Influenza Vaccine Performance:

Summary of the Influenza Vaccines and Immunization SAGE Working Group

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Risk Groups Assessed for Vaccine Effectiveness/Efficacy

1) Pregnant Women
2) Health Care Workers
3) Children
4) Elderly
5) Underlying medical conditions

1. Influenza Vaccine and Pregnant Women


Public Health
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Issue Brief – Influenza Vaccination for Pregnant Women, 2010-11 Season

Please Note
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The correct by-line with contact information is stated above.

Pregnant Women and Influenza

Pregnant women are at increased risk for severe infections and hospitalization from seasonal influenza and pregnant women were at increased risk for hospitalization and death during the 2009 H1N1 pandemic.1 Both the 2009 H1N1 virus and other seasonal influenza viruses are expected to circulate during the current flu season. Influenza vaccination is the most effective way to protect pregnant women from influenza.

Inactivated flu vaccine is considered safe and effective during any stage of pregnancy. Both the American College of Obstetricians and Gynecologists (ACOG) and the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (CDC/ACIP) recommended that women who are or plan to be pregnant during influenza season receive influenza vaccine as soon as possible and during any trimester of pregnancy.[1,2]

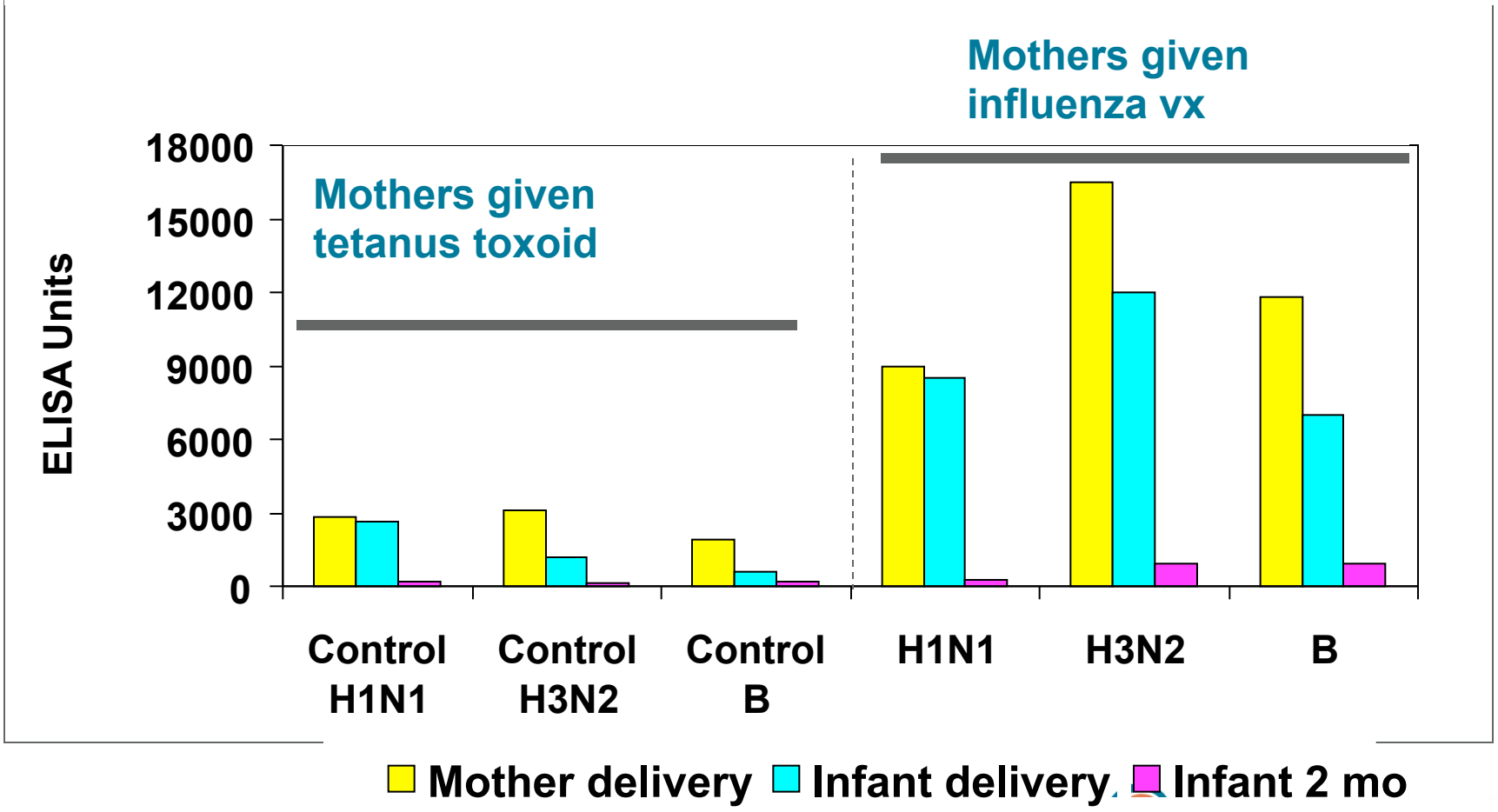
- The ACOG Committee on Obstetric Practice considers influenza vaccination an integral element of prenatal care.[3]
- In addition to protecting women during pregnancy and after delivery, two recent studies have demonstrated flu vaccination of women during pregnancy also protects their newborns for up to six months.[4,5]
- Despite their increased risk and the formal recommendations from CDC/ACIP and ACOG, only 10-25% of pregnant women typically receive influenza vaccination.[6]

