Maternal Immunization Promises and Challenges

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Overview

- Rationale and concept of maternal vaccination
- Vaccines recommended in pregnancy
- Key issues on maternal immunization
- Opportunities and Challenges

Rationale for Maternal Immunization

1. Children are at **higher risk of morbidity and mortality from infections** in the newborn period than at any other time in life

2. **Infants depend on maternal IgG antibody** to resist infections in early life

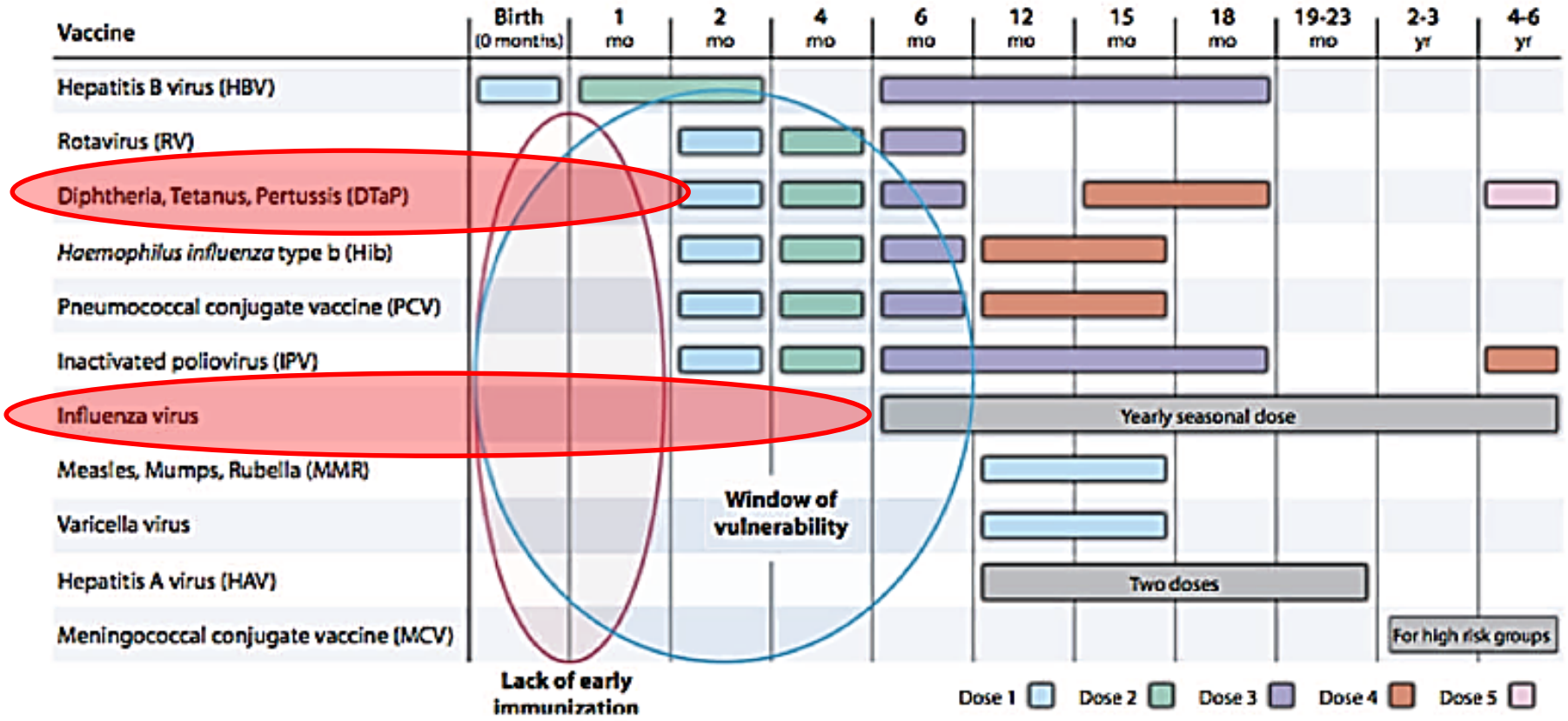
3. Most **active vaccinations are ineffective at birth** given qualitative and quantitative **differences in infant immune system** AND the presence of maternal antibody

4. Specific **antibody protects mothers and infants** against serious disease, preventing infection, delaying onset or decreasing severity (eg. Tetanus, GBS, Influenza, *H. influenzae*, Pneumococcus, RSV natural and passive Ab)

5. Existing concentrations of **antibody are low in many pregnant women** (eg. Pertussis) who might **also** be **at risk** of infection

6. Concentration of **maternal antibodies can be optimized in pregnant women who have an intact humoral response to vaccines** AND many **opportunities** for vaccination through prenatal care

Period of vulnerability for infant infectious diseases



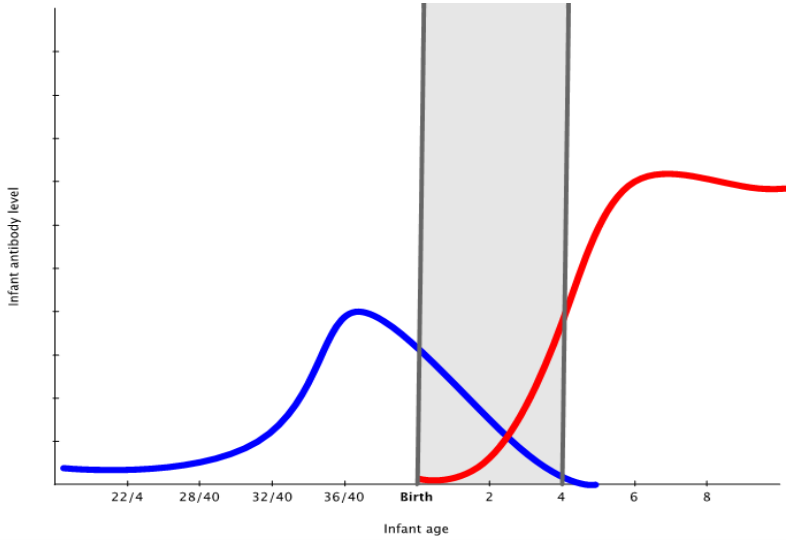
Jones C, *et al. Hum Vaccin Immunother* 2014;10: 2118–2122.

Concept of Maternal Immunization

To boost maternal levels of pathogen-specific IgG antibodies

To provide protection to the mother, the newborn and infant

Against infections occurring during a period of increased vulnerability, until infant is able to adequately respond to active immunization or infectious challenge



Influenza

Tetanus
GBS

Pertussis
Influenza
RSV

MOTHER NB INFANT

Maternal Immunization and Breastfeeding Protection

Review Vaccine 2014,32:1786

Breastfeeding after maternal immunisation during pregnancy: Providing immunological protection to the newborn: A review

Kirsten Maertens[a,*], Sara De Schutter[b], Tessa Braeckman[a], Lesley Baerts[b], Pierre Van Damme[a], Ingrid De Meester[b], Elke Leuridan[a]

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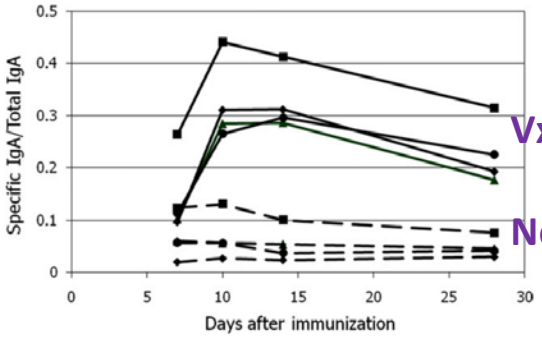
Vaccine specific
Secretory IgA
IgG

Pneumococcus
Influenza
Hib
RSV
Meningococcus
Pertussis

Potential for protection
~ 6+ months?

sIgA to Pertussis Ag
Post-partum Tdap Vx



Halperin, CID 2011, 53:885

TABLE 2. Geometric Mean Concentration with the 95% CI Between Brackets for Anti-PT sIgA, Total sIgA and Adjusted anti-PT sIgA in Breast Milk Samples in the 4 Study Groups

	Vaccination During Pregnancy (Group 1)	Vaccination Shortly After or at Delivery (Group 2)	Vaccination Less Than 5 Years Before Delivery (Group 3)	No Vaccination 5 Years Before Delivery (Group 4)
Anti-PT sIgA in IU/mL (95% CI)	0.55 (0.31–0.98)	0.66 (0.44–0.97)	0.51 (0.29–3.22)	0.19 (0.16–0.23)
Total sIgA in mg/mL (95%CI)	0.22 (0.17–0.28)	0.31 (0.25–0.38)	0.29 (0.18–0.48)	0.20* (0.15–0.28)
Adjusted anti-PT sIgA in IU/mg (95% CI)	2.56 (1.42–3.00)	2.15 (1.53–3.02)	1.73 (1.07–2.80)	0.96* (0.67–1.38)

*The concentration of total sIgA was not determined for one sample in study group 4.

De Shutter PIDJ 2015,34:e149

WHO Statement on Vaccines In Pregnancy

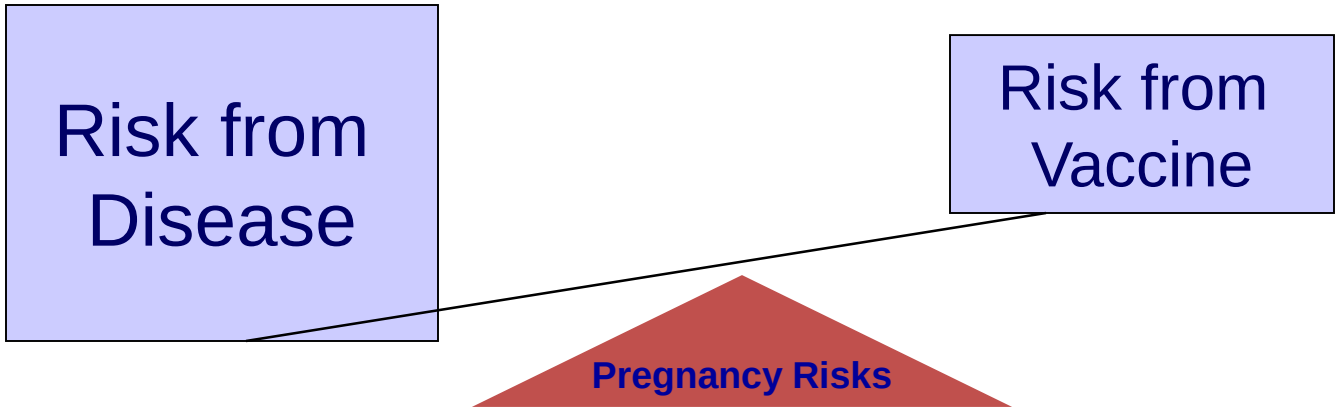
- **Pregnancy should not deter a woman from receiving vaccines** that are safe and will **protect both her health and that of her unborn child**.
- **Killed or inactivated vaccines** (influenza, toxoids, polysaccharides and conjugated vaccines) can generally be given during pregnancy.
- **Live vaccines are generally contraindicated** because of largely **theoretical risks** to the baby (MMR, varicella).
- The **risks and benefits** should be examined in each **individual case**. Eg: Vaccination against YF may be considered in pregnancy depending on risk of disease.

