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

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



BC Centre for Disease Control  
An agency of the Provincial Health Services Authority

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# Key milestones in the immunization response:

- June 11<sup>th</sup>: 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<sup>st</sup>:
  - Release of adjuvanted vaccine and product monograph / recommendations for use
- Oct 26<sup>th</sup>:
  - 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

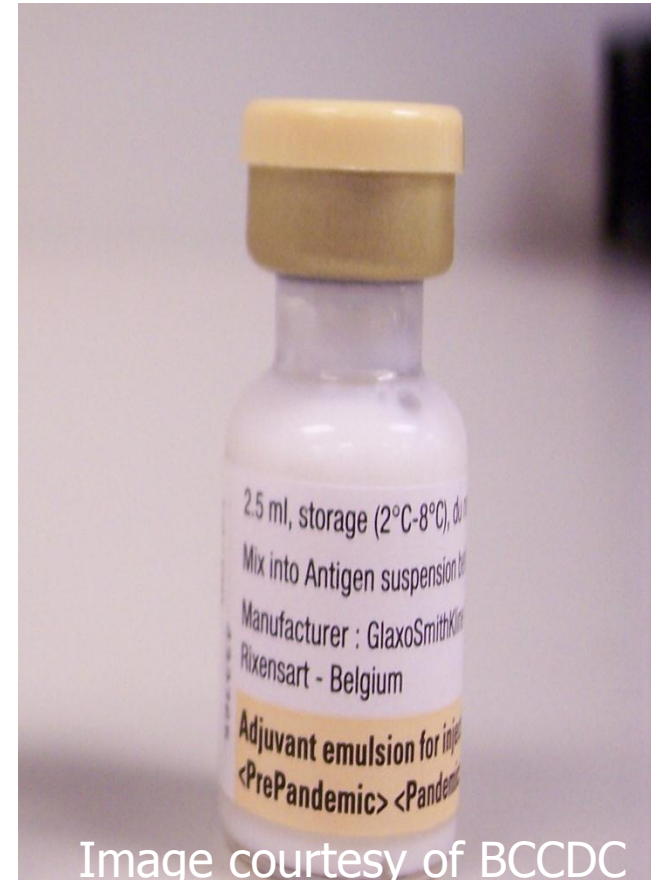


Image courtesy of BCCDC

# 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)

<b>Anti-HA Antibody</b>	<b>Adjuvanted Vaccine (n=61)</b>	<b>Non-Adjuvanted Vaccine (n=66)</b>
Seroprotection rate	100%	93.9%
Seroconversion rate	96.7%	84.8%

**Seroprotection rate: % of individuals with haemagglutination 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**

# Common adverse events with H5N1 AS03 vaccine

Local Symptoms	Incidence		General Symptoms	Incidence	
	Adjuvanted Vaccine	Non-adjuvanted Vaccine		Adjuvanted Vaccine	Non-adjuvanted Vaccine
Pain	90%	38%	Arthralgia	28%	10%
Redness	18%	18%	Fatigue	45%	28%
Swelling	20%	8%	Fever	4%	0%
Induration	28%	10%	Headache	53%	36%
Bruising	16%	8%	Myalgia	39%	16%
<i>Based on trials with Prepandrix, with subjects 18-60 years of age</i> Leroux-Roels et al., (2007). The Lancet, Vol. 370: 580-588.			Shivering	20%	12%
			Sweating	18%	10%



# AEFI Surveillance for pH1N1 in Canada

## ■ Passive surveillance



## ■ 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](http://immunizebc.ca)

### □ AEFI reporting guidelines

- Link to [bccdc.ca](http://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

