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.

Ajoke Sobanjo-ter Meulen

Flor Munoz

Workshop introduction

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

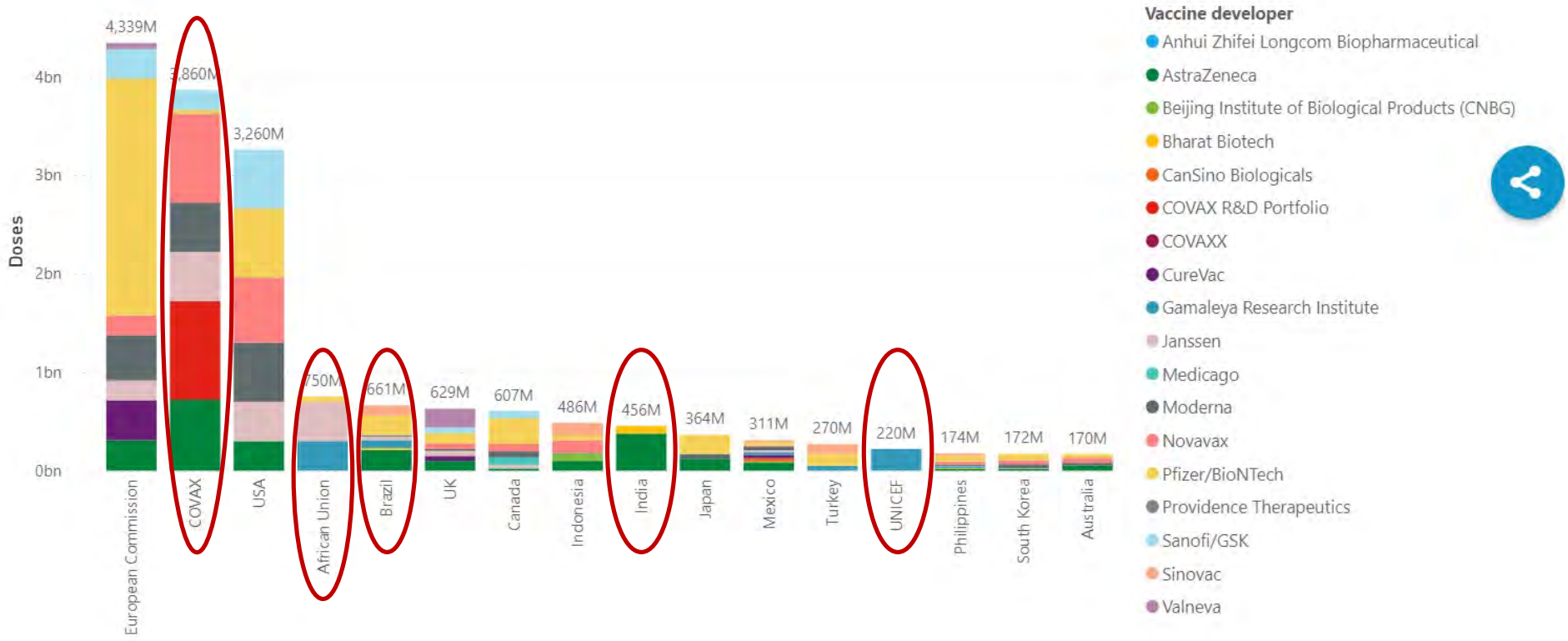
- To provide information to support evidence-based COVID-19 vaccine policy making for pregnant women in LMIC, taking into account the risks of:

  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



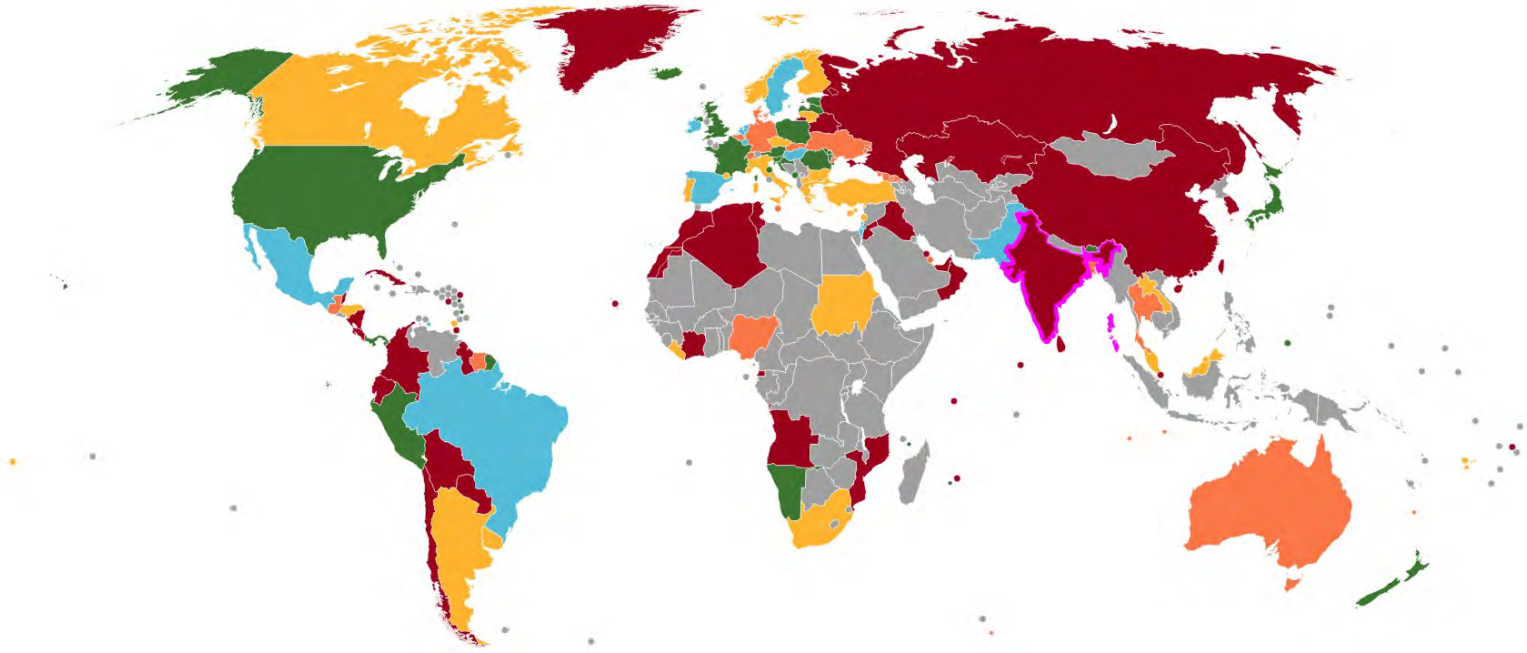
Unicef dashboard: accessed June 7, 2021

Current Guidance Regarding COVID-19 Vaccines in Pregnancy (As of June 9, 2021)