Prenatal health care providers play a pivotal role in influencing their patients' decisions to receive influenza vaccine, as well as other recommended vaccines. By recommending and providing influenza vaccine to their patients, prenatal

- Used since ~ 1960 in pregnant women
- Excellent safety profile
- Equally immunogenic as in non-pregnant women in small clinical studies
- No clinical effectiveness studies in women using laboratory-confirmed influenza outcomes
- 2009 pandemic A/H1N1 impacted recommendations and uptake of influenza vaccine during pregnancy

Immunogenicity: Maternal Influenza Vaccine Increases Antibody Concentrations in Mothers and their Infants *

Antibody to influenza A and B in mothers and their infants following maternal immunization with influenza vaccine or tetanus vx.



* Englund et al: J Infect Dis 1993;168:647-56

EFFICACY: Maternal Immunization with Influenza in Low Resource Countries*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effectiveness of Maternal Influenza Immunization in Mothers and Infants

K. Zaman, M.B., B.S., Ph.D., Eliza Roy, M.B., B.S., D.C.H., Shams E. Arifeen, M.B., B.S., Dr.P.H., Mahbubur Rahman, M.B., B.S., Ph.D., Rubhana Raqib, Ph.D., Emily Wilson, M.H.S., Saad B. Omer, M.B., B.S., Ph.D., Nigar S. Shahid, M.B., B.S., M.P.H., Robert E. Breiman, M.D., and Mark C. Steinhoff, M.D.

N Engl J Med 2008;359:1555-64.

Study design:

- Randomized controlled trial carried out in Bangladesh, 2004-5.
- 340 pregnant women received either inactivated influenza vaccine or pneumococcal polysaccharide vaccine (control) during 3rd trimester.
- Followed through pregnancy and first 6 months after birth.

Results:

- Maternal TIV decreased respiratory illness with fever:
  - 29% among infants;
  - 36% among their mothers.
- Vaccine efficacy against laboratory-confirmed influenza among newborns was 63%

Caveats:

- Small sample size
- Laboratory testing not optimal

Maternal Immunization with Influenza Vaccine Protects Infants Against Influenza*

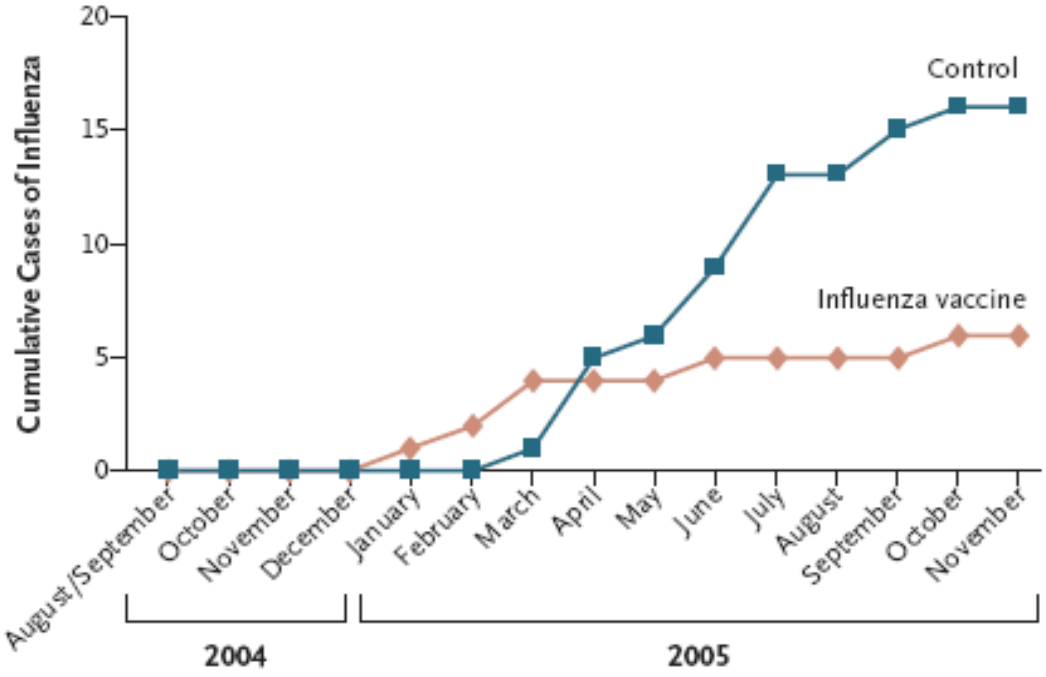


Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.

Testing for influenza antigen was performed from December 2004 to November 2005.

*Zaman et al, NEJM 2008;359 (Sept. 2008)

SUMMARY: Other studies of antenatal influenza immunization and infant outcomes

Author	Site/ Dates	Design	# VX	# Control	Infant Effect
Zaman 2008	Bangladesh 2004-5	RC Vx Trial	172	168	↓ 36% ILI ↓ 69% lab + flu
Poehling 2011	TN, OH, NY USA 2002-9	Case Control	151	1359	↓45-48% hospitalization
Eick 2011	Apache/ Najavo USA 2002-5	Prospec-tive obser-vational cohort	573	587	↓41% lab + flu
Benowitz 2010	CN/ USA 2000-9	Case-control	91	156	↓91.5% hospitalized flu+

Maternal immunization with influenza vaccine: Benefits to the infant

- Influenza immunization of pregnant women in Bangladesh was associated with a lower risk of SGA infants (↓34%) and an increase in mean birth weights (↑200g) in a tropical country, where influenza circulates nearly year round.

- These data from a RCT data provide initial evidence that influenza infections during pregnancy are a preventable cause of decreased intrauterine growth.

- Additional randomized prospective studies are needed to expand these novel observations, and are underway

Increased birth weight in babies born to TIV-immunized mothers support results of Bangladesh study

Data from 3 studies of pregnant women who were either immunized or experienced influenza supports birthweight observations from Bangladesh:

Author	Site	Design	Intervention	Control	Newborn	Outcome
Steinhoff 2011	Bangladesh 2004-05	**RC Trial**	Flu vaccine 172	Spn vaccine 168	**Birth weight** ↑ 200g	% SGA ↓ 34%
McNeill 2011	NS, Canada 1990-2002	Retrospective	"flu" adm 208	No adm 132,099	↑ 90gm	↓ 40%
S. Omer 2011	GA, USA 2004-06	Cohort analysis	Flu vaccine 578	No vaccine 3,748	—	↓ 70%
Anderson 2011	RI, USA 2009-10	Prospective cohort (pH_1N_1)	Lab flu 16	ILI, lab negative 25	↑ 285g	—

1. Influenza Vaccine and Pregnant Women: Conclusions

- Pregnant women are at highest risk for severe sequelae of influenza
- Influenza vaccines are safe and immunogenic in this population
- Vaccination during pregnancy is likely to be effective against severe disease in this population
- Protection against influenza in infants following maternal immunization during the first 6 months of life has been demonstrated

2. Influenza Vaccine and Health Care Workers (HCW)

- HCW have additional exposure risk for influenza
- HCW are able to respond to influenza vaccine better than patients, who may be ill, immunocompromised, young, or elderly.
- Vaccination of HCW could prevent transmission of virus from HCW to patients, or patients to HCW and their families.
- Vaccination of HCW should prevent morbidity in the workers themselves and morbidity and mortality in patients

Influenza vaccine effectiveness in healthy working adults

- Meta-analysis of 38 studies including consideration of vaccine match to circulating strains estimated point estimate of 80% efficacy during well-matched years and 50% efficacy during poor match years.*
- Meta-analysis of TIV efficacy showed efficacy in 8/12 seasons in 10 randomized controlled trials in adults 18-65, with a pooled efficacy of 59% **
- Serological study in Baltimore of HCW showed effectiveness against influenza A/B of 88-89%***
- Absenteeism of healthy workers could potentially be prevented by influenza vaccine, but few trials available to document this and existing trials have variable results.