WHO's specific vaccine position papers:
http://www.who.int/immunization/documents/positionpapers_intro/en/.

Guidelines for Immunization during Pregnancy (US)

Documentation that:

1. Women have a high risk of exposure to the disease
2. Infection poses a special risk to the mother
3. Infection poses a special risk to the fetus
4. A vaccine is available and is unlikely to cause harm



MMWR 1994;43,No RR-1-28; ACOG Obstet Gynecol 2004;104:1125-6

Vaccines Recommended During Pregnancy

Routinely

- TT/Td/Tdap
- Inactivated influenza vaccine

Contraindicated

- MMR
- Varicella
- Live Influenza vaccine
- BCG

In Special Circumstances

- Inactivated Polio
- Pneumococcal
- Meningococcal
- Hepatitis A and B
- Inactivated Cholera
- Rabies
- YF

CDC..gov Vaccines in Pregnancy

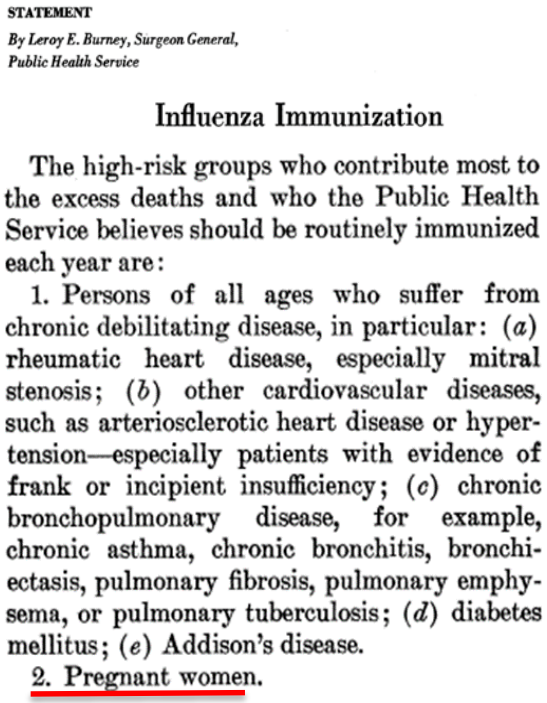
Vaccines in Post-partum and Breastfeeding women

- **Tdap and influenza IF** not given in pregnancy
  - Inactivated or live (no contraindication)
- **Rubella** vaccine if non-immune (MMR)
- HPV vaccine to complete interrupted series
- Any other vaccine based on need/risk
- No currently used vaccine (live or inactivated) is contraindicated in post-partum and breastfeeding women, **except** yellow fever should be avoided in breastfeeding women unless exposure inevitable

Maternal Immunization is NOT New - Early Milestones

- **1879** - MI with **Vaccinia** protected mothers and infants against smallpox
- **1940's** - MI studies with **DTPw** vaccine in US to protect infants against pertussis
- **1960s – Influenza** vaccine recommended for pregnant women (at risk) since the 1957 pandemic
- **1961**- MI with **Tetanus Toxoid** to prevent neonatal tetanus in Papua New Guinea, added to WHO Expanded Program on Immunization in 1970's; MNT elimination goal set in 1980's

Public health reports 1960



STATEMENT

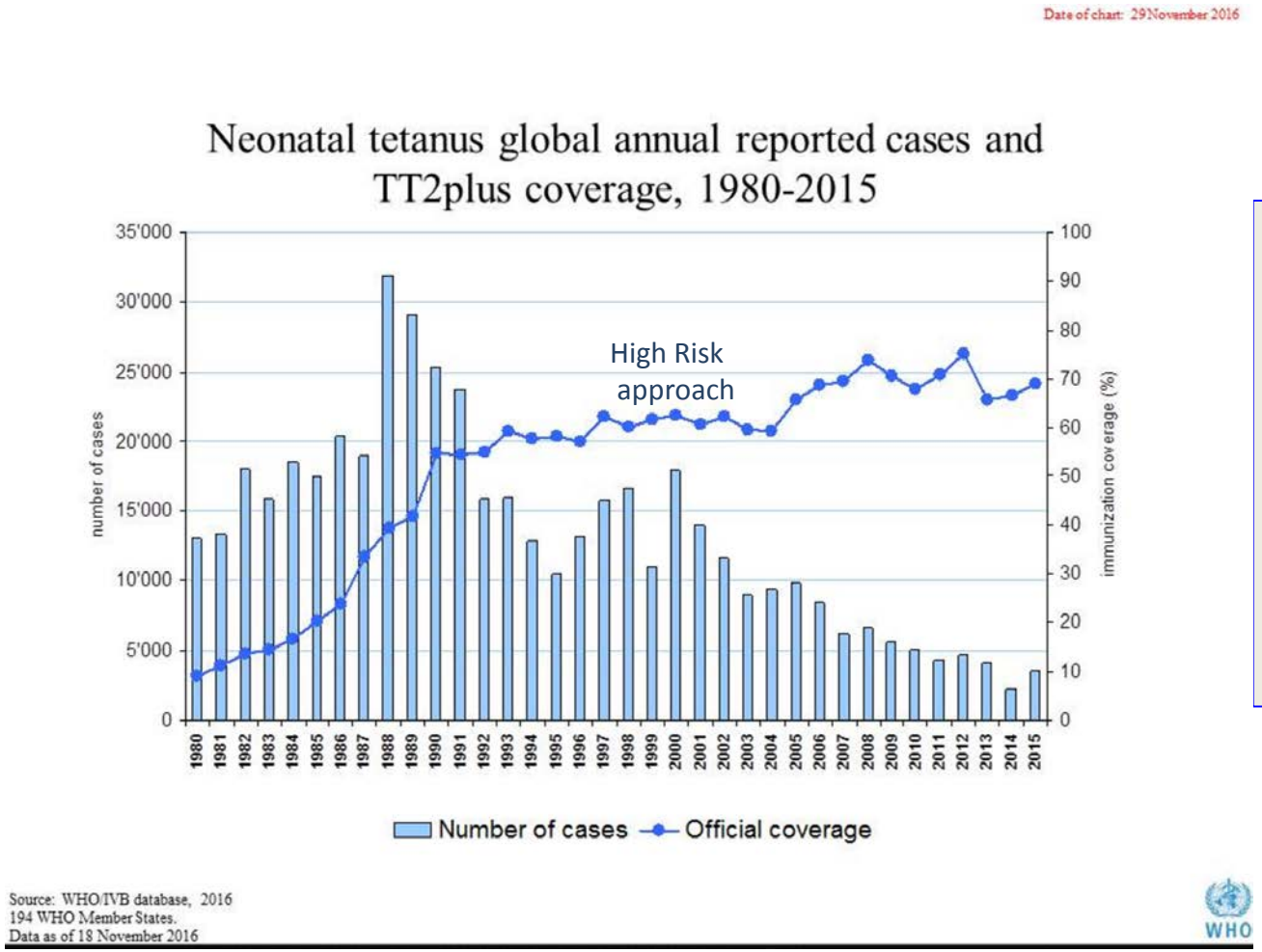
By Leroy E. Burney, Surgeon General, Public Health Service

Influenza Immunization

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.

MNT Elimination – A Successful Platform



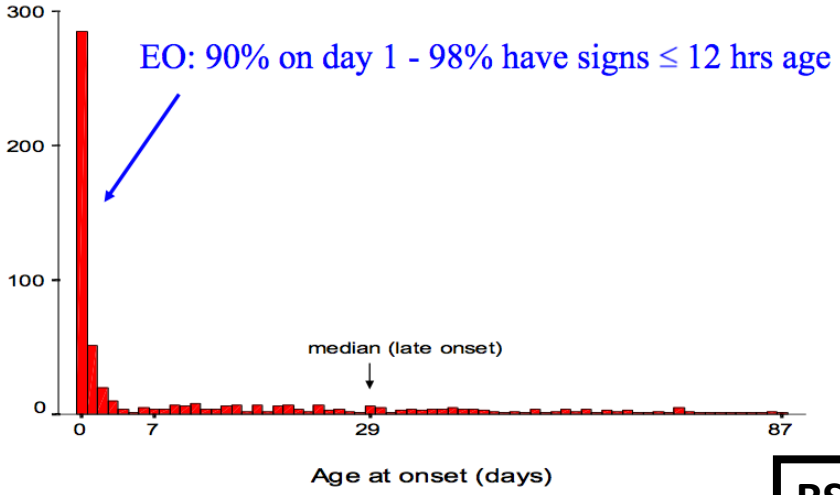
1980: 787,000 deaths
(~30% of infant mortality)
1989: 161 countries

2015
69% maternal coverage
34,000 neonatal deaths
21 countries

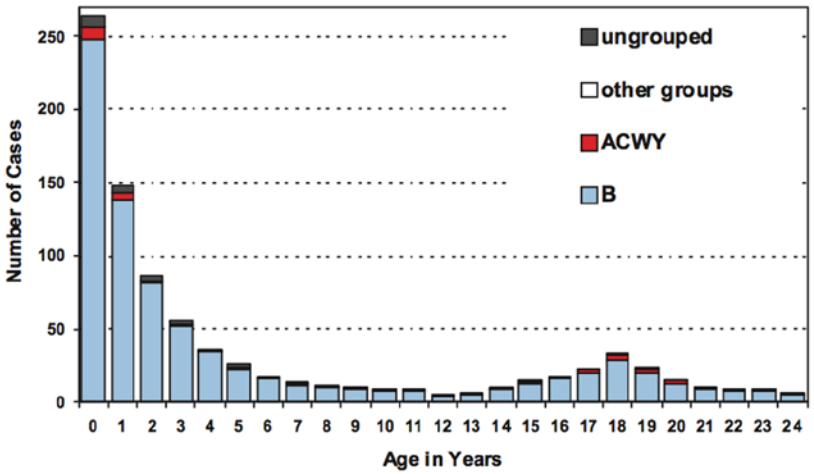
TT2 strategy: 2 doses of TT in pregnancy + 3 doses in women of childbearing age, reduces the rate of neonatal tetanus by 94%

Opportunities for Maternal Immunization: Newborns Increased Risk of Infection

Group B Streptococcus



Meningococcus B



RSV

	Infection rate per 1000 children (95% CI)			
Treatment Site	0-5 months	6-11 months	12-23 months	24-59 months
Hospital	16.9 (15.3-18.5)	5.1 (4.6-5.5)	2.7 (2.3-2.7)	0.4 (0.3-0.4)
Emergency department	55 (24-126)	57 (20-161)	32 (11-92)	13 (4-41)
Pediatric practice	132 (46-383)	177 (61-511)	66 (18-245)	57 (19-167)

