Maternal immunization: current status and future directions

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Trend in PubMed citations, 1990–2017


H1N1 pandemic
Recent reviews

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

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

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 $\rightarrow$ 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

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.

Current recommendations for existing vaccines

<table>
<thead>
<tr>
<th>Vaccines routinely recommended for all pregnant women **</th>
<th>No recommendation for use in pregnancy (use if indicated)</th>
<th>Contraindicated during pregnancy</th>
</tr>
</thead>
</table>
| - Inactivated influenza virus (IIV) - One dose each pregnancy in any trimester, as early as possible during influenza season | - Cholera (oral)  
- Hib  
- Meningococcal conjugate  
- Meningococcal polysaccharide  
- Meningococcal B  
- 13- Valant pneumococcal conjugate  
- 23- Valant pneumococcal polysaccharide  
- Typhoid Vi  
- Hep A  
- Hep B  
- JEV  
- Polio  
- Rabies  
- HPV  
- Yellow fever | - BCG  
- Oral typhoid  
- JEV  
- MMR  
- Rotavirus  
- Varicella  
- Zoster |
| - 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 | | |

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

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

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AND

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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.
National policies for maternal influenza immunization

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

Safety of maternal influenza immunization

- Safety studies have been reassuring overall

<table>
<thead>
<tr>
<th>Systematic review</th>
<th>Summary</th>
</tr>
</thead>
</table>
| 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

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Pertussis

United States, 1990-2012

England and Wales, 1998-2012

WHO Regions, 2000-2012

WHO Regions, 2011 and 2012

Countries recommending maternal TDap

*Europe:* UK, Belgium, Spain, Portugal, Czech Republic, Switzerland, Greece and Israel

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Effectiveness of maternal Tdap immunization

England, 2001-2014

United States, 1990-2015

Effectiveness of maternal Tdap immunization

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

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

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage of cases vaccinated</th>
<th>Average matched coverage</th>
<th>Vaccine effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &lt; 3 months of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination at least 7 days before birth</td>
<td>15% (12/82)</td>
<td>62%</td>
<td>91% (84 to 95)</td>
</tr>
<tr>
<td>Vaccination at least 7 days before birth with coverage reduced by a relative 20%</td>
<td>15% (12/82)</td>
<td>49%</td>
<td>84% (71 to 93)</td>
</tr>
<tr>
<td>Infants &lt; 3 months of age by timing of maternal immunisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination at least 28 days before birth</td>
<td>14% (10/71)</td>
<td>62%</td>
<td>91% (83 to 95)</td>
</tr>
<tr>
<td>Vaccination 7–27 days before birth</td>
<td>3% (2/72)</td>
<td>19%</td>
<td>91% (70 to 96)</td>
</tr>
<tr>
<td>Vaccination 0–6 days before or 1–13 days after birth</td>
<td>3% (2/68)**</td>
<td>5%</td>
<td>38% (−95 to 80)</td>
</tr>
<tr>
<td>Infants ≥ 2 months of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination at least 7 days before birth</td>
<td>15% (11/71)</td>
<td>61%</td>
<td>90% (82 to 95)</td>
</tr>
<tr>
<td>Vaccination at least 7 days before birth with coverage reduced by a relative 20%</td>
<td>15% (11/71)</td>
<td>49%</td>
<td>82% (67 to 90)</td>
</tr>
</tbody>
</table>

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. §Cases minus one case vaccinated within a week of birth and seven cases matched to zero coverage. ‡Cases minus three cases vaccinated at other times before birth and 18 cases matched to zero coverage. §§Cases minus 11 cases vaccinated at other times before birth and seven cases matched to zero coverage. §§Cases minus 12 cases vaccinated at other times before birth and ten cases matched to zero coverage.

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TABLE 3 Protection Against Pertussis From Maternal Tdap Vaccination During Pregnancy Before And After Infant DTaP Vaccination In 14881 Newborns Followed From Birth Until 12 Months Of Age

<table>
<thead>
<tr>
<th>No. of Pertussis Cases (Rate per 100 000 Person-Years)</th>
<th>VE, % (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Maternal Tdap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Tdap during pregnancy (8+ days before birth)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 DTaP doses (birth until day 7 after the first DTaP dose)</td>
<td>31 (177.2)</td>
<td>2 (14.8)</td>
</tr>
<tr>
<td>Protected by 1 DTaP dose§</td>
<td>28 (170.3)</td>
<td>5 (43.2)</td>
</tr>
<tr>
<td>Protected by 2 DTaP doses§</td>
<td>12 (88.5)</td>
<td>8 (72.8)</td>
</tr>
<tr>
<td>Protected by 3 DTaP doses§</td>
<td>14 (48.7)</td>
<td>7 (32.1)</td>
</tr>
<tr>
<td>Maternal Tdap before pregnancy</td>
<td>89 (89.4)</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Maternal Tdap after pregnancy</td>
<td>80 (72.1)</td>
<td>23 (106.2)</td>
</tr>
</tbody>
</table>

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### Safety of maternal Tdap immunization

- **Safety studies have been reassuring overall**

<table>
<thead>
<tr>
<th>Systematic review</th>
<th>Summary</th>
</tr>
</thead>
</table>
- Prenatal vaccination induces high antibody concentrations that are efficiently transferred to the fetus  
- Safe, no evidence of adverse pregnancy, birth, or neonatal outcomes |
- 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
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

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)

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Invasive infant GBS disease

<table>
<thead>
<tr>
<th></th>
<th>Early onset disease (EOD)</th>
<th>Late onset disease (LOD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of onset</strong></td>
<td>Affects infants 0-6 days old</td>
<td>Affects infants 7-89 days old</td>
</tr>
<tr>
<td><strong>Mode of exposure</strong></td>
<td>Acquired in utero (within a few days before birth) or during vaginal birth</td>
<td>Acquired from the mother, or through hospital or community exposure</td>
</tr>
<tr>
<td><strong>Pattern of disease</strong></td>
<td>Sepsis, pneumonia, meningitis</td>
<td>Bacteremia, meningitis, pneumonia, cellulitis</td>
</tr>
</tbody>
</table>
| **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

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
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

https://www.cdc.gov/groupbstrep/guidelines/downloads/Figure_1_GBS_Decline.pdf
Vaccine strategy versus IAP

A) Term births (≥37 weeks of gestation)

Vaccine protects through maternal antibodies (transplacental/breastmilk) and possible ongoing protection.

First trimester

Second trimester

Third trimester

Screening (35-37 weeks) + IAP (for screen positives)

BIRTH (term)
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

65% prior to 35 weeks

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

GBS vaccines in development

- From [www.clinicaltrials.gov](http://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

Areas for future research on GBS

- 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
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

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

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

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*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

# RSV vaccines in development

## RSV Vaccine and mAb Snapshot

<table>
<thead>
<tr>
<th>RSV Vaccine and mAb Snapshot</th>
<th>TARGET INDICATION:  P = PEDIATRIC  M = MATERNAL  E = ELDERLY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRECLINICAL</strong></td>
<td><strong>PHASE 1</strong></td>
</tr>
<tr>
<td><strong>PHASE 2</strong></td>
<td><strong>PHASE 3</strong></td>
</tr>
<tr>
<td><strong>MARKET APPROVED</strong></td>
<td></td>
</tr>
</tbody>
</table>

### LIVE-ATTENUATED/CHIMERIC
- Codagenix
  - LIDY/NARDPH
  - BRSV
- LIDY/NARDPH
- Merville Vaccines
- St. Jude Hospital
  - LAD-1001

### WHOLE-INACTIVATED
- MedImmune
  - RSV

### PARTICLE-BASED
- AbCellera Biotech
  - RSV F Protein
- Janssen Pharmaceutical
  - RSV F Protein
- University of Saskatchewan
  - RSV F protein

### SUBUNIT
- Biopharmaceuticals
  - RSV F Protein
- University of Georgia
  - RSV F protein
- MedImmune
  - RSV F Protein

### NUCLEIC ACID
- ChimerX
  - RNA
- Iovio Pharmaceuticals
  - DNA

### GENE-BASED VECTORS
- Corates
  - Adenovirus
- Janssen Pharmaceutical
  - Adenovirus

### COMBINATION/IMMUNO-PROPHYLAXIS
- AstraZeneca
  - RSV mAb
- MedImmune
  - RSV mAb, palivizumab, pentavalent vaccine, anti-N mAb, anti-F mAb
- VSXART
  - Adenosine

### MARKET APPROVED
- MedImmune
  - RSV F Protein
- Bavarian Nordic
  - Vaxart

RSV vaccines in development

- From [www.clinicaltrials.gov](http://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

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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)
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

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)

Areas for future research on RSV

- 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
4. Safety monitoring issues and conclusions
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 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester
- Follow-up restricted to 6 months of age

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

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
Acknowledgements

- **Advanced Course of Vaccinology (ADVAC) 2017 lectures:**
  - Dr. Kathy Edwards
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  - Dr. Gayatri Amirthalingam
  - Dr. Fiona Cutley

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- Dr. Justin Ortiz, University of Maryland
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