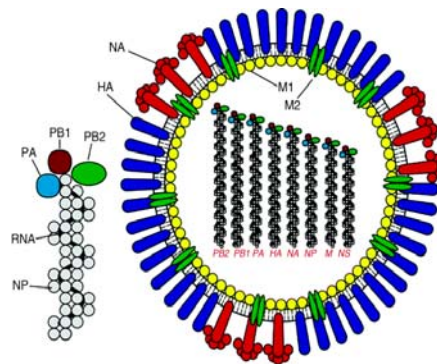


New Strategies to Prevent Influenza: can vaccinating kids protect us?

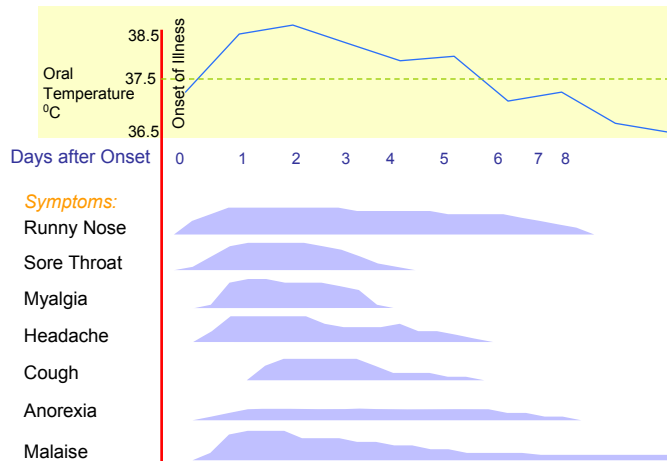
Mark Loeb MD

Influenza

- 3 types: A, B, C
- 8 viral RNA segments
- Subtypes of type A determined by surface components



Natural History of Clinical Influenza



Complications

- Bacterial pneumonia
- Exacerbations of asthma, chronic lung disease
- Myocardial infarction, heart failure, sudden death
- Febrile convulsions, otitis media, croup, bronchiolitis, Reye's syndrome
- Myocarditis, encephalitis

Mortality in Canada from Influenza

- Influenza infection is a health burden and has significant economic impact on society
- Mortality due to influenza and pneumonia is the 6th leading cause of death in Canada after cancer, heart disease, CV diseases, COPD, and accidents
- Estimated 4,000-8,000 deaths per year
- 70,000-75,000 hospital admissions per year
- Total annual costs of influenza are estimated at approximately **\$1 billion in Canada**

Statistics Canada, Health Statistics Division. Available at <http://www.statcan.ca/english/Pgdb/People/Health/death.htm>
Noël GE. Life-threatening "flu"? *Can J Diagnosis* 1999;March:104-115.

Burden of Influenza in the Elderly

- Influenza and pneumonia are the leading infectious cause of death
- Most important cause of medically attended acute respiratory illness
- Interpandemic rates of morbidity highest in extremes of age

Thompson et al, JAMA 2004; 292:1333-40

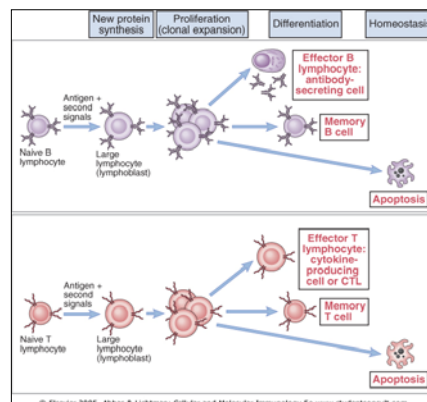
Influenza Immunization Policy

- Adults and Children with selected chronic health conditions
- Residents of nursing homes and other chronic care facilities
- People ≥ 65 years of age
- Healthy children aged 6 to 23 months
- Women who will be pregnant
- Healthcare providers, household contacts of high risk individuals

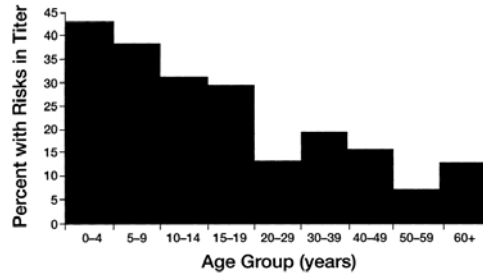
National Advisory Committee on Immunization 2009

