Maternal Immunization: Unique considerations of public health value of vaccines given to pregnant women

Estimating the full public health value of vaccines

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- Significant neonatal, young infant, and maternal morbidity and mortality globally.
- Maternal antibodies transmitted across the placenta prior to birth confer protection against certain infectious diseases during the first months of life.
- Pregnant women are an accessible population.

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Immunization against selected infectious diseases during pregnancy is a potential strategy to reduce severe disease in mothers and their newborn infants.

Immunization of Pregnant Women is NOT New . . . for Protection of the Mother and the Infant

- **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 and infant mortality in New Guinea.

Immunization of Pregnant Women is NOT New . . . for Protection the Mother

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.

Burney LE. Public Health Rep. 1960 Oct;75(10):944.
First U.S. influenza vaccine recommendation.

Considerations for Vaccination During Pregnancy

- Disease burden in mothers and infants versus disease burden predominantly in infant or mother.
- Effects on the fetus
- Immunogenicity/effectiveness:
  - Immune response in mother, including durability.
  - 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.

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What influences government adoption of vaccines in developing countries? A policy process analysis

Syarifah Liza Munira[a,*], Scott A. Fritzen[b]

"Disease burden has been consistently mentioned by policymakers in countries to be the number one factor in setting priorities for vaccines to be introduced into immunization programs; the higher the burden, the more attractive a potential addition to the immunization regime of the country would be."

Vaccines Currently Administered to Pregnant Women: Where is disease burden?

Vaccine	Status	Mother?	Infant?
Influenza	Licensed and recommended	Yes	Yes
Tetanus	Licensed and recommended	Yes	Yes
Pertussis	Licensed and recommended (certain countries)	Potential	Yes
Meningococcal meningitis	Licensed	Yes	Yes

Future targets for maternal immunization: Where is disease burden?

Vaccine	Status	Mother?	Infant?
RSV	Phase I/II/III	Potential	Yes
Group B streptococcus	Phase II	Yes (fetus?)	Yes
Herpes Simplex Virus	Pre/Phase I	Yes*	Yes
CMV	Phase I/II	Yes*	Yes
Hepatitis E	Licensed (China)	Yes*	?
Zika virus?	Phase I/II	Yes*	Yes

*Ideally pre-pregnancy for early fetal effects

Other Considerations for Vaccines During Pregnancy

- Role as caregivers for family
- Economic productivity
  - Household poverty
  - Work absenteeism
- Longer-term consequences of maternal or infant disease
- Preventing health care visits/hospital stays
- Antimicrobial use and antimicrobial resistance
- Lack of alternatives (prevention in early weeks of life)
- Outbreak control and pandemic preparedness?

TABLE 2. Odds ratio* for any cardiopulmonary event occurring during influenza season among women aged 15–44 years enrolled in the Tennessee Medicaid program, by pregnancy status, 1974–1993

Pregnancy status	Prevalence (%)		OR†	95% CI†
	Cases (n = 4,369)	Controls (n = 21,845)		
Postpartum	4.4	7.7	1.0‡	
Nonpregnant	86.6	85.3	1.11	0.94–1.32
Week 1–7	0.7	1.1	1.06	0.68–1.67
Week 8–13	0.7	1.0	1.23	0.79–1.93
Week 14–20	0.9	1.2	1.44	0.97–2.15
Week 21–26	1.2	0.9	2.52	1.74–3.65
Week 27–31	1.3	0.9	2.62	1.82–3.76
Week 32–36	2.0	1.0	3.21	2.32–4.44
Week 37–42	2.2	0.9	4.67	3.42–6.39

* Odds ratios were adjusted for all factors listed in table 3.
† OR, odds ratio; CI, confidence interval.
‡ Referent.

