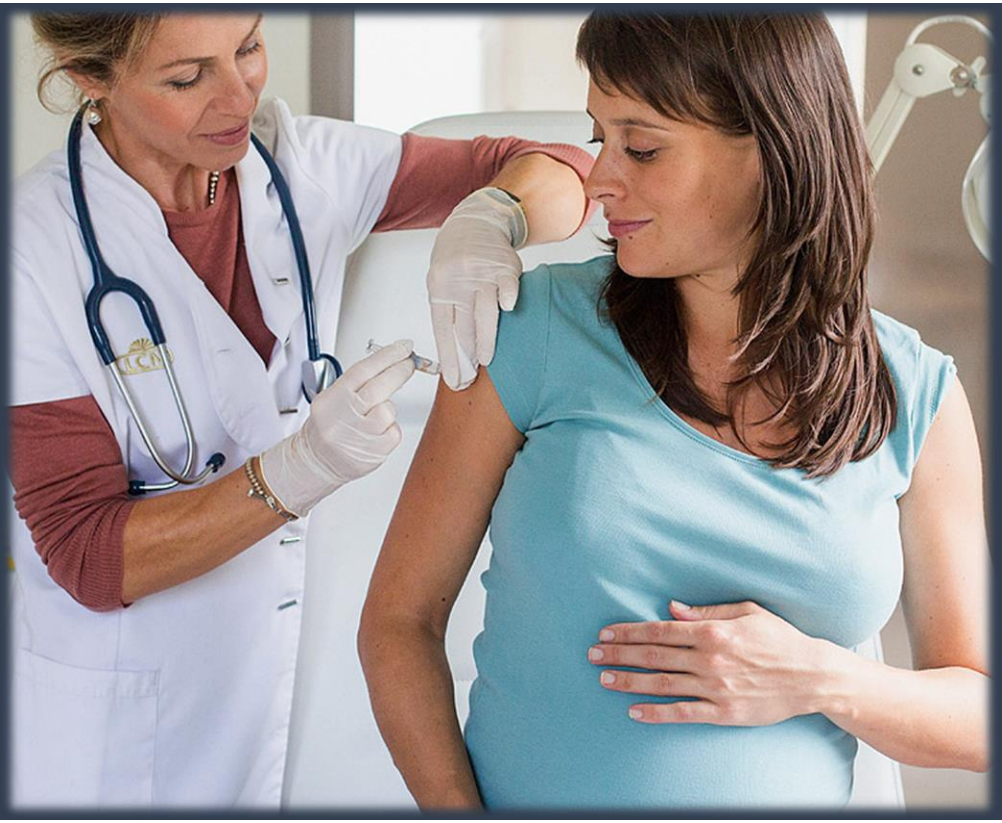

Maternal immunization: current status and future directions

Vaccinology 2017
III International Symposium for Asia Pacific Experts
Hanoi, Vietnam
October 17, 2017

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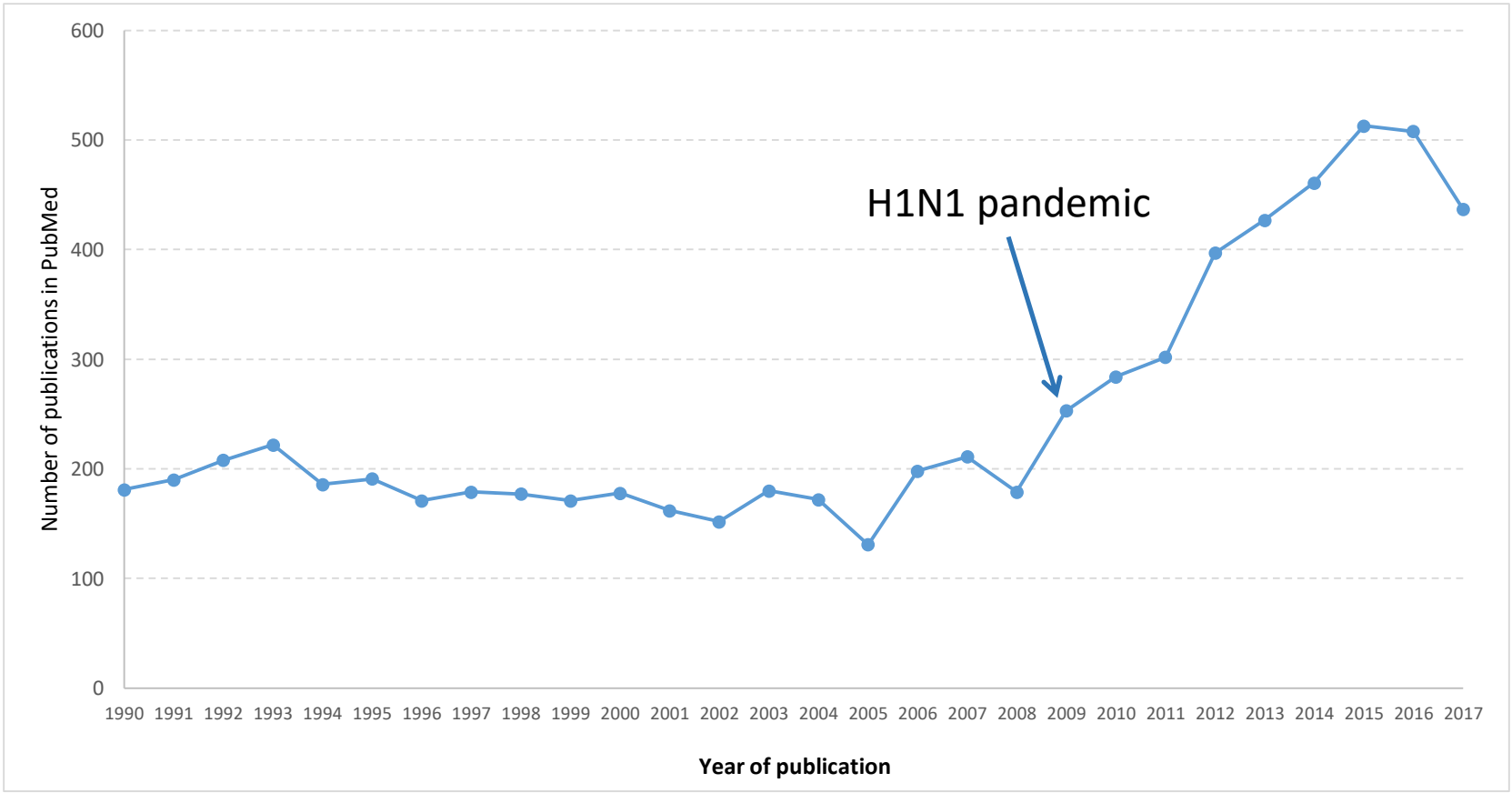
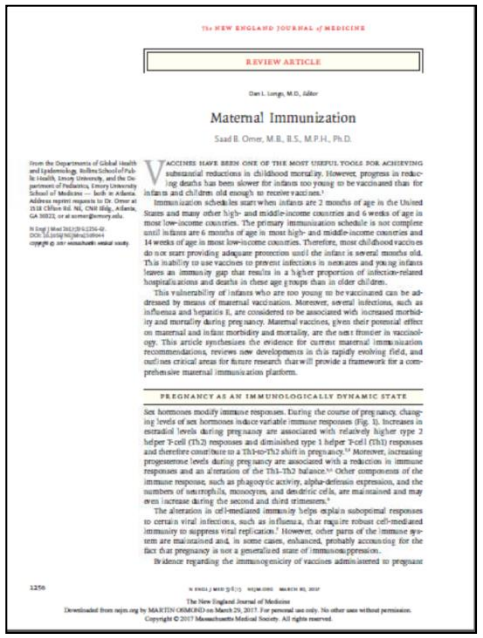
Trend in PubMed citations, 1990–2017



PubMed search term: "Maternal immunization", September 19, 2017

Recent reviews



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Maternal Immunization

Saad B. Omer, M.B., B.S., M.P.H., Ph.D.

VACCINES HAVE BEEN ONE OF THE MOST USEFUL TOOLS FOR ACHIEVING substantial reductions in childhood mortality. However, progress in reducing deaths has been slower for infants too young to be vaccinated than for infants and children old enough to receive vaccines.[1]

Immunization schedules start when infants are 2 months of age in the United States and many other high- and middle-income countries and 6 weeks of age in most low-income countries. The primary immunization schedule is not complete until infants are 6 months of age in most high- and middle-income countries and 14 weeks of age in most low-income countries. Therefore, most childhood vaccines do not start providing adequate protection until the infant is several months old. This inability to use vaccines to prevent infections in neonates and young infants leaves an immunity gap that results in a higher proportion of infection-related hospitalizations and deaths in these age groups than in older children.

This vulnerability of infants who are too young to be vaccinated can be addressed by means of maternal vaccination. Moreover, several infections, such as influenza and hepatitis E, are considered to be associated with increased morbidity and mortality during pregnancy. Maternal vaccines, given their potential effect on maternal and infant morbidity and mortality, are the next frontier in vaccinology. This article synthesizes the evidence for current maternal immunization recommendations, reviews new developments in this rapidly evolving field, and outlines critical areas for future research that will provide a framework for a comprehensive maternal immunization platform.

PREGNANCY AS AN IMMUNOLOGICALLY DYNAMIC STATE

Sex hormones modify immune responses. During the course of pregnancy, changing levels of sex hormones induce variable immune responses (Fig. 1). Increases in estradiol levels during pregnancy are associated with relatively higher type 2 helper T-cell (Th2) responses and diminished type 1 helper T-cell (Th1) responses and therefore contribute to a Th1-to-Th2 shift in pregnancy.[2] Moreover, increasing progesterone levels during pregnancy are associated with a reduction in immune responses and an alteration of the Th1–Th2 balance.[3,4] Other components of the immune response, such as phagocytic activity, alpha-defensin expression, and the numbers of neutrophils, monocytes, and dendritic cells, are maintained and may even increase during the second and third trimesters.[5]

The alteration in cell-mediated immunity helps explain suboptimal responses to certain viral infections, such as influenza, that require robust cell-mediated immunity to suppress viral replication.[6] However, other parts of the immune system are maintained and, in some cases, enhanced, probably accounting for the fact that pregnancy is not a generalized state of immunosuppression.