Organization	Recommendations
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)***

COMIT

Covid-19 Maternal Immunization Tracker



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)

Time (PDT)	Session	Speaker
7:00 am PT (5 min)	Workshop Introduction	Ajoke Sobanjo-ter Meulen Flor Munoz
7:05 am PT (60 min)	**Session 1**	Moderator: Flor Munoz
7:05 am PT (10 min)	Vaccine safety surveillance	Kathryn Edwards
7:15 am PT (15 min)	Safety profile of adenovirus vectored vaccines	David Kaslow
7:30 am PT (10 min)	Theory of TTS/VITT mechanism	Andreas Greinacher
7:40 am PT (10 min)	Thrombosis/thrombocytopenia in pregnancy	Annemarie Fogerty
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)

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

Kathryn Edwards

Professor of Pediatrics

Vanderbilt University

Nashville, TN, USA

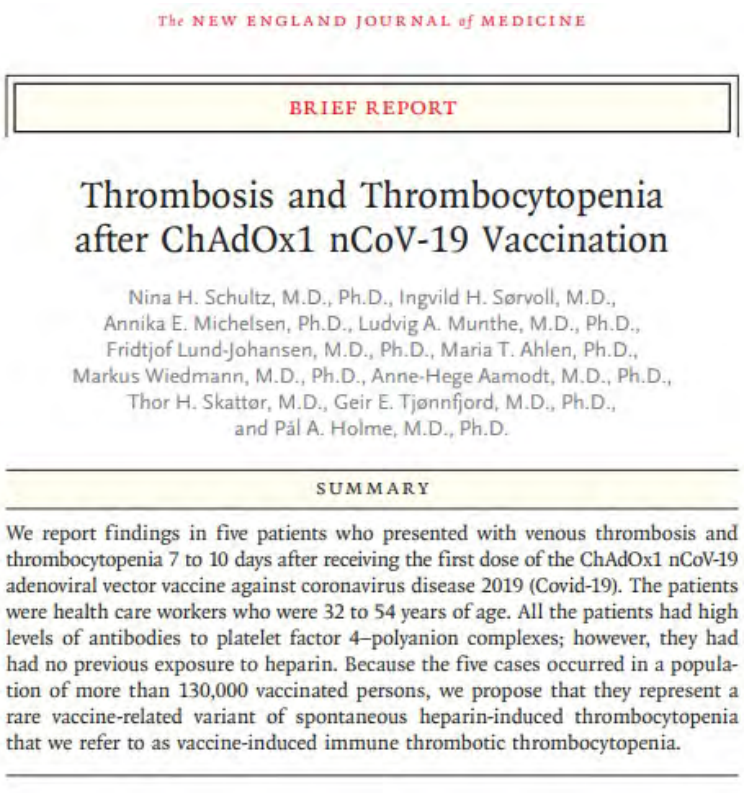
Vaccine safety surveillance

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



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

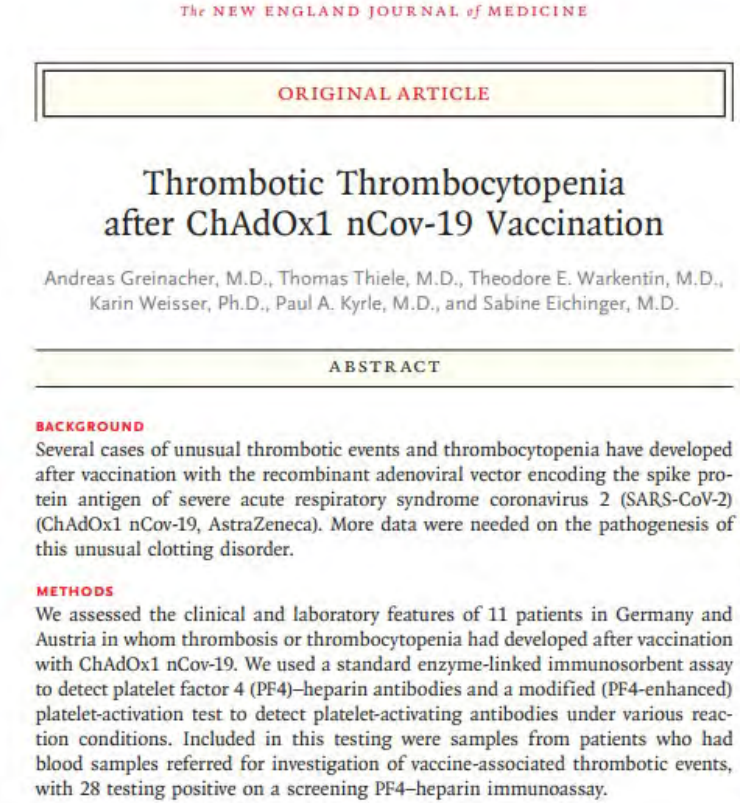
SUMMARY

We report findings in five patients who presented with venous thrombosis and thrombocytopenia 7 to 10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine against coronavirus disease 2019 (Covid-19). The patients were health care workers who were 32 to 54 years of age. All the patients had high levels of antibodies to platelet factor 4–polyanion complexes; however, they had had no previous exposure to heparin. Because the five cases occurred in a population of more than 130,000 vaccinated persons, we propose that they represent a rare vaccine-related variant of spontaneous heparin-induced thrombocytopenia that we refer to as vaccine-induced immune thrombotic thrombocytopenia.