Neuzil et al. Am J Epi 1998

Maximizing Public Health Impact of Maternal Immunization

- Balance between immunizing early (before exposure) and ensuring adequate time for immune response with duration of protection

Placental transport across gestation

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

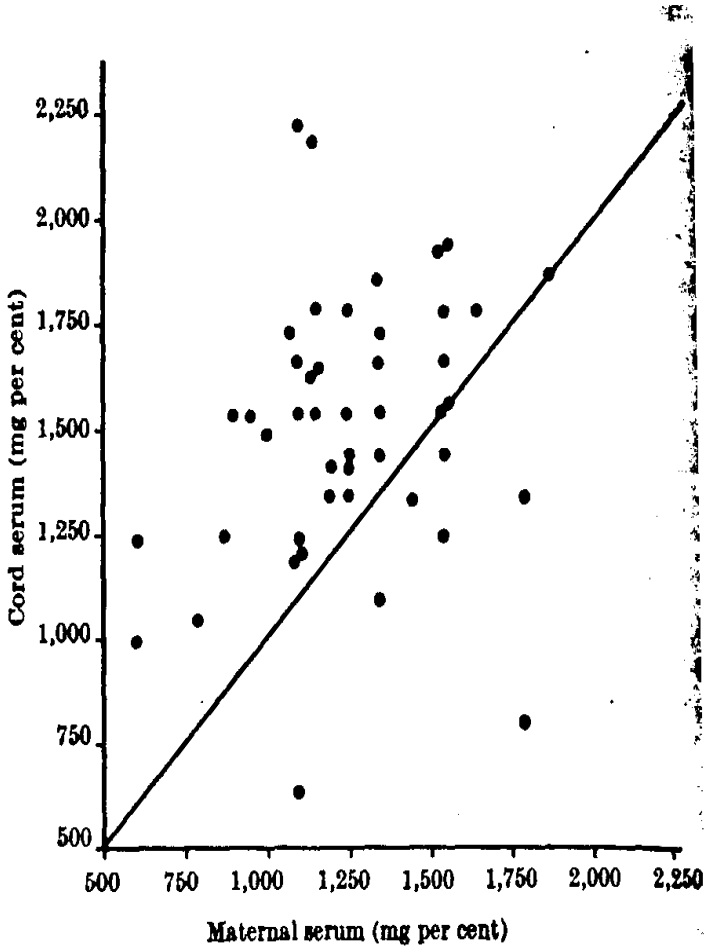


Fig. 1. Comparison of IgG concentrations in forty-six paired maternal cord sera

Kohler and Farr. Nature 1966;21:1070

Factors affecting transplacental transport

- Placental abnormalities
  - Malaria
  - HIV infection.
- Time:
  - Gestational age of infant.
  - Interval Between Vaccination and Delivery.
- Maternal IgG levels.

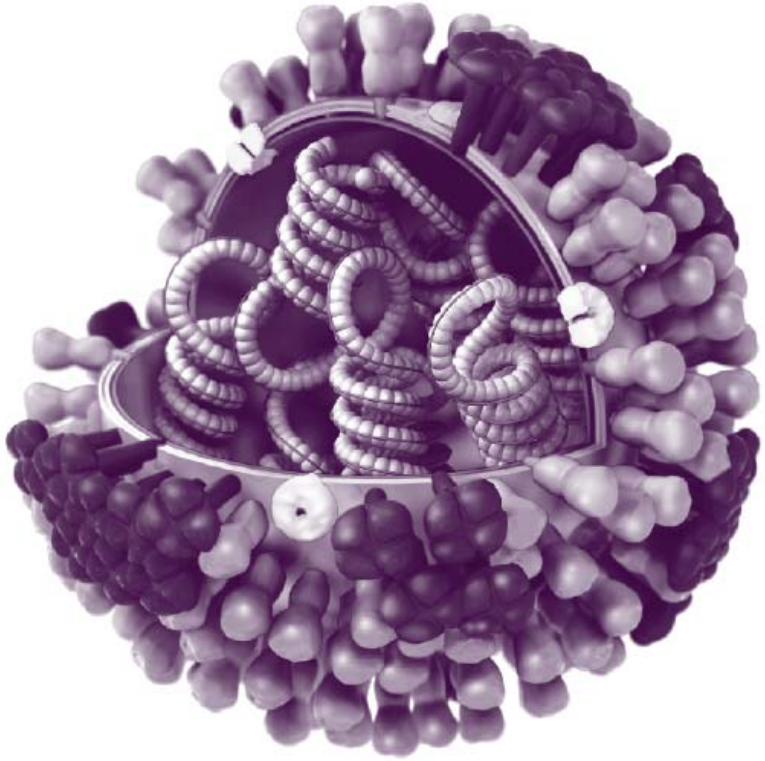
Impaired Placental Antibody Transport in HIV-Infected Mothers

- Lower specific antibody levels to some antigens in HIV-infected pregnant women.
- Reduced placental transfer of antibodies.