Evidence regarding the immunogenicity of vaccines administered to pregnant

1256

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New England Journal of Medicine
March 30, 2017
Volume 376, Issue 25

Series

Maternal immunisation 1

Maternal immunisation: collaboratin

Maternal Immunisation 2

Pertussis and influenza immunisation during preg

a landscape review

Maternal Immunisation 3

Group B streptococcus and respiratory syncytial virus

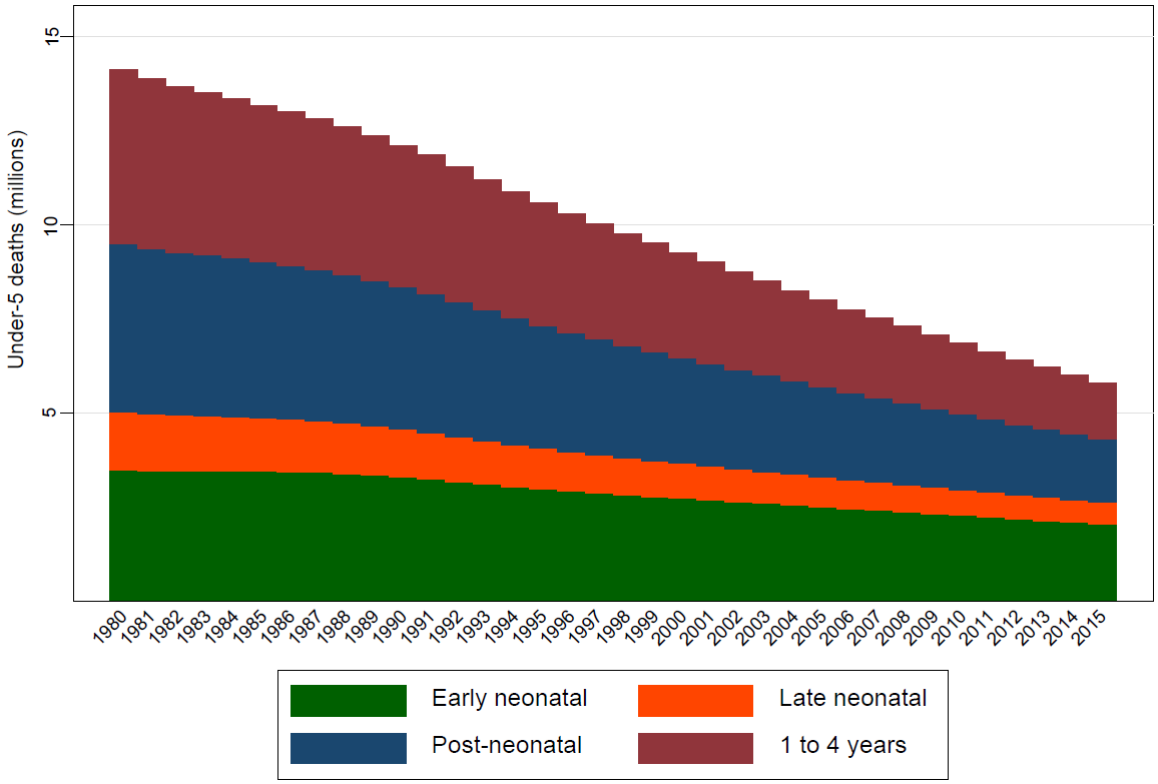
immunisation during pregnancy: a landscape analysis

Series

Lancet Infectious Diseases
April 19, 2017
Volume 17, Issue 7

1. Overview of immunization during pregnancy

Trends in under 5 mortality



- ~45% of under 5 deaths globally occur in the neonatal period (<28 days)
- Lower respiratory infection, sepsis and other infectious disorders of the newborn: ~24% of all neonatal deaths

Wang. Global Burden of Disease 2015 Child Mortality Collaborators. Lancet 2016;388:1725–74; Lozano. Lancet 2012; 380: 2095–128.

Why immunize pregnant women?

1. Direct protection to pregnant women, who may be unimmunized, under-immunized, or have waning immunity

2. Reduced maternal carriage or disease → reduced transmission of pathogens from mother to fetus/newborn

3. Leads to passive immunity for the neonates through transplacental transfer of maternal antibodies to the fetus

Sobanjo-ter Meulen A, et al. Vaccine 2016; 63: S123–33.; Sobanjo-ter Meulen A, et al. Vaccine 2015; 33: 6388–95; Marchant et al., Lancet ID 2017

History of maternal immunization

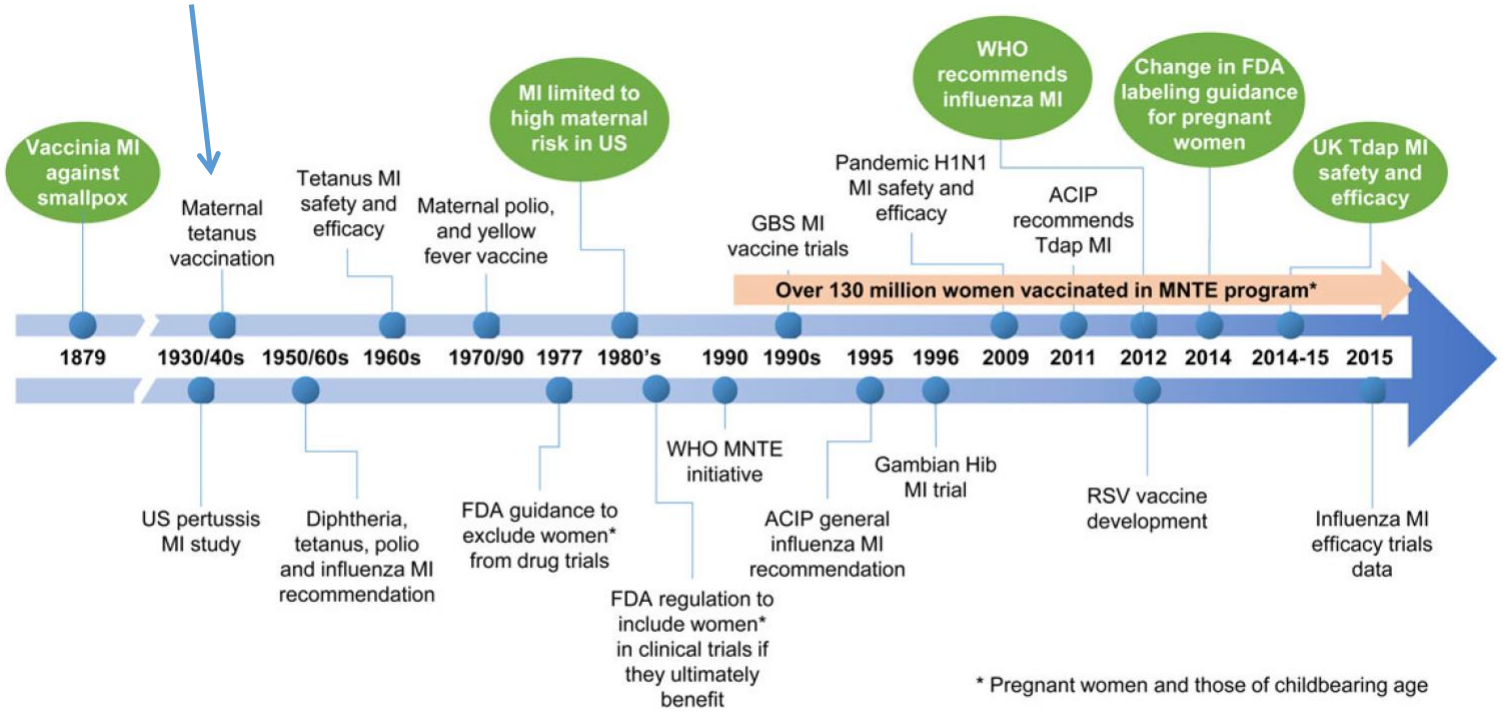


Figure 2. The history of maternal immunization [12]. Abbreviations: ACIP, Advisory Committee on Immunization Practices; FDA, US Food and Drug Administration; GBS, group B *Streptococcus*; Hib, *Haemophilus influenzae* type b; MI, maternal immunization; MNTE, maternal neonatal tetanus elimination; RSV, respiratory syncytial virus; Tdap, reduced-dose tetanus-diphtheria-acellular pertussis vaccine; WHO, World Health Organization.

Sobanjo-ter Meulen A, et al. Vaccine 2016; 63: S123–33.

Current recommendations for existing vaccines

Vaccines routinely recommended for all pregnant women **	No recommendation for use in pregnancy (use if indicated)	Contraindicated during pregnancy
▪ **Inactivated influenza virus (IIV)** - *One dose each pregnancy in any trimester, as early as possible during influenza season* ▪ **Acellular pertussis containing vaccine (Tdap)** - *One dose each pregnancy, optimally at 27-36 weeks' gestation* ▪ **Td** - *Routinely recommended during pregnancy in some countries for MNT elimination*	▪ Cholera (oral) ▪ Hib ▪ Meningococcal conjugate ▪ Meningococcal polysaccharide ▪ Meningococcal B ▪ 13- Valent pneumococcal conjugate ▪ 23- Valent pneumococcal polysaccharide ▪ Typhoid Vi ▪ Hep A ▪ Hep B ▪ JEV ▪ Polio ▪ Rabies ▪ HPV ▪ Yellow fever	▪ BCG ▪ Oral typhoid ▪ JEV ▪ MMR ▪ Rotavirus ▪ Varicella ▪ Zoster

***** Recommendations listed are primarily derived from the USA and Canada, but also apply in many other settings.***

Perret & Nolan. Pediatr Drugs 2017; 19: 313-24; Omer SB. NEJM 2017;376:1256–67. Canadian Immunization Guide, PHAC.

2. Practices and evidence for existing vaccines administered to pregnant women

Influenza

EPIDEMIC PNEUMONIA (SPANISH INFLUENZA) IN PREGNANCY

EFFECT IN ONE HUNDRED AND ONE CASES

WESLEY J. WOOLSTON, M.D.
Attending Gynecologist, Cook County and Wesley Hospitals; Assistant Professor of Gynecology and Surgery, University of Illinois College of Medicine

AND

D. O. CONLEY, A.B., M.D.
Resident Physician, Cook County Hospital

CHICAGO

During the recent epidemic of pneumonia, or so-called Spanish influenza, 2,154 patients were admitted to Cook County Hospital between Sept. 18 and Nov. 5, 1918. Of this number, 101 were pregnant women.

Of these 101 cases of pneumonia, complicated by pregnancy, fifty-two died, giving a mortality of 51.4 per cent., as compared with a mortality of 719, or 33.3 per cent., of the 2,154 patients admitted to the general hospital. This shows a relatively higher death rate by 18.1 per cent. in the pregnant women. These apparently high percentages of mortality may be explained in part by the condition of the average patient on entrance to this hospital.

