Expert Consultation on Post-Vaccine Thrombosis Thrombocytopenia Syndrome & Impact on Maternal Immunization

A COVAX Maternal Immunization Working Group Webinar

June 9th 2021
Meeting Norms and Recording Disclaimer

Throughout the workshop, please ask any questions in the “Q&A” function. If you see that your question is already asked, you can “like” the question in the “Q&A” function.

During the discussion sessions, please “Raise Your Hand” if you want to say something. If called on by the moderator, you will be unmuted to intervene.

Please contact Amanda Berzins Amanda.Berzins@gatesfoundation.org for any technology or logistical issues.

This workshop will be recorded. Recording might be shared after the webinar. Please be mindful of the diverse audience attending the meeting when participating in open discussions.
Workshop introduction

Ajoke Sobanjo-ter Meulen

Flor Munoz
Workshop objectives

• To characterize the state of the science of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with adenoviral vectored COVID-19 vaccines, and how TTS might affect pregnant women

• To provide information to support evidence-based COVID-19 vaccine policy making for pregnant women in LMIC, taking into account the risks of:

  a. TTS following administration of adenovirus vectored vaccines in pregnancy
  b. COVID-19 infection and disease
  c. Availability of other COVID-19 vaccines
Number of COVID-19 Vaccine Approvals: Adenoviral vectored vaccines are important global players

Unicef dashboard: accessed on June 7, 2021
Country agreements for COVID-19 vaccine supply: significant proportion in LMIC are based on adenoviral vectored vaccine
### Current Guidance Regarding COVID-19 Vaccines in Pregnancy (As of June 9, 2021)

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| US FDA             | Upon EUA Approval (Dec 2020): “If you are pregnant or breastfeeding, discuss your options with your healthcare provider.”  
                        | **No specific contraindications** to vaccination other than anaphylaxis/allergic reactions.                                                 |
| US CDC – ACIP      | If the pregnant or lactating woman is part of a priority group (i.e., healthcare personnel) who is recommended to receive a COVID-19 vaccine and is pregnant, she may choose to be vaccinated. A discussion with her healthcare provider can help her make an informed decision.”  
                        | **TTS events with JJ AdV vaccine (April 2021) – Warning: inform women 18-49 years of risks and availability of other vaccines**                       |
| US ACOG / SMFM     | “COVID-19 vaccines should not be withheld” from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups.” Shared decision making with clinicians is advisable; however, it should not be required as this may create an undue barrier to access for these women. Breastfeeding women can get vaccinated.  
                        | **No change in recommendations or preference for specific vaccines after TTS events, in line with ACIP**                                           |
| WHO                | SAGE Meeting Dec 17th, 2020 - pregnant or lactating women should not be vaccinated with COVID-19 vaccines unless they are in high risk group.  
                        | **January 2021, language modified to indicate that pregnant and lactating women at risk may be vaccinated if at high risk of exposure (health care workers).**   |
| UK MHRA            | Dec 2020: “There are no data as yet on the safety of COVID-19 vaccines in pregnancy, either from human or animal studies. Given the lack of evidence, JCVI favours a precautionary approach, and does not currently advise COVID-19 vaccination in pregnancy. Women should be advised not to come forward for vaccination if they may be pregnant or are planning a pregnancy within three months of the first dose.  
                        | **Dec 30th, 2020 - Language changed to be in line with ACIP recommendations.**                                                                 |
                        | **May 2021 – Change to indicate preference of use of mRNA vaccines in pregnancy (based on US V-safe data)**                                        |
Recommended for some or all: e.g. “Pregnant people should be offered vaccine…

Permitted: e.g. “Pregnant people may receive vaccine... (including “where the benefits outweigh the risk”)

Permitted with qualifications: e.g. “Pregnant people may receive the vaccine only if…”

Not recommended but with exceptions: e.g. “Pregnant people should not receive the vaccine unless…”

Not recommended: e.g. “Pregnant women should not receive the vaccine…”

In transition: Where current policies are being revised.

No position found: Where no policies regarding vaccination in pregnancy could be found, or where the position remains unclear.
## Meeting agenda (I)

<table>
<thead>
<tr>
<th>Time (PDT)</th>
<th>Session</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 am PT (5 min)</td>
<td>Workshop Introduction</td>
<td>Ajoke Sobanjo-ter Meulen Flor Munoz</td>
</tr>
<tr>
<td>7:05 am PT (60 min)</td>
<td><strong>Session 1</strong></td>
<td><strong>Moderator: Flor Munoz</strong></td>
</tr>
<tr>
<td>7:05 am PT (10 min)</td>
<td>Vaccine safety surveillance</td>
<td>Kathryn Edwards</td>
</tr>
<tr>
<td>7:15 am PT (15 min)</td>
<td>Safety profile of adenovirus vectored vaccines</td>
<td>David Kaslow</td>
</tr>
<tr>
<td>7:30 am PT (10 min)</td>
<td>Theory of TTS/VITT mechanism</td>
<td>Andreas Greinacher</td>
</tr>
<tr>
<td>7:40 am PT (10 min)</td>
<td>Thrombosis/thrombocytopenia in pregnancy</td>
<td>Annemarie Fogerty</td>
</tr>
</tbody>
</table>
| 7:50 am PT (30 min) | **Discussion 1**                             | **Panelists:**
|                     |                                               | - Hanna Nohynek
|                     |                                               | - Annemarie Fogarty
|                     |                                               | - David Kaslow
|                     |                                               | - Asma Khalil
|                     |                                               | - Arnaud Marchant
|                     |                                               | **Moderator: Paul Henri Lambert**            |
| 8:20 am PT          | Break (5 min)                                |                                              |
## Meeting agenda (II)

<table>
<thead>
<tr>
<th>Time (PDT)</th>
<th>Session</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:25 am PT (50 min)</td>
<td><strong>Session 2</strong></td>
<td>Moderator: Ajoke Sobanjo-ter Meulen</td>
</tr>
<tr>
<td>8:30 am PT (10 min)</td>
<td>TTS/pregnancy surveillance update UK</td>
<td>Katherine Donegan</td>
</tr>
<tr>
<td>8:40 am PT (10 min)</td>
<td>TTS/pregnancy surveillance update Brazil</td>
<td>Cristiana Toscano</td>
</tr>
<tr>
<td>8:50 am PT (10 min)</td>
<td>TTS/pregnancy surveillance update US</td>
<td>Christine Olson</td>
</tr>
<tr>
<td>9:00 am PT (10 min)</td>
<td>TTS/pregnancy surveillance update EMA</td>
<td>Kelly Plueschke</td>
</tr>
<tr>
<td>9:10 am PT (10 min)</td>
<td>TTS/pregnancy surveillance update India</td>
<td>Narendra Arora</td>
</tr>
<tr>
<td>9:20 am PT (40 min)</td>
<td><strong>Expert Roundtable</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Panelists:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Jeff Roberts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Daniel Brasseur</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cristiana Toscano</td>
<td></td>
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<tr>
<td></td>
<td>• Laura Riley</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Narendra Arora</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Moderator:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ruth Karron and Mark Turrentine</td>
<td></td>
</tr>
<tr>
<td>10:00 am PT (5 min)</td>
<td>Concluding remarks</td>
<td>Ajoke Sobanjo-ter Meulen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flor Munoz</td>
</tr>
</tbody>
</table>
Vaccine safety surveillance

Kathryn Edwards
Professor of Pediatrics
Vanderbilt University
Nashville, TN, USA
Expert Consultation on Post-Vaccine Thrombosis Thrombocytopenia Syndrome & Impact on Maternal Immunization

• **Vaccine Safety Surveillance**
• Kathryn M. Edwards M.D.
• Professor of Pediatrics
• Vanderbilt University
• Nashville, TN, USA
Vaccine-induced immune thrombotic thrombocytopenia

Reports of low platelets (thrombocytopenia) and blood clots (thrombosis) after AZ vaccine in Europe

Two publications describing cases of thrombotic thrombocytopenia from Germany & Austria, and Norway

Many cases had platelet activating antibodies directed against platelet factor 4 (PF4)

Authors propose syndrome entitled “Vaccine-induced immune thrombotic thrombocytopenia” (VITT)


Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>10.1 gm/dL</td>
<td>12-15.5 gm/dL</td>
</tr>
<tr>
<td>Mean Corpuscular Volume</td>
<td>87.6 fL</td>
<td>81-96 fL</td>
</tr>
<tr>
<td>White Blood Cell count</td>
<td>8540/cmm</td>
<td>4000-10,000/cmm</td>
</tr>
<tr>
<td>Absolute Neutrophil Count</td>
<td>5320/cmm</td>
<td>1400-7000/cmm</td>
</tr>
<tr>
<td>Absolute Lymphocyte Count</td>
<td>2250/cmm</td>
<td>800-3300/cmm</td>
</tr>
<tr>
<td>Platelet count</td>
<td>13,000/cmm</td>
<td>150000-400000/cmm</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>89 mg/dL</td>
<td>220-397 mg/dL</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>117,512 ng/mL</td>
<td>&lt;500 ng/mL</td>
</tr>
</tbody>
</table>

ELISA PF4 Antibody = 2.550 OD units

US Vaccine Safety System

• V-safe
• Vaccine Adverse Event Reporting System (VAERS)
• Vaccine Safety Datalink (VSD)
• Clinical Immunization Safety Assessment (CISA) Project
Use your smartphone to tell CDC about any side effects after getting the COVID-19 vaccine. You’ll also get reminders if you need a second vaccine dose.

Advisory Committee on Immunization Practices (ACIP)
March 1, 2021
1. text message check-ins from CDC (daily 1st week; weekly thru 6 weeks; then 3, 6, and 12 mo.)

vaccine recipient completes web survey*

v-safe™ after vaccination health checker

Vaccine recipients

2. clinically important health impact reported

✓ received medical care

Call center

3. v-safe call center conducts active telephone follow-up on a clinically important event and takes a VAERS report if appropriate

4. pregnancy registry team conducts outreach to assess eligibility for registry and obtain consent for enrollment and follow-up