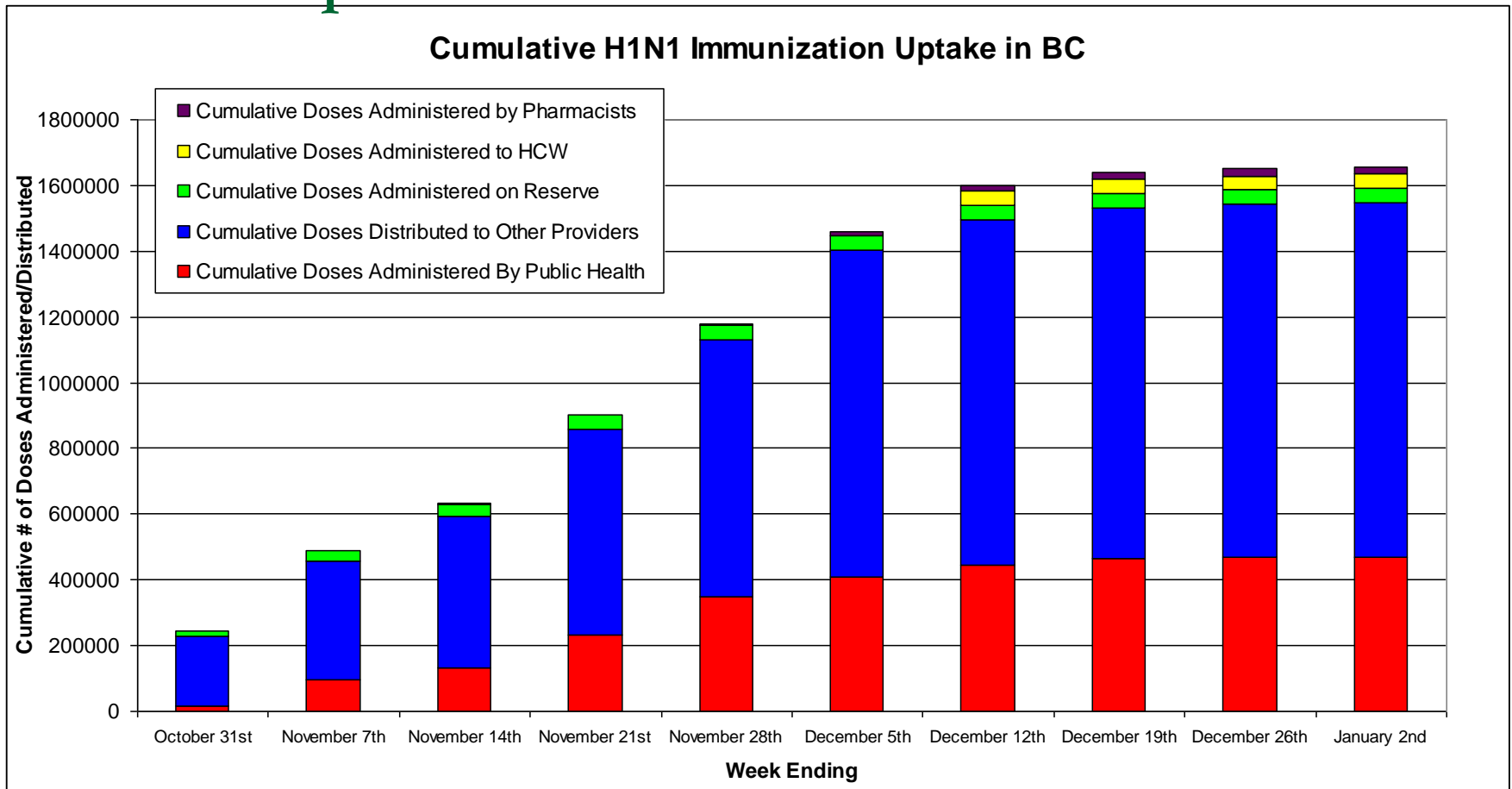


# Reportable adverse events:

- 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



# Vaccine uptake: Cumulative doses administered



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<sub>95</sub> 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