Opportunities: Potential Benefits and Targets of Maternal Immunization

- **Directly protects** mother and infant
- **Interrupts transmission**
- **Prevents disease** not eliminated by antibiotics or other available interventions
- **Fills need** for lack of or ineffective neonatal and early life vaccination
- **Indirect Protection**:
  - Prevents maternal infection
  - Breast milk antibodies

- Tetanus (Diphtheria)
- Pertussis
- Influenza
- GBS
- RSV
- Meningococcus (A; B)
- Pneumococcus
- CMV, HSV
- Zika
- Hepatitis E
- Malaria, Cholera
- *E.coli*, Listeria

Key Issues on Maternal Immunization

- No vaccine licensed specifically for pregnancy
  - Existing vaccines are **recommended** for pregnant women based on **risk-benefit** assessment (tetanus, influenza, pertussis)
  - New vaccines specifically targeting pregnant women are in development (RSV, GBS)
- **Background risks** inherent to pregnancy challenge the assessment of safety
- **Safety** and **efficacy** needs to be demonstrated for mother and infant (ideally)
- **Research and Implementation** in pregnancy:
  - Inclusion of pregnant women in clinical trials
  - Design of vaccines for pregnancy (not live, no viral vectors, adjuvants?)
  - Maternal immunization schedules and impact on infant immunization schedules

Maternal Immunization Challenges

- **Research in pregnancy**
- **Knowledge Gaps**
  - Disease burden to assess impact
  - Placental function-immunology; optimal timing for maternal immunization
  - Maternal immune responses with repeated vaccination
  - Contribution of transplacental and breast milk antibodies
- **Safety in mothers and infants**
  - Observational vs prospective clinical trials
  - Background rates of key outcomes of pregnancy and infant health
  - Harmonised case definitions
- **Efficacy**
  - Duration of protection in mothers and infants
  - Outcome measures (death, hospitalization, severity, infection, costs?)
  - Effect of maternal antibody on infant immune responses to vaccine or infection
- **Implementation**
  - Strategy, maternal vaccine schedule, policy, resources, priorities
  - Post-implementation surveillance of safety and efficacy - sustainability

Recent Milestones in Maternal Immunization

- **2008-2010 - BMGF** supports pivotal study in Bangladesh (pneumococcus vs. influenza) and 3 large studies of **influenza** MI in Nepal, Mali and South Africa.
- **2009-10** – **MenA**frivac Program includes pregnant women
- **2009-10 Influenza Pandemic** – Influenza MI and research prioritized.
- **2012 SAGE-WHO** make **Influenza** vaccination of pregnant women a global priority for all countries were influenza vaccination is administered
  - 34 countries have implemented influenza MI programs: 29 in PAHO, rest in Africa, Asia, Eastern Europe
- **2012** – Given re-emergence of **Pertussis**, infant protection through MI with Tdap **recommended in US, UK**, Australia, some provinces of Canada, LAM. **2015 – 2017 Effectiveness data from UK** supports intervention.

Ongoing:

- **BMGF** projects **Pertussis** MI in South Africa, Pakistan, Kenya
- **BMGF and Industry** studies on **RSV and GBS vaccines** for MI
- **FDA**, **NIH, CDC, WHO and Brighton + multiple other stakeholders support** assessment of vaccines and safety of vaccines in pregnancy

Vaccine 31 (2013) 4274–4279

Contents lists available at ScienceDirect

Vaccine

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

Research on vaccines during pregnancy: Protocol design and assessment of safety☆,☆☆

Flor M. Munoz[a,*], Jeanne S. Sheffield[b], Richard H. Beigi[c], Jennifer S. Read[d], Geeta K. Swamy[e], Indira Jevaji[f,1], Sonja A. Rasmussen[g], Kathryn M. Edwards[h], Kimberly B. Fortner[i], Shital M. Patel[j], Catherine Y. Spong[k], Kevin Ault[l], R. Phillips Heine[e], Mirjana Nesin[m]

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Research on vaccines during pregnancy: Reference values for vital signs and laboratory assessments

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Protocol design, safety monitoring, assessment and reporting tools for studies of vaccines in pregnancy

Safety: Speaking the Same Language

Vaccine 33 (2015) 6441–6452

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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

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ABSTRACT

Background: The variability of terms and definitions of Adverse Events Following Immunization (AEFI) represents a missed opportunity for optimal monitoring of safety of immunization in pregnancy. In 2014, the Brighton Collaboration Foundation and the World Health Organization (WHO) collaborated to address this gap.

Methods: Two Brighton Collaboration interdisciplinary taskforces were formed. A landscape analysis included: (1) a systematic literature review of adverse event definitions used in vaccine studies during pregnancy; (2) a worldwide stakeholder survey of available terms and definitions; (3) and a series of taskforce meetings. Based on available evidence, taskforces proposed key terms and concept definitions to be refined, prioritized, and endorsed by a global expert consultation convened by WHO in Geneva, Switzerland in July 2014.

Results: Using pre-specified criteria, 45 maternal and 62 fetal/neonatal events were prioritized, and key terms and concept definitions were endorsed. In addition recommendations to further improve safety monitoring of immunization in pregnancy programs were specified. This includes elaboration of disease concepts into standardized case definitions with sufficient applicability and positive predictive value to be of use for monitoring the safety of immunization in pregnancy globally, as well as the development of guidance, tools, and datasets in support of a globally concerted approach.

Conclusions: There is a need to improve the safety monitoring of immunization in pregnancy programs. A consensus list of terms and concept definitions of key events for monitoring immunization in pregnancy is available. Immediate actions to further strengthen monitoring of immunization in pregnancy programs are identified and recommended.

- **Guideline for MI clinical trials**
- **Matrix of key variables**

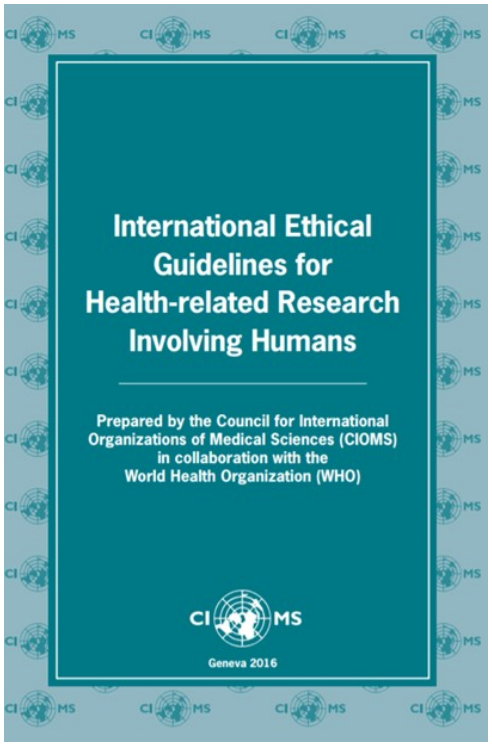
Neonatal (11)	**Maternal (10)**
Stillbirth	SAB
Neonatal Death	Maternal Death
Congenital Anomalies	FGR
Preterm Birth	Premature labor
Neonatal Infection	Eclampsia/pre-eclampsia
LBW	Postpartum hemorrhage
SGA	Antenatal bleeding
FTT	Gestational DM
Neonatal Encephalopathy	Fetal distress (non-reassuring fetal status)
Respiratory Distress	Dysfunctional labor
Microcephaly	

Related terms and enabling terms

gaia

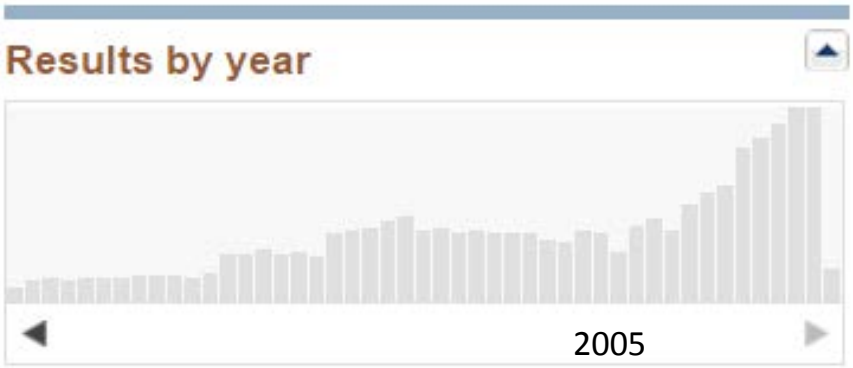
Recent Progress in Maternal Immunization Research

- Pregnancy and Lactation Labeling Rule (PLLR)
- 2015 VRBAC Meeting
- NVAC 2015-16 MI group
- Common Rule Update 2016
- 21 Century Cures Act 2017
- CIOMS 2017
- WHO IVR - MI



Maternal Immunization Research

Total Hits: 8765



ClinicalTrials.gov

A service of the U.S. National Institutes of Health

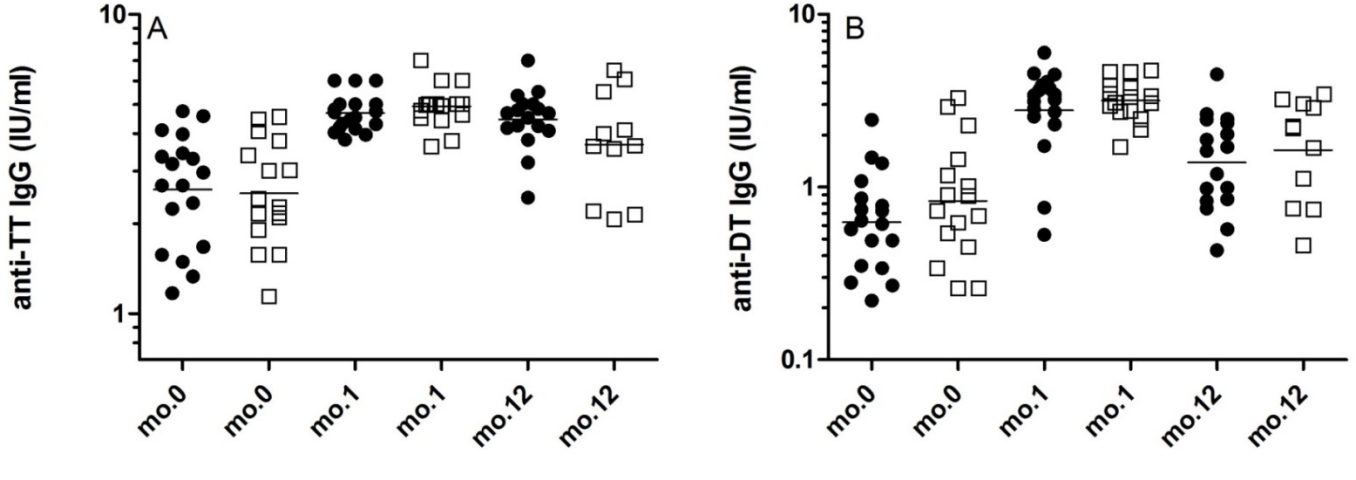
271 studies found for: maternal immunization

