MATERNAL IMMUNIZATION: FOR THE WOMAN, FETUS, AND INFANT

ASVAC 2019
Yangon, Myanmar
Sept. 14, 2019

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UNIVERSITY OF WASHINGTON

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FINANCIAL DISCLOSURES AND CONFLICTS OF INTEREST

My institution has received research support for clinical studies from GSK, Alios, Novavax, MedImmune, and Chimerix.

I have served as a consultant for SanofiPasteur and Meissa vaccines.

I support influenza vaccination for healthcare workers including pregnant women in my hospital.

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MATERNAL IMMUNIZATION:

DEFINITION:

Giving a vaccine to a pregnant women to provide protection to the mother, fetus, and infant through active antibody production and transplacental antibody transfer

CONCEPT OF MATERNAL IMMUNIZATION

Boosts maternal levels of pathogen-specific anti-bodies

Provides newborn and infant with sufficient concen-tration of antibodies to protect against infections

until able to adequately respond to active immunization or infectious challenge

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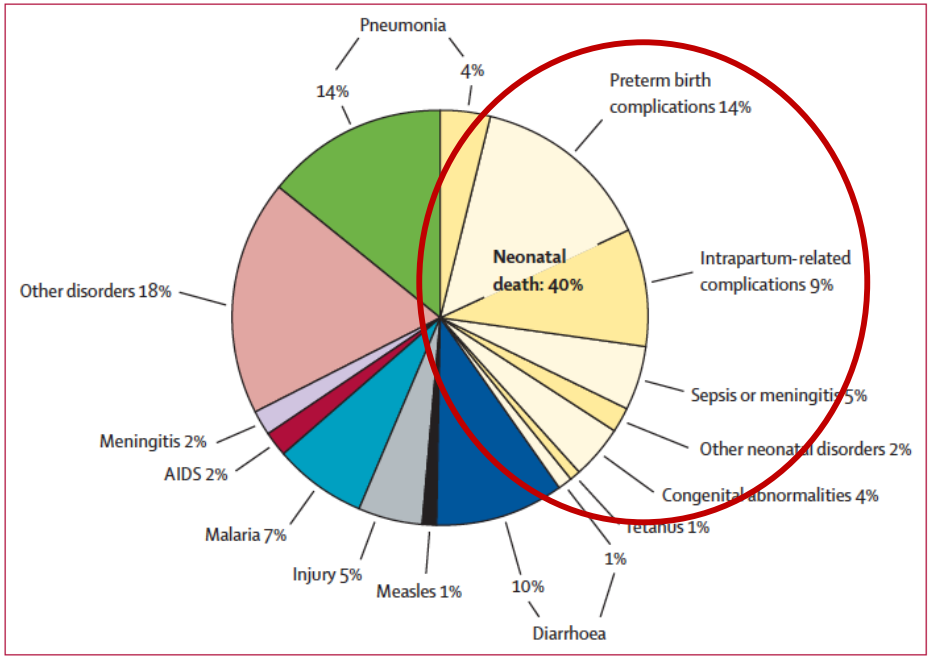
WHY CONSIDER MATERNAL IMMUNIZATION? YOUNG INFANTS AT HIGHEST RISK FROM INFECTIONS

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

Global Causes of Mortality in Children < 5 years*



*Liu L et al. Lancet 2012

WHY IMMUNIZE A PREGNANT WOMAN?

- Immunization during pregnancy has the potential to protect the mother, fetus, and infant during a vulnerable period in their lives – “Two for one” protection
- Pregnant women are accessible to medical care and intervention –in both developed and developing countries
- Transplacental transfer of antibodies is NATURAL: it is safer and less expensive than administration of immunoglobulin to the infant

PEOPLE magazine

WHO: Sustainable Development Target Goals

Achieving universal health coverage -
Sustainable Development Goal 3 targets

World Health Organization

By 2030….

Target 3.1 Reduce global maternal mortality ratio to < 70 per 100,000 live births

Target 3.2 End preventable deaths of newborns and children < 5 years of age

Neonatal mortality to at least as low as 12 per 1000 live births and
Under-5 mortality to at least as low as 25 per 1000 live births

UNIGME: To achieve targets, targeted low cost interventions to prominent causes of mortality needed

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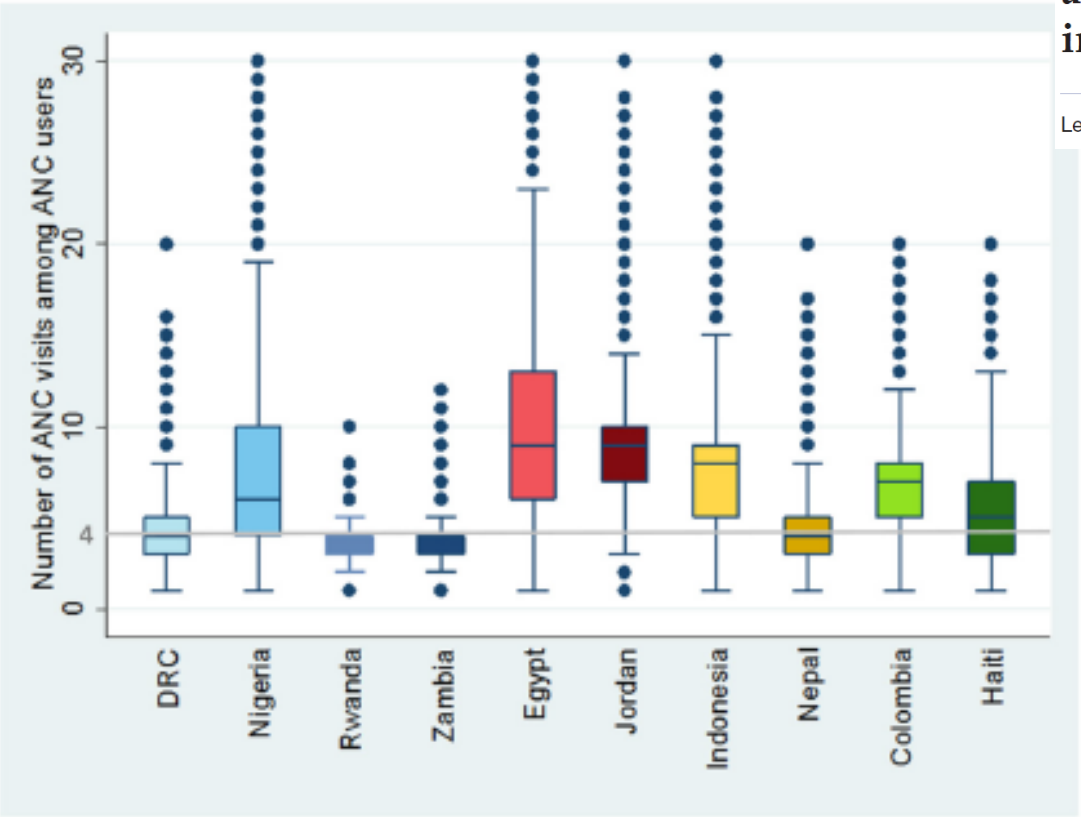
Antenatal care visits among women increasing, 2019



Box plot of number of antenatal care (ANC) visits among ANC users, by country. DRC, Democratic Republic of Congo.

Not just a number: examining coverage and content of antenatal care in low-income and middle-income countries

Lenka Benova [1] Özge Tuncalp [2] Allisyn C Moran [3] Oona Maeve Renee Campbell[1]

BMJ Global Health

2018 BMJ

Results In all 10 countries, the majority of women in need of ANC reported 1+ ANC visits and over two-fifths reported 4+ visits. Receipt of the six routine components varied widely; blood pressure measurement was the most commonly reported component, and urine test and information on complications the least. Among the subset

Conclusion Our findings suggest that even among women with patterns of care that complied with global recommendations, the content of care was poor. Efficient

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

Thanks to my sister-in-law

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IMMUNIZATION DURING PREGNANCY: RECENT HISTORY

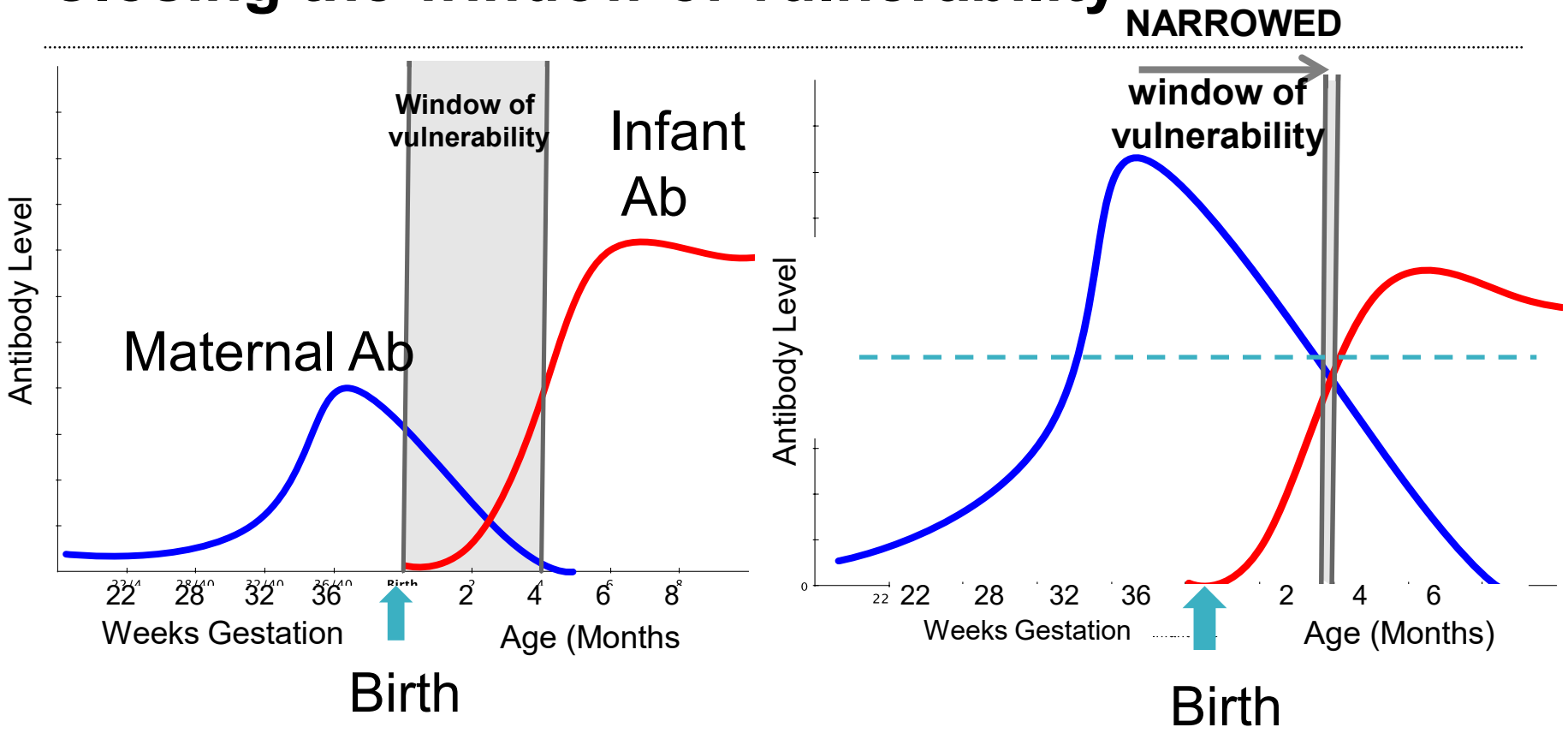
- Routine immunization during pregnancy with diphtheria, influenza and polio vaccines (1950-60's)
- Safety and benefit of polio vaccine to entire population including pregnant women during polio outbreaks (Finland, Israel), and meningococcal outbreaks (Brazil) between 1970 – 90's
- Concerns of vaccine safety, vaccine components, and lack of efficacy data: cessation of maternal vaccination EXCEPT tetanus vaccine globally by 1980's
- 2009-10 pandemic H1N1 outbreak demonstrated risk of influenza (flu) during pregnancy and benefits of flu vx
- 2012-2014 pertussis epidemic emphasized high risk of neonatal pertussis deaths and benefit of maternal Tdap

Current Status of Vaccines Recommended during Pregnancy - 2019

Vaccine: Licensed	Maternal Benefits	Fetal/ Neonatal Benefits	When to give	Safety Concerns
Tetanus	X	X	3rd trimester	None identified
Influenza multivalent	X	X	Any trimester	None identified
Pertussis -Acellular	X	X	2nd-3rd trimester	None identified
SPECIAL CONDITIONS: Hep A; Meningococcal conjugate; Polio; Rabies Yellow Fever	X	No Data	If necessary	None identified (Except ?Yellow Fever)
Vaccines in Development				
RSV	Possibly	Possibly	1st study completed, not published	Preliminary data looking good
GBS	X	X	In development	Some data
CMV	X	X	In development (?prepregnancy)	No Data
HSV	X	X	In development	No Data
Mening GrpA –Tetanus conj	X	X	Analysis ongoing	No Data

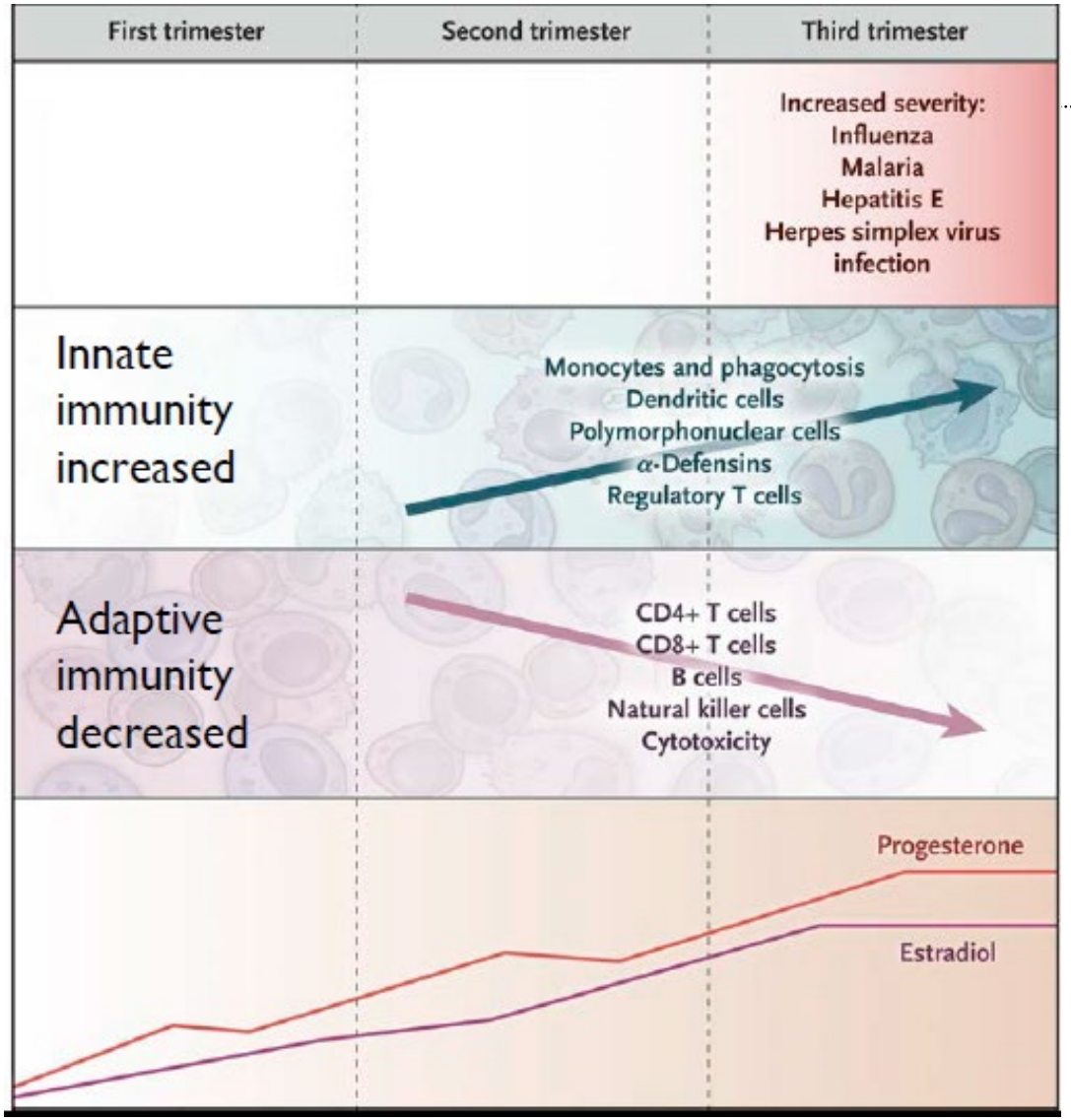
MATERNAL-INFANT ANTIBODIES

Closing the window of vulnerability



Thanks to B&M Gates Fndn

Changes in Hormone Levels and Immune Characteristics during Pregnancy*

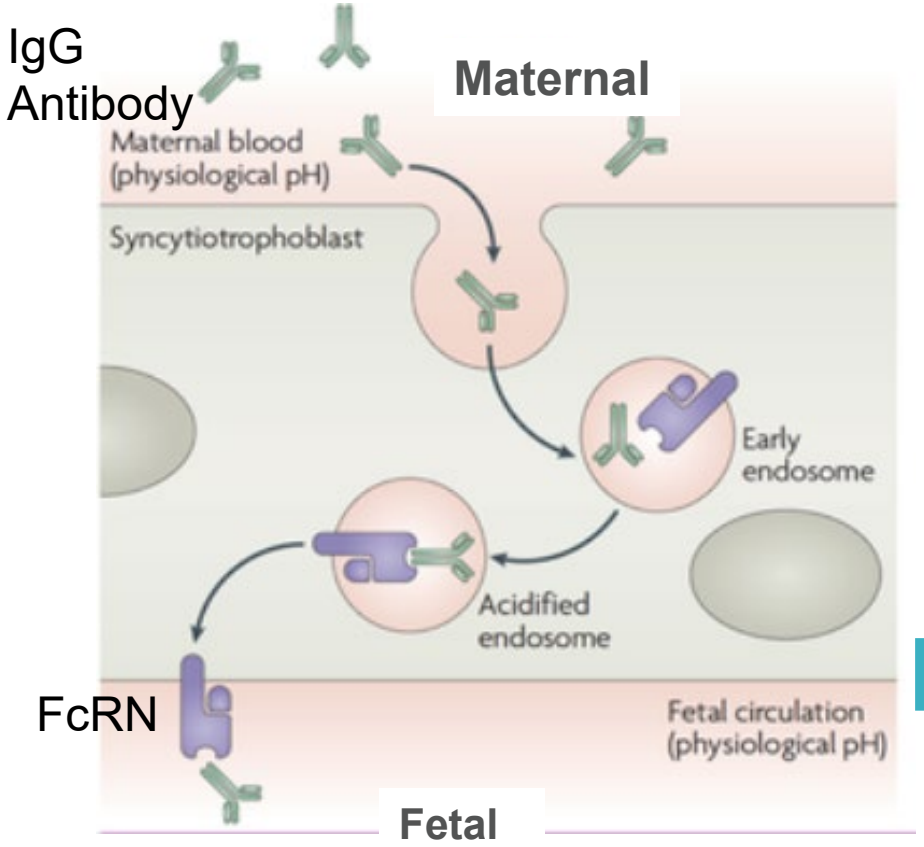


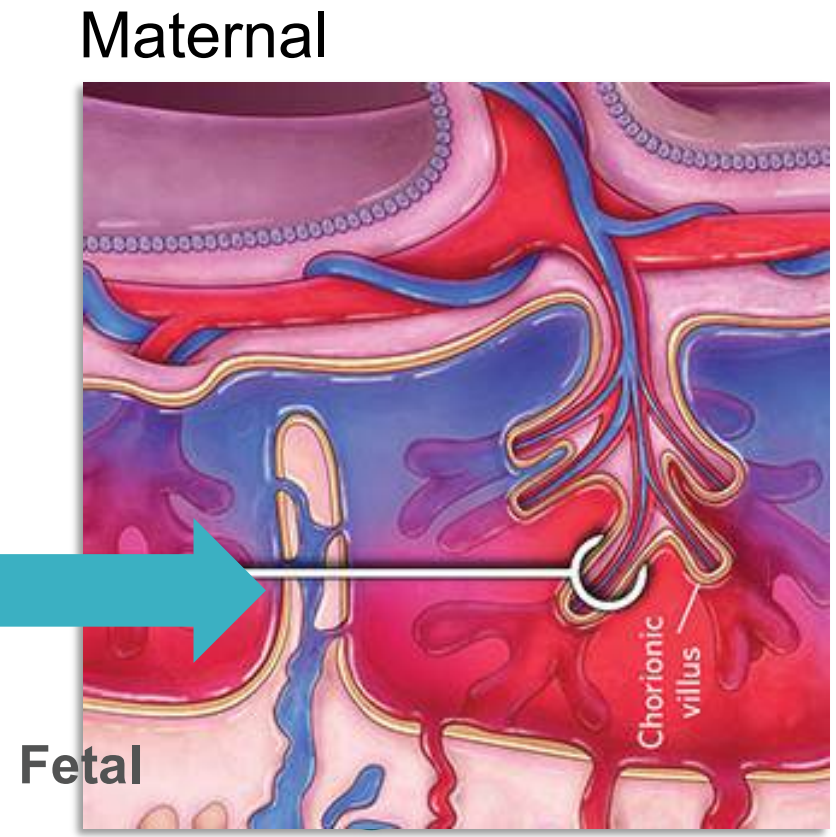
- Increasing estradiol levels augment TH2 and humoral response to infection and decrease TH1 response
- Innate immune response preserved during pregnancy
- Pregnant women respond appropriately to Flu and Tdap vacines and achieve same rates of serologic response as non-pregnant women