Call center

* Selected web surveys capture information on pregnancy status
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pfizer-BioNTech Vaccine</th>
<th>Moderna Vaccine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2136 (54.0)</td>
<td>1822 (46.0)</td>
<td>3958 (100)</td>
</tr>
<tr>
<td><strong>Age at first vaccine dose</strong>‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–24 yr</td>
<td>17 (0.8)</td>
<td>19 (1.0)</td>
<td>36 (0.9)</td>
</tr>
<tr>
<td>25–34 yr</td>
<td>1335 (62.5)</td>
<td>1238 (67.9)</td>
<td>2573 (65.0)</td>
</tr>
<tr>
<td>35–44 yr</td>
<td>777 (36.4)</td>
<td>560 (30.7)</td>
<td>1337 (33.8)</td>
</tr>
<tr>
<td>45–54 yr</td>
<td>7 (0.3)</td>
<td>5 (0.3)</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td><strong>Race and ethnic group‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>1663 (77.9)</td>
<td>1463 (80.3)</td>
<td>3126 (79.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>164 (7.7)</td>
<td>151 (8.3)</td>
<td>315 (8.0)</td>
</tr>
<tr>
<td>Non-Hispanic Asian</td>
<td>225 (10.5)</td>
<td>138 (7.6)</td>
<td>363 (9.2)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>24 (1.1)</td>
<td>26 (1.4)</td>
<td>50 (1.3)</td>
</tr>
<tr>
<td>Non-Hispanic multiple races</td>
<td>42 (2.0)</td>
<td>30 (1.6)</td>
<td>72 (1.8)</td>
</tr>
<tr>
<td>Non-Hispanic American Indian or Alaskan Native</td>
<td>5 (0.2)</td>
<td>1 (0.1)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Non-Hispanic Native Hawaiian or other Pacific Islander</td>
<td>6 (0.3)</td>
<td>3 (0.2)</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td>Missing data or participant declined to answer</td>
<td>7 (0.3)</td>
<td>10 (0.5)</td>
<td>17 (0.4)</td>
</tr>
<tr>
<td><strong>Timing of first eligible dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periconception: within 30 days before last menstrual period</td>
<td>55 (2.6)</td>
<td>37 (2.0)</td>
<td>92 (2.3)</td>
</tr>
<tr>
<td>First trimester: &lt;14 wk</td>
<td>615 (28.8)</td>
<td>517 (28.4)</td>
<td>1132 (28.6)</td>
</tr>
<tr>
<td>Second trimester: ≥14 and &lt;28 wk</td>
<td>932 (43.6)</td>
<td>782 (42.9)</td>
<td>1714 (43.3)</td>
</tr>
<tr>
<td>Third trimester: ≥28 wk</td>
<td>533 (25.0)</td>
<td>486 (26.7)</td>
<td>1019 (25.7)</td>
</tr>
<tr>
<td>Missing data</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td><strong>Covid-19 infection during pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Covid-19 infection</td>
<td>2084 (97.6)</td>
<td>1779 (97.6)</td>
<td>3863 (97.6)</td>
</tr>
<tr>
<td>Before vaccination</td>
<td>32 (1.5)</td>
<td>24 (1.3)</td>
<td>56 (1.4)</td>
</tr>
<tr>
<td>≤14 days after first eligible dose of vaccination</td>
<td>3 (0.1)</td>
<td>7 (0.4)</td>
<td>10 (0.3)</td>
</tr>
<tr>
<td>&gt;14 days after first eligible dose of vaccination</td>
<td>9 (0.4)</td>
<td>3 (0.2)</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td>Missing data</td>
<td>8 (0.4)</td>
<td>9 (0.5)</td>
<td>17 (0.4)</td>
</tr>
</tbody>
</table>
Figure 1. Most Frequent Local and Systemic Reactions Reported in the V-safe Surveillance System on the Day after mRNA Covid-19 Vaccination.
<table>
<thead>
<tr>
<th>Participant-Reported Outcome</th>
<th>Published Incidence*</th>
<th>V-safe Pregnancy Registry†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy loss among participants with a completed pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous abortion: &lt;20 wk\textsuperscript{15-17}</td>
<td>10–26</td>
<td>104/827 (12.6)‡</td>
</tr>
<tr>
<td>Stillbirth: ≥ 20 wk\textsuperscript{18-20}</td>
<td>&lt;1</td>
<td>1/725 (0.1)§</td>
</tr>
<tr>
<td>Neonatal outcome among live-born infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth: &lt;37 wk\textsuperscript{21,22}</td>
<td>8–15</td>
<td>60/636 (9.4)¶</td>
</tr>
<tr>
<td>Small size for gestational age\textsuperscript{23,24}</td>
<td>3.5</td>
<td>23/724 (3.2)</td>
</tr>
<tr>
<td>Congenital anomalies\textsuperscript{25****}</td>
<td>3</td>
<td>16/724 (2.2)</td>
</tr>
<tr>
<td>Neonatal death\textsuperscript{25††}</td>
<td>&lt;1</td>
<td>0/724</td>
</tr>
</tbody>
</table>

*Published Incidence
†V-safe Pregnancy Registry

This article was published on April 21, 2021, at NEJM.org.
DOI: 10.1056/NEJMoa2104583
VAERS is the nation’s early warning system for vaccine safety

About VAERS  Report an Adverse Event  VAERS Data  Resources  Submit Follow-Up Information

Have you had a reaction following a vaccination?
1. Contact your healthcare provider.
2. Report an Adverse Event using the VAERS online form or the new downloadable PDF. [New!]

Import: If you are experiencing a medical emergency, seek immediate assistance from a healthcare provider or call 9-1-1. CDC and FDA are not able to provide immediate medical treatment advice or diagnosis. If you need individual medical or health care advice, consult a qualified healthcare provider.

¿Ha tenido una reacción después de recibir una vacuna?
1. Contacta a tu proveedor de salud.
2. Reporte la reacción en línea o descarga la formular de VAERS en español [Nueva!]

What is VAERS?

Advisory Committee on Immunization Practices (ACIP)
March 1, 2021

co-managed by CDC and FDA
http://vaers.hhs.gov
Vaccine Adverse Event Reporting System (VAERS)

Strengths
- National data
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

Limitations
- Reporting bias
- Inconsistent data quality and completeness of information
- Lack of unvaccinated comparison group
- Not designed to assess causality

- VAERS accepts all reports from everyone regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event
- As a hypothesis-generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

Advisory Committee on Immunization Practices (ACIP)
March 1, 2021
VSD
Vaccine Safety Datalink

9 participating integrated healthcare organizations data on over 12 million persons per year

Advisory Committee on Immunization Practices (ACIP)
March 1, 2021
Types of information in VSD

- enrollment and demographics
- immunization records
- outpatient and clinic visits
- emergency room visits
- procedure codes
- hospital discharge diagnosis codes
- birth and death certificate information & family linkage

Linked by study IDs

+ charts and electronic health records

Advisory Committee on Immunization Practices (ACIP)
March 1, 2021
VSD COVID-19 vaccine doses administered by manufacturer through February 13, 2021*

* Source: VSD participating integrated healthcare organizations; total includes a small number of unknown vaccine type
Preliminary results of the VSD **sequential vaccinated concurrent comparator** analysis for COVID-19 vaccine safety after either dose of any mRNA vaccine as of February 13, 2021

- No statistical signals detected

<table>
<thead>
<tr>
<th>VSD Rapid Cycle Analysis prespecified outcomes for COVID-19 vaccines</th>
<th>Concurrent comparator analysis</th>
<th>Risk interval</th>
<th>Events in risk interval</th>
<th>Adjusted expected events in risk interval</th>
<th>Statistical signal (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>21</td>
<td>30.8</td>
<td>N</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>25</td>
<td>53.5</td>
<td>N</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>17</td>
<td>23.1</td>
<td>N</td>
</tr>
<tr>
<td>Convulsions/seizures</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>10</td>
<td>9.4</td>
<td>N</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>1</td>
<td>0</td>
<td>N</td>
</tr>
<tr>
<td>Immune thrombocytopenia</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>1</td>
<td>0</td>
<td>N</td>
</tr>
<tr>
<td>Myocarditis/pericarditis</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>2</td>
<td>0</td>
<td>N</td>
</tr>
<tr>
<td>Stroke, hemorrhagic</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>7</td>
<td>0</td>
<td>N</td>
</tr>
<tr>
<td>Stroke, ischemic</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>37</td>
<td>43.5</td>
<td>N</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>23</td>
<td>12.4</td>
<td>N</td>
</tr>
<tr>
<td>Pulmonary embolism (subset of VTE)</td>
<td>Vaccinated</td>
<td>1-21 days</td>
<td>19</td>
<td>0</td>
<td>N</td>
</tr>
</tbody>
</table>

* Only includes outcomes with events in the risk window
CISA

Clinical Immunization Safety Assessment (CISA) Project

7 participating medical research centers with vaccine safety experts

- clinical consult services†
- clinical research

†More information about clinical consults available at http://www.cdc.gov/vaccinesafety/Activities/CISA.html
Reports of CVST to VAERS after COVID-19 vaccines as of April 12, 2021

- Janssen COVID-19 vaccine
  - 6 reports of CVST with thrombocytopenia (platelet counts <150K/mm³) following 6.86 million doses administered
    - Reporting rate of 0.87 cases per million doses administered

- Pfizer-BioNTech COVID-19 vaccine
  - 0 reports following 97.9 million doses administered

- Moderna COVID-19 vaccine
  - 3 reports following 84.7 million doses administered
  - All 3 with normal platelet counts; onset 2, 6, and 12 days after vaccination

Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations

Presented at Advisory Committee on Immunization Practices; April 14, 2021
Characteristics of patients with CVST and thrombocytopenia* after Janssen COVID-19 vaccine, N=6

- Median age 33 years (range 18–48)
- Median time to symptom onset 8 days (range 6–13 days)
- All cases occurred in white females
- Current estrogen/progesterone use (n=1)
- **Pregnant or post-partum (n=0)**
- Pre-existing conditions
  - Obesity (n=3)
  - Hypothyroidism (n=1)
  - Hypertension (n=1)
  - Asthma (n=1)
  - Coagulation disorders (none known)

*Note: Thrombosis usually does not occur in the presence of low platelets; these case presentations are atypical and consistent with cases observed after AstraZeneca COVID-19 vaccine*
Janssen/J&J COVID-19 vaccine:
HAN released April 13, 2021

Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine

- Recommendations for Clinicians: diagnosis and treatment
- Recommendations for Public Health: case reporting through VAERS
- Recommendations for the Public: clinical signs and symptoms to monitor

HAN Archive- 00442 | Health Alert Network (HAN) (cdc.gov)
US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COVID2.S Vaccination, March 2 to April 21, 2021

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Key Points

Question What were the clinical characteristics of the first US patients reported to have cerebral venous sinus thrombosis (CVST) with thrombocytopenia following receipt of the Ad26.COVID2.S (Janssen/Johnson & Johnson) COVID-19 vaccine?

Findings In this case series of 12 patients, all were women, younger than 60 years, and had symptom onset ranging from 6 to 15 days after vaccination requiring hospitalization. Of 11 patients with heparin-platelet factor 4 enzyme-linked immunosorbent assay (ELISA) heparin-induced thrombocytopenia (HIT) antibody test results, all were positive. At last follow-up, outcomes were death (n = 3), intensive care unit (ICU) care (n = 3), non-ICU hospitalization (n = 2), and discharge to home (n = 4).

Meaning This case series may inform clinical guidance and investigations into the potential relationship between the Ad26.COVID2.S vaccine and CVST with thrombocytopenia.
Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients — United States, April 2021

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Summary

What is already known about this topic?
On April 13, 2021, CDC and the Food and Drug Administration (FDA) recommended pausing use of the Janssen COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome (TTS) among vaccine recipients.

What is added by this report?
On April 23, the Advisory Committee on Immunization Practice concluded that the benefits of resuming Janssen COVID-19 vaccination among persons aged ≥18 years outweighed the risks and reaffirmed its interim recommendation under FDA's Emergency Use Authorization, which includes a new warning for rare clotting events among women aged 18–49 years.

What are the implications for public health practice?
Resuming use of the Janssen COVID-19 vaccine will ensure flexibility, choice, and improved access. Education about TTS risk with Janssen COVID-19 vaccine is critical.
COVID-19 vaccine safety update

VAXZEVRIA
AstraZeneca AB

Individuals who previously had blood clots with low blood platelets (thrombosis with thrombocytopenia syndrome, TTS) after Vaxzevria must not be given a second dose of Vaxzevria.

Individuals with low blood platelets within 3 weeks after vaccination with Vaxzevria should be actively investigated for signs of blood clots; similarly, individuals who present with blood clots within 3 weeks of vaccination should be evaluated for low blood platelets.

Patients who have blood clots with low blood platelets after vaccination require specialist medical care.

Hypersensitivity reactions presenting as hives or rapid swelling under the skin in areas such as the face, lips, mouth and throat are newly identified side effects of Vaxzevria.

