Systematic Review of Effectiveness of Live-Attenuated vs. Inactivated Vaccines for Healthy Children

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Advisory Committee on Immunization Practices

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First Influenza Vaccine Recommendation

Burney LE.
Public Health Rep. 1960 Oct;75(10):944.

STATEMENT

By Leroy E. Burney, Surgeon General, Public Health Service

Influenza Immunization

Two outbreaks of influenza swept the United States in the fall of 1957 and the winter of 1958, resulting in 60,000 more deaths than would be expected under normal conditions. There were, in addition, more than 26,000 excess deaths during the first 3 months of 1960 which also were considered to be the result of influenza.

These departures from the usually predictable norms prompted the Surgeon General's Advisory Committee on Influenza Research to analyze the cause and to seek measures to prevent such an occurrence in the future.

The committee found that a new antigenic variant, the Asian strain, because of its widespread introduction and the general lack of resistance to it, was the direct cause of the excess number of deaths, not only in the total population but most markedly among the chronically ill, the aged, and pregnant women. As a result of these findings, the Public Health Service is urging a continuing program to protect these high-risk groups in order to prevent a recurrence of this excess mortality.

The high-risk groups who contribute most to the excess deaths and who the Public Health Service believes should be routinely immunized each year are:

1. Persons of all ages who suffer from chronic debilitating disease, in particular: (*a*) rheumatic heart disease, especially mitral stenosis; (*b*) other cardiovascular diseases, such as arteriosclerotic heart disease or hypertension—especially patients with evidence of frank or incipient insufficiency; (*c*) chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis; (*d*) diabetes mellitus; (*e*) Addison's disease.
2. Pregnant women.
3. All persons 65 years or older.

The adult dosage recommended by the advisory committee for initial immunization is 1.0 cc. (500 cca units) of polyvalent vaccine, administered subcutaneously on two occasions separated by two or more months. Preferably, the first dose would be given no later than September 1 and the second no later than November 1. Persons previously immunized with polyvalent vaccine should be reinoculated with a single booster dose of 1.0 cc. subcutaneously each fall, prior to November 1. The only contraindication to vaccination would be a history of food allergy to eggs or chicken or a prior history of allergic reaction to an egg-produced vaccine, such as the commercial influenza product.

The time to start such a program is before the onset of the influenza season this fall. In the past, influenza vaccination has been sparse and sporadic, and primarily in response to an epidemic or the threat of an epidemic. The unpredictability of recurrence of influenza and its continued endemic occurrence are well known. Therefore, the Public Health Service strongly recommends that immunization of these high-risk groups be started now and continued annually, regardless of the predicted incidence of influenza for specific years.

The members of the Surgeon General's Advisory Committee on Influenza Research are: Colin M. MacLeod, M.D., chairman, University of Pennsylvania, Fred M. Davenport, M.D., University of Michigan, Morris Schaeffer, M.D., bureau of laboratories of the City of New York Health Department, George Burch, M.D., Tulane University, Dorland J. Davis, M.D., National Institute of Allergy and Infectious Diseases, Public Health Service, Thomas F. Sellers, M.D., Georgia State Department of Health, and Glenn S. Usher, M.D., Communicable Disease Center, Public Health Service.

History of U.S./ACIP Recommendations for Influenza Vaccination of Children

- 1960:
  - Children with high-risk conditions
- 2003:
  - Children aged 6-23 months
- 2006:
  - Children aged 6-59 months
- 2008:
  - All children aged 6 months through 18 years

Available Influenza Vaccines for Children

- **Inactivated Influenza Vaccine (IIV)**
  - Intramuscular injection
  - First approved in U.S. in 1945
  - Various preparations available for children as young as 6 months
  - May be administered to children with chronic medical conditions
- **Live attenuated vaccines (LAIV)**
  - Administered intranasally
  - Approved in U.S. 2003
  - Recommended for healthy non-pregnant persons 2-49 years
  - Not recommended for persons at high risk of influenza-related complications
- **LAIV preference outside US**
  - Canada: LAIV preferred vaccine for children 2-17 without contraindications
  - United Kingdom: recently recommended vaccination of all children 2-17 yrs; LAIV preferred for those without a contraindication
- **ACIP/CDC currently express no preference for LAIV vs. TIV**

LAIV vs. IIV for Children

- Several RCTs have noted greater relative effectiveness of LAIV as compared with IIV in children
- ACIP examining the relative effectiveness of LAIV vs. IIV as the first recommendation to be evaluated through GRADE methodology
- Consideration of a preferential recommendation requires consideration of a variety of factors, including
  - Relative effectiveness
  - Safety
  - Supply
  - Cost
  - Programmatic feasibility

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Question For Discussion in Today's Presentation

- What is the evidence for the relative effectiveness of LAIV vs. IIV for healthy children?
  - Ages 2-8
  - Ages 9-18

Study Inclusion/Exclusion Criteria

Included:

- Randomized trials of IIV and LAIV conducted among healthy children
- Bivalent vaccines (e.g., LAIV containing influenza A(H3N2) and A(H1N1) only) acceptable

Excluded:

- Studies specifically enrolling children with chronic medical conditions
- Data pertaining to
  - adjuvanted, whole-virus, and virosomal vaccines
  - live-attenuated vaccines derived from different master strains from those used for U.S. products
  - vaccines with antigen quantified by means other than mcg hemagglutinin (HA)
- Studies enrolling only children under 2 years of age.

