PREVENTION OF INFANT DISEASE: IMMUNIZATION IN PREGNANT WOMEN AND ITS APPLICATION IN DEVELOPING COUNTRIES

Annecy ADVAC 15
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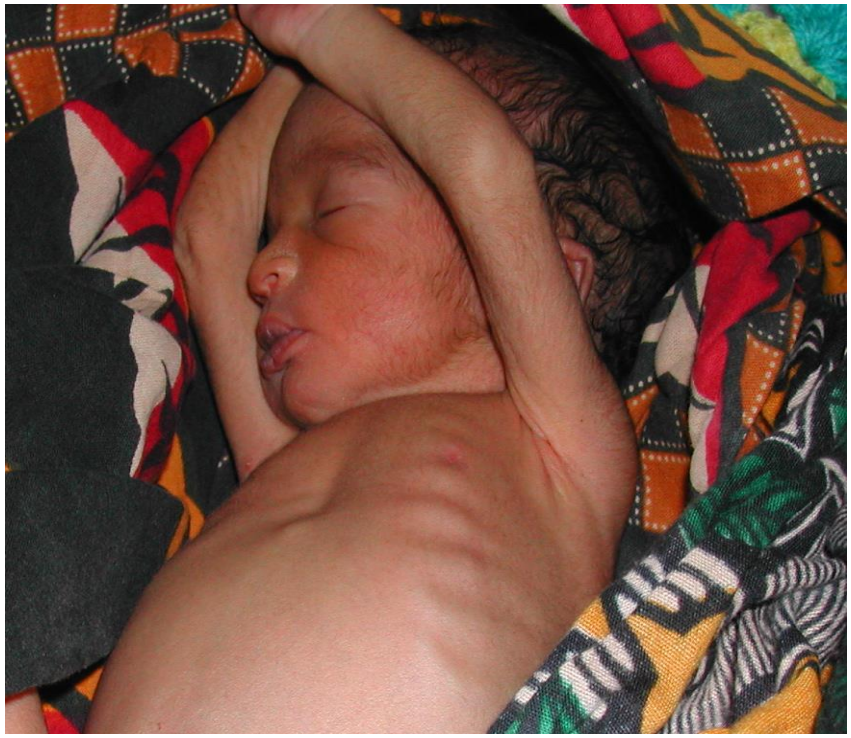
NEONATES AND YOUNG INFANTS ARE AT HIGH RISK FROM INFECTIOUS DISEASES

- Neonates are uniquely at risk for many different infections which cause substantial morbidity and mortality worldwide
- Immune system of neonates is immature and relatively ineffective
- Active immunization is rarely successful in newborns



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PREGNANT WOMEN

- Deserve appropriate routine medical care as medically indicated - regardless of pregnancy status.
  EXAMPLES: antibiotics

- Should not be excluded from beneficial treatments/ potentially beneficial therapies based on pregnancy status. EXAMPLE: antiretroviral drugs

- Can help protect their infants against some diseases by medical intervention during pregnancy.
  EXAMPLE: Rh disease/Rhogam, tetanus vx

- Have mature immune systems which are far more competent than the fetus or neonate. They respond well to protein, polysaccharide, and conjugate vx
  EXAMPLE: Flu vx, Tdap vx

- Are capable and should have the right to make informed consent for themselves and their unborn child (although this is country and culture-specific)

Thanks to my sister-in-law

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Immune Responses During Pregnancy*

- Physiologic changes
  - Increased heart rate, stroke volume; decreased lung capacity but increase in O2 carriage.
  - Alter host response to antigens (increase in estrogen and progesterone result in decreased interleukins).
  - Increase in blood cortisol levels due to decreased clearance
- Decreased cell mediated immunity: relatively minor but can predispose to listeria, TB, toxoplasmosis, etc.
- Decrease in concentration of IgG (hemodilution)
- No significant alteration in antibody responses to vaccines or infections

Southwest Washington Health District , WA

*Halsey and Klein D, Maternal Immunization Workshop. Pediatr Inf Dis J 1990;9:574

WHY IMMUNIZE A PREGNANT WOMAN?

- Immunization during pregnancy has the potential to protect both mother and infant during a vulnerable period in their lives
- Pregnant women are accessible to medical care and intervention
- Transplacental transfer of antibodies is safer and less expensive than administration of immunoglobulin preparations to the infant

Health Service Coverage Among Pregnant Women*

	MDG 5 Antenatal care coverage (%) 2000-2009	
Income Group	**At least 1 visit**	**At least 4 visits**
Low income	69	39
Lower middle income	79	47
Upper middle income	94	75
High income	--	--
Global	78	48

* World Health Statistics 2010.

OBSTETRICAL CONSIDERATIONS FOR USING A VACCINE IN PREGNANT WOMEN*

- High risk for exposure of pregnant woman to disease
- Infection poses a special risk to the mother
- Infection poses a special risk to the fetus
- Vaccine is available, and unlikely to cause harm

*ACOG Technical Bulletin 1991; 160.

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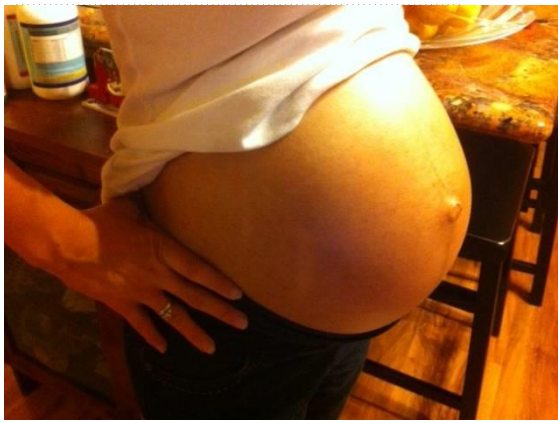
IMMUNIZATION DURING PREGNANCY: RECENT HISTORY

- Routine immunization during pregnancy with diphtheria, influenza and polio vaccines during 1950's - 60's
- Safety and benefit of polio vaccine during polio outbreaks (Finland, Israel), and meningococcal outbreaks (Brazil) between 1970 – 1990
- Concerns of vaccine safety, vaccine components, and lack of efficacy data resulted in cessation of maternal vaccination except for high maternal risk in USA by 1980's
- 2009-10 Pandemic H1N1 outbreak demonstrated risk of flu during pregnancy and benefits of flu vaccination
- 2012-2014 pertussis epidemic emphasized high risk of neonatal pertussis deaths



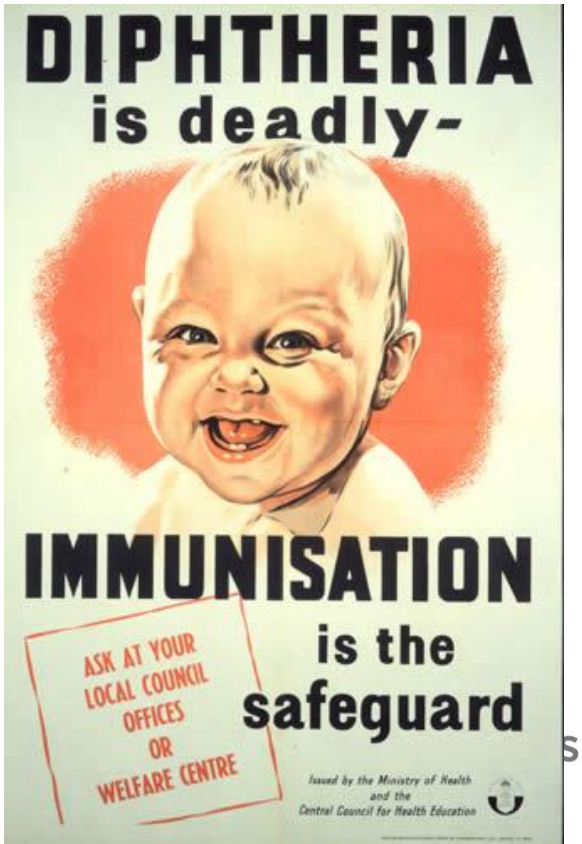
Outline

Examples of maternal immunization to be discusssed :

- Diphtheria
- Tetanus
- Hib
- Influenza
- Pertussis, RSV

- Not discussed:
  - Group B Streptococcus
  - Meningococcus
  - CMV, HSV

UK poster 1950



DIPHTHERIA

Barr et al, Lancet 1950

DIPHTHERIA IMMUNISATION IN YOUNG BABIES

A STUDY OF SOME FACTORS INVOLVED

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TABLE I—ANTITOXIC RESPONSE OF BABIES TO TWO INJECTIONS, EACH OF 0·5 ML. OF A.P.T. : BABIES GROUPED ACCORDING TO THE TITRE OF PASSIVE ANTITOXIN PRESENT AT THE TIME OF THE FIRST INJECTION

Group	Passive antitoxin at time of 1st injection (unit/ml.)	Age (weeks)	No. of babies producing titres (unit/ml.)								Total no.	Geometric mean (unit/ml.)	Av. interval (weeks) between	
			<0·01	0·01	0·02	0·04	0·1	0·2	0·5	1·0			1st and 2nd injections	2nd injection and blood sample
A	Under 0·02	6–13	..	..	..	1	3	11	4	1	20	0·329	8·1	8·9
B		14–26	..	..	..	3	6	9	3	2	23	0·267	8·7	8·5
C		Over 26	..	..	2	3	1	10	1	1	18	0·207	9·6	8·9
A + B + C	Total under 0·02	6 upwards	..	..	2	7	10	30	8	4	61	0·265	..	..
D	0·02–0·04	Av. 18·4	..	..	1	2	1	1	2	0	7	0·166	9·9	9·1
E	0·04–0·10	Av. 12·9	..	1	1	1	2	0	0	1	6	0·098	7·8	7·7
F	0·10–0·20	Av. 18·2	3	1	..	1	..	..	..	..	5	<0·020	8·2	8·2

More maternal Ab → Less infant Ab after infant immunization

Who Could Benefit From What Vaccine?

Licensed Vaccines	Mother	Infant
Tetanus	✓	✓
Influenza	✓	✓
Pertussis	✓	✓
Meningococcus	✓	?
Vaccines in Development		
Group B strep	✓	✓
RSV	?	✓
CMV		✓

NEONATAL TETANUS: A PREVENTABLE DISEASE

- Important cause of neonatal death worldwide for centuries
  - 1960: 38% of neonatal mortality in Thailand
  - 1980: 30% of all deaths in first year of life in many developing countries
- 1961: Landmark study in New Guinea demonstrated benefit of maternal immunization with tetanus toxoid
  (Schofield et al, Brit Med J 1961,2: 785-9)
- 1989: World Health Organization set goal to eliminate neonatal tetanus using maternal immunization – renewed X 3

Highlands,
New Guinea

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Schofield et al, Brit Med J 1961,2: 785-9

NEONATAL TETANUS IN NEW GUINEA

EFFECT OF ACTIVE IMMUNIZATION IN PREGNANCY

BY

F. D. SCHOFIELD, M.D., M.R.C.P., D.T.M.&H.

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AND

G. R. WESTBROOK, S.R.N.

A.O.G. Mission, Wingei, Sepik District, New Guinea

New Guinea, 1961: Incidence of neonatal tetanus pre-study was 80 cases per 1000 live births

# Doses Tetanus Toxoid Given To Pregnant Women	0 or 1 dose	2 doses	3 doses
Number (%) of infants with neonatal tetanus	16/160 (10%)	8/234 (3.4%)	1/175 (0.6%)

Elimination of Neonatal Tetanus

1989 WHO & 1990 World Summit for Children made declarations for the global elimination of neonatal tetanus by 1995… 2000…2005…2010….*

*Roper MH et al. Lancet 2007;370:1947

FACTORS AFFECTING TRANSPLACENTAL TRANSPORT OF MATERNAL ANTIBODY TO THE INFANT

- Placental abnormalities
  - Malaria
  - HIV infection
- TIME:
  - gestational age of infant
  - time between vaccination and delivery
- Maternal IgG level
- IgG subclass

Infant born in Nepal during maternal immunization trial

Maternal-Fetal IgG Transport: AN ACTIVE PROCESS

- Placental transfer is highly selective for monomeric IgG, and occurs by receptor-mediated active transport
- Transport requires HEALTHY placenta
- IgG1 = IgG3 > IgG4 > IgG2
- No transfer of IgM, IgA, IgE
- Begins at 17 wks; increases with gestation
- By 33 weeks maternal= fetal IgG levels and by 40 weeks fetal > maternal IgG levels