INFLUENZA OCCURRING IN PREGNANT WOMEN

A STATISTICAL STUDY OF THIRTEEN HUNDRED AND FIFTY CASES *

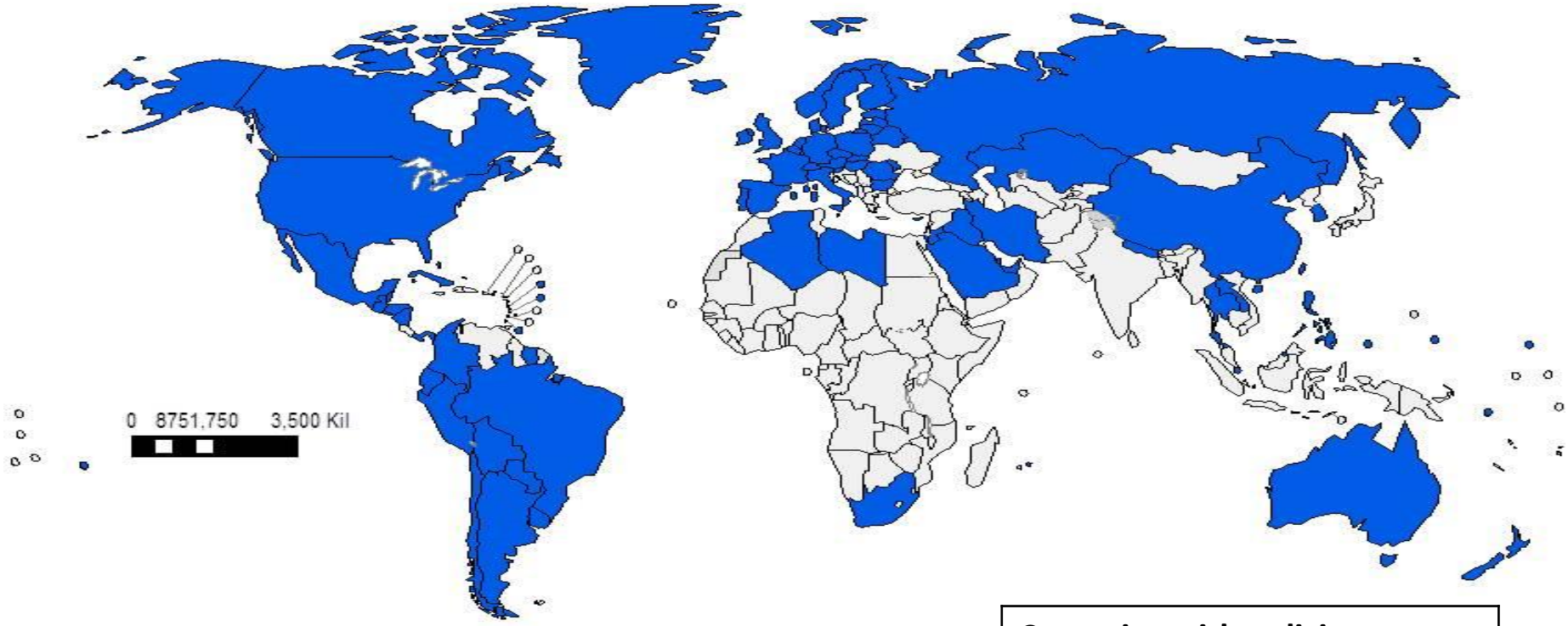
JOHN W. HARRIS, M.D.
BALTIMORE

pregnant women than among nonpregnant women or men of the same age. This question cannot be determined until we have reliable statistical data concerning influenza in general. Our own figures show only what happened in this group of 1,350 patients.

TABLE 1.—INCIDENCE OF PNEUMONIA AND PERCENTAGE OF MORTALITY IN CASES OF INFLUENZA REPORTED FOR THE DIFFERENT MONTHS OF PREGNANCY

Woolston. JAMA 1918; 71(23):1898-9; Harris. JAMA 1919; 72:978-80.

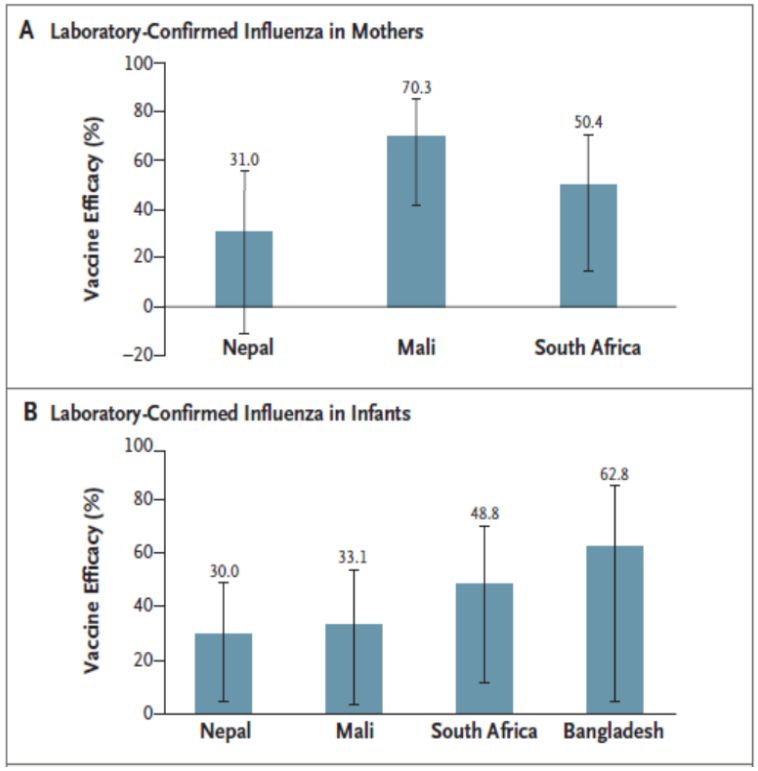
National policies for maternal influenza immunization



Countries with policies targeting pregnant women	
2006	15
2014	84

WHO-UNICEF joint reporting forms (JRFs) 2014.
Map production: Immunization Vaccines and Biologicals, World Health Organization

Maternal influenza vaccine efficacy



- Four RCTs of IIV during pregnancy
  - Bangladesh: Zaman et al., NEJM 2008
  - South Africa: Madhi et al., NEJM 2014
  - Mali: Tapia et al., Lancet ID 2016
  - Nepal: Steinhoff et al., Lancet ID 2017

Omer SB. NEJM 2017;376:1256–67.

Safety of maternal influenza immunization

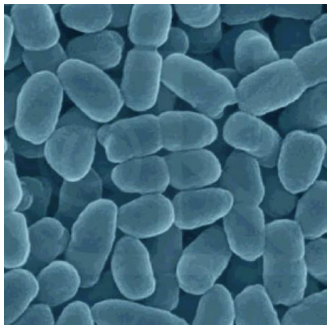
- Safety studies have been reassuring overall

Systematic review	Summary
Fell et al. BJOG 2015; 122(1):17-26	▪ Systematic review of published studies up to April 2014 (n=27 studies) ▪ Outcomes: preterm birth; fetal death ▪ No evidence of any adverse effect of influenza vaccination during pregnancy on preterm birth or late fetal death
McMillan et al. Vaccine 2015; 33(18):2108-17	▪ Systematic review of published studies up to March 2014 (n=19 studies) ▪ Outcomes: fetal death; congenital malformations ▪ No evidence of any adverse effect of influenza vaccination during pregnancy
Bratton et al. CID 2015; 60(5):e11-9	▪ Systematic review of published studies up to November 2013 (n=7 studies) ▪ Outcomes: stillbirth and spontaneous abortion ▪ No evidence of any adverse association between influenza vaccination during pregnancy and study outcomes

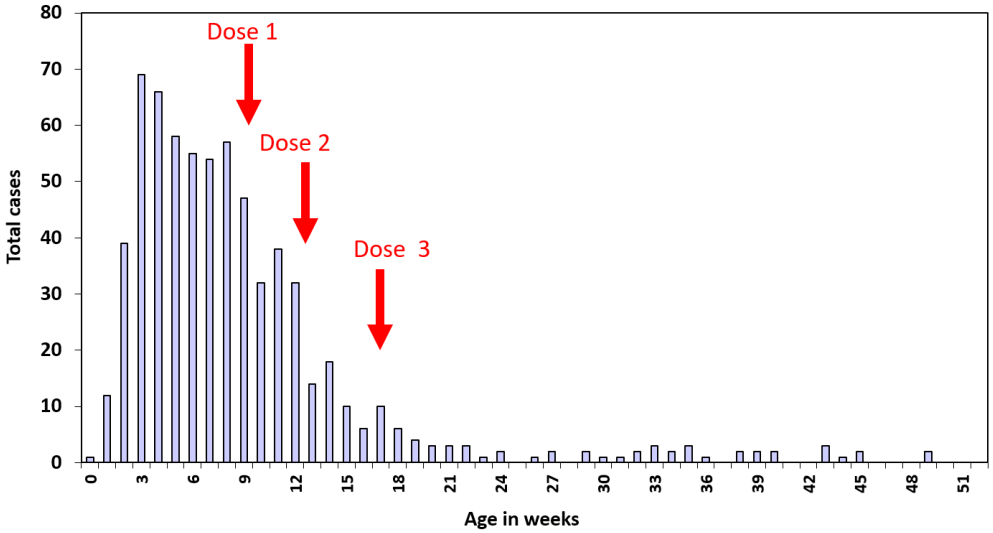
- One study recently reported increased risk of spontaneous abortion following 1st trimester receipt of pH1N1-containing vaccines in two consecutive influenza seasons (Donahue et al. Vaccine 2017;35:5314-22)

Pertussis

- Bacterial infection caused by *Bordetella pertussis*
  - Wide clinical spectrum of illness, ranging from mild cold-like symptoms to severe illness resulting in death
  - Young infants are at the greatest risk of suffering from severe pertussis illness



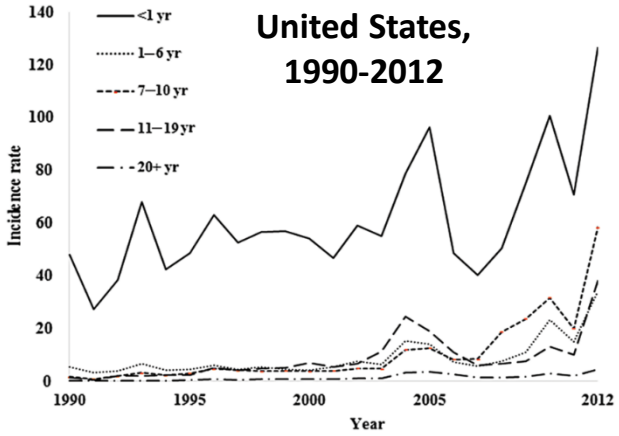
England and Wales, 2011-2012



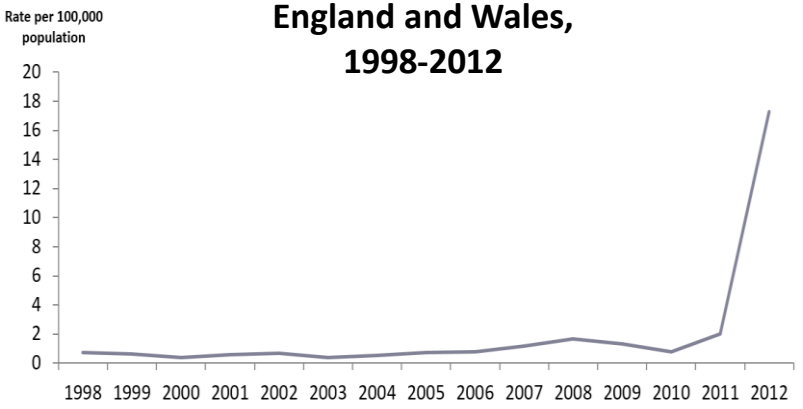
Edwards. ADVAC 2017; Cherry. CID 2016:63 (Suppl 4):S119-22; Public Health England 2016.