Specific Antibody	Placental Transfer, Median (IQR)[a]		Reduction, %
	HIV-Infected Mother–Exposed Uninfected Infant Pairs	HIV-Uninfected Mother–Unexposed Infant Pairs	
Haemophilus influenzae type b	0.57 (0.45-0.79)	0.74 (0.61-1.00)	23
Bordetella pertussis	0.91 (0.61-1.20)	1.51 (1.15-2.06)	40
Pneumococcus	0.62 (0.41-0.77)	0.73 (0.53-0.94)	15
Tetanus toxoid	0.95 (0.60-1.12)	1.30 (1.03-1.86)	27

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

Influenza: A few points…



Influenza in Low Resource Countries: Bangladesh

ICDDR,B - Matlab, July 2006.

- **Study participants and design:**
  - Bangladesh, 2004-05.
  - Randomized controlled trial.
  - 340 pregnant women received either influenza vaccine or pneumococcal polysaccharide vaccine during third trimester.
  - Follow-up through pregnancy and first 6 months after birth.
- **Outcomes:**
  - Febrile respiratory illness among infants and mothers.
  - Lab-confirmed influenza among infants.

Influenza Vaccine Reduced Febrile Respiratory Disease

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.		%	
Infants				
Person-months	870	881		
Respiratory illness with fever				
Any fever	153	110	28.9 (6.9 to 45.7)	−28.1 (−48.2 to −8.0)§
Temperature >38°C	77	56	28.1 (−4.6 to 50.6)	−13.7 (−28.0 to 0.5)
Diarrheal disease	138	137	1.9 (−30.0 to 26.0)	−1.6 (−22.1 to 18.9)
Clinic visit	92	54	42.0 (18.2 to 58.8)	−24.5 (−39.5 to −9.5)§
Influenza test ordered	79	41	48.7 (25.4 to 64.7)	−24.4 (−38.0 to −10.8)§
Influenza test positive	16	6	62.8 (5.0 to 85.4)	−6.4 (−12.2 to −0.5)§
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)

K Zaman et al. *N Engl J Med* 2008.