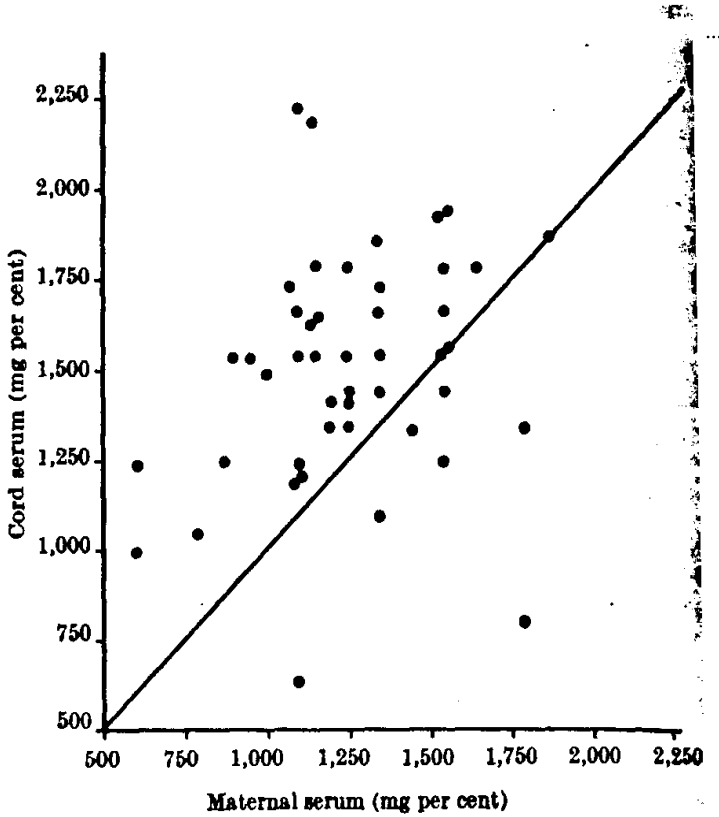

Fig. 1. Comparison of IgG concentrations in forty-six paired maternal cord sera

Kohler and Farr. Nature 1966;21:1070

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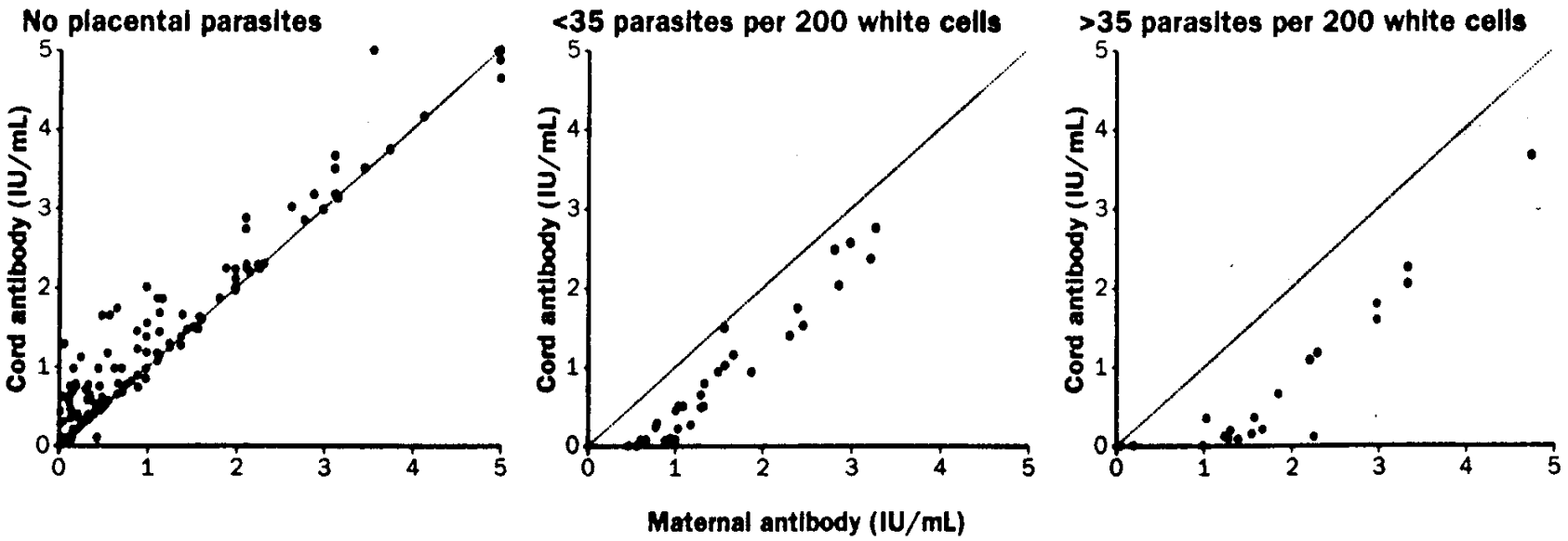
PLACENTAL STRUCTURE:
Reduced Transfer of Tetanus Antibodies with Malaria



Cord/Maternal IgG ratio:

0.82 **0.23** **0.18**

Brair et al. Lancet 1994;343:208

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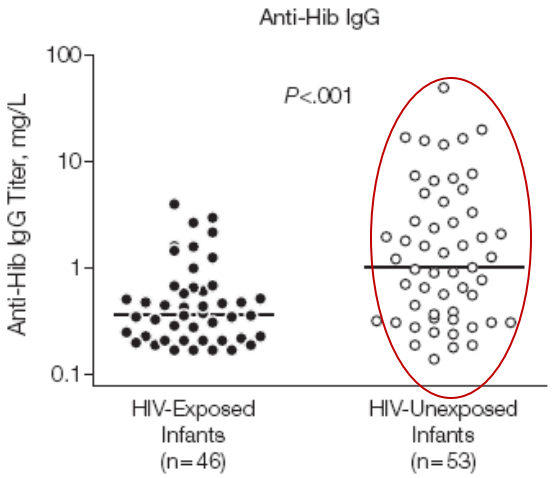
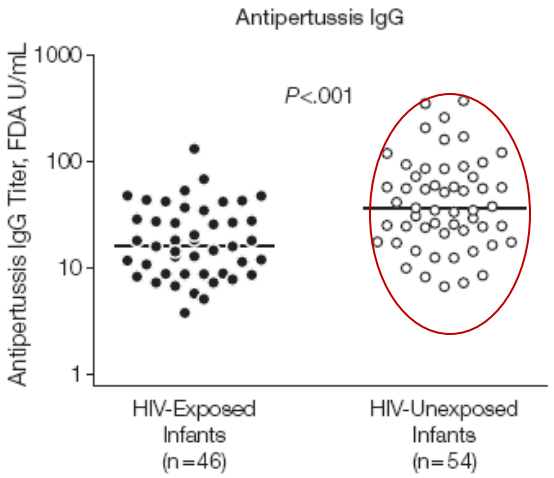
Decreased Antibody Titers in Uninfected, HIV-exposed vs Healthy HIV-unexposed Infants at Birth*

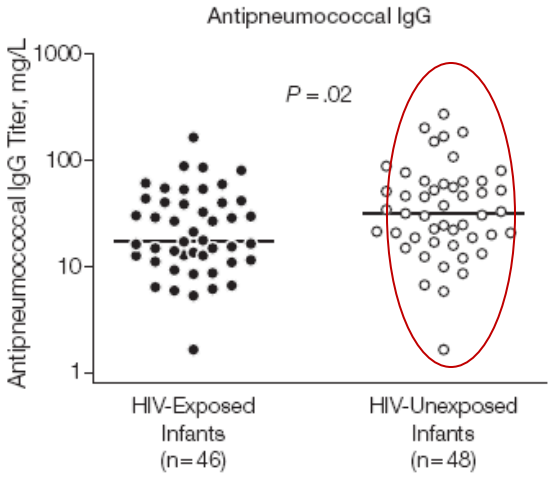
HIB

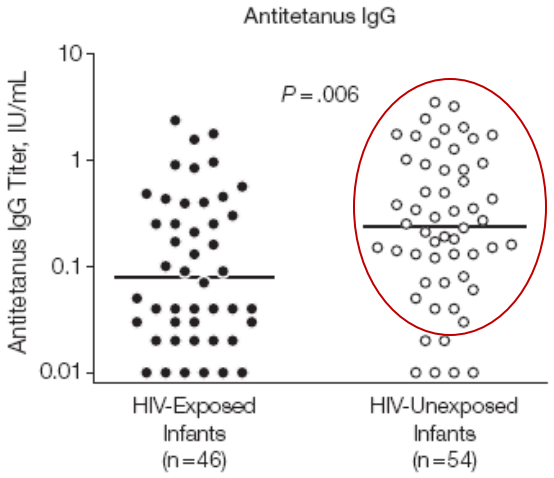




Pertussis

Pneumo -coccus





Tetanus

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*Jones CE, et al. JAMA. 2011 Feb 9;305(6):576-84.

IMMUNIZATION DURING RATHER THAN PRIOR TO PREGNANCY HAS ADVANTAGES

NOTE: Pre-pregnancy immunization has higher % IgG transmission but decreased total IgG levels

Timing of Hib Vaccine	IgG Anti-PRP (ug/ml) Mother	Infant	% Transmision
Pre-Pregnancy			
Sacaton, AZ[1]	20	11	73%
3rd Trimester			
Houston, TX[2]	78	47	60%
The Gambia[3]	4	2	61%

[1] Santosham et al,PIDJ 2001;20:931; [2] Englund et al JID 1995; [3] Mulholland et al. JAMA 1996

Influenza Vaccine and Pregnant Women*


Contents lists available at ScienceDirect

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leview

nfluenza vaccine for pregnant women in resource-constrained countries: A review of the evidence to inform policy decisions

ustin R. Ortiz [a,b,*], Janet A. Englund [c], Kathleen M. Neuzil [a,b,d]

- High burden of influenza illness among pregnant women.
- Excellent immunogenicity and safety profile of TIV.
- Effectiveness in infants born to vaccinated mothers.
- No good alternatives for neonates, young infants.
- Main barriers: logistics and costs.

Level of evidence	High resource	Low resource
Disease burden, mother	++	+
Disease burden, infant	++	+
Vaccine safety	++	+
Maternal immunogenicity	++	+
Antibody interference with routine childhood immunization	N/A	N/A
Effectiveness in pregnant women	+	+
Effectiveness in infants born to vaccinated mother	+	+

Legend:

++ Substantial information available

\+ Partial information available

– Little or no information available

N/A Not applicable

*Ortiz JR, Englund JA, Neuzil KM. Influenza vaccine for pregnant women in resource-constrained countries: A review of the evidence to inform policy decisions. Vaccine. 2011 Jun 15;29(27):4439-52. PMID: 21550377

Options for Prevention: Influenza Vaccine

- Trivalent inactivated vaccine (TIV)
  - Approved for > 6 months of age
  - Only vaccine for pregnant women (recommended by CDC; not licensed by FDA for use during pregnancy)
  - At least 5 manufacturers in US
  - Single dose-thimerosal free and multidose vials available
  - Dose: 0.5 ml IM once early in season
- Adjuvanted inactivated influenza vaccine
  - MF59
  - AS03 – enhanced immunity; licensed in EU
  - Not studied prior to 2009 pandemic
- Live attenuated influenza vaccine
  - Not recommended for use in pregnancy

Influenza Disease During Pregnancy

Influenza infection in pregnant women:

- Increased severity during 3rd trimester
- Increased severity with pre-existing conditions
- Increased severity with new influenza strain
- Impacts the fetus

Photo thanks to my fellow

Systematic Review of Risks of Pandemic H1N1 in Pregnancy

RISK OF ICU:

TABLE 1
Relative risk of hospitalization, intensive care unit admission, death, or any severe outcome in pregnant women due to 2009 H1N1 influenza

Paper	Risk of hospitalization	Risk of ICU admission	Risk of death	Risk of severe disease
New South Wales Public Health Network[110]		RR, 5.8[a]	RR, 10.2[a]	
ANZIC[8]		RR, 7.4[a]		
Campbell et al[123]		RR, 0.7 (0.4–1.2)[a]	RR, 1.1 (0.3–4.1)[a]	RR, 0.7 (0.4–1.3)
Creanga et al[13]	RR, 7.2[a]			RR, 4.3[a]
Fuhrman et al[62]			aOR, 0.3 (0.04–3.0)	aOR, 0.5 (0.2–0.8)
Gérardin et al[46]		RR, 0.4 (0–2.6)[a]		
Hanslik et al[23]		OR, 5.2 (4.0–6.9)	OR, 1.4 (0.3–4.2)	
Jamieson et al[3]	RR, 4.3 (2.3–7.8)[b]			
Kelly et al[28]	RR, 5.2 (4.6–5.8)[b]	RR, 6.5 (4.8–8.8)[b]	RR, 1.4 (0.4–4.5)[b]	
Koegelenberg et al[29]			OR, 1.13 (0.14–8.88)	
Oliveira et al[81]			RR, 1.07 (.82–1.41)[a]	
Yang et al[53]			OR, 0.8 (0.2–3.5)	OR, 0.4 (0.2–3.4)
Zarychanski et al[106]		OR, 3.64 (0.86–15.4)[a,c]		

ANZIC, ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System; *aOR*, adjusted odds ratio; *ICU*, intensive care unit; *OR*, odds ratio; *RR*, relative risk.

[a] Compared to nonpregnant women of reproductive age; [b] Compared to general population; [c] This number reports increased odds that pregnant women would require ICU admission over that they would require only outpatient treatment.

Mosby. 2009 H1N1 and pregnancy. Am J Obstet Gynecol 2011.

Mosby AJOG 2011

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Fetal Risk of Maternal Influenza (Surveillance Studies)

Study	Site	Case	Control	Results
McNeill AJOG 2011	Canada 1990-2002	Maternal influenza season respiratory hospitalization (208)	No hospitalization (132,099)	Newborns of hospitalized cases were 90gm smaller, 40% more likely to be small for gestational age
Mendez-Figueroa AJOG 2011	USA 2009-10	Maternal ILI with lab confirmed pandemic H1N1 (15)	Maternal ILI with lab test negative (25)	Newborns exposed to influenza were 285gm smaller
Pierce BMJ 2011	UK 2009-2010	Pregnant women with Lab-confirmed hospitalization for pandemic H1N1 (256)	Historical comparison of pregnant women from 2005-2006 (1220)	Newborns exposed to influenza were 255 g smaller. Higher perinatal mortality and premature birth in exposed.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Fetal Death after Pandemic Influenza Virus Infection or Vaccination

Siri E. Håberg, M.D., Ph.D., Lill Trogstad, M.D., Ph.D., Nina Gunnes, Ph.D., Allen J. Wilcox, M.D., Ph.D., Håkon K. Gjessing, Ph.D., Sven Ove Samuelsen, Ph.D., Anders Skrondal, Ph.D., Inger Cappelen, Ph.D., Anders Engeland, Ph.D., Preben Aavitsland, M.D., Steinar Madsen, M.D., Ingebjørg Buajordet, Ph.D., Kari Furu, Ph.D., Per Nafstad, M.D., Ph.D.,

Haberg et al. NEJM
Jan. 17, 2013; 368: 333-40

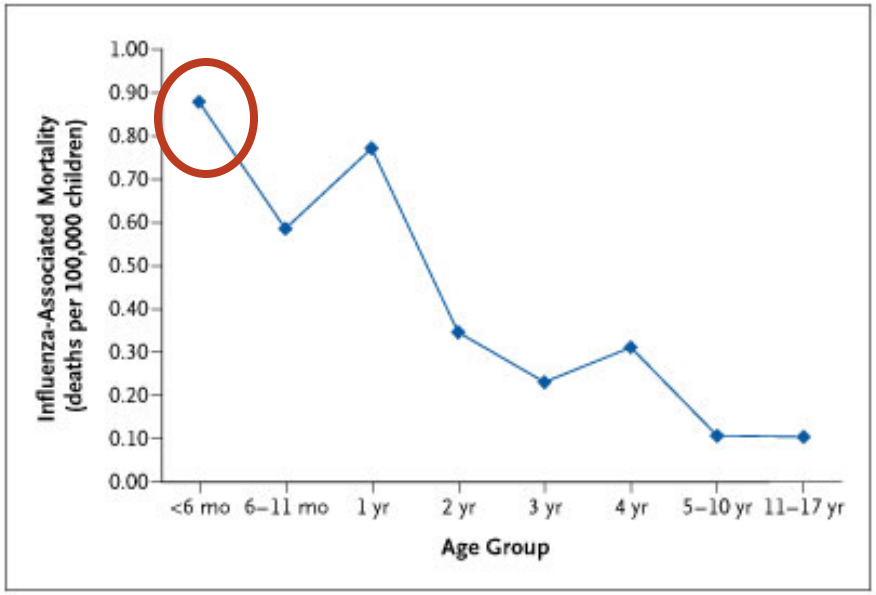
There were 117,347 eligible pregnancies in Norway from 2009 through 2010. Fetal mortality was 4.9 deaths per 1000 births. During the pandemic, 54% of pregnant women in their second or third trimester were vaccinated. Vaccination during pregnancy substantially reduced the risk of an influenza diagnosis (adjusted hazard ratio, 0.30; 95% confidence interval [CI], 0.25 to 0.34). Among pregnant women with a clinical diagnosis of influenza, the risk of fetal death was increased (adjusted hazard ratio, 1.91; 95% CI, 1.07 to 3.41). The risk of fetal death was reduced with vaccination during pregnancy, although this reduction was not significant (adjusted hazard ratio, 0.88; 95% CI, 0.66 to 1.17).