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**)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

ABSTRACT

BACKGROUND

Several cases of unusual thrombotic events and thrombocytopenia have developed after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). More data were needed on the pathogenesis of this unusual clotting disorder.

METHODS

We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events, with 28 testing positive on a screening PF4–heparin immunoassay.

https://www.nejm.org/doi/full/10.1056/NEJMoa2104882?query=featured_home

https://www.nejm.org/doi/full/10.1056/NEJMoa2104840?query=featured_home

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination

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

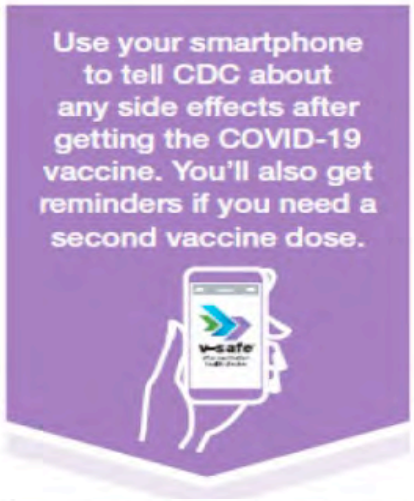
ELISA PF4 Antibody = 2.550 OD units

doi/10.1056/NEJMc2105869?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

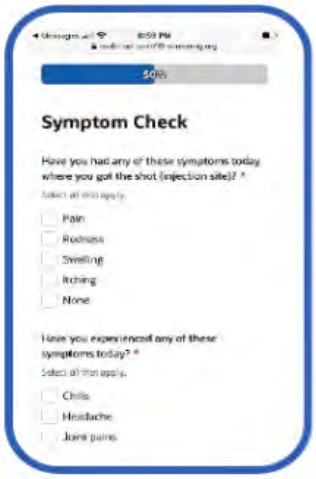
US Vaccine Safety System

- V-safe
- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink (VSD)
- Clinical Immunization Safety Assessment (CISA) Project

v-safe℠ after vaccination health checker



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*

Vaccine recipients

v-safe℠ after vaccination health checker

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 3. Characteristics of V-safe Pregnancy Registry Participants.*

Characteristic	Pfizer–BioNTech Vaccine	Moderna Vaccine	Total
	number (percent)		
Total	2136 (54.0)	1822 (46.0)	3958 (100)
Age at first vaccine dose†			
20–24 yr	17 (0.8)	19 (1.0)	36 (0.9)
25–34 yr	1335 (62.5)	1238 (67.9)	2573 (65.0)
35–44 yr	777 (36.4)	560 (30.7)	1337 (33.8)
45–54 yr	7 (0.3)	5 (0.3)	12 (0.3)
Race and ethnic group‡			
Non-Hispanic White	1663 (77.9)	1463 (80.3)	3126 (79.0)
Hispanic	164 (7.7)	151 (8.3)	315 (8.0)
Non-Hispanic Asian	225 (10.5)	138 (7.6)	363 (9.2)
Non-Hispanic Black	24 (1.1)	26 (1.4)	50 (1.3)
Non-Hispanic multiple races	42 (2.0)	30 (1.6)	72 (1.8)
Non-Hispanic American Indian or Alaskan Native	5 (0.2)	1 (0.1)	6 (0.2)
Non-Hispanic Native Hawaiian or other Pacific Islander	6 (0.3)	3 (0.2)	9 (0.2)
Missing data or participant declined to answer	7 (0.3)	10 (0.5)	17 (0.4)
Timing of first eligible dose			
Periconception: within 30 days before last menstrual period	55 (2.6)	37 (2.0)	92 (2.3)
First trimester: <14 wk	615 (28.8)	517 (28.4)	1132 (28.6)
Second trimester: ≥14 and <28 wk	932 (43.6)	782 (42.9)	1714 (43.3)
Third trimester: ≥28 wk	533 (25.0)	486 (26.7)	1019 (25.7)
Missing data	1 (<0.1)	0	1 (<0.1)
Covid-19 infection during pregnancy			
No Covid-19 infection	2084 (97.6)	1779 (97.6)	3863 (97.6)
Before vaccination	32 (1.5)	24 (1.3)	56 (1.4)
≤14 days after first eligible dose of vaccination	3 (0.1)	7 (0.4)	10 (0.3)
>14 days after first eligible dose of vaccination	9 (0.4)	3 (0.2)	12 (0.3)
Missing data	8 (0.4)	9 (0.5)	17 (0.4)

This article was published on April 21, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2104983