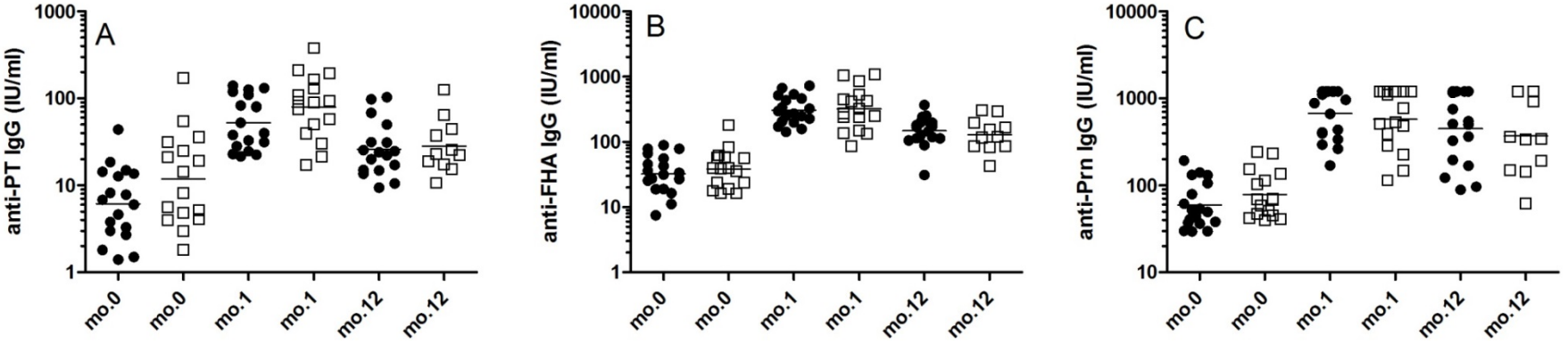
Modify this search | How to Use Search Results

- **Safety/Immunogenicity**
- **Effect on infant immune responses**
- **Optimal time for vaccination during pregnancy**
- **Placental biology/maternal-infant interactions**
- **Implementation**

1	Not yet recruiting	A Post-marketing, Observational, Retrospective Study to Assess the Safety of Refortrix TM (Tdap) When Administered During Pregnancy in a Maternal Immunization Program in Brazil.	Condition: Diphtheria Intervention: Biological: Combined diphtheria, tetanus and tricomponent acellular pertussis vaccine [Refortrix (Tdap)]
2	Completed	RSV F Vaccine Maternal Immunization Study in Healthy Third-trimester Pregnant Women.	Condition: Respiratory Syncytial Virus Infections Interventions: Drug: Saline Placebo (0.5mL injection); Drug: RSV F vaccine (0.5mL injection)
3	Completed	Maternal Immunization To Prevent Infant Otitis Media	Condition: Otitis Media Interventions: Biological: PNCRM9; Biological: Placebo comparator
4	Recruiting	Impact of Boostrix™ Maternal Vaccination on Morbidity and Mortality of Pertussis Disease in Infants ≤6 Weeks of Age, in Bogota, Colombia.	Conditions: Diphtheria; Acellular Pertussis; Tetanus Intervention: Other: Pertussis maternal immunization
5	Active, not recruiting	Pertussis Maternal Immunization Study	Condition: Pregnant Women Interventions: Biological: Tdap; Biological: Td
6	Recruiting	A Study to Determine the Safety and Efficacy of the RSV F Vaccine to Protect Infants Via Maternal Immunization	Condition: Respiratory Syncytial Virus Infections Interventions: Biological: RSV F vaccine with adjuvant; Biological: Formulation buffer
7	Unknown †	Maternal Immunization: Giving Immunity For Tomorrow	Conditions: Pregnancy; Influenza
8	Completed	Pertussis Vaccine in Healthy Pregnant Women	Conditions: Diphtheria; Pertussis; Tetanus Interventions: Drug: Placebo; Biological: Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed
9	Recruiting	Maternal Tdap Immunization in Guatemala	Conditions: Pertussis; Whooping Cough Interventions: Biological: Tdap; Biological: Td
10	Active, not recruiting	Genotyping of Human Platelet Alloantigens : Non-invasive Prenatal Diagnosis	Condition: Neonatal Thrombocytopenia Isoimmunization Maternal-fetal Interventions: Biological: Extra blood draw samples; Biological: extra amniotic fluid samples
11	Withdrawn	Active Immunization of HIV-Infected Pregnant Women: A Phase I Study of Safety and Immunogenicity of a rgp120/HIV-1 Vaccine (NOTE: Some Patients Receive Placebo)	Conditions: HIV Infections; Pregnancy; HIV Seronegativity Interventions: Biological: MF59; Biological: rgp120/HIV-1 SF-2
12	Active, not recruiting	A Trial Comparing Two Pertussis-containing Vaccines in Pregnancy and Vaccine Responses in UK Mothers and Their Infants	Condition: Responses to Infant Immunisations Interventions: Drug: Repevax; Drug: Boostrix-IPV
13	Not yet recruiting	Low Birth Weight Follow-up	Conditions: Non Specific Effects of Vaccine; Bacillus-Calmette-Guerin; Low Birth Weight; Maternal Immunisation Intervention:
14	Active, not recruiting	Field Trial of Maternal Influenza Immunization in Asia	Condition: Influenza Human Interventions: Biological: influenza vaccine; Biological: saline placebo

Concerns and Misconceptions: Effect of “pregnancy” on humoral immune responses





Huygen et al Vaccine 2015

Transplacental Antibody Transfer

- Maternal IgG crosses the placenta by a *selective* and *active* receptor-mediated transport system (hFcRn)
- Passage begins at ~ 17 wk, increases with gestation
- 33-35 wk: Mat = Fetal IgG
- 40 wk: Fetal > Mat IgG
- Cord/Maternal Ab correlation favors infant
- Half life ~ 30-40 days
- High Ab → longer protection

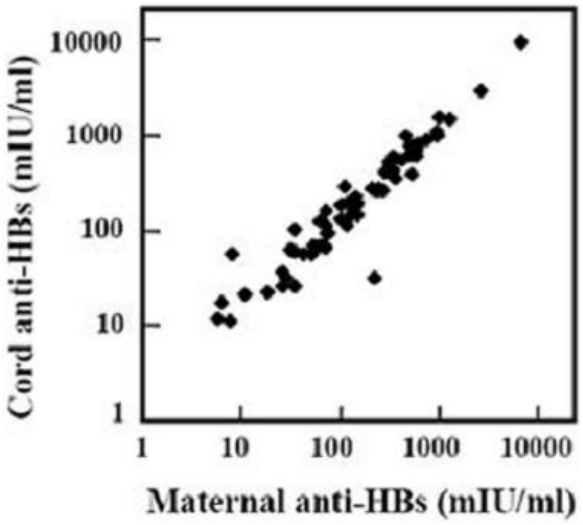


Figure 2. Correlation of transplacentally transferred anti-HBs in infants with the maternal antibody (linear regression analysis, $y = 1.393x - 37.286$, $r = 0.992$, $P < 0.001$, $n = 63$).

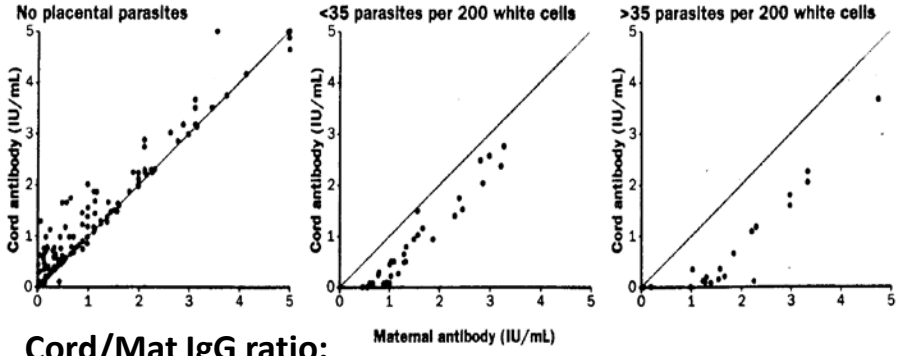
Malek A, et al. AJRI 1996
Ellinger I, Fuchs R. WMW 2012,162/9-10

Wang Z, et al. PLoS One 2011;6(9):e25130

Factors that Alter Transplacental Antibody Transfer

- Gestational age at birth (little benefit for preterms)
- Interval vaccination to delivery
- Maternal IgG level at delivery
- IgG Subclass
  - IgG1 ~ IgG3 > IgG4> IgG2
- Placental abnormalities
- Infections (malaria, HIV)
- Maternal health

Malaria



Cord/Mat IgG ratio:

0.82 **0.23** **0.18**

Brair et al. Lancet 1994;343:208

HIV

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. JAMA 2011;205(6) 576-84

Transplacental antibody: Infant Duration of Protection Differs in Vaccinated vs. Naturally Immune Mothers

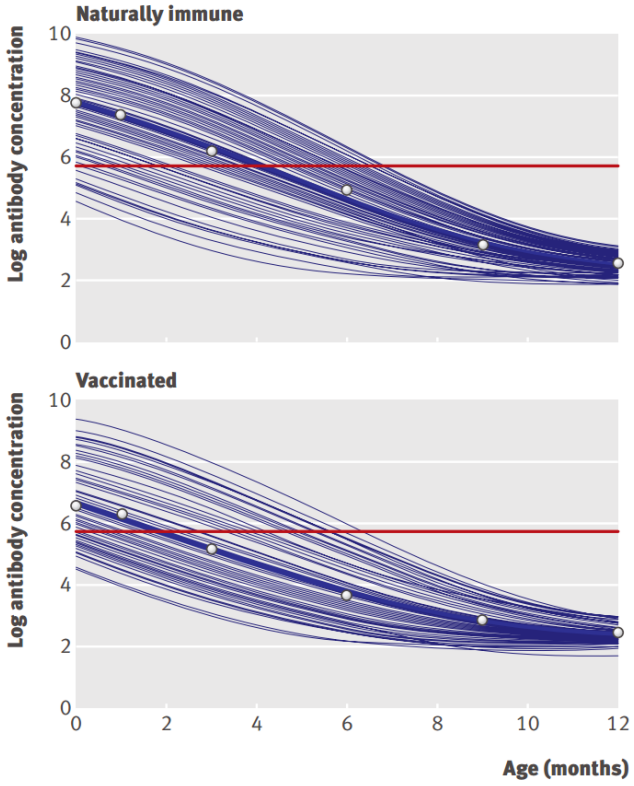


Fig 1| Fitted individual profiles for decay in log antibody concentration (log(AL+1)) based on linear mixed model (blue lines) in all infants, infants from naturally immune women, and infants from vaccinated women. Horizontal red line indicates threshold of 300 mIU/ml. Thick curve is predicted mean curve in each group with observed means at birth and 1, 3, 6, 9, and 12 months as open circles