Pertussis

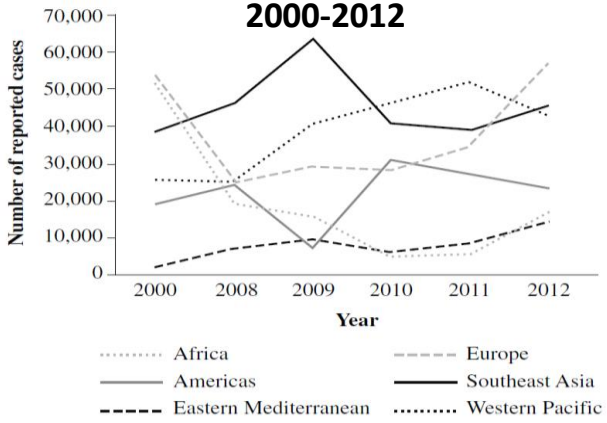
United States, 1990-2012



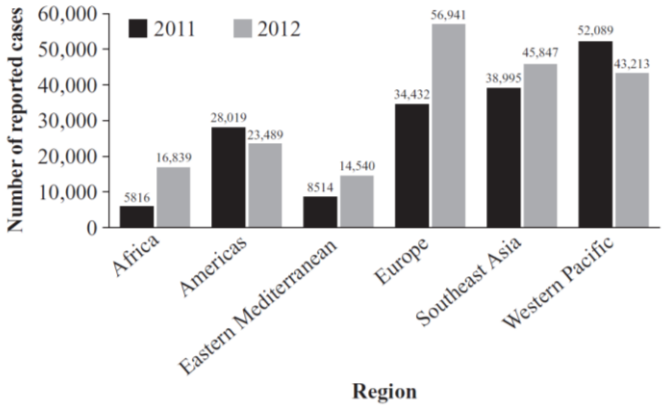
England and Wales, 1998-2012



WHO Regions, 2000-2012

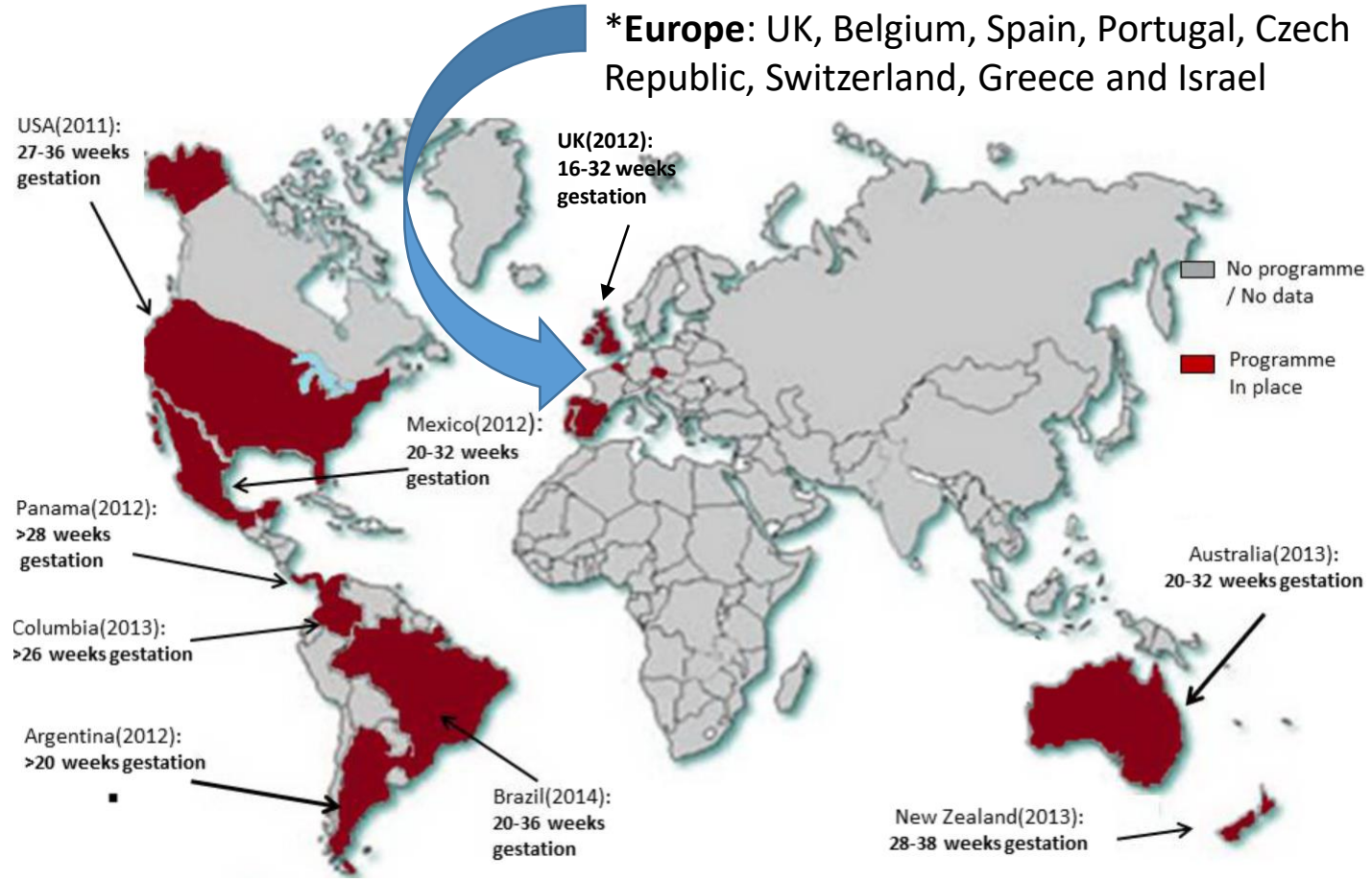


WHO Regions, 2011 and 2012



Clarke. JID 2014;209:978-81; Public Health England 2016; Tan. PIDJ 2015;34:e222-32.

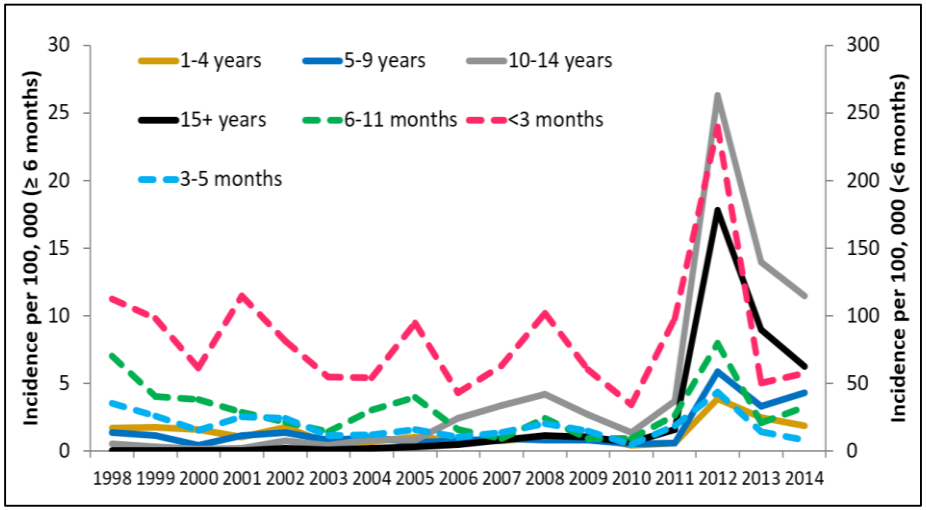
Countries recommending maternal TDap



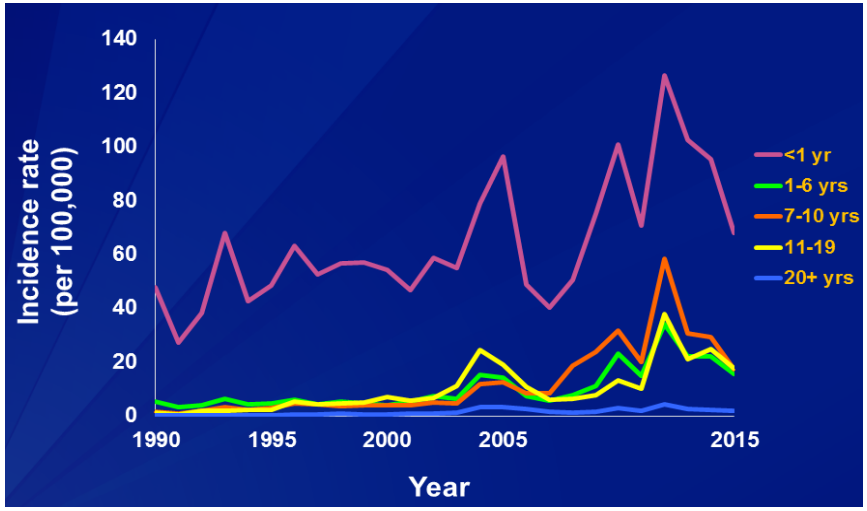
Courtesy of G. Amirthalingam, Public Health England, Sept 2017; Gkentzi D, et al. Arch Dis Child Fetal Neonatal Ed. 2017; 102(5), F456-63

Effectiveness of maternal Tdap immunization

England, 2001-2014



United States, 1990-2015



Public Health England: https://www.gov.uk/government/publications/vaccination-against-pertussis-whooping-cough-for-pregnant-women; CDC: https://www.cdc.gov/pertussis/images/incidence-graph-age.png.

Effectiveness of maternal Tdap immunization

	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)

Data are % (n/N), %, or % (95% CI). *Average matched coverage is the average of the matched population coverage estimates for all cases included in the analysis. †For cases in which the mother matched to zero coverage, that case was dropped from the analysis because it did not contribute information. ‡Vaccine effectiveness calculated on the basis of matched coverage on each individual, not with average matched coverage. §90 cases minus one case vaccinated within a week of birth and seven cases matched to zero coverage. ¶90 cases minus three cases vaccinated at other times before birth and 18 cases matched to zero coverage. ‖90 cases minus 11 cases vaccinated at other times before birth and seven cases matched to zero coverage. **90 cases minus 12 cases vaccinated at other times before birth and ten cases matched to zero coverage.