*Jefferson et al. Cochrane database of systematic reviews 2007. **Osterholm et al. Lancet ID 2012; 12:36;***Wilde et al. JAMA 1999;28:908; ****

2. HCW: Conclusions

- HCW have additional risks for influenza exposure
- HCW are likely to respond to influenza vaccine
- HCW are an important priority group for influenza vaccine because vaccination has the potential to protect the HCW and vulnerable patients.
- HCWs are also an important target for pandemic preparedness: ensuring countries have existing robust programs to vaccinate HCWs during pandemics is a key global strategy to ensuring resilience of health care systems

3. Influenza Vaccine and Children: Children 6 Months - 2 Years

- Highest risk group for severe disease or hospitalization is in youngest children
- Older children respond better to inactivated flu vaccines than children ages 6 M – 2 Y
- Vaccine choices are limited in this age group:
  - Only inactivated vaccine without adjuvants currently licensed for this age group.
  - Two doses a minimum of 3-4 weeks apart required to provide protection.
- Effectiveness of influenza vaccines among children varies due to changes in circulating viruses
  - Vaccine effectiveness among children <2 particularly affected by vaccine match to circulating strains.

Observational Studies: Trivalent inactivated influenza vaccine effectiveness in children < 2 years

Author (Year)	Study Year	No. subjects	Age range	Outcome	VE (%)	95% CI
Shuler (2007)	2003-04	290	6-23 m	OP	52	20,97
Szilagyi (2008)	2003-04	165 80	6-23 m	OP IP	68 -42	NS NS
	2004-05	74 95	6-23 m	OP IP	-40 53	NS NS
Eisenberg (2008)	2003-4 2004-5	228 197	6-23 m	OP, ED, IP	28 55	NS 13,77
Cochran (2010)	2003-04 2004-05 2005-06	1,164 153 331	6-23 m	OP?	8 -197 76	NS NS 37-91
Heinonen (2011)	2007-08	631	9m – 3y 9 m – 2y 2 – 3y	OP	66 66 63	29,84 9,88 -5,88
Kelly (2011)	2008	289	6m- 5y 6 – 23m	OP, ED	58 63	9, 81 NS
Kantayose (2011)	2002-08	14,788	6m – 6y 6 – 11m 12 – 12m	OP	52 80 63	47,56 P<0.01 P<0.01

3. Influenza Vaccine and Young Children Less than 2 years: Summary

- No vaccines currently available for children < 6 months
- Inactivated vaccines are only current option for children ages 6 months - 2 years
- Two intramuscular doses of TIV are required to provide adequate protection for children, based on Ab levels and observational studies
- Timing of 2nd dose does not matter as much as the antigen content of the vaccine
- Lower VE observed in some studies compared with older children, but no decline in VE by age in others
- Vaccine effectiveness varies by season and good match of circulating virus to vaccine strain needed for good effectiveness in young children

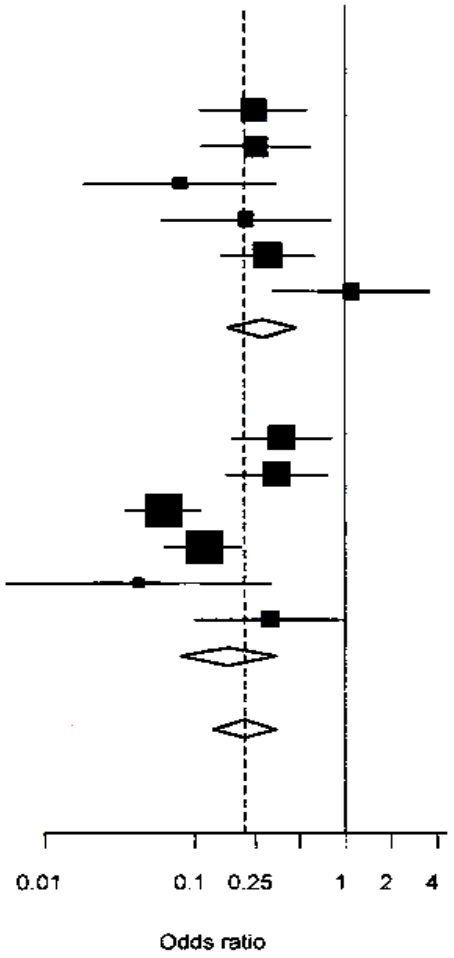
3. Influenza Vaccine and Children: 2 -5 Years of Age

- Either trivalent inactivated influenza vaccine (TIV) or live-attenuated influenza vaccine (LAIV) is an appropriate choice for vaccination programs.
- LAIV may be more effective than TIV in healthy preschool and school-aged children, but limited availability of LAIV currently
- Children < 9 years of age previously unimmunized against influenza require two doses of vaccine to generate a protective immune response.
- Antibody responses among children with chronic medical conditions may be decreased compared with children without chronic medical conditions.