Vaxzevria is effective in preventing COVID-19.
Conclusions

• Rare cases of thrombotic thrombocytopenia were seen after COVID vaccines
• Initial cases were seen more commonly in females of younger ages
• Pregnancy surveillance systems were established
• An advisory was issued, and vaccinations were halted
• Vaccinations were resumed
• Patients were informed about the small risk of associated thrombotic complications with COVID vaccines
• We are eager to learn more about the risk in pregnancy
Safety profile of adenovirus vectored vaccines

David C Kaslow MD,
Chief Scientific Officer, PATH
Safety profile of adenovirus vectored vaccines
with a focus on:

• hAd5, hAd26, and ChAdY25
• platelets & coagulation factors (and other factors) associated with thrombosis and/or thrombocytopenia

David C Kaslow, MD
Chief Scientific Officer, PATH Essential Medicines
Head, PATH's Center for Vaccine Innovation and Access

07 JUN 2021

Graphic credits: Adenovirus by C San Martin https://doi.org/10.3390/v4050847
Disclosures

Inventor, U.S. and International patents related to adenoviruses

including Ad5 and Ad26
all assigned to MERCK & CO., INC. (US) | MSD (exUS)
no financial interests
Potential etiologies of thrombosis and/or thrombocytopenia

<table>
<thead>
<tr>
<th>Adenovirus-related</th>
<th>SARS-CoV-2 Spike-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Platelet and endothelial interactions</td>
<td>• S protein interactions with platelets, endothelium, etc.</td>
</tr>
<tr>
<td>• Coagulation factor interactions</td>
<td>• Immune-mediated</td>
</tr>
<tr>
<td>• Inflammatory response(s)</td>
<td></td>
</tr>
<tr>
<td>• Immune-mediated</td>
<td>• Immune-mediated</td>
</tr>
</tbody>
</table>

• Atypical Spike protein fragments and fusion proteins from neo-splicing events during “DNA vector”-based nuclear transcription

Graphic credits: Adenovirus by Ramon Andrade uploaded on 3dciencia/science Photo Library 17 Sep 2018
SARS-CoV-2 by CDC / A. Eckert, MS; D. Higgins, MAM
Background on Ad5, Ad26, & ChAdOx1

Platelets & Ad vectors

Coagulation factors & Ad vectors

Other mechanisms of potential interests
Phylogenetic relationship of vector backbones

- "Sputnik V" (hAd5 [recombinant]) vaccine,
- ChAdOx1-S/nCoV-19 [recombinant] vaccine
- (h)Ad26.COV2.S [recombinant] vaccine

Considerations relevant to thrombosis/thrombocytopenia:

- Tropism
  - Cell entry receptors (also on platelets & endothelium)
    - Coxsackie Adenovirus Receptor (CAR)
      - hAd5 (strong)\(^1\)
      - ChAdY25 (modest)\(^1\)
      - hAd26 (weak)\(^2\)
    - Sialic acid-bearing glycans
      - hAd26 (strong)\(^2\)
      - ChAdY25?\(^1\)
- Pre-existing adenovirus immunity\(^3,4\)
  - hAd5>hAd26>ChAdY25
- Immune response(s), including directed at vector\(^3,4\)
  - hAd5>ChAdY25>Ad26

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\(^1\)Sci Rep 5:16756 (2015) https://doi.org/10.1038/srep16756

* aka ChAdOx1
Adenovector platforms: COVID-19 vaccines

<table>
<thead>
<tr>
<th></th>
<th>E1</th>
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<th>E3</th>
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<td>?</td>
<td>?</td>
<td>?</td>
<td>FL PPS?</td>
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<tr>
<td>hAd26</td>
<td>Δ</td>
<td>wt</td>
<td>Δ</td>
<td>orf6</td>
<td>FL PPS</td>
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<td>ChAdOx1</td>
<td>Δ</td>
<td>wt</td>
<td>Δ</td>
<td>hybrid^3</td>
<td>FL</td>
</tr>
</tbody>
</table>

Δ = deleted; WT = wildtype; FL = Full length; PPS = pre-fusion stabilized

1 No technical reference publicly available
2 EMA Public Assessment Report (EPAR) [link]
3 *PLoS ONE* 7: e40385 (2012) [link]

Adenovirus and vector genetic structure

Adapted from: [link]

E1-complementing cell lines required

Adapted from: [link]

Graphic credit: [link]
Vaccine adenovectors require nuclear transcription, mRNA-based vaccines don’t

DNA-based vaccines
(e.g., Gam-COVID-Vac, Ad26.COV2-S, and ChAdOx1-S/nCoV-19)

RNA-based vaccines
(e.g., BNT162b2 and mRNA-1273)

N.B. Adenovirus replication and expression: episomal rather than chromosomal


## Vaccine adenovectors: clinical experience (non-COVID/non-therapeutic)

<table>
<thead>
<tr>
<th>hAd5 +/-</th>
<th>hAd26</th>
<th>ChAdOx1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ebola virus:</strong> GamEvac-Combi, heterologous VSV</td>
<td><strong>Ebola virus:</strong> Ad26.ZEBOV</td>
<td><strong>Malaria:</strong> ChAdOx1 LS2</td>
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<tr>
<td><strong>MERS:</strong> BVRS-GamVac-Combi</td>
<td><strong>HIV:</strong> Ad26.Mos.HIV, Ad26.Mos4.HIV, and Ad26.ENVA.01</td>
<td><strong>MERS:</strong> ChAdOx1 MERS</td>
</tr>
<tr>
<td><strong>Flu:</strong> GamFluVac</td>
<td><strong>RSV:</strong> Ad26.RSV.FA2 and Ad26.RSV.preF</td>
<td><strong>TB:</strong> ChAdOx1 85A (+ MVA)</td>
</tr>
<tr>
<td><strong>hAd5 by others</strong></td>
<td><strong>Filovirus:</strong> Ad26.Filo</td>
<td><strong>Flu:</strong> ChAdOx1 NP+M1</td>
</tr>
<tr>
<td>HIV, TB, Flu, Malaria, RSV, Ebola virus, Norovirus…</td>
<td><strong>Zika:</strong> Ad26.ZIKV.001</td>
<td><strong>Chikungunya:</strong> ChAdOx1 Chik</td>
</tr>
<tr>
<td></td>
<td><strong>HPV:</strong> Ad26.HPV16 and Ad26.HPV18</td>
<td><strong>Zika:</strong> ChAdOx1 Zika</td>
</tr>
</tbody>
</table>

4. Source: clinicaltrials.gov
Background on Ad5, Ad26, & ChAdOx1

Platelets & Ad vectors

Coagulation factors & Ad vectors

Other mechanisms of potential interests
Adenovirus (wildtype) and platelets

- Wildtype Ad bind platelets
  - via CAR\(^1\) and other receptors\(^2,3\) (sialic acid-bearing glycans?)
  - associated with activation\(^3,*,\) thrombosis\(^1,4,*,\), and thrombocytopenia\(^1,*\)

- CAR\(^5,**\) and sialic acid\(^6\) positive
- Anucleated; therefore, adenovirus may bind but do not replicate
- Activation may lead to aggregation (thrombosis) or clearance (thrombocytopenia)

<table>
<thead>
<tr>
<th></th>
<th>CAR</th>
<th>Sialic glycans</th>
<th>Thrombi</th>
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<tr>
<td>hAd5</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>hAd26</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>ChAdY25</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

3[^Virol J 6:25] (2009) [https://doi.org/10.1186/1743-422x-6-25](https://doi.org/10.1186/1743-422x-6-25);
4[^Hum Gene Ther. 27:193] (2016) [https://doi.org/10.1089/hum.2015.154](https://doi.org/10.1089/hum.2015.154);
5[^Virol J 8:456] (2011) [https://doi.org/10.1186/1743-422X-8-456](https://doi.org/10.1186/1743-422X-8-456);
6[^J Clin Med 10:1661] (2019) [https://doi.org/10.3390/jcm10081661](https://doi.org/10.3390/jcm10081661);

N.B. *Dispute adenovirus induce, inhibit, or potentiate human platelet aggregation, Hum Gene Ther 13:125 (2002) [https://doi.org/10.1089/10430340152712674](https://doi.org/10.1089/10430340152712674);
**Dispute presence of CAR on platelets: Ref 3 above

[^Blood109:2832]: [https://doi.org/10.1182/blood-2006-06-032524](https://doi.org/10.1182/blood-2006-06-032524);
[^J Virol 70:4502]: [https://doi.org/10.1186/1743-422X-7-148](https://doi.org/10.1186/1743-422X-7-148);
[^Virol J 6:25]: [https://doi.org/10.1186/1743-422x-6-25](https://doi.org/10.1186/1743-422x-6-25);
[^Hum Gene Ther. 27:193]: [https://doi.org/10.1089/hum.2015.154](https://doi.org/10.1089/hum.2015.154);
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Graphic credits:
Adenovirus by Ramon Andrade uploaded on 3dciencia/science Photo Library 17 Sep 2018
Adenovector-associated thrombocytopenia

- Route and dose-dependent thrombocytopenia with 1\textsuperscript{st} gen adenovectors:
  - Intraportal\textsuperscript{1} > (intratumor)\textsuperscript{2} > intravascular\textsuperscript{3} > intramuscular\textsuperscript{4} > (oral\textsuperscript{5})

\begin{tabular}{|c|c|}
\hline
\textbf{Product} & \textbf{Dose} \\
\hline
hAd5/26 & $1 \times 10^{11}$ virus particles/each \\
\hline
hAd26 & $2.5 \times 10^{10}$ viral particles* \\
\hline
ChAdOx1 & $2.5 \times 10^{10}$ viral particles** \\
\hline
\end{tabular}

\*Reported as 8.92 log10 (8.3 \times 10\textsuperscript{8}) infectious units (from EPAR)

\**Reported as 2.5 \times 10\textsuperscript{8} infectious units (from EPAR)


\textsuperscript{4} see slide 14

\textsuperscript{5} limited data
“extremely mild thrombocytopenia was noted after the initial adenovector inoculation, and in Study E (Ebola), these mean values fell slightly outside the historical reference range, the severity was so slight that it is not likely to be clinically meaningful.”
Repeat-dose in male and female rabbits:
- transient decreases, followed by transient increases
- pathophysiological responses to vaccine administration
- not associated with any apparent adverse consequence

Vaccine adenovectors and platelets: *Clinical data*

Non-COVID vaccine trials reporting thrombocytopenia

- All infrequent and transient; most mild without clinical consequences (range to severe)

<table>
<thead>
<tr>
<th>Ad 5 and other C type</th>
<th>Ad26</th>
<th>ChAdOX1</th>
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</thead>
<tbody>
<tr>
<td>rAd5-EnvA/rAd35-EnvA (HIV)</td>
<td>Ad26.ZEBOV</td>
<td>ChAdOX1 85A</td>
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<tr>
<td>Ad5 (Ebola)</td>
<td></td>
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<tr>
<td>ChAd3-EBO-Z</td>
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Access bias?
Background on Ad5, Ad26, & ChAdOx1
Platelets & Ad vectors
Coagulation factors & Ad vectors
Other mechanisms of potential interests
Adenovector-associated coagulopathies

- Route and dose-dependent coagulopathies with 1st gen adenovectors:
  - Intraportal\(^1\) > (intratumor)\(^2\)> intravascular\(^3\) > intramuscular\(^4\) > (oral\(^5\))

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“consistent with an in vitro effect on the laboratory assay for aPTT due to a transient induction of anti-phospholipid antibody (APA)”

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\(^5\) limited data
Vaccine adenovectors and coagulation factors: *Preclinical tox data* I

### Coagulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study</th>
<th>Product</th>
<th>Timepoint</th>
<th>Gender</th>
<th>Direction</th>
<th>Mean</th>
<th>S.D.</th>
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<td><strong>Activated</strong></td>
<td>D</td>
<td>SD24</td>
<td>F</td>
<td>†</td>
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<td>83.71</td>
<td>7.65</td>
<td>73.35</td>
<td>10.65</td>
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<tr>
<td></td>
<td>E</td>
<td>SD3</td>
<td>M</td>
<td>†</td>
<td>↑</td>
<td>105.96</td>
<td>27.18</td>
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<td></td>
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<td>F</td>
<td>↑</td>
<td>↓</td>
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<td>SD24</td>
<td>F</td>
<td>↑</td>
<td>↓</td>
<td>107.19</td>
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<td>84.32</td>
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<td></td>
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<td>0.16</td>
<td>6.62</td>
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<tr>
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<td>SD108</td>
<td>M</td>
<td>↓</td>
<td>↑</td>
<td>6.3</td>
<td>0.12</td>
<td>6.56</td>
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<td>↓</td>
<td>↑</td>
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<td>7.05</td>
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<td>M</td>
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<td>6.56</td>
<td>0.11</td>
<td>6.99</td>
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<td>335.15</td>
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<td>↓</td>
<td>↑</td>
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<td>81.96</td>
<td>271.62</td>
<td>65.69</td>
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<td>SD90</td>
<td>F</td>
<td>↓</td>
<td>↑</td>
<td>665.8</td>
<td>77.32</td>
<td>347.82</td>
<td>28.53</td>
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<td></td>
<td>G</td>
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<td>F</td>
<td>↓</td>
<td>↑</td>
<td>559.6</td>
<td>73.26</td>
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<td>SD90</td>
<td>F</td>
<td>↓</td>
<td>↑</td>
<td>472</td>
<td>77.46</td>
<td>361.69</td>
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<td></td>
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<td>SD90</td>
<td>F</td>
<td>↓</td>
<td>↑</td>
<td>359.1</td>
<td>47.83</td>
<td>294.11</td>
<td>48.54</td>
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<td>F</td>
<td>↓</td>
<td>↑</td>
<td>407.3</td>
<td>95.76</td>
<td>307.25</td>
<td>49.2</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>SD90</td>
<td>F</td>
<td>↓</td>
<td>↑</td>
<td>353.8</td>
<td>144.62</td>
<td>247.15</td>
<td>21.58</td>
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<tr>
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<td>G</td>
<td>SD45</td>
<td>F</td>
<td>↓</td>
<td>↑</td>
<td>620.8</td>
<td>41.91</td>
<td>339.84</td>
<td>50.42</td>
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<td>G</td>
<td>SD45</td>
<td>F</td>
<td>↓</td>
<td>↑</td>
<td>569.6</td>
<td>91.11</td>
<td>269.81</td>
<td>17.92</td>
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<tr>
<td></td>
<td>G</td>
<td>SD57</td>
<td>F</td>
<td>↓</td>
<td>↑</td>
<td>297.8</td>
<td>42.58</td>
<td>238.21</td>
<td>14.92</td>
</tr>
</tbody>
</table>

*Note: D = Day 1; E = Day 2; F = Day 3; G = Day 4; † = p < 0.05; ↑ = increase; ↓ = decrease.*

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**Journal of Immunotoxicology**

**Biodistribution and Toxicological Safety of Adenovirus Type 5 and Type 35 Vectored Vaccines Against Human Immunodeficiency Virus-1 (HIV-1), Ebola, or Marburg Are Similar Despite Differing Adenovirus Serotype Vector, Manufacturer’s Construct, or Gene Inserts**


*J Immunotoxicology* 5:315 (2008) [https://doi.org/10.1080/15376510802312464](https://doi.org/10.1080/15376510802312464)
• “shortened PTT times are not clinically meaningful … do not reflect any coagulation abnormalities.”
• “consistent observation of prolonged activated partial thromboplastin time (APTT) … also been observed clinically in association with adenovirus infection or adenovector delivery.”
• “possible that the prolonged APTT represents a clinically benign effect of transient inflammation-induced anti-phospholipid antibody in the in vitro assay.”

Therefore, we suggest that the adenovector delivery intramuscularly is not inducing clinically-relevant coagulation abnormalities, but that the APTT assay is indirectly detecting a transient rise in anti-phospholipid antibodies that are a byproduct of the vaccine-induced inflammation and immune responses. Further, the elevated fibrinogen values that are likely a reflection of a vaccine-induced inflammatory response support this interpretation.”
“fibrinogen concentration was found to increase considerably after administration of ChAd3-EBO-Z in both males and females”

“increase started 8 hours after the injection and lasted for up to 7 days”

“could have been related to the inflammation seen microscopically at the injection sites and correlated with the increased neutrophil counts”

“demonstrates the establishment of an inflammatory reaction consecutive to vaccine administration”
"Statistically significant prolongation of APTT was noted 24 hours after both injections and 48 hours after the first injection in males and females treated with ChAd3-EBO-Z candidate vaccine"
Vaccine adenovectors and platelets: *Clinical data*

Non-COVID vaccine trials reporting coagulopathies

- All infrequent, transient; most mild and without clinical consequences (range to moderate)

<table>
<thead>
<tr>
<th>Ad 5 and other C type</th>
<th>Ad26</th>
<th>ChAdOX1</th>
</tr>
</thead>
<tbody>
<tr>
<td>rAd5-EnvA/rAd35-EnvA (HIV)</td>
<td><img src="https://doi.org/10.1371/journal.pone.0166393" alt="Link" /></td>
<td><img src="https://doi.org/10.1016/j.vaccine.2010.10.037" alt="Link" /></td>
</tr>
<tr>
<td>Ad5 (Ebola)</td>
<td><img src="https://doi.org/10.1016/j.vaccine.2010.10.037" alt="Link" /></td>
<td><img src="https://doi.org/10.1016/j.vaccine.2010.10.037" alt="Link" /></td>
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<tr>
<td>ChAd3-EBO-Z</td>
<td><img src="https://doi.org/10.1016/j.vaccine.2010.10.037" alt="Link" /></td>
<td><img src="https://doi.org/10.1016/j.vaccine.2010.10.037" alt="Link" /></td>
</tr>
</tbody>
</table>

Access and/or assessment bias?

(i.e., absence of effect or absence of data)
Background on Ad5, Ad26, & ChAdOx1
Platelets & Ad vectors
Coagulation factors & Ad vectors
Other mechanisms of potential interests
Other mechanisms proposed

• Immune-mediated
  • Adenovector-mediated vaccine-induced thromboembolic thrombocytopenia
    • Adenovirus-associated complexes
    • Cross-reaction of anti-adenovector antibodies to platelets or host factors (e.g., platelet factor 4 complexes)

• Transgene-mediated
  • Alternatively spliced mRNA
    • Spike protein fragments
    • Fusion proteins
    • Neoantigens
Adeno-vectored vaccines require nuclear transcription, mRNA vaccines don’t

DNA-based vaccines
(e.g., Gam-COVID-Vac, Ad26.COV2-S, and ChAdOx1-S/nCoV-19)

RNA-based vaccines
(e.g., BNT162b2 and mRNA-1273)


Multiple types of alternative splicing in nuclear pre-mRNA processing

N.B. Pre-mRNA splicing initially described in hAd2 late mRNA processing¹


Splice reactions within SARS-CoV-2 Spike open reading frame

Source: Research Square preprint Version 1 posted by Kowarz et al 26 May 2021 https://doi.org/10.21203/rs.3.rs-558954/v1
Interim summary

• Preponderance of data suggest wildtype adenoviruses and replication-deficient recombinant adenovectors can affect platelet counts and coagulation factors, in an apparent route and dose-dependent manner

• Pre-clinical toxicology and/or clinical evaluation of hAd5, hAd26, and ChAdOX1 adenovectors have all reported some degree of thrombocytopenia and/or variability in coagulation-related lab results

• Gaps (some significant) exist in understanding:
  • effect(s) of adenovectors on
    • platelets
    • coagulation
  • thrombosis and/or thrombocytopenia
  • anti-adenovector immune response(s) and host immunopathology
  • synthesis, processing, distribution, and host responses to adenovector transgenes
Theory of TTS/VITT mechanism

Prof. Dr. med. Andreas Greinacher
Universitätsmedizin Greifswald
Sauerbruchstraße
Thrombosis/thrombocytopenia in pregnancy

Annamarie E. Fogerty, MD.
Director, Reproductive Hematology
Massachusetts General Hospital
Boston, MA USA
COVAX MATERNAL IMMUNIZATION WORKING GROUP WEBINAR

Thrombosis/Thrombocytopenia in Pregnancy

Annemarie E. Fogerty, M.D.

June 2021
THROMBOCYTOPENIA IN PREGNANCY: Affects 10% of all pregnancies

Etiologies can include

- Pregnancy specific
  - Gestational thrombocytopenia
  - Preeclampsia/HELLP (hemolysis, elevated liver enzymes, low platelets)
  - AFLDP (acute fatty liver disease of pregnancy)
- Pre-existing: Lupus, ITP, liver disease, VWD 2B, congenital thrombocytopenia
- New/acquired: ITP, thrombotic microangiopathies, infections, antiphospholipid antibody syndrome, aplasia, drug
Maternal thrombocytopenia: Most Common Causes

- 70% Benign Gestational
- 21% Pre-eclampsia
- 6% ITP
- 3% Other
Features that may contribute to thrombocytopenia development in normal pregnancies

- Published reviews reveal an average decline of platelets by 10-13% in pregnancy
  
- Minor increase in thrombopoietin (TPO), which can be insufficient in disease states
  
- ADAMTS13 activity level declines
  
- Increased vWF production and prolongation of the vWF half life
  
- Increasing mean platelet volume (MPV) as pregnancy progresses likely reflects progressive increase in platelet turnover

6. Fogerty AE. Accepted for publication, BJH. 2021
Benign gestational thrombocytopenia (GT)

- Platelets 70-80K+
  - Occurs in late gestation (mid-2nd-3rd trimester)
  - About 10% of cases will result in platelet <100K

- Features of GT:
  - No increased risk of newborn thrombocytopenia
  - No treatment needed
  - No contraindication to epidural anesthesia
  - Rapid and spontaneous resolution after delivery
  - Recurs in future pregnancies
    - Suggesting a fixed maternal physiology
  - Exaggerated increase in MPV compared to normal pregnancies

3. Fogerty AE. Accepted for publication, BJH. 2021.
Pre-eclampsia
(about 20-25% of cases of thrombocytopenia in pregnancy)

- HTN (140/90) and proteinuria after 20 weeks (HAs, rapid weight gain, limb edema)
  - Responsible for 1/3rd of pregnancy related deaths (40% of deaths attributed to cerebrovascular event)

- Proposed mechanism: Failure of embryonic trophoblasts to adequately invade the uterus and spiral arteries leads to placental ischemia from:
  - Increases in sheer force of the endothelium
  - Disturbed platelet function
  - Imbalance of angiogenic vs antiangiogenic factors
  - Abnormal complement regulation
ITP in pregnancy
(about 3% of cases of thrombocytopenia in pregnancy)

- 1-2/1000 pregnancies
  - Most common cause of thrombocytopenia in first/early second trimesters
- No “rule in” test: onset, trend over time, size of platelets and ruling out other causes. Remains a diagnosis of exclusion
- Can result in fetal thrombocytopenia (autoantibodies can readily cross the placenta)
  - 8.7-14.7% fetal thrombocytopenia in neonates of ITP mothers
  - Fetal intracranial hemorrhage: 1.5%  

No documented association with vaccinations as causing ITP in adults

- 198 newly diagnosed ITP patients
- 878 matched controls without ITP
- Vaccinations in past 12 months
  - ITP: 66/198 (33.3%)
  - No ITP: 303/878 (34.5%)

Covid data from Vaccine Adverse Events Reporting System (VAERS)

- Report on 17 cases of new ITP (20 million vaccinations)
  - Median (range) 5 (1–23) days after first dose vaccine
  - Median (range) platelet counts: 2 (1–36) x 10^9/L
  - Most respond to corticosteroids or IVIG
  - One died
- Comparable to background rate of ITP
- No cases seen in licensing trials
MGH COVID Vaccination Experience in 50 patients with pre-existing ITP diagnosis

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>J&amp;J</td>
<td>8%</td>
</tr>
<tr>
<td>Pfizer</td>
<td>46%</td>
</tr>
<tr>
<td>Moderna</td>
<td>46%</td>
</tr>
</tbody>
</table>

- **No symptoms**
  - No platelet counts: 17/50 (34%)
  - No change in platelet counts: 26/50 (52%)

- **Symptoms**
  - Platelets fell*: 7/50 (14%)
    - 3/7 admitted to hospital, all 7 had increased ITP treatment, all recovered in 3–35 days

Kuter DK. BJH. 2021.
THROMBOSIS IN PREGNANCY
Estrogen induces a hypercoagulable state

- **Coagulation promoted**
  - Increased fibrinogen, vWF, factors II, VII, VIII, IX, X

- **Decrease in natural anticoagulant mechanisms**
  - Increased resistance to activated protein C and decreased PS