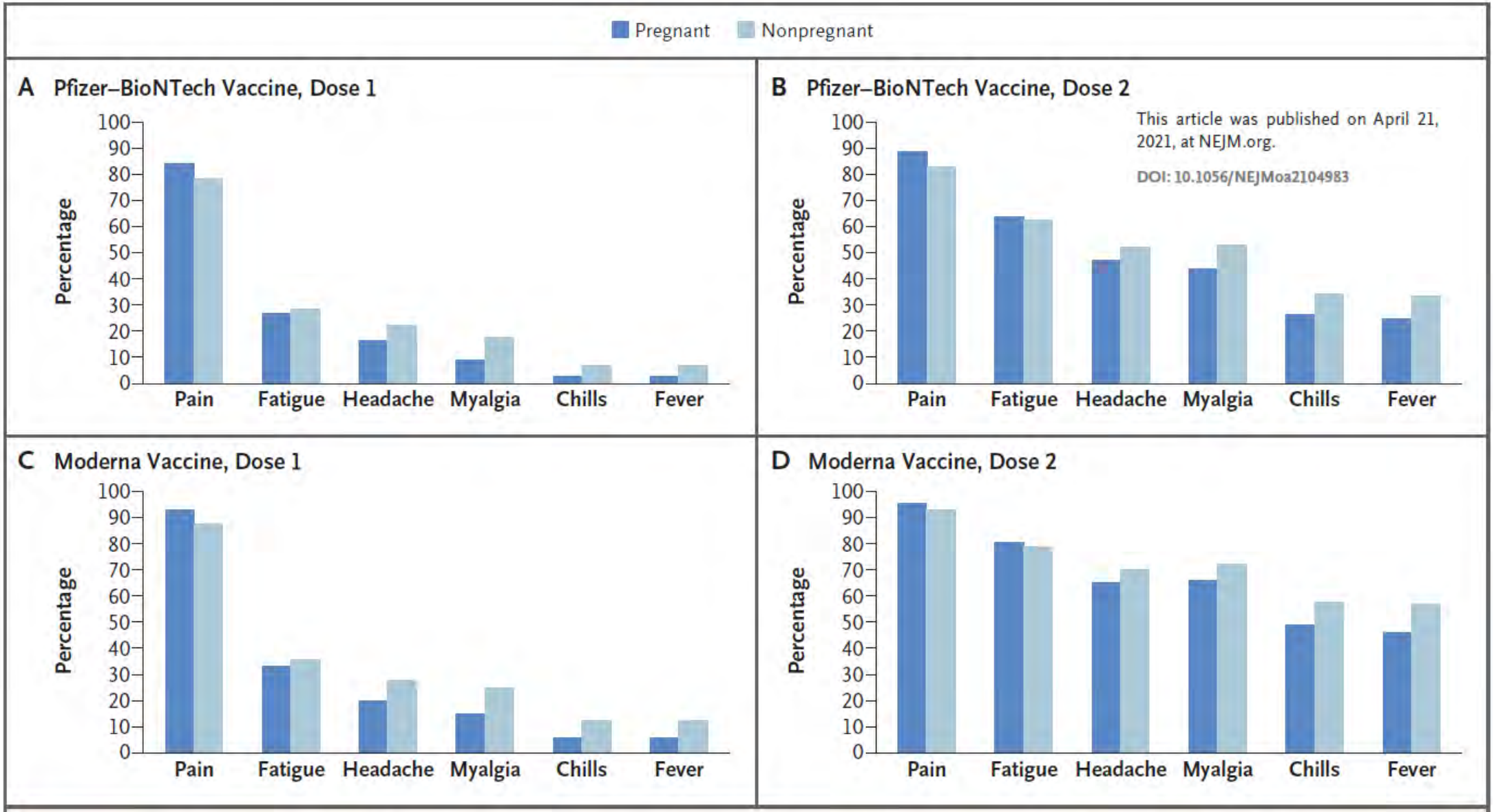


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Figure 1. Most Frequent Local and Systemic Reactions Reported in the V-safe Surveillance System on the Day after mRNA Covid-19 Vaccination.

Table 4. Pregnancy Loss and Neonatal Outcomes in Published Studies and V-safe Pregnancy Registry Participants.

Participant-Reported Outcome	Published Incidence*	V-safe Pregnancy Registry†
	%	*no./total no. (%)*
Pregnancy loss among participants with a completed pregnancy		
Spontaneous abortion: <20 wk[15-17]	10–26	104/827 (12.6)‡
Stillbirth: ≥ 20 wk[18-20]	<1	1/725 (0.1)§
Neonatal outcome among live-born infants		
Preterm birth: <37 wk[21,22]	8–15	60/636 (9.4)¶
Small size for gestational age[23,24]‖	3.5	23/724 (3.2)
Congenital anomalies[25]**	3	16/724 (2.2)
Neonatal death[26]††	<1	0/724

This article was published on April 21, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2104983

VAERS is the nation's early warning system for vaccine safety

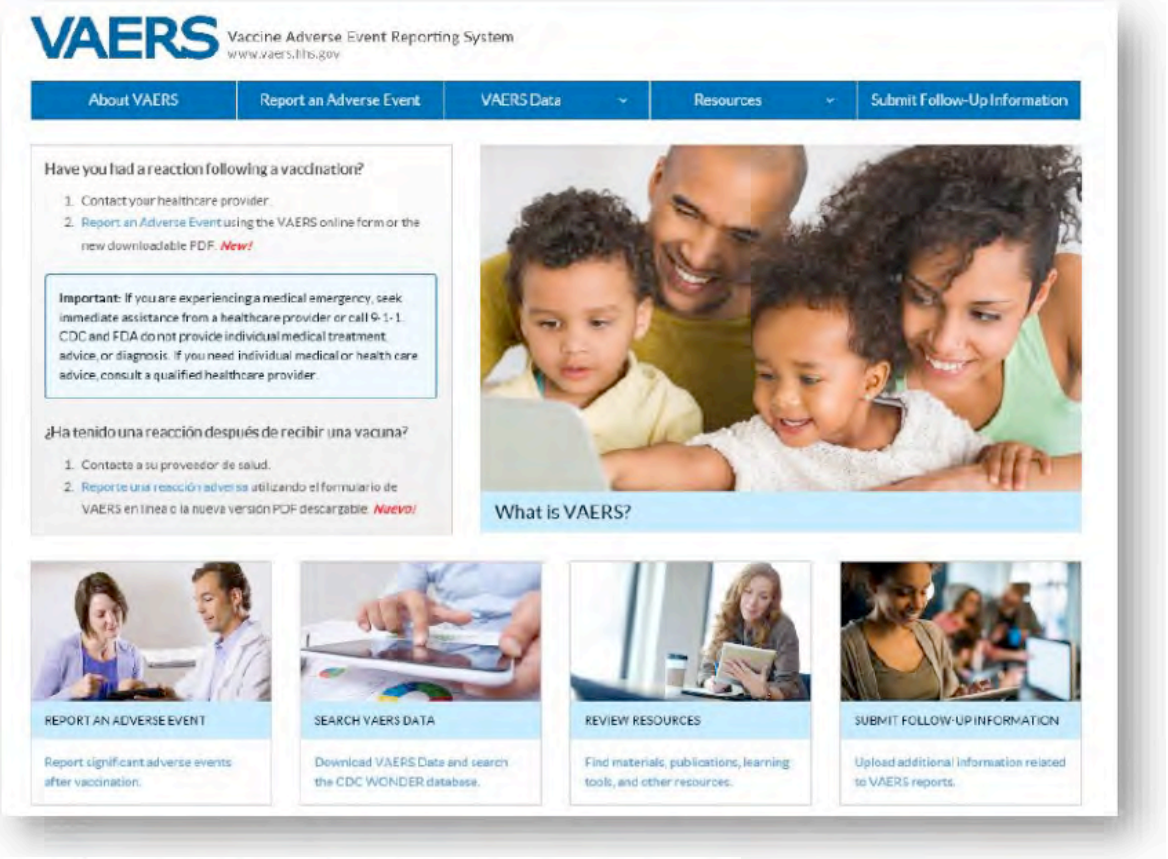
CDC + FDA

VAERS

Vaccine Adverse Event Reporting System

co-managed by CDC and FDA

http://vaers.hhs.gov



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

Vaccine Adverse Event Reporting System (VAERS)