Meta-analysis of TIV and LAIV efficacy in children (Negri et al. Vaccine 2005; 23)

Inclusion: RCTs with placebo or non-flu vaccine as control; ages 6m – 18 yrs; healthy children; >=30 subjects per arm; published 1990-2003; both lab-confirmed and non-lab confirmed endpoints

Study	Vaccine	Placebo	OR	95%CI
Inactivated vaccine				
Gruber 1990; I	10/54	37/77	0.25	0.11-0.56
Clover 1991; II	9/54	36/82	0.26	0.11-0.59
Neuzil 2001; II	2/327	21/294	0.08	0.02-0.34
Neuzil 2001; IV	3/308	12/280	0.22	0.06-0.79
Hoberman 2003; I	15/273	22/138	0.31	0.15-0.61
Hoberman 2003; II	9/252	4/123	1.10	0.33-3.65
All Inactivated	48/1268	132/994	0.28	0.17-0.47
Live-attenuated vaccine				
Gruber 1990; II	15/58	37/77	0.38	0.18-0.79
Clover 1991; I	12/56	36/82	0.35	0.16-0.75
Belshe 1998; I	14/1070	94/531	0.06	0.03-0.11
Belshe 1998; II	15/917	56/441	0.11	0.06-0.20
Neuzil 2001; I	1/311	21/294	0.04	0.01-0.31
Neuzil 2001; III	4/289	12/280	0.31	0.10-0.98
All Live-attenuated	61/2701	256/1705	0.16	0.08-0.34
All	109/3969	388/2699	0.21	0.13-0.34



Summary VE estimates:

Culture-confirmed

TIV - 65% (45 -77)

LAIV – 80% (53 -91)

Serologically confirmed

TIV - 63% (43 - 76)

LAIV – 54% (20 – 74)

Conclusions -

Influenza vaccines are effective

No significant difference between LAIV and TIV

Did not provide results by age group

Summary of evidence for Vaccine Effectiveness (VE) among children 2- 5 yrs old

- Influenza vaccines are effective, but
  - VE of TIV depends on vaccine match to circulating viruses
  - VE of LAIV less affected by strain mismatch
- Children 2-5 years may respond better to TIV than younger children

- Superior VE of LAIV has been demonstrated in children < 9 years with diverse T cell responses demonstrated and broader cross protection than TIV

- Superior VE of adjuvanted TIV in children < 6 years compared with standard TIV has been demonstrated (Vesikari 2011)
  - Effect of adjuvant perhaps greater in the youngest children

3. Conclusion: Influenza vaccine for children

- Priority group for vaccination based on high disease burden
- Vaccine effectiveness is more dependent on vaccine strain match to circulating strain
- Preventing influenza disease in influenza-naïve population is challenging
- Need for 2 doses of inactivated vaccine prior to influenza season to provide protection is also challenging
  - LAIV in children > 2 years or adjuvanted vaccine could potentially reduce need for 2 doses
  - No current vaccine for highest risk infants < 6 M of age, indicating need for maternal immunization at highest priority

4. Influenza Vaccine and the Elderly

- Influenza contributes to **substantial** morbidity and mortality in the elderly
- Increasing population of living persons > 65 yrs
- Currently available inactivated influenza vaccine reduce the risk of morbidity and mortality in the elderly. However:
  - Decreasing effectiveness with increasing age and multiple medical conditions
  - Institutionalized elderly may be at greatest risk from influenza, yet benefit less from vaccine.