Kourtis AP et al NEJM 2014; 370:2211-8

Transplacental Maternal Antibody Transfer to the Fetus

Maternal IgG is actively transferred across the placenta via FcRn receptors of of syncychiotrophoblast cells in the chorionic villi.





https://www.the-scientist.com/?articles.view/articleNo/43618/title/The-Prescient-Placenta/

https://www.quora.com/Why-do-IgG-antibodies-cross-through-the-placenta

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

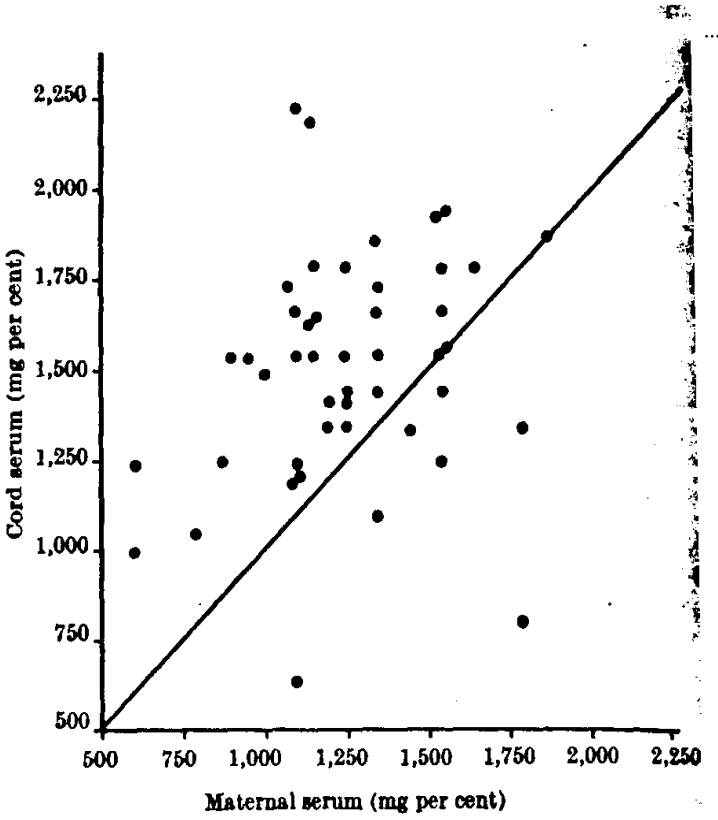


Fig. 1. Comparison of IgG concentrations in forty-six paired maternal cord sera

Kohler and Farr. Nature 1966;21:1070

Influence of Maternal HIV Infection on Placental Antibody Transfer*

- An abnormal placenta may not efficiently transport maternal antibodies to the fetus.
- EXAMPLE: In HIV+ women in Africa, lower antibody titers to certain antigens were seen in cord blood: reduction of 15-40%

Specific Antibody	HIV-Infected Mother–Exposed Uninfected Infant Pairs	HIV-Uninfected Mother–Unexposed Infant Pairs	Reduction, %
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

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

BETTER ANTIBODY IN BABIES AFTER MATERNAL IMMUNIZATION COMPARED TO PRE-PREGNANCY

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

Outline

Examples of maternal immunization to be discussed :

- Tetanus
- Influenza
- Pertussis
- Future: RSV, GBS

- Not discussed:
  - Meningococcus
  - Pre-pregnancy:
    - CMV, HSV, Hepatitis E, Zika

UK Poster
1950

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

BRITISH MEDICAL JOURNAL 785 SEPT. 23, 1961

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.

V. M. TUCKER, S.R.N.

Department of Public Health, Territory of Papua and New Guinea

AND

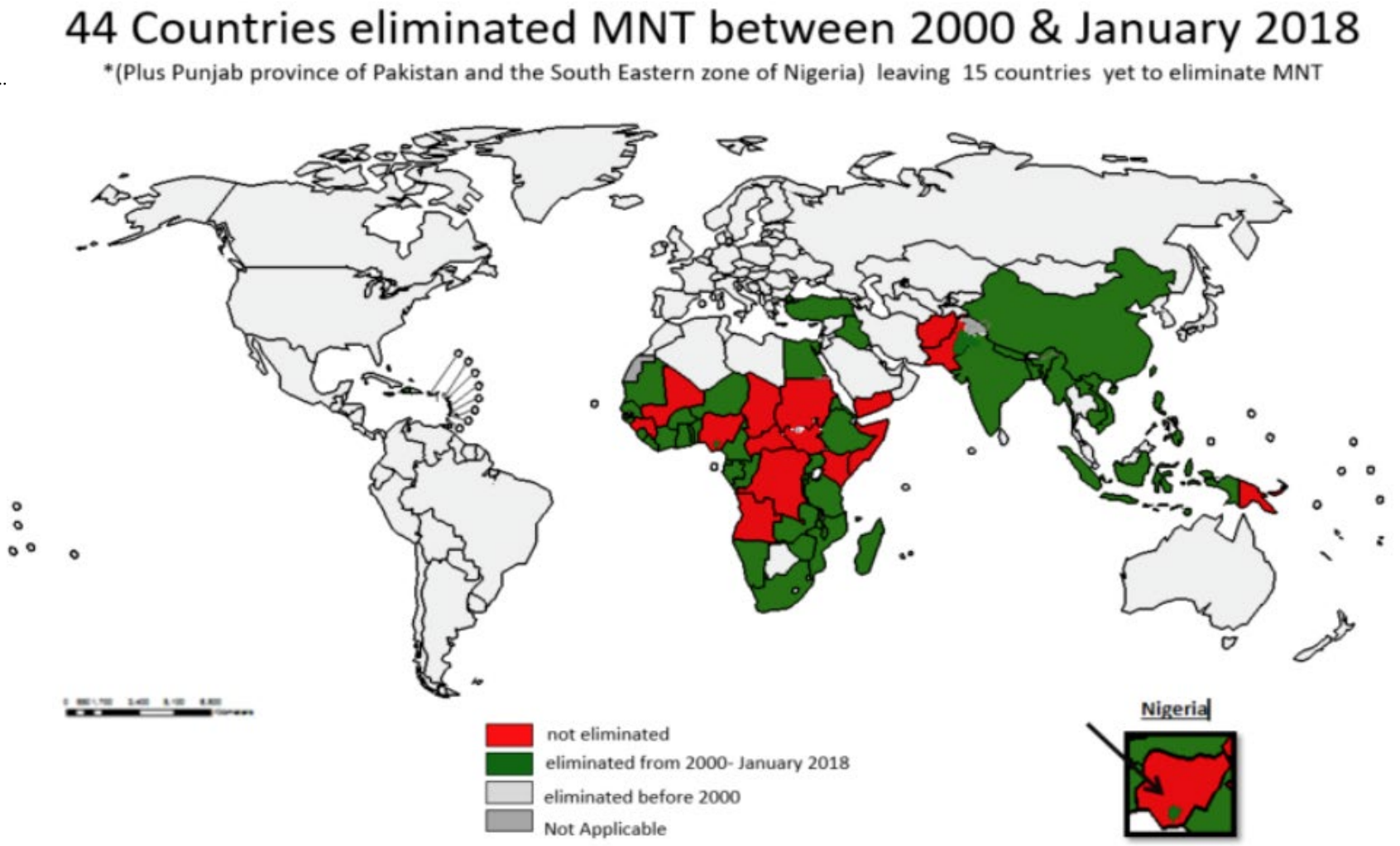
G. R. WESTBROOK, S.R.N.

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

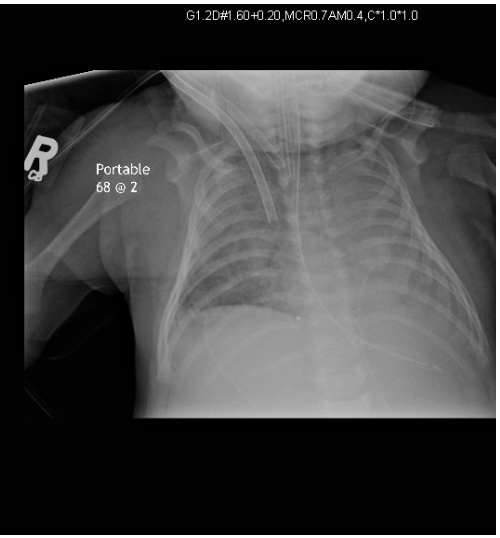
# Doses Tetanus Toxoid Given To Pregnant Women	0 or 1 dose	2 doses	3 doses
Number (%) of infants with neonatal tetanus	16/160 (10%)	8/234 (3.4%)	1/175 (0.6%)

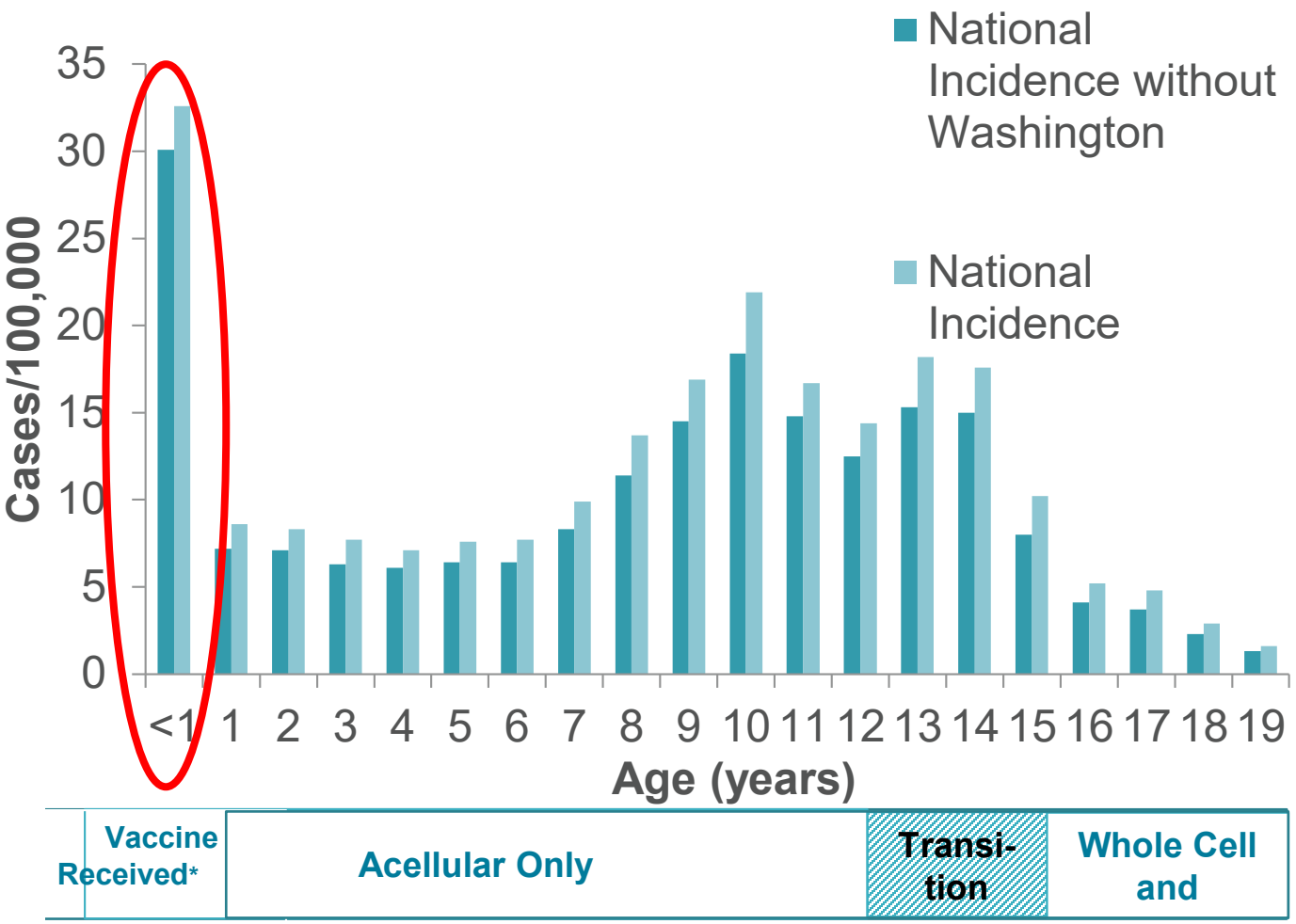
2018: 44 Countries Eliminated Maternal Neonatal Tetanus (45?)



Pertussis cases by age — United States, 2012

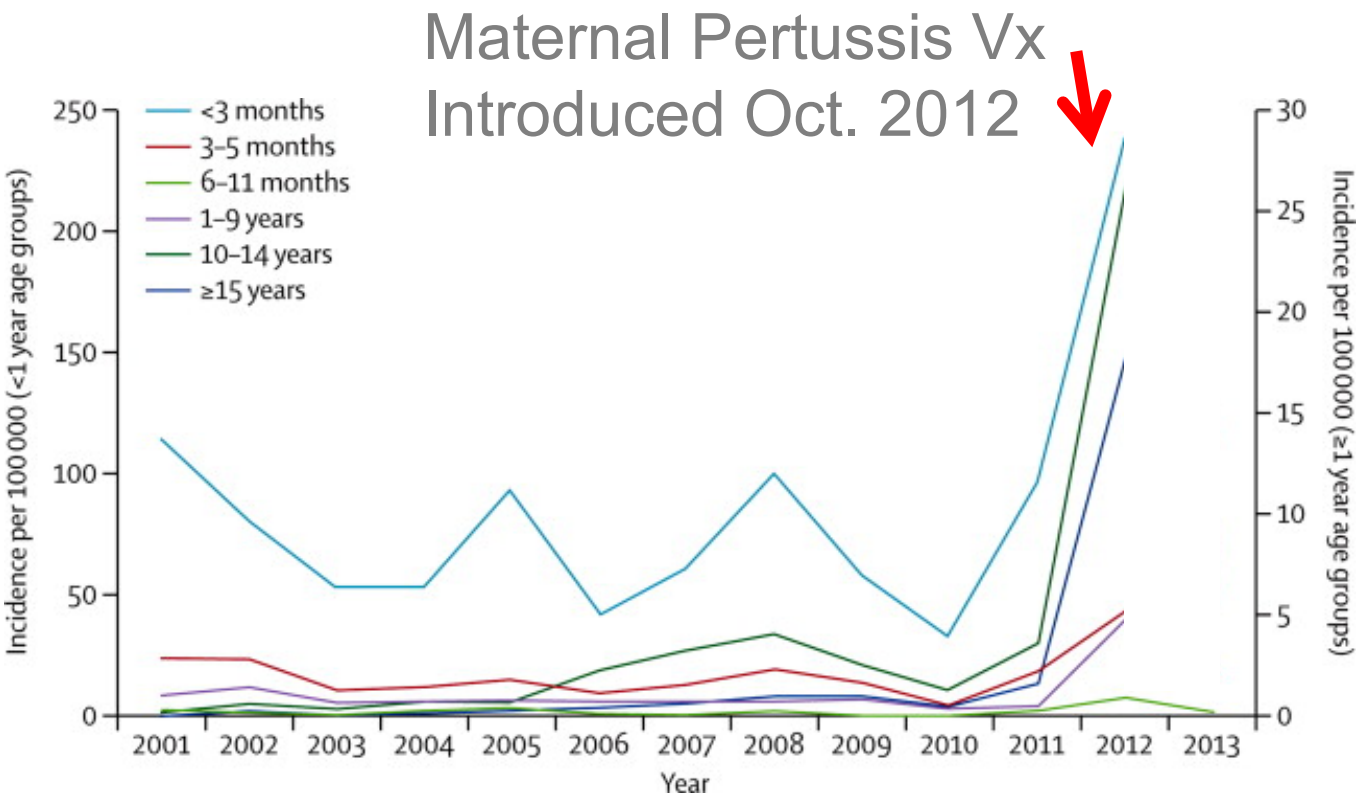
Fatal Neonatal Pertussis





EXAMPLE: UK Pertussis Disease and Maternal Tdap *

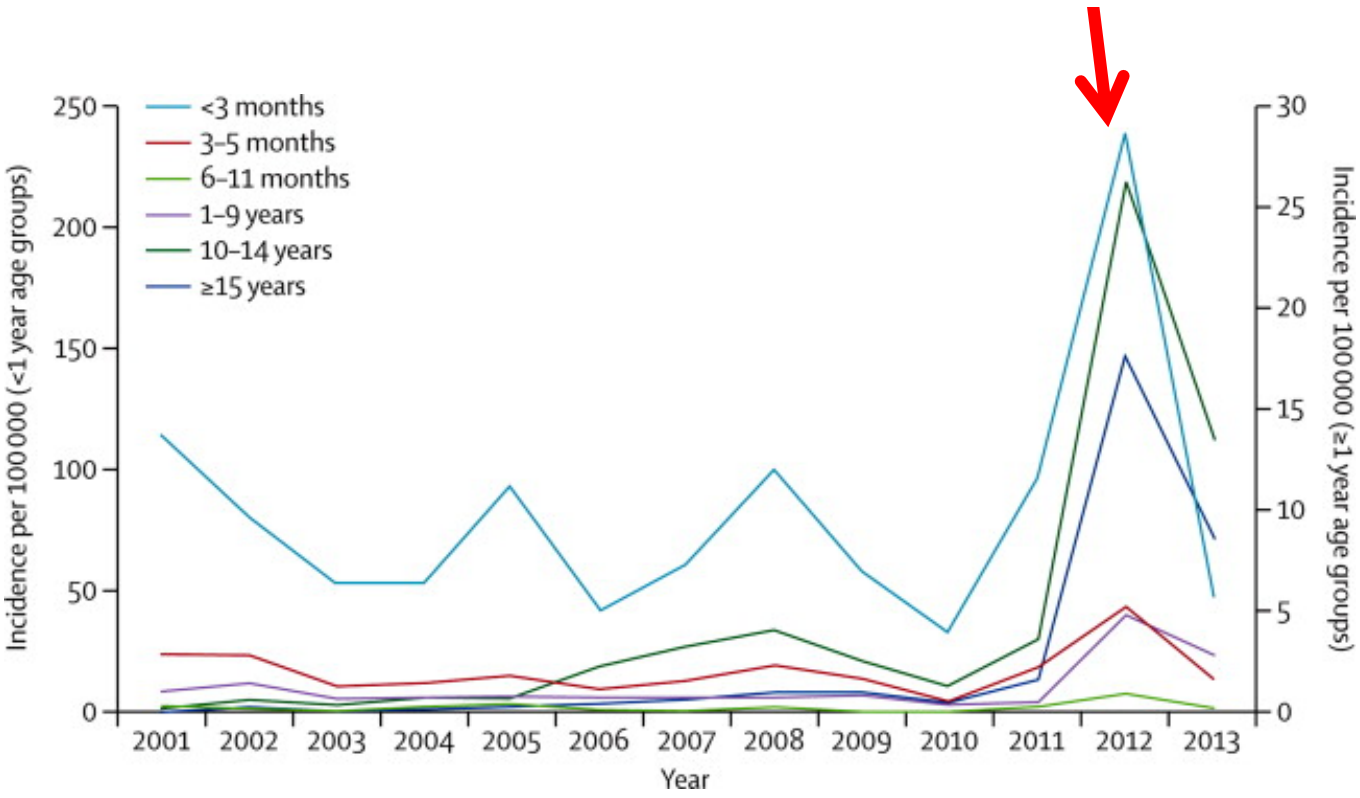
UK Neonatal Pertussis Epidemic, 2012



*Amirthalingam G et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014; 384:1521