Table 2. Hazard Ratios for Fetal Death, According to Status Regarding Vaccination, Pregnancy during the Pandemic Wave, and a Clinical Diagnosis of Influenza.*

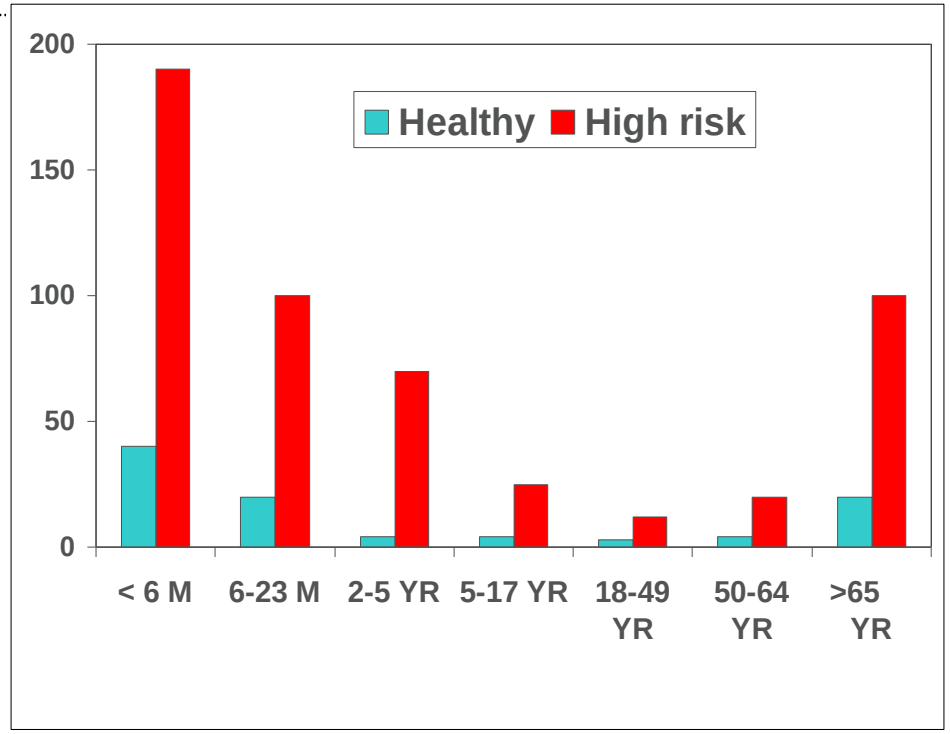
Variable	No. of Pregnancy-Days at Risk†	Hazard Ratio (95% CI)		
		Without Adjustment	With Initial Adjustment‡	With Further Adjustment§
Total no. of days	18,970,404			
Vaccinated during pregnancy				
No	15,942,252	1.00	1.00	1.00
Yes	3,028,152	0.95 (0.74–1.21)	0.84 (0.64–1.10)	0.88 (0.66–1.17)
Pregnant during the pandemic				
No	10,422,035	1.00	1.00	1.00
Yes	8,548,369	1.15 (0.96–1.37)	1.21 (1.00–1.48)	1.26 (1.02–1.55)
Without an influenza diagnosis	8,221,514	1.11 (0.93–1.33)	1.18 (0.96–1.44)	1.23 (0.99–1.52)
With an influenza diagnosis	326,855	2.00 (1.20–3.32)	2.10 (1.27–3.49)	1.91 (1.07–3.41)

Influenza-associated Mortality and Hospitalizations Are High in the Youngest Children*

Influenza-associated deaths among US children, 2003-2004*



Hospitalizations per 10,000**



*Bhat et al. *N Engl J Med* 2005; 353: 2559-67

** Glezen et al. Am Rev Respir Dis 1987;155:1119-26;
Neuzil et al. NEJM 2000;342:225-231;
Neuzil et al. J Pediatr 2000;137:856-864.

Safety of influenza vaccines in pregnancy

- Data available includes
  - Prospective clinical trials *
  - Retrospective and database studies*
  - Post-marketing passive reporting systems **
    - VAERS or VSD in the US
    - Yellow Card System in the UK
  - Other vaccine safety systems using databases that link vaccination history and medical outcomes
  - Post-marketing Pregnancy Registries**

- Data available supports safety of vaccination of pregnant women with inactivated influenza vaccine, with potential to benefit both mother and infant.
  (Maternal Influenza Immunization Convening London, June 2011)

*** Limitations: Design and statistical power (N)**

**** Limitations: 1. Under reporting; 2. In addition to number of events, calculation of a rate or attributable risk (using # persons vaccinated as denominator) is necessary to evaluate relationship/causality; 3. Confounders; 4. Insufficient power**

World Health Organization

SAGE MEETING | April 2012

Maternal Immunization with Influenza Vaccine Protects Mothers and Babies Against Influenza*

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.

Babies born to mothers who received TIV

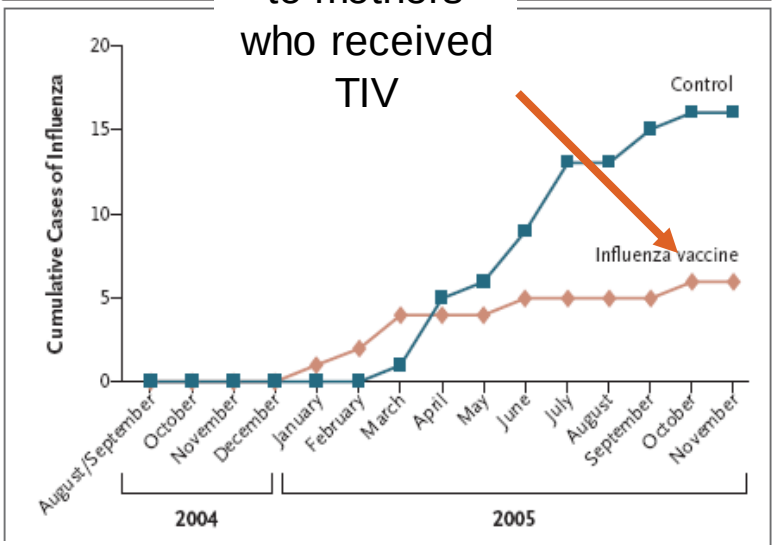


Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.
Testing for influenza antigen was performed from December 2004 to November 2005.

Table 2. Clinical Effectiveness of Influenza Vaccine in Infants and Mothers.*

Variable	Episodes		Clinical Effectiveness (95% CI)†	Risk Difference (95% CI)‡
	Control	Influenza Vaccine		
	no.		%	
Mothers				
Person-months	1076	1089		
Respiratory illness with fever				
Any fever	77	50	35.8 (3.7 to 57.2)	−14.2 (−25.5 to −2.9)§
Temperature >38°C	33	19	43.1 (−9.0 to 70.3)	−7.3 (−14.5 to −0.1)§
Diarrheal disease	60	49	19.3 (−24.6 to 47.8)	−5.9 (−16.4 to 4.5)
Clinic visit	25	19	24.9 (−43.9 to 60.8)	−3.2 (−9.8 to 3.4)

*Zaman et al, NEJM 2008;359

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

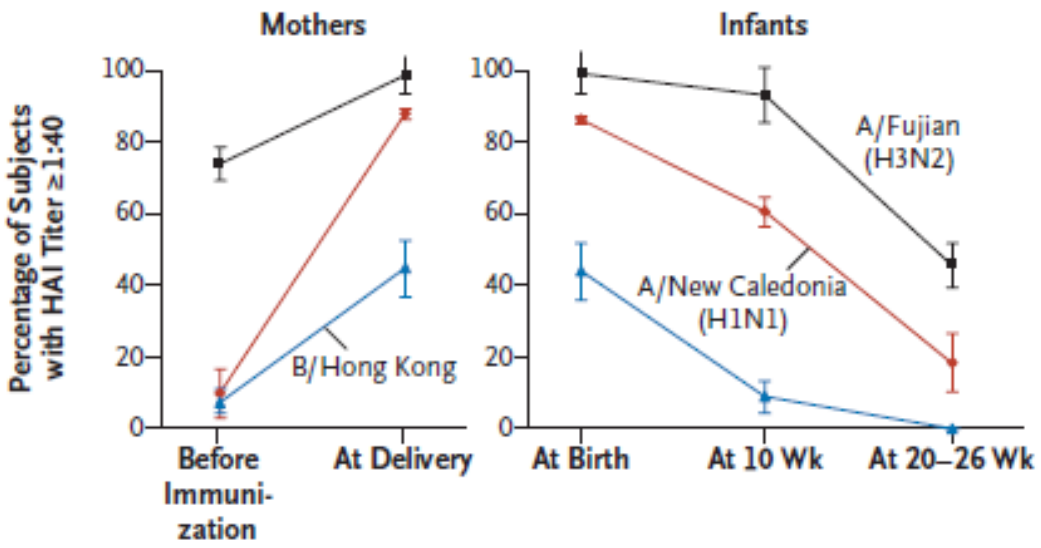


Figure 1. Proportions of Immunized Mothers and Their Infants with Hemagglutination-Inhibition (HAI) Titer of 1:40 or Greater.

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 et al NEJM 2010; 362: 17

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HOS

Maternal 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+

J. Englund. Presentation to SAGE. April 2012.

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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	—

WHO Position Paper: Maternal Immunization

This recommendation is based on evidence of:

- **High risk of severe disease**
- **Safety** of seasonal influenza vaccine throughout pregnancy
-
- **Effectiveness** of preventing influenza in the women as well as in their young infants, in whom the disease burden is also high.

WHO. Vaccines Against Influenza, WHO position paper – November 2012. Wkly Epidemiol Rec. No. 47, 2012, 87, 461–476.

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

May 2012

25 MAY 2012, 87th YEAR / 25 MAI 2012, 87e ANNÉE
No. 21, 2012, 87, 201–216
http://www.who.int/wer

SAGE recommended pregnant women as the most important risk group for inactivated seasonal influenza vaccination. Other risk groups to be considered, in no specific priority order were: health-care workers, children aged 6–59 months, the elderly and those with high-risk conditions. SAGE recommended that countries with existing influenza vaccination programmes targeting any of these groups should continue to do so and should incorporate immunization of pregnant women into such programmes. Countries should decide which other risk groups to prioritize for vaccination based on burden of disease, cost-effectiveness, feasibility and other appropriate considerations.

The priority accorded to pregnant women was based on compelling evidence of substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe and effective in preventing disease in pregnant women as well as their young infants, in whom disease burden is also high. Additional considerations for targeting this group included operational feasibility and the opportunity to prioritize and strengthen maternal immunization programmes.

- Pregnant women represent the most important risk group for receipt of inactivated seasonal influenza vaccine.
- The priority accord to pregnant women was based on “compelling evidence of substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe and effective in preventing disease in pregnant women as well as their young infants, in whom disease burden is also high.”
- No recommendation for timing of influenza vaccine during pregnancy.
- Revision of WHO Position Paper and Grade Tables published in Nov. 2012.

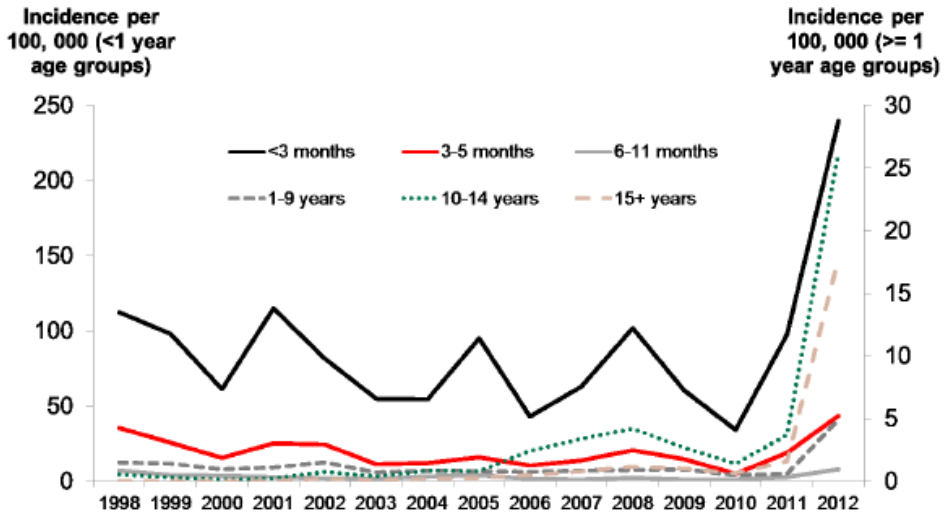
Clinical Studies of Maternal Influenza Immunization Underway

- Ongoing clinical studies of influenza in pregnant women may help answer questions regarding effectiveness, safety, and benefits in outcomes.
- EXAMPLE: Prospective, randomized clinical studies of TIV in pregnant women sponsored by Gates Fndn underway in Mali, Nepal, and South Africa in 2nd year, with thousands of pregnant women enrolled at each site.

Infant Pertussis : A serious outbreak in the UK, 2012-2014

Public Health England

Annual age specific pertussis incidence rates 1998 – 2012: England



Public Health England

Pertussis Immunisation in Pregnancy

Department of Health Recommendations

- From 1 October 2012
- Offer a single dose of Repevax® (dTaP/IPV) between 28-38 weeks pregnancy
- Offer in every pregnancy
- Outbreak response measure

- In 2012: 235 babies < 12 weeks of age diagnosed with pertussis; in 2013 with maternal Tdap in ~60% pregnant women: 79% drop in infant cases
- In 2012: 14 babies died; in 2013- 3 babies died of pertussis and none born to immunized mothers

http://www.nhs.uk/conditions/pregnancy-and-baby/pages/whooping-cough-vaccination-pregnant.aspx#So

Get Vaccinated Against Whooping Cough While Pregnant – USA – ACIP: 2013*

Pregnant women should get a whooping cough vaccine since vaccines are the best way to prevent this disease.