Immune Deficits in Aging

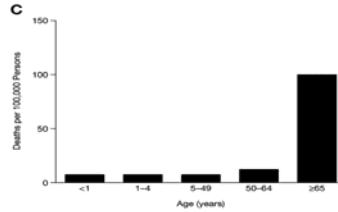
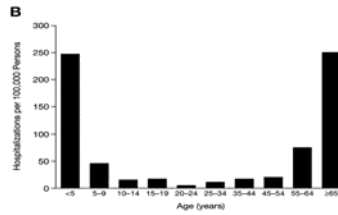
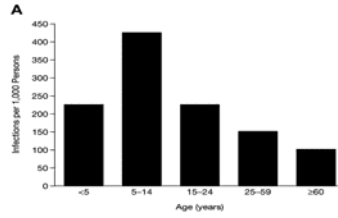
- Shift from naive to memory T-cells
 - possibly due to CMV?
- Reduction of apoptosis and increase CD8 T cells
- Chronic low-grade inflammatory state “Inflammaging”
- Immune Risk Profile - high CD8, low CD4 and poor T-cell proliferative response



Community Influenza Attack Rates and Complications by Age



Monto, et al. *Epidemiol Infect.* 1993;110:145-60.



Influenza Vaccination of Schoolchildren in Japan Reduction in Excess Pneumonia and Influenza Mortality Among Older Adults



Reichert T et al. *NEJM* 2001;344:889-96.

Limitations of Existing Studies

- No RCTs of indirect benefit to the community
- Observational studies subject to bias
- Unblinded trials
- Lack of laboratory confirmation

Immunization Level for Herd Immunity

- Mathematical modeling suggests 70%
- Even lower levels may provide benefit
 - 20% coverage reduce cases by 46%
 - 80% coverage reduce cases by 90%

A Cluster Randomized Trial of Vaccinating Hutterite Children against Influenza

M. Loeb, M. Russell, L. Moss, K. Fonseca, J. Fox, D. Earn, F. Aoki, G.
Horsman, P. Van Caesele, K. Chokani, M. Voight, L. Babiuk, R. Webby,
S. Walter

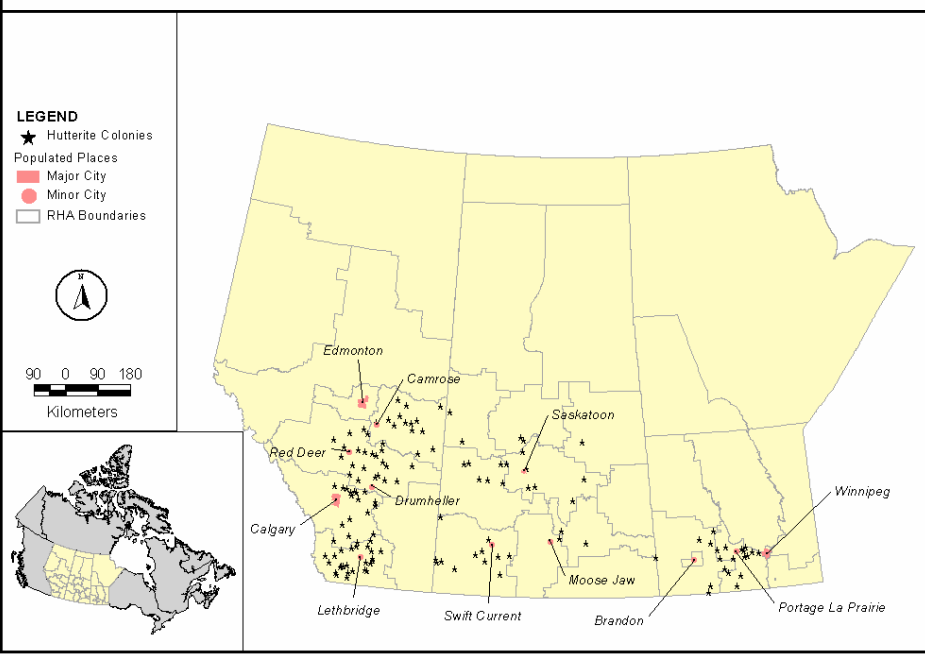
McMaster University; University of Calgary; Provincial Laboratory for Public Health, Alberta; University of Manitoba;
Saskatchewan Disease Control Laboratory; Cadham Provincial Laboratory; Saskatchewan Health; University of Alberta; St. Jude
Children's Hospital and WHO Collaborating Center



Primary Objective

- To test whether immunizing children in Hutterite colonies with inactivated influenza vaccine can prevent laboratory confirmed influenza in other community members
- Hypothesis: *immunizing $\geq 70\%$ of healthy children in intervention colonies will reduce lab confirmed influenza in other colony members*

Distribution of Hutterite Colonies Alberta, Saskatchewan & Manitoba



Study Colonies

- Colony inclusion criteria
 - within 150 km of designated city or town
 - ≥ 10 high risk members
- Colony exclusion criteria
 - no childhood immunizations given
 - colonies with high risk individual where all colony members immunized