EXAMPLE: UK Maternal Tdap Immunization*

Maternal Pertussis Vx
Introduced Oct. 2012



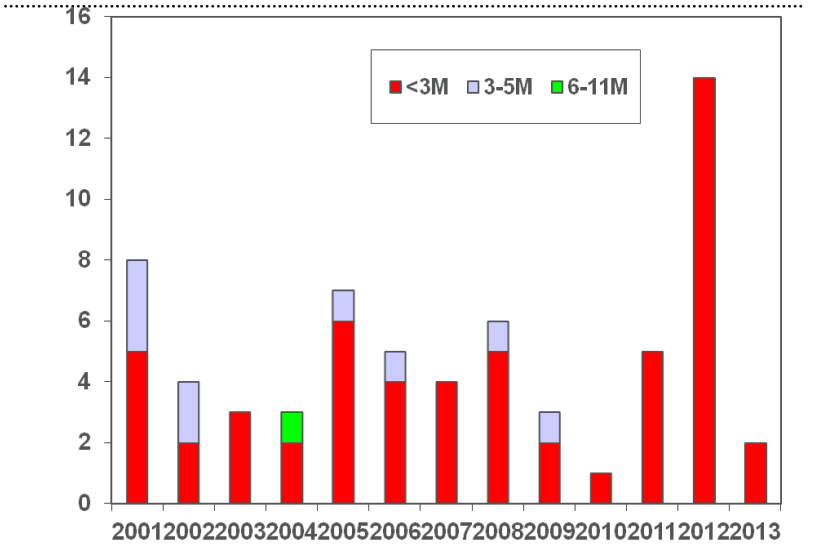
*Amirthalingam G et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014; 384:1521

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

July 16, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60686-3

- Oct. 2012: Immunization of pregnant women started using TdapIPV
- Vaccine coverage in first year = 64%
- Vaccine effectiveness in infants: calculated based on cases of disease in babies in first 3 months of life = 91% (95% CI 84-95)



Clinical Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America

Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis

Kathleen Winter,[1,2] Steve Nickell,[1] Michael Powell,[1] and Kathleen Harriman[1]
[1]California Department of Public Health, Immunization Branch, Richmond; and [2]Department of Epidemiology, University of Kentucky, Lexington

Clinical Infectious Diseases® 2017;64(1):3–8

- Utilized California immunization registry
- Maternal immunization with Tdap 85% more effective than postpartum Tdap at preventing pertussis in infants < 8 wks

Timing of Tdap During Pregnancy: Earlier is Better (NEW)

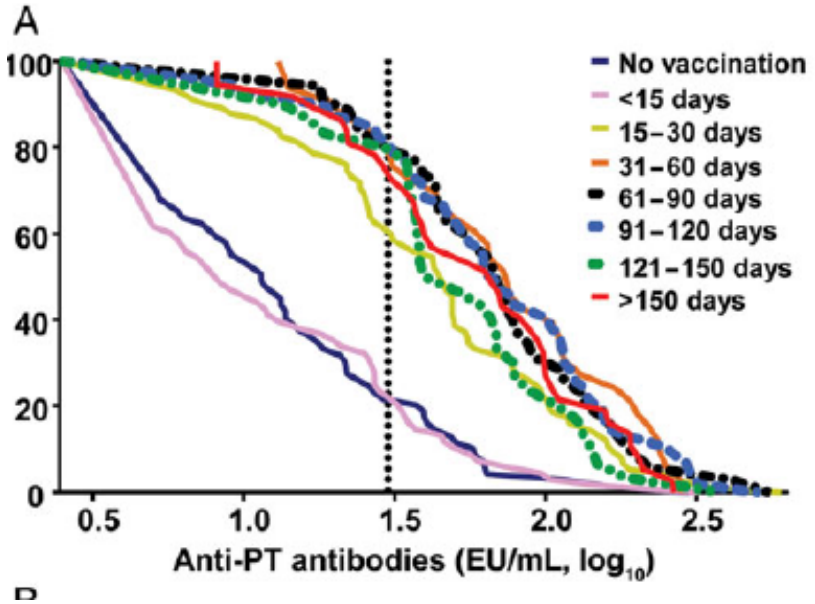
Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis

Clin Inf Dis 2016

Christiane S. Eberhardt,[1,2] Geraldine Blanchard-Rohner,[3] Barbara Lemaître,[1] Meriem Boukrid,[4] Christophe Combescure,[5] Véronique Othenin-Girard,[4] Antonina Chilin,[4] Jean Petre,[6] Begoña Martinez de Tejada,[4] and Claire-Anne Siegrist[1,3]

[1]Center for Vaccinology and Neonatal Immunology, Department of Pediatrics and Pathology-Immunology, Departments of [2]Neonatology and Pediatric Intensive Care, and [3]Pediatrics, Children's Hospital of Geneva, [4]Department of Gynecology and Obstetrics, and [5]Clinical Research Center, University Hospitals of Geneva and Faculty of Medicine, University of Geneva, Switzerland; and [6]BioNet-Asia Co, Ltd, Bangkok, Thailand

N = 335 women ,
2nd or 3rd trimester



Conclusion: Early 2nd trimester immunization significantly increased neonatal pertussis PT and FHA AB

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 66 / No. 2
January 20, 2017

Coverage with Tetanus, Diphtheria, and Acellular Pertussis Vaccine and Influenza Vaccine Among Pregnant Women — Minnesota, March 2013–December 2014

Alexandra Barber, MPH[1]; Miriam Halstead Muscoplat, MPH[1]; Anna Fedorowicz, MPH[1]

TABLE 1. Tdap and influenza vaccination coverage among pregnant women, based on vital records data and immunization records — Minnesota, March 2, 2013–December 31, 2014

Characteristic	Total study population No. (%)	Received Tdap vaccination during pregnancy No. (%)	Received Influenza vaccination during pregnancy No. (%)
Overall	113,730	66,222 (58.2)	52,248 (45.9)

Vaccination Rates

Tdap **58%**

Flu **46%**

UW Medicine

WHO Position Paper 2012: Maternal Immunization

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

25 MAY 2012, 87th YEAR / 25 MAI 2012, 87e ANNÉE
No. 21, 2012, 87, 201–216

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.
- **2019:** Pregnancy is an indication on flu vaccine label in some EU countries

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

Clinical Studies of Maternal Influenza Vaccine Efficacy Bill and Melinda Gates Foundation

EXAMPLE: Three prospective, randomized clinical studies of trivalent inactivated influenza vaccine (TIV) in pregnant women sponsored by Bill & Melinda Gates Foundation conducted in Mali, Nepal, and South Africa, with thousands of pregnant women and their infants enrolled at each site.

Effectiveness of Maternal Influenza Vaccine in Controlled Clinical trials in Nepal, Mali, and South Africa*

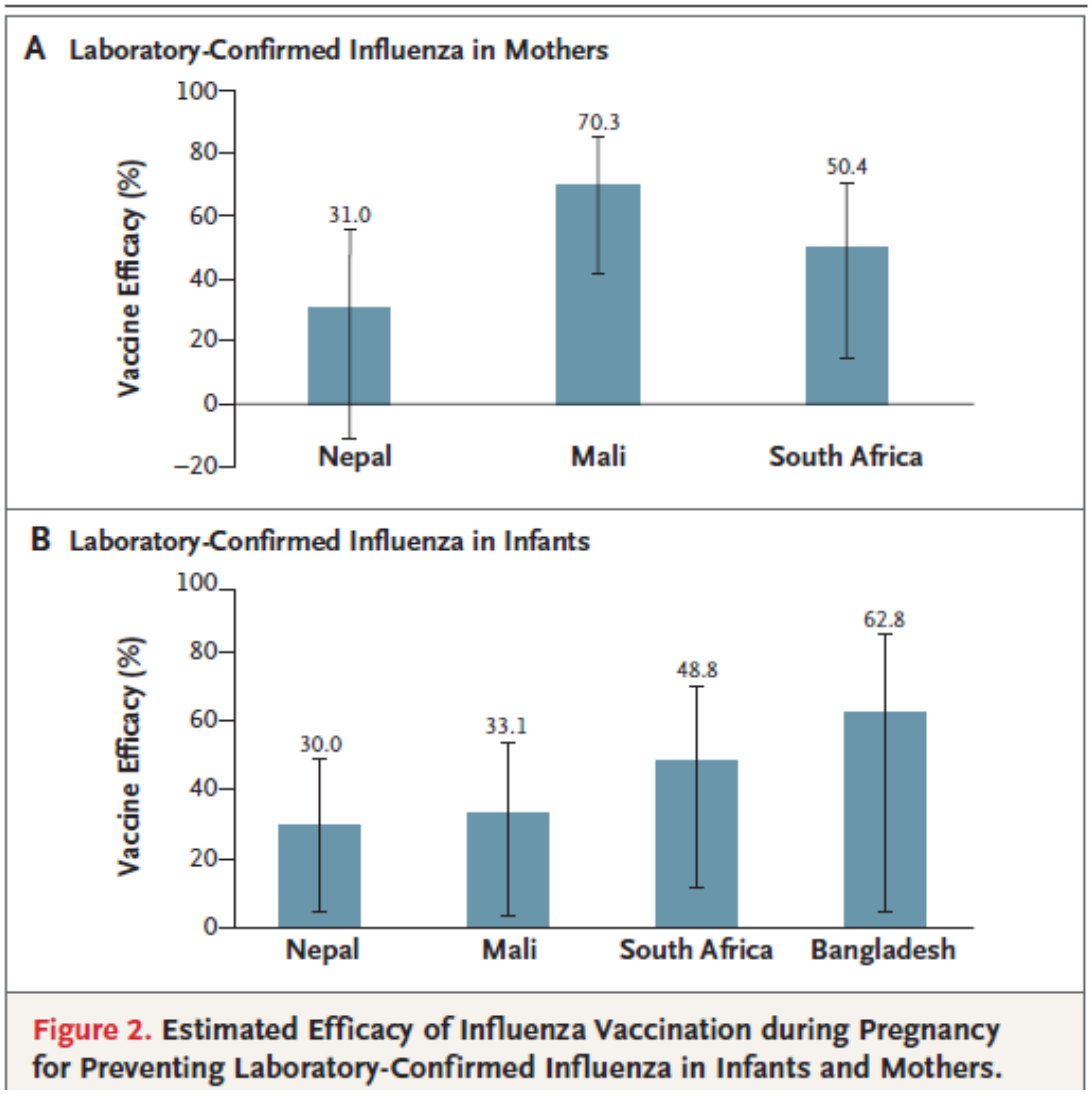


Figure 2. Estimated Efficacy of Influenza Vaccination during Pregnancy for Preventing Laboratory-Confirmed Influenza in Infants and Mothers.

Omer NEJM 2017

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Maternal flu immunization reduces severe pneumonia and may improve newborn growth trajectory

Slide courtesy of A. TerMeulen, Gates Fndn 2018

Reduced all-cause severe pneumonia 25%

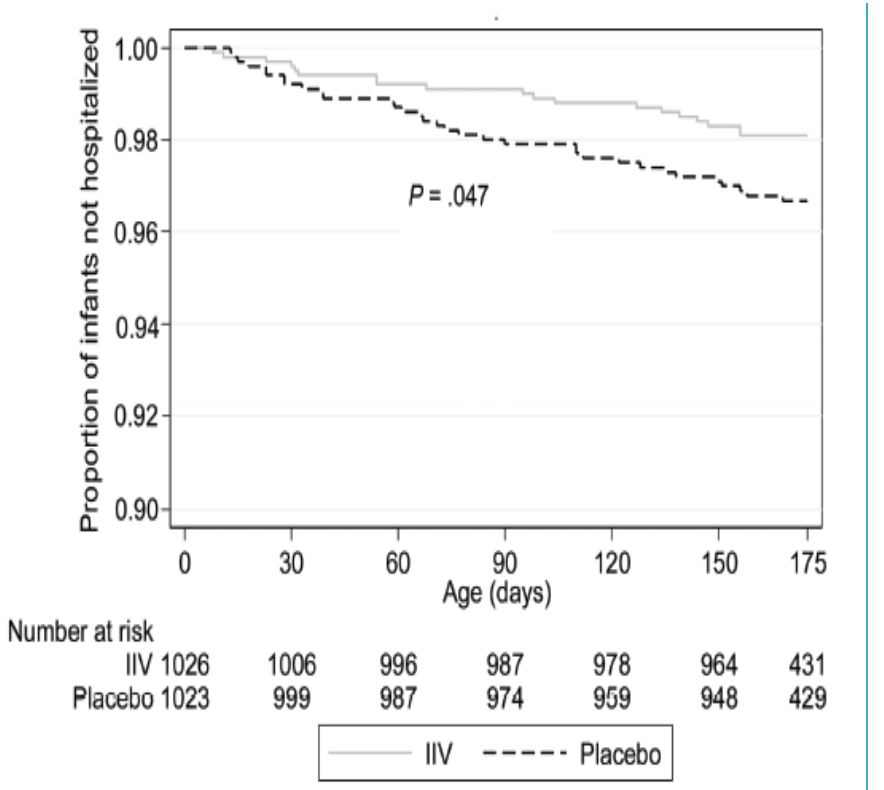
Infants of mothers vaccinated during pregnancy – pooled analysis flu efficacy trials

Reduced severe wasting RR=0.45

Infants of mothers vaccinated with seasonally matched flu strain in Nepal

Improved growth at 16 weeks 12.2 vs. 5.9 centiles

HIV-neg. infants of vaccinated mothers in South Africa

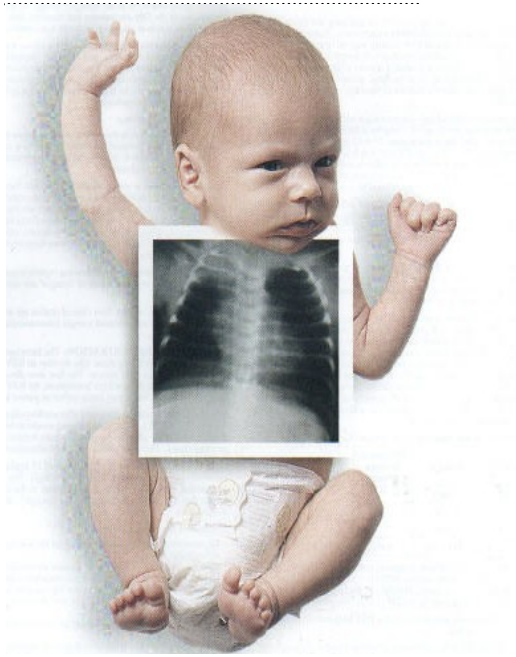


Less pneumonia hospitalization in infants of mothers vaccinated during pregnancy in South Africa

MatFlu Trials Pooled Analysis Working Group, Omer et al PIDJ 2017; Nunes et al. *CID* 2017;65: 1069; Katz J et al. *Vaccine* 2017 ;

Maternal Immunization to Prevent Infant RSV Disease

- Most urgent need for protection against RSV is during first few months of life; >75% of RSV disease hospitalization occurs in full term, healthy infants.
- Efficient RSV-specific IgG transfer from mothers to neonates.
- RSV subunit vaccines in pregnant women show good immunogenicity and lack of reactogenicity (Munoz et al Vaccine 2003).
- US government regulation (FDA): No evidence teratogenicity in animal models (required prior to human trials).



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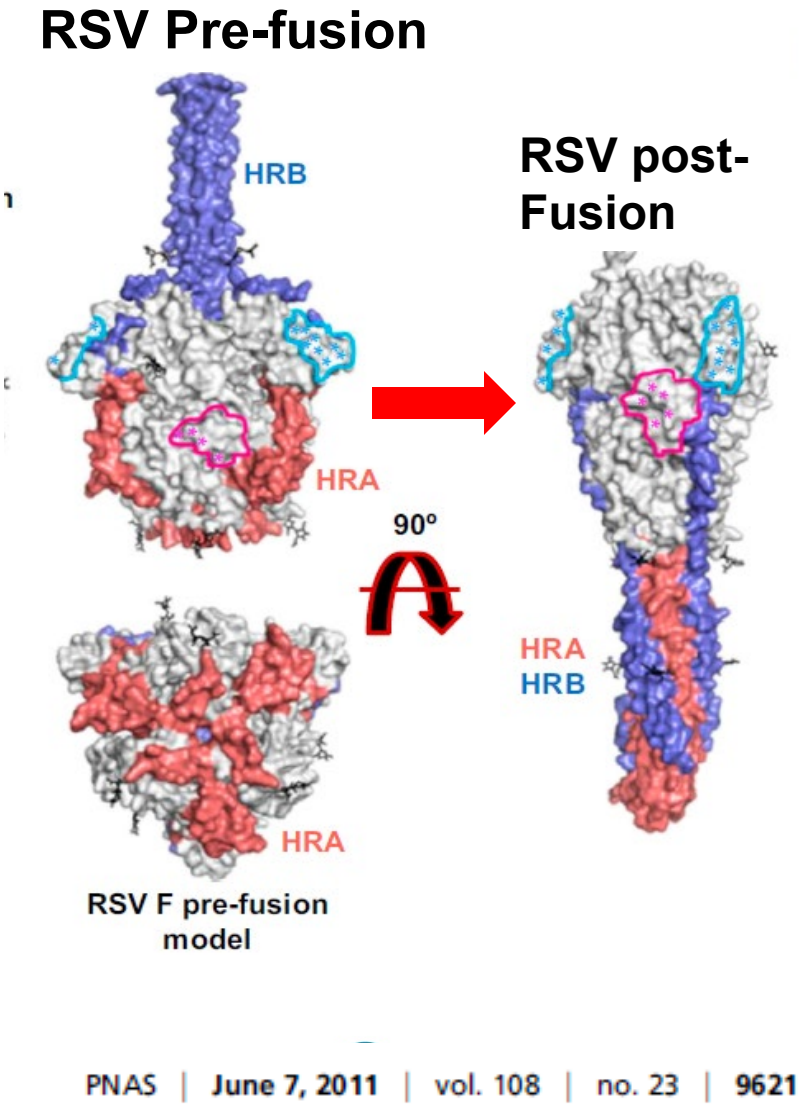
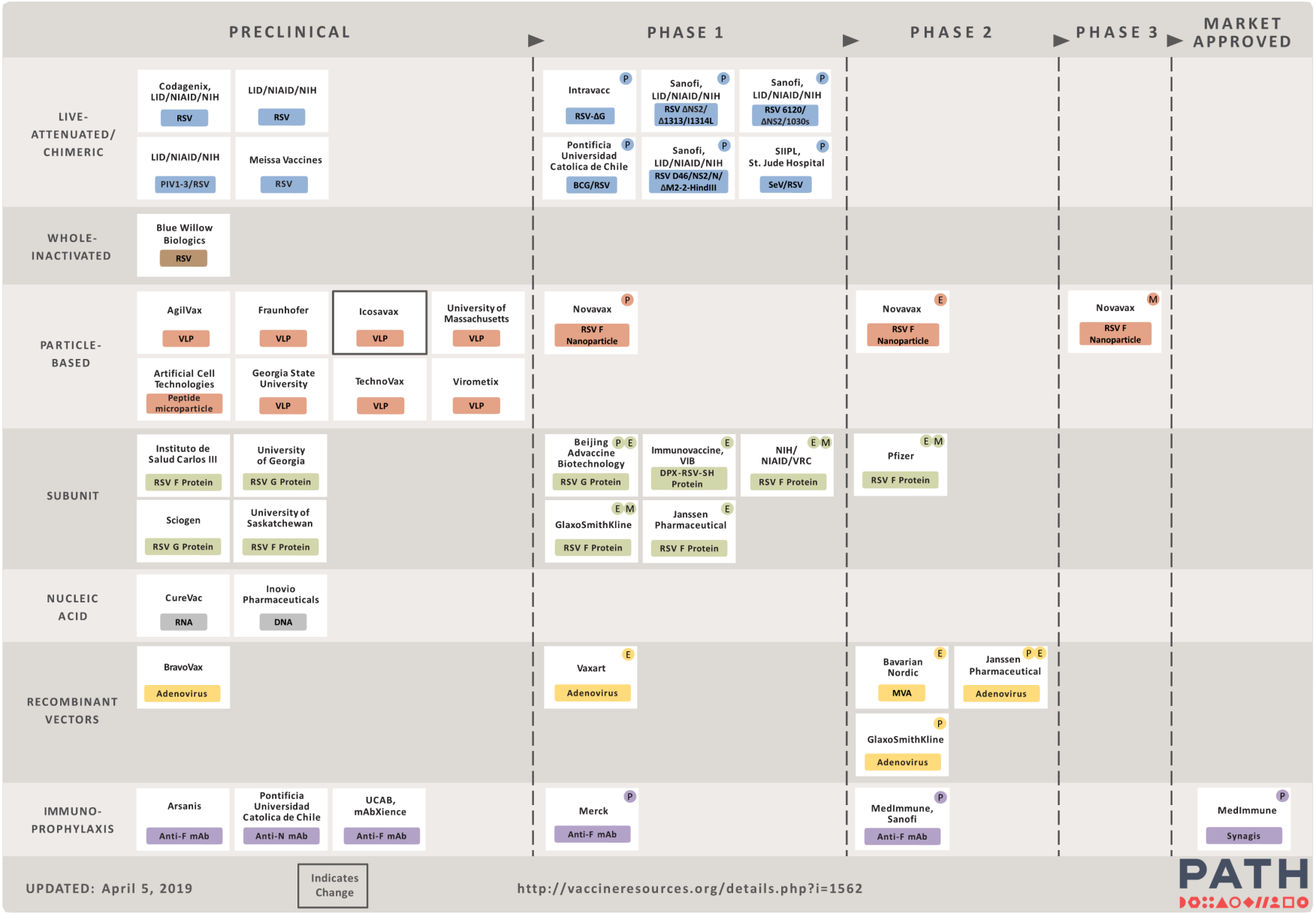
ADVANCES IN RSV F PROTEIN STRUCTURE AND PRODUCTION