There are 2 different whooping cough vaccines for different age groups:

- Tdap: for everyone 11 years and older, including pregnant women
- DTaP: for children 2 months through 6 years of age

Whooping cough vaccine is recommended during each of your pregnancies

- The best time to get the shot is your 27th through 36th week of pregnancy.

* http://www.cdc.gov/vaccines/adults/rec-vac/pregnant/whooping-cough/get-vaccinated.html

Preliminary Communication

Safety and Immunogenicity of Tetanus Diphtheria and Acellular Pertussis (Tdap) Immunization During Pregnancy in Mothers and Infants

A Randomized Clinical Trial

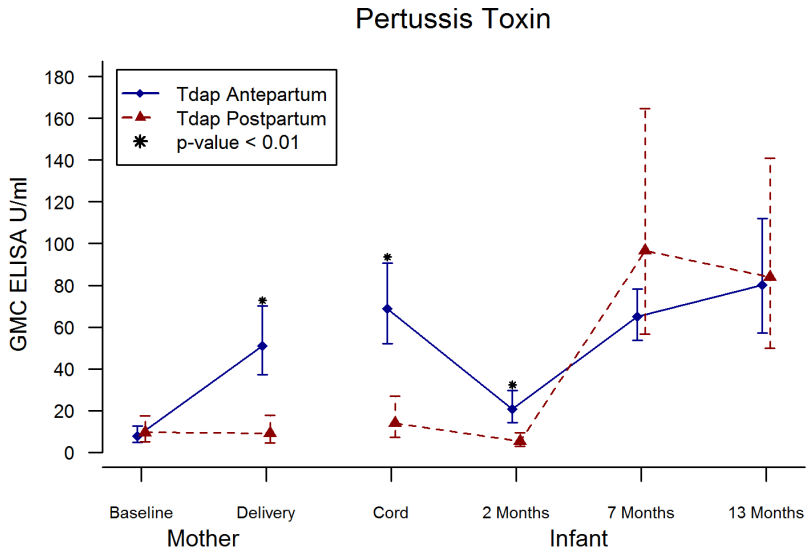
JAMA®
The Journal of the American Medical Association

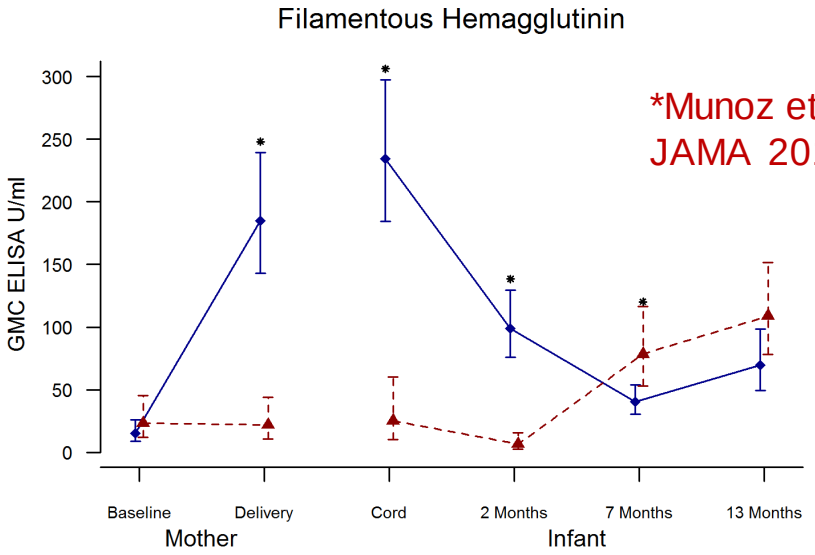
Flor M. Munoz, MD; Nanette H. Bond, PAC; Maurizio Maccato, MD; Phillip Pinell, MD; Hunter A. Hammill, MD; Geeta K. Swamy, MD; Emmanuel B. Walter, MD; Lisa A. Jackson, MD; Janet A. Englund, MD; Morven S. Edwards, MD; C. Mary Healy, MD; Carey R. Petrie, PhD; Jennifer Ferreira, ScM; Johannes B. Goll, MS; Carol J. Baker, MD

Arm	Group	N	Single dose administered to pregnant women with crossover design	
			Antepartum	**Postpartum**
Interven-tion	1	32	Tdap	Saline
Control	2	16	Saline	Tdap
Control	3	32	**Single dose administered to non-pregnant women** Tdap vaccine	

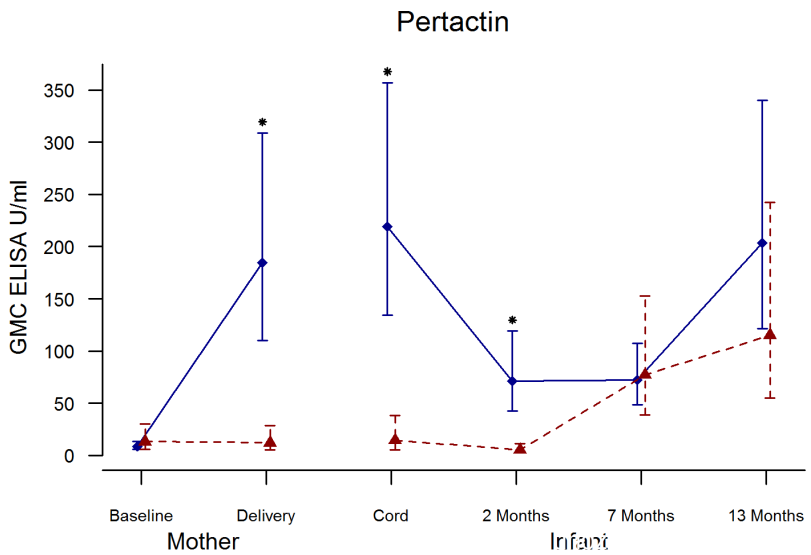
Munoz FM et al. JAMA 2014; 311:1760-9

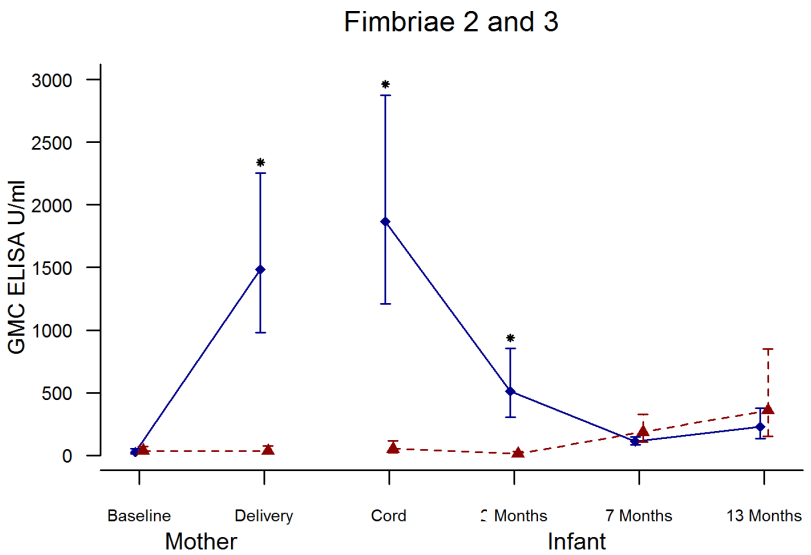
RESULTS : Immunogenicity (GMC) Pertussis Antibodies in Mothers and Infants*





*Munoz et al
JAMA 2014



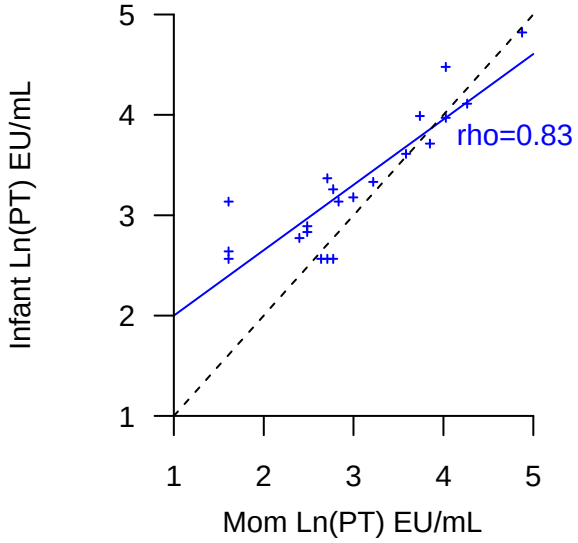


Transplacental Transmission of PT Ab: US* vs Nepal**

Table 5. Transplacental Transfer of Antibodies (Ratio of Infant Cord Blood Antibodies to Maternal Antibodies) and Antibody Concentrations in Infants at 2 Months of Age Compared With Concentrations at Birth (Ratio of Infant 2-Month Antibodies to Cord Blood Antibodies)

	Ratio (95% CI)			
	Tdap Antepartum/Placebo Postpartum (n = 31)		Placebo Antepartum/Tdap Postpartum (n = 14)	
Vaccine Antigen	Infant Cord Blood Antibodies to Maternal Antibodies at Delivery	Infant Antibodies at 2 Mo to Cord Blood Antibodies	Infant Cord Blood Antibodies to Maternal Antibodies at Delivery	Infant Antibodies at 2 Mo to Cord Blood Antibodies
Pertussis Toxin	1.23 (1.03 to −1.47)	0.34 (0.29 to 0.41)[a]	1.54 (1.15 to 2.05)	0.40 (0.29 to 0.56)[b]
Filamentous hemagglutinin	1.27 (1.13 to 1.42)	0.42 (0.36 to 0.49)	1.15 (0.74 to 1.76)	0.32 (0.19 to 0.53)[c]
Pertactin	1.19 (0.93 to 1.52)	0.31 (0.25 to 0.39)	1.19 (0.88 to 1.44)	0.42 (0.29 to 0.60)[b]
Fimbriae 2 and 3	1.26 (1.02 to 1.55)	0.26 (0.20 to 0.32)	1.49 (1.27 to 1.73)	0.25 (0.19 to 0.33)[b]
Tetanus	1.36 (1.14 to 1.62)	0.27 (0.22 to 0.31)[d]	1.19 (1.02 to 1.40)	0.38 (0.26 to 0.57)[c,d]
Diphtheria	1.26 (0.91 to 1.75)	0.28 (0.22 to 0.36)	1.28 (0.91 to 1.79)	0.28 (0.22 to 0.36)[c]

Nepal cord : maternal PT Ab transfer = 1.35 [95% CI, 1.04 – 1.28] **



US vaccinated mothers:
cord: maternal PT transfer = 1.23 [95% CI 1.03-1.47]

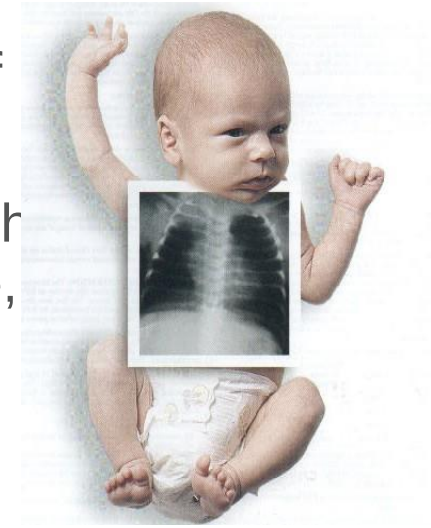
US unvaccinated mothers:
cord: maternal PT transfer = 1.54 [95% CI 1.15-2.05]

*Munoz et al JAMA 2014; ** Mergler PAS 2014 Abstract, Vancouver BC

Burden of RSV Disease Worldwide

- Pneumonia is leading single cause of mortality in children < 5 years

- Emerging data indicate clinical importance of RSV in children worldwide:*
  - Studies have detected RSV and demonstrated high burden of disease worldwide regardless of climate, socioeconomic burden
  - More disease at an earlier age documented in crowded setting, lower socioeconomic status.
  - Increased concern about antibiotic resistance and the proper use of antibiotics in children (RSV is not susceptible to ampicillin!)



Nair et al Lancet 2011

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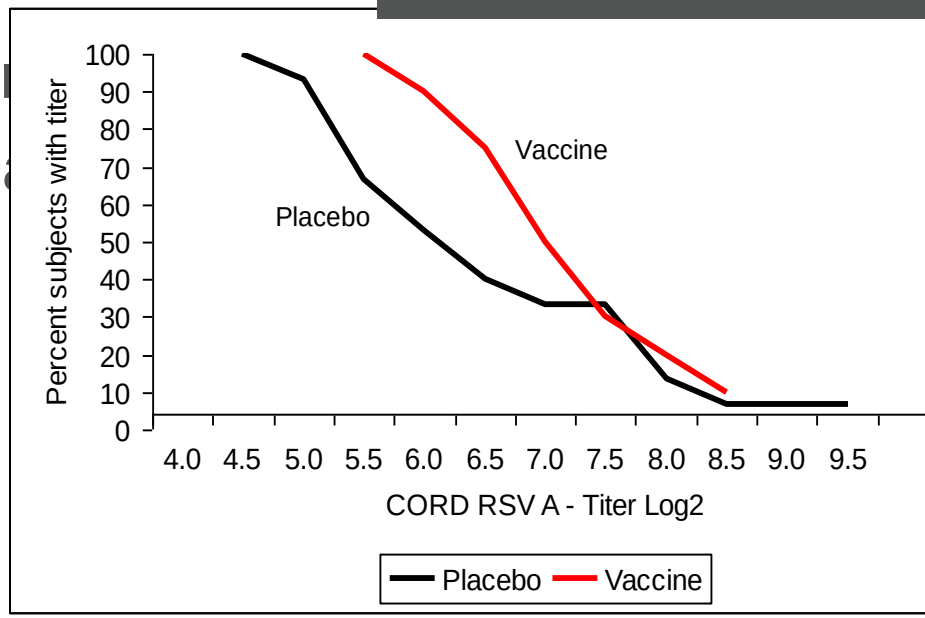
RSV VACCINE vs PLACEBO IN PREGNANT WOMEN*

- Primary Endpoints:
  - Safety in women and their offspring
  - Effect of antibody on primary RSV disease in infants
- Secondary Endpoints:
  - Immunogenicity
  - Efficiency of antibody transfer
  - Persistence of antibody in infa
  - Breast milk antibody