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



# AEFI of Special Interest Following pH1N1 vaccine, BC 2009-10

<b>Severe AEFI</b>	<b>Frequency</b>	<b>% of all AEFI</b>
<b>Seizure</b>	14	2.9%
<b>Anaesthesia/ Paraesthesia</b>	18	3.8%
<b>Oculo- respiratory syndrome (ORS)</b>	8	1.7%
<b>Cellulitis</b>	2	0.42%
<b>Total</b>	<b>42</b>	<b>8.8%</b>



# 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’



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- Thank you



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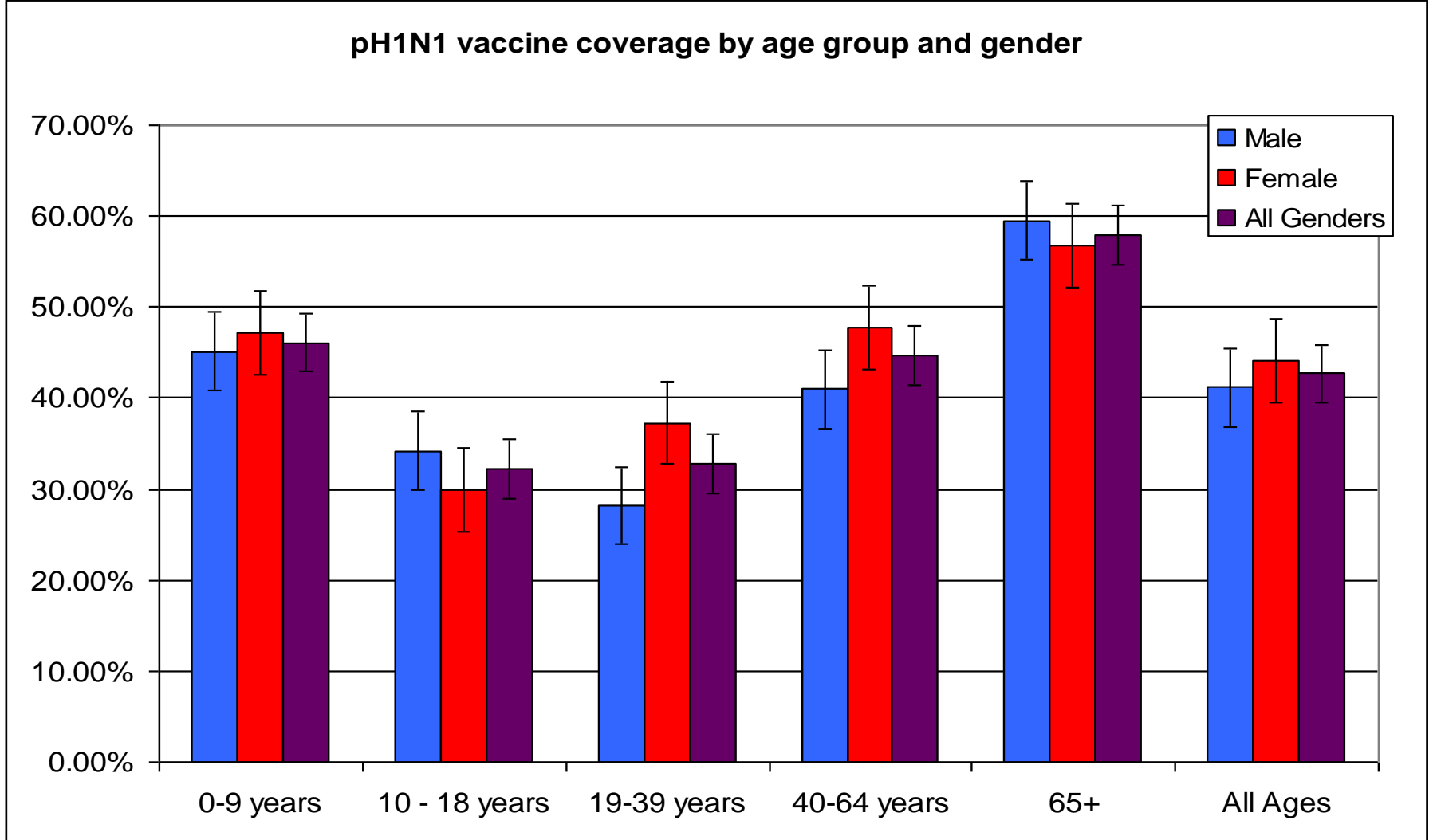
# Extra slides

