - PHAC/CIHR funded influenza research network
    - Included SOS – serious outcome surveillance from selected hospitals in Canada; adult
  - Immunization Monitoring Program ACTive: pediatric inpatient beds; 12 hospitals; was not specifically involved
  - Advisory Committee on Causality Assessment
Sources of information for health care providers:

- PHO web site
  - Immunization guidelines
    - Link to immunizebc.ca
  - AEFI reporting guidelines
    - Link to bccdc.ca
    - Health care providers in BC should report adverse events that they believe to be associated with these vaccines to the local medical officer of health/health unit
Changes made to BC reporting system for the pH1N1 campaign:

- Emphasized reporting ASAP of events: severe or unusual/medical attention/hospitalization
- De-emphasized reporting of local and non-serious systemic events
- Added specific events: ORS/Bell’s palsy
- Obtained baseline data on ‘expected’ rates of specific diagnoses
- Daily review of serious events; weekly analysis and reporting of all events
- Established a pH1N1 Advisory Committee on Causality Assessment
Faster processes for review of passive surveillance data

- Daily review of serious events
  - Anaphylaxis
  - Convulsion/seizure
  - Encephalopathy
  - Meningitis and/or encephalitis
  - Anaesthesia/paraesthesia
  - Paralysis
  - Guillain-Barré syndrome
  - Other severe or unusual events

- Automated alerting of events

- Weekly aggregate national reporting and teleconferences
Reportable adverse events:

- **High fever**
- **Local reactions:**
  - Large, severe, long lasting, infected abscess, sterile abscess
- **Adenopathy**
- **Allergic, anaphylaxis**
- **ORS**
- **Rash**
- **HHE**
- **Miscellaneous:**
  - Parotitis, orchitis
  - Arthritis
  - Vomiting/ diarrhea
  - Intussusception
- **Neurologic**
  - Persistent crying
  - Seizure
  - Encephalopathy
  - Meningitis
  - Encephalitis
  - Anaesthesia
  - Paralysis
  - Bell’s palsy
  - GBS
  - SSPE
- **Other severe or unusual event**
38% of the BC population could be covered by pH1N1 doses reported as administered or distributed.
pH1N1 adjuvanted vaccine effectiveness

- Case control study using SPSI fall 2009
- BC AB ON QU
- PCR positive influenza diagnosed in 38% of 552 participants

- 2/209 (1%) cases and 58/343 (17%) of controls had been immunized 2+ weeks prior to onset
- VE 93% (CI$_{95}$ 69-98) against medically attended laboratory confirmed pH1N1 influenza

AEFI reports in BC associated with pH1N1 vaccine

- 478 adverse events (391 people): rate of 29.3 events per 100,000 doses distributed
  - 62 anaphylaxis requiring emergency intervention (3.8 per 100,000) (Brighton levels 1 through 4)
  - 98 non-anaphylactic allergic events (6.0 per 100,000)
  - 42 other events of special interest (2.5 per 100,000)
  - 27 ‘serious’ AEFIs (1.7 per 100,000)

- Compared to 5 year baseline seasonal reports:
  - overall 1.1 times the expected rate
  - anaphylaxis 5.4 times higher than expected
  - other severe 2.5 times higher
  - serious 3.4 times higher
Serious AEFI Following pH1N1 vaccine, BC 2009-10

<table>
<thead>
<tr>
<th>Serious AEFI</th>
<th>Frequency</th>
<th>% of all AEFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis Brighton Level 1-3</td>
<td>13</td>
<td>2.7%</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>0.42%</td>
</tr>
<tr>
<td>Syncope (with injury)</td>
<td>2</td>
<td>0.42%</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis (ADEM)</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Fetal death</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Guillain-Barre Syndrome</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Seizure (Hospitalized)*</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Severe adenopathy (Hospitalized)*</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Severe headache (Hospitalized)*</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td>Severe myalgia (Hospitalized)*</td>
<td>1</td>
<td>0.21%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27</strong></td>
<td><strong>5.6%</strong></td>
</tr>
</tbody>
</table>