- RSV F glycoprotein mediates viral entry into host cells: key structure BREAKTHROUGH described by McLellan et al 2013
- F undergoes a conformational change at cell entry resulting in fusion of viral -cellular membranes (Lamb, 2007)
- Activation of RSV F from pre-fusion state requires vast structural change (Gonzales-Reyes, PNAS 2001)
  - The structure of RSV protein in circulating virus and virus attached to cell surface differs remarkably (Swanson PNAS 2011)
  - Antigenic targets for pre and post fusion also differ



RSV Vaccine and mAb Snapshot 2019 (PATH)

TARGET INDICATION: (P) =PEDIATRIC (M) =MATERNAL (E) =ELDERLY



UPDATED: April 5, 2019

Indicates Change

http://vaccineresources.org/details.php?i=1562

PATH

Humanized RSV Monoclonal Antibody: Palivizumab licensed for RSV prophylaxis

- Proof of principal: RSV F-protein antibody will protect high-risk infants from lower respiratory tract disease
- Approved in USA in 1998 for use in infants and children <2 years of age with chronic lung disease
  and babies born at <35 weeks gestation:
  - Palivizumab (Synagis^{R}; MedImmune,Gaithersburg, MD
  - Administered IM at 15 mg/kg monthly; expensive

- New long acting MAb Medi15887 being studied in clinical trials

INFECTIOUS DISEASE

A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants

Qing Zhu,[1*†] Jason S. McLellan,[2†] Nicole L. Kallewaard,[1] Nancy D. Ulbrandt,[1] Susan Palaszynski,[1] Jing Zhang,[1] Brian Moldt,[1] Anis Khan,[3] Catherine Svabek,[1] Josephine M. McAuliffe,[1] Daniel Wrapp,[2] Nita K. Patel,[1] Kimberly E. Cook,[4] Bettina W. M. Richter,[1] Patricia C. Ryan,[5] Andy Q. Yuan,[4] JoAnn A. Suzich[1*]

CHALLENGES OF MATERNAL RSV IMMUNIZATION

1) Placental transfer of antibody: generalizable to all populations?
   a) Impact of HIV
   b) Impact of maternal IgG
2) Timing of vaccination
3) Inhibition of secondary vaccine (if/when infant vaccines available)
4) Safety – in both mother and baby
5) Efficacy-
   a) requiring large controlled clinical studies in geographical diverse and developing/developed countries
   b) Clinical and laboratory endpoints

NOVAVAX PREPARE Trial Completed: RSV Vaccine in Pregnant Women

Primary Objective:

Efficacy of maternal immunization against medically significant RSV LRTI through 90-180 days of life in infants

Randomized, Observer-Blind, Placebo-Controlled	
Number of Participants	• **4,636** third trimester pregnant women **randomized 2:1 (vaccine:placebo)**
Length of Study Participation	• Mothers: up to 9 months • Infants: 1 year after delivery
Dosing	• 1 intramuscular (IM) Injection of RSV F vaccine or placebo at **28-36 weeks** Estimated Gestational Age (EGA)
Safety Assessment	• Through 6 months post-partum in mothers • Through 1 year in infants
Efficacy Assessment	• **Active/passive surveillance in mothers and infants** • Confirmation of RSV infection by RT-PCR • Medically significant tachypnea or pulse oximetry (infants only) • Confirmation of LRTI (infants only)

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Results of Novavax RSV Maternal Immunization Trial – Presented at ESPID 2019 *

% Efficacy (97.5% CI; 95% CI) for MS RSV LRTI Primary Endpoint only **Placebo/Vaccine**	**Medically Significant LRTI**	**LRTI Hospital-izations**	**LRTI with severe hypox-emia**
Primary and secondary RSV+ with site data through 90 Days	**39.4** (-1, 63.7)[1] (5.3, 61.2)[2] 35/1430; 42/2765	**44.4** (19.6, 61.50) 53/1430, 57/2765	**48.3** (-8.2, 75.3) 14/1430, 14/2765

ESPID Presentation, May 2019
Munoz et al

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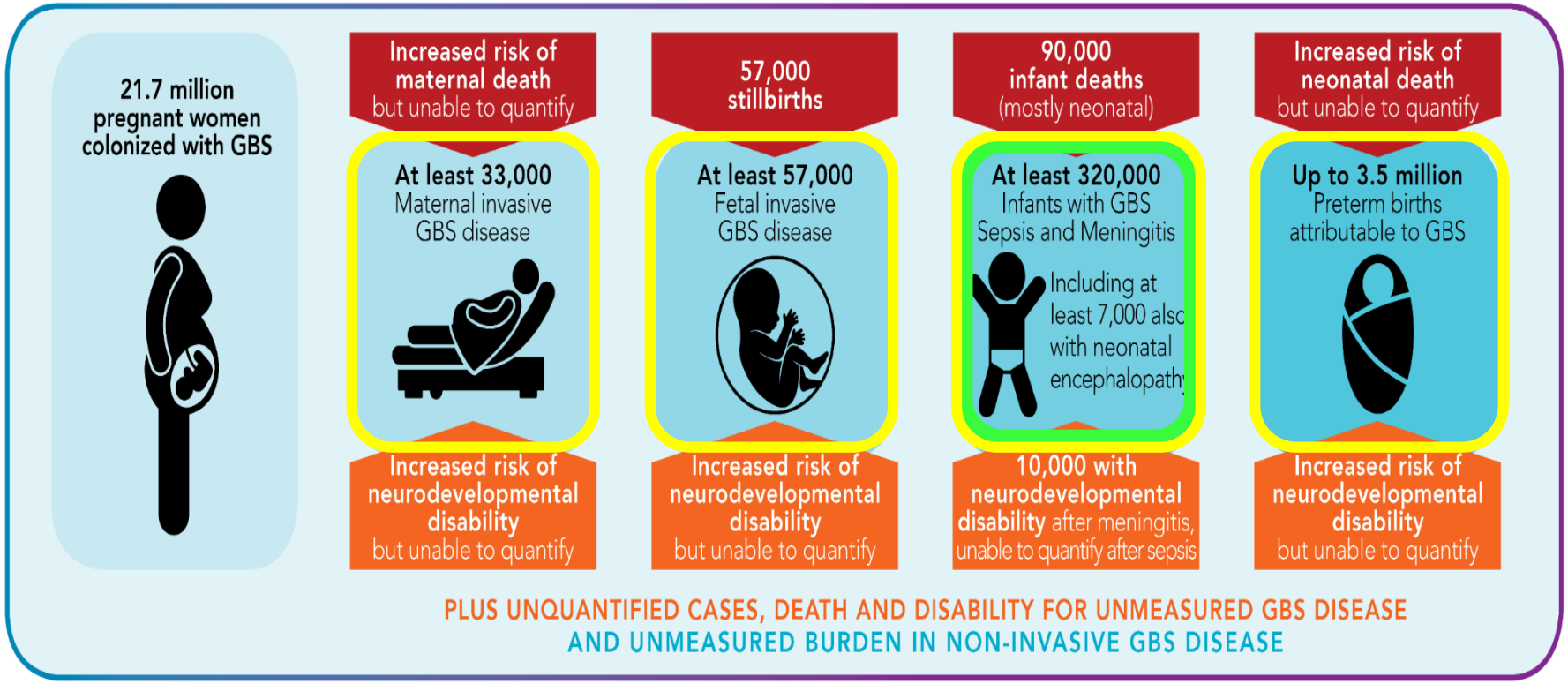
WHAT ABOUT A MATERNAL GBS VACCINE?



Seale AC et al Clinical Infectious Diseases. 2017;65(S2):S200-19

Slide from A. TerMeulen, BMG Fndn

1. Higher impact than IAP as affects more outcomes
2. Higher coverage especially in challenging settings → more equitable than IAP
3. Leverage existing programmatic platforms (e.g. antenatal care)
4. Reduce antibiotic exposure (21.7 million women)

Could be prevented by IAP

Could be prevented by maternal vx

Group B streptococcus vaccination in pregnant women with or without HIV in Africa: a non-randomised phase 2, open-label, multicentre trial

Robert S Heyderman, Shabir A Madhi, Neil French, Clare Cutland, Bagrey Ngwira, Doris Kayambo, Robert Mboizi, Anthonet Koen, Lisa Jose, Morounfolu Olugbosi, Frederik Wittke, Karen Slobod, Peter M Dull

Lancet Infect Dis 2016; 16: 546–55

- Multivalent conjugate GBS vaccine to serotypes 1A, 1B, and III administered to pregnant women in Malawi and South Africa
- GBS vaccine was safe and immunogenic in these women
- Vaccine was less immunogenic in HIV-infected women
- GMT of overall transfer of maternal antibody to infant in HIV-negative women varied from 2.67-3.91ug ml for various GBS subtypes but was lower at 1.52-2.62 ug/ml in HIV-infected women.

What vaccines have priority for maternal vaccination?

- RSV fusion protein vaccine: First large study under analysis; newer RSV vaccine candidates to start
- Group B Streptococcal vaccine: First study sponsored by Novartis completed in South Africa; company upheaval

- Meningitis vaccines: MenAfrivac given to pregnant women in Africa
- Acellular pertussis vaccine - Monovalent vs polyvalent?
- Herpes simplex virus
- Hepatitis E vaccine
- Pneumococcal vaccine – conjugate, polysaccharide
- Pre-pregnancy vs pregnancy: Cytomegalovirus, Zika, Ebola?

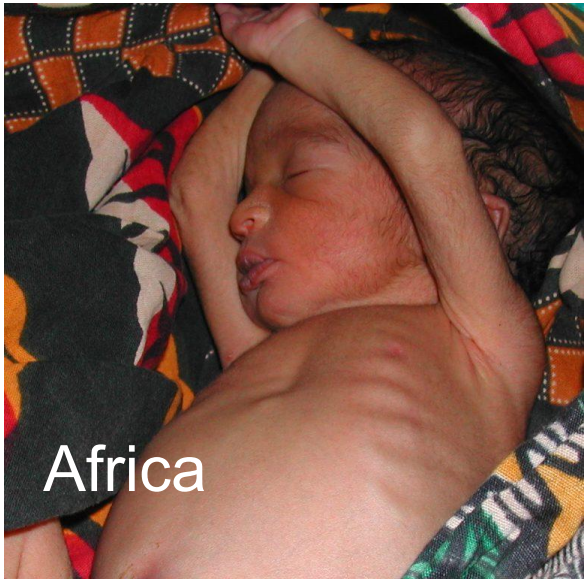
POTENTIAL OBSTACLES FOR MATERNAL IMMUNIZATION

- 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

Legal Liability for Vaccine Manufacturers

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

OUR GOAL: HEALTHY MOTHERS, HEALTHY BABIES



Acknowledgements:

- H. Chu, MD, L. Eckert, MD, and J. Kuypers PhD- Univ. Washington
- K. Neuzil, MD, MPH , Univ. Maryland
- F. Munoz, MD, P. Piedra, 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
- ClaireAnne Siegrist- enthusiast for maternal immunization

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

DIPHTHERIA: A fatal disease in the early 1900's

Gunnar and Balto

Iditarod Dog Sled Race

- Diphtheria causes respiratory disease due to blockage of throat with thick secretions that make breathing difficult / impossible
- Treatment in 1920's was antitoxin
- Alaska outbreak with shortage of antitoxin – 2 children died in 1925
- Balto and Gunnar Kaasen delivered antitoxin to Nome (now the Iditarod sled race.
- Vaccine introduction in 1950's given to both children and pregnant women

http://www.cdc.gov/features/diphtheria/diphtheria_b200px.jpg

OTHER POTENTIAL PATHOGENS: What has priority?

- Group B Streptococcal vaccines: Study sponsored by Novartis completed in South Africa
- Acellular pertussis vaccines: under exploration with Gates Fndn
- Herpes Simplex virus
- Meningococcal vaccine
- Pneumococcal vaccine – conjugate?
- Cytomegalovirus ? – perhaps pre-pregnancy

Efficacy of Maternal Flu Vx Immunization: Dependent on match to circulating viruses, Nepal*

	Vx Efficacy Cohort 1 (p value)	Vx Efficacy Cohort 2 (p value)	Vx Efficacy Cohorts 1 & 2 (p value)
Maternal +ILI	7.4% (0.497)	33% (0.02)	17% (0.05)
Maternal + flu overall	**42% (0.07)**	-8% (0.84)	27% (0.18)
Infant lab - confirmed flu	12% (0.47)	**60% (<0.01)**	**28% (0.03)**

* Steinhoff et al, IDWeek 2015. Open Forum ID 2 (suppl 1): doi:10.1093/ofid/ofv133.1445

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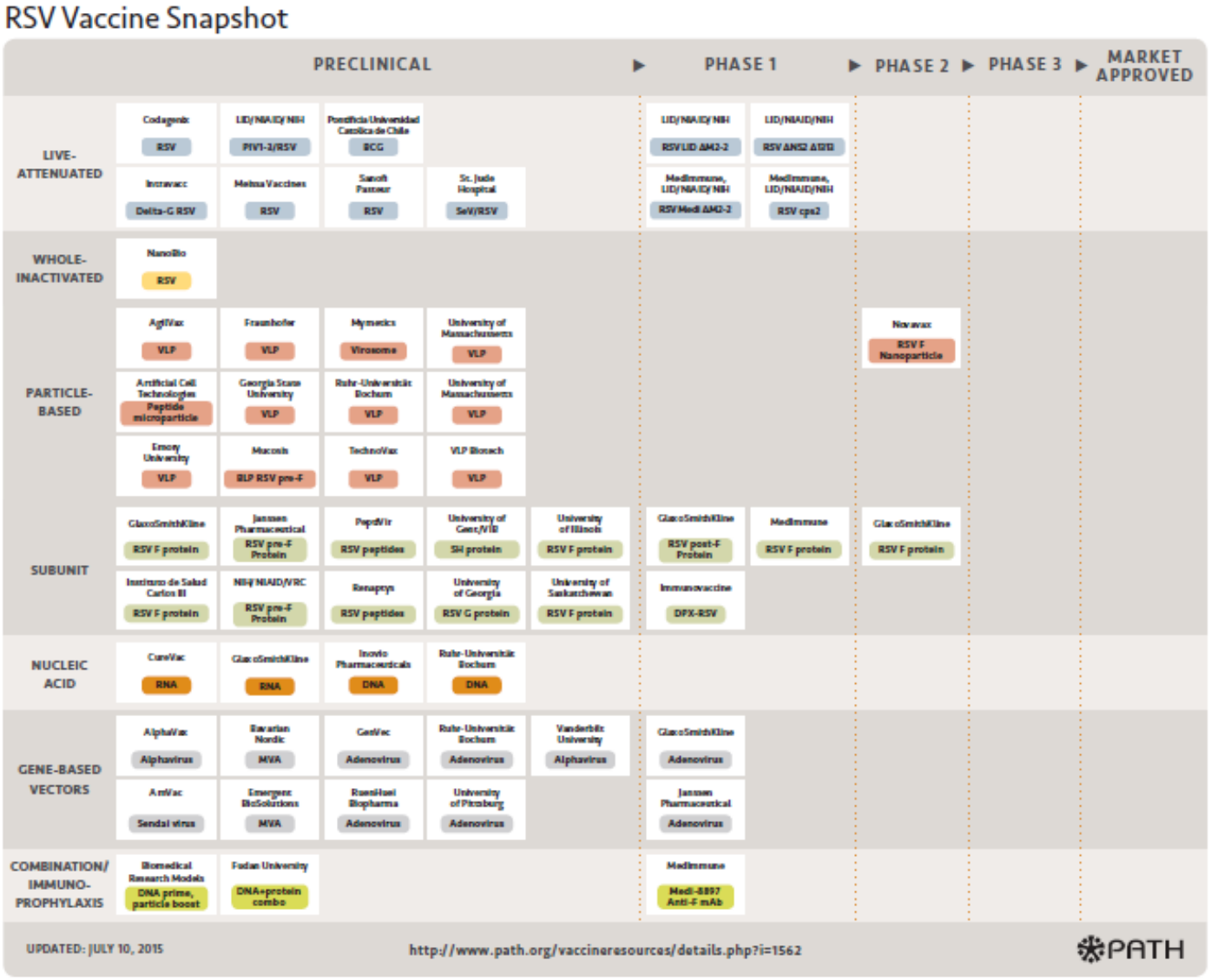
UPDATE ON POTENTIAL RSV VACCINES*

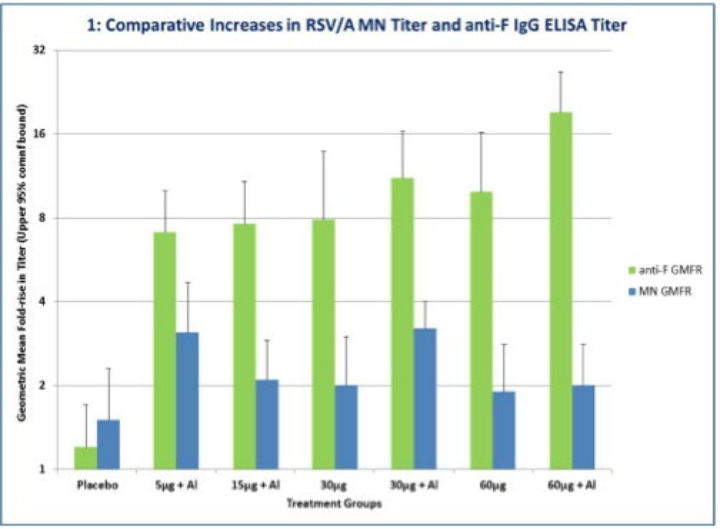
2015 RSV Vaccine Update by PATH:
62 candidates



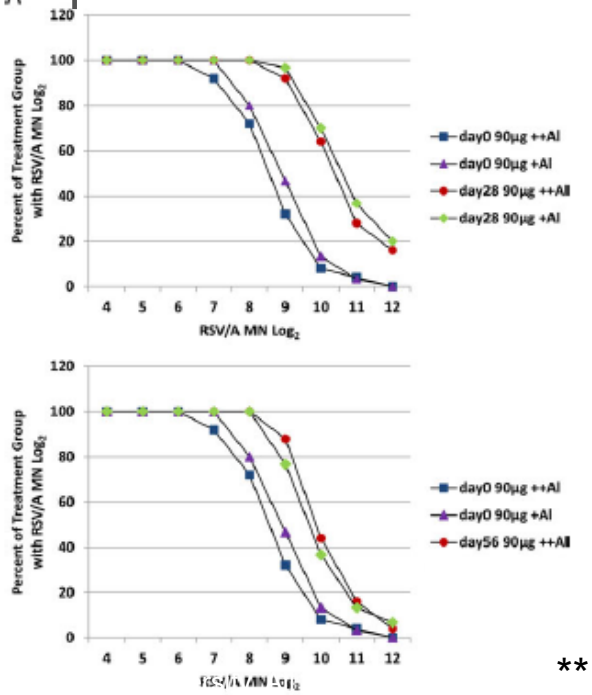
*http://sites.path.org/vaccinedevelopment/files/2014/07/RSV-Vaccine-Snapshot_8July2015.pdf

RSV F Nanoparticle Vaccine Currently in Clinical Trials – Novavax*

- Developed by Novavax (Gaithersburg, MD)
- Engineered RSV postfusion F protein expressed in baculovirus forms nanoparticles
- Preclinical studies in cotton rats showed protection against RSV
- Phase I studies in healthy adults (men) completed*
- Phase II placebo-controlled studies in 330 women of childbearing age and ~50 pregnant women completed



*Vaccine 2013



** JID 2016

*Glenn GM et al Vaccine 2013 31: 524
** Glenn GM et al JID 2016 213; 411

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Vaccines Against Respiratory Syncytial Virus: The Time Has Come