Vaccine Effectiveness in the Elderly

- Influenza vaccine studies in the elderly vary greatly depending on the population, vaccine to circulating strain match, and outcome measured.
- VE estimates range widely- from 20 to 80%
  - Efficacy varies based on endpoint: ILI vs lab-confirmed flu
  - Varies between community dwelling and nursing home elderly
  - Is all cause mortality an expected endpoint?
- "Healthy vaccinee" effect: healthier individuals may seek out vaccine more readily (Jackson, 2006)
- Limited data on LAIV in elderly but this data suggests comparability with TIV in this population

Vaccine Effectiveness in the Elderly: Studies and Reviews

- Cochrane review, 2010: vaccine effectiveness (VE):
  - 41% against ILI of 41%
  - 58% against lab-confirmed flu of 58%
- 2002 meta-analysis by Vu et al (2002) in community-dwelling adults > 65 years found VE of :
  - 35% against ILI
  - 33% against pneumonia/influenza hospitalizations
  - 47% against pneumonia and influenza mortality
  - 50% against all-cause mortality
- 2007 report of annual mass vaccination campaigns for adults > 65 years in Sao Paulo, Brazil detected 26% reduction in age-specific influenza-attributable mortality

4. Influenza vaccine and the elderly: Conclusions

- High risk population group with highest risk of mortality due to influenza
- Traditional focus of vaccination effort and potential benefit in terms of mortality
- However, influenza vaccines are less effective in this population than most other groups, particularly healthy young adults
- Vaccination is the best tool to reduce influenza-associated morbidity and mortality in this group

5. Influenza Vaccine and Persons with Underlying Health Conditions

- Individuals of any age with underlying health conditions are more likely to develop severe disease following influenza infection
- Effectiveness of influenza vaccine has been demonstrated in subsets of individuals with underlying health conditions in a variety of settings

High Risk Conditions Considered for Influenza Vaccine

- Respiratory disease
- Cardiac disease
- Neurodevelopmental disorders
- Metabolic disorders
- Immunocompetency disorders
- Chronic liver diseases
- Chronic renal insufficiency
- Hematological diseases
- Chronic aspirin therapy in children
- Others: socially disadvantaged minority groups, members of long term care facilities, morbid obesity

Vaccine performance in persons with high-risk conditions

- Inactivated influenza vaccine effectiveness has been demonstrated in persons with:
  - Asthma
  - COPD
  - Chronic lung disease
  - Cardiac disase
- Compared to healthy populations, VE may be decreased and meta-analyses indicate insufficient evidence to conclude vaccines are fully effective in these populations
  - Limited evidence in elderly with comorbid conditions, COPD
  - Immunogenicity of flu vaccines are decreased in immunocompromised individuals, but also seroconversion rates my underestimate efficacy of the vaccine (Madhi 2011)
- Evidence of improved effectiveness with higher dose ag vaccines is pending.

South Africa TIV Randomized Controlled Trial: HIV+

- 506 HIV infected adults with CD4+ cell counts >100 cells per microliter (349 on ART) randomized to TIV or placebo
- 13 pregnant HIV-infected women (4 in immunogenicity cohort)
- Seroconversion ~50% for each vaccine strain tested
- Seroconversion rate for H1N1 underestimated observed strain-specific efficacy (73%)

- This study provides rationale for clinical effectiveness studies despite moderate immunologic response to TIV

*Madhi CID 2011

5. Influenza vaccine in persons with high risk conditions

- Increasing population of older persons, immunocompromised persons, and those with single or multiple high risk conditions
- Heterogenous population presents difficulties with targeted vaccination campaigns
- Safety and effectiveness of LAIV in these populations not well studied

- Use of influenza vaccine in these populations may be hampered because of programatic challenges

Thank you

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Followup: Influenza Ab in Immunized Mothers and Babies over Time*

