Maternal immunisation – protection of the young child through vaccination of the mother

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1. General principles
2. FAQ
   a) Why vaccinate during pregnancy?
   b) Safety of the strategy
   c) Immunogenicity and effectiveness
   d) Secondary effects
   e) Adherence to and acceptance of the recommendations
1. General Principles

It is not a new concept!

1879: Maternal immunisation with vaccinia virus

1938: Maternal immunisation with whole cell pertussis vaccine

1961: Maternal immunisation with tetanus toxoid in new Guinea
General rules

- **Risk of infection**: epidemiological or individual
- **Risk attached to vaccination** of a pregnant woman = theoretical risk or real risk?
- Advantages of vaccination usually outweigh the potential risk of a side effect
- Every woman should start a pregnancy in a perfectly protected status: pre-conceptional consult (food- folic acid- *vaccination status*- serological status- irregular antibodies...)

General rules

- Vaccines containing **inactivated** material do not appear to be harmful to foetus or pregnant women
- **Attenuated** vaccines are contra-indicated in pregnant women
- Immune response of a pregnant woman = equally adequate as a non-pregnant woman for vaccine response; BUT less adequate for response to infection!!
Who could benefit from a maternal immunization strategy?

<table>
<thead>
<tr>
<th></th>
<th>Mother</th>
<th>Unborn child</th>
<th>Neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tetanus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>(+)</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Pertussis</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>RSV</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>GBS</td>
<td>(+)</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Zika</td>
<td>+</td>
<td></td>
<td>(+)</td>
</tr>
</tbody>
</table>
Determinants of the amount of maternal antibodies in infants

Maternal titer

Placenta: FcRn Receptor

Gestational age: (Pre)maturity

(Malek 1996)
Antibody persistence in the newborn

- Variation according to disease: Varicella-Pertussis-Measles

- Variation according to region: e.g. measles (before universal vaccination)
  - industrialised countries: 12 months
    (Sato, 1979)
  - developing countries: 2-9 m: infections, malnutrition...
    - transfer, concentration and persistence of IgG in Germany > Nigeria
      (Hartter, 2000)
    - hiv load and decrease maternal antibodies in Kenya
      (Farquhar, 2005) (Scott, 2005)
Proportion of infants (≤ 12 m of age) with maternal measles antibodies and number of cases in 2011 outbreak (≤ 12 m of age)

Solid line: proportion with measles antibodies in children from vaccinated mothers
Dotted line: proportion with measles antibodies in children from naturally immune mothers (Leuridan, Vaccine 2012)
Columns: number of measles cases (N=60) by age in months during the 2011 measles outbreak in Belgium
Effect of maternal antibodies in infants

- Passive protection
- Hamper humoral immune response on vaccination (life attenuated vaccines- wP vaccine...)
  - maternal antibody/vaccine antigen ratio: sufficient B cell vaccine epitopes free for binding by infant B cells
    (Siegrist, 1998)
  - maternal antibodies trigger a regulatory mechanism of B cell responses
    (Kim, 2011)

→ Timing first dose of vaccination
  (Leuridan, Vaccine, 2007)
1. General principles

2. FAQ
   a) Why vaccinate during pregnancy?
   b) Safety of the strategy
   c) Immunogenicity and effectiveness
   d) Secondary effects
   e) Adherence to and acceptance of the recommendations
a) Why vaccinate during pregnancy

Figure 2: Global causes of child deaths in 2013

Li Liu et al Lancet 2015;358:430-40
Pertussis

https://www.wiv-isp.be/pedisurv/
AnnualReports/CurrentReport/jaarverslag_nl.pdf
14 infants died in 2012
Historical data on pertussis epidemiology

**Figure 1. Proportion of reported infant pertussis deaths, by age — United States, 1938–1940,* 1990–1999,† and 2000–2006§**