Janet A. Englund[1,2] and Helen Y. Chu[2]

[1]Seattle Children's Research Institute, and [2]University of Washington, Seattle

What is this thing we call immunity?
Does it exist for ills from RSV?
Caroline Breese Hall, 1939–2012

J. Infect Dis.: 2016, In press.

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Impact of Influenza B circulating strains and match to Vaccine in Immunized Pregnant Women- Nepal

Summary of Influenza circulation, immunization dates, and vaccine status
Mothers and Infants Nepal 2011-2014

Number of influenza detections/month by vaccine for each influenza subtype

Efficacy of Maternal Flu Vx Immunization: Variation by match to circulating viruses, Nepal*

	Vx Efficacy Cohort 1 (P value)	Vx Efficacy Cohort 2 (P value)	Vx Efficacy Cohorts 1 & 2 (P value)
Maternal lab-confirmed flu	42% (0.068)	-8% (0.841)	26.6% (0.186)
Maternal ILI	7.4% (0.497)	**32.8% (0.017)**	26.6% (0.052)
Infant lab - confirmed flu	11.8 % (0.474)	**59.9% (0.002)**	**28.2% (0.027)**

•Steinhoff et al, IDWeek, 2015

THREE MATERNAL FLU VACCINE TRIALS
(Omer et al 2015 Vaccine)

	South Africa	Mali	Nepal
Design	Randomized, double-blind, placebo-controlled trial, HIV uninfected and a second HIV infected trial	Randomized, controlled with mening vaccine, observer-blind trial	Randomized, placebo-controlled, community-based trial
Enrollment	20-36 wks gest.	3rd Trimester	17-34 wks gest., year round
Primary Objectives	Determine TIV efficacy in pregnant women against lab+ flu, and infants up to 24 wks; evaluate immunogenicity of TIV	Compare lab+ flu in infants thru 6 M born to mothers receiving TIV vs mening vx	Compare incidence of lab+flu in infants thru 6 M, and ILI in women receiving TIV vs placebo; compare incidence of LBW
Maternal Mortality	400 per 100,000 live births (adjusted)	540 per 100,000 live births (adj.	280 per 100,000 live births (adj.)
Infant Mortality	50 per 1000	27 per 1000	19 per 1000

South Africa: Maternal Immunization with Influenza Vaccine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

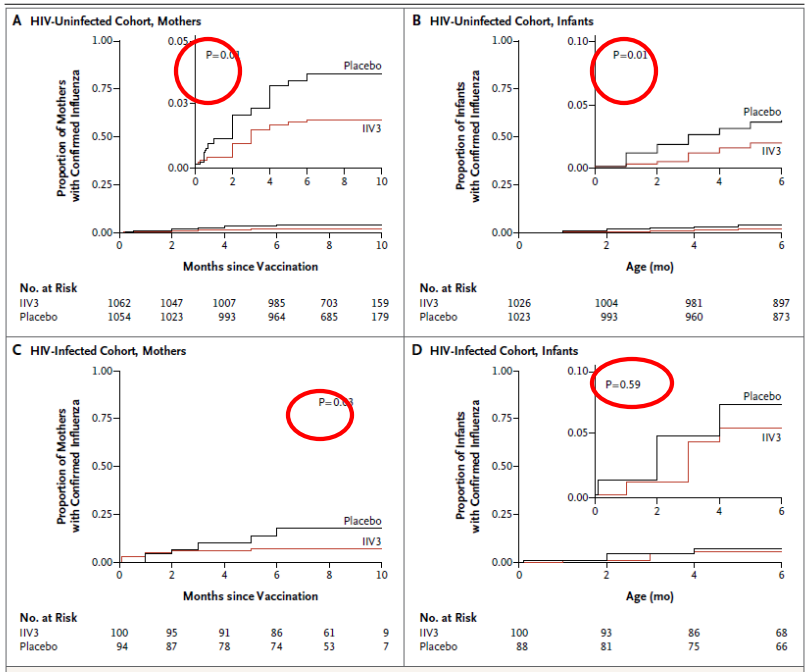

Figure 1. Kaplan–Meier Estimates of Percentages of Confirmed Cases of Influenza According to Cohort and Study Group.
Confirmed influenza was defined as influenza diagnosed by means of reverse-transcriptase–polymerase-chain-reaction assay. The insets show the same data on an expanded y axis. HIV denotes human immunodeficiency virus, and IIV3 trivalent inactivated influenza vaccine.

CONCLUSIONS

Influenza vaccine was immunogenic in HIV-uninfected and HIV-infected pregnant women and provided partial protection against confirmed influenza in both groups of women and in infants who were not exposed to HIV. (Funded by the Bill and Melinda Gates Foundation and others; ClinicalTrials.gov numbers, NCT01306669 and NCT01306682.)

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MALI: Maternal Flu Vaccine Effective in Mothers and their Infants

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 Schlueterman, Andrea Buchwald, Karen L Kotloff, Wilbur H Chen, Evan W Orenstein, Lauren A V Orenstein, Julie Villanueva, Joseph Bresee, John Treanor, Myron M Levine

Comparison of maternal TIV vs meningoococcal conjugate vaccine.

	Women				Vaccine efficacy (95% CI)	Infants				Vaccine efficacy (95% CI)
	TIIV group (n=2108)	Incidence per 1000 person-days of follow-up	MCV group (n=2085)	Incidence per 1000 person-days of follow-up		TIIV group (n=2064)	Incidence per 1000 person-days of follow-up	MCV group (n=2041)	Incidence per 1000 person-days of follow-up	
Type A	7	0·03	25	0·09	72·0% (35·2 to 87·9)	17	0·06	48	0·17	64·5% (38·3 to 79·6)
H3N2	4	0·01	7	0·03	42·8% (−95·4 to 83·3)	10	0·04	27	0·10	62·9% (23·4 to 82·0)
H1N1	3	0·01	18	0·06	83·3% (43·4 to 95·1)	7	0·02	21	0·07	66·6% (21·5 to 85·8)
Type B	4	0·01	15	0·05	73·3% (19·6 to 91·1)	8	0·03	10	0·04	19·9% (−103·0 to 68·4)

TIIV=trivalent inactivated influenza vaccine. MCV=quadrivalent meningococcal conjugate vaccine.

Table 3: Number of cases of influenza and influenza vaccine efficacy against first episodes of laboratory-confirmed influenza by type in women and their infants up to 5 months of age

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NEPAL MATERNAL IMMUNIZATION STUDY: YEAR ROUND VACCINATION

Flu Vaccines used in Nepal Field Trial, 2010-2013

Vaccine Formulation	Vaccine Strains (a)			Lot No.	Date Used	Cohort	
	A/H3N2	A/H1N1	B				
Northern 2010-2011	Perth	California	Brisbane(V)	G7142	25 Apr 2011 to 29 Jul 2011	1	Vaccine 1
Southern 2011	Perth	California	Brisbane(V)	H9100	7 Aug2 011 to 30 Dec 2011	1	
Northern 2011-2012	Perth	California	Brisbane(V)	H7099-1	1 Jan 2012 to 31 May 2012	1 through April 24 2012, then Cohort 2	
				H7116-2	1 Jun 2012 to 29 Jun 2012	2	
Southern 2012	Perth	California	Brisbane(V)	J70265-1	1 Jul 2012 to 15 Oct 2012	2	
Northern 2012-2013	Victoria	California	Wisconsin(Y)	J7186-1	15 Oct 2012 to 30 Dec 2012	2	Vaccine 2
Southern 2013	Victoria	California	Wisconsin(Y)	J7154-4	30 Dec 2012 to 27 Jan 2013	2	
				J7217-1	27 Jan 2013 to 21 May 2013	2	
				K7021-3	21 May 2013 to 3 Sep 2013	2	
				K2009-3	3 Sep 2013 to 9 Sep 2013	2	

(a) Sanofi Pasteur Vaxigrip®

Birth Weight Following Maternal Flu Vaccination, Nepal Trial*

	Cohort 1		Cohort 2		Cohorts 1 & 2	
	Placebo	**VX**	**Placebo**	**VX**	**Placebo**	**VX**
Birth Wt gm (SD)	2741 (463)	2770 (441)	2790 (442)	2852 (459)	2762 (456)	2804 (450)
	RR Cohort 1 (95%CI)		**RR Cohort 2 (95%CI)**		**RR Cohorts 1 & 2 (95%CI)**	
Birth Wt (RR): babies born to immunized vs placebo mothers	28·9 (-15·6, 73·5) p=0·203		**62·0 (10·0, 113·9) p=0·01**		**42·1 (8·2, 76·0) p=0·015**	

* Presented by Steinhoff et al, IDWeek, 2015

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

World Health Organization

Organisation mondiale de la Santé

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.

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

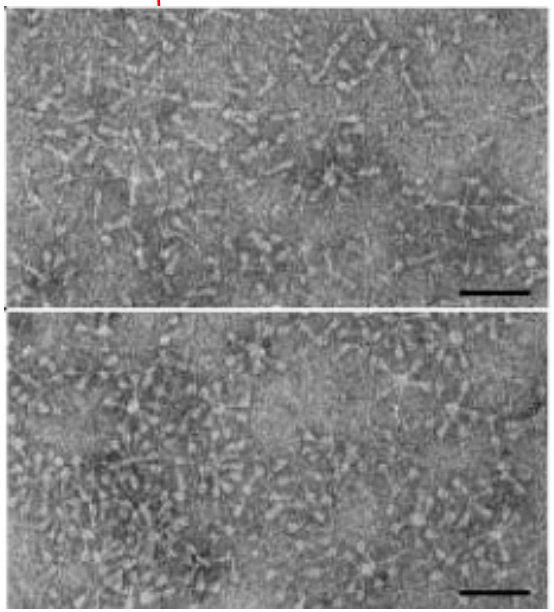
May 2012

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

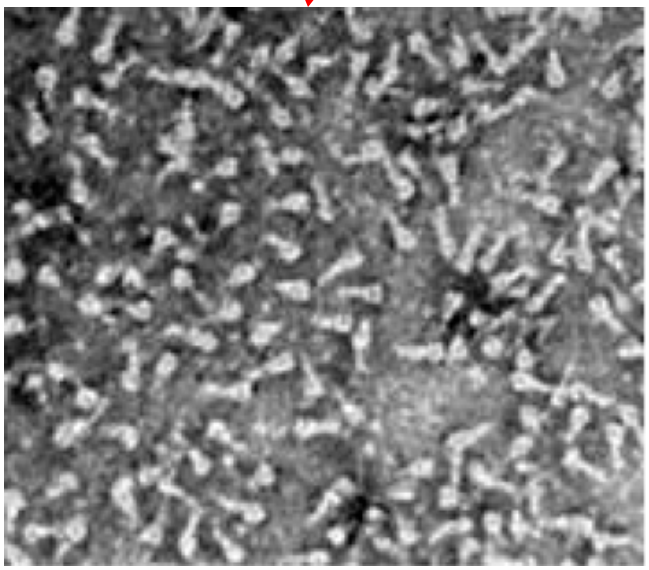
- Pregnant women represent the most important risk group for receipt of inactivated seasonal influenza vaccine.
- The priority accord to pregnant women was based on “compelling evidence of substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe and effective 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.

RSV Pre-Fusion and Post-Fusion F by Electron Microscopy

Prefusion RSV “lollipop”*



Postfusion RSV F “crutch***:



* Ruiz-Arguello MB et al , J Gen Vir 2004;85:3677

***Swanson Et al PNAS 2011; 108:9619-9624; supplemental figures at:
http://www.pnas.org/content/suppl/2011/05/17/1106536108.DCSupplemental

AAC
Journals.ASM.org

A Novel Investigational Fc-Modified Humanized Monoclonal Antibody, Motavizumab-YTE, Has an Extended Half-Life in Healthy Adults

Gabriel J. Robbie,[a] Ryan Criste,[a] William F. Dall'Acqua,[b] Kathryn Jensen,[c] Nita K. Patel,[d] Genevieve A. Losonsky,[e] M. Pamela Griffin[e]

Clinical Pharmacology and DMPK,[a] Antibody Discovery and Protein Engineering,[b] Biostatistics,[c] Research and Development, Infectious Disease,[d] and Clinical Research and Development,[e] MedImmune, Gaithersburg, Maryland, USA

The study objective was to evaluate the pharmacokinetics (PK), antidrug antibody (ADA), and safety of motavizumab-YTE (motavizumab with amino acid substitutions M252Y/S254T/T256E [YTE]), an Fc-modified anti-respiratory syncytial virus (RSV) monoclonal antibody. Healthy adults ($n = 31$) were randomized to receive a single intravenous (i.v.) dose of motavizumab-YTE or motavizumab (0.3, 3, 15, or 30 mg/kg) and followed for 240 days. Clearance of motavizumab-YTE was significantly lower (71% to 86%) and the half-life ($t_{1/2}$) was 2- to 4-fold longer than with motavizumab. However, similar peak concentrations and volume-of-distribution values, indicative of similar distribution properties, were seen at all dose levels. The

December 2013 Volume 57 Number 12 Antimicrobial Agents and Chemotherapy p. 6147–6153

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

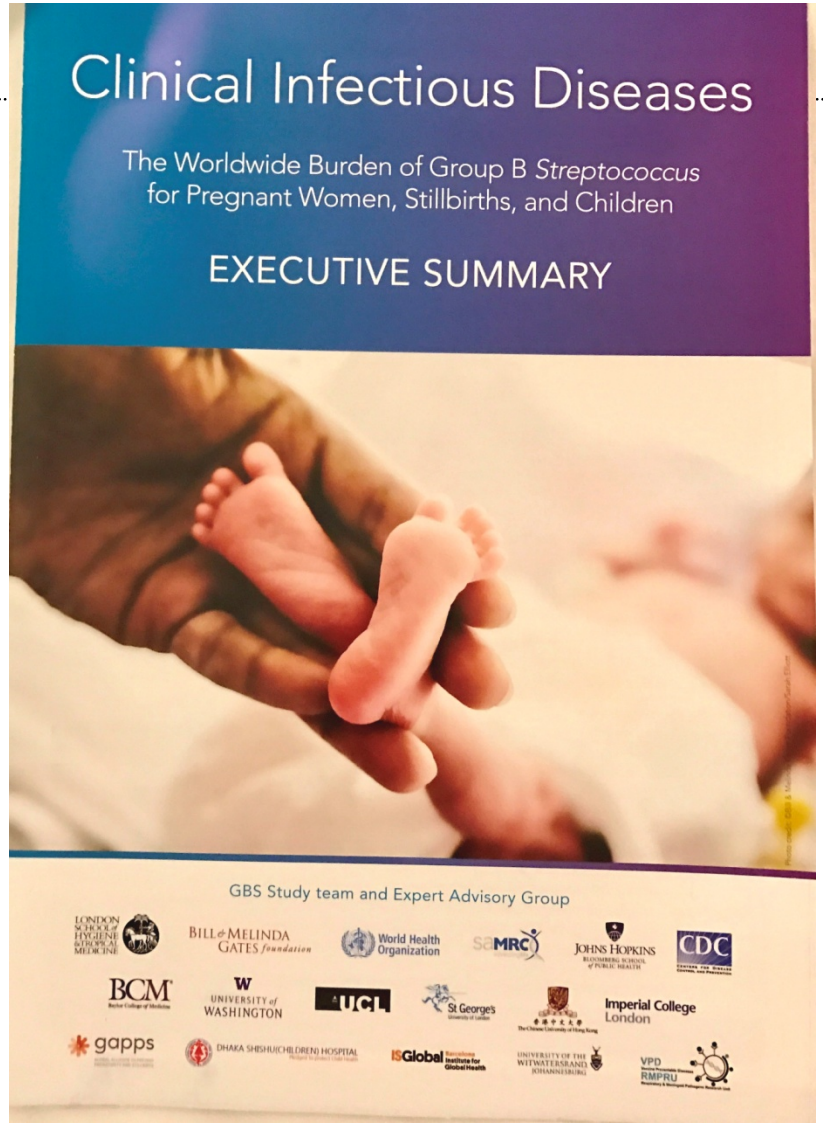
Arm	Group	N	Single dose administered to pregnant women with crossover design	
			Antepartum	Postpartum
Inter-vention	1	32	Tdap	Saline
Control	2	16	Saline	Tdap
Control	3	32	Single dose Tdap administered to non-pregnant women	

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

Who Could Benefit From What Vaccine?

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

Increased information regarding GBS in pregnant women and children - CID 2018 Supplement



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Bangladesh: Maternal Immunization with Influenza Vaccine Protects Mothers and Babies*

The NEW ENGLAND JOURNAL of MEDICINE
VOL. 348 NO. 12

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)

Babies born to mothers who received TIV

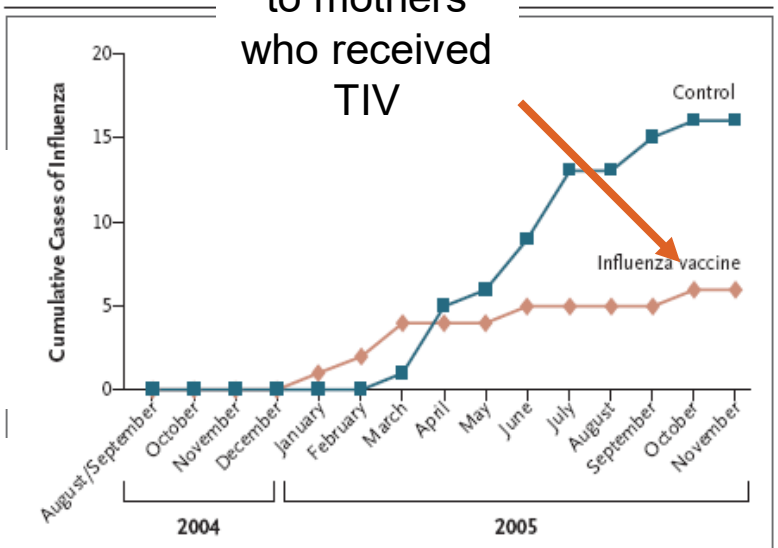


Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.
Testing for influenza antigen was performed from December 2004 to November 2005.

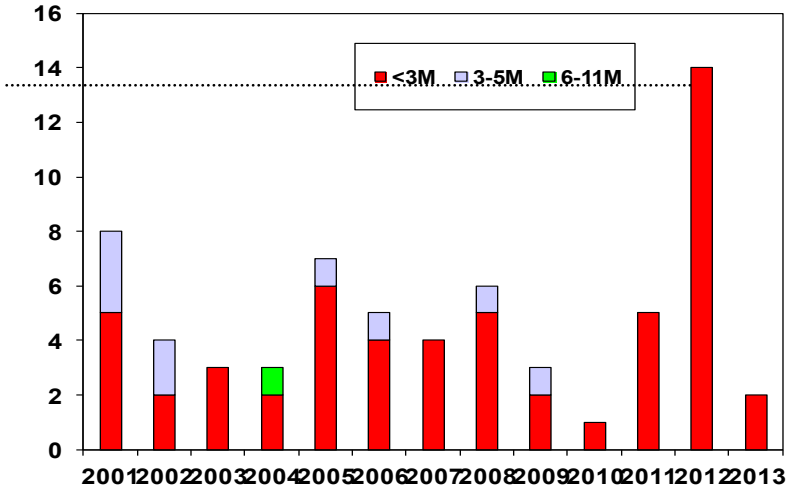
*Zaman et al, NEJM 2008;359

Effectiveness of maternal pertussis vaccination in England: an observational study

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

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

- UK: Oct. 2012: Immunization of pregnant women started using TdapIPV; vaccine coverage in first year = 64%
- Vaccine effectiveness in infants based on cases of disease in babies in first 2-3 months of life.



Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis

Clinical Infectious Diseases® 2017;64(1):3–8

Kathleen Winter,[1,2] Steve Nickell,[1] Michael Powell,[1] and Kathleen Harriman[1]

Table 5. Vaccine Effectiveness Estimates Compared With Postpartum Administration[a]

	Pertussis at Age <8 wk	
Timing of Prenatal Tdap	Adjusted VE (95% CI), %	Infants With Pertussis, No.
27–36 wk gestation	85.4 (33.0–96.7)	18
Any time during pregnancy	63.8 (10.6–85.4)	23

Maternal Influenza Immunization and Prevention of Severe Clinical Pneumonia in Young Infants

Analysis of Randomized Controlled Trials Conducted in Nepal, Mali and South Africa

Omer et al.