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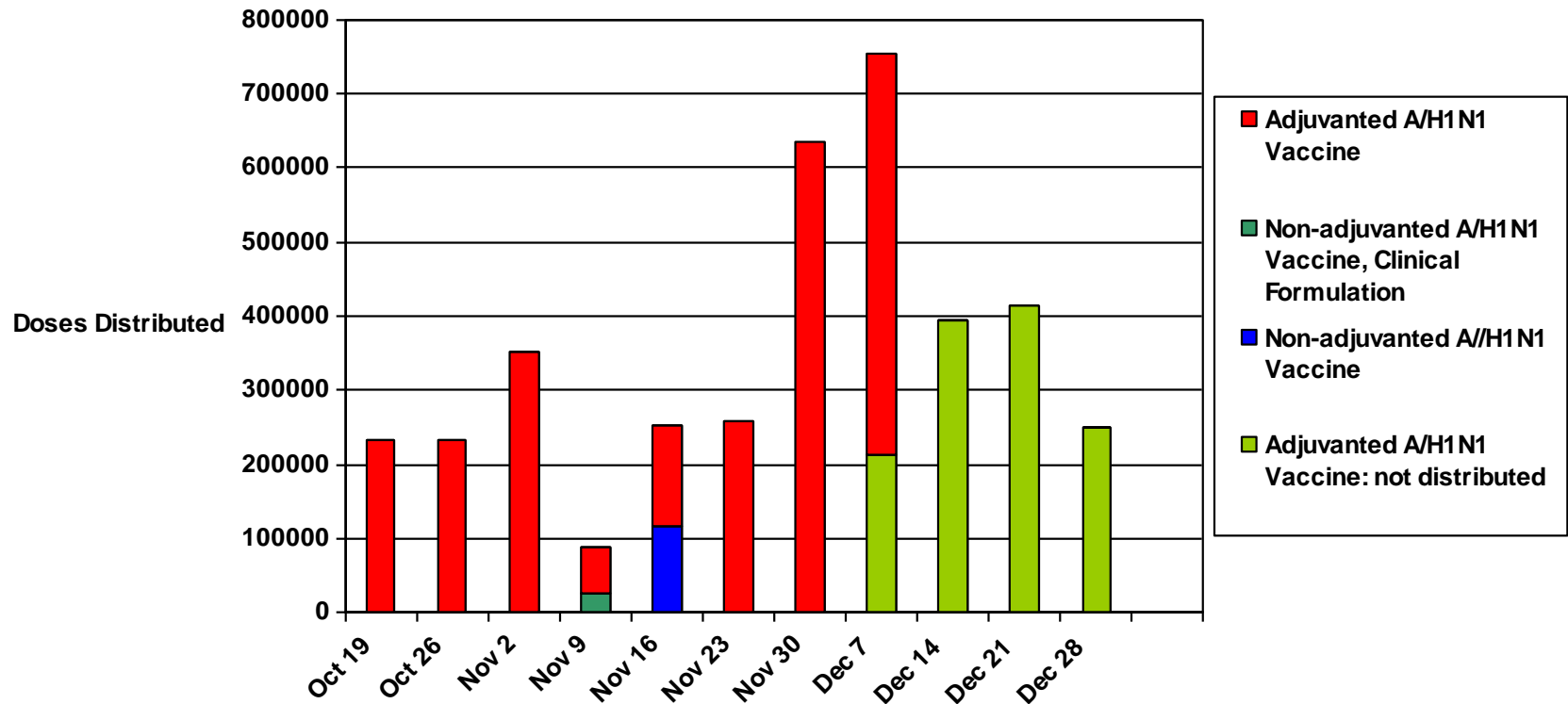