**Historical data on pertussis vaccination in pregnancy with wP vaccines**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No</th>
<th>Vaccine /Doses</th>
<th>Safety</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichty</td>
<td>1938</td>
<td>42</td>
<td>3 wP</td>
<td>Arm pain</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cohen/</td>
<td>1941-</td>
<td>~170</td>
<td>6 wP</td>
<td>Arm pain, lump, no adverse pregnancy outcomes</td>
<td>0/8 immunized and 3/6 unimmunized exposed infants</td>
</tr>
<tr>
<td>Mishulow</td>
<td>1946</td>
<td></td>
<td></td>
<td></td>
<td>developed pertussis</td>
</tr>
<tr>
<td>Kendrick</td>
<td>1945</td>
<td>57</td>
<td>3 wP</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Adams</td>
<td>1947</td>
<td>16</td>
<td>3 wP</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cohen</td>
<td>1951</td>
<td>106</td>
<td>3 wP</td>
<td>Mild injection site; no adverse pregnancy</td>
<td>0/2 exposed infants of immunized women developed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>outcomes</td>
<td>pertussis</td>
</tr>
</tbody>
</table>
Neonatal tetanus

- Generalised tetanus in newborn
- Infection of umbilical stump

WHO goal on MNT Elimination
- = <1 neonatal tetanus case per 1000 live births in a year in every district of a country
- IF NT is eliminated, maternal tetanus is also considered eliminated
Epidemiology tetanus

Start tetanus vaccination for pregnant women in 1961
43 Countries eliminated MNT between 2000 & June 2017

*(16 regions out of 17 in Philippines and Punjab province of Pakistan) leaving 16 countries yet to eliminate MNT

Source: WHO/UNICEF Database
Date of view: 08 July 2017
Map produced by Immunisation Geospatial and Epidemiology, (IGE), World Health Organization
MNT Risk in most of the remaining countries is narrowed down to few districts (High Risk)

District level elimination status of MNT in the remaining 18 priority countries

Source: WHO/UNICEF Database
Date of slide: 06 June 2016
Map production: Immunization Vaccines and Biologicals (IVB), World Health Organization

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 lines on maps represent approximate border lines for which there may not yet be full agreement.
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Epidemiology RSV

Global burden in children < 5 years of age:
- 33.8 (95% CI 19.3–46.2) million episodes with acute lower respiratory tract infection (ALRI)
- 3.4 million episodes of severe RSV infection requiring hospitalisation

Le Doare Vaccine 2013

Acute respiratory illness in adults:
- annual attack rate 10%
- 5–15% of cases of community-acquired pneumonia/ 9–10% of hospitalizations (elderly)

The burden of RSV disease in pregnant women is unknown

Muñoz, Current Opinion in Infectious Diseases 2015
Transplacental transport of maternal RSV-neutralizing antibodies:

+ **RSV-specific antibody protect** infants during the first few months of life
+ **Safety and protective effectiveness** of passive administration of RSV-specific antibodies
+ median time to reduction of natural maternally derived serum-neutralizing antibody below a protective titer= **17 weeks**

→ Maternal vaccination could offer protection for at least 3–6 months
The development of Group B streptococcus (GBS) vaccines for maternal immunization: priority for WHO Initiative for Vaccine Research, based on
*a high unmet medical need, *technical feasibility assessment and *potential value of WHO involvement

Early-onset GBS infection in babies (0-6 days of life): sepsis with pneumonia.

Late onset GBS infection in babies (6 days to 3 months of life): sepsis, pneumonia and/or meningitis, or osteomyelitis and septic arthritis
Epidemiology GBS

- Global data and regional data
- Early onset disease (EOD < 6 days): 60-70%: serotype Ia, II, III, V; 20-30% colonisation in industrialised countries; incidence 0.5-4/1000
  Edmonds Lancet 2012; Mahieu Acta Clin Belg 2014
- Late onset disease (LOD > 6 days): less prevalent: 0.5/1000; 50% meningitis, serotype III
- Overall on average incidence in Europe: 0.53/1000
  Le Doare Vaccine 2013

**National Estimates of Invasive Disease**

Early-Onset Cases: 990 (0.25/1,000 live births)
Late-Onset Cases: 1,110 (0.28/1,000 live births)

CDC surveillance 2014
Zika virus
Specific human monoclonal antibodies (namely Z23 and Z3L1) have neutralisation capacity in vitro

b) Safety

Vaccines containing **inactivated** material: harmless for foetus and pregnant women.

**Live attenuated** vaccines are contra-indicated for pregnant women. In women at fertile age, 1 month of contraception should be advised, yet no interruption of pregnancy should be performed after accidental administration.
Safety pertussis vaccination

UK:
- N= 17,560 women: FU 28 d post vaccination
- N= 6,185 women: FU 44 weeks post LMD
- Risk assessment: stillbirth, maternal or neonatal demise, (pre-) eclampsia, haemorrhagia, fetal distress, uterus rupture, placenta (vasa) praevia, C-section, low birth weight, neonatal kidney failure, etc

This study found no evidence of an increased risk of any of the extensive predefined list of adverse events related to pregnancy. In particular, there was no evidence of an increased risk of stillbirth.