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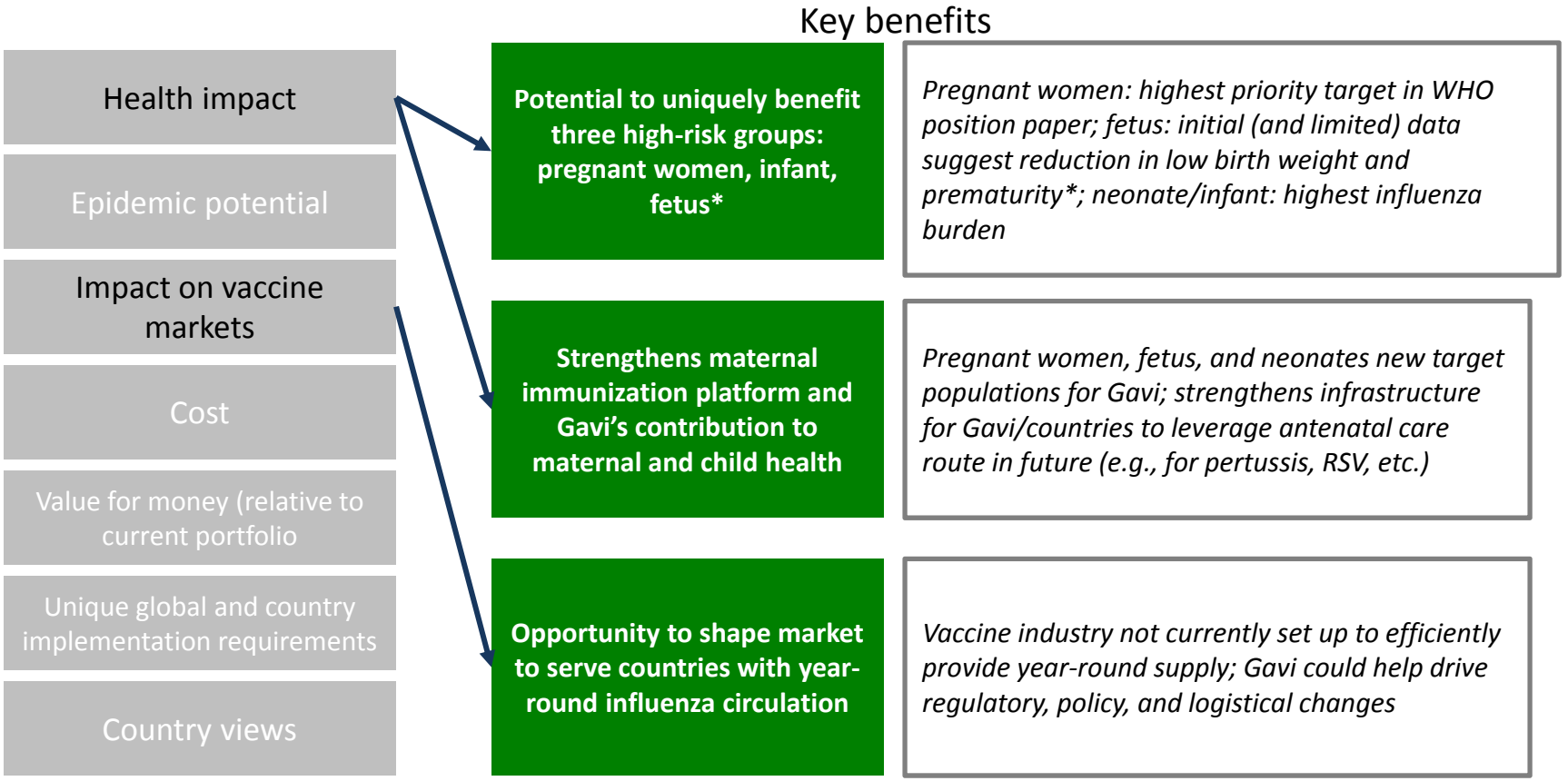
Key influenza vaccine benefits

Benefits moms and babies, strengthens maternal immunization, catalytic market-shaping opportunities.