# pH1N1 vaccine uptake in BC

pH1N1 vaccine coverage by age group and gender



# AH1N1 Vaccine Distribution, 2009, BC

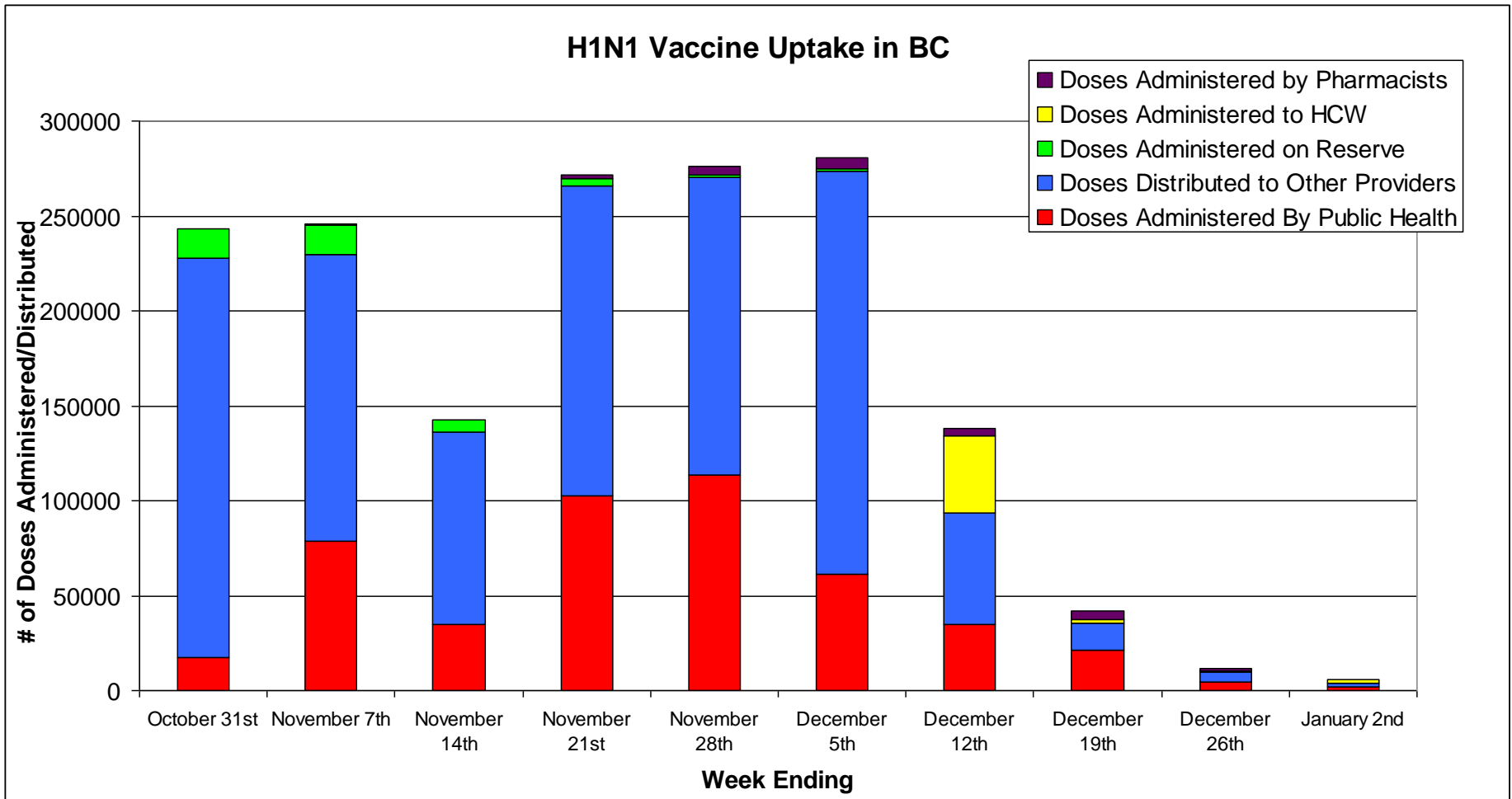


Until early October, the anticipated quantities of adjuvanted vaccine for BC were 1.3-2.3M doses for first shipment, thereafter 455,000 doses per week for a total of 6.3M doses, and all of unadjuvanted supply of 156,000 doses in early November