Table 4: Effectiveness of maternal pertussis vaccine by infant age at onset and timing of vaccination

United Kingdom

- Vaccine effectiveness: 91% for infants under three months of age

TABLE 3 Protection Against Pertussis From Maternal Tdap Vaccination During Pregnancy Before and After Infant DTaP Vaccination in 148 981 Newborns Followed From Birth Until 12 Months of Age

	12-mo Follow-up (Total Pertussis Cases = 103)			
	No. of Pertussis Cases (Rate per 100 000 Person-Years)		VE, % (95% CI)	*P*
	No Maternal Tdap	Maternal Tdap		
Maternal Tdap during pregnancy (8+ days before birth)[a]				
0 DTaP doses (birth until day 7 after the first DTaPdose)	31 (177.2)	2 (14.8)	87.9 (41.4 to 97.5)	.009
Protected by 1 DTaP dose[b]	23 (170.3)	5 (43.2)	81.4 (42.5 to 94.0)	.004
Protected by 2 DTaP doses[b]	12 (88.5)	8 (72.8)	6.4 (−165.1 to 66.9)	.901
Protected by 3 DTaP doses[b]	14 (48.7)	7 (32.1)	65.9 (4.5 to 87.8)	.041
Maternal Tdap before pregnancy	89 (89.4)	14 (42.4)	55.6 (20.1 to 75.4)	.007
Maternal Tdap after pregnancy	80 (72.1)	23 (106.2)	24.1 (−28.5 to 55.1)	.305

[a] We calculated the VE of maternal Tdap vaccination during pregnancy after each infant DTaP vaccine dose based on a Cox regression model that included an 8-level variable created by interacting a 2-level Tdap variable (0 = unvaccinated during pregnancy, 1 = vaccinated during pregnancy 8+ days before birth) and a 4-level DTaP variable (0, 1, 2, or 3 doses). The model was stratified on the year and month of birth of the infant and included covariates to adjust for sex, race, delivery hospital, and maternal Tdap before and after pregnancy. We used contrast statements to estimate the VE of maternal Tdap vaccination during pregnancy after each infant DTaP dose. Case counts do not include 1 infant whose mother received the Tdap vaccine 1 to 7 days before birth because the VE estimates do not include infants whose mothers were vaccinated 1 to 7 days before birth as either vaccinated or unvaccinated during pregnancy; there were too few infants in this group to give a meaningful result, so the 1 case where this occurred is not included.

[b] Protected by DTaP dose: from day 8 after the DTaP dose until day 7 after the next dose.

Northern California

- Vaccine effectiveness: 88% for infants under two months of age

Amirthalingam. Lancet 2014; 384:1521–28; Baxter. Pediatrics 2017;139:e20164091.

Safety of maternal Tdap immunization

- Safety studies have been reassuring overall

Systematic review	Summary
Gkentzi D, et al. Arch Dis Child Fetal Neonatal Ed 2017; 102(5): F456-63	▪ January 2011 – May 2016 ▪ Prenatal vaccination induces high antibody concentrations that are efficiently transferred to the fetus ▪ Safe, no evidence of adverse pregnancy, birth, or neonatal outcomes
McMillan M, et al. Obstet Gynecol 2017; 129(3): 560-73	▪ Inception of database – May 5, 2016 ▪ Prenatal combined Tdap administered 2nd or 3rd trimester not associated with adverse outcomes in fetus or neonate ▪ Medically attended events in pregnant women are similar between vaccinated and unvaccinated groups

- Two studies have reported increased risk of chorioamnionitis
  - Kharbanda et al. JAMA 2014;312:1897-1904
  - Layton et al. Vaccine 2017;35:4072-8

Infant immune responses

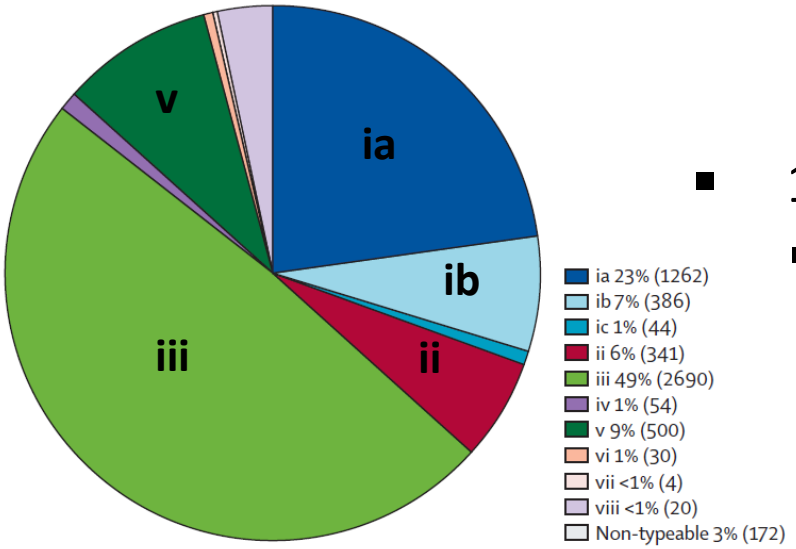
- Increased concentrations of maternal pertussis antibodies induced by maternal immunization in infants have been shown to interfere with infant immune responses
  - Blunting effect resolved after booster dose at 12 months in RCTs in the US (Munoz et al., 2014) and Vietnam (Maertens et al., 2016)
  - Clinical relevance unclear

Omer SB. NEJM 2017;376:1256–67; Raya, et al. Lancet Infect Dis 2017;17:e209-e222; Maertens K. CID 2016; 63 (Suppl 4): S197-S204; Munoz F. JAMA 2014;311(17):1760-9.

3. New vaccines under development for future implementation in the obstetrical population

Group B Streptococcus (GBS)

- Gram-positive bacterium that commonly colonizes the gastrointestinal tract
  - 10-35% of women screened during pregnancy are colonized



- 10 GBS serotypes have been identified:
  - 5 account for more than 85% of infant GBS disease (Ia, Ib, II, III, V)

Berardi A, et al. Expert Rev Anti Infect Ther. 2015;13:1387-99; Edmond KM, et al. Lancet 2012; 379(9815): 547-56.

Invasive infant GBS disease

	Early onset disease (EOD)	Late onset disease (LOD)
Timing of onset	Affects infants 0-6 days old	Affects infants 7-89 days old
Mode of exposure	Acquired in utero (within a few days before birth) or during vaginal birth	Acquired from the mother, or through hospital or community exposure
Pattern of disease	Sepsis, pneumonia, meningitis	Bacteremia, meningitis, pneumonia, cellulitis
Global epidemiology	Incidence: 0.43 per 1,000 live births Case-fatality: 12.1%	Incidence: 0.24 per 1,000 live births Case-fatality: 6.8%

- Up to 12% stillbirths are associated with maternal GBS

Berardi A, et al. Expert Rev Anti Infect Ther. 2015;13:1387-99; Edmond KM, et al. Lancet 2012; 379(9815): 547-56; Kobayashi M, et al. F1000Res. eCollection 2016; 5:2355; Nan, et al. BJOG; 2015; 122:1437-45.

Updated estimates of GBS carriage and disease

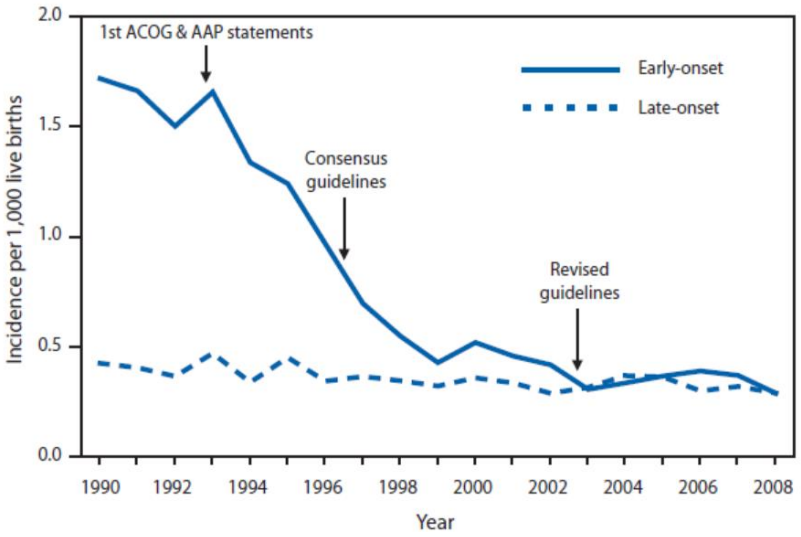
- Article on global estimates of GBS will be published in a Clinical Infectious Diseases Supplement in November, 2017
  - Global and regional estimates of GBS carriage in pregnant women, GBS-attributable stillbirths, and invasive infant disease

Madhi SA. INMIS Conference, September 2017.

Current approach to prevention

- In high income countries (HIC), routine screening for pregnant women, performed at 35–37 weeks' gestation
- Treatment for GBS+ women involves use of intrapartum antimicrobial prophylaxis (IAP) prior to labour
- Difficult to implement in LMIC settings