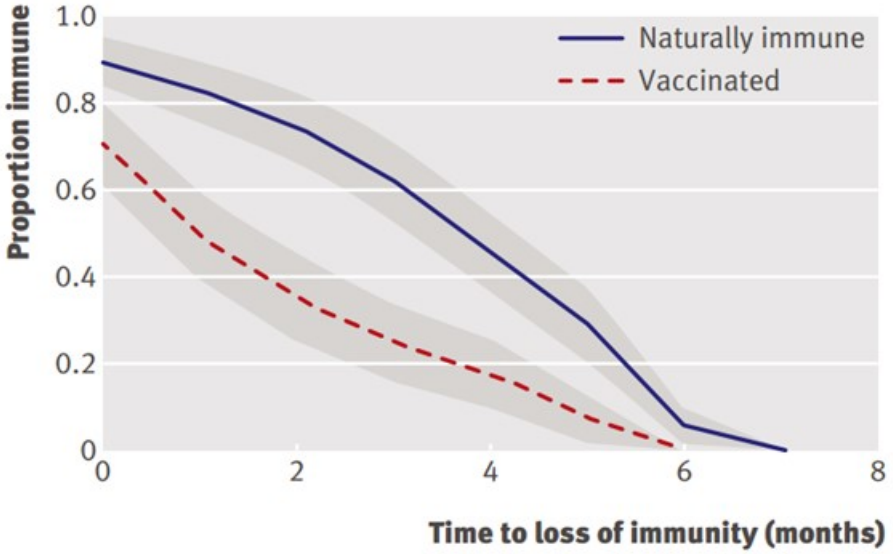
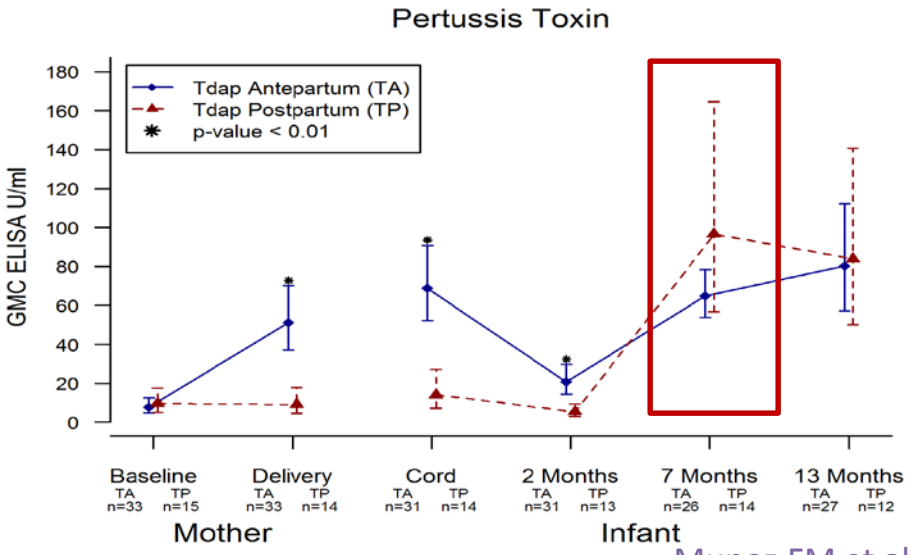
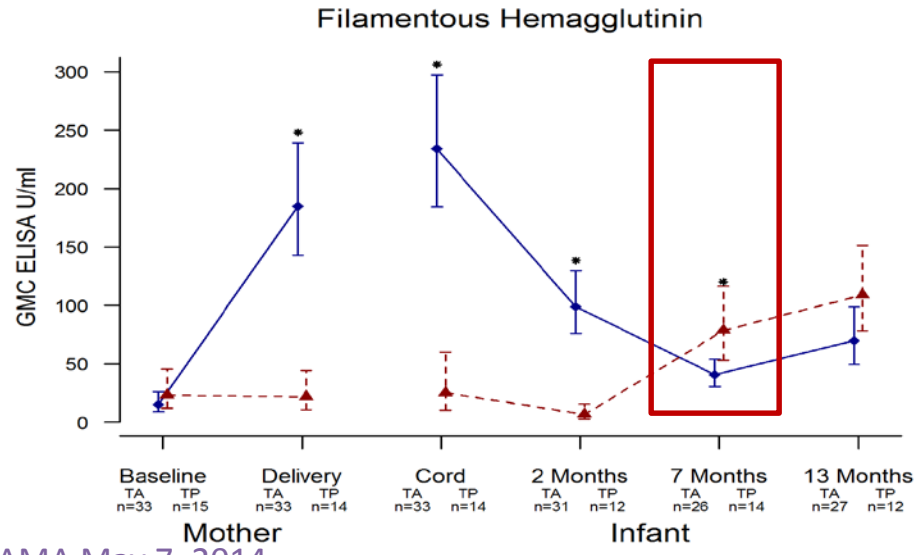


Fig 2| Proportion of infants of vaccinated women and naturally immune women still immune as a function of time to loss of immunity. Shaded area is 95% confidence interval

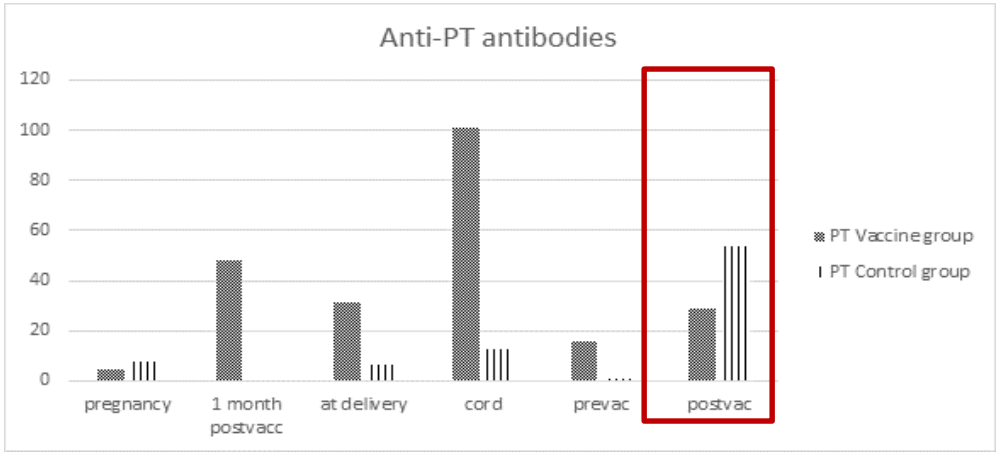
Leuridan E. BMJ 2010

Maternal and Infant Responses to Maternal Tdap Immunization

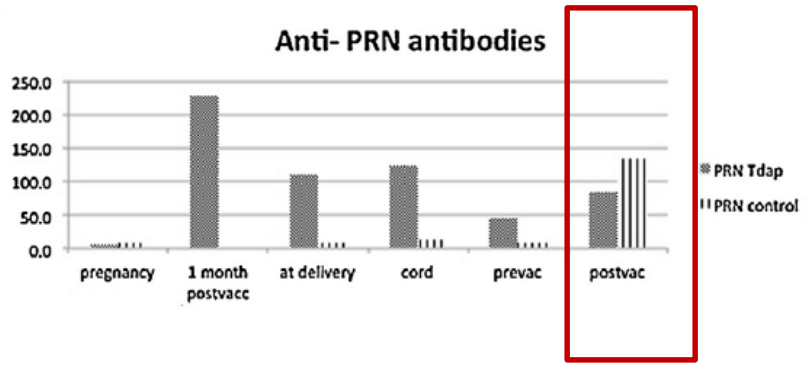




Munoz FM et al. JAMA May 7, 2014



Maertens & Leuridan et al, Vaccine 2016



Hoang HT, *et al . Vaccine* 2016,34:151-159.

Optimal Time for Maternal Immunization

Abu Raya, Vaccine 2014 (Boostrix) – 63 vaccinated PW vs. 20 unvaccinated controls

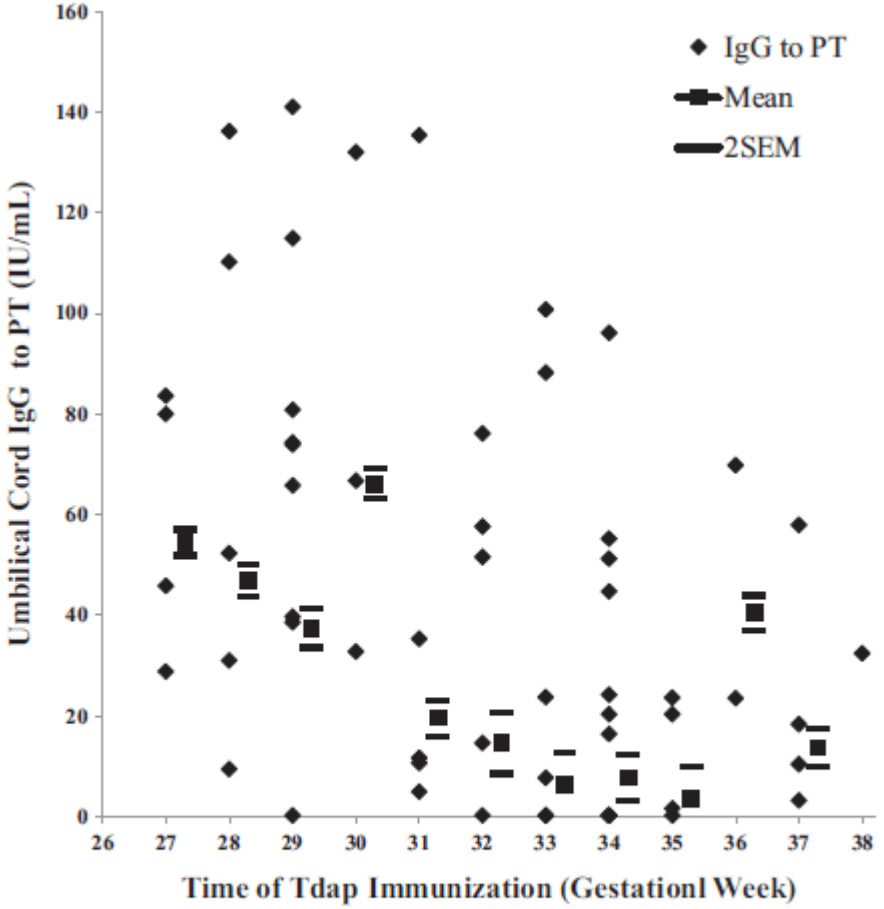


Fig. 2. Scatter graph of the mean (±2 standard error of the mean) of umbilical cord immunoglobulin G to pertussis toxin concentrations as a function of timing of gestational tetanus, diphtheria and acellular pertussis immunization (weeks). *Abbreviations*: IgG, immunoglobulin G; PT, pertussis toxin; SEM, standard error of the mean; Tdap, tetanus, diphtheria and acellular pertussis; IU/mL, international unit/milliliter.