- **Fibrinolysis inhibited**
  - Increased level and activity of TAFI, PAI-1, PAI-2 (fibrinolytic inhibitors)

Similar trend, but less dramatic change from estrogen-containing OCPs
INITIATION
TF exposed at the site of injury

AMPLIFICATION
Increased in Pregnancy:
Fibrinogen
Factors II, VII, VIII, IX, X
VWF

TFPI decreased:
• Inhibits fX
• Inhibits TF/fVIIa union
Changes in Pregnancy:

- 40-60% decrease protein S activity
  - Estrogen induced decrease in total protein S and increase in C4b binding protein, which binds protein S
- Increased factor VIII
- Thrombomodulin increases (sign of vascular damage)
Pregnancy: A hypercoagulable state

- **Anatomic changes** also contribute to the hypercoagulable state:
  - Decreased rate of venous return from the legs due to hormonal changes decreasing venous tone
  - Venous obstruction by the gravid uterus
  - Endothelial damage to pelvic veins at the time of delivery due to venous hypertension
Risk for VTE in pregnancy

• VTE risk increases 6-10 fold
  – estimated incidence 0.76-1.72 per 1000 pregnancies
  – * about 1/3500 with use of estrogen-OCPs

• Death from PE:
  – 1.1-1.5 per 100,000 deliveries in USA and Europe

• 2/3rd DVT occur antepartum
  – evenly distributed between trimesters

• 50% of PE occur postpartum

• Primary thrombophilia will be identified in 50% of cases of pregnancy-associated VTE
HIT and VITT

- HIT during pregnancy is extremely rare
  - Heparin is not used in the vast majority of pregnancies
  - No data on probability of pre-existing PF4 antibodies
  - When it occurs, an alternative anticoagulant should be used: fondaparinux, danaparoid (not in the US), direct thrombin inhibitors

- IVIg has been used for persistent thrombocytopenia despite heparin discontinuation and alternative anticoagulant

- Still emerging data, but considerations …
  - VITT is quite rare, but most common among reproductive age females
  - We have seen autoimmune “flares” with COVID vaccinations (ITP data)
Panel discussion

Panelists

Hanna M. Nohynek  Annemarie Fogarty  David Kaslow  Asma Khalil  Arnaud Marchant

Paul-Henry Lambert
Moderator

Questions

- Can we have a consensus on the mechanisms involved in post-vaccination TTS?

- Is there an increased risk of TTS in pregnant women or in women at child-bearing age

- Provide suggestions for research agenda
5 minutes break
Dr Katherine Donegan
Pharmacoepidemiology Research and Intelligence Manager, MHRA
TTS / pregnancy surveillance update UK

Dr Katherine Donegan
UK AZ vaccine deployment

• First AZ doses deployed 30\textsuperscript{th} December 2020

• Up to 28\textsuperscript{th} May, 24.3 million 1\textsuperscript{st} AZ doses and 13.4 million 2\textsuperscript{nd} doses
  – In under 40s, 13.1 million and 1.4 million respectively.

• UK deployment priority groups based on age and risk of COVID-19 infection (health and social care workers) and severity (medical history)
  – Pregnant women at risk of severe COVID-19 eligible

• May 2021, alternative vaccines offered to those under 40 years
  – Pregnant women eligible based on age
TTS: Experience in the UK


• Up to 28th May, 348 TTS cases (330 1st dose / unknown vs. 18 2nd dose)
  – 128 CVST (28% fatal) vs 220 non-CVST (11% fatal)
  – 189 women, 156 men, age range 18-93 years
  – Overall reported incidence rate 13.6 per 1m 1st doses, 2.4 per 1m 1st doses fatal

• Age-related risk following first dose: 8.0 per 1m doses 18-49 years vs. 10.2 50+ years

• Only borderline increased reporting in females, 15.8 per 1million males vs 19.9 females
### Reported incidence of TTS

#### Weighing up the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine

For 100,000 people with high exposure risk

| Age group | Potential benefits (ICU admissions due to COVID-19 prevented every 16 weeks) | Potential harms (Specific blood clots associated with the vaccine:)
<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>20-29yr</td>
<td>6.9</td>
<td>1.9</td>
</tr>
<tr>
<td>30-39yr</td>
<td>24.9</td>
<td>1.5</td>
</tr>
<tr>
<td>40-49yr</td>
<td>51.5</td>
<td>1.2</td>
</tr>
<tr>
<td>50-59yr</td>
<td>95.6</td>
<td>1.0</td>
</tr>
<tr>
<td>60-69yr</td>
<td>127.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission.

Other potential harms not shown include short-term side effects. Data from reactions to first dose only. Data from UK up until 28th April 2021.

* Based on coronavirus incidence of 20 per 10,000 per day (1391 per 100,000 per week): roughly UK at peak.
## Reported incidence of TTS – 1st vs 2nd dose

<table>
<thead>
<tr>
<th>Age group</th>
<th>Estimated number of first doses in UK (1,000,000s)</th>
<th>Total number of cases (exc. unlikely cases)</th>
<th>Case incidence rate (per 1 million doses)</th>
<th>Estimated number of second doses in UK (1,000,000s)</th>
<th>Total number of cases (exc. unlikely cases)</th>
<th>Case incidence rate (per 1 million doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49 yrs</td>
<td>8.4</td>
<td>151</td>
<td>18.0 (15.3, 21.1)</td>
<td>2.7</td>
<td>0</td>
<td>0 (0, 1.4)</td>
</tr>
<tr>
<td>50+ yrs</td>
<td>15.9</td>
<td>163</td>
<td>10.2 (8.7, 11.9)</td>
<td>10.7</td>
<td>15</td>
<td>1.4 (0.8, 2.3)</td>
</tr>
<tr>
<td>Total</td>
<td>24.3</td>
<td>330*</td>
<td>13.6 (12.2, 15.1)</td>
<td>13.4</td>
<td>18**</td>
<td>1.3 (0.8, 2.1)</td>
</tr>
</tbody>
</table>
UK COVID-19 vaccines in pregnancy surveillance strategy

- MHRA: Four-tiered approach
  - Enhanced passive surveillance – observed vs expected
  - **Targeted active surveillance** – Yellow Card Vaccine Monitor
  - Rapid Cycle Analysis - in the CPRD
  - Epidemiological studies

- Public Health England – Vaccination in Pregnancy study
  - Inadvertent exposures in pregnancy

- Collaborative epidemiological studies with PHE, devolved regions, and UKTIS
  - POC pregnancy data capture mandatory – linkage to secondary /primary care data
  - Pregnancy-specific AESI
Yellow Card Vaccine Monitor

- 935 women reporting pregnancy registered, 319 (34%) report an ADR
Cristiana Toscano, MD PhD
Professor, Federal University Goiás, Brazil
Member of the PAHO TAG and WHO SAGE working group on COVID-19 vaccines.

TTS/pregnancy surveillance update Brazil
TTS/Pregnancy Surveillance in Brazil

Expert Consultation on Post-Vaccine TTS & Impact on Maternal Immunization
June 9th, 2021

Cristiana Toscano, MD, PhD
Professor, Head, Collective Health Department
Federal University of Goiás (UFG), Brazil
Member of the PAHO Technical Advisory Group of Experts on Immunization (TAG)
Member of the COVID-19 working group, Strategic Advisory Group of Experts (SAGE)-WHO
Disclaimer and Acknowledgements

• Disclaimer
  • Infectious Disease Epidemiologist, Professor at the University
  • Technical consultation meetings and technical committees
  • Not part of the Brazilian MoH
  • Not representing policies and positions of any of the institutions below

• Slides, Data and Thanks:
  • Ministry of Health, National Imunization Program – Brazil
  • Pan-American Health Organization, country office – Brazil
  • Biomanguinho, Fiocruz - Brazil
Outline

- Brazilian national COVID-19 vaccine safety surveillance system
- COVID-19 surveillance and vaccine safety monitoring in pregnancy
- COVID-19 infection/disease risk in pregnant women
- Adverse events following vaccination in pregnant women
- Case report - TTS death in pregnancy after vaccination
- Considerations for covid-19 maternal vaccination recommendations
COVID-19 vaccination in pregnancy, Brazil

Jan 17, 2021
Covid-19 vaccination starts

Early May 2021
257.9 cases & 20.3 deaths/100,000 pregnant women

Ntl Rec to vaccinate Pregnant women (and post-partum)¹
April 26th, 2021

¹Nota Técnica 467/2021 - CGPNI/DEIDT/SVS/MS
²Nota Técnica 627/2021 - CGPNI/DEIDT/SVS/MS
Severe Acute Respiratory Syndrome in Pregnant Women, Brazil, 2021, by mid-May 2021

- Estimated pregnant women in Brazil: 2,488,052

<table>
<thead>
<tr>
<th></th>
<th>Número</th>
<th>Incidência/100 mil habitantes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casos SRAG</td>
<td>6.880</td>
<td>276.52</td>
</tr>
<tr>
<td>Casos de SRAG por covid-19</td>
<td>4.442</td>
<td>178.53</td>
</tr>
<tr>
<td>Óbitos por SRAG</td>
<td>541</td>
<td>21.74</td>
</tr>
<tr>
<td>Óbitos de SRAG por covid-19</td>
<td>514</td>
<td>20.75</td>
</tr>
</tbody>
</table>

Fonte: SIVEP-Gripe, atualizado em 17/05/2021, dados sujeito a alterações

Mortality among pregnant and recently pregnant women with SARIs is high among those with COVID-19, particularly in regions where maternal mortality is already high.
COVID-19 vaccine doses administered in pregnant post-partum women, Brazil, by June 6th, 2021

<table>
<thead>
<tr>
<th></th>
<th>Total: 126,185</th>
<th>Dose 1: 124,890 (99%)</th>
<th>Dose 2: 1,295 (1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>73,4K (58%)</td>
<td></td>
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</tr>
<tr>
<td>AstraZeneca</td>
<td>39,1 K (31%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinovac</td>
<td>13,8 K (11%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fonte: Ministério da Saúde, disponível em https://localizasus.saude.gov.br/ (06/06/2021)
COVID-19 vaccine doses administered in pregnant post-partum women, by State - Brazil, by June 6th, 2021

*Exceto estado de São Paulo
Fonte: Ministério da Saúde, disponivel em https://localizasus.saude.gov.br/ (06/06/2021)
COVID-19 Post-Vaccination Adverse Events in pregnant women Brazil, by May 23rd 2021

General Population:
Total: 166,8/100K doses
Severe: 9,9/100K doses
Death: 5,1/100K doses

Deaths: 4 (3,2/100K doses)
Severe events: 41 (32,5/100K doses)
Total events: 773 (612,6/100K doses)

By vaccine:
- AstraZeneca: 473 → 1.209,7
- Sinovac: 275 → 1.992,8
- Pizer: 25 → 34,1

- AstraZeneca: 26 → 66,5
- Sinovac: 11 → 79,7
- Pizer: 4 → 5,4

- AstraZeneca: 3 → 7,7
- Sinovac: 0 → --
- Pizer: 1 → 1,4

*Excluindo São Paulo
Fonte: Planilha compartilhada pela CGPNI/DEIDT/SVS/MS

#UniversalHealth
Severe adverse events in pregnant women reported, Brazil, by June 7th 2021

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Abortion</th>
<th>Premature labor</th>
<th>Fetal Death</th>
<th>TTS/death</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiocruz/AstraZeneca</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Coronavac/Butantan</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Pfizer</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>21</strong></td>
<td><strong>5</strong></td>
<td><strong>4</strong></td>
<td><strong>1</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

Fonte: eSUS Notifica/CGPNI/DEIDT/SVS/MS. Dados preliminares, sujeitos a alterações

¹Síndrome Trombótica com trombocitopenia

²Outras complicações da gravidez não relacionadas às vacinações
Descrição dos eventos adversos graves em gestantes notificados no e-SUS notifica até 16/05/2021*