Pediatr Infect Dis J 2018;37:436–440

Int J Gynecol Obstet 2018; 140: 65–72

Impact of maternal vaccination timing and influenza virus circulation on birth outcomes in rural Nepal

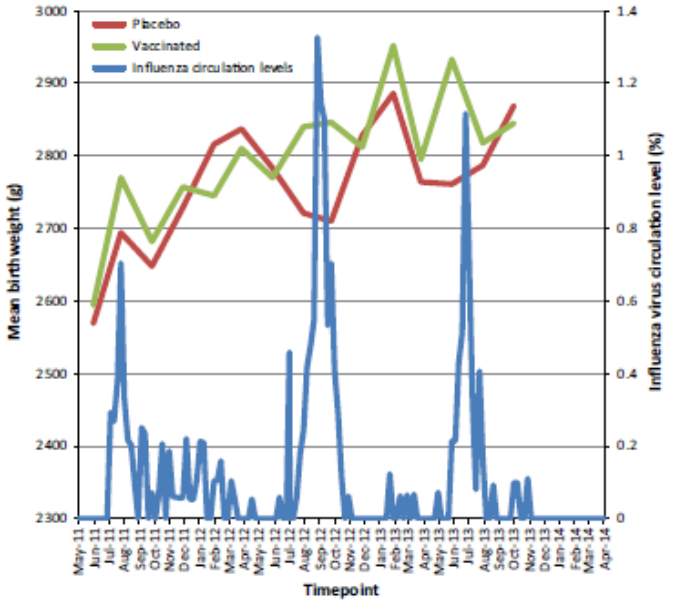


FIGURE 1 Mean birth weight in relation to influenza virus

Timing of Tdap During Pregnancy: Earlier is Better !

Clin Inf Dis 2016

1. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis

Christiane S. Eberhardt,[1,2] Geraldine Blanchard-Rohner,[3] Barbara Lemaître,[1] Meriem Boukrid,[4] Christophe Combescure,[5] Véronique Othenin-Girard,[4] Antonina Chilin,[4] Jean Petre,[6] Begoña Martinez de Tejada,[4] and Claire-Anne Siegrist[1,3]

[1]Center for Vaccinology and Neonatal Immunology, Department of Pediatrics and Pathology-Immunology, Departments of [2]Neonatology of Geneva, [4]Department of Gynecology and Obstetrics, and [5]Clinical Research Center, University Hospitals of Geneva and Faculty of M Ltd, Bangkok, Thailand

N = 335 women , 2nd or 3rd trimester

2. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – A prospective study

Bahaa Abu Raya[a,b,*,1], Isaac Srugo[a,b,c,1], Aharon Kessel[b,d], Michael Peterman[b,c], David Bader[b,e], Ron Gonen[b,f], Ellen Bamberger[b,c]

[a] Department of Pediatrics, Bnai Zion Medical Center, Golomb St. 47, Haifa 31048, Israel
[b] The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Efron St. 1, Haifa 31096, Israel
[c] Clinical Microbiology Laboratory, Bnai Zion Medical Center, Golomb St. 47, Haifa 31048, Israel

N = 61 immunized women/cords

Vaccine 32 (2014) 5787–5793

3. **The optimal gestation for pertussis vaccination during pregnancy - A prospective cohort study**

Madison A. NAIDU[a], Ms Ruth MULJADI[b], Miranda L. DAVIES-TUCK[ab], Euan M. WALLACE[abc], Michelle L. GILES[ac].

[a] Department of Obstetrics and Gynaecology, Monash University, Melbourne, Victoria, Australia

N = 109 immunized mat/cord prs

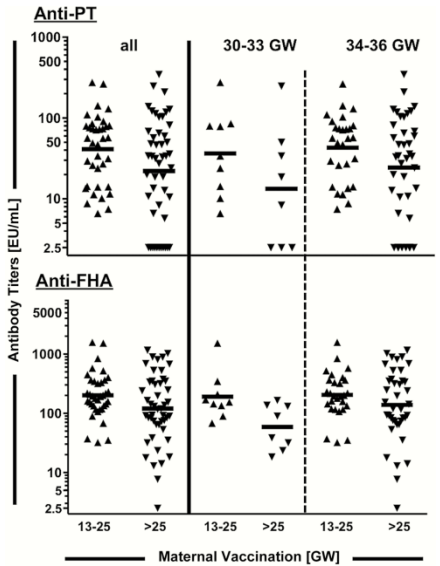
Am J Ob Gyn 2016

Clinical Infectious Diseases® 2017;64(8):1129–32

4. Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization

Christiane S. Eberhardt,[1,2] Geraldine Blanchard-Rohner,[3] Barbara Lemaître,[1] Christophe Combescure,[4] Véronique Othenin-Girard,[5] Antonina Chilin,[5] Jean Petre,[6] Begoña Martinez de Tejada,[5] and Claire-Anne Siegrist[1,3]

Optimal time to immunize preterm infants is 2nd trimester (85 mat/cord pairs)



Maternal Immunization Studies Sponsored by Gates Foundation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

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, Fianon Cissoko, Awa Traoré, Adama Mamby Keita, Fadima Cheick Haidara, Fatoumata Diallo, Moussa Doumbia, Doh Sanogo, Ellen DeMatt, Nicholas H Schluterman, Andrea Burchwald, Karen L Kotloff, Wilbur H Chen, Evan W Orenstein, Lauren A V Orenstein, Julie Villanueva, Joseph Bresee, John Treanor, Myron M Levine

THELANCETID-D-16-01105R3

S1473-3099(17)30252-9

Embargo: May 15, 2017—23:30 (BST)

This version saved: 14:55, 12-May-17

Funded by Bill Gates Foundation/ GOLD OA XX XX

Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial

Mark C Steinhoff, Joanne Katz, Janet A Englund, Subarna K Khatry, Laxman Shrestha, Jane Kuypers, Laveta Stewart, Luke C Mullany, Helen Y Chu, Steven C LeClerq, Naoko Kozuki, Monica McNeal, Adriana M Reedy, James M Tielsch

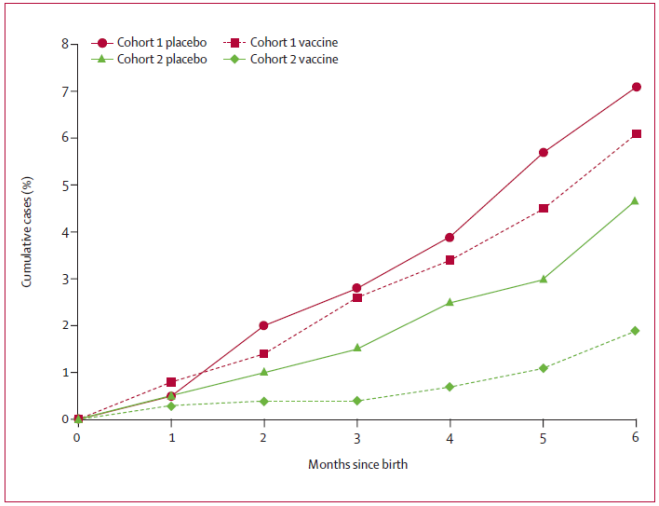


Figure 2: Laboratory-confirmed influenza in infants in cohort 1 and cohort 2

MONOCLONAL AB: ANOTHER STRATEGIES FOR RSV

INFECTIOUS DISEASE

A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants

Qing Zhu,[1*†] Jason S. McLellan,[2†] Nicole L. Kallewaard,[1] Nancy D. Ulbrandt,[1] Susan Palaszynski,[1] Jing Zhang,[1] Brian Moldt,[1] Anis Khan,[3] Catherine Svabek,[1] Josephine M. McAuliffe,[1] Daniel Wrapp,[2] Nita K. Patel,[1] Kimberly E. Cook,[4] Bettina W. M. Richter,[1] Patricia C. Ryan,[5] Andy Q. Yuan,[4] JoAnn A. Suzich[1*]

Zhu *et al.*, *Sci. Transl. Med.* **9**, eaaj1928 (2017) 3 May 2017

MEDI8897 was optimized from antibody targeting the prefusion conformation of RSV F protein, and confirmed by crystallographic analysis of Fab. Has > 50-fold higher activity than PVZ

Safety, Tolerability, and Pharmacokinetics of MEDI8897, the Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody with an Extended Half-Life, in Healthy Adults

M. Pamela Griffin,[a] Anis A. Khan,[a] Mark T. Esser,[a] Kathryn Jensen,[a] Therese Takas,[a] Martin K. Kankam,[b] Tonya Villafana,[a] Filip Dubovsky[a]

MedImmune (AstraZeneca), Gaithersburg, Maryland, USA[a]; Vince and Associates Clinical Research, Overland Park, Kansas, USA[b]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

March 2017 Volume 61 Issue 3 e01714-16

One injection resulted in extended $t_{1/2}$ of 85-117 days in adults with high RSV neutralizing activity

RSV Neutralizing Ab Over Time in Days

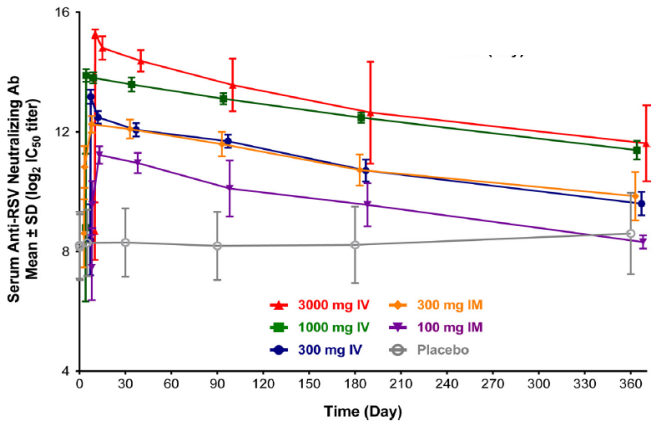


FIG 3 Anti-RSV neutralizing antibody titers after a single i.v. or i.m. dose of MEDI8897 or placebo. Data points represent the mean anti-RSV A2 neutralizing antibody titers on a log_2 scale. Data have been jittered. Error bars represent the standard deviations. Ab, antibody.

Introduction of Maternal Pertussis Vaccination – UK, 2012-2013*

~70% rate of maternal TdapIPV uptake over time

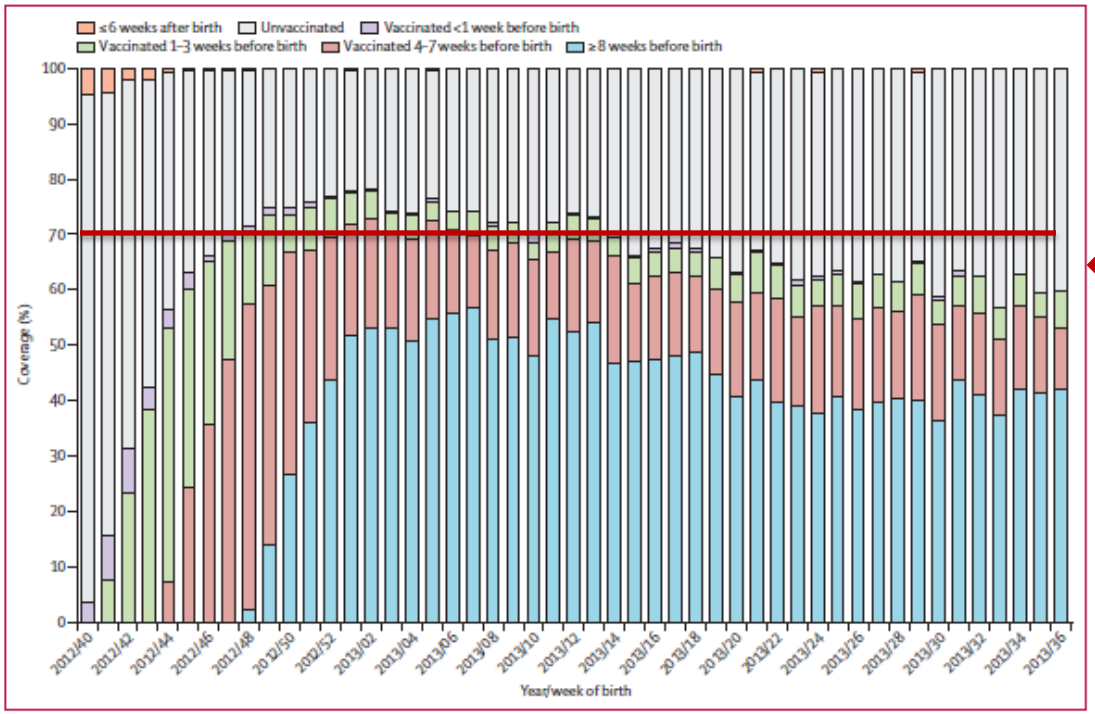


Figure 1: Estimated maternal vaccine coverage by week of birth
Figure shows coverage from week 40, 2012, to week 36, 2013. Figure based on data provided by the Clinical Practice Research Datalink.

Lancet 2014

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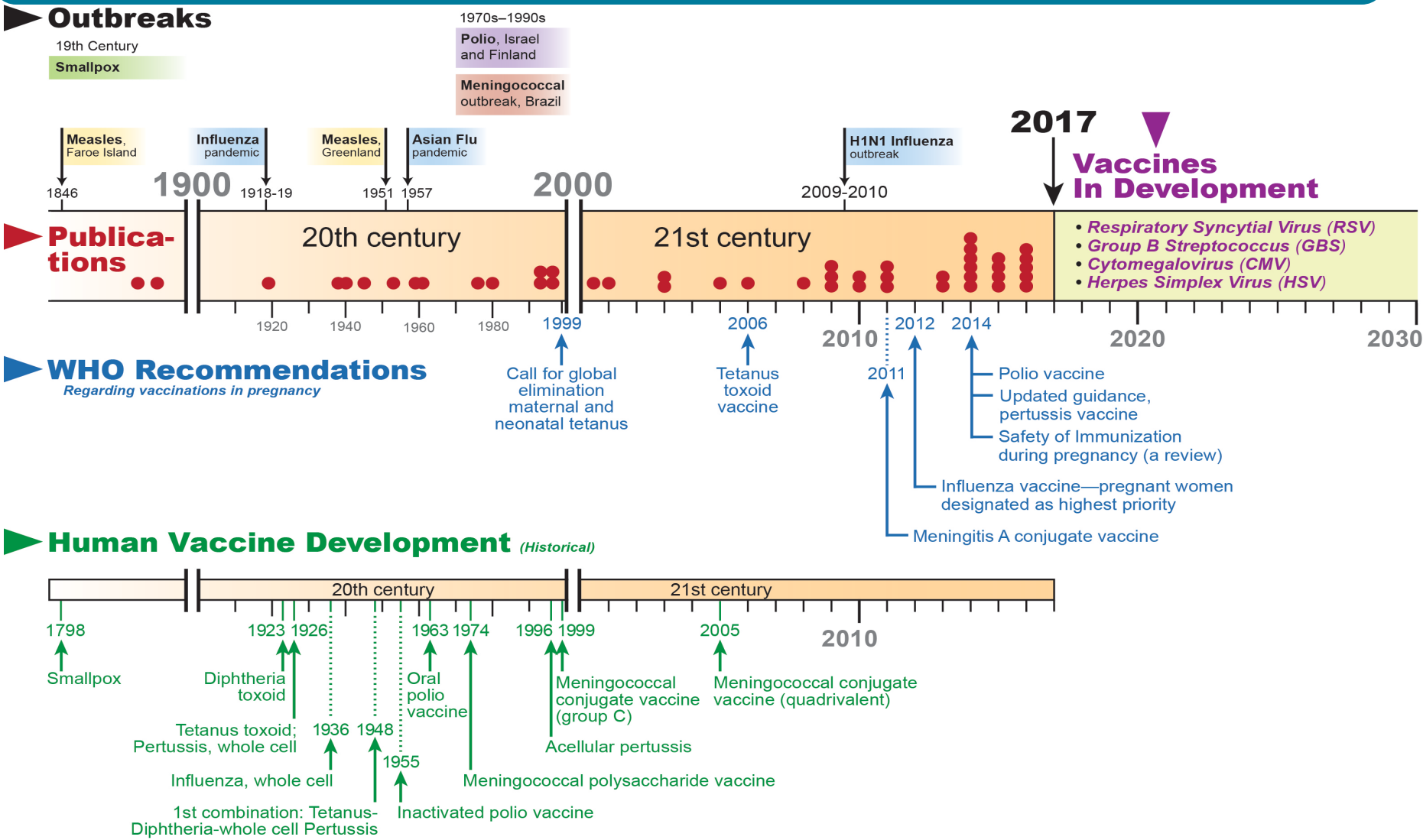
History of Maternal Immunization



Kachikas A, Eckert L, Englund JA.
Who's the Target – Mother or Baby? Viral Immunology 2017

NEW APPROACHES TO MATERNAL PERTUSSIS IMMUNIZATION

The Journal of Infectious Diseases

MAJOR ARTICLE

Maternal Vaccination With a Monocomponent Pertussis Toxoid Vaccine Is Sufficient to Protect Infants in a Baboon Model of Whooping Cough

Parul Kapil,[1] James F. Papin,[2] Roman F. Wolf,[2,a] Lindsey I. Zimmerman,[1] Leslie D. Wagner,[1] and Tod J. Merkel[1]

BioNet Received Thai FDA Approval of the World's Only Available Recombinant Monovalent Acellular Pertussis (aP) Vaccine –Dec. 2016

https://www.prnewswire.com/news-releases/bionet-received-thai-fda-approval-of-the-worlds-only-available-recombinant-monovalent-acellular-pertussis-ap-vaccine-300383345.html

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CONCEPT OF MATERNAL IMMUNIZATION

Boosts maternal levels of pathogen-specific anti-bodies

Provides newborn and infant with sufficient concen-tration of antibodies to protect against infections

until able to adequately respond to active immunization or infectious challenge

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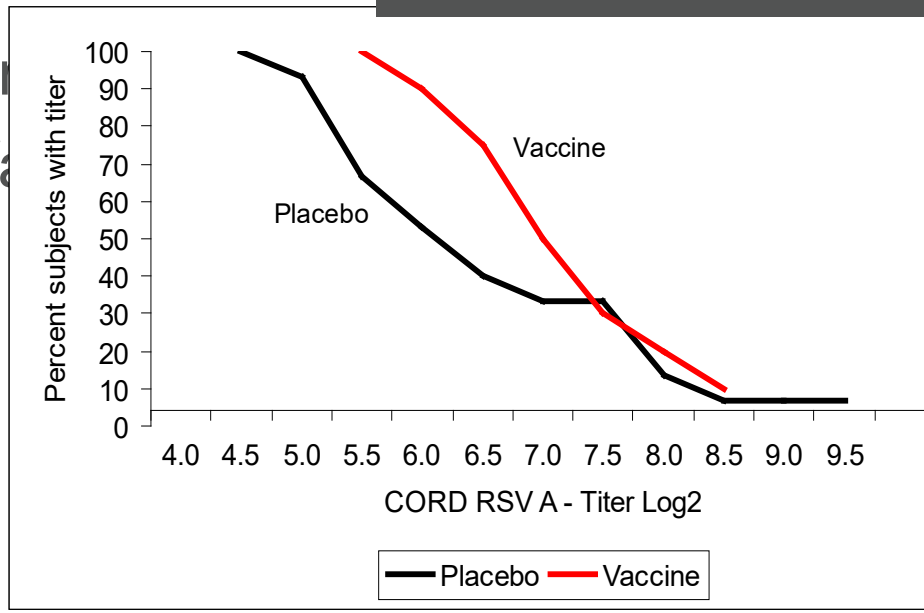
RSV VACCINE vs PLACEBO IN PREGNANT WOMEN*

- 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

Maternal Immunization with RSV F protein Vaccine (Phase 2 study, Novavax, 2016)*

²2 Infants: Time from Vaccination to Delivery (Days) Impacts Placental Antibody Transfer

Assay	Source	Del. < 30d post vacc., n=7*	Del. > 30d post vacc., n=14	All n=21*
Anti F IgG	Cord	7,227	8,659	8,153
	Mothers	12,979	6,993	8,594
	Ratio	**0.6**	**1.2**	**0.9**
PCA	Cord	177	195	189
	Mothers	303	178	213
	Ratio	**0.6**	**1.1**	**0.9**
RSV/A	Cord	928	672	748
	Mothers	1,448	580	786
	Ratio	**0.6**	**1.2**	**1.0**
RSV/B	Cord	565	512	529
	Mothers	724	410	495
	Ratio	**0.8**	**1.2**	**1.1**

GA = gestational age
Ad hoc analysis
*Excludes 1 mother/infant pair with delivery 5 days post-immunization, late pre-term delivery

Important Findings:

- Maternal antibody peaks 14d after vaccination
- Period of placental transfer >30 days maximizes antibody titer in infants
- P3 recruitment window opened to 31 weeks to maximize antibody transfer

*http://novavax.com/download/files/presentations/FIGO_7OCT2015_AA_P2_Data_10_14_15_FINAL(1).pdf