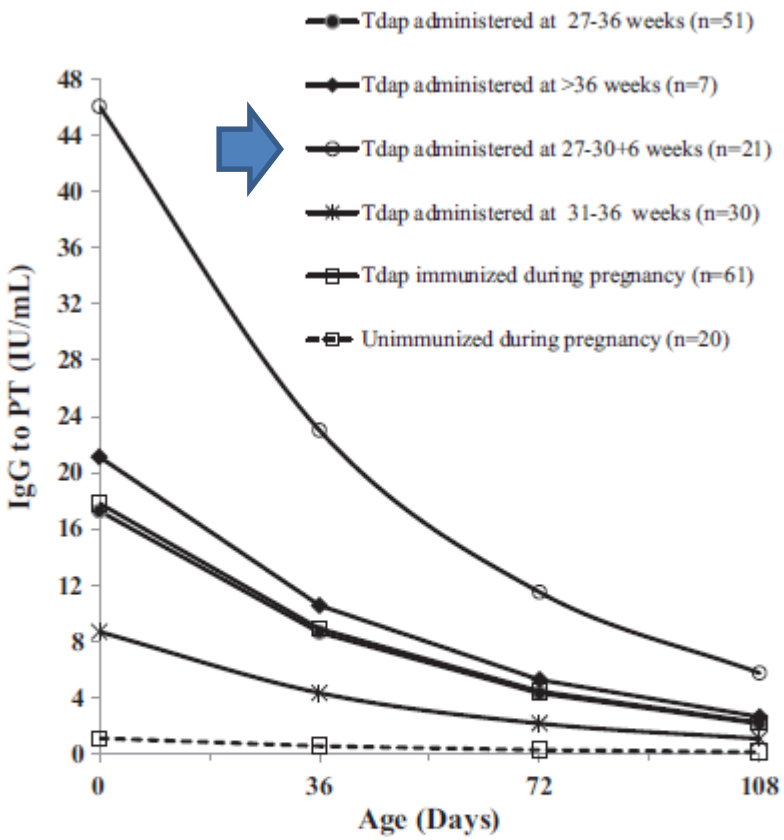


Fig. 3. Geometric mean concentrations (GMCs) of pertussis toxin immunoglobulin G in newborn cord sera interpolated up to 108 days post-partum stratified by sequential time frames of tetanus, diphtheria and acellular pertussis administration in late pregnancy. Confidence intervals for newborns' umbilical cord GMCs are presented in Table 3. *Abbreviations*: Tdap, tetanus, diphtheria and acellular pertussis; PT, pertussis toxin; IgG, immunoglobulin G; IU/mL, international unit/milliliter.

Maternal Tdap vaccination reduces pertussis severity in infants

Retrospective cohort study evaluate **pertussis-infected infants** born in 2011-2015 whose mothers received Tdap vaccine during pregnancy in California

	Maternal Tdap N=49	No Maternal Tdap N=371		
	N (%)	**N (%)**	**P-value**	**RR (95%CI)**
Infant DTaP >14days prior onset	3 (6)	6 (2)	0.08	1.1 (0.9, 1.1)
Course of pertussis illness				
Hospitalized	21 (43)	271 (73)	<0.001	0.5 (0.4, 0.6)
Days hospitalized, median [IQR]	3 [1-6]	6 [3-14]	0.02	
ICU admissions	6 (13)	102 (30)	0.01	0.8 (0.7, 0.9)
Seizures	0	14 (4)	0.6	0.9 (0.9, 1.0)
Intubated	0	28 (8)	0.06	0.9 (0.9, 1.0)
Died	0	6 (2)	1	1

Winter K, *et al*. *Clin Infect Dis* 2017.

UK EFFECTIVENESS DATA

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)
Infants <3 months of age by timing of maternal immunisation			
Vaccination at least 28 days before birth	14% (10/69)¶	63%	91% (83 to 95)
Vaccination 7–27 days before birth	3% (2/72)||	19%	91% (70 to 96)
Vaccination 0–6 days before or 1–13 days after birth	3% (2/68)**	5%	38% (–95 to 80)
Infants <2 months of age			
Vaccination at least 7 days before birth	15% (11/71)	61%	90% (82 to 95)
Vaccination at least 7 days before birth with coverage reduced by a relative 20%	15% (11/71)	49%	82% (67 to 90)

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

Efficacy of maternal IIV3 vaccination in preventing influenza illness in the women until 6 months post-partum

Study	Period, country	Control group	Population	Outcomes	Vaccine efficacy
Zaman K, *et al. N Engl J Med* 2008	2004-2005 Bangladesh	23-valent pneumococcal vaccine	IIV3 172 Control 168	Respiratory illness with fever	**35.8%** **(95%CI: 3.7%, 57.2%)**
Madhi SA, *et al. N Engl J Med* 2014	2011-2012 South Africa	Saline placebo	IIV3 1062 Control 1054	PCR-confirmed influenza	**50.4%** **(95%CI: 14.5%, 71.2%)**
Tapia MD, *et al. Lancet ID* 2016	2011-2013 Mali	Meningococcal vaccine	IIV3 2108 Control 2085	PCR-confirmed influenza	**70.3%** **(95%: 42.2%, 85.8%)**
Steinhoff MC, *et al Lancet ID* 2017	2011-2013 Nepal	Saline placebo	IIV3 1847 Control 1846	Influenza like Illness	**19.0 %** **(95% CI 1%, 34%)**

IIV3, inactivated influenza vaccine.

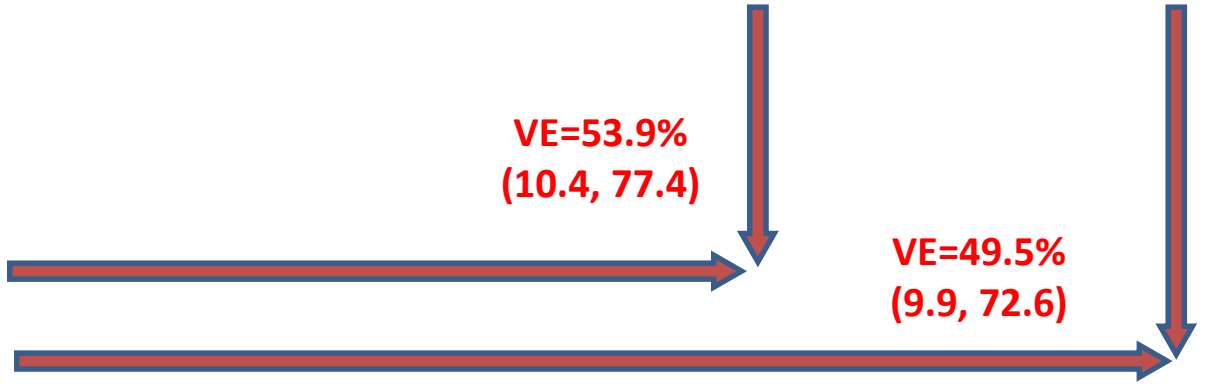
Efficacy of maternal IIV3 vaccination in preventing influenza illness in the infants until 6 months of age

Study	Period, country	Control group	Population	Outcomes	Vaccine efficacy
Zaman K, *et al. N Engl J Med* 2008; 359:1555 –64	2004-2005 Bangladesh	23-valent pneumococcal vaccine	IIV3 161 Control 166	Rapid test-confirmed influenza	**62.8%** **(95%CI: 5.0%, 85.4%)**
Madhi SA, *et al. N Engl J Med* 2014; 371:918–31	2011-2012 South Africa	Saline placebo	IIV3 1026 Control 1023	PCR-confirmed influenza	**48.8%** **(95%CI: 11.6%, 70.4%)**
Tapia MD, *et al. Lancet ID* 2016	2011-2013 Mali	Meningococcal vaccine	IIV3 2064 Control 2041	PCR-confirmed influenza	**33.1%** **(95%: 3.7%, 53.9%)**
Steinhoff MC, *et al Lancet ID* 2017	2011-2013 Nepal	Saline placebo	IIV3 1,831 Control 1,835	PCR-confirmed influenza	**30%** **(95% CI: 5%, 48%)**

IIV3, inactivated influenza vaccine.

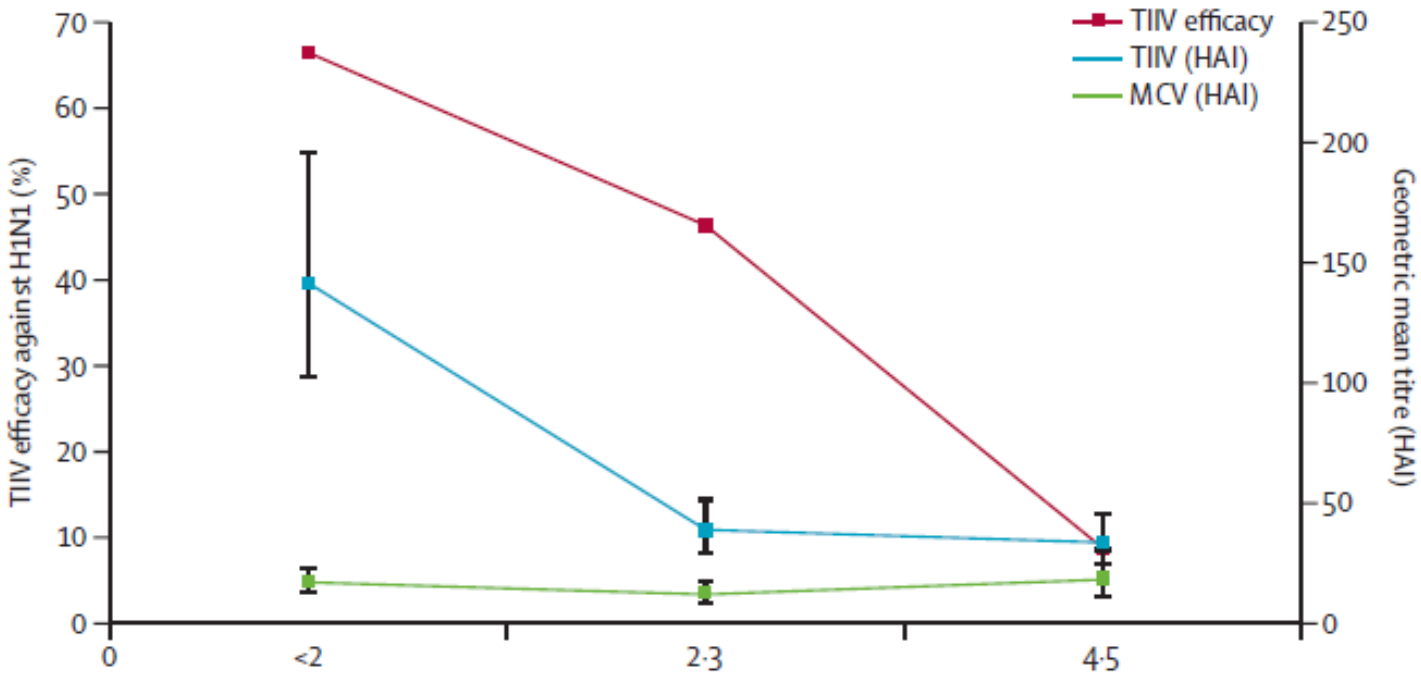
Duration of IIV3 efficacy against influenza illness in infants

	Influenza cases		
IIV3	2 1.0 per child/months	12 3.1 per child/months	5 0.9 per child/months
Placebo	14 6.8 per child/months	16 4.1 per child/months	7 1.3 per child/months
VE (95% CI)	85.8% (38.3, 98.4)	25.3% (-68.2, 67.8)	29.2% (-159.3, 82.3)
P-value	0.002	0.5	0.6



Nunes MC, *et al. JAMA Pediatr* 2016,170:840-847.