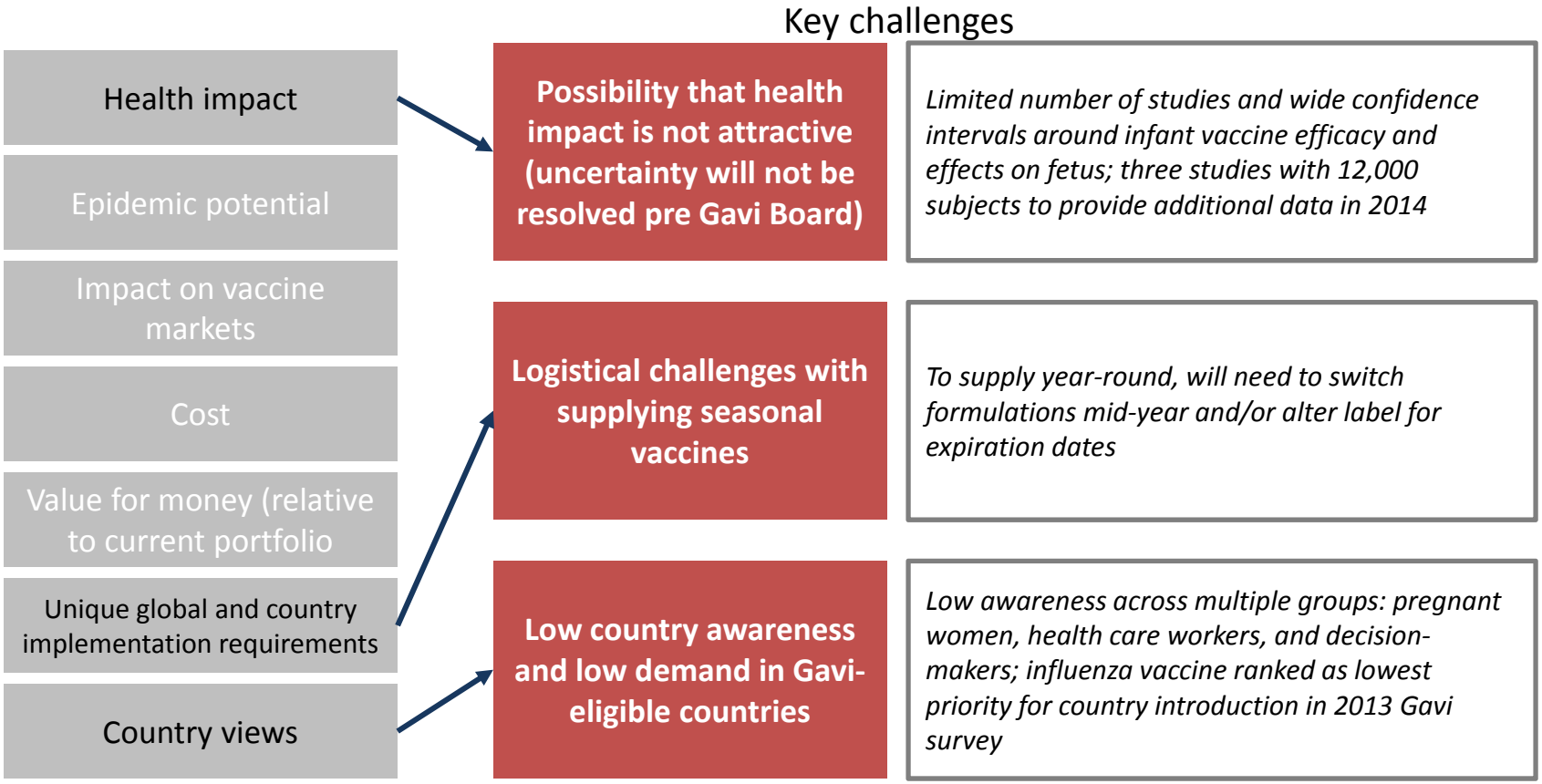


*Effects on fetus highly uncertain and not included in VIS impact studies.

Source: J. Kallenberg, Gavi Board 2013.

Key influenza vaccine challenges

Uncertainty in impact, complex provision of year-round supply, low awareness/demand.