*These cases were categorized as serious only because of hospitalization
## AEFI of Special Interest Following pH1N1 vaccine, BC 2009-10

<table>
<thead>
<tr>
<th>Severe AEFI</th>
<th>Frequency</th>
<th>% of all AEFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>14</td>
<td>2.9%</td>
</tr>
<tr>
<td>Anaesthesia/Paraesthesia</td>
<td>18</td>
<td>3.8%</td>
</tr>
<tr>
<td>Oculo-respiratory syndrome (ORS)</td>
<td>8</td>
<td>1.7%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>2</td>
<td>0.42%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>42</strong></td>
<td><strong>8.8%</strong></td>
</tr>
</tbody>
</table>
Ongoing activities:

- Case control study of anaesthesia/paraesthesia (Quebec)
- BC-WA comparison of pH1N1 associated AEFI reports: ISDA/US Immunization Conference
- Establishment of a provincial advisory committee on causality assessment
Lessons learned:

- ‘Surge’ capacity is reallocation
- Can be lean and mean but limited by time lags
- ‘Ns’: in-province experience insufficient to identify signals
- Limited national capacity for case review
- Improvements needed in data access
- Remain open to ‘unusual/ unexpected’:
  - Anaesthesia/ paraesthesia
  - Narcolepsy (Sweden/ Finland)
- Establishment of early safety assessment
  - ‘canary in the gold mine’
Thank you
Extra slides
**pH1N1 vaccine uptake in BC**

**pH1N1 vaccine coverage by age group and gender**

- 0-9 years
- 10 - 18 years
- 19-39 years
- 40-64 years
- 65+
- All Ages

**Male**

**Female**

**All Genders**
Until early October, the anticipated quantities of adjuvanted vaccine for BC were 1.3-2.3M doses for first shipment, thereafter 455,000 doses per week for a total of 6.3M doses, and all of unadjuvanted supply of 156,000 doses in early November.
H1N1 Vaccine Uptake in BC

Vaccine uptake: doses administered each week

H1N1 Vaccine Uptake in BC

Week Ending

# of Doses Administered/Distributed

Doses Administered by Pharmacists
Doses Administered to HCW
Doses Administered on Reserve
Doses Distributed to Other Providers
Doses Administered By Public Health
A/H1N1 ‘epidemic curve’ in BC

Week starting October 19th
How ‘sequencing’ translated into ‘eligibility’

- **Week of:**
  - **October 26:**
    - Pregnant women
    - People under 65 with chronic medical conditions
    - People residing in remote and isolated communities
  - **November 2:**
    - Health care workers in critical areas such as ER, ICU, and specialized units
    - Children between 6 months and less than 5 years of age
    - Household contacts younger than 65 years old of: babies less than six months old and of severely immunocompromised people
  - **November 9:**
    - Other health care workers, with priority given to those in critical functions and direct patient care roles
    - Women in the first half of pregnancy (using unadjuvanted vaccine)
  - **November 16:**
    - All other health care workers
    - Children and adolescents between 6 months and 18 years of age
    - First responders (police, fire)
  - **November 19:**
    - All others
Squalene & Polysorbate 80

Squalene:
- is a naturally occurring substance found in plants, animals, and humans. It is manufactured in the liver of every human body. It is a precursor for cholesterol and steroid hormones and circulates in our bloodstream.
- is also found in a variety of foods, cosmetics, over-the-counter medications, and health supplements
- is commercially extracted from fish oil, and in particular shark liver oil. Squalene used in pharmaceutical products and vaccines is purified from this source.
- is present in MF59, an adjuvant used in Fluad™, an influenza vaccine produced by Novartis approved in 14 European countries for use in 65+ year olds, of which more than 47 million doses have been distributed since 1997 with no safety concerns identified.

Polysorbate 80:
- is an emulsifier that stabilizes the adjuvant
- is used widely in vaccines, medicinal products, and foods