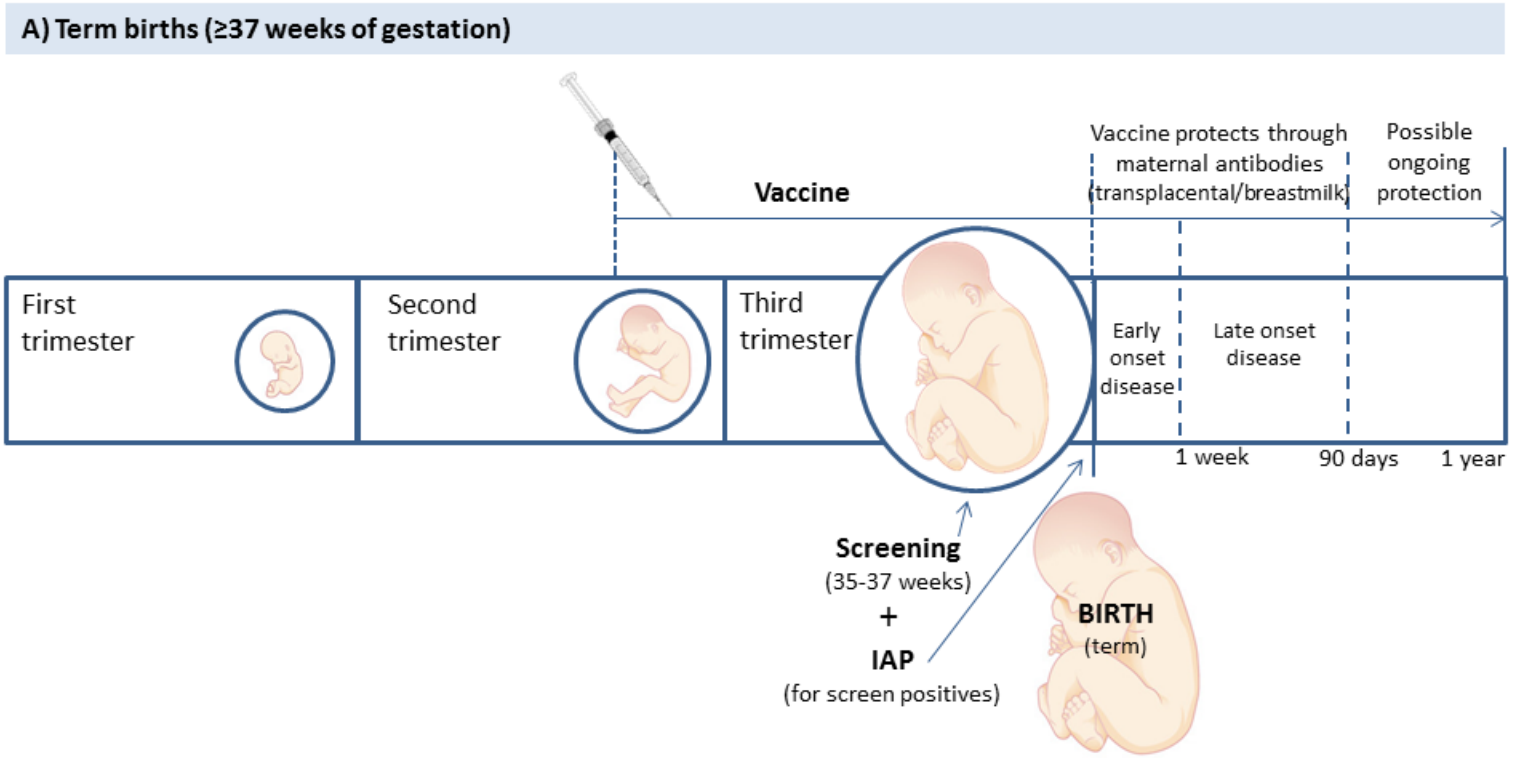
FIGURE 1. Incidence of early- and late-onset invasive group B streptococcal (GBS) disease — Active Bacterial Core surveillance areas, 1990–2008, and activities for prevention of GBS disease



https://www.cdc.gov/groupbstrep/guidelines/downloads/Figure_1_GBS_Decline.pdf

Kobayashi M, et al. F1000Res. eCollection 2016; 5:2355; Lin FY, et al. Am J Obstet Gynecol 2001; 184(6): 1204—10.

Vaccine strategy versus IAP

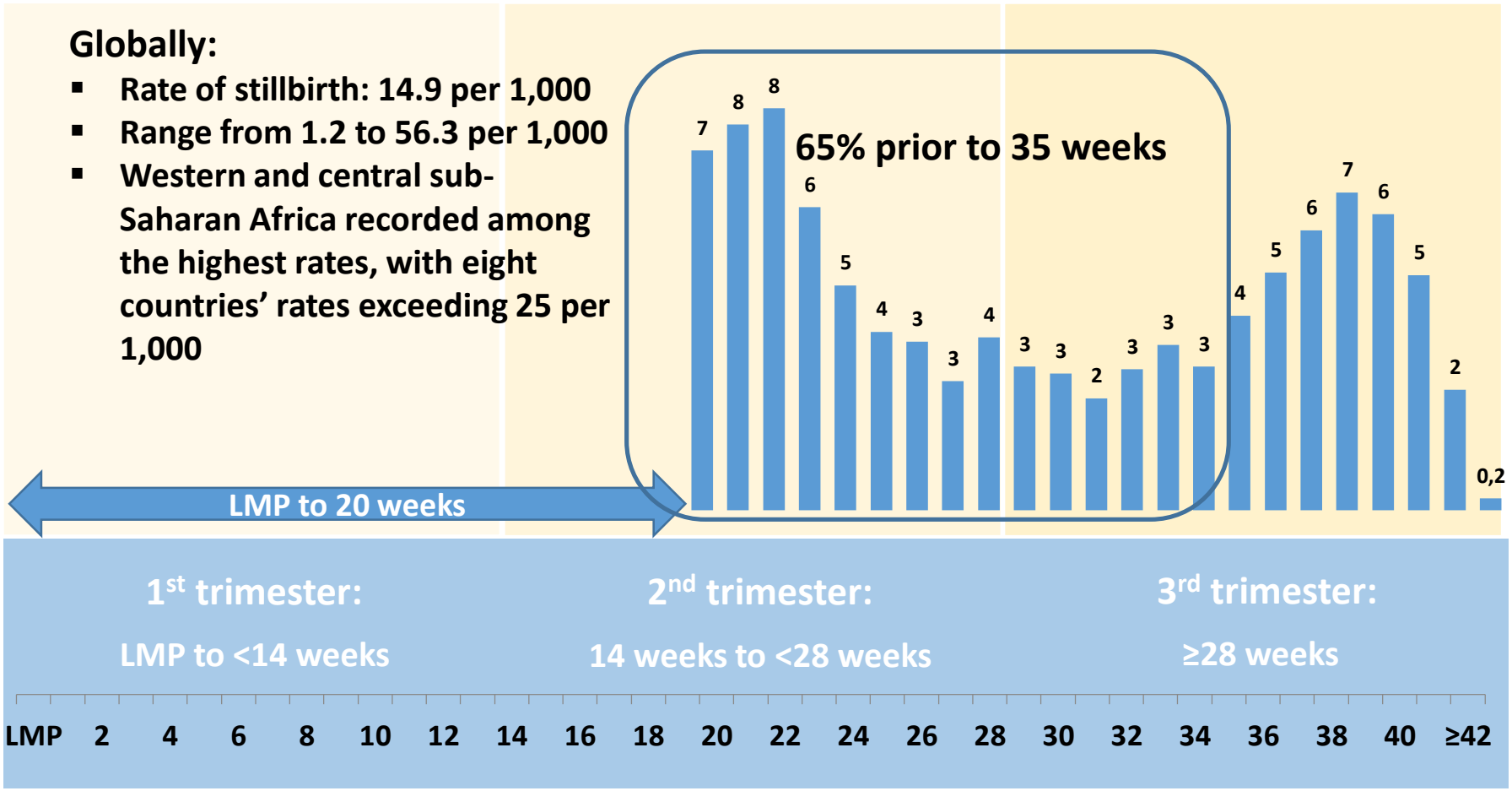


Courtesy of Dr. N Crowcroft, Public Health Ontario, 2017.

Distribution (%) of stillbirths by gestational age

Globally:

- **Rate of stillbirth: 14.9 per 1,000**
- **Range from 1.2 to 56.3 per 1,000**
- **Western and central sub-Saharan Africa recorded among the highest rates, with eight countries' rates exceeding 25 per 1,000**



Canadian Institute for Health Information, Canada, 2006–2007 and 2007–2008; Global Burden of Disease 2015 Study, Lancet. 2016;388:1725-74.

GBS vaccines in development

- Current leading vaccine candidates are conjugated capsular polysaccharides (CPS) vaccines
- Phase I and II trials of a trivalent GBS vaccine (serotypes Ia, Ib and III) have been conducted in >600 non-pregnant and >500 pregnant women in four countries

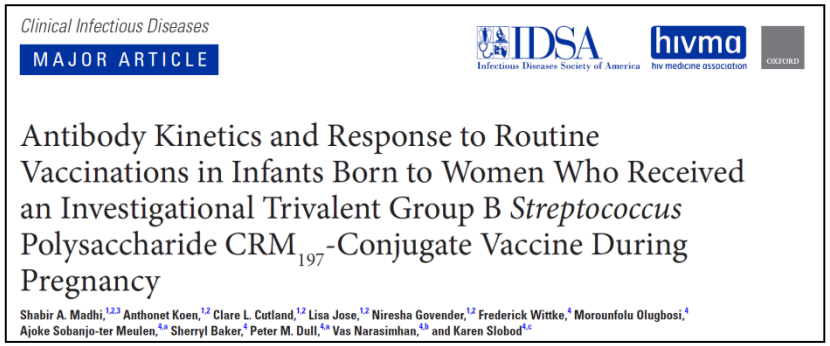
Table 1
Development status of current vaccine candidates (POC, proof of concept trial).

Developer	Candidate name/identifier	Preclinical	Phase I	Phase II	POC	Phase III
NIH	Tetanus toxoid-CPS conjugates: monovalent (multiple studies), bivalent (one study); CRM197–CPS conjugate: monovalent (one study)	x	x	x	x (trial in pregnant women)	
Novartis/GSK	CRM197-CPS conjugates: monovalent (multiple), trivalent (several)	x	x	x	x (trial in pregnant women)	
Minervax	N-terminal domains of the Rib and AlphaC surface proteins	x	x			
Novartis/GSK	Pilus proteins	x				
Various academic groups	Other protein(s) and/or protein-CPS conjugates	x				

Heath PT. Vaccine 2016 Jun 3;34(26): 2876-9.

GBS vaccines in development

- Randomized, placebo-controlled, observer blind, phase Ib/II trial of trivalent conjugate GBS vaccine (serotypes Ia, Ib, and III)
- 295 infants born to women from Soweto, South Africa, enrolled between 28–35 weeks' gestation
- Results:
  - Antibody levels for all vaccine serotypes across the 3 dosages:
    - On day 43: ranged from 41%–61% of the levels measured at birth
    - On day 91: ranged from 26% –76% of values at birth
  - Persistence of GBS antibody levels in infants were not impacted by gestational age at vaccination
  - No interference with infants' immune responses to diphtheria or pneumococcal vaccination



Madhi, et al. CID 2017; In press.

GBS vaccines in development

- From www.clinicaltrials.gov October 4, 2017:
  - 15 GBS vaccine trials listed
  - Only 1 is still recruiting (Phase I/II trial of multivalent GBS vaccine in healthy, non-pregnant adults)

- Challenges:
  - Specifically being developed for use in pregnancy
  - Large sample size would be required for Phase III study to assess efficacy against invasive infant disease (even larger for stillbirth)
  - Phase III study could not be conducted in a setting with IAP as the standard of care
  - Geographic heterogeneity in serotype distribution

Heath PT. Vaccine 2016;34(26): 2876-9; Madhi SA. Vaccine 2017;35:4457-60; Heath PT, et al. Lancet Infect Dis 2017;17:e223-e234;.