Source: J. Kallenberg, Gavi Board 2013

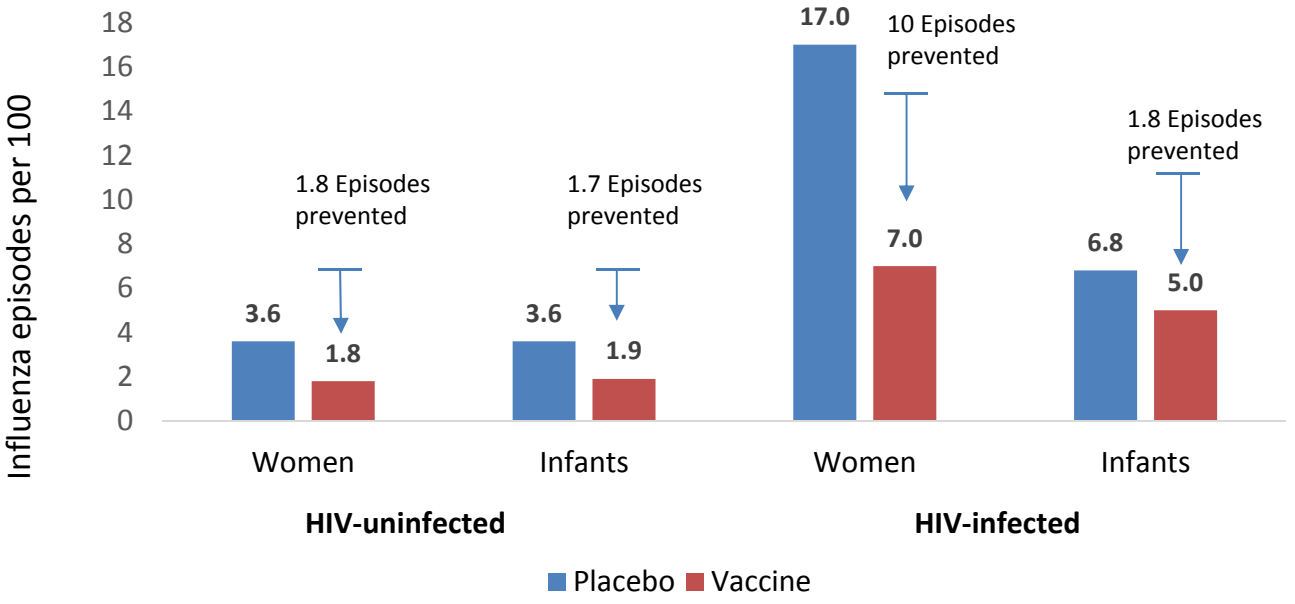
Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuwanda, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Florette Treurnicht, Ph.D., Justin R. Ortiz, M.D., Marietjie Venter, Ph.D., Avy Violari, M.D., Kathleen M. Neuzil, M.D., Eric A.F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (Matflu) Team*

- Two double-blind, randomized, placebo-controlled trials of IIV3 in South Africa
  - 2011: 194 pregnant women with HIV infection
  - 2011 and 2012: 2116 pregnant women who were not HIV- infected.
  - 18- 36 years of age, 20 to 36 weeks gestation
- Immunogenicity, safety and efficacy until 24 weeks after birth evaluated
- Influenza diagnosed by RT-PCR assays of respiratory samples

Source: N Engl J Med 2014; 371:918-31.

Efficacy of influenza vaccine and influenza episodes prevented per 100 persons, South Africa



Efficacy	**50.4%**	**48.8%**	**57.7%**	**26.7%**
	(14.5 - 71.2)	(11.6 - 70.4)	(0.2 - 82.1)	(-132.0 - 76.8)

Source: Madhi et al. N Engl J Med 2014; 371:918-31.

Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial

Milagritos D Tapia, Samba O Sow, Boubou Tamboura, Ibrahima Téguété, Marcela F Pasetti, Mamoudou Kodio, Uma Onwuchekwa, Sharon M Tennant, William C Blackwelder, Flanon Coulibaly, Awa Traoré, Adama Mamby Keita, Fadima Cheick Haidara, Fatoumata Diallo, Moussa Doumbia, Doh Sanogo, Ellen DeMatt, Nicholas H Schluterman, Andrea Buchwald, Karen L Kotloff, Wilbur H Chen, Evan W Orenstein, Lauren AV Orenstein, Julie Villanueva, Joseph Bresee, John Treanor, Myron M Levine

Tapia et al, Lancet Infect Dis, 2016

- Double-blind, randomized, controlled trial
- 4425 Pregnant women received TIV or MCV in third trimester
- Infants followed through 6 months of age (LCI primary outcome)

Efficacy against Laboratory-Confirmed Influenza

Age (m)	Infants born to women vaccinated any time pre-partum		Infants born to women vaccinated ≥ 14 days pre-partum	
	%	95% CI	%	95% CI
< 1	100	15.8 - 100	100	-8.4 - 100
1	78.0	-6.3 – 97.7	75.2	-24.2 – 97
2	68.7	18.4 – 89.8	69.0	11.3 – 91.1
3	67.9	35.1 – 85.3	70.2	35.7 – 87.6
4	57.3	30.6 – 74.4	60.7	33.8 – 77.5
5	33.1	3.7 – 53.9	37.3	7.6 – 57.8