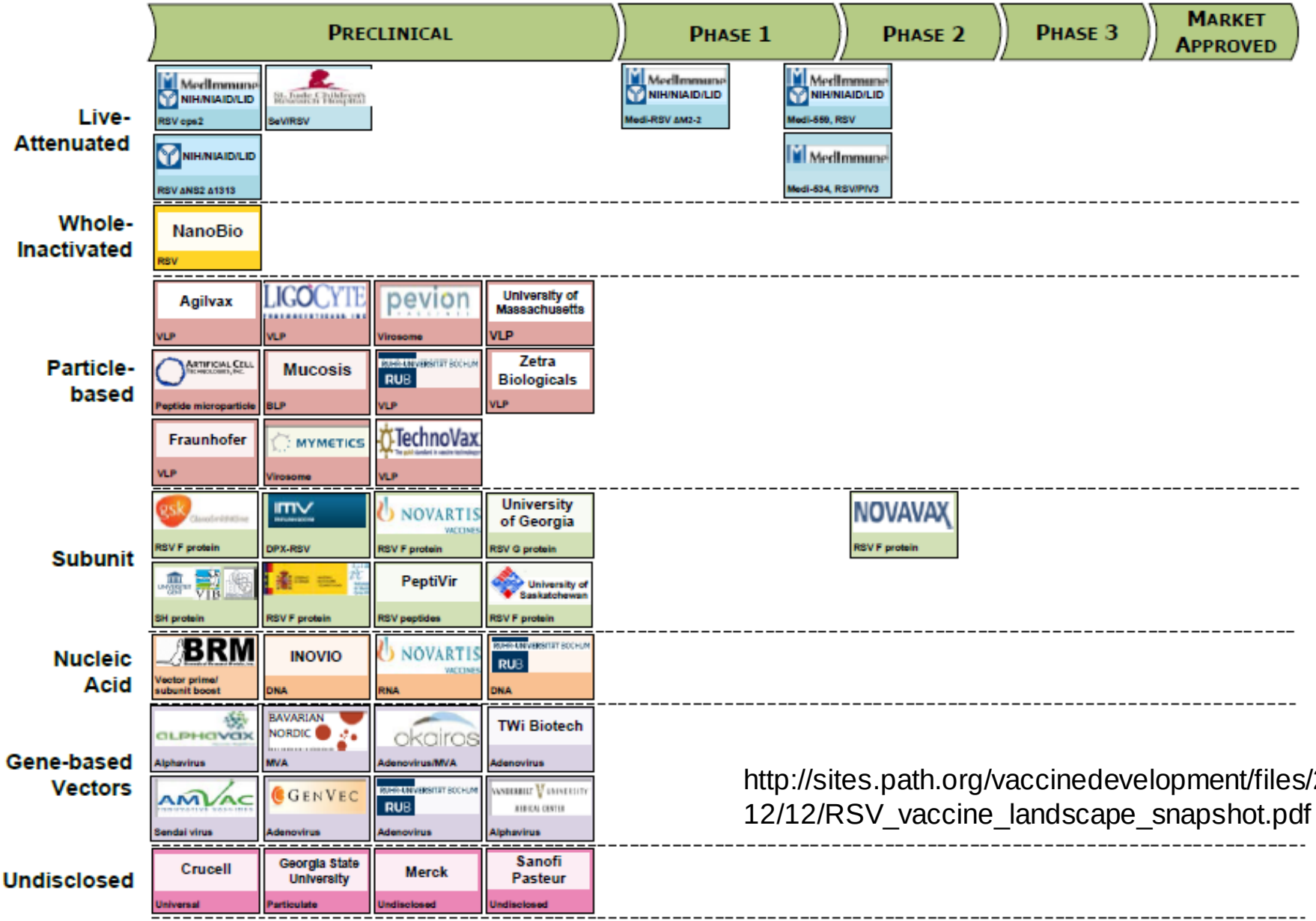
RSV-A Neutralization antibodies in Cord



*Munoz, Piedra, Glezen. Vaccine 2003;21:3465

RSV Vaccine Snapshot 2013

PATH



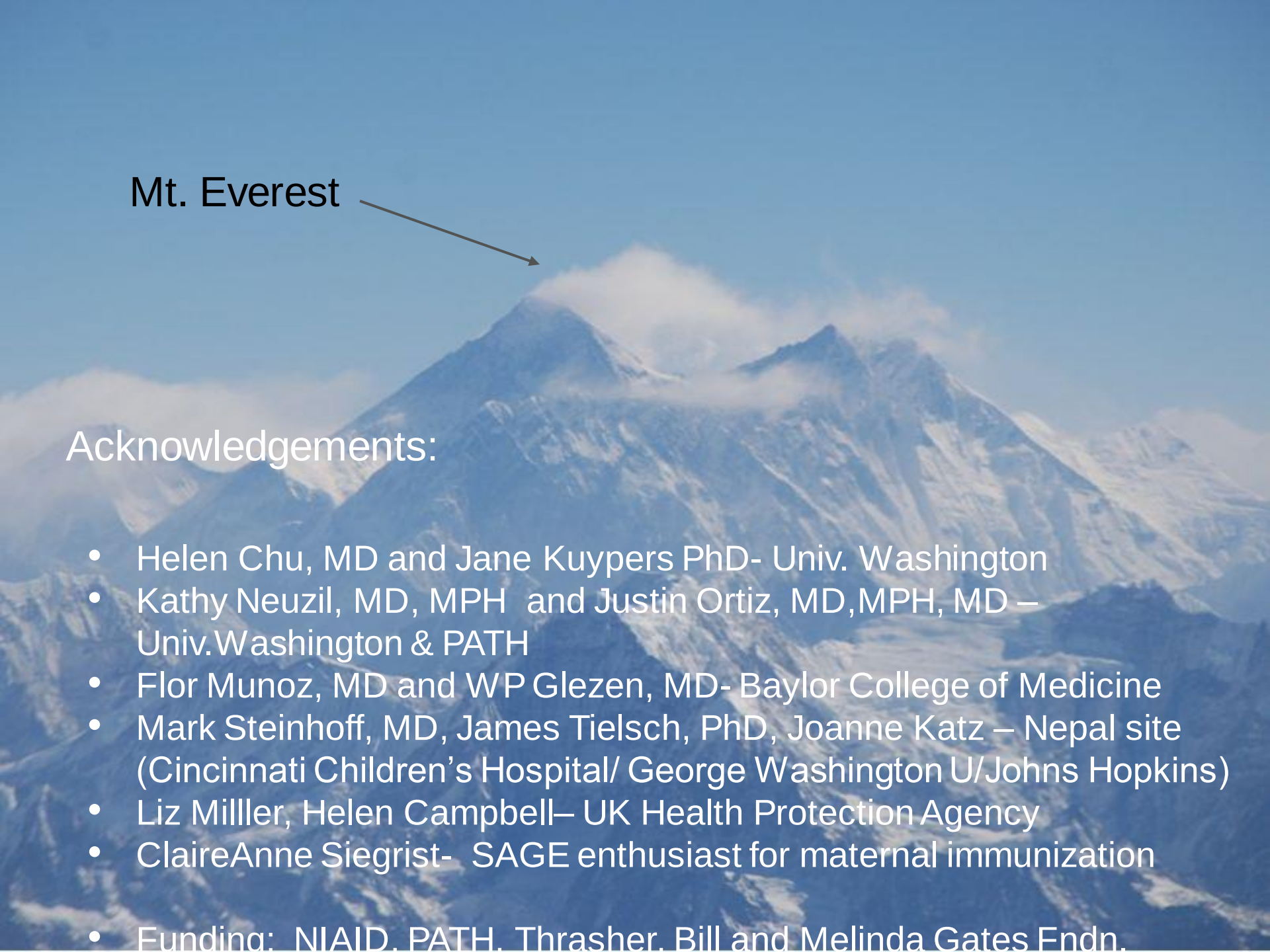
http://sites.path.org/vaccinedevelopment/files/2012/12/RSV_vaccine_landscape_snapshot.pdf

Legal Liability for Vaccine Manufacturers

- Background rates of major congenital anomalies, spontaneous abortions, and still births EVEN without vaccination are substantial
- Temporal relationships, rather than causation, will be difficult to prove or disprove
- Background of a litiginous society AND “medical terrorism” makes supporting studies difficult for manufacturers
- Indemnification needed before companies will participate in production and testing

POTENTIAL OBSTACLES FOR MATERNAL IMMUNIZATION

- **Lack of effective vaccines against important common pathogens**
- **Immune response to some vaccines appears short- lived, necessitating intrapartum (not pre-conception) vaccination and perhaps repeated immunization**
- **Regulatory and legal issues**
- **Liability issues and issues affecting interaction with pharmaceutical companies**



Acknowledgements:

- Helen Chu, MD and Jane Kuypers PhD- Univ. Washington
- Kathy Neuzil, MD, MPH and Justin Ortiz, MD,MPH, MD – Univ.Washington & PATH
- Flor Munoz, MD and WP Glezen, MD- Baylor College of Medicine
- Mark Steinhoff, MD, James Tielsch, PhD, Joanne Katz – Nepal site (Cincinnati Children's Hospital/ George Washington U/Johns Hopkins)
- Liz Millller, Helen Campbell– UK Health Protection Agency
- ClaireAnne Siegrist- SAGE enthusiast for maternal immunization

- Funding: NIAID, PATH, Thrasher, Bill and Melinda Gates Fndn.

Thank you to:

Acknowledgements:
Women participating in our studies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Inhibition of Active Immune Response to Diphtheria Toxoid in Infants Based on Presence of Passive Antibody

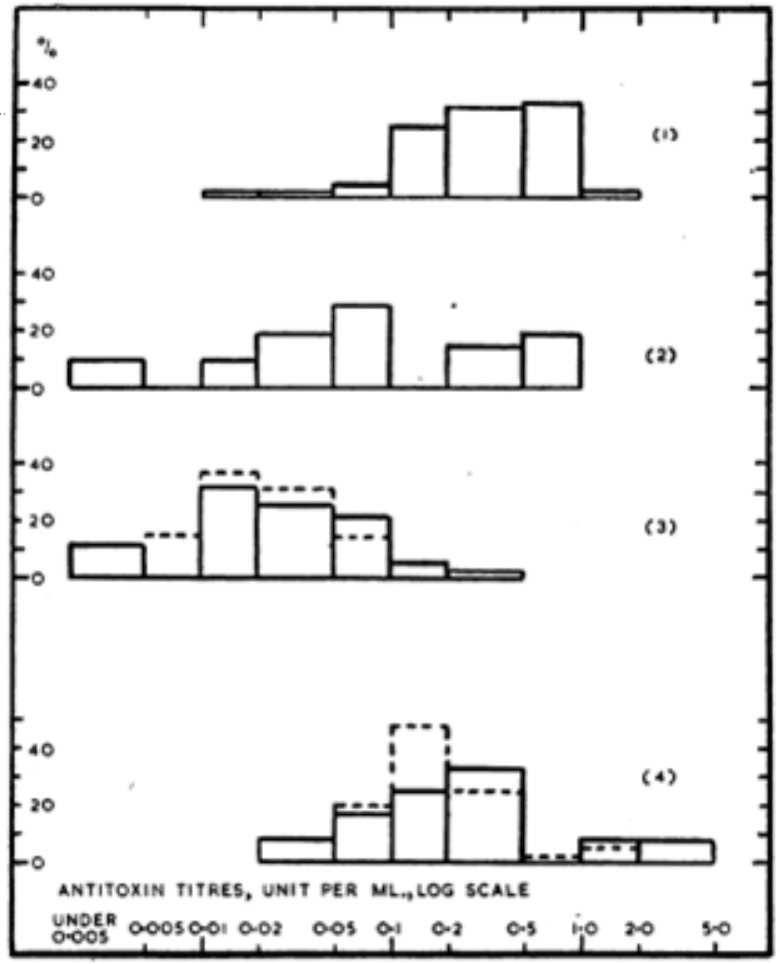

FIG. I.—Distribution of diphtheria antitoxin titres in the serum of babies when 3 months old after immunization under scheme A.
(1) 110 babies with cord blood titre of 0.01 unit per ml. or less
(2) 21 " " " " " " 0.02 or 0.04 unit per ml.
(3) 34 " " " " " " 0.1, 0.2, or 0.5 unit "
(4) 12 " " " " " " 1, 2, or 10 units "
Broken lines show the distribution of residual passive antitoxin titres.

DISEASE

BRITISH MEDICAL JOURNAL

IMMUNIZATION OF YOUNG BABIES AGAINST DIPHTHERIA

BY

N. R. BUTLER, M.D., M.R.C.P., D.C.H.
MOLLIE BARR, M.Sc., A.R.I.C.
AND
A. T. GLENNY, B.Sc., F.R.S.
(From the Obstetric Hospital of University College Hospital, London; the L.C.C. Infant Welfare Clinic of University College Hospital Medical School; and the Wellcome Research Laboratories (Biological Division), Beckenham, Kent)

BMJ 1954; pp 476-481

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PERTUSSIS

The Effect of Maternal Antibody on the Serologic Response and the Incidence of Adverse Reactions After Primary Immunization With Acellular and Whole-Cell Pertussis Vaccines Combined with Diphtheria and Tetanus Toxoids

Janet A. Englund, Edwin L. Anderson, George F. Reed, Michael D. Decker, Kathryn M. Edwards, Michael E. Pichichero, Mark C. Steinhoff, Margaret B. Rennels, Adamadia Deforest and Bruce D. Meade

Pediatrics 1995;96;580

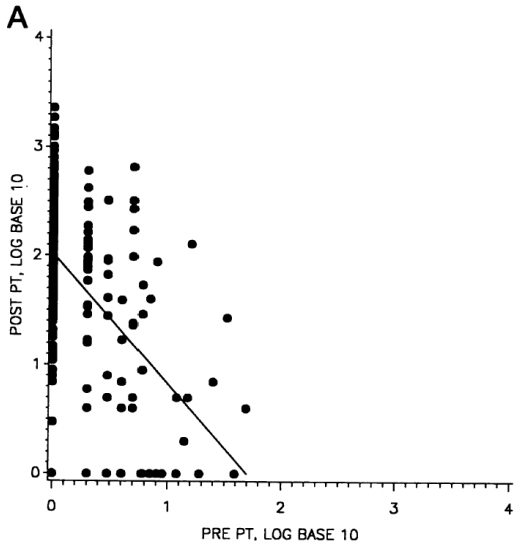

Figure A: Pre vs post PT antibody in infants receiving DTaP vaccine (no effect of maternal Ab)

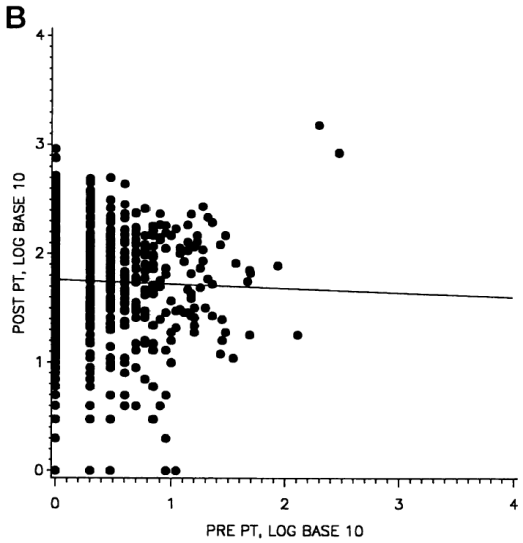

Figure B. Pre vs. post-PT antibody in infants receiving DTP Vaccine (Neg. effect of maternal Ab)

Figure. Relationship between preimmunization and postimmunization PT antibody levels after WCL (A) and DTaP (B). The slope of the linear regression for preimmunization versus postimmunization antibody is −0.04 for DTaP (P = .26), indicating no significant effect of preimmunization antibody on the postimmunization response. In contrast, the slope of the regression line is −1.19 for WCL (P < .001), indicating a significant negative effect of preimmunization antibody on the postimmunization antibody level. See Table 2 for the various regression coefficients (slopes).