Astrazeneca/Oxford/Fiocruz
-1 óbito em uma paciente com a síndrome de trombose com trombocitopenia
-1 óbito sem relação causal com a vacina (doença pré-existente)
-5 abortos espontâneos em gestantes vacinadas (não sabiam que estavam grávidas) no primeiro trimestre.
-3 partos prematuros
-7 eventos não especificados em investigação
-1 descolamento de placenta

Sinovac/Butantan
-7 abortos espontâneos em gestantes vacinadas (não sabiam que estavam grávidas) no primeiro trimestre.
-1 parto prematuro com óbito neonatal, em investigação.
-1 erro de registro no sistema (não foi evento adverso grave)

Pfizer/Wyeth
-1 episódio convulsivo isolado, cura sem sequelas, em investigação
-1 óbito fetal em uma paciente com antecedente de descolamento de placenta antes da vacinação

Obs.: abortos no primeiro trimestre gestacional são extremamente frequentes em gestações normais (15%) e é improvável haver uma correlação causal com as vacinas
COVID-19 vaccination in pregnancy, Brazil

Jan 17, 2021
Covid-19 vaccination starts

Early May 2021
257.9 cases & 20.3 deaths/100,000 pregnant women

May 14th, 2021
Suspension of COVID-19 vaccination in pregnant women

Ntl Rec to vaccinate Pregnant women (and post-partum)¹
April 26th, 2021

Death of pregnant women post Vx
May 7th, 2021

¹Nota Técnica 467/2021 - CGPNI/DEIDT/SVS/MS
²Nota Técnica 627/2021 - CGPNI/DEIDT/SVS/MS
Algoritmo para identificação e diagnóstico de eventos TTS, Brasil 2021

**A.** Contagem de plaquetas abaixo de 150.000/μL confirmada por esfregaço periférico demonstrando plaquetopenia sem evidência de agregados plaquetários (que podem levar a contagem falsamente baixa de plaquetas)?

**B.** A presença de trombose/tromboembolismo foi confirmada por qualquer um dos seguintes?

- Exame de imagem:
  - Ultrassom - Doppler
  - Tomografia computadorizada – com contraste / angiografia
  - Venografia ou arteriografia por ressonância magnética
  - Ecocardiograma
  - Cardiografia pulmonar de ventilação e perfusão
  - Angiografia convencional / Angiografia por subtração digital
  - Procedimento cirúrgico: que confirma a presença de um trombo (como trombectomia)
  - Exame de patologia: incluindo biópsia ou autópsia.

**C.** Há outros exames de exames de imagem ou laboratoriais complementares sugestivos, mas não confirmatórios, de trombose/tromboembolismo?

- Radiografia de tórax
- Ecocardiograma
- Tomografia computadorizada sem contraste
- Outro exame elevado acima do limite superior de normalidade.

**D.** A apresentação clínica sugere uma das síndromes clínicas abaixo?

NOTA: os sinais/sintomas descritos são sugestivos de cada síndrome, mas não contemplam todos os sinais clínicos ou todos os sintomas possíveis. Outros sintomas podem ser presentes, não é necessário que todos estejam presentes. O diagnóstico clínico de uma síndrome por um especialista também é aceitável.

- Trombose de sela venoso cerebral / Trombose venosa cerebral: surgiimento de cefaleia, inesquecível, frequentemente grave, déficit cerebral focal, encefalopatia, convulsão.
- Trombose venosa profunda periférica: início de edema, geralmente (mas nem sempre) em membros inferiores (em); edema localizado acompanhado de dor (pode ser em distâncias) e aumento da sensibilidade; vermelhidão ou descamação/edema na pele; edema dependente.
- Tromboembolismo pulmonar: início súbito de dispneia (em repouso ou ao esforço), dor torácica pleurítica (alérgica, de forte intensidade, em costas/tecidos/descamação, taquicardia, taquicardia, arritmia, cansaço, hipotensão).
- Trombose intra-abdominal: dor abdominal (pode ser desproporcional) aos exames de exames físicos, distensão abdominal, náuseas, vômitos, diarreia, presença de sangue nas fezes; acidez, hepatomegalia (se localizada em vias hepáticas).
- Acidente vascular cerebral (AVC) lacunar: início súbito de déficit neurológico focal, como dificuldade na fala (afasia ou disartria), hemiparesia, marcha atáxica, parestesia facial.
- Infarto agudo do miocárdio (IAM): dor torácica (frequentemente em aperto), dispneia, arritmias (incluindo assistência), canseço.

**Nível 1 (Caso Confirmado) de TTS**

**Nível 2 (Caso Provável) de TTS**

**Nível 3 (Caso Possível) de TTS**

**Nível 4: excluído – evidência insuficiente para determinar o caso de TTS possível, provável ou definitivo**
Detailed description of notified adverse events in pregnant women, by vaccine type, by May 16th, 2021

Astrazeneca/Oxford/Fiocruz
- 1 death in patient with TTS
- 1 death due to pre-existing illness (no relation to vaccine)
- 5 spontaneous abortions in unknowingly pregnant women vaccinated in the first trimester
- 3 premature labors
- 7 non-specified events under investigation
- 1 placental abruption

Sinovac/Butantan
- 7 spontaneous abortions in unknowingly pregnant women vaccinated in the first trimester
- 1 premature labor with neonatal death, under investigation

Pfizer/Wyeth
- 1 episode of convulsion, resumed without sequelae, under investigation
- 1 fetal death in a patient with a history of placental abruption prior to vaccination

Risk Benefit Analysis

Hospitalization due to COVID-19 in pregnant women in Brazil, 2021: ~200/100,000

Deaths due to COVID-19 in pregnant women in Brazil, 2021: ~20/100,000

TTS post-COVID-19 vaccination with AstraZeneca/Oxford: ~1/100,000
Discussion

- Brazilian national COVID-19 vaccine safety surveillance system
  - Data availability and sensitivity of surveillance system – probably not representative of true events in the whole country
  - Data quality issues
  - Challenges in case investigation and case classification
    - Many events notified
    - Low quality of local investigation procedures
- High rates of maternal COVID-19 hospitalization and deaths
- Availability of selected vaccines in limited supply
- Challenges in evidence based recommendations to support using vaccines and which vaccines to pregnant women in general (irrespective of other high risk conditions)
- PAHO and MoH will implement a regional protocol for monitoring, evaluation and classification of adverse events in pregnant women with newborn evaluation and follow up
Protocol for safety monitoring of COVID-19 vaccination in pregnancy and post-partum

Gestação
• 3 moments of maternal follow up

1º Trimester

2º Trimester

2º Trimester

Labour

3º Trimester

3º month - NB

6º month - NB

Pilot project, PAHO/CLAP, in 5 states of the county:
• RO, PE, DF, SP e RS
• Start date: 15/06
Thank you!!!!!
ctoscano@ufg.br
TTS/pregnancy surveillance update US
TTS/pregnancy surveillance update: United States

Christine Olson MD, MPH
Co-lead, v-safe pregnancy registry
Medical Officer, VAERS/ISO/NCEZID/CDC
June 9, 2021
Surveillance systems

• Vaccine Adverse Event Reporting System (VAERS)
• Clinical Immunization Safety Assessment (CISA) Project
• Vaccine Safety Datalink (VSD)
• V-safe and V-safe Pregnancy Registry
Vaccine safety monitoring systems

- VAERS
- Immunization Safety Office
- CISA
- VSD
- v-safe
  - after vaccination health checker
  - pregnancy registry
Case finding for TTS following COVID-19 vaccines* 

• Healthcare providers directly contact CDC about potential TTS cases
• FDA physicians screen incoming VAERS reports daily to identify potential TTS cases (i.e., screening of pre-processed reports)
• CDC searches the VAERS database of processed reports daily for possible TTS cases
• Medical records requested for all potential TTS case reports to confirm thrombosis with laboratory evidence of thrombocytopenia, using working case definition
• CDC and FDA medical officers review TTS case reports and available medical records; CISA experts including hematologists consulted – review cases and provide expert consultation

* Analytic period March 2–May 7, 2021

T Shimabukuro, Advisory Committee on Immunization Practices (ACIP) May 12, 2021
CDC working case definition for TTS following COVID-19 vaccination

• Tier 1 TTS case
  • Thrombosis in an unusual location, including cerebral venous sinuses, portal vein, splenic vein, and other rare venous and arterial thromboses
    • May also concurrently have thrombosis in more common locations (e.g., venous thromboembolism, axillary vein thrombosis, deep vein thrombosis, pulmonary embolism)
  • Platelet count <150,000 per microliter
  • Positive (+) heparin-PF4 ELISA HIT antibody* result is supportive, but not required

• Tier 2 TTS case
  • Thrombosis in a common location only (e.g., venous thromboembolism, axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, etc.)
    • Excludes isolated acute myocardial infarction or ischemic stroke
  • Platelet count <150,000 per microliter
  • Positive (+) heparin-PF4 ELISA HIT antibody* result is required

* Heparin platelet factor 4 enzyme-linked immunosorbent assay heparin-induced thrombocytopenia antibody test

T Shimabukuro, Advisory Committee on Immunization Practices (ACIP) May 12, 2021
VAERS pregnancy identification

![VAERS form](https://vaers.hhs.gov/reportevent.html)
U.S. COVID-19 vaccine administration by product type and TTS reports to VAERS
(as of May 7, 2021)*

No confirmed TTS reports to VAERS

Pfizer-BioNTech
135,725,061

No confirmed TTS reports to VAERS

Moderna
110,124,671

J&J/Janssen
8,739,657

Not Identified
189,944

0.0
20M
40M
60M
80M
100M
120M

Total Doses Administered

* Data source: [https://covid.cdc.gov/covid-data-tracker/#vaccinations](https://covid.cdc.gov/covid-data-tracker/#vaccinations)
† One CVST with thrombocytopenia case was observed in Janssen COVID-19 vaccine pre-authorization clinical trials in a 25-year-old male; this case is not included in the VAERS post-authorization confirmed case count

T Shimabukuro, Advisory Committee on Immunization Practices (ACIP) May 12, 2021
Characteristics of U.S. TTS cases after Janssen COVID-19 vaccination, N=28 (Tier 1=25, Tier 2=3, as of May 7, 2021)

- Median age: 40 years (range 18–59 years)
- Median time from vaccination to symptom onset: 9 days (range 3–15 days)
- All received the Janssen COVID-19 Vaccine before the pause on April 13, 2021
  - Female (n=22), male (n=6)
- 19 of the 28 TTS cases has a cerebral venous sinus thrombosis (CVST)
- Pregnant or postpartum* (n=0)
- Past SARS-CoV-2 infection (n=5); 3 by history, 2 by nucleocapsid serology testing only
- Risk factors for thrombosis†
  - Systemic estrogen‡ (n=3)
  - Obesity (n=12)
  - Hypertension (n= 7)
  - Hypothyroidism (n=3)
  - Diabetes (n=3)
  - Current cigarette smoking (n=2)
  - Malignancy (n=1)
  - Fertility treatment (n=1)
  - Coagulation disorders (n=0)

* Within 12 weeks of delivery; † Reference source: https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis; ‡ 2 patients were taking combined oral contraceptives (COCs), 1 patient was on hormone therapy (HT) estradiol patch

T Shimabukuro, Advisory Committee on Immunization Practices (ACIP) May 12, 2021
VSD: Cerebral venous sinus thrombosis (CVST) after mRNA COVID-19 vaccination

• 3.7 million doses of Pfizer-BioNTech and 3.3 million doses of Moderna COVID-19 vaccinations administered in VSD as of May 8, 2021

• 17 total ICD-10 coded CVST diagnoses identified following mRNA vaccines (6 after Pfizer-BioNTech and 11 after Moderna vaccination)
  • 14/17 have been reviewed to date, 3 chart reviews are pending.
    • 8/14 were ruled out as incident cases (historical n=2, other known cause=5, chronic cavernous sinus syndrome n=1)
    • This leaves 6 potential CVST incident cases, but all without thrombocytopenia