Strengths

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

Limitations

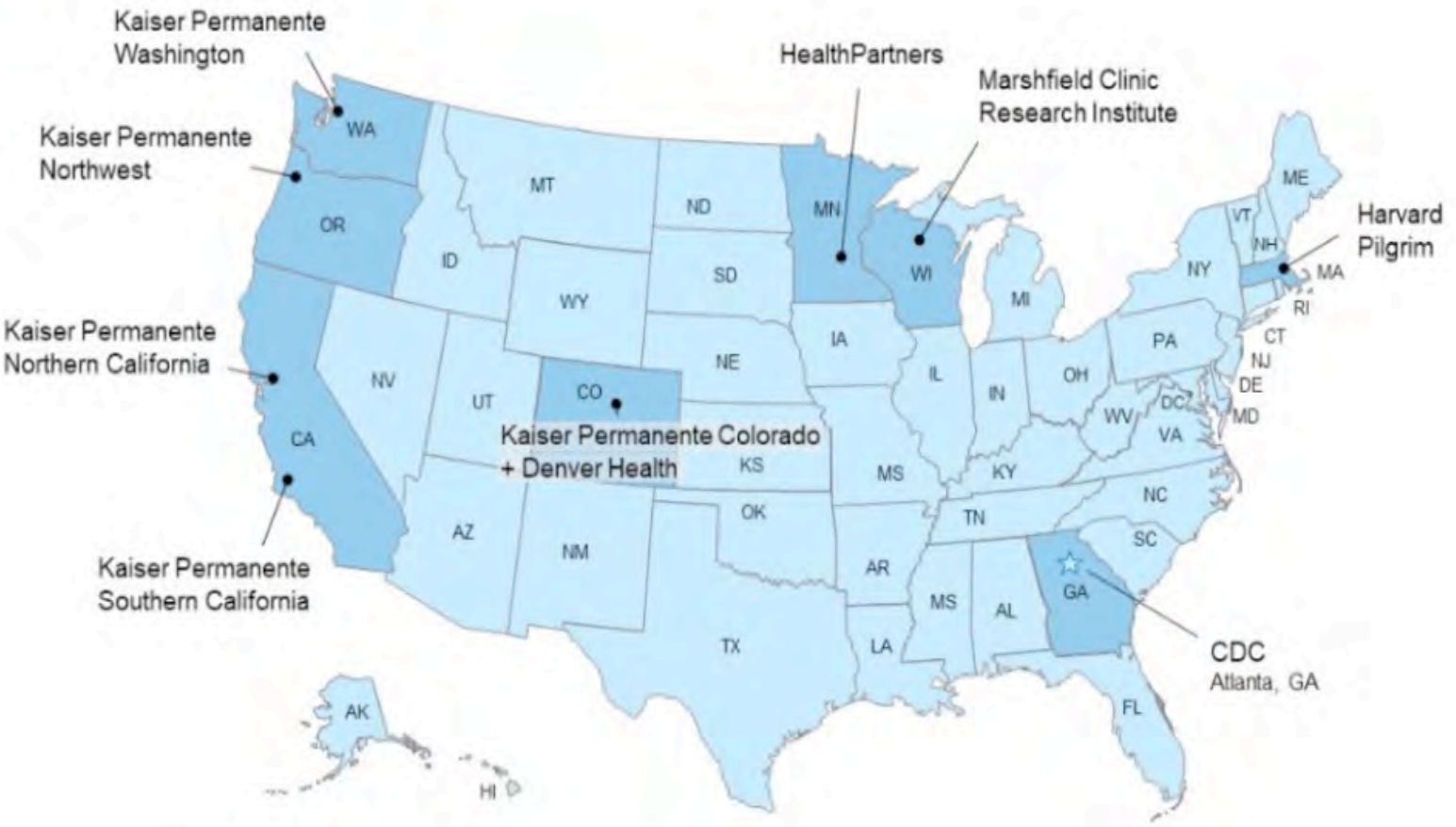
- Reporting bias
- Inconsistent data quality and completeness of information
- Lack of unvaccinated comparison group
- Not designed to assess causality