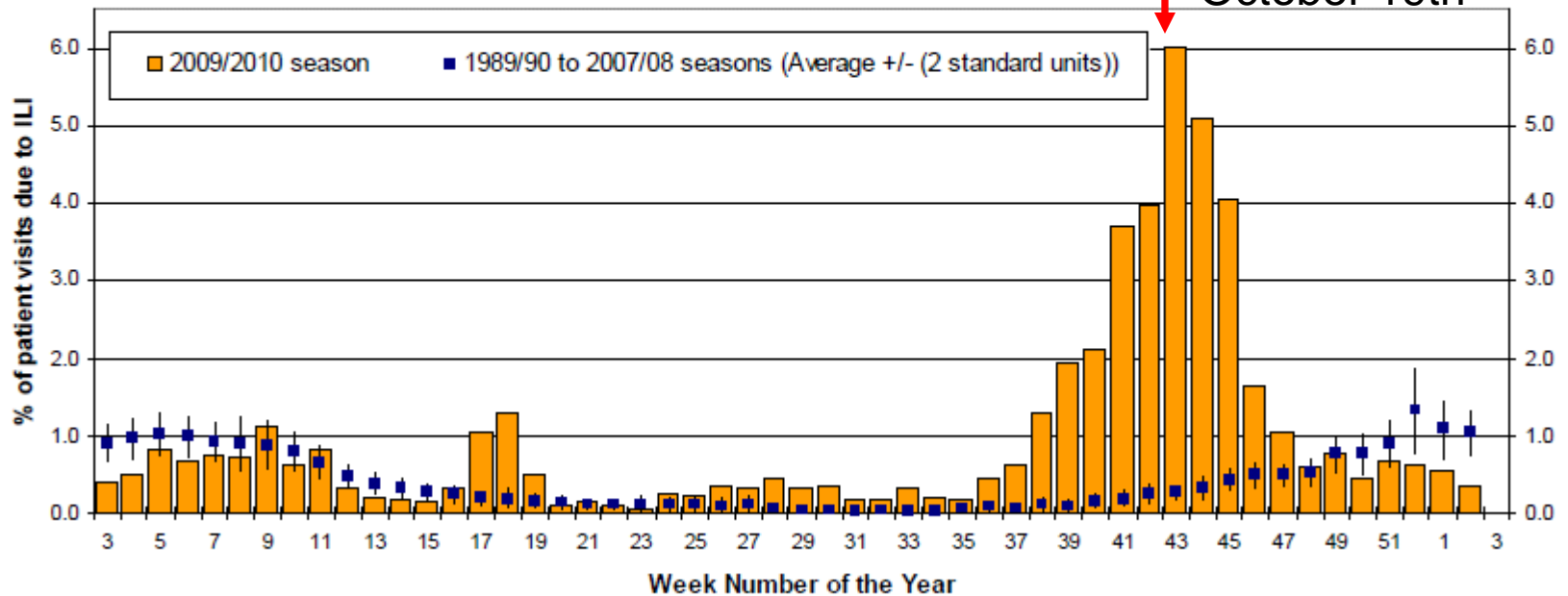
# Vaccine uptake: doses administered each week



# A/H1N1 'epidemic curve' in BC

Percentage of Patient Visits due to Influenza Like Illness (ILI) per Week  
Compared to Average Percentage of ILI Visits for the Past 19 Seasons  
Sentinel Physicians, British Columbia, 2009-2010

Week starting  
October 19th



\*\*Data subject to change as reporting becomes increasingly complete



# 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 Fludac<sup>TM</sup>, 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