• **No confirmed cases** of incident CVST with thrombocytopenia after ~7 million doses of mRNA COVID-19 vaccines administered in VSD

_T Shimabukuro, Advisory Committee on Immunization Practices (ACIP) May 12, 2021_
V-safe & v-safe pregnancy registry

Text message check-ins from CDC (daily 1st week; weekly through 6 weeks; then at 3, 6, and 12 months) and vaccine recipients choose to complete web survey

- Received medical care
- v-safe call center follows up and takes a VAERS report if appropriate
- Reported pregnancy

Pregnancy registry team calls to assess eligibility and, for those eligible, obtains consent for enrollment and follow-up

Registry participants are contacted once per trimester, after delivery, and when the infant is 3 months old.
V-safe pregnancy registry

- **V-safe** participants who report pregnancy following COVID-19 vaccination are actively contacted to enroll in pregnancy registry*
- Outcomes of interest include miscarriage and still birth, pregnancy complications, maternal intensive care unit admission, adverse birth outcomes, neonatal death, infant hospitalizations, and birth defects
- No reports to date of TTS

* Must be registered in **v-safe** and have been pregnant at the time of COVID-19 vaccine receipt or within 30 days of vaccination; enrollment may discontinue when sufficient enrollment numbers are achieved
† Phone surveys are conducted along with maternal and infant medical record review
Timing of first eligible COVID-19 dose among v-safe pregnancy registry participants as of June 7, 2021

Among 5,095 pregnancies

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-conceptional</td>
<td>276</td>
<td>5.4%</td>
</tr>
<tr>
<td>First Trimester</td>
<td>1,431</td>
<td>28.1%</td>
</tr>
<tr>
<td>Second Trimester</td>
<td>2,118</td>
<td>41.6%</td>
</tr>
<tr>
<td>Third Trimester</td>
<td>1,268</td>
<td>24.9%</td>
</tr>
</tbody>
</table>
Updated v-safe pregnancy registry participants as of June 7, 2021

<table>
<thead>
<tr>
<th></th>
<th>Pfizer-BioNTech</th>
<th>Moderna</th>
<th>J&amp;J Janssen</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>2,585 (50.7)</td>
<td>2,234 (43.8)</td>
<td>276 (5.4)</td>
<td>5,095 (100)</td>
</tr>
</tbody>
</table>

Resources

- **CDC COVID Data Tracker**  [https://covid.cdc.gov/covid-data-tracker/#vaccinations](https://covid.cdc.gov/covid-data-tracker/#vaccinations)
- **VAERS**  [https://vaers.hhs.gov/](https://vaers.hhs.gov/)
Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTS/pregnancy surveillance update EMA

Kelly Plueschke
Scientific Administrator
Data Analytics and Methods Task Force
European Medicines Agency
Thrombosis Thrombocytopenia Syndrome and pregnancy surveillance

COVAX Maternal Immunization Consultation Meeting meeting 9th June 2021

Kelly Plueschke - EMA Data Analytics and Methods Task Force
Outline

• Safety signal of TTS with COVID-19 adenovirus vectored vaccines
• Contextualisation exercise to support Member States vaccination programmes
• Surveillance measures for pregnant women
• International collaboration to better study medicines use in pregnancy
Safety signal of Embolic and thrombotic events with a focus on thrombosis with thrombocytopenia with Vaxzevria

• Started in March 2021 following 22 cases of thromboembolic events and evolved into investigation of very rare blood clots with unusual features (low numbers of platelets) and locations (cerebral venous sinus thrombosis, splanchnic vein thrombosis)

• EMA Pharmacovigilance and Risk Assessment Committee (PRAC) recommendation: benefits continue to outweigh the risks in adults of all age groups

• Risk minimisation measures:
  - Update of Product Information (contraindication, listing of TTS) - [LINK]
  - Update to Risk Management Plan (TTS added as new important risk to be further characterised)
  - Direct healthcare professional communication (DHPC)
Vaxzevria: further advice to HCP on blood clots and low blood platelets – EMA 21/05/2021

• Must not give Vaxzevria to anyone who has had blood clots with low blood platelets (thrombosis with thrombocytopenia syndrome, TTS) after receiving the vaccine.

• Should check for signs of blood clots in any person who has low blood platelets within 3 weeks of vaccination.

• Should check for signs of low blood platelets in any person who has blood clots within 3 weeks of vaccination.

• Should ensure that patients who have blood clots with low blood platelets after vaccination receive specialist care.

• COVID-19 Vaccine Janssen: similar risk minimisation measures adopted in April 2021
Contextualisation exercise

• Triggered by European Commission on 9 April 2021

• Aim: to provide more specific recommendations to the Member States to guide their vaccinations programmes

• Put the risk of TTS in the context of vaccine’s benefits for different age groups (most of cases in < 55yo) and different rates of infection: [Link](#)

• Data sources: COVID-19 infection and vaccination from the Member States (obtained directly or via ECDC), literature, and EudraVigilance

• Different approaches adopted at national level based on EMA information ([ECDC overview](#) – May 2021)
**Classified as internal/staff & contractors by the European Medicines Agency**

**Visuals benefit risk contextualisation**

**Benefits depending on age, infection rate and parameter of interest**

### Medium infection rate*

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases of COVID-19 hospitalisations prevented</th>
<th>Cases of blood clots with low platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>54</td>
<td>1.8 **</td>
</tr>
<tr>
<td>40-49</td>
<td>81</td>
<td>2.1 **</td>
</tr>
<tr>
<td>50-59</td>
<td>114</td>
<td>1.1 **</td>
</tr>
<tr>
<td>60-69</td>
<td>183</td>
<td>1 **</td>
</tr>
<tr>
<td>70-79</td>
<td>278</td>
<td>0.5</td>
</tr>
<tr>
<td>80+</td>
<td>332</td>
<td>0.4 **</td>
</tr>
</tbody>
</table>

* "Medium" exposure: using virus circulation for March 2021 (incidence 40/100,000 population)

### Low infection rate*

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases of COVID-19 ICU admissions prevented</th>
<th>Cases of blood clots with low platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>0</td>
<td>1.9 **</td>
</tr>
<tr>
<td>30-39</td>
<td>0</td>
<td>1.8 **</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
<td>2.1 **</td>
</tr>
<tr>
<td>50-59</td>
<td>1</td>
<td>1.1 **</td>
</tr>
<tr>
<td>60-60</td>
<td>3</td>
<td>1 **</td>
</tr>
<tr>
<td>70-79</td>
<td>6</td>
<td>0.5 **</td>
</tr>
<tr>
<td>80+</td>
<td>12</td>
<td>0.4 **</td>
</tr>
</tbody>
</table>

* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)
What about the risk management of TTS in pregnant women?

**Continuous characterisation** of the risk and re-evaluation as new evidence arises (Conditional Marketing Authorisation):

- Routine Pharmacovigilance activities
- Enhanced:
  - Monthly Summary Safety Reports including reports received during pregnancy
  - Prospective observational studies
### Vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comirnaty – remained in trial, total</strong></td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Spontaneous pregnancy loss</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawn from trial</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Moderna – no pregnancy-related trial withdrawals</strong></td>
<td>6</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td><strong>Vaxzevria, total</strong></td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Spontaneous loss</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Elective termination of pregnancy</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>COVID-19 Vaccine Janssen, total</strong></td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Spontaneous abortion and ectopic pregnancy TOPs and incomplete abortion Exposed during breastfeeding</td>
<td>1 + 1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2 + 1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td>157</td>
<td>285</td>
</tr>
</tbody>
</table>

### Vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Post-authorisation studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comirnaty</strong></td>
<td><em>Phase 2/3, Placebo-Controlled, Randomized</em>, Observer-Blinded Study to Evaluate the Safety, Tolerability, and Immunogenicity of a SARS CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older</td>
</tr>
<tr>
<td></td>
<td><strong>4000 healthy pregnant</strong> women followed up until end of pregnancy and 6 months infants age</td>
</tr>
<tr>
<td><strong>Moderna</strong></td>
<td><em>Prospective observational pregnancy outcome study (IQVIA)</em> to evaluate impact of exposure on pregnancy complications and birth outcomes</td>
</tr>
<tr>
<td><strong>Vaxzevria</strong></td>
<td><em>Phase IV Enhanced Active Surveillance Study including pregnancy sub-cohort and Prospective observational pregnancy registry (C-VIPER)</em> to estimate the risk of obstetric outcomes and infants outcomes among vaccinated pregnant women relative to non-vaccinated pregnant women</td>
</tr>
<tr>
<td></td>
<td>Pregnancy registry: <strong>500 pregnant women</strong> followed up until end of pregnancy and 12 months infants age</td>
</tr>
<tr>
<td><strong>COVID-19 Vaccine Janssen</strong></td>
<td><em>Open-label, Phase 2 Study</em> to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26.COV2.S in Healthy Pregnant Participants - HORIZON 1</td>
</tr>
<tr>
<td><strong>Janssen</strong></td>
<td><strong>400 pregnant women</strong> followed up until end of pregnancy and 12 months infantage</td>
</tr>
</tbody>
</table>
Going forward…

Observational studies using real word data

ICMRA technical working groups
CONSIGN project – July 2020 to July 2022
Covid-19 infectiON and medicineS In pregnancy

Objectives:
• Assess use of medicines for COVID-19 treatment;
• Describe severity and clinical outcomes of COVID-19 disease
• Assess and compare pregnancy and neonatal outcomes in different treatment groups
• Ultimate plan: Worldwide infrastructure to study medicines in pregnancy beyond COVID-19

3 Work Packages:
• Retrospective study using on e-health databases
• Prospective studies using antenatal clinics and hospital databases
• ENCePP news item dated 29/04/2021: LINK

Status: Interim results expected in July 2021*

International collaboration: Meta-analyses
☐ Scale-up and further increase retrospective and prospective studies power!
☐ CONSIGN-INTERNATIONAL: Document outlining practical steps for international collaboration
☐ Ongoing work with US FDA, US CDC (SET-NET*, CDC study), George Washington University GWU (PMA study) and others
☐ Protocols and code books shared, mapping of variables
Other EMA study: Two-year vaccine safety monitoring study

1) WP1: active surveillance, prospective cohort at least 10 EU MSs
   - Hypothesis-generating, potential longer-term effects of the vaccines (up to 12 months f/up)
   - General population N≥60,000 (extension of early study)
   - Special populations N=60,000 (COVI-PREG and ORCHESTRA countries + PT, CZ, SK, RO)
   - Incidence rates of suspected ADRs and symptomatic COVID-19

2) WP2: readiness & rapid signal assessment
   - To characterise emerging safety concerns and provide evidence supporting signal management and regulatory decision-making
   - Common protocols, common data models and distributed analytics
   - O/E analyses, case-only analyses or other suitable pharmacoepidemiological methods
   - Generation of novel background incidence rates as needed
Further collaboration at international level

- International Coalition of Medicines Regulatory Authorities (ICMRA)
  - Technical working group on COVID-19 and Pregnancy research
  - COVID-19 Vaccine Pharmacovigilance Network
- EMA strategy on Pregnancy and Lactation implementation group
- New ICMRA sub-group on Pregnancy and Lactation – Explore work at ICH level
Conclusion

• NEW Safety signals identified with new vaccines → Risk minimisation

• Continuous intense monitoring to ensure proactive and reactive advice to HCP

• Contextualisation is key to inform regulatory decision making and national vaccination campaigns: TTS incidence higher in younger population → Restrictions in use of COVID-19 adenovirus vectored vaccines in younger population → Decrease of risk in pregnant women

• International collaboration to study COVID-19 and vaccines impact on pregnancy (e.g. TTS)

• Change the way we work to improve information on B/R of medicines use in pregnancy & breastfeeding → **We need data pre-approval** to better assess efficacy and **safety** in this population!
Any questions?