A COMPELLING CASE

- THERE IS COMPELLING DATA TO VACCINATE PREGNANT WOMEN TO PROTECT THE WOMAN AND HER INFANT
- Flu vaccines are safe and immunogenic
- WHY DON'T WE? In countries with physician malpractice concerns, are health care providers at risk by not promoting maternal flu vaccination?
- If you had a limited vaccine supply or health care budget, who would you immunize?

Vaccines Administered during Pregnancy in NIH Funded Trials, USA

- Capsular Polysaccharide of Hib
- Protein Conjugate-Polysaccharide of Hib
- 23 valent Pneumococcal Polysaccharide
- Group B Streptococcal polysaccharide and conjugate vaccines
- RSV-subunit vaccine (PFP-2)
- Pneumococcal conjugate vaccines
- Acellular pertussis vaccines

- Today's talk:
  Tetanus, influenza, RSV

RSV Is Predominant Cause of Community-Acquired Pneumonia in Children Ages 2Mo -3Yr in Nepal

RNA viruses in community-acquired childhood pneumonia in semi-urban Nepal; a cross-sectional study

Maria Mathisen*[1], Tor A Strand[1,2], Biswa N Sharma[3], Ram K Chandyo[1,4], Palle Valentiner-Branth[5], Sudha Basnet[4], Ramesh K Adhikari[4], Dag Hvidsten[6], Prakash S Shrestha[4] and Halvor Sommerfelt[1,7]

N = 2219 children

Table 2: Distribution of the different RNA viruses in 2,219 cases of community-acquired pneumonia in children 2 to 35 months of age diagnosed at a field clinic in Bhaktapur, Nepal, from July 2004 to June 2007

	Number of isolates	All pneumonia cases (*n* = 2,219)	Virus positive cases (*n* = 887)
Virus	*n*	% (95% CI)	% (95% CI)
RSV	334	15.1 (13.6 to 16.6)	37.7 (34.5 to 40.9)
Influenza A	164	7.4 (6.3 to 8.6)	18.5 (16.0 to 21.2)
PIV type 3	129	5.8 (4.9 to 6.9)	14.5 (12.3 to 17.0)
PIV type 1	98	4.4 (3.6 to 5.4)	11.0 (9.1 to 13.3)
hMPV	93	4.2 (3.4 to 5.1)	10.5 (8.5 to 12.7)
Influenza B	84	3.8 (3.0 to 4.7)	9.5 (7.6 to 11.6)
PIV type 2	17	0.8 (0.4 to 1.2)	1.9 (1.1 to 3.1)

CI = confidence interval; hMPV = human metapneumovirus; PIV = parainfluenza virus; RSV = respiratory syncytial virus.

BMC Medicine 2009, 7:35 doi:10.1186/1741-7015-7-35

Are there sufficient data?*

- "Whereas reliance on supranational/regional data may be necessary for many countries to assess the overall epidemiological situation, individual national decisions on the use of influenza vaccines will be determined by national capacity and resources."
- "To this end, country- specific information about risk groups, disease burden and cost-effectiveness are important to aid national policy makers and health programme planners."

*WHO. Vaccines Against Influenza, WHO position paper – November 2012. Wkly Epidemiol Rec. No. 47, 2012, 87, 461–476.

Guidelines for Vaccinating Pregnant Women

Modified after: Advisory Committee on Immunization Practices (ACIP)

CDC, July 2012

Hepatitis A	May be used if benefits outweigh risks
Hepatitis B	Recommended in some circumstances
Human Papillomavirus (HPV)	Not recommended
Influenza (Inactivated)	Recommended
MCV4, PCV 13, PPS23	Inadequate data for specific recommendation
IPV	May be used if needed
Td	Should be used if otherwise indicated
TdaP	Recommended
Varicella, LAIV, MMR, Zoster	Contraindicated

Source: Gruber M. Annecy maternal immunization meeting. 2012

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Transplacentally-Acquired Influenza Antibody in Infants: Small prospective studies

- **Infants are protected from symptomatic influenza A virus infection by transplacentally acquired antibody *(Puck 1980)***

- **Passive maternal antibody to influenza:**
  - **delays the onset of influenza disease**
  - **decreased the severity of influenza disease (*Reuman 1987)***
- **Maternal immunization increases antibody transmission to the infant (Englund 1993)**

Immunization of Women During Pregnancy is NOT New

- **1879**: Maternal immunization with vaccinia conferred protection to smallpox in infants
- **1938**: Maternal immunization with crude whole cell pertussis vaccine given multiple times conferred protection of infants to pertussis
- **1961**: Maternal immunization with tetanus toxoid prevented maternal mortality as well as neonatal tetanus in New Guinea

Considerations for Vaccination During Pregnancy

- Disease burden in mothers and infants versus disease burden predominantly in infant or mother.
- Immunogenicity/effectiveness:
  - Immune response in mother.
  - Kinetics of antibody transfer.
  - Influence of maternal antibody on infant immune responses.
- Safety.
- Regulatory and legal considerations.
- Programmatic.
- Public perception/risk communication.
- Advocacy/demand creation.
- Financial.

Partially adapted from: ACIP. MMWR 2008; 57: 580 and Ortiz JR Vaccine 2012.

INFLUENZA DURING PREGNANCY

- 1918: ~50% mortality associated with infection during pregnancy with highest rates in later pregnancy*
- 1957: 50% of women of childbearing age who died of influenza were pregnant; 10% of all influenza deaths that season were in pregnant women (most in latter half of pregnancy)**
- 1970-1980's: Case reports of complications– many in later stages of pregnancy, with high rates of resp. failure***
- 2009 H1N1 Pandemic: increased rates, severe outcomes in US, UK, Argentina, Australia****

*Harris. JAMA 1919;14:978;
** Freeman and Barno, Am J Ob Gyn 1959;78:1172; Greenberg et al. Am J Ob Gyn 1958;76:897
***Neuzil et al Inf Dis Clin N Am 2001;15:123
****Jamieson Lancet 2009

Influenza-Specific Maternal Antibody in Infants

Good evidence that infants are protected from symptomatic influenza by transplacentally acquired antibody:

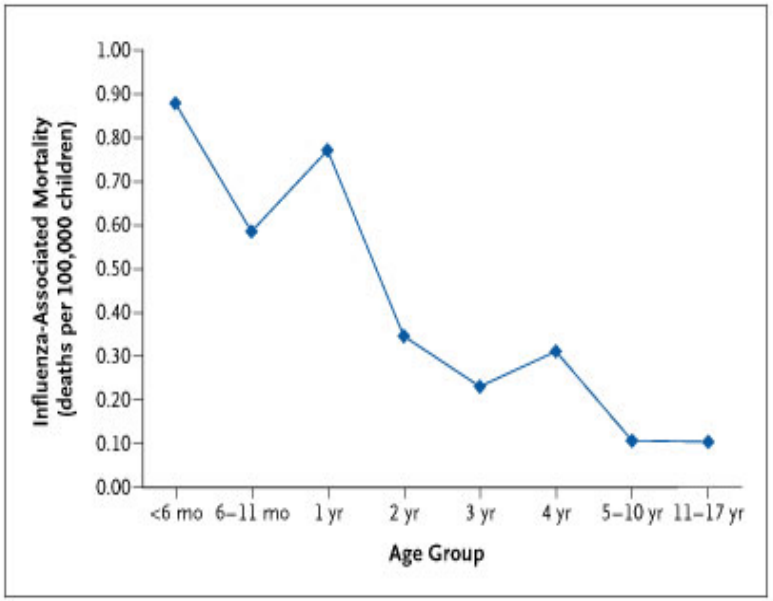
- Undetectable flu antibody in cord blood of infants who are hospitalized with influenza[1]
- Delayed onset and decreased severity of disease in infants with higher antibody levels [2]

Maternal immunization increases the amount of antibody transmitted to infants[3]

1. Puck et al, J Infect Dis 1980; 142:844-9;
2. Reuman PD, et al. PIDJ 1987;6:398-403
3. Englund et al: J Infect Dis 1993;168:647-56

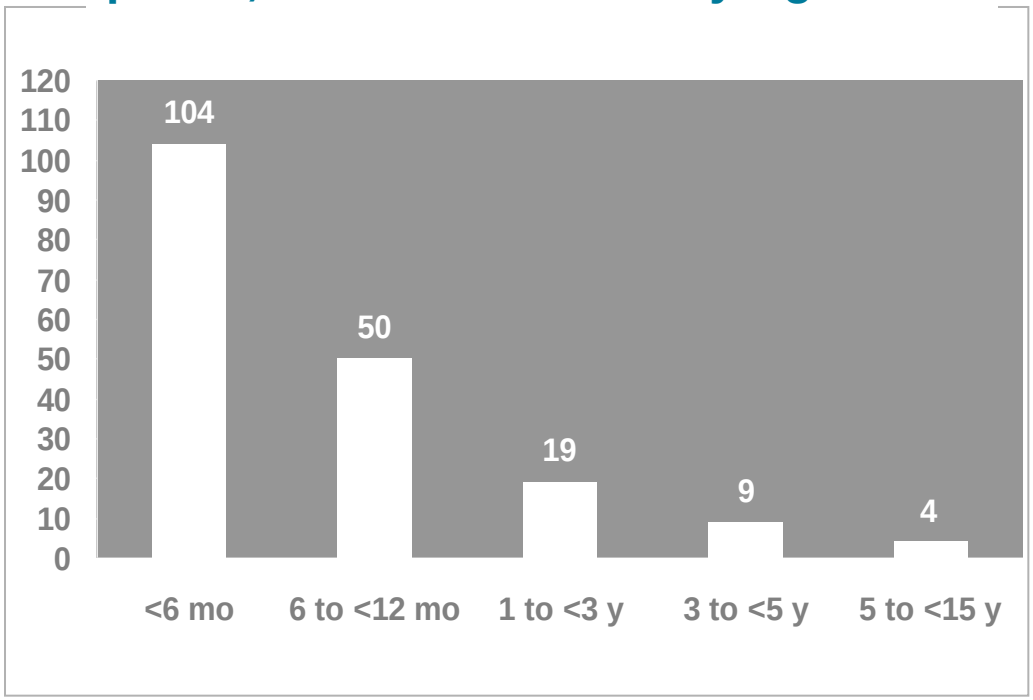
Influenza is a serious disease in the youngest children

Influenza-associated deaths per 100,000 US children, 2003-4



*Bhat et al. *N Engl J Med* 2005; 353: 2559-67

Excess Hospitalizations of Influenza per 10,000 Children/Year By Age



Neuzil KM et al. *N Engl J Med.* 2000;342:225-231

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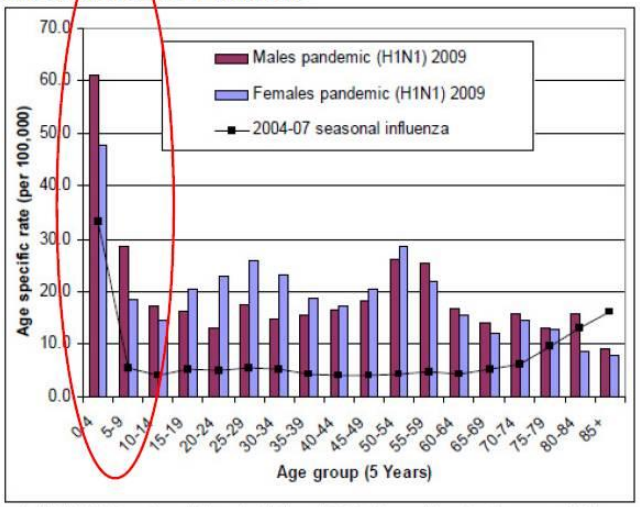
Pandemic Influenza A (H1N1) : Age Specific Hospitalization Rates

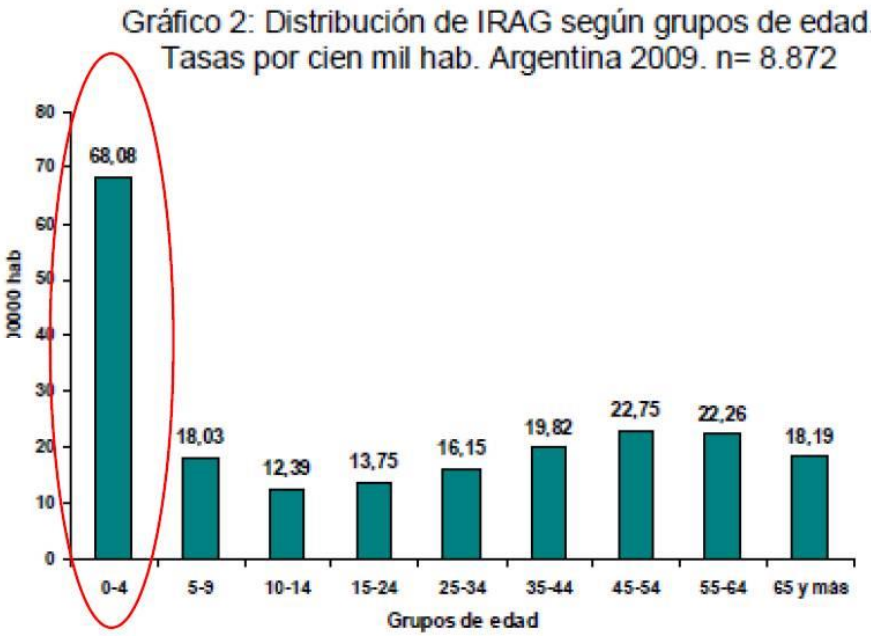
Australia

Figure 9. Age specific rates of hospitalised confirmed cases of pandemic (H1N1) 2009 to 18 September 2009, compared with average annual age specific rates of hospitalisations from seasonal influenza 2004-05 to 2006-07*, Australia



*The rates for pandemic (H1N1) 2009 are from 15 June to 21 August 2009 whereas the rates for seasonal influenza are averaged annual rates (i.e. for a full influenza season).