Areas for future research on GBS

Panel 1: Identified knowledge gaps for group B streptococcus disease

Epidemiology and surveillance

- Epidemiological data from South American, African, and Asian countries where the burden, strain, and serotype distribution is not adequately assessed
- Contribution to prematurity, birth asphyxia, and stillbirths

Laboratory assays

- Standardisation of assay methods (quantitative ELISA and functional assays) and standardised reference ranges for capsular polysaccharide-specific IgG antibody concentrations

Immunology and vaccination

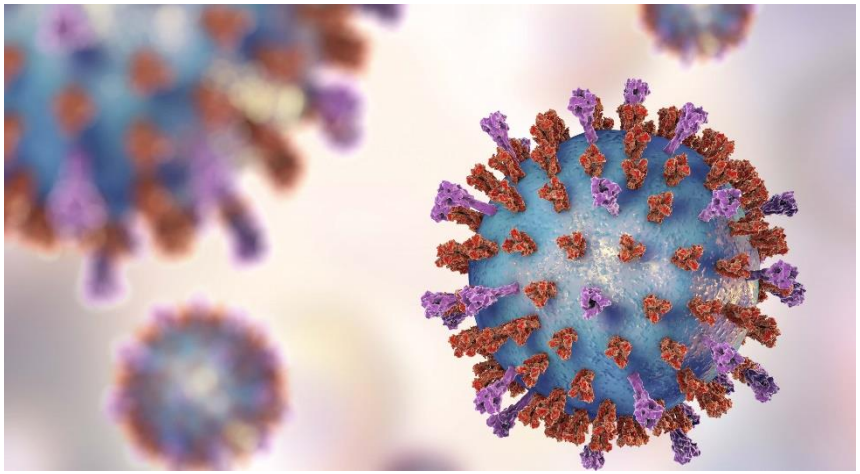
- Correlates of protection against maternal and infant colonisation, early-onset and late-onset infections, and other perinatal outcomes (eg, prematurity and stillbirths)
- Immunogenicity of conjugate vaccines and protein-based vaccines in pregnant women, duration of protective antibody concentrations, need for further doses in subsequent pregnancies, placental transfer and duration of antibody protection in infants
- Potential for interference of maternal vaccine-induced antibodies with active immune responses in infants
- Effect of immunisation in pregnancy on group B streptococcus colonisation at delivery, on vertical transmission, and infant colonisation
- Immunogenicity of immunisation in pregnant women with HIV who are severely immunocompromised, the role of different doses or schedules in women with HIV to maximise protection
- Influence of breastfeeding on vaccine-induced protection
- Immune responses of pregnant women of different ethnicities and different health backgrounds (including effect of malaria and nutritional status) to candidate group B streptococcus vaccines
- Overall public health benefit (including cost-effectiveness) of a group B streptococcus vaccine in pregnancy, including direct and indirect protection against both confirmed (culture proven) and unconfirmed (probable) group B streptococcus disease

- Safety, clinical efficacy, and effectiveness of new vaccines
- Determining the optimal timing of vaccination
  - During pregnancy for fetal and infant protection
    - Preterm infants are at a high risk for GBS infection
    - ~12% of stillbirths are attributable to GBS infection

Heath PT, et al. Lancet Infect Dis 2017;17:e223-e234; Kobayashi M, et al. F1000Res. eCollection 2016; 5:2355.

Respiratory syncytial virus (RSV)

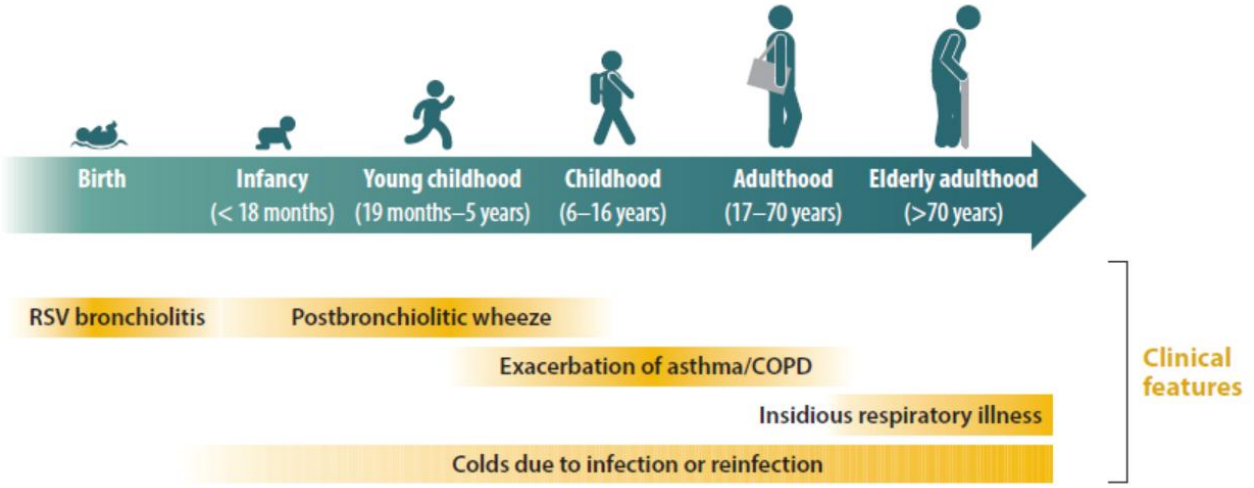
- Most common cause of viral acute lower respiratory infection (ALRI) in young children
  - In 2015 among children under five, RSV resulted in over 33 million episodes of ALRI globally, over 3 million hospital admissions and almost 60,000 in-hospital deaths
- Primary infection prior to two years of age is extremely common
  - Cumulative rate of infection estimated to be 97%
  - ~50% of 2-year olds will have been infected twice



Shi T, et al. Lancet 2017;390:946-58; Karron. Lancet 2017;390:917-8; Lozano R, et al. Lancet 2012; 380: 2095-128.

Respiratory syncytial virus (RSV)

- Clinically, RSV infection presents as pneumonia and bronchiolitis in young children
- RSV ALRI is a risk factor for ongoing respiratory morbidity
  - Transient early wheezing and recurrent wheezing
  - Asthma



Oppenshaw. Ann Rev Immunol 2017; 35:501–32; Heath PT, et al. Lancet Infect Dis 2017;17:e223-e234; Meissner HC. N Engl J Med 2016; 374: 62–72; Blanken MO, et al. N Engl J Med 2013; 368: 1791–99.; Feldman AS, et al. Am J Respir Crit Care Med 2015; 191: 34–44; Fauroux, et al. Infect Dis Ther 2017; 6: 173-97.

Respiratory syncytial virus (RSV)

- Association between RSV and later wheeze supported by data from RCT of palivizumab prophylaxis among healthy, late preterm infants
  - Reduced number of subsequent wheezing days over the first year of life

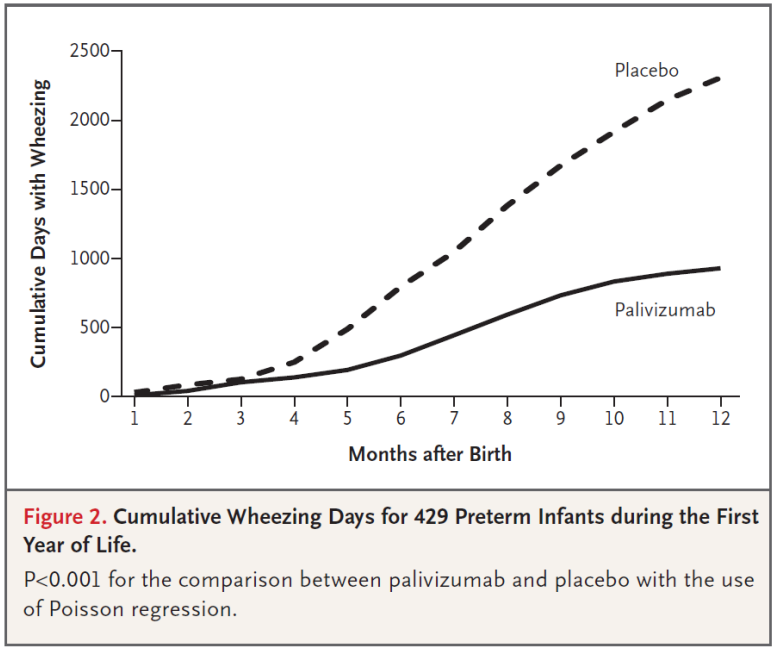


Figure 2. Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.

P<0.001 for the comparison between palivizumab and placebo with the use of Poisson regression.

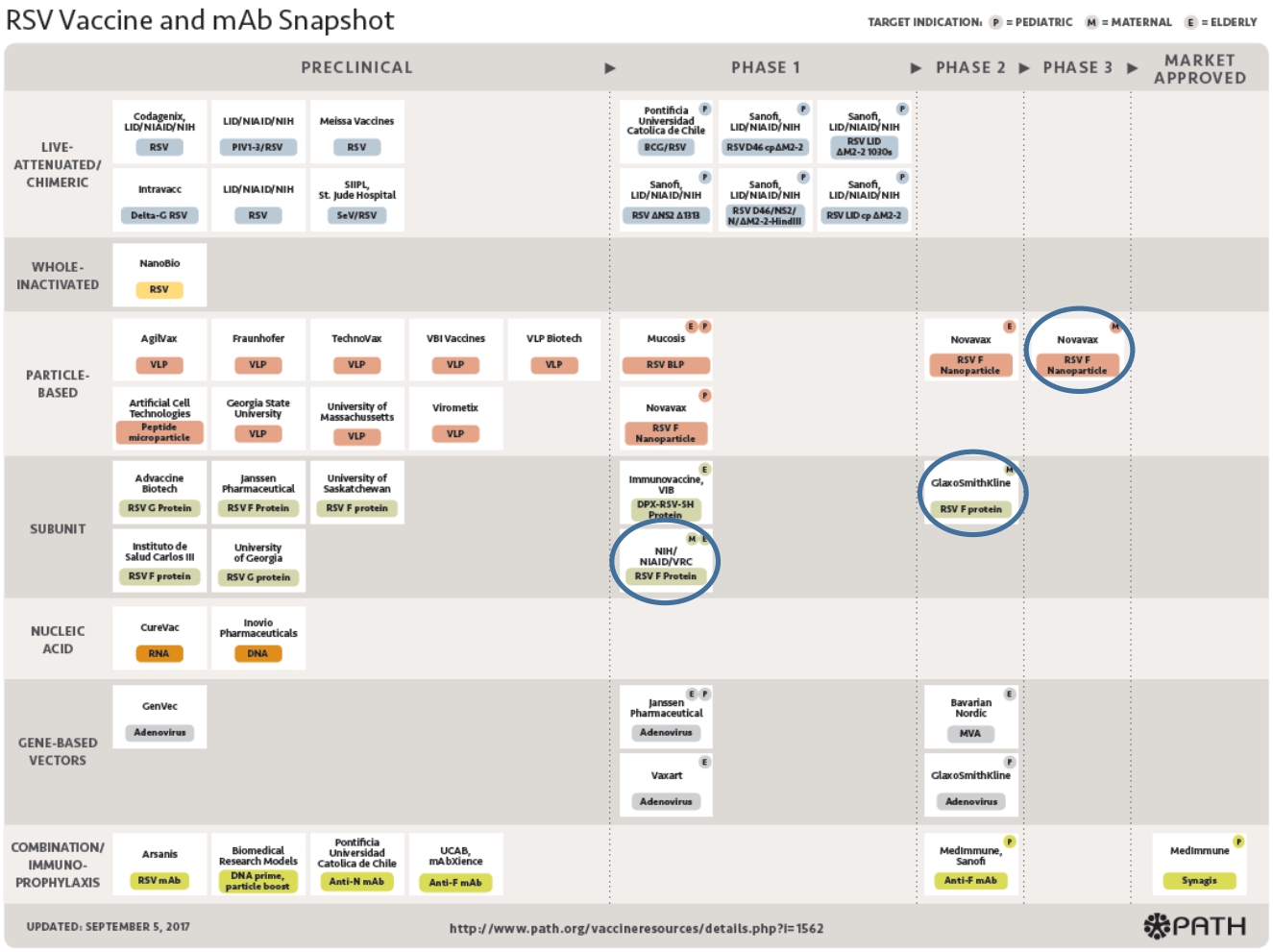
Blanken. NEJM 2013;368:1791-9.

Current approach to RSV prevention

- Palivizumab
  - Immunoprophylaxis
  - Monoclonal neutralizing antibody
  - Approved for infants at highest risk for RSV morbidity and mortality (preterm infants, those with chronic lung disease or congenital heart defects)
  - Requires 5 monthly IM injections (>$5000 USD)
  - Used in some HICs and MICs, but cost and requirement for monthly injections render it unfeasible in resource-constrained countries

Karron. Vaccines (6th ed.), 2013; Higgins. Vaccine; 2016;34:2870-5.

RSV vaccines in development



PATH: http://www.path.org/publications/files/CVIA_rsv_snapshot_final_0917r.pdf (Updated September 2017).

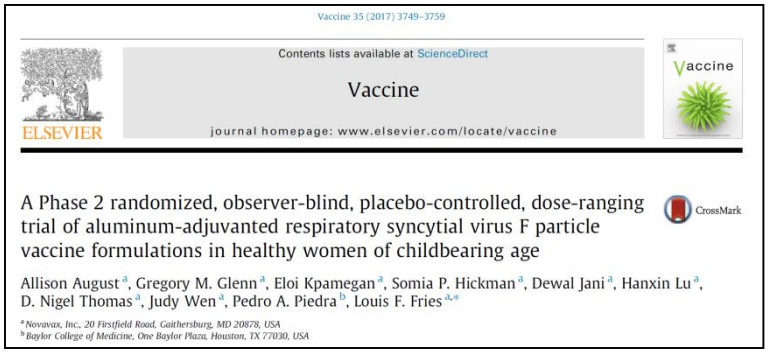
RSV vaccines in development

- From www.clinicaltrials.gov October 6, 2017:
  - Among registered studies that are 'active not recruiting', 'recruiting', or 'not yet recruiting', there are ~25 ongoing RSV trials of vaccines and vaccine-like monoclonal antibodies in different target groups

Study	Phase	Description
A Study to Determine the Safety and Efficacy of the RSV F Vaccine to Protect Infants Via Maternal Immunization (NCT02624947)	3	▪ Currently enrolling third-trimester pregnant women in the Northern and Southern hemispheres, for up to four consecutive RSV seasons in each hemisphere ▪ Phase 3, randomized, observer-blind, placebo-controlled ▪ Projected to enroll an estimated maximum of 8,618 third-trimester pregnant subjects ▪ 1° outcome: Incidence of RSV LRTI up to 90 days ▪ 2° outcomes: RSV hypoxemia, hospitalization, death up to 90 days; health care for wheezing up to 1 year

RSV vaccines in development

- Phase II randomized, observer-blind, placebo-controlled trial of RSV F nanoparticle vaccine
- 720 women of childbearing age, randomized to one of six dosing schedules
- Results:
  - All formulations were well tolerated
  - Single dose regimen of 120 µg RSV F with 0.4 mg of aluminum elicited robust immune responses, which outweigh the slight advantage of a two dose regimen (longer antibody persistence)



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

A Phase 2 randomized, observer-blind, placebo-controlled, dose-ranging trial of aluminum-adjuvanted respiratory syncytial virus F particle vaccine formulations in healthy women of childbearing age

Allison August [a], Gregory M. Glenn [a], Eloi Kpamegan [a], Somia P. Hickman [a], Dewal Jani [a], Hanxin Lu [a], D. Nigel Thomas [a], Judy Wen [a], Pedro A. Piedra [b], Louis F. Fries [a,*]

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[b] Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

August. Vaccine 2017;35:3749-59.

RSV vaccines in development

- Clinical trials so far show promising results:
  - Well-tolerated and immunogenic in Phase I and II studies in human adults (including women of reproductive age)
  - No signs of teratogenicity or enhanced RSV disease in animal studies
  - No infant adverse health effects resulting from maternal RSV vaccination have been detected
  - Evidence of protection against serologically-detected RSV infection in women of childbearing age

Karron. Lancet 2017;390:917-8; Heath PT, et al. Lancet Infect Dis 2017;17:e223-e234; Munoz FM. Vaccine 2003; 21: 3465–67; Englund. ADVAC 2017; Omer SB. NEJM 2017;376:1256–67; August. Vaccine 2017;35:3749-59.

RSV vaccines in development

- Challenges:
  - Likely that different vaccines will be needed for various target populations (i.e., pregnant women, infants, elderly adults)
  - Maternal vaccination will only confers short-term protection and must be complemented by development of a pediatric vaccine
  - Identifying clinically meaningful and reproducible indicators of vaccine impact on severity of disease
    - Case definitions and diagnostic criteria currently vary (e.g., bronchiolitis, wheeze)

Karron. Vaccines (6th ed.), 2013; Roberts JN, et al. Vaccine 2016; 34(41): 4843-9; Heath PT, et al. Lancet Infect Dis 2017;17:e223-e234; Kinyanjui TM, et al. PLoS One 2015; 10: e0138018; Karron. Lancet 2017;390:917-8.

Areas for future research on RSV

***Panel* 2: Identified knowledge gaps for respiratory syncytial virus disease**

- Mechanisms of protection against lower respiratory tract infection and severe disease in infants, and intrinsic and environmental influences on infant respiratory immunity
- Identification of key, measurable correlates of protection against infection and severe disease in infants and of key endpoints and outcomes for studies of vaccine efficacy
- Development of an effective, safe respiratory syncytial virus vaccine to induce high-affinity neutralising antibody in pregnant women
- Identification of the properties of a protective maternal immune response and the factors influencing the transfer and decay of maternal antibodies in infants
- Assessment of the potential effect of widespread maternal immunisation on infant immunity to respiratory syncytial virus and on respiratory syncytial virus epidemiology
- The effect of respiratory syncytial virus vaccination and prevention of longer-term outcomes such as asthma and wheeze

- Safety, clinical efficacy, and effectiveness of new vaccines
- How diseases (e.g., malaria, HIV) affect maternal immunogenecity and antibody transfer
- Determining the optimal timing of vaccination, taking into account:
  - Gestational timing for optimal antibody transfer for term and preterm infants
  - Local RSV seasonality

Heath PT, et al. Lancet Infect Dis 2017;17:e223-e234; Englund. ADVAC 2017.

4. Safety monitoring issues and conclusions

Constraints of RCTs for safety evaluation in pregnancy

- Some limitations of RCTs for safety evaluation in pregnancy
- E.g., Existing RCTs of maternal influenza immunization are:
  - Small
  - Restricted to healthy pregnant women immunized during the 2nd or 3rd trimester
  - Follow-up restricted to 6 months of age

- These characteristics preclude the ability to study rare pregnancy outcomes, outcomes relevant to 1st trimester exposure, and longer-term pediatric health outcomes

Constraints of observational studies for safety evaluation in pregnancy

- Observational studies of influenza immunization during pregnancy have played a central role in post-hoc safety assessment

- Within studies, inherent problems of observational studies:
  - Confounding bias
  - Large sample size requirements seriously limit ability of available epidemiologic studies to rule out unacceptable vaccine-associated risks to the fetus

- Across studies:
  - Lack of consistent definitions and ascertainment of adverse birth outcomes

Brighton Collaboration: GAIA Project

- The Global Alignment of Immunization safety Assessment in pregnancy (GAIA) is a working group founded by the Brighton Collaboration
  - Standardization of:
    - AEFI case definitions specific to maternal and neonatal outcomes***
    - Conduct of safety trials (collection, analysis, and presentation of data)
    - Data sharing***
    - Data collection for population-based surveillance

Table 2
Standardized case definitions developed for the first 21 obstetric and neonatal outcomes.

	Obstetric outcomes	Neonatal outcomes	Enabling terms
First set of 10 case definitions	• Hypertensive disorders of pregnancy • Non-reassuring fetal status • Postpartum hemorrhage • Pathways to premature birth • Maternal death	• Stillbirth • Preterm birth • Congenital anomalies • Neonatal infections • Neonatal death	• Assessment of Gestational Age • Live birth
Second set of 10 case definitions	• Abortion • Antenatal bleeding • Gestational diabetes • Dysfunctional labor • Intra uterine growth retardation	• Low birth weight • Small for gestational age • Neonatal encephalopathy • Respiratory distress in the newborn • Failure to thrive	
Additional case definition		• Microcephaly	

http://www.who.int/vaccine_safety/committee/topics/pregnancy/Jul_2016_gaia_project/en/; *Bonhoeffer. Vaccine 2016;34:5993-7.*

Future directions for safety monitoring

- Background rates of adverse pregnancy outcomes
- Better data to study miscarriages/stillbirth
- Widespread acceptance of Brighton case definitions (to allow for data combining and systematic reviews)
- Robust research methodologies to account for inherent biases in observational studies
- Mechanisms for national and international data sharing and combining (e.g., distributive data networks)
- Data from LMICs

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- Advanced Course of Vaccinology (ADVAC) 2017 lectures:
  - Dr. Kathy Edwards
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  - Dr. Fiona Cutley
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  - Dr. Saad Omer
- Dr. Justin Ortiz, University of Maryland

Cảm ơn bạn
Merci
Thank you

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