Immunized Children

- Healthy children aged 36 months to 15 years were eligible for study vaccine
- Exclusion
 - previous anaphylactic reaction to dose of influenza or hepatitis A vaccine
 - previous anaphylactic reaction to neomycin
 - previous known IgE mediated hypersensitivity to eggs
 - GBS within 8 weeks of a previous influenza vaccine

Other Hutterite Colony Members

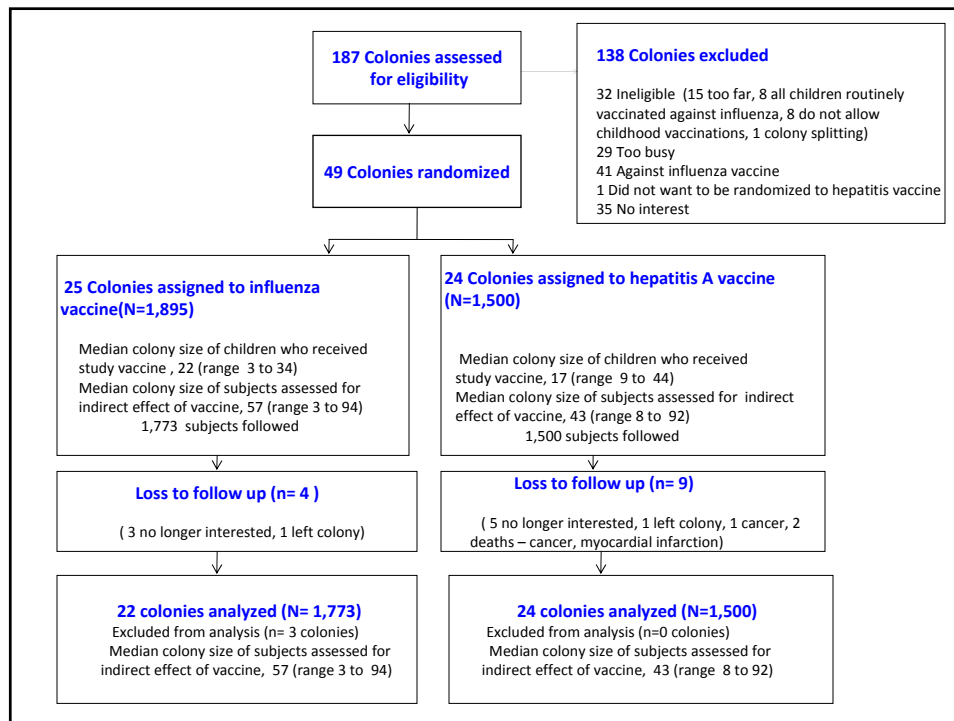
- Other colony members were enrolled to assess indirect benefit of immunizing children
- No exclusion criteria, included both individuals with chronic medical conditions, persons ≥ 65 years, children ≤ 23 months, pregnant women

Interventions

- Hutterite colonies randomized to either influenza (2008-2009 vaccine) or hepatitis A vaccine immunization of healthy children between ages of 36 months and 15 years
- Schedule of influenza immunization mimicked using hepatitis vaccine and sterile saline

Outcomes

- Primary outcome – laboratory confirmed influenza (RT-PCR)
- HAI assays to seasonal subtypes (infection was defined as a ≥ 4 -fold increase)
- Secondary outcomes - MD visits for respiratory illness, influenza-like illness, school/work absenteeism, antimicrobial prescriptions, hospitalizations for pneumonia/LRTI, deaths



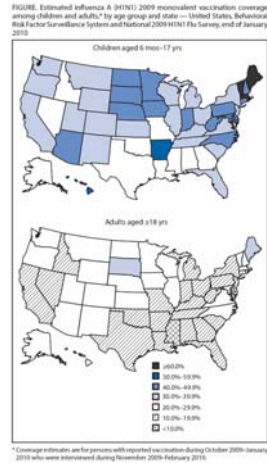
Indirect Protectiveness

| Study Group | Influenza Vaccine | Hepatitis A Vaccine | | P value | |
|--|-------------------|---------------------|--|-------------|------|
| Participants who did not receive study vaccine | N=1271 | N=1,055 | Protective Effectiveness of Influenza Vaccine (95% CI) | | |
| Participants with influenza detected by PCR- no. (%) | 39 (3.1) | 80 (7.6) | | | |
| Person days of follow up – no. | 182,866 | 151,902 | | | |
| Incidence of influenza – no. of cases/10,000 person-days | 2.13 | 5.27 | Simple | 61 (8 - 83) | 0.03 |
| | | | Adjusted | 61 (8 - 83) | 0.03 |