- 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

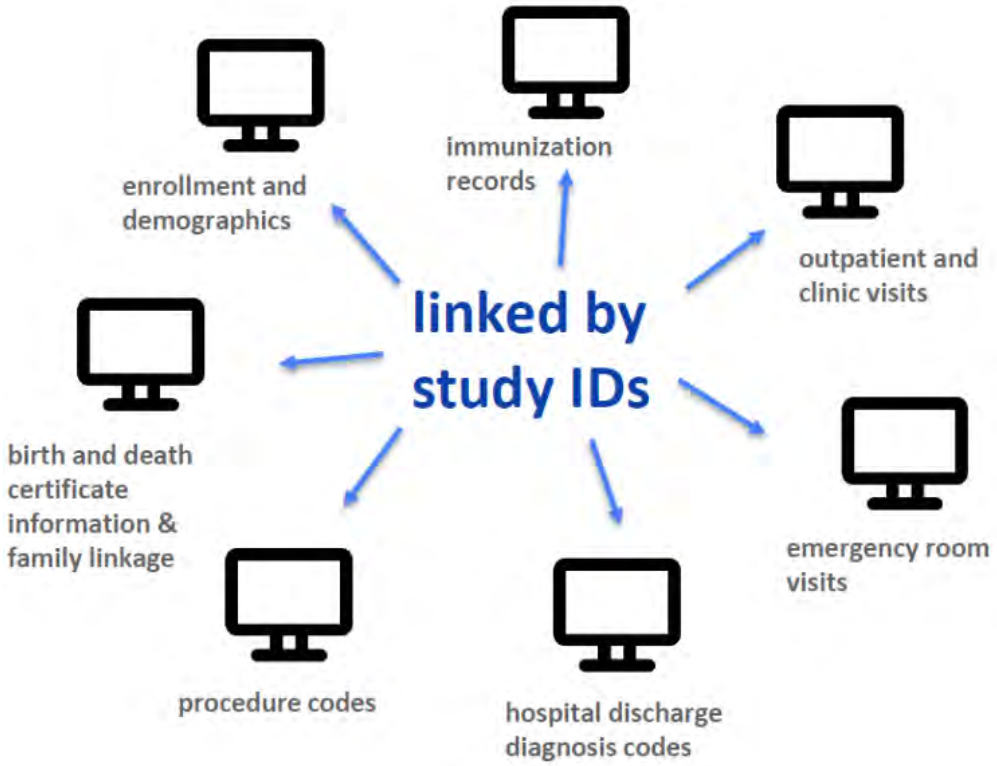


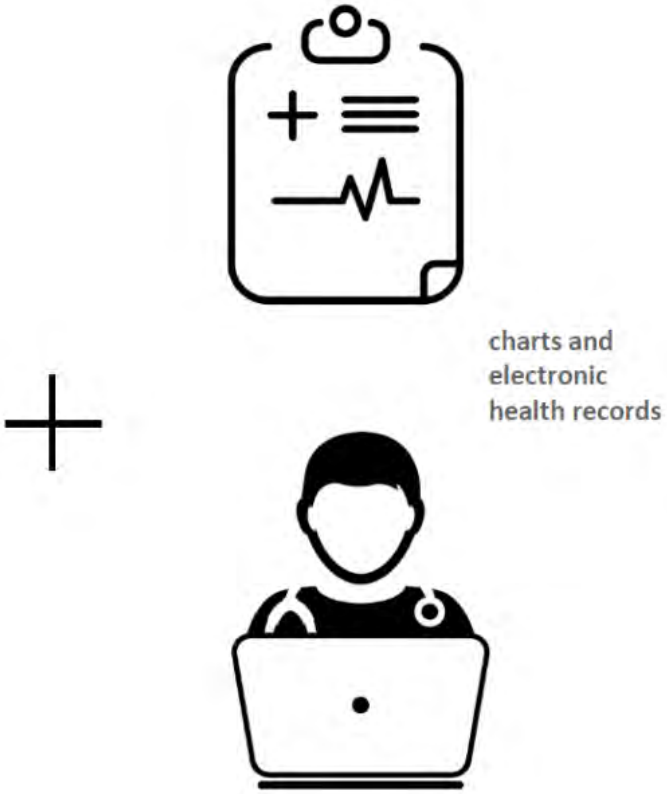
9 participating integrated healthcare organizations

data on over **12 million** persons per year

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

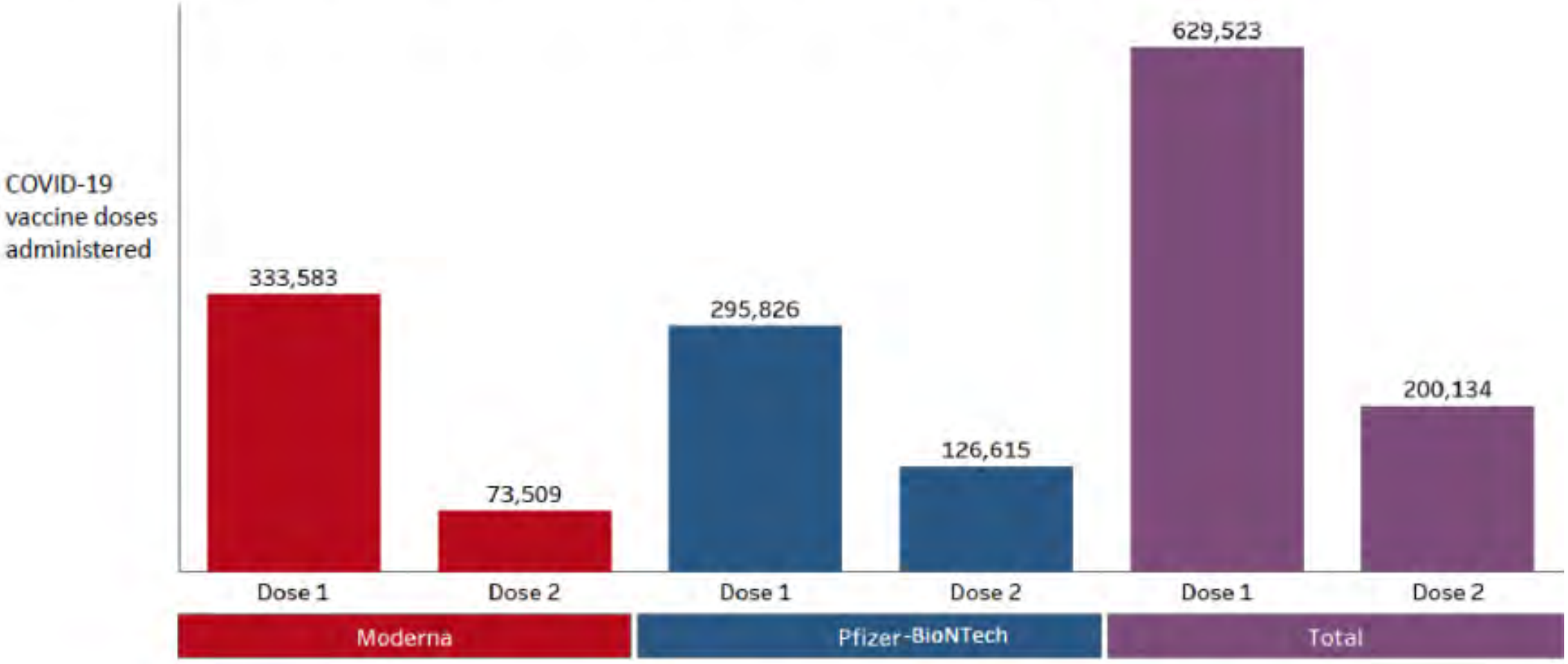
Types of information in VSD





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 unknow 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