Duration of IIV3 efficacy against influenza illness in infants



	<2	2-3	4-5
TIIV efficacy	66·5% (−317·6 to 99·4)	46·4% (−44·7 to 81·9)	8·8% (−69·8 to 51·2)
TIIV (HAI)	141·6 (102·6 to 195·4)	39·0 (29·5 to 51·5)	33·7 (18·3 to 45·7)
MCV (HAI)	17·2 (12·8 to 23·1)	12·1 (8·3 to 17·6)	18·3 (10·9 to 30·7)

Tapia MD, *et al. Lancet ID* 2016.

Vaccination of pregnant women in preventing Influenza-related hospitalization in their infants

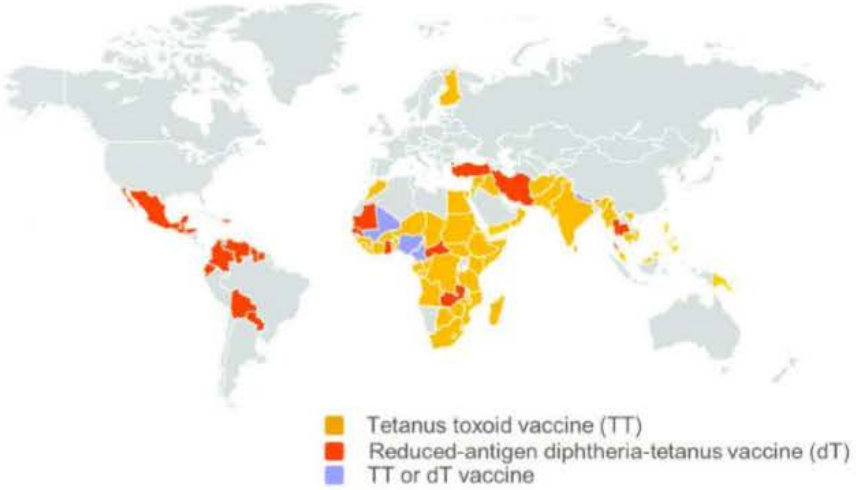
Study	Year, country	Design	Population	Outcomes	VE
Black SB, et al. 2004	1997-2002 USA	Retrospective cohort	3652 infants of immunized moms 44987 infants of non-immunized moms	Hospitalization for pneumonia and influenza	**4% (95%CI: -3, 11)**
France EK, et al. 2006	1995-2001 USA	Retrospective matched cohort	3160 infants of immunized moms 37969 infants of non-immunized moms	Medically attended ARI	**4% (95%CI: -1, 1)**
Benowitz I, et al. 2010	2000-2009 USA	Matched case-control	<12 months old (113 cases; 192 matched controls)	Lab-confirmed influenza hospitalization	**92% (95%CI: 62, 98) in <6 months**
Eick AA, et al. 2011	2002-2005 USA	Prospective cohort	1169 infant mother pairs	Lab-confirmed influenza; ILI hospitalization	**41% (95%CI: 7, 63) 39% (95%CI: 16, 55)**
Poehling KA, et al. 2011	2002-2009 USA	Active population-based case-control	<6 months old (151 cases; 1359 controls)	Lab-confirmed influenza hospitalization	**48% (95%CI: 9, 70)**
Dabrera G, et al. 2014	2013-2014 England	Retrospective study using the screening method	<6 months old (43 cases)	Lab-confirmed influenza; Lab-confirmed influenza hospitalization	**71% (95%CI: 24, 89) 64% (95%CI: 6, 86)**
Regan AK, et al. 2016	2012-2013 Australia	Retrospective population-based cohort	3169 infants of immunized moms 27859 infants of non-immunized moms	Hospitalization for respiratory illness during influenza season	**aHR: 0.75 (95%CI: 0.56, 0.99)**

Black SB, *et al. Am J Perinatol* 2004;21:333–9; France EK, *et al. Arch Pediatr Adolesc Med* 2006;160:1277–8; Benowitz I, *et al. Clin Infect Dis* 2010;51:1355–61; Eick AA, *et al. Arch Pediatr Adolesc Med* 2011;165:104–11; Poehling KA, *et al. Am J Obstet Gynecol* 2011;204:S141–8; Dabrera G, *et al. Euro Surveill* 2014;19:20959; Regan AK, *et al. Pediatr Infect Dis J* 2016,35:1097-1103

Implementation: Maternal Immunization Recommendations Worldwide

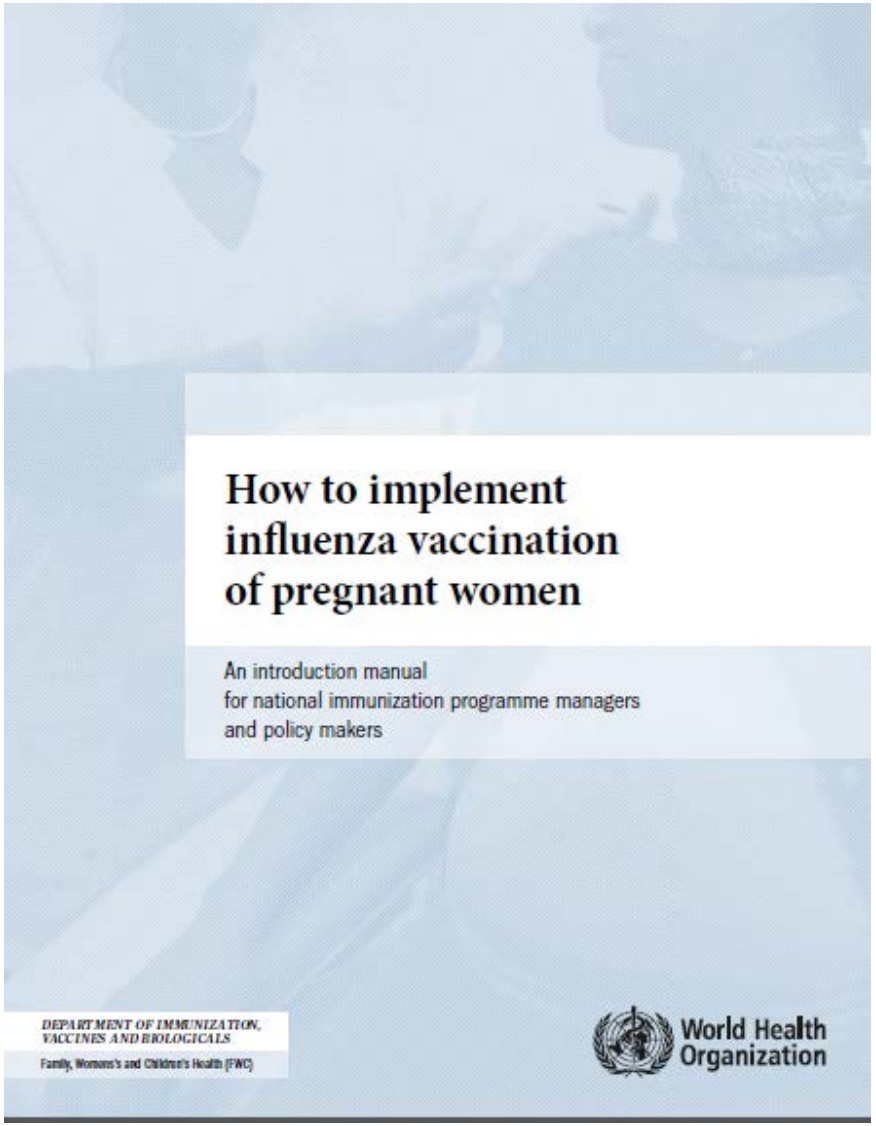
Influenza

Tetanus



Pertussis

Note: Despite recommendation, Coverage is variable for each vaccine and country



- Published September 2016
- Produced by the Initiative for Vaccine Research (IVR) of the Department of Immunization, Vaccine and Biologicals, WHO
- Supported by BMGF

<u>Addresses:</u>

- **Decision making** at country level, aimed at policy-makers
- Issues concerning **vaccine introduction planning and implementation**, aimed at national immunization programme managers and immunization partners

Annexes and links provide **planning and assessment tools** for policy makers and programme managers

This publication is available on the Internet at:
http://www.who.int/immunization/research/development/influenza_maternal_immunization/en/index1.html

Active Research is Ongoing

WHO

RFPs on assessment of safety of MI

Areas of work

Maternal and newborn

Mother and Newborn Information for Tracking Outcomes and Results (MONITOR) technical advisory group

Maternal Immunization and Antenatal Care Situation Analysis (MIACSA)

The Maternal Death Surveillance and Response (MDSR) and perinatal audit

Industry studies

Group B-Streptococcus

- 1980-90 studies – monovalent (type III) polysaccharide and conjugate vaccines clinical trials in healthy adults and pregnant women
- Recent clinical trials in pregnant women (phase I-II) conducted in US and South Africa demonstrate response and Ab transfer
- Phase II and III clinical trials needed – likely with multivalent conjugate vaccine

Respiratory Syncytial virus

One F-Protein-based vaccine in phase III targeting pregnant women (global study), others in phase I-II

2016-17
US CDC
Convened Technical Consultation
to assess gaps in knowledge prior to
the introduction of RSV vaccines

Table 1. Summary of Respiratory Syncytial Virus Epidemiologic Gaps

Epidemiologic Gap	Summary
Surveillance for burden estimates	• Needed for all age groups, with finer age strata for extremes of age • Include MAARI and hospitalizations • Include high-risk populations, including preterm infants, children, and adults with underlying heart and lung disease, neurologic diseases, immunocompromised, Alaska Natives, American Indians, pregnant women, and residents of congregate settings (eg, long-term-care facilities) • Ensure design of surveillance platforms: -Can test for multiple respiratory pathogens -Avoid influenza-like illness and severe acute respiratory infection definitions
RSV-associated mortality	• Collect hospital and community-associated RSV deaths in all age groups
Short- and long-term outcomes of RSV infection	• Investigate effects of RSV on recurrent wheezing and asthma, particularly long-term effects • Conduct studies in pregnant women to determine impact of maternal RSV disease on pregnancy and neonatal outcomes • Assess impact on frailty in older adults
Correlates of protection	• Assess durability of respiratory mucosal antibodies and role in protection • Study correlation of neutralization and viral protein– or epitope-specific antibodies with disease protection • Investigate role of cellular immunity in RSV disease outcome
Cost-effectiveness	• Costs and benefits of vaccine introduction in target populations, which will need up-to-date burden estimates, indirect and out-of-pocket costs associated with RSV-associated MAARI, hospitalizations, and deaths
Assessing RSV diagnostic practices	• Needed to document potential underestimation of disease burden due to testing behaviors
Surveillance once vaccine is introduced	• Adverse events • Genomic sequencing of breakthrough infections to document changes in the virus

Abbreviation: RSV, respiratory syncytial virus.