Source: NETEPI database



Argentina

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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.
  - Women followed through pregnancy and women/babies through 6 M 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
  - Not placebo-controlled

H1N1 2009 influenza virus infection during pregnancy in the USA

*Denise J Jamieson, Margaret A Honein, Sonja A Rasmussen, Jennifer L Williams, David L Swerdlow, Matthew S Biggerstaff, Stephen Lindstrom, Janice K Louie, Cara M Christ, Susan R Bohm, Vincent P Fonseca, Kathleen A Ritger, Daniel J Kuhles, Paula Eggers, Hollianne Bruce, Heidi A Davidson, Emily Lutterloh, Meghan L Harris, Colleen Burke, Noelle Cocoros, Lyn Finelli, Kitty F MacFarlane, Bo Shu, Sonja J Olsen, and the Novel Influenza A (H1N1) Pregnancy Working Group**

- ~ 6% of deaths in US from pandemic (H1N1) 2009 Influenza are among pregnant women (based on 484 H1N1 deaths reported to CDC by August 21, 28 of whom were pregnant)

- Pregnant women ~1% of the general population

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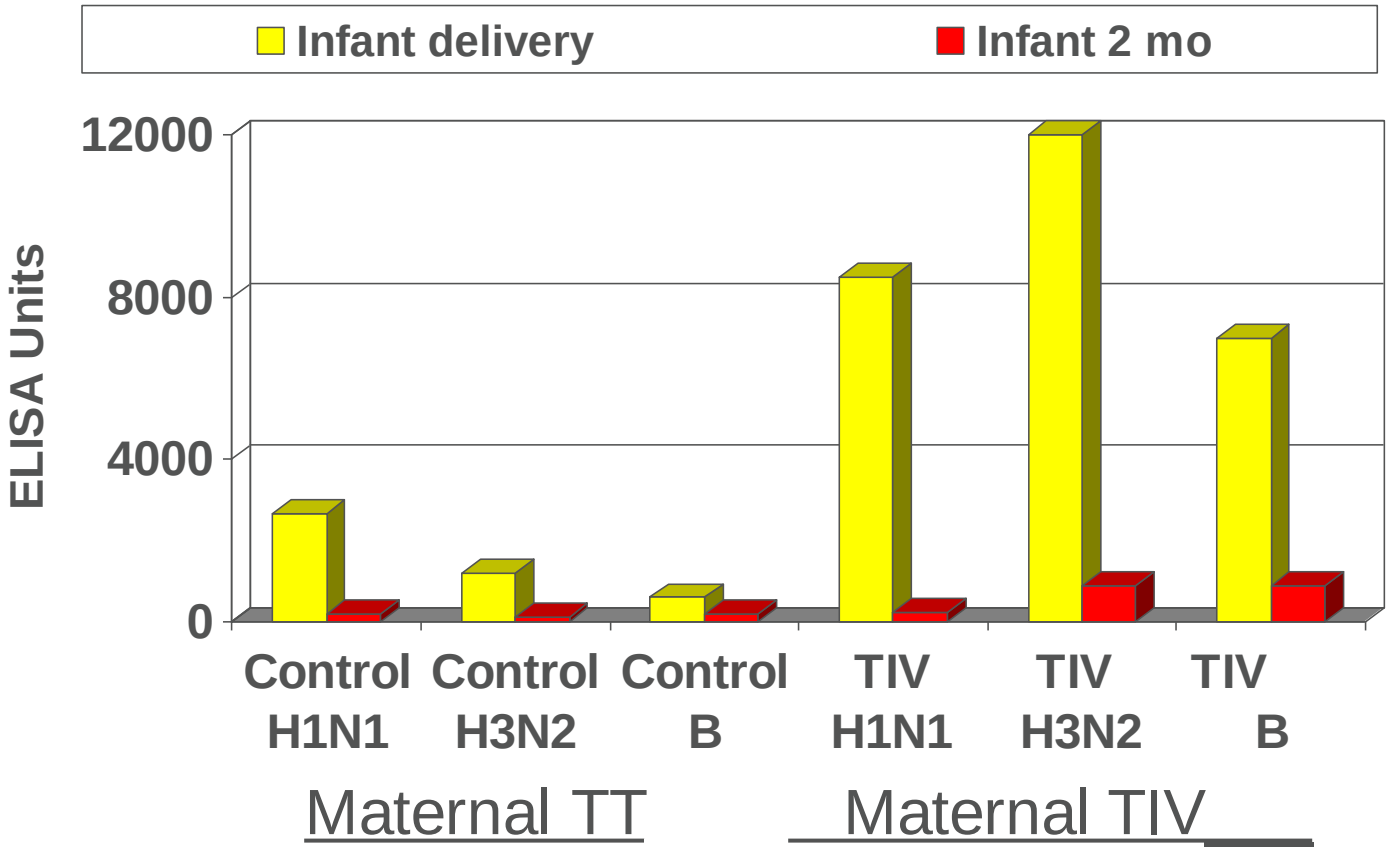
Jamieson et al., Lancet 374:451-8, 2009

Transplacentally-acquired Influenza Vaccine-specific Antibody in US Infants*

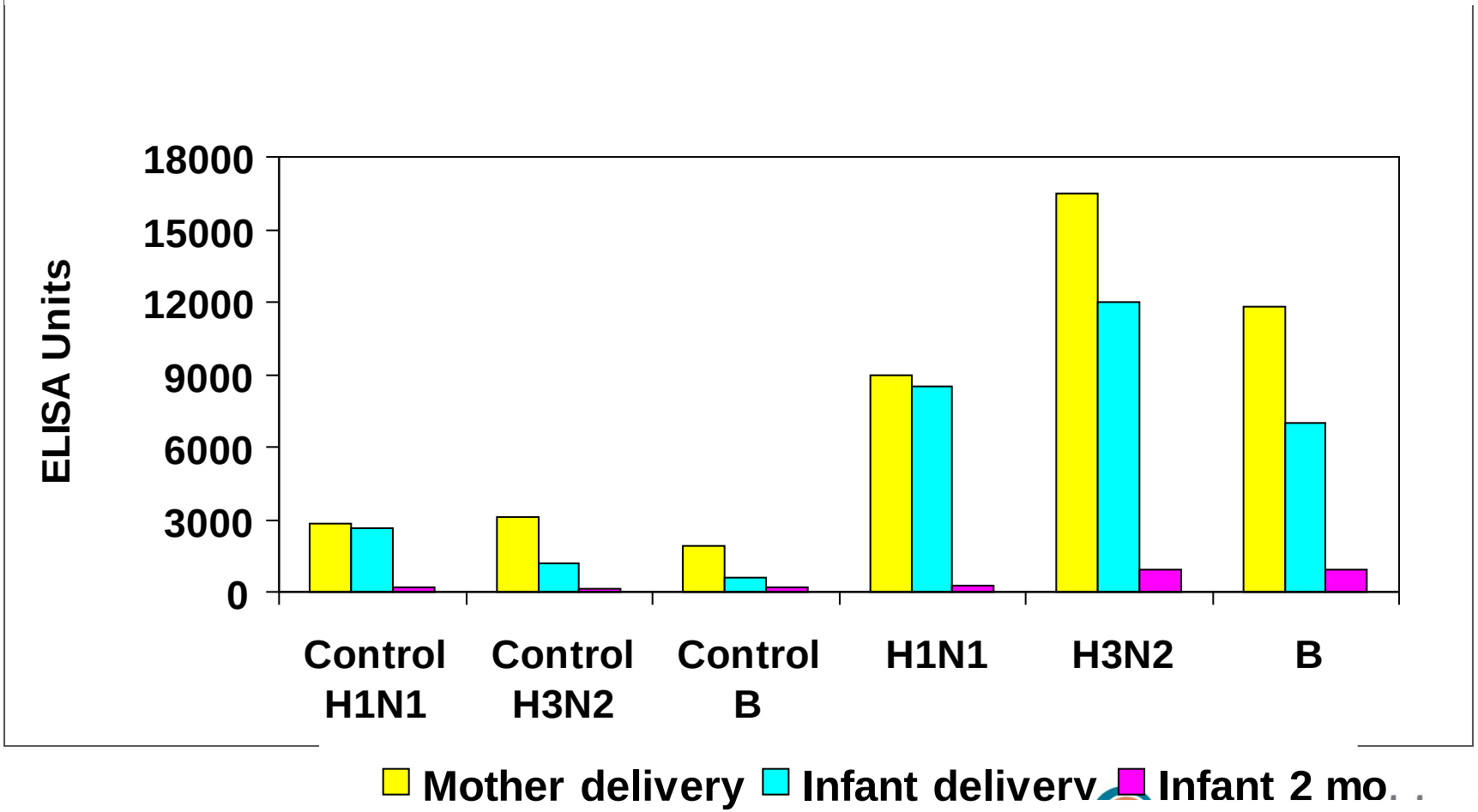


Antibody to influenza A and B in infants following maternal immunization with TIV or TT (control)

*Englund et al, JID 1993;68:647

Maternal Influenza Vaccine Increases the Antibody Transferred To Infants *

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



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

Safety of influenza vaccines in pregnancy (1)

- Influenza vaccination (TIV) is an essential element of prenatal care because pregnant women are at increased risk of serious illness due to influenza
- Vaccination is recommended at any time in pregnancy, before and during the influenza season
- No study to date has shown an adverse consequence of inactivated influenza vaccine in pregnant women or their offspring
- Data from an observational cohort study in Canada and from a birth and infant health registry in the United States did not point to any safety concerns related to pandemic vaccines among women during gestation or their offspring. Several studies on the safety of pandemic vaccines among pregnant women are still being completed in other regions.
- GACVS has established a subgroup on safety during pregnancy issues that is reviewing safety issues related to the use of influenza vaccines during pregnancy and lactation.

ACOG Committee Opinion, Obstet Gynecol Vol116;No.4:1006,Oct.2010

World Health Organization

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GACVS advice:
Safety of Influenza vaccines in pregnancy (3)

- Safety information for influenza vaccines continues to be reassuring.
- Significant morbidity due to vaccine-preventable diseases among women and infants could be prevented by immunization of pregnant women.
- Despite lack of apparent safety issues precautions and contraindications limiting vaccines' benefits to women are often included in product labelling on pregnancy and lactation.
- Further action by GACVS (Dec 2011):
  - continue to monitor and report adverse events in pregnant women following the use of influenza vaccines
  - review relevant evidence
  - include methodological points for planning and analysis of clinical trials and post marketing studies.

World Health Organization

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NEPAL MATERNAL INFLUENZA IMMUNIZATION STUDY

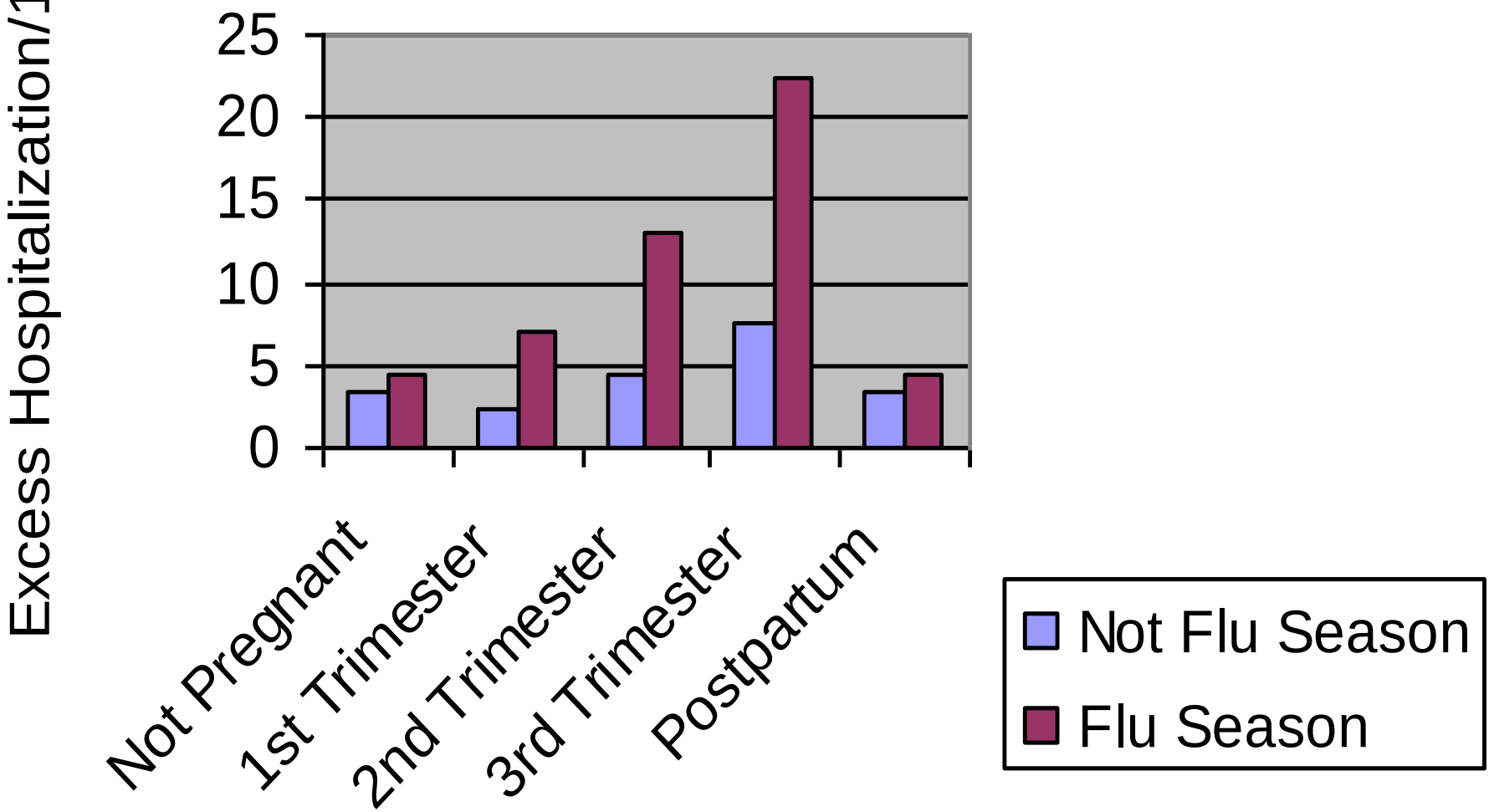
Helen Teaching

Pregnancy testing

Informed Consent

Study Blood draw

Excess Hospitalization of Low Risk Women During Influenza and Non-Influenza Season