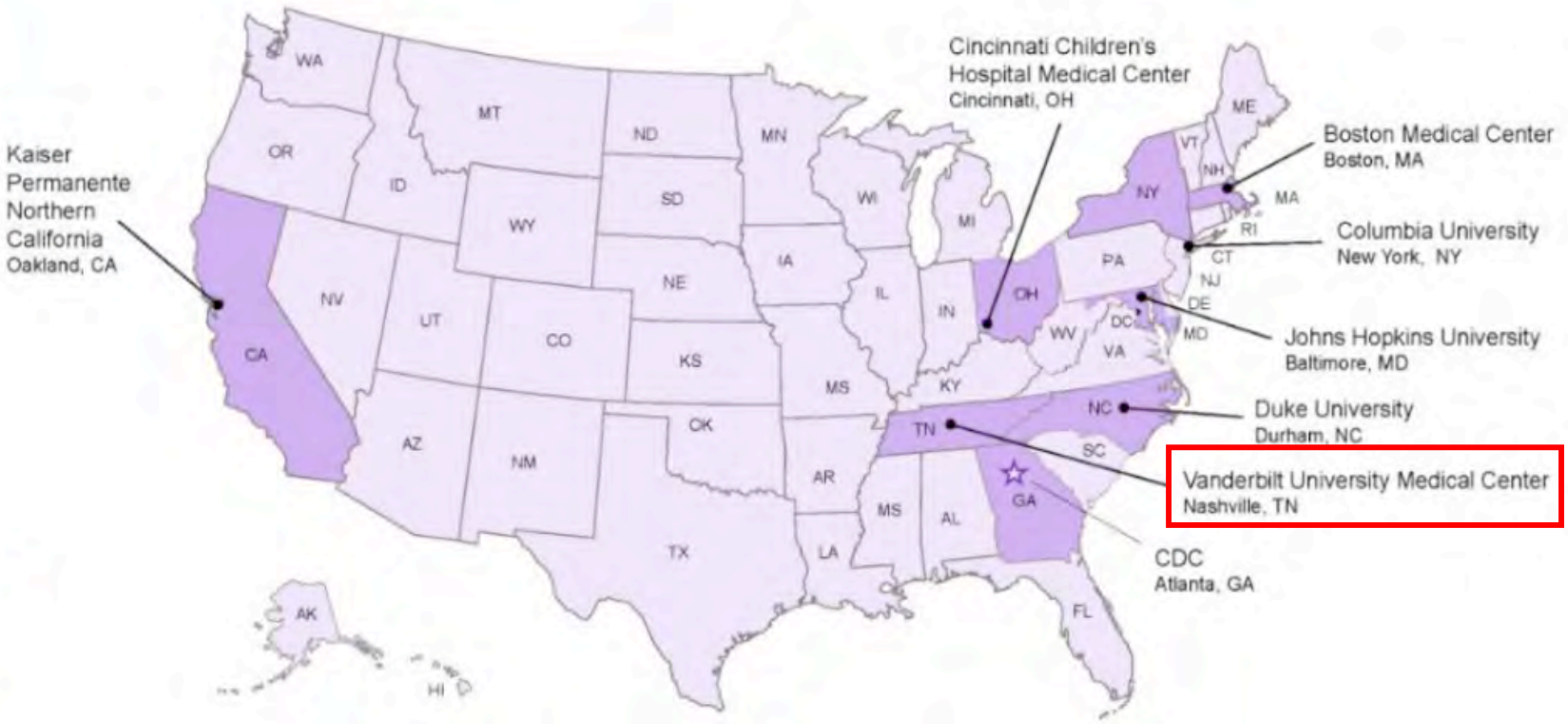
- No statistical signals detected

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

* 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/mm^3) 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

Presented at Advisory Committee on Immunization Practices; April 14, 2021

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)

JAMA | Original Investigation

US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021

Isaac See, MD; John R. Su, MD, PhD, MPH; Allison Lale, MD, MPH; Emily Jane Woo, MD, MPH; Alice Y. Guh, MD, MPH; Tom T. Shimabukuro, MD, MPH, MBA; Michael B. Streiff, MD; Agam K. Rao, MD; Allison P. Wheeler, MD, MSCI; Suzanne F. Beavers, MD; Anna P. Durbin, MD; Kathryn Edwards, MD; Elaine Miller, RN, MPH; Theresa A. Harrington, MD, MPH&TM; Adamma Mba-Jonas, MD, MPH; Narayan Nair, MD; Duong T. Nguyen, DO; Kawsar R. Talaat, MD; Victor C. Urrutia, MD; Shannon C. Walker, MD; C. Buddy Creech, MD; Thomas A. Clark, MD, MPH; Frank DeStefano, MD, MPH; Karen R. Broder, MD

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.COV2.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.COV2.S vaccine and CVST with thrombocytopenia.

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
April 27, 2021

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

Jessica R. MacNeil, MPH[1]; John R. Su, MD, PhD[1]; Karen R. Broder, MD[1]; Alice Y. Guh, MD[1]; Julia W. Gargano, Stephen C. Hadler, MD[1]; Heather M. Scobie, PhD[1]; Amy E. Blain, MPH[1]; Danielle Moulia, MPH[1]; Matthew F. Dalc José R. Romero, MD[4]; H. Keipp Talbot, MD[5]; Grace M. Lee, MD[6]; Beth P. Bell, MD[7]; Sara E.