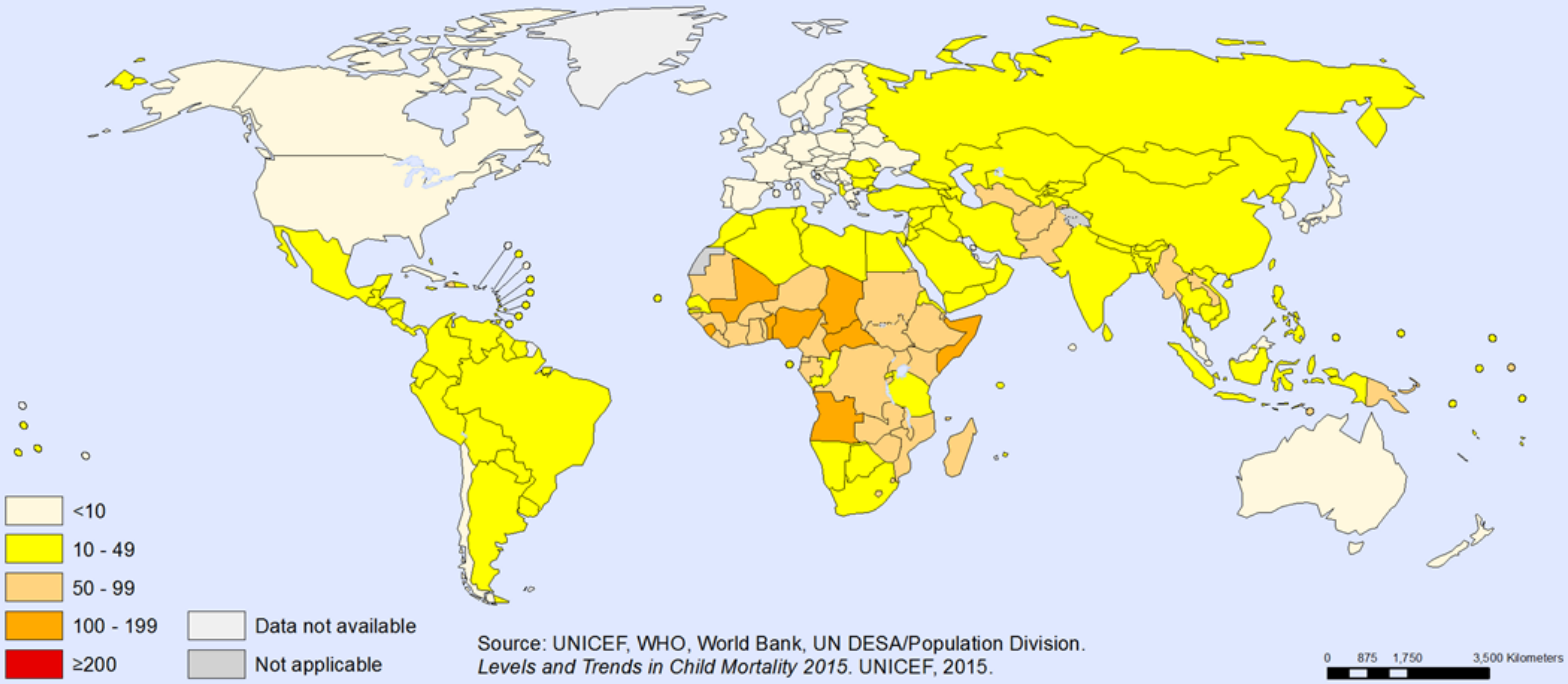
Kim et al. Clinical Infectious Diseases®
2017;65(6):1020–5

Opportunities for Maternal Immunization Overcoming Challenges

- Improve **coverage** with recommended vaccines for pregnant women
- Improve **confidence** about maternal immunization among providers and public
- Maintain **surveillance on safety** and immunogenicity post-implementation
- Evaluate most efficient **implementation strategies**, sites, platform, access, resources, efficacy, cost-benefit, impact
- Target most relevant pathogens in mothers-infants
- Increase **awareness** of burden of disease and potential **impact** of maternal immunization on relevant **outcome measures**
- Develop successful vaccines
- Well designed epidemiologic and clinical studies
- **Collaborative** work and partnership among stakeholders
- **Prioritize** maternal immunization as feasible public health strategy to **improve maternal and child health**

Texas Children’s Hospital, Houston, TX

Under-five mortality rate (probability of dying by age 5 per 1000 live births), 2015



Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

Mortality

5.9 million

children under age five died in 2015, nearly 16 000 every day

Causes of death

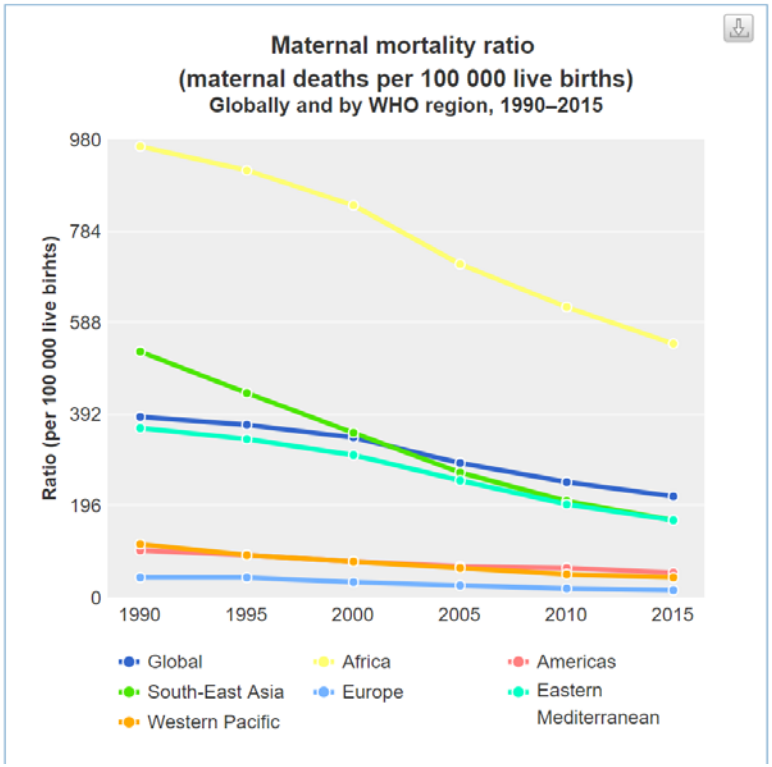
83%

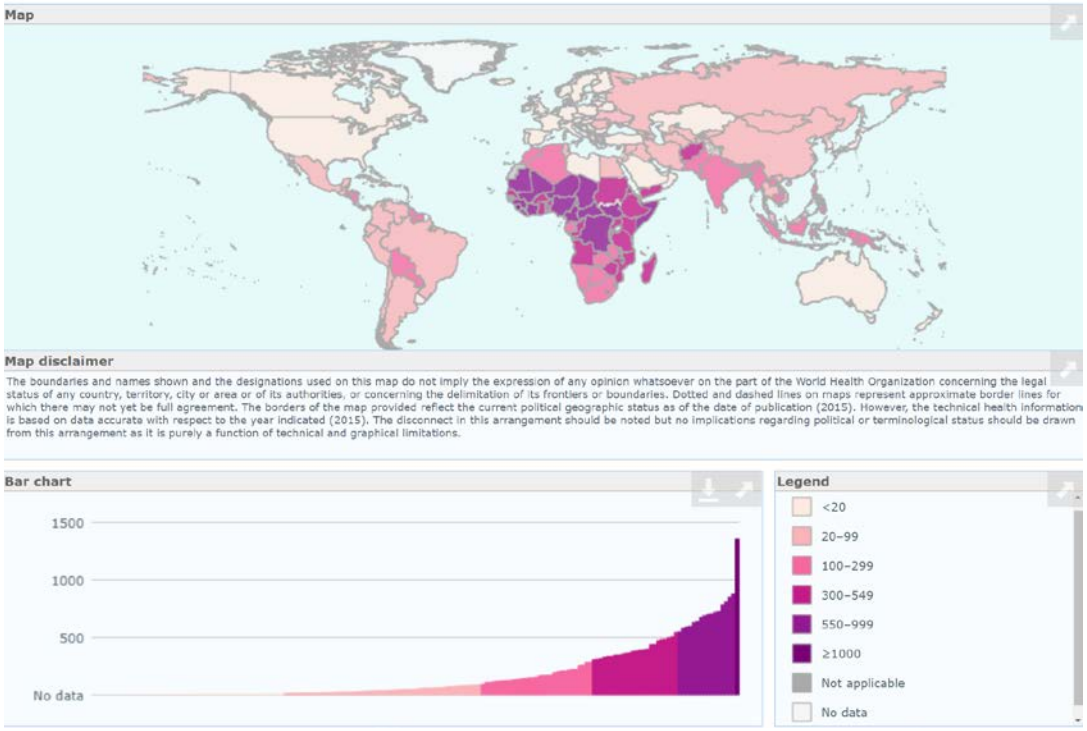
of deaths in children under age five are caused by infectious, neonatal or nutritional conditions

Preventing under-five deaths

58%

of children with suspected pneumonia are taken for treatment to an appropriate care provider


Maternal mortality ratio
(maternal deaths per 100 000 live births)
Globally and by WHO region, 1990–2015
Ratio (per 100 000 live birhts)
980
784
588
392
196
0
1990
1995
2000
2005
2010
2015
Global
Africa
Americas
South-East Asia
Europe
Eastern Mediterranean
Western Pacific


Map
Map disclaimer
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. The borders of the map provided reflect the current political geographic status as of the date of publication (2015). However, the technical health information is based on data accurate with respect to the year indicated (2015). The disconnect in this arrangement should be noted but no implications regarding political or terminological status should be drawn from this arrangement as it is purely a function of technical and graphical limitations.
Bar chart
1500
1000
500
No data
Legend
<20
20–99
100–299
300–549
550–999
≥1000
Not applicable
No data