Effectiveness Outcomes

Outcome	Importance
Effectiveness outcomes:	
Laboratory-confirmed influenza	Critical
Mortality	Critical
Hospitalization	Critical
Medically-attended acute respiratory illness	Critical
Influenza-like illness	Important
Otitis media	Important

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Systematic Review and Meta-analysis—Approach

- Review of literature to identify randomized trials evaluating LAIV and IIV
- Studies identified through existing systematic reviews, review of previous ACIP influenza statements, and literature search
- Two reviewers independently evaluated study eligibility and extracted descriptive, methodological, and efficacy data
- Comparisons conducted using a random effects model
- Quality of evidence assessed following the GRADE approach

Trials Analyzed

22 randomized trials including LAIV, IIV, or both

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6 included LAIV and IIV
- 3 directly comparing LAIV and IIV
- 3 with LAIV, IIV, and placebo arms

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Excluded trials:
- 1 of children with asthma
- 1 of bivalent LAIV (influenza A only) which reported only influenza B infections
- 1 of bivalent LAIV (influenza A only) which used placebo or inactivated B controls, for which influenza A data not extractable

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3 trials included in analyses
- 2 directly comparing LAIV and IIV
- 1 with LAIV, IIV, and placebo arms

Study Characteristics

Study	Location	Season	Arms	Ages	N
Ashkenazi (2006)	Europe, Israel	2002-03	Trivalent LAIV Trivalent IIV	6-59 mo	2187
Belshe (2007)	U.S., Europe, Middle East, Asia	2004-05	Trivalent LAIV Trivalent IIV	6-71 mo	8352
Clover (1991)	U.S. (Houston)	1986-87	Bivalent LAIV* Trivalent IIV Placebo	3-19 yr	192

* Bivalent LAIV containing A(H1N1) and A(H3N2) antigens.

Evidence Profile: LAIV vs. IIV—Lab-confirmed Influenza
2-8 year olds

Laboratory-confirmed influenza							
Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect (Use of LAIV vs. IIV)		Quality
					RR (95% CI)	Abs. Risk per 1000	
3	Serious	None serious	None serious	None serious	0.50 (0.37-0.67)	20 fewer (13 fewer to 25 fewer)	2 (Moderate)

- Ashkenazi (2006), Belshe (2007), Clover (1991).
- 1 trial was open label; a second did not report randomization, allocation concealment, blinding, or loss to follow up.
- Ashkenazi: results not age-stratified; data included was without regard to match.
- Belshe: results for 24-59 mos included; data for well-matched strains included.
- Clover: results for 3-9 yrs included; infections reported were a different H1N1 strain from vaccine.

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Evidence Profile: LAIV vs. IIV—Lab-confirmed Influenza
9-18 year olds

Laboratory-confirmed influenza							
Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect (Use of LAIV vs. IIV)		Quality
					RR (95% CI)	Abs. Risk per 1000	
1	Very serious	None serious	None serious	Very serious	10 (0.60-165)	610 more (27 fewer to 1000 more)	3 (Low)

- Clover (1991)
- Trial did not report randomization, allocation concealment, blinding, or loss to follow up.
- Very wide confidence interval
- Clover: results for 10-18 yrs included; infections reported were a different H1N1 strain from vaccine.

Summary

- LAIV provided greater relative protection than IIV against culture-confirmed influenza among healthy younger children (ages 6 months through 9 years) as assessed across 3 randomized studies.

- Less data available from randomized studies of older children (only one study; LAIV not significantly more effective).

Limitations

- Small number of studies, particularly for older children.
- Some children under 2 years of age included in analysis.
- Studies conducted during different seasons in geographically diverse regions.

Additional Issues to be Considered

- **Safety assessment**
  - Quadrivalent LAIV (Q-LAIV) expected to replace current trivalent LAIV (T-LAIV) for 2013-14 season
  - Do not yet have postmarketing safety experience with Q-LAIV
- **Supply**
- **Relative cost**

Next Steps

- Plans for assessment and ongoing safety evaluation of quadrivalent LAIV
- Review of supply and economic data
- Gathering of additional information requested by ACIP

Thank You!

For more information please contact Centers for Disease Control and Prevention

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