Tapia et al, Lancet Infect Dis, 2016

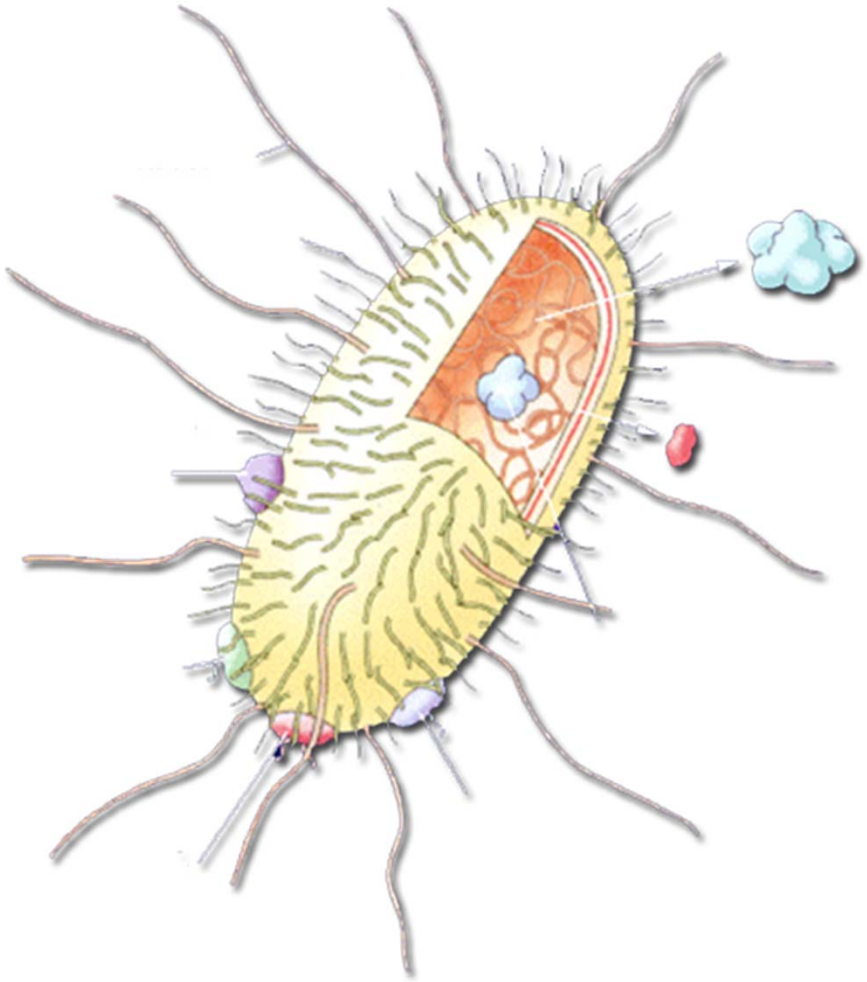
Effects on Birthweight

	TIIV	MCV	p-value
Low birthweight (<2500g), N (%)			
All live births	191 (9.3)	166 (8.2)	0.2
Births during peak flu season*	90 (9.6)	77 (8.2)	0.29
Birthweight, mean g (SD)			
All live births	3017 (472)	3015 (444)	0.91
Births during peak flu season*	3013 (483)	3002 (437)	0.61