Adapted from Neuzil et al Am J Epi 1998;148: 1094

TIV Clinical Effectiveness in Immunized Mothers

Zaman 2008: TIV in Bangladesh

- 25-45% clinical effectiveness against nonspecific criteria

Sheffield 2011: TIV given to pregnant women 2003-2004 (non-randomized)

- 2889 women received TIV; 1998 matched controls
- Decrease flu+ disease in women: 99% efficacy

Observational studies using administrative databases with mixed findings:

- Black 2004: no benefit to mother or child

BMGF-Sponsored Maternal Immunization Trials

	Nepal (Steinhoff)	Mali (Levine)	South Africa (Madhi)
RCT Endpoint	Safety and efficacy in mothers and infants	Safety and efficacy in mothers and infants	Safety and efficacy in mothers (without HIV) and infants. Safety and immuno in mothers with HIV and infants.
Years	2010-2013	2011-13	2011-2013
Sample Size	3,000	5,440	HIV-:2,100 HIV+:180 (year 1)/ 789 (year 2)
Vaccines	Vaxigrip/placebo	Vaxigrip/Menactra	Vaxigrip/placebo
Geography	Rural	Urban	Urban
Infant Mortality	47/1,000 l-b	102/1,000 l-b	44/1,000 l-b
HIV prevalence	<1%	2.3%	29%
Climate/Influenza Seasonality	Sub-tropical/Year Round	Tropical/Unknown	Temperate/ Seasonal

- Adegbola R, Nesin M, Wairagkar N. Immunogenicity and efficacy of influenza immunization during pregnancy: recent and ongoing studies. Am J Obstet Gynecol. 2012 Sep;207(3 Suppl):S28-32.
- Clinicaltrials.gov

Evaluation of Safety of Influenza Vaccination During Pregnancy

- No systematic review currently available
- Prospective clinical trials *
- Retrospective and database studies*
- Post-marketing passive reporting systems **
  - VAERS or VSD in the US
  - Yellow Card System in the UK
- Other vaccine safety systems using databases that link vaccination history and medical outcomes
- Post-marketing Pregnancy Registries**

* Limitations: Design and statistical power (N)

** Limitations: 1. Under reporting; 2. In addition to number of events, calculation of a rate or attributable risk (using # persons vaccinated as denominator) is necessary to evaluate relationship/causality; 3. Confounders; 4. Insufficient power

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

28 JANUARY 2011, 86th YEAR / 28 JANVIER 2011, 86e ANNÉE
No. 5, 2011, 86, 37–44
http://www.who.int/wer

recommending that the vaccine should not be administered during pregnancy unless there is definite risk of group A meningococcal disease, and lactating women should not be given the vaccine since it is not known whether it is excreted in breast milk. The Committee noted that this kind of precautionary statement has also been used for other inactivated vaccines, including other meningococcal conjugate vaccines, and is not based on any known risks to these groups. **Given the clear benefits of the vaccine, the increased risk of disease in the geographical area and past experiences using similar vaccines in comparable conditions, GACVS supported WHO's technical guidance that MenAfriVac should be offered to pregnant and lactating women residing in the meningitis belt during any stage of pregnancy or lactation. . . .**"

Immunogenicity in Pregnant women: Whole Virus and TIV

Study	Design	Pregnant women	Non-pregnant	Results
Hulka Obstet Gynecol 1964	Nonrandomized cohort; 2 doses whole virus	225	44	Similar pattern of rise and fall of influenza titers
Murray J Clin Micro 1979	Prospective cohort; '76 monovalent whole virus	26	18	No significant difference in GMT HAI antibody between pregnant and non-pregnant or by trimester
Sumaya 1976	Conven. sample, '76 monovalent whole virus	40		HAI antibody similar to nonpregnant adults in another trial.
Englund JID 1993	TIV in third trimester	13		All 13 seroconverted
Steinhoff NEJM 2010	TIV	311	0	Good immunogenicity in mothers with antibody persisting for up to 6 months in infants

Risk Factors for Severe Outcomes following 2009 Influenza A (H1N1) Infection: A Global Pooled Analysis

Risk Factor	RR Hospitalization	RR Death
Gender	1.0 (0.8-1.1)	0.8 (0.7–1.0)
Respiratory Disease	3.3 (2.0–5.8)	7.8 (4.9–26.6)
Asthma	1.8 (1.2–2.6)	1.7 (1.5–2.1)
Diabetes	0.9 (0.5–1.7)	4.0 (3.1–6.9)
Cardiac Disease	2.0 (1.5–2.2)	9.2 (5.4–10.7)
Renal Disease	4.4 (4.2–4.5)	22.7 (21.0–25.4)
Liver Disease	3 5.7 (3.2–15.7)	17.4 (11.6–28.0)
Neurological Disease	1.1 (0.9–1.3)	13.1 (8.4–32.4)
Immune Compromised	24.3 (16.1–32.6)	27.7 (14.0–66.5)
Pregnancy	**6.8 (4.5–12.3)**	**1.9 (0.0–2.6)**

Relative Risk differs by country from 3.5 in Germany to 25.3 in France, and may reflect clinical practice variations and health care utilization

Van Kerkhove, Mounts PLoS Med 2011

Neonatal Outcomes after Influenza Immunization During Pregnancy - Steinhoff et al. CMAJ 2012; 184:645

Variable	No. (%) of infants*		p value	OR (95% CI)
	Control vaccine *n = 166*	Influenza vaccine *n = 161*		
Birth weight, mean, g	3027	3117	0.09	–
Gestational age, mean, wk	39.4	39.5	0.6	–
Small for gestational age	63 (38.0)	45 (28.0)	0.05	0.63 (0.4–1.0)
Weighed less than < 2500 g	13 (7.8)	1 (4.4)	0.2	0.53 (0.2–1.4)
Born before 37 weeks' gestation	14 (8.4)	10 (6.2)	0.4	0.72 (0.3–1.7)

Note: CI = confidence interval, OR = odds ratio.
*Unless stated otherwise.

Comments:

1) Secondary analysis
2) Control vaccine = pneumococcal vaccine
3) Increased impact in infant when flu virus circulating

GACVS Advice: Safety of influenza vaccines in pregnancy

- Safety information for influenza vaccines continues to be reassuring
- Sgnificant morbidty due to vaccine-peventable diseases among women and infants could be prevented by immunization of pregnant women
- Despite lack of apparent safety issues, precautions and contraindications limiting vaccine benefits to women are often included in product labeling
- Further action by GACVS (Dec 2011):
  - Continue to monitor and report adverse events in pregnant women following the use of influenza vaccine
  - Review relevant evidence
  - Include methodological points for planning and analysis of clinicalt trials and post-marketing studies
  - GACVS meeting to discuss maternal immunization

World Health Organization

UPDATE ON SAFETY OF INFLUENZA VACCINES DURING PREGNANCY

Safety of flu vaccines assessed using:*

- Prospective clinical trials**
- Retrospective and database studies
- Post-marketing passive reporting systems
- VAERS or VSD in the US
- Yellow Card System in the UK
- Other vaccine safety systems using databases that link vaccination history and medical outcomes
- Post-marketing Pregnancy Registries

** Limitations:

1. Under reporting
2. In addition to number of events, calculation of a rate or attributable risk (using # persons vaccinated as denominator) is necessary to evaluate relationship or causality;
3. Confounders
4. Insufficient power

*** Ortiz et al, Vaccine 2011; Blancard-Rohner, Siegrist Vaccine 2011; Munoz 2012**

**** Zaman NEJM 2009; Englund JID 1993**

Safety of Adjuvanted Influenza H1N1 vaccines in Pregnant Women, 2010-2012

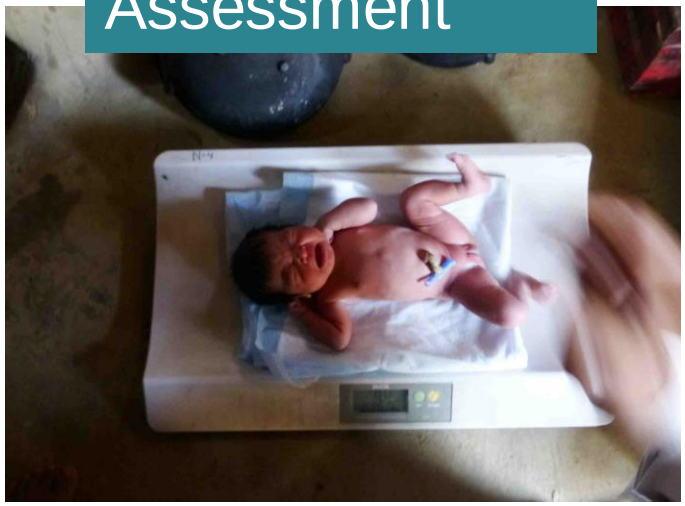
Study	Design	Study Group	Control Group	F/Up Period	Maternal Outcomes	Infant Outcomes
Tsai et al Vaccine 2010	Novartis clinical trial database of MF59 adjuvanted Flu vaccines (N=23,300) and unadjuvanted (N=40,285)	43 preg-nancies after MF59 and 60 pregnancies after nonadj flu vx; majority received vx 1st trimester	None	Delivery	No signals of risk but small numbers; similar rates after nonadj. & MF59 adj vx	Not reported
Gisslser et al ESPID 2012		76,043 newborn; 12,510 spon abortions	No maternal vx	Delivery	Pandemrix vaccine did not affect course of pregnancy	Protective effect on newborns regardless of smoking hx
Mackenzie et al Br J Clin Pharm 2012	Safety surveillance feasibility study in Scotland	3754 vaccinated people, with 117 pregnant women	312 who declined vaccine		No significant safety issues ; 4 miscarriages overall	No significant risk6 possible congenital abnormalities
Oppermann et al Vaccine 2012	F/up of German pregnant women immunized with ASO3 or nonadj. Flu vx	323 pregnant women any trimester	1329 controls	Delivery	No attributable risk vs. controls	No attributable risk vs. controls

Transplacentally-Acquired Influenza Antibody in Infants: Small prospective studies

- **Infants are protected from symptomatic influenza A virus infection by transplacentally acquired antibody *(Puck 1980)***
- **Passive maternal antibody to influenza:**
  - **delays the onset of influenza disease**
  - **decreased the severity of influenza disease (*Reuman 1987)***
- **Maternal immunization increases antibody transmission to the infant (*Englund 1993*)**

BIRTH ASSESSMENT and WEEKLY ASSESSMENTS

Birth Assessment



Weekly Assessment

Transport of specimens

NEPAL FLU VACCINE STUDY

Maternal influenza immunization in southern Nepal:

- Sponsored by B&M Gates Foundation
- ~3500 pregnant women enrolled to receive flu vaccine or placebo
- Babies and mother outcome followed
- Influenza present nearly every month

Safety of maternal influenza immunization in controlled studies

- Many "older" studies reported but often not well controlled
- Over 100 pregnant women received 1976 swine influenza vaccine (A/New Jersey/8/76)[1-3]
- Recent prospective[4] and retrospective[5-6] studies of safety of TIV during pregnancy
- No significant adverse reactions, including fever, local or systemic reactions, or fetal complications associated with flu vaccine in literature[7]
- Canadian, European, US studies of influenza vaccine in healthy and HIV+ pregnant women with H1N1: good safety, immunogenicity
- At least 3 international field trials underway (S. Africa, Nepal, Nepal)

1. Sumaya CV et al. JID 1979;140:141-46
2. Murray DL et al. J Clin Micro 1979;10:184-87
3. Deinhard AS et al. Am J Obstet Gynecol 1981;140:240
4. Englund JA, Glezen WP. JID 1993;168:647-56
5. Munoz FM et al. Am J Ob Gyn 2006;194:1200
6. Tamma PD et al. Am J Ob Gyn 2009;201:547
7. Ortiz et al. Vaccine 2011 (in press)

EFFECTIVENESS BY WHO GRADE TABLE*

Is inactivated influenza vx vs. no intervention or non-influenza vx in pregnant women effective to prevent influenza infection and severe outcomes of infection in pregnant women?

- Zaman 2008:
  - Effectiveness against respiratory illness with fever was 36%, implying a significant reduction achieved by influenza vaccination of pregnant women.
- Englund 1993:
  - No information on vaccine efficacy in pregnant women and the impact on laboratory-confirmed influenza (Note: not studied).
- Hulka 1964:
  - No significant difference in effectiveness of influenza vaccine vs. other vaccine against MAARI.
- *Excluded: Decades of immunogenicity studies, observational studies, effectiveness studies in non-pregnant adults, outcomes including newborn influenza or birthweight.*

*http://www.who.int/immunization/position_papers/influenza_grad_maternal_outcomes.pdf

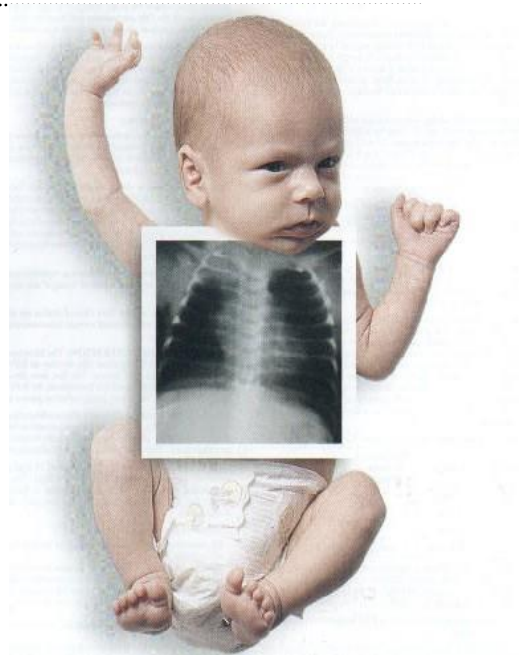
ACIP Guidelines for Vaccinating Pregnant Women: Pertussis Vaccine

" ACIP recommends that providers of prenatal care implement a Tdap immunization program for all pregnant women. Health-care personnel should administer a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap. If not administered during pregnancy, Tdap should be administered immediately postpartum."

ACIP. October 24, 2012

EXAMPLE: Maternal Immunization to Prevent Infant RSV Disease

- Most urgent need for protection against RSV is during first months of life, when vaccines are poorly immunogenic
- >75% of hospitalization for significant RSV disease occurs in full term, healthy infants:
- Clinical studies with RSV subunit vaccines show good immunogenicity and lack of reactogenicity in postpartum women
- US government regulation (FDA): Teratogenicity of PFP vaccine in animal model required and performed prior to human trial



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