COMPARISON OF THREE MATERNAL FLU VX TRIALS

	South Africa	Mali	Nepal
Mat Flu VE rate	**50.4% P = 0.01**	**Flu A: 72 % Flu B: 73%**	**26.6 % P = 0.186**
Infant VE rate	**48.8% P = 0.01**	**Flu A: 64% Flu B: 20%**	**28.2% P = 0.027**
Infant attack rate	3.6 %	(not shown)	Yr 1: 6.7 %; Yr 2: 4.7 %
Birth Wt difference: Vx vs Placebo	NS	NO (not shown)	**YES: 2804 vs 2761 g; difference 42 g; P = 0.015**
Decreasing infant VE over time	YES VE decreased after age 2 M	YES VE decreased after age 5 M	NO No decrease change over 6 M

* **South Africa**: Madhi S et al NEJM 2014; Nunes MC et al JAMA Pediatr 2016;
Mali: Tapia M et al Lancet ID 2016; **Nepal**: Steinhoff Lancet ID 2017 (in press)

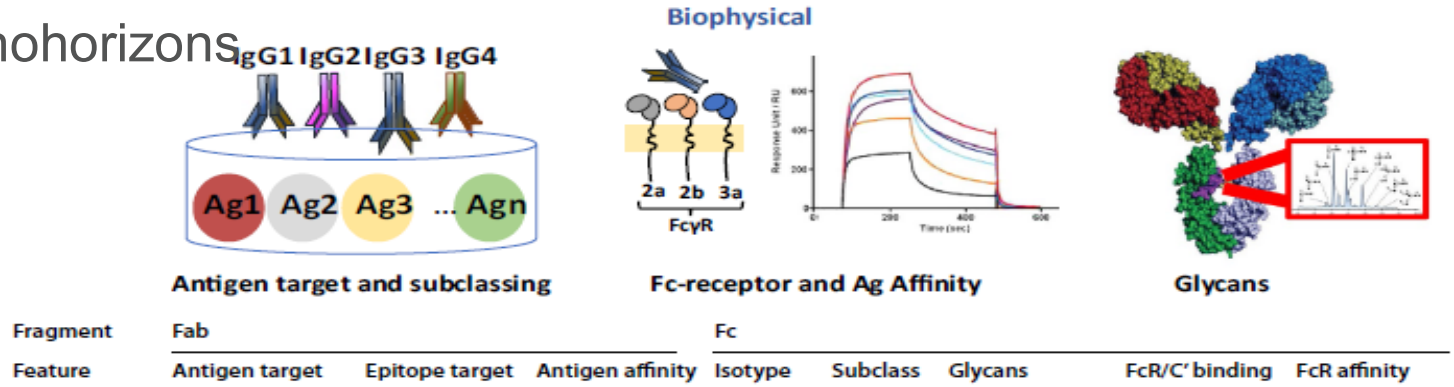
Pregnancy and Inflammation, NK cells, and Implantation: The Good, the Bad, and the Ugly

- Not a simple Th1/Th2 paradigm
- The good: inflammation important for implantation
  - Cytokines provide growth factors necessary for implantation of fetus in placenta
  - Adaptive immunity has potential to potentiate inflammation
  - Treg cells control some aspects of adaptive immunity
- The bad:
  - NK cell hyperactivation, IF17 have role in **implantation failure**
- The ugly:
  - Endometriosis from prolonged inflammation leads to **infertility**

Chaouat. J Reprod Immunology 2013; 97:2
Englund, Kachikis J Inf 2016; 72:S83.

Better Understanding of Maternal AB Transport Across the Placenta: Systems Serology

*Fouda & Alter Immunohorizons 2018



- FcRn is a MHC class I-related molecule that plays a central role in regulation of IgG homeostasis and IgG transport across polarized epithelial barriers.*
  - FcRn in cytosol binds Fc portion of IgG at acidic pH.
  - Maternal IgG undergoes endocytosis into syncytiotrophoblast cells making endosomes; FcRn then binds to maternal IgG and complex carried to basal plasma membrane where IgG released from FcRn upon exposure to normal pH; Fc RIIIa important.
- IgG1 most efficiently across placental but new data shows differential transport of IgG1 and functional Ab across Ab.**
  - EXAMPLES: Increased transfer of ADCC Ab; specific glycans

Summary of Key Efficacy Findings

Efficacy (%) (97.52%CI and 95%CI for MS RSV LRTI primary endpoint at 90 days, all others 95%CI) Placebo, Vaccine cases[3]	Time Interval	MS RSV LRTI	RSV LRTI hospitalizations	RSV LRTI w/ severe hypoxemia
Primary and secondary RSV⁺ w/ Site data	**0 to 90 days**	**39.4** (-1, 63.7)[1] (5.3, 61.2)[2] 35/1430, 41/2765	**44.4** (19.6, 61.5) 53/1430, 57/2765	**48.3** (-8.2, 75.3) 14/1430, 14/2765
	0 to 180 days	**26.6** (-7.8, 50.1) 43/1430, 61/2765	**40.4** (16.0, 57.7) 59/1430, 68/2765	**42.2** (-10.9, 69.9) 17/1430, 19/2765
Pre-specified exploratory RSV⁺ w/expanded data	**0 to 90 days**	**40.9** (15.9, 58.5) 56/1430, 64/2765	**41.7** (16.7, 59.2) 55/1430, 62/2765	**59.6** (32.1, 76.0) 32/1430, 25/2765
	0 to 180 days	**26.5** (-0.6, 46.2) 64/1430, 91/2765	**35.6** (10.3, 53.7) 61/1430, 76/2765	**51.2** (21.9, 69.6) 35/1430, 33/2765

1. (97.5% CI); 2. (95.0% CI); 3. Per-protocol population

Presented by F. Munoz, ESPID 2019

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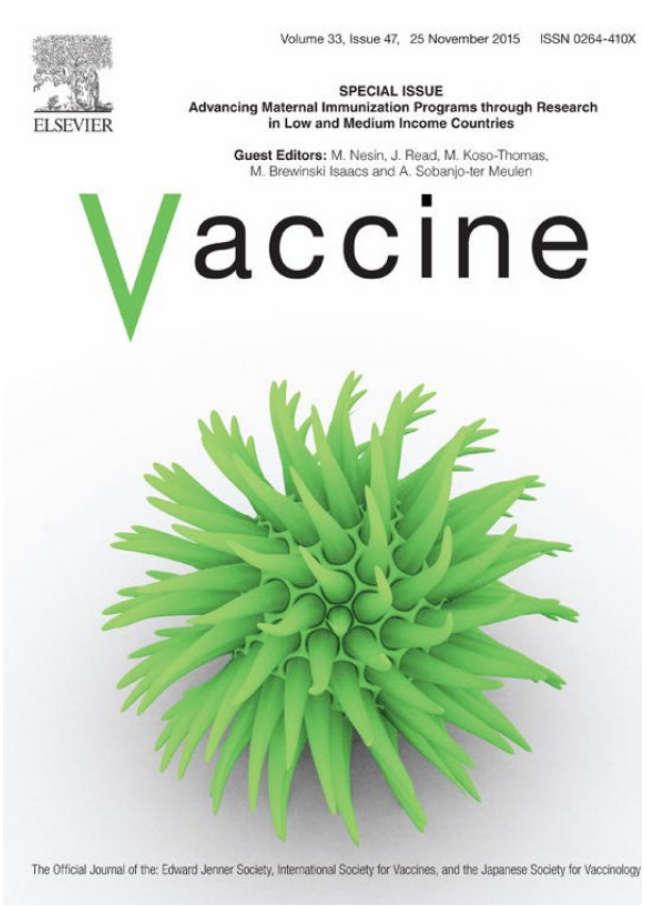
IMPORTANCE OF RSV FUSION PROTEIN FOR VACCINES*

RSV F proteins: Potential candidates for immunization of adults, women, and pregnant women

- Experience with monoclonal Ab prophylaxis of preterm infants with palivizumab (Synagis) provides rationale for this approach
- Vaccine prefusion F protein candidates may increase AB response even more:
  - Immunogenic in inducing protective neutralizing Ab in cotton rats, adult humans (already exposed)
  - Safe, non-reactogenic in adults
- Vast experience with maternal immunization against tetanus and influenza makes this approach promising

*Englund and Chu, CID 2016

Potential Problem: Uniform Definitions Needed for Maternal Immunization Trials



GAIA collaboration: Brighton initiative, in collaboration with WHO and co-sponsored by B&M Gates Fndn has worked to provide case definitions by experts for monitoring safety and adverse events during clinical trials. Definitions involve events related to pregnancy/childbirth/fetus and infants amd will to enable more uniform descriptions and analysis of maternal immunization clinical trials.

Key terms for the assessment of the safety of vaccines in pregnancy: Results of a global consultative process to initiate harmonization of adverse event definitions

Flor M. Munoz[a,*], Linda O. Eckert[b], Mark A. Katz[c], Philipp Lambach[d], Justin R. Ortiz[d,***], Jorgen Bauwens[e], Jan Bonhoeffer[e,f,**]

[a] Departments of Pediatrics and Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX, USA
[b] Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA
[c] Independent Consultant, Tel Aviv, Israel
[d] Initiative for Vaccine Research, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
[e] Brighton Collaboration Foundation, Basel, Switzerland
[f] University of Basel Children's Hospital, Basel, Switzerland

Vaccine 33 (2015) 6441–6452

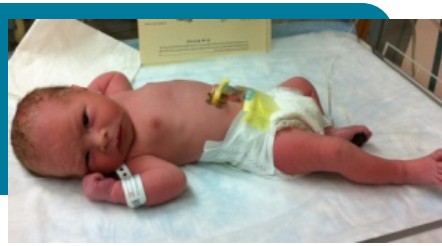
IMPACT OF 2009 INFLUENZA A (H1N1): MOTHERS *

MATERNAL Risk Factor	RR Hospital-ization	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 Dis.	2.0 (1.5–2.2)	9.2 (5.4–10.7)
Renal Dis.	4.4 (4.2–4.5)	22.7 (21–25.4)
Liver Dis.	3 5.7 (3.2–16)	17.4 (11.6–28)
Neurological Disease	1.1 (0.9–1.3)	13.1 (8.4–32.4)
Immune Compromised	24.3 (16.1–33)	27.7 (14–66.5)
Pregnancy	**6.8 (4.5–12.3)**	**1.9 (0.0–2.6)**

Relative Risk differed 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**

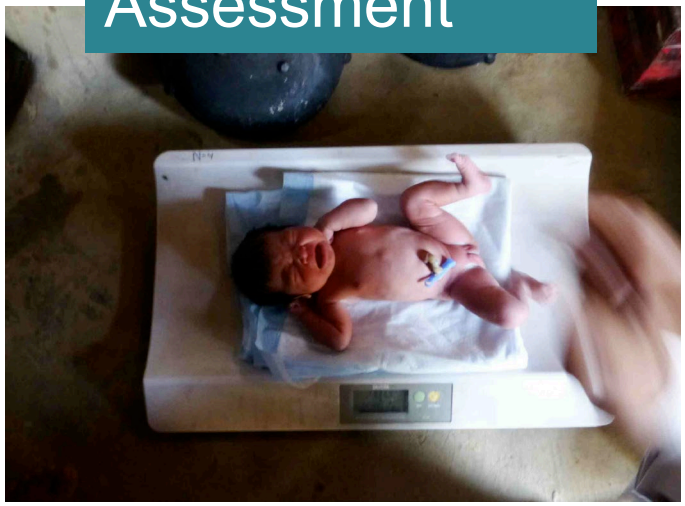
IMPACT OF 2009 INFLUENZA A (H1N1): INFANTS



Study	Site	Case	Control	Results
McNeill AJOG 2011	Canada 1990-2002	Maternal flu season respiratory hospitalization (N=208)	No hospitalization (N=132,099)	Newborns of hosp. women: 90 gm smaller, 40% more likely SGA
Mendez-Figueroa AJOG 2011	USA 2009- 10	Maternal ILI with lab confirmed pandemic H1N1 (N=15)	Maternal ILI with neg. lab test (N=25)	Newborns exposed to flu were 285 gm smaller
Pierce BMJ 2011	UK 2009-10	Pregnant women with lab+ confirmed pandemic H1N1 (N=256)	Historical comparison of pregnant women from 2005-2006 (N=1220)	Newborns exposed to flu were 255 gm smaller, with incr. perinatal mortality and premature birth

BIRTH ASSESSMENT and WEEKLY ASSESSMENTS

Birth Assessment



Weekly Assessment

Transport of specimens

Immune Responses During Pregnancy

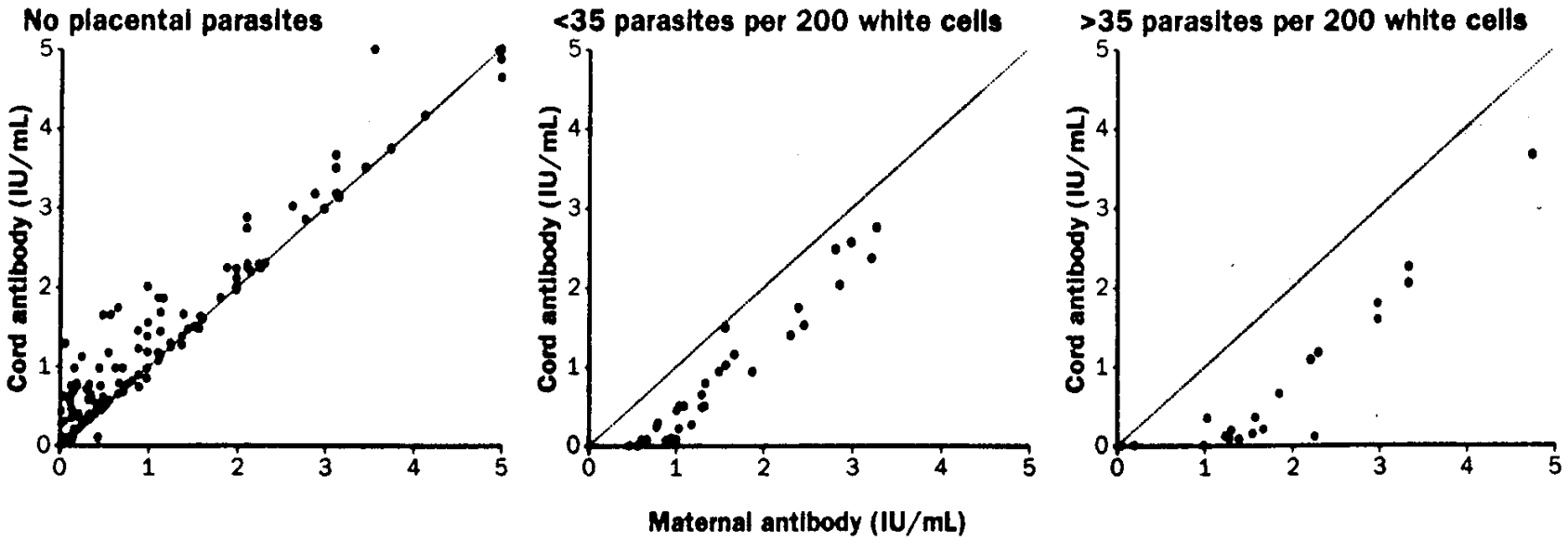
- Physiologic changes *
  - Increased heart rate, stroke volume; decreased lung capacity but increase in O2 carriage.
  - Alter host response to antigens (increase in estrogen and progesterone result in decreased interleukins).
  - Increase in blood cortisol levels (decreased clearance)

- Decreased cell mediated immunity: relatively minor predisposition to listeria, TB, toxoplasmosis, etc.*
- Decrease in concentration of IgG by hemodilution (18% IgG decrease from 2nd to 3rd trimester**)
- Historically: Th2 humoral immune response thought to predominate but now evidence of shifts between pro-inflammatory and anti-inflammatory states to facilitate implantation of blastocyst, fetal growth, and parturition (facilitated by estrogens and progesterone)***
- No significant alteration in antibody responses to vaccines or infections

*Halsey and Klein D,et al. PIDJ 1990;9:574l ** Amino N. et al 1978 Ob Gyn 52: 415

***Zenclussen AC Am J Reprod Immunol l2013;69:291-303; Chaouat G. J Reprod Imm 2002;53:241-56.

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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DIPHTHERIA

Barr et al, Lancet 1950

DIPHTHERIA IMMUNISATION IN YOUNG BABIES

A STUDY OF SOME FACTORS INVOLVED

MOLLIE BARR
M.Sc. Lond., A.R.I.C.

A. T. GLENNY
B.Sc. Lond., F.R.S.

OF THE WELLCOME RESEARCH LABORATORIES, BECKENHAM

K. J. RANDALL
M.D. Lond.

SENIOR REGISTRAR IN PATHOLOGY, ST. ALFEGE'S HOSPITAL, GREENWICH

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

Infants protected after maternal immunization

BUT: More maternal Ab → Less infant Ab after infant immunization

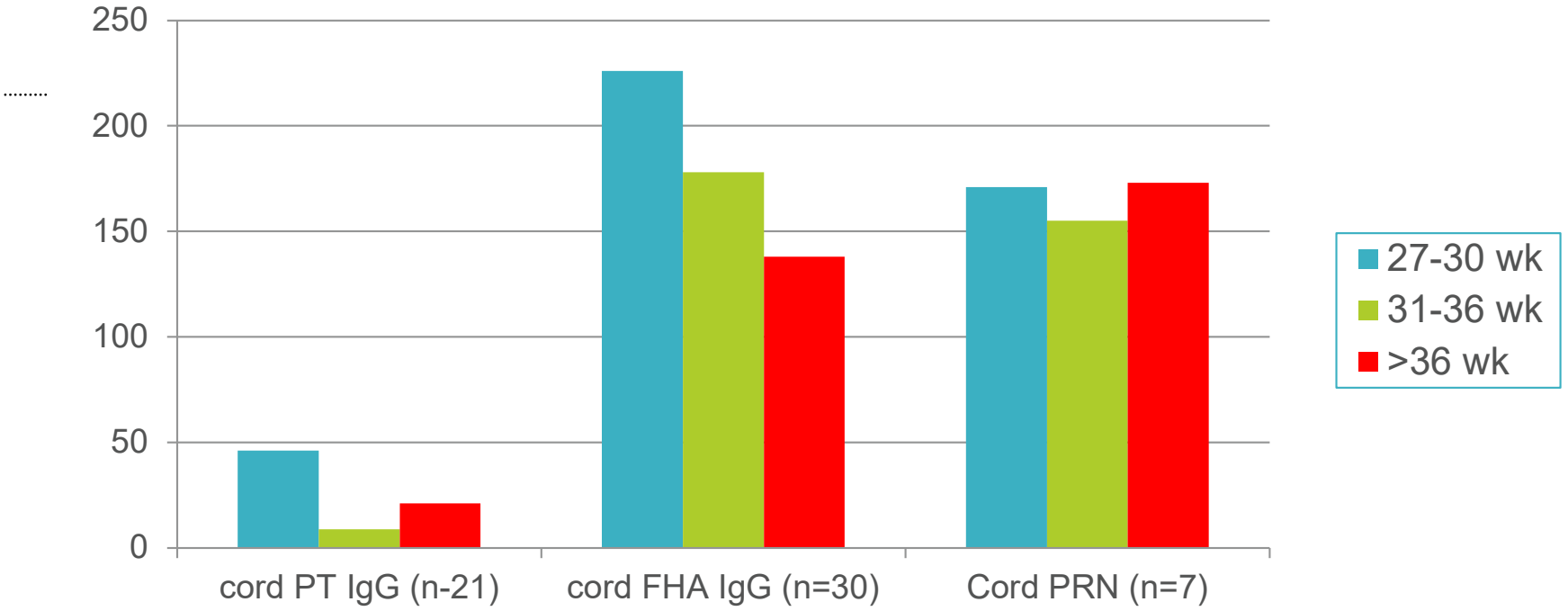
Placental Transfer of Anti-Measles AB in Mothers with High Total IgG is Reduced*

- Total IgG in mothers associated with reduced efficiency of transfer of total & measles-specific IgG
- Relatively more measles Ab transferred to babies born to German mothers than Nigerian mothers

	Total IgG in Mother At Delivery Mean (Range) (g/L)	Maternal Measles NT Ab	Cord Measles NT Ab	% Trans-mission
Nigerian	15.8 (18-26)	6.0	6.0	100%
German	8.7 (4.8- 16)	7.0	7.7	140%

*Harter et al. PIDJ 2000;19:635-41

Timing of Maternal Tdap and Cord Ab Levels*



CONCLUSION:

Immunization of pregnant women with Tdap between 27-30^{+6} weeks associated with highest umbilical cord GMCs of IgG to PT and FHA compared with immunization beyond 31 wks.