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 Practices 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.

https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7017e4-H.pdf

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2021

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

David C Kaslow MD,

Chief Scientific Officer, PATH

Safety profile of adenovirus vectored vaccines

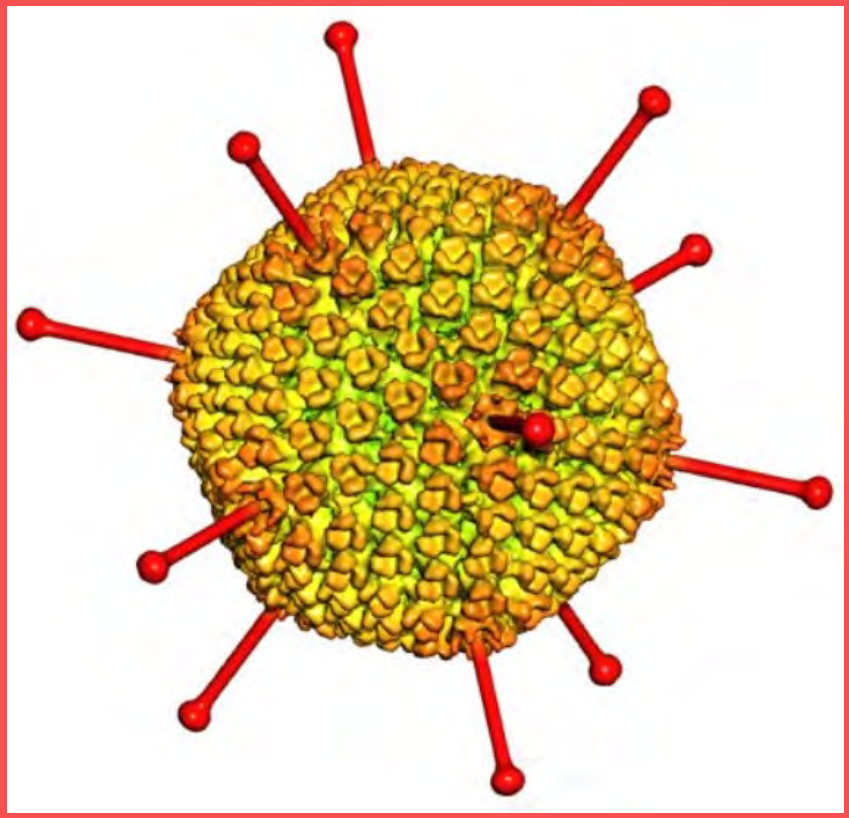
Safety profile of adenovirus vectored vaccines

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



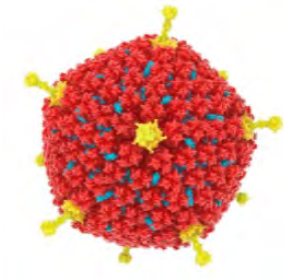
Graphic credits: *Adenovirus* by C San Martin https://doi.org/10.3390/v4050847

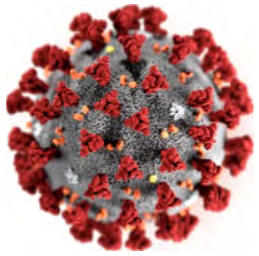
Disclosures

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





Adenovirus-related	SARS-CoV-2 Spike-related
• Platelet and endothelial interactions • Coagulation factor interactions • Inflammatory response(s) • Immune-mediated	• S protein interactions with platelets, endothelium, etc. ⇕ • Immune-mediated
• 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

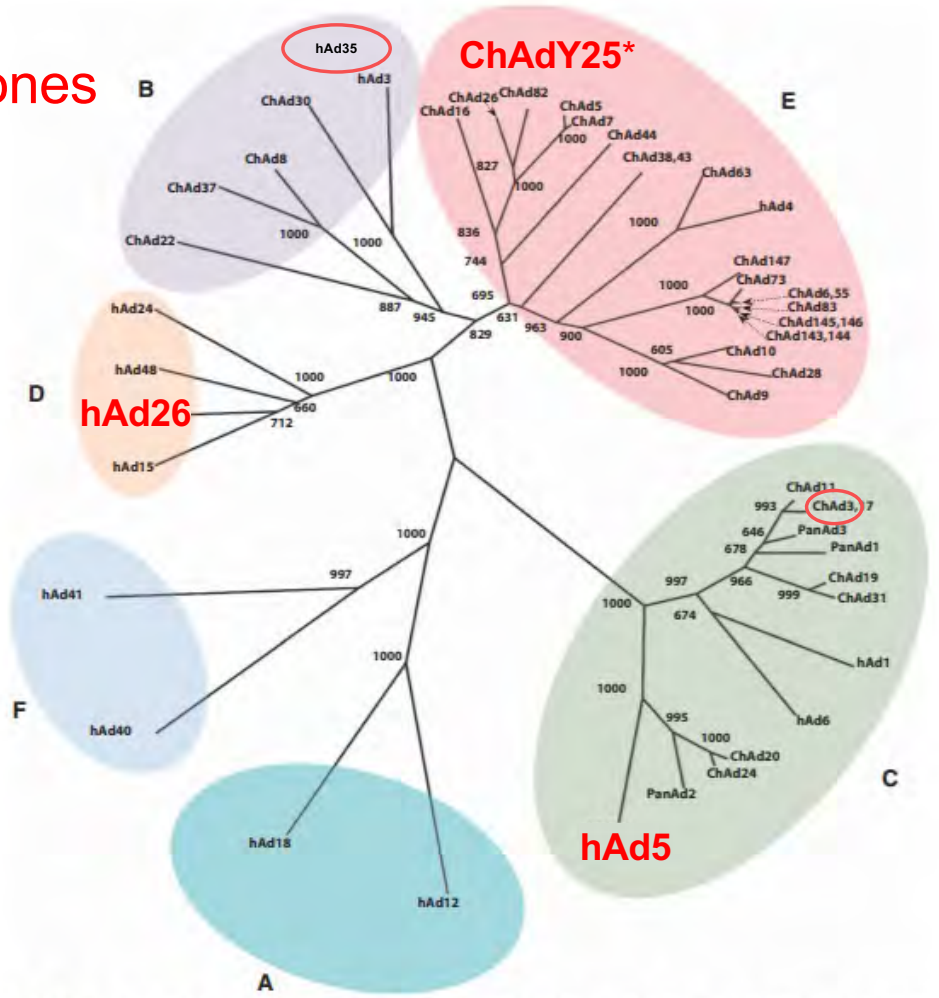