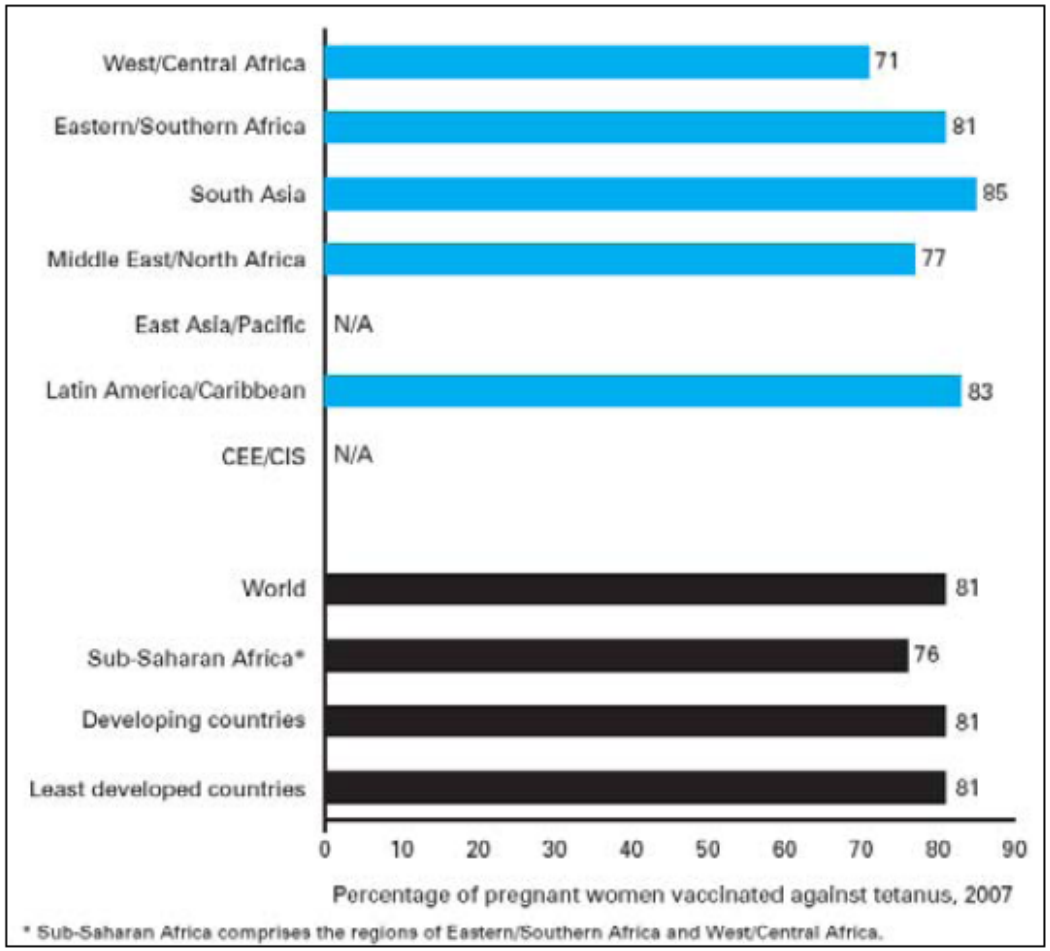
*Peak influenza season was Sept 1 – Oct 31 and Feb 1 – Apr 30

Tapia et al, Lancet Infect Dis, 2016

Pertussis: A few points….



Maternal Immunization: It's Possible Tetanus Vaccination in Pregnancy



Source: Moccia P. The state of the world's children 2009 maternal and newborn health. New York, NY: United Nations Children's Fund (UNICEF); 2008.

Pertussis: Why maternal immunization?

- Severe disease incidence highest in young infants
- It's feasible: Pregnant women already receive TT or TD
- It works!

- Unanswered questions:
- Burden of disease
- Interference with infant immunization series
  - Whole cell vaccines
  - Younger age at immunization

Effectiveness of maternal pertussis vaccination in England: an observational study

Gayatri Amirthalingam, Nick Andrews, Helen Campbell, Sonia Ribeiro, Edna Kara, Katherine Donegan, Norman K Fry, Elizabeth Miller, Mary Ramsay

	Percentage of cases vaccinated	Average matched coverage*†	Vaccine effectiveness‡
Infants <3 months of age			
Vaccination at least 7 days before birth	15% (12/82)§	62%	91% (84 to 95)
Vaccination at least 7 days before birth with coverage reduced by a relative 20%	15% (12/82)§	49%	84% (71 to 93)

www.thelancet.com **Published online July 16, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60686-3**

Summary

- Approach to valuing maternal immunization will need to be flexible and innovative
  - Unique aspects of each vaccine
  - Unique aspects of maternal vaccines (pregnant women, fetus, infant)
    - Are these additive?
    - Longer-term consequences
- More complete measurements of public health impact will apply to pregnant women as well
  - Economic productive, for example