* Abu Raya, Srugo, Kessel, et al.
Vaccine 2014;32:5787

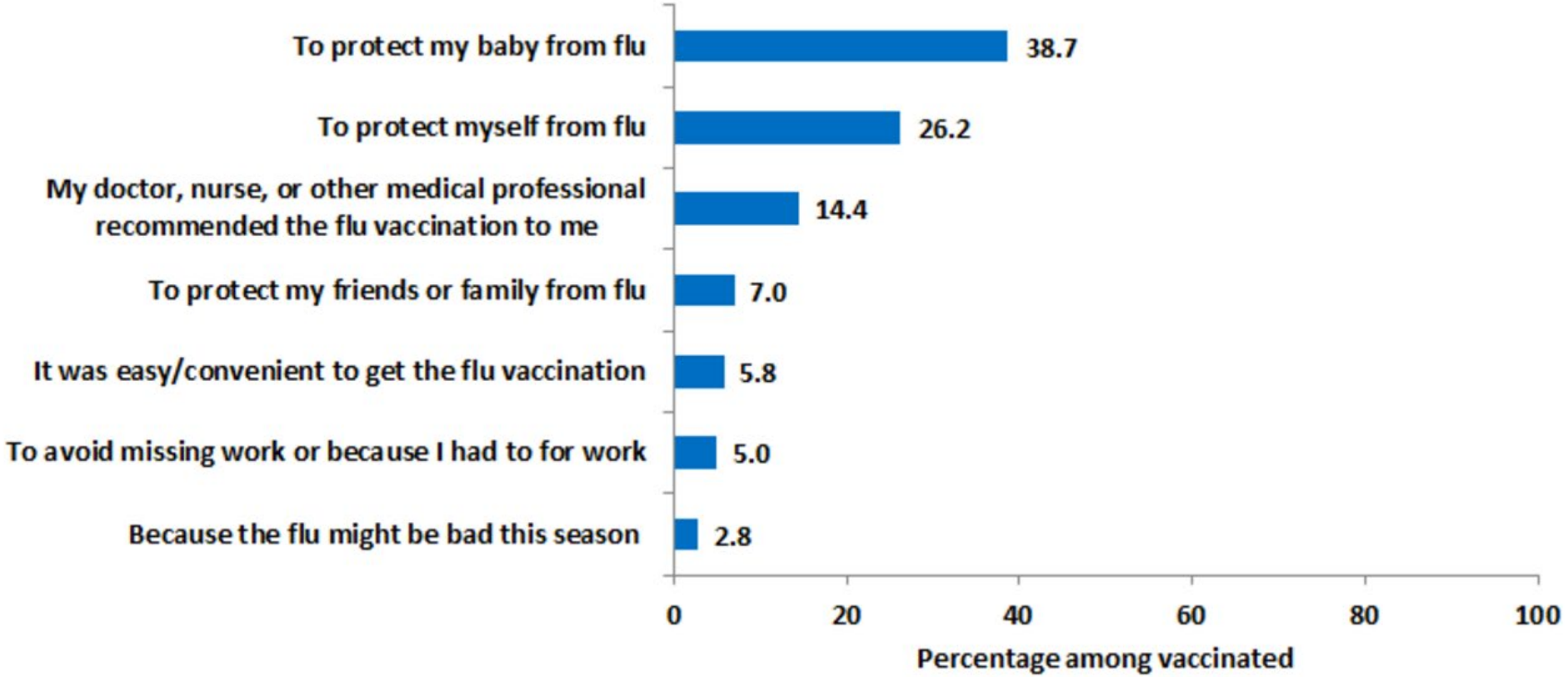
Case Presentation

Your patient says: “I don’t believe in vaccines” when you offer the flu vaccine to your pregnant patient who is at 24 weeks gestation. “Last year I got the vaccine, and I still got sick.”

What would your response be? Would your response differ in a pregnant vs a non pregnant patient?

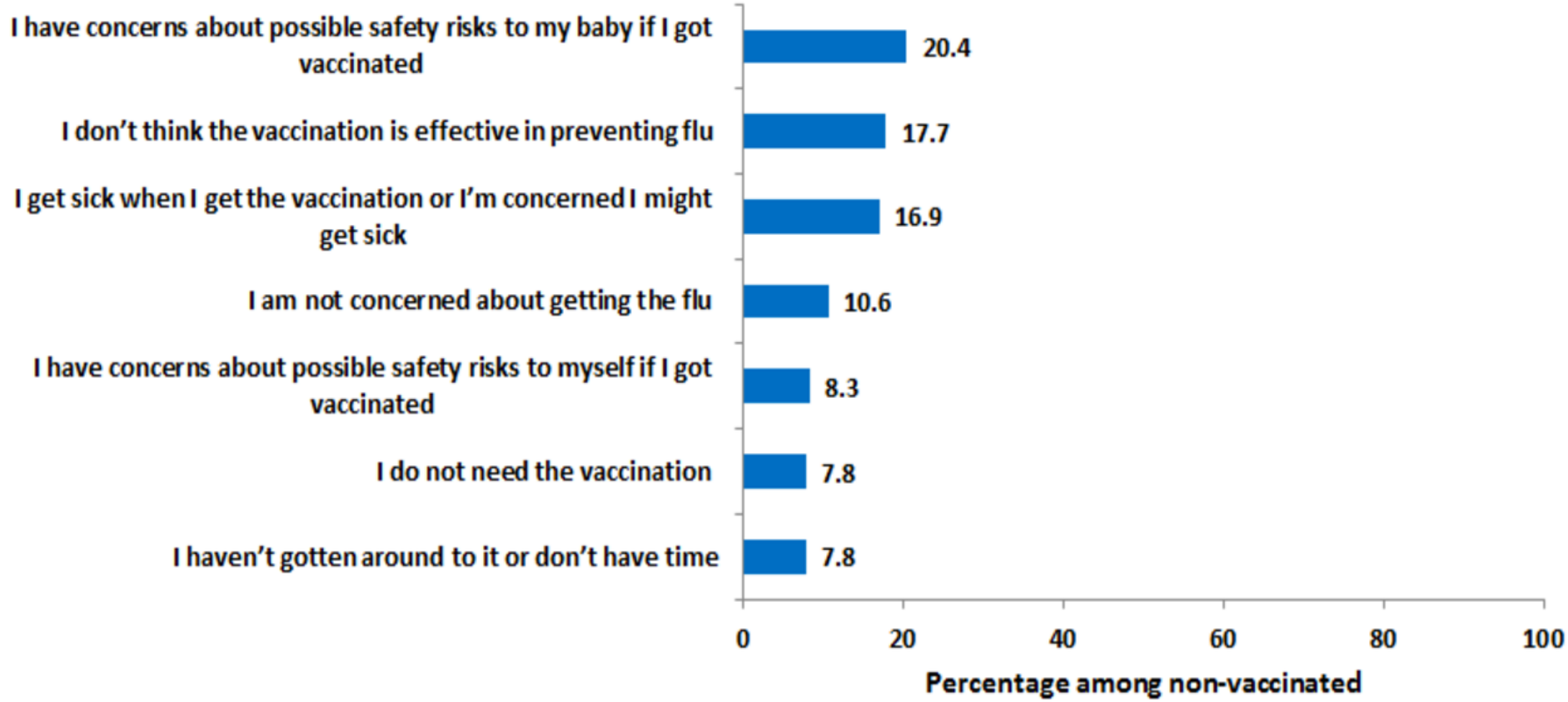
Thanks to Linda Eckert

Main Reason for RECEIVING Flu Vaccine During Pregnancy in USA



Ding, Helen et al. Internet Panel Survey conducted by CDC Mar 29–Apr 7, 2016

Main Reason for NOT Receiving Flu Vaccine during Pregnancy in USA



Ding, Helen et al. Internet Panel Survey conducted by CDC Mar 29–Apr 7, 2016

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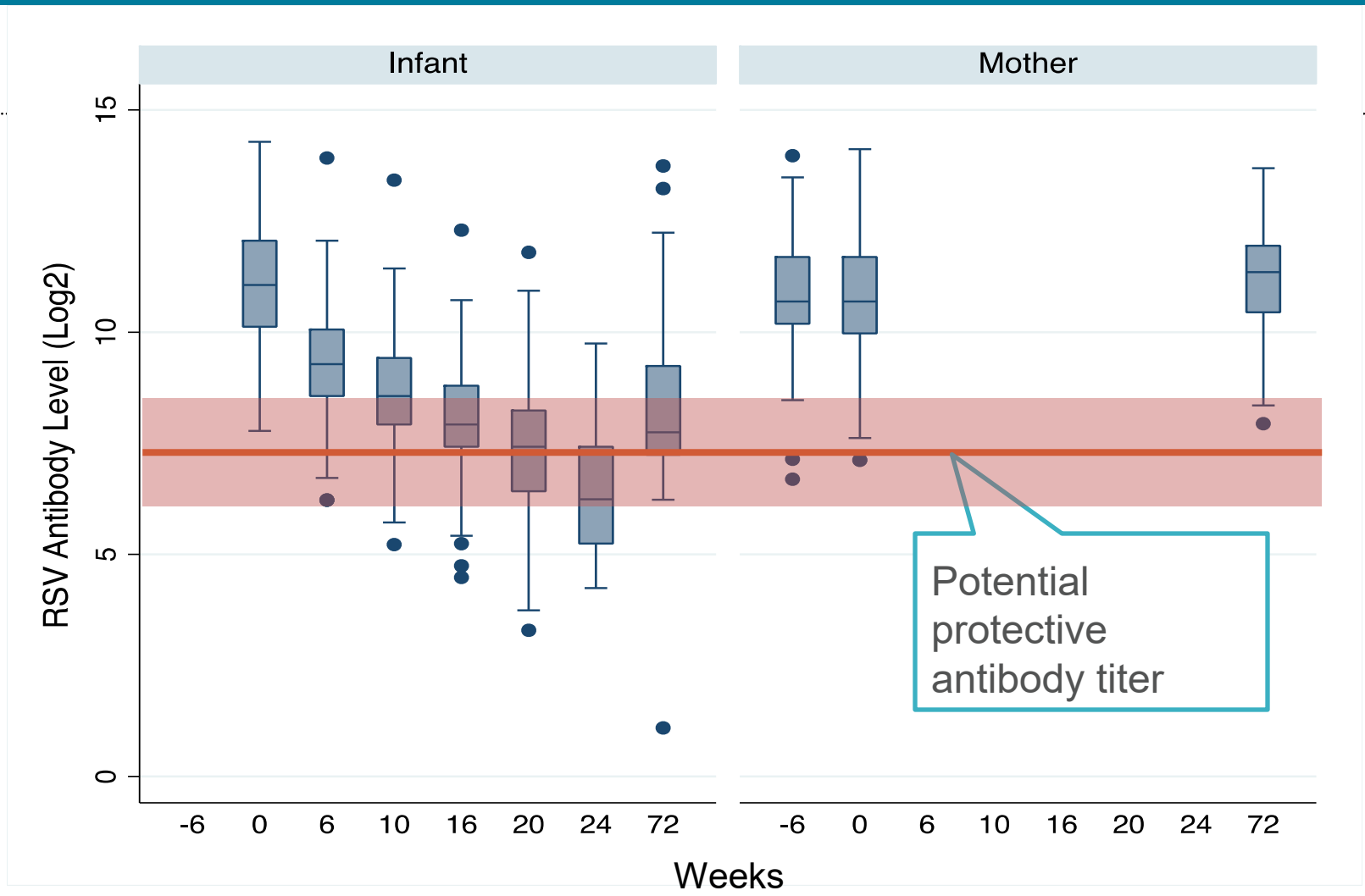
COMPARISON OF THREE MATERNAL FLU VX TRIALS

	S. Africa	Mali	Nepal
Climate	Temperate	Tropical	Subtropical
Comparator	Placebo	Meningococcal vx	Placebo
When vx given	Pre-seasonal	Seasonal- long	Year-round
Maternal BMI	27.6	-	**21**
Placebo: Preterm < 37 wk	10%	-	**13.6%**
Birthwt (median)	3.1 kg	-	2.76 kg
LBW (< 2.5 kg)	12.5%	-	**26.8%**

South Africa: Madhi S et al NEJM 2014; Nunes MC et al JAMA Pediatr 2016;
Mali: Tapia M et al Lancet ID 2016; **Nepal:** Manuscript submitted

Infant and Mother RSV Antibody Levels Over Time in 149 Mother/Infant Pairs (Bangladesh*)



*Chu H, Steinhoff M, et al. JID 2015

CLINICAL TRIALS OF RSV F-PROTEIN VACCINES

RECENT RSV CLINICAL TRIALS

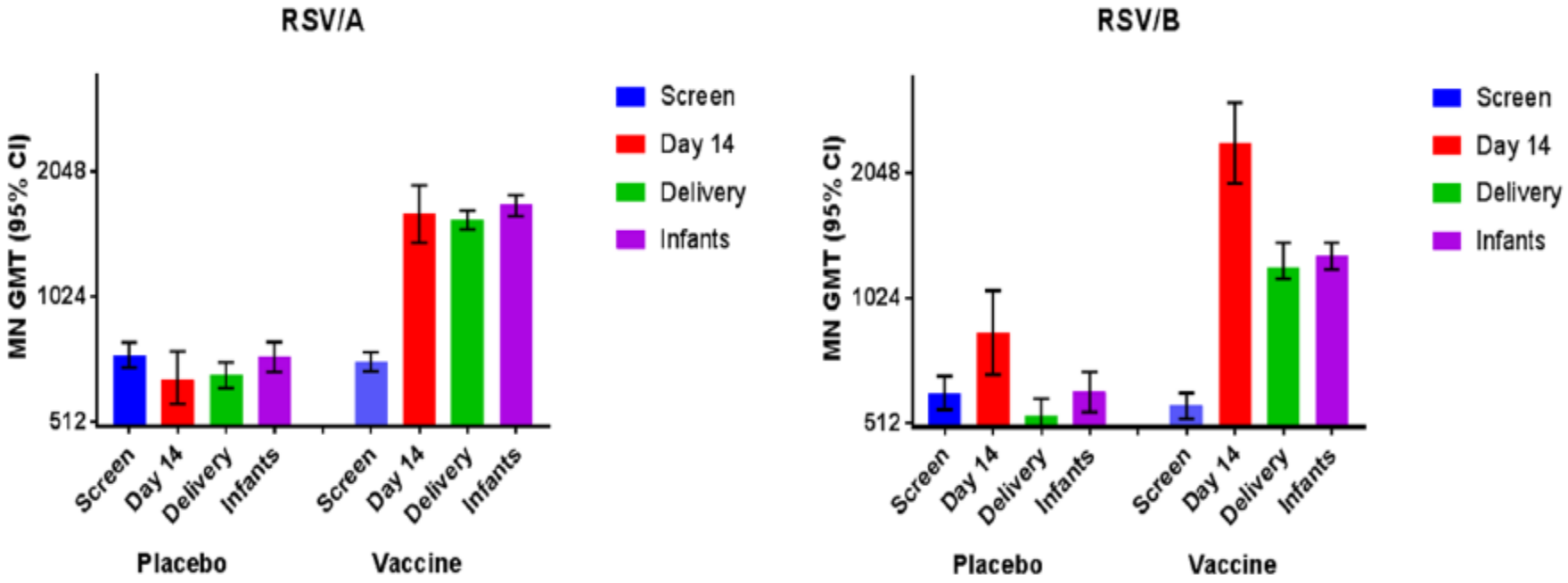
1. Elderly: MedImmune and Novavax: Results did not demonstrate efficacy against RSV disease (2017 Int'l RSV Meeting)

2. Healthy adults of childbearing age – Novavax, (Glenn JID 2016; Langley JID 2016 and 2018)

3. Pregnant women – International phase 2, 3 trial completed with > 4000 women (Novavax with support from B&M Gates). Pregnant women vaccines under consideration by other pharmaceutical companies.

Vaccine Immunogenicity and Transplacental Transfer of Antibodies: Neutralizing Antibodies

Microneutralization Responses from Subset of Season 1 and 2 Subjects



Presented by F. Munoz at ESPID, 2019, Slovenia

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Pregnant Women in Alaska…….

Alaska Dispatch N

Saturday, September 20, 2014 www.adn.com AL

Pregnant Homer woman joins mating call to bag moose with single shot

By CRAIG MEDRED
Alaska Dispatch News

If you're 8½ months pregnant, craving meat and find the freezer empty, what do you do?

Well, if you're a woman in Homer, you go out and shoot a moose. That's what Ashley Switzer did.

The 22-year-old, soon-to-be first-time mom was home alone in early September when it came time to put food on the table. Husband Scott was off working on a fishing boat somewhere near Kodiak Island, about 130 miles to the southwest.

Ashley wasn't sure when he'd be home, so she decided she best do something

See Back Page, MOOSE

Photo courtesy of YVONNE KETELL

Ashley Switzer shot a moose while she was 8½-months pregnant

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Influenza Vaccine and Pregnant Women*

Vaccine 29 (2011) 4439–4452

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

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

Justin 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

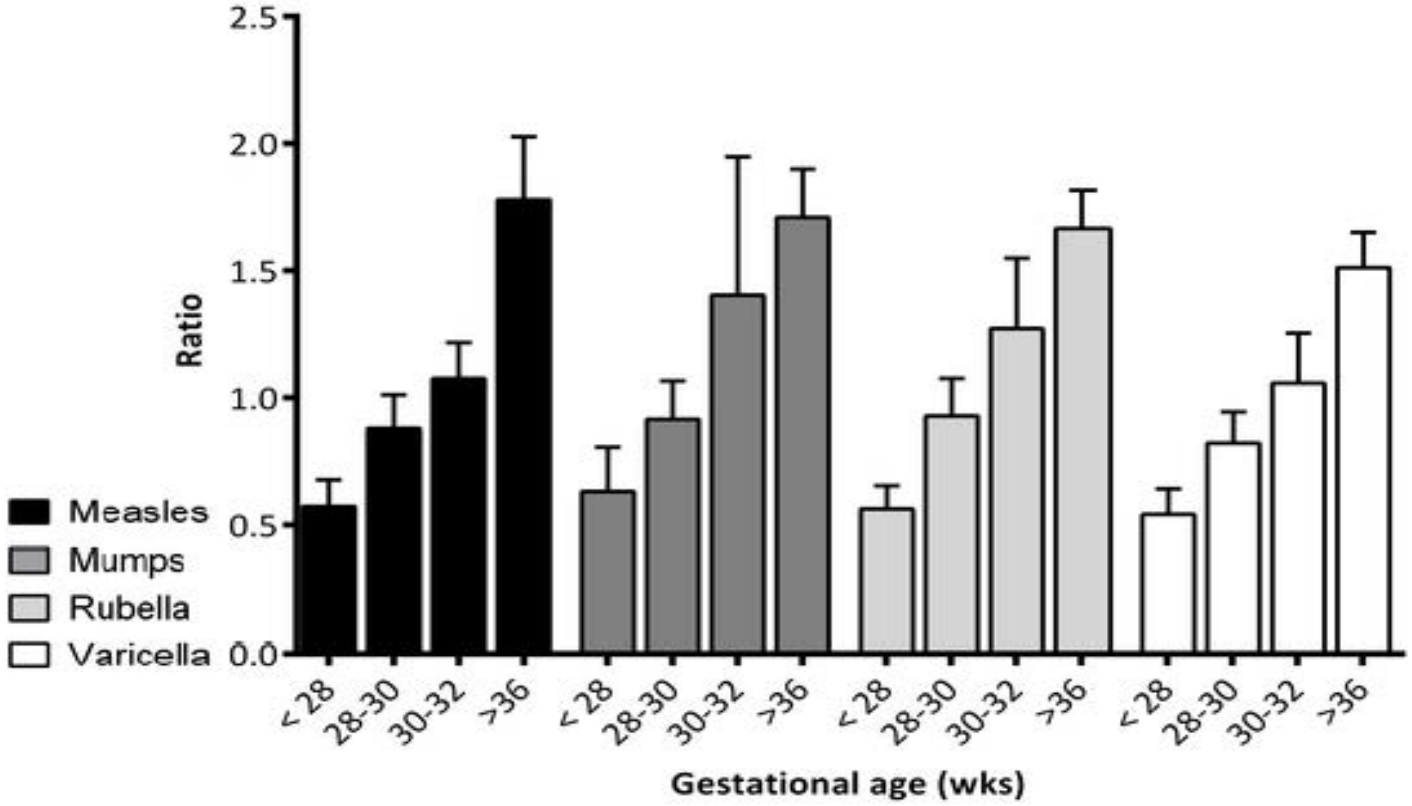
– Little or no information available

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

Transplacental Antibody Transfer by Gestational Age*

Gestational age: 10% at beginning of 2nd trimester, 50% by end of 2nd trimester, & >100% by birth



Vanden Berg JP PLos One 2014;

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