Total Protectiveness

| All participants | N=1773 | N=1500 | | P Value | |
|--|----------|------------|--|-------------|--------|
| Participants with influenza detected by RT-PCR– no.(%)* | 80 (4.5) | 159 (10.6) | Protective Effectiveness of Influenza Vaccine (95% CI) | | |
| Person days of follow up – no. | 253,243 | 210,856 | | | |
| Incidence of influenza – no. of cases/10,000 person-days | 3.16 | 7.54 | Simple | 59 (5 - 82) | P=0.04 |
| | | | Adjusted | 59 (4 - 64) | P=0.04 |

Uptake of Influenza A (H1N1) 2009 Vaccine



- Among persons ≥ 6 months, estimates of uptake range from 13% to 39% by state
- Median coverage in children (6 months to 17 yrs) was 37%
- 20% for adults ≥ 18 yrs
- 33% for ACIP target groups

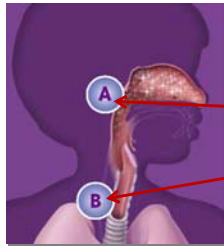
MMWR 2010 Apr 9;59 (13)397

Question 4: What are the Current Options for Vaccination

Current vaccines:

- Trivalent Inactivated Influenza Vaccine (TIV) administered by injection
 - FLUVIRAL® S/F (influenza trivalent split virion)
 - INFLUVAC™ (influenza vaccine, inactivated, surface antigen)
 - VAXIGRIP® (inactivated influenza trivalent types A and B [split virion]),
 - AGRIFLU® (purified trivalent subunit influenza vaccine, thimerosal and preservative free)
 - INTANZA® (intradermal (ID) influenza vaccination by disposable-syringe jet injector (DSJI))
- Live Attenuated Intranasal Vaccine (LAIV)
 - FluMist® (trivalent live attenuated influenza vaccine)
- Antiviral agents may be used for prophylaxis
 - Often in combination with the flu vaccine in an outbreak situation

New Intranasal Flu Vaccine: LAIV (FluMist®)



- FluMist® is a seasonal influenza virus vaccine
 - The virus is attenuated: weakened (not cause the flu)

(A)

Cold adapted: Replicates efficiently in nasopharynx
(first line of immune response)

(B)

Temperature sensitive: does not replicate
the lungs

- Protects against three anticipated seasonal influenza strains
 - (2 "A" strains and 1 "B" strain)
- Contains **no preservatives**
 - e.g., no thimerosal, which is a mercury-containing organic compound

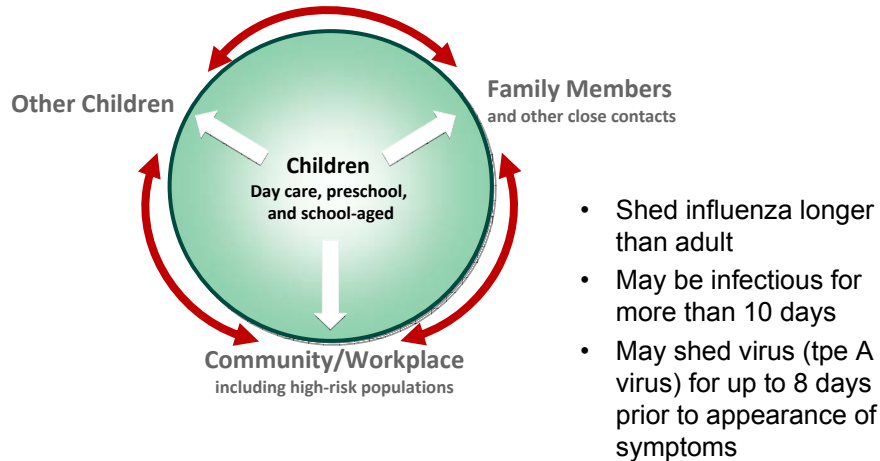


CONFIDENTIAL INFORMATION Contains no adjuvants

LAIV Paediatric Use: Clinical Pearls

- High efficacy demonstrated in multiple randomized, controlled trials
 - 60% efficacy in vaccine-naïve children after one dose
 - 77% efficacy in vaccine-naïve children after two doses
 - 87% efficacy for revaccination with single dose
- More efficacious than TIV in 3 randomized studies in children 6 months to 17 years
 - 31.9% to 54.9% fewer cases of influenza illness
- Cross-protection against mismatched strains, including greater cross-protection versus TIV

Societal Benefits of immunizing children



Glezen WP, et al. *N Engl J Med.* 1978;298:587-592.
Weycker D, et al. *Vaccine.* 2005;23:1284-1293.

Conclusions

- Significant herd immunity can be achieved when the uptake of influenza vaccine is 80% in clusters where children aged 3 to 15 yrs are immunized
- Study offers experimental proof to support influenza immunization of school age children with inactivated vaccine to interrupt influenza transmission
- Immunizing children with live intranasal vaccine likely will lead to greater herd immunity