Further information

kelly.plueschke@ema.europa.eu

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Back up slides - CONSIGN

Contributing organizations

- University Medical Center Utrecht, Utrecht, the Netherlands (UMCU)
- UKOSS, NPEU, University of Oxford, ITSS, Rome, Italy. NOSS, Nordic countries, Inserm, France
- Universiteit Utrecht, Utrecht, The Netherlands (UU)
- Agenzia Regionale di Sanita' Toscana Italy (ARS)
- Aarhus University (AUH)
- University Copenhagen, Denmark (UCPH)
- Leibniz-Institute for Prevention Research and Epidemiology – BIPS, Germany (BIPS)
- Hospital Sanitaria Vall d’Hebron, Spain (IFIC)
- Foundation for the Promotion of Health and Biomedical Research of Valencian Region (FISABIO), Spain
- Karolinska Institute, Sweden (KI)
- RTI Health Solutions [RTI-HS], Barcelona, Spain; North Carolina and Massachusetts, USA
- University Oslo, Norwegian Institute of Public Health, Norway (UiO)
- Instituto Aragonés de Ciencias de la Salud, Zaragoza Spain (IACS)
- University Swansea, UK (USWANSEA)
- University Bordeaux (BPE)
- University Lausanne/Bern. (UniBern)
- University of Manchester, UK. (UMAN)
CONSIGN project

- **Work Package 1: Secondary use of real world data collected in health care DBs**
  - Current stage: Protocol agreed
  - Databases 9 Population based electronic health and medical birth registers in 8 countries (DK, DE, FR, IT, NO, ES, SE, UK (Wales))
  - Cohort studies and case control to estimate drug use, outcomes of COVID-19 and pregnancy outcomes related to medicines
  - Next steps:
    - Jan 2021: Finalization of Statistical analysis plans
    - March 2021: Data retrieval
    - April 2021 onwards: Data analysis
    - July 2021: Preliminary report of study results
    - July 2022: Updated report of study results to include all 2020 pregnancy data

- **International collaboration to increase study power: discussions with ICMRA technical WG on feasibility to implement the CONSIGN protocol in their region (e.g. FDA-Sentinel)**
CONSIGN project

- **Work Packages 2 (COVI-PREG) and 3 (INOSS): Primary data collection**

**A. COVI-PREG:** Prospective multinational longitudinal cohort study of pregnant women suspected of COVID-19 across > 200 health facilities with antenatal clinics worldwide. Purpose to:
- Launch a prospective structured data collection to allow future research projects leading to a better characterization of the risks associated to SARS-CoV-2 infection in pregnancy;
- Create a responsive data collection system through a health care facilities network to ensure a rapid assessment of the risks linked to future emergent pathogens.

*from Panchaud et al. Lancet 2020*
CONSIGN project

• **Work Packages 2 (COVI-PREG) and 3 (INOSS):** Primary data collection

**B. INOSS:** Individual patient data meta-analysis of prospective national population-based observational cohort studies including all listed participating International Network of Obstetric Survey Systems countries

• 18 countries: 12 in Europe, 6 outside Europe (Australia, Ethiopia, Ghana, New Zealand, South Africa, Suriname)

• Use of uniform case definitions, common datasets, specifically collected detailed data and prospectively agreed comparative and combined analyses all add to the validity of studies and their utility to guide policy and clinical practice and hence improve the quality of care.

• **International collaboration:** ongoing discussions between EMA, COVI-PREG, INOSS, CDC and George Washington University (GWU) to perform meta-analyses on pregnant women exposure to treatments for Covid-19 and pregnancy outcomes
Prof (Dr) Narendra Kumar Arora
Executive Director
The INCLEN Trust International
New Delhi – India
Maternal Immunization in India
Decision to Include Pregnant Women for COVID 19 Vaccines
(COVISHIELD & COVAXIN)

Narendra Arora
COVAX Working Group

Wednesday, 9th June, 2021
COVID 19 Working Group of NTAGI

• Terms of Reference
  • Understand and discuss the current state of Covid-19 vaccine development in India & providing evidence-based recommendation on use of Covid-19 vaccines.
  • Understand safety, efficacy, effectiveness, route, dose and frequency of administration of available or soon to be available candidate Covid-19 vaccines and repurposed vaccines.
  • Track the capacity and supply potential of the Covid-19 vaccine manufacturers.
  • Identify gaps if any that may arise during the development cycle and/or implementation stage.
  • Evaluate the disease surveillance data for identification of high-risk or target population and evaluate vaccine economics.
  • Identify the platform for vaccine delivery to reach the identified priority population.
  • Provide recommendation on post licensure vaccine safety surveillance.
  • Advise studies necessary to fill any gaps in evidence to NTAGI-STSC.
Timeline of Meetings (Since August 2020)

Per 100,000 Population

24 Meetings
Aug 24, 2020 - May 27, 2021
Progression of Second Wave of Covid-19 Pandemic in India
(1st Jan 2021 – 7th June 2021)
COVID 19 Vaccine Eligibility for Pregnant Women
Weighing up the potential benefits and harms of the AstraZeneca COVID-19 vaccine

For 100,000 people with very low exposure risk:

<table>
<thead>
<tr>
<th>Age group</th>
<th>ICU admissions prevented every 16 weeks</th>
<th>Specific blood clots associated with the vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29yr</td>
<td>0.2</td>
<td>1.9</td>
</tr>
<tr>
<td>30-39yr</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>40-49yr</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>50-59yr</td>
<td>3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>60-69yr</td>
<td>4.3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission.

Other potential harms not shown include short-term side effects.

* Based on coronavirus incidence of 0.6 per 10,000 per day (42 per 100,000 per week): roughly UK in April 2021.

Data from UK up until 28th April 2021.
**Weighing up the potential benefits and harms of the AstraZeneca COVID-19 vaccine**

For 100,000 people with low exposure risk*

<table>
<thead>
<tr>
<th>Age group</th>
<th>Potential benefits</th>
<th>ICU admissions due to COVID-19 prevented every 16 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29yr</td>
<td>0.8</td>
<td>1.9</td>
</tr>
<tr>
<td>30-39yr</td>
<td>2.7</td>
<td>1.5</td>
</tr>
<tr>
<td>40-49yr</td>
<td>5.7</td>
<td>1.2</td>
</tr>
<tr>
<td>50-59yr</td>
<td>10.5</td>
<td>1.0</td>
</tr>
<tr>
<td>60-69yr</td>
<td>14.1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission

*Based on coronavirus incidence of 2 per 10,000 per day (140 per 100,000 per week): roughly UK in March 2021

Specific blood clots associated with the vaccine:

Other potential harms not shown include short-term side effects

Data from reactions to first dose only

Data from UK up until 28th April 2021
Weighing up the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine

For 100,000 people with medium exposure risk:

**ICU admissions due to COVID-19 prevented every 16 weeks:**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Potential benefits</th>
<th>Potential harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29yr</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>30-39yr</td>
<td>8.0</td>
<td>1.5</td>
</tr>
<tr>
<td>40-49yr</td>
<td>16.7</td>
<td>1.2</td>
</tr>
<tr>
<td>50-59yr</td>
<td>31.0</td>
<td>1.0</td>
</tr>
<tr>
<td>60-69yr</td>
<td>41.3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission.

Specific blood clots associated with the vaccine:

* Based on coronavirus incidence of 6 per 10,000 per day (419 per 100,000 per week): roughly UK in February 2021

Data from UK up until 28th April 2021

Other potential harms not shown include short-term side effects.

Data from reactions to first dose only
Weighing up the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine

For 100,000 people with high exposure risk*

<table>
<thead>
<tr>
<th>Age group</th>
<th>Potential benefits</th>
<th>Potential harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29yr</td>
<td>6.9</td>
<td>1.9</td>
</tr>
<tr>
<td>30-39yr</td>
<td>24.9</td>
<td>1.5</td>
</tr>
<tr>
<td>40-49yr</td>
<td>51.5</td>
<td>1.2</td>
</tr>
<tr>
<td>50-59yr</td>
<td>95.6</td>
<td>1.0</td>
</tr>
<tr>
<td>60-69yr</td>
<td>127.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

ICU admissions due to COVID-19 prevented every 16 weeks:

Data from UK up until 28th April 2021

Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission

Other potential harms not shown include short-term side effects Data from reactions to first dose only

* Based on coronavirus incidence of 20 per 10,000 per day (1391 per 100,000 per week): roughly UK at peak
Progression of Second Wave of Covid-19 Pandemic in India

(1st Jan 2021 – 7th June 2021)
Delhi COVID 19 Cases & Hospitalization
(1\textsuperscript{st} April to 4\textsuperscript{th} June 2021)

**New Cases and Number of Hospital Admissions Per One Lakh Population in Delhi**

![Graph showing new cases and hospital admissions per lakh population in Delhi from 1\textsuperscript{st} April to 4\textsuperscript{th} June 2021.](image)
Anvisa said the 35-year-old woman, who was 23 weeks pregnant, died of a hemorrhagic stroke on Monday after checking into a hospital five days earlier. "The serious adverse event of a hemorrhagic stroke was assessed as possibly related to the use of the vaccine given to the pregnant woman," Anvisa said in a statement.
The safety of the COVID-19 vaccine in pregnant women, especially regarding mid- to long-term adverse reactions and fetal and neonatal safety, is currently not well established.

Initial experiences from mRNA vaccines is encouraging and have been approved by WHO.

There have been thrombosis-thrombocytopenia related complication with Adeno-vectored vaccines (Brazil, Belgium, USA).
Considering the current situation of the pandemic, WG & STSC recommended pregnant women should not be excluded from vaccination.

- Exposure probability is very high: benefit>>risk
- Before vaccination, pregnant women should be fully informed that the long-term adverse reactions are unknown and that the safety of the vaccine for the fetus and the child is not yet established.
- Mandatory 30 minutes of in-hospital observation after vaccination is recommended.

As strongly expressed by Prof Neerja Bhatla on behalf of FOGSI, there is no justification for any further delay in rolling out the vaccination of pregnant women.
Recommendation: Pregnancy and Lactation

All pregnant women visiting for Antenatal care centre may be informed about the risks and benefits associated with the COVID 19 vaccines (COVISHIELD and COVAXIN) available in the country.

An educational tool comprising information on the risk of COVID 19 infection during pregnancy, benefits associated with the COVID vaccination and rare complications associated with vaccines e.g., thrombosis and thrombocytopenia (with COVISHIELD) may be developed. This information is communicated to every pregnant woman before administering the vaccine.

All lactating women are eligible to receive the COVID 19 vaccines any time after the delivery.

Studies to be put in place immediately to monitor the safety of COVISHIELD and COVAXIN among pregnant women (CEM/Sentinel Surveillance)

Based on the information provided a pregnant woman may be offered the available COVID 19 vaccine at the center. The COVID 19 vaccine can be given anytime during the pregnancy.
NTAGI COVID-19 Working Group

**Working Group**
- Dr NK Arora (Chair)
- Dr J P Muliyil
- Dr Gagandeep Kang
- Dr Rakesh Aggarwal
- Dr Amulya Panda
- Dr V G Somani
- Dr Navin Khanna
- Dr Pradeep Halder

**DBT**
- Dr Alka Sharma
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- Dr Nivedita Gupta

**Immunization Division, MoHFW**
- Dr M K Aggarwal
- Dr Veena Dhawan

**NTAGI Secretariat**
- Dr Dinesh Paul
- Dr Awnish Kumar Singh

Thank You
Experts’ roundtable

Members

Jeff Roberts     Daniel Brasseur     Cristiana Toscano     Laura Riley     Narendra Arora

Ruth Karron     Mark Turrentine

Moderators

Questions

- Based on what we learned in the first session, should considerations for the use of adenovirus-vectored SARS-CoV-2 vaccine differ for pregnant women and non-pregnant women of the same age? If so, how?

- Does the outcome of heparin-induced thrombocytopenia (HIT) in pregnant compared to non-pregnant individuals help guide our thinking?

- What are the regulatory (labelling) implications of distinguishing between pregnant and non-pregnant individuals?

- Thinking about implementation and surveillance for AEFI in LMICs
Concluding remarks

Ajoke Sobanjo-ter Meulen
Flor Munoz