The NEW ENGLAND JOURNAL of MEDICINE N ENGL J MED 362;17 NEJM.ORG APRIL 29, 2010

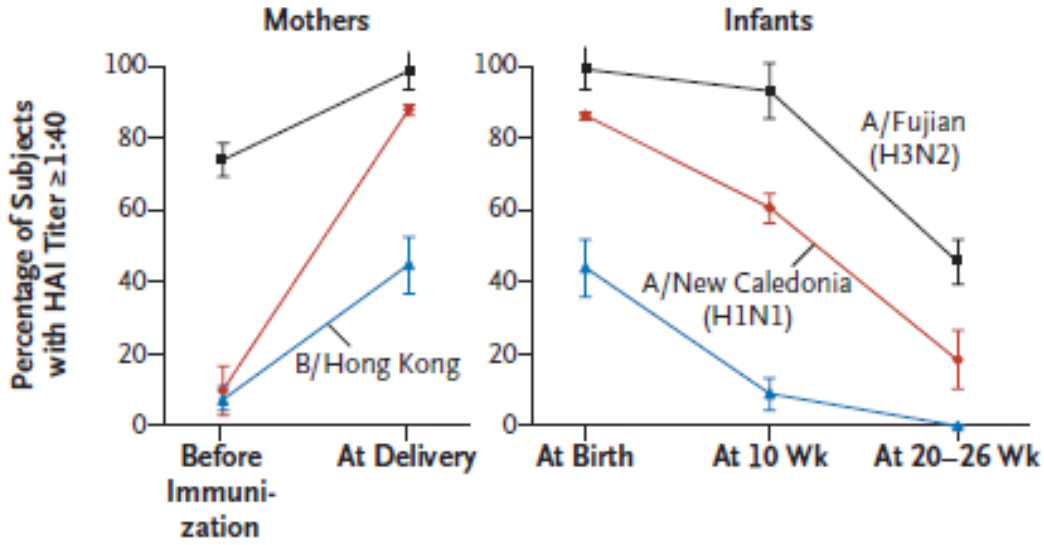
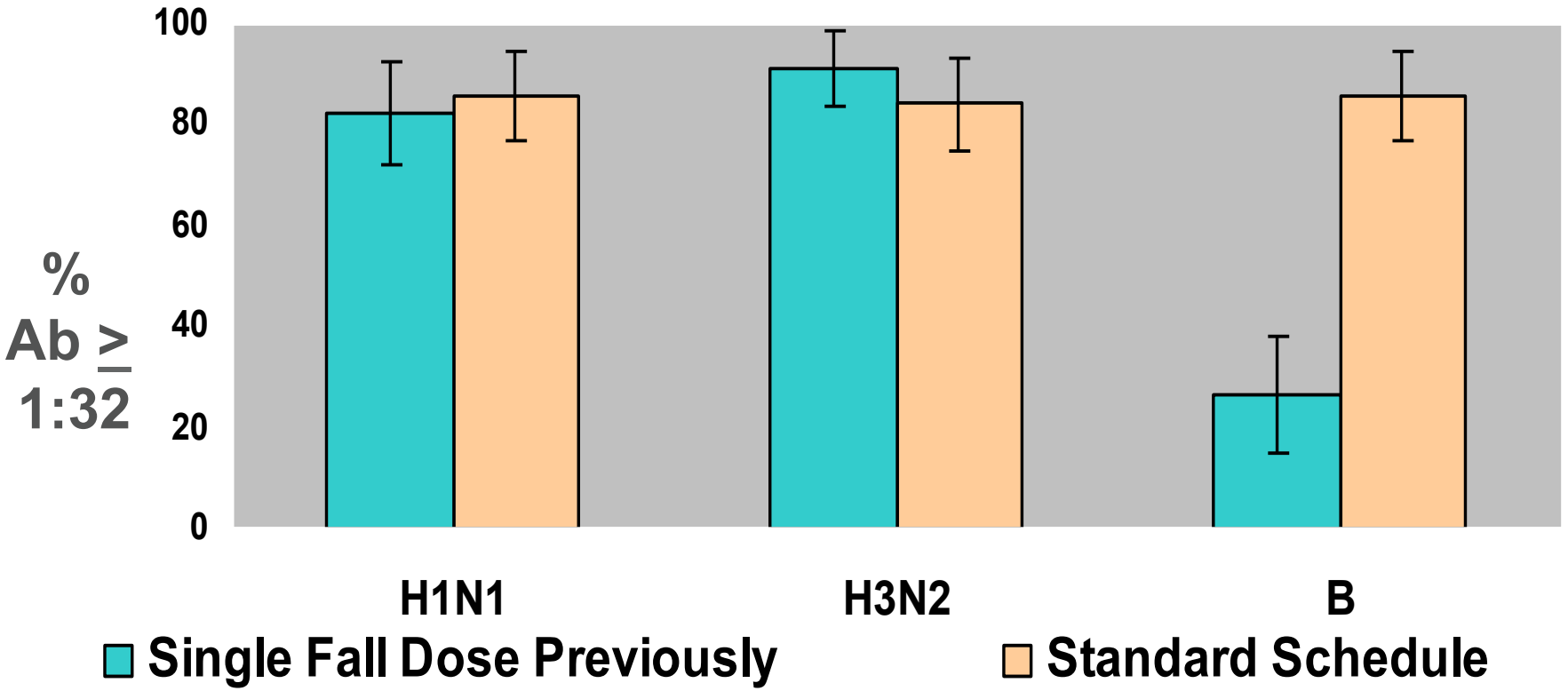


Figure 1. Proportions of Immunized Mothers and Their Infants with Hemagglutination-Inhibition (HAI) Titer of 1:40 or Greater.

Data at birth are from cord-serum samples. Before immunization, the proportions with an HAI titer of 1:40 or greater were significantly ($P<0.001$) higher for A/Fujian (H3N2) than either of the other two strains, among mothers, and the proportions were significantly higher for A/Fujian (H3N2) than for A/New Caledonia (H1N1) at all other time points. The proportions with seroprotection were significantly lower for B/Hong Kong than for either of the other two strains at all time points after immunization. (Immunization occurred during the third trimester.) I bars indicate 95% confidence intervals.

*Steinhoff M et al. NEJM 2010; 362:17

Antigen Composition of Vaccine But Not Timing Important in Antibody Response in Toddlers*



Note: Vaccines in blue group differed by drifted A/H3N2 and major lineage switch in B Ag

*Englund et al, Pediatrics 2006

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Influenza vaccine efficacy or effectiveness in children < 2 years: TIV

Author/Year/ Journal	Study Design	Study Year	Lab-confirmed outcome?
Hoberman (2003)	RCT	1999-01	Cx
Vesikari (2011)	RCT	2007-09	RT-PCR
Heinonen (2011)	Cohort	2007-08	IFA, Cx, PCR
Shuler (2007)	Case-Control	2003-04	RIDT
Allison (2006)	Cohort	2003	No
Szilagyi (2008)	Case-Control	2003-05	PCR, Cx
Ritzwoller (2005)	Cohort	2003-04	No
Eisenberg (2008)	Case cohort	2003-05	PCR, Cx
Cochran (2010)	Case-Control	2003-05	DFA, Cx
Kelly (2011)	Case-Control	2008	PCR, Cx
Kantayose (2011)	Cohort	2002-8	RIDT

Refs:
Hoberman et al. JAMA 2003; 290:1608; Vesikari et al. NEJM 2011; 365:1406;
Heinonen, et al. Lancet ID 2011;11:23;
Szilagyi et al. Arch Pediatr Adolesc Med 2008; 162:943;
Allison et al. J Pediatr 2006; 149:755; Ritzwoller et al. Pediatrics 2005;116:153;
Eisenberg. Pediatrics 2008; 122:911; Shuler et al. Pediatrics 2007;119:e587
Cochran et al Human Vaccines 2011; 9:729; Kantayose et al. Vaccine 2011; 29:1844
Kelly et al. Pediatr Infect Dis J 2011; 30:107;

The effectiveness of TIV in children over six consecutive influenza seasons (Katayose, et al. Vaccine 2011; 29: 1844-49

Study Design:

Prospective observational study of commercial TIV given as 2 doses to all ages 6 mos-6 years in Japan, with ~2300 children/year over 6 years.

Outcomes

Rapid influenza detection tests based on ARI and fever

Results:

H3N2 predominant 4 years; B and H1 predominant one year each

Vaccine match (good match <= 4-fold HI titer):

- H1: good match 5/6 years
- H3: good match 3/6 yrs
- B: good match 3/6 yrs

Overall VE: 71% (59-80%) over entire study period for all ages

Influenza vaccine efficacy in children: Randomized Control Trials of TIV

Author/Year/ Journal	Study Year	Loca-tion	Age range	Vaccine Type	Lab Confirmation	VE (%)	95% CI
Neuzil (2001)	1988-89	USA	<16 y	TIV	Cx, HI	91	64,98
	1989-90	USA	<16 y	TIV	Cx, HI	77	20,94
Clover (1991)	1986-87	USA	3-18 y	TIV	Cx, HI	62	P<0.01
Hoberman (2003)	1999-00	USA	6 -24 m	TIV	Cx	66	34, 82
	2000-01	USA	6 - 24 m	TIV	CX	-7	-247, 67
Loeb (2010)	2008-09	Canada	36 m-15 y	TIV	RT-PCR	61%	8,83
Vesikari (2011)	2007-09	Germany, Finland	6-71 m	TIV-Adj	RT-PCR	86	74, 93
	2007-09			TIV		43	15 , 61

- Range of VE point estimates: 0% - 91%
- 6/8 study-years with significant protection [VE of 43-91%]
- 2 study years with no measurable effect (low AR in control group)