- Confirmed by Kharbanda JAMA 2014, Datwani Vaccine 2015, Keller Stanlowski Vaccine 2014
Safety repeat Tdap boosters

Safety repeat tetanus containing vaccines

- Sukumaran JAMA 2015 & 2016
- VSD sites: 29155 pregnant women
- No increased risk for: local reactions, premature delivery, SGA
- NO increased AE when repeat booster Tdap interval <2 years, 2-5 years in comparison with > 5 years
Safety influenza vaccination

- All considered safe except live attenuated vaccines
- Adjuvanted pandemic A/H1N1 2009 influenza vaccine: Denmark: N=54,585 pregnancies, no increased risk on fetal death, spontaneous abortion, stillbirth (Pasternak BMJ 2012)
- Seasonal vaccine: meta analysis: no increased risk on fetal death, spontaneous abortion, congenital malformation, but first trimester data are lacking (McMillan Vaccine 2015)
## Safety rubella vaccination

<table>
<thead>
<tr>
<th>Country (Year)</th>
<th>Number of Vaccinated Women</th>
<th>Number of reported pregnant women who were vaccinated</th>
<th>Number of susceptible pregnant Women</th>
<th>Number of Live Births with follow up</th>
<th>Number of Infants with congenital infection*</th>
<th>Infants with CRS\¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa Rica (Badilla 2007)</td>
<td>800,000</td>
<td>3,810</td>
<td>163</td>
<td>93</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Brazil</td>
<td>26,361,761</td>
<td>22,708</td>
<td>2,332</td>
<td>1,647</td>
<td>66 (4.0%)</td>
<td>0</td>
</tr>
<tr>
<td>El Salvador</td>
<td>1,400,000</td>
<td>909</td>
<td>59</td>
<td>59</td>
<td>1 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Ecuador</td>
<td>2,400,000</td>
<td>1,291</td>
<td>172</td>
<td>43</td>
<td>2 (0.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Paraguay</td>
<td>1,862,178</td>
<td>945</td>
<td>148</td>
<td>119</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Argentina</td>
<td>6,718,314</td>
<td>476</td>
<td>20</td>
<td>19</td>
<td>2 (11.7%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>39,542,253</strong></td>
<td><strong>30,139</strong></td>
<td><strong>2894</strong></td>
<td><strong>1980</strong></td>
<td><strong>70 (3%)</strong></td>
<td><strong>0</strong></td>
</tr>
</tbody>
</table>

PAHO: Castillo-Solorzano et al JID 2011

§ Within 4 weeks prior to pregnancy or up to 12 weeks of gestation

* Congenital Infection confirmed by rubella IgM+

¶ Vaccine associated CRS
Safety yellow fever vaccination

Fœtal damage: stillbirth, malformations

Maternal disease++

Indication: booster is allowed (no viraemia), primo- vaccination if really necessary

Outbreaks in Nigeria, Trinidad, European Network of Teratology Information Services: no complications

- Robert et al Vaccine 1999: 58 vaccinations during pregnancy: no side effects
- Cavalcanti Trop Med Int Health 2007: 3,3% vaccinated women (n=304) with congenital malformations (~ general population of Brazil)
Yellow fever vaccine and lactation

A few cases in literature: breastfed infants infected with the YF vaccine strain!

Kuhn S et al. CMAJ 2011;183:E243-E245
More and better data are welcomed:

- Standardised and harmonised AEFI definitions and reporting
  
  Muñoz Vaccine 2015, Jones Vaccine 2016

- Terminology and consistency in language:
  diagnostics (LMIC)

  Roice fulton Vaccine 2015

- LMIC: more comorbidity and adverse pregnancy outcomes: local/ regional data are needed

  Cutland Vaccine 2015

- CDC: enhanced surveillance: VAERS, VSD, CISA and prospective studies

  Moro Hum vacc Immunother 2015
Overview: vaccinate safely?

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Status</th>
<th>Vaccine</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polio</td>
<td>YES</td>
<td>Haemophilus</td>
<td>YES</td>
</tr>
<tr>
<td>Rubella</td>
<td>Contraindicated</td>
<td>Hepatitis</td>
<td>YES</td>
</tr>
<tr>
<td>Measles</td>
<td>Contraindicated</td>
<td>Pneumococcus</td>
<td>YES</td>
</tr>
<tr>
<td>Mumps</td>
<td>Contraindicated</td>
<td>Yellow fever</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Tetanus</td>
<td>YES</td>
<td>Pertussis</td>
<td>YES</td>
</tr>
<tr>
<td>Influenza</td>
<td>YES</td>
<td>Varicella</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
And more vaccines...

<table>
<thead>
<tr>
<th>Disease</th>
<th>YES/NO</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabies</td>
<td>YES</td>
<td>100% lethal infection, vaccinate if necessary</td>
</tr>
<tr>
<td>Tick Borne Encephalitis</td>
<td>YES</td>
<td>Seasonality: high risk in Eastern Europe</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>YES</td>
<td>Prevention mosquitos!</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>YES</td>
<td>Seasonality! Men-afrivac recommendation in meningitis belt (WER 2011 Jan)</td>
</tr>
<tr>
<td>Cholera</td>
<td>Yes/No</td>
<td>50% immunogenicity, no obligation to immunize</td>
</tr>
<tr>
<td>TBC</td>
<td>Yes/No</td>
<td>Skintest/RX. Treatment treats foetus!</td>
</tr>
<tr>
<td>Small pox</td>
<td>(Yes)</td>
<td>No malformations</td>
</tr>
<tr>
<td>Anthrax</td>
<td>(Yes)</td>
<td>No data</td>
</tr>
</tbody>
</table>
c) Immunogenicity and effectiveness

Humoral immune response on aP vaccines during pregnancy is comparable to response in non pregnant population (Gall et al Am J Obstet Gynecol 2011; Healy et al JID 2004, Muñoz et al Jama 2014; Abu Raya et al JID 2015...)

- Pregnant
- Control

Huygen et al Vaccine 2015
Tetanus

Start vaccination in 1961
Reconciled deaths from pertussis in infants, England only

Sources: Lab confirmed cases, certified deaths, Hospital episode statistics, GP registration details
* Both with unvaccinated mothers

Bron: http://www.who.int/immunization/sage/meetings/2014/april/3_SAGE_April_Pertussis_Miller_Strategies.pdf?ua=1
Effectiveness of Tdap in pregnancy on hospitalisation of infants due to pertussis disease

<table>
<thead>
<tr>
<th>Infants &lt;3 months of age</th>
<th>Percentage of cases vaccinated</th>
<th>Average matched coverage*†</th>
<th>Vaccine effectiveness‡</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infants &lt;3 months of age by timing of maternal immunisation</th>
<th>Percentage of cases vaccinated</th>
<th>Average matched coverage*†</th>
<th>Vaccine effectiveness‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination at least 28 days before birth</td>
<td>14% (10/69)¶</td>
<td>63%</td>
<td>91% (83 to 95)</td>
</tr>
<tr>
<td>Vaccination 7–27 days before birth</td>
<td>3% (2/72)</td>
<td></td>
<td></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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infants &lt;2 months of age</th>
<th>Percentage of cases vaccinated</th>
<th>Average matched coverage*†</th>
<th>Vaccine effectiveness‡</th>
</tr>
</thead>
<tbody>
<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>

Amirthalingam et al Lancet 2015
Effectiveness of Tdap in pregnancy on hospitalisation of infants of vaccinated women, due to pertussis disease

<table>
<thead>
<tr>
<th>Timing of Maternal Tdap Vaccination</th>
<th>Mothers Vaccinated, No.</th>
<th>Unadjusted VE (95% CI), %</th>
<th>Adjusted VE (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any point in pregnancy²</td>
<td>49</td>
<td>72.3 (49.0-85.0)</td>
<td>58.3 (14.9-79.6)</td>
</tr>
<tr>
<td>3rd trimester only²</td>
<td>35</td>
<td>75.4 (49.8-88.0)</td>
<td>52.1 (−16 to 80.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Tdap, tetanus, diphtheria, and acellular pertussis; VE, vaccine effectiveness.

² Adjusted for infant’s chronological age, gestational age, and receipt of diphtheria and tetanus toxoids and acellular pertussis vaccine.
² Calculations based on 420 (unadjusted) and 344 (adjusted) infants.
² Calculations based on 406 (unadjusted) and 330 (adjusted) infants.

Infected infants of vaccinated women: less likely to be hospitalized, shorter hospital stay

Winter et al CID 2016
Effectiveness influenza in pregnancy

Pregnant women

- Bangladesh: 36% decrease respiratory infections (Zaman New Engl J Med 2008)
- S Africa: 50% effectiveness against proven influenza, less in hiv + (Mahdi NEJM 2014)
- US: 50% reduction of acute respiratory infections among vaccinated pregnant women (Thompson CID 2013)

Fetus: positive effect on SGA and prematurity, more benefit for high risk profile women (african americans and lower SE situation) (Omer Saad Plos Medicine 2011) (Adedinsewo Vaccine 2013)
Neonate:

Positive effect: protection of infants

**d) Secondary effect: blunting of infant immune response by maternal antibodies**

**UK: prospective, historically controlled study:**
- high pre-vaccination antibody concentrations; blunting of PT antibody responses
- CRM conjugated vaccines: less IgG immune responses (pneumococci)
- MCC-TT and Hib-TT higher IgG responses

**BE/VN: prospective controlled study**
- Equal blunting of PT antibody responses
- Resolved with booster dose 2nd year of life
- Equal blunting of pneumococcal responses

Ladhani et al CID 2015

Maertens et al Vaccine (Jan en Jun) 2016, Maertens et al PIDJ 2017; Ha Hoang & Leuridan, Vaccine 2016-2017
Prospective study Belgium

Vaccine group (Boostrix): N= 57 women, 55 infants

Control group (no vaccine): N=42 women, 26 infants

Infants received Infanrix hexa

* Significant

Maertens et al Vaccine (Jan en Jun) 2016
e) Acceptance/ coverage/ implementation

Tetanus

Cumulative number of WRA protected with at least 2 doses of TT during SIA/year

Source: WHO/UNICEF MINFO Database, as at 17 February 2015
For 2014, data is provisional.
Date of slide 17 February 2015

**Protected means receiving at least 2 properly spaced doses of TT.
** Some of the unprotected are likely to have received the 2nd and subsequent doses of TT vaccine during some timeframes.
** The number of women of reproductive age at risk but not targeted is added in retrospect following country-level data collected over the years, and includes the fact that by 2014 there were still 60.5 million women of reproductive age to be reached.
Pertussis

ACIP (CDC), USA, Augustus 2011 51%
Third or late second trimester
Or immediately postpartum
UPDATE Oct 2012: every pregnancy

Department of Health, UK, Oktober 2012 73,8%
• 28-32 weeks gestational age
• Every pregnancy

Superior Health Council Belgium, July 2013 64%
• Every pregnancy
• 24-32 weeks gestational age

Gezondheidsraad Nederland, 2015
• 28-32 weeks GA
• Every pregnancy
Coverage of Pertussis and Influenza vaccination among pregnant women in Flanders, Belgium

**Pertussis**
- 64% vaccine coverage:
  - 87.9% advised by Obs/gynecologist, 5.9% GP and 2% midwife
  - 82% administered by GP, 10.4% by Obs/Gyne, 5% midwife
- 36% not vaccinated: 50% not informed; 7.8% advise against vaccination
- 62.6% of all partners vaccinated during present or previous pregnancy

**Flu**
- 45% vaccine coverage
  - 64% advised by Obs/gynecologist, 14.7% occupational physician, 13.2% GP
  - 68.1% administered by GP, 21.9% occupational physician, 4.6% Obs/Gyne
- 55% not vaccinated: 40% not informed, 6.8% advise against vaccination
Significantly influencing factors

- Migration background, also second generation

- Lower education and disemplyoment
  Laenen J, Vaccine, 2015

- Parity

- Hospital and HCW

Maertens et al Vaccine 2016
Conclusions

No vaccine has ever proven to have embryotoxic or teratogenic effects
Theoretically avoid live attenuated vaccines in pregnancy
Accidental exposure to attenuated vaccines: no indication for abortion (registration!)
Future vaccines designed specifically for vaccination during pregnancy
Acknowledgements

All participating women and children
Kirsten Maertens, Marjolein Orije & Aline Bontenakel: the MATAB team
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Wetenschappelijk Instituut Volksgezondheid (WIV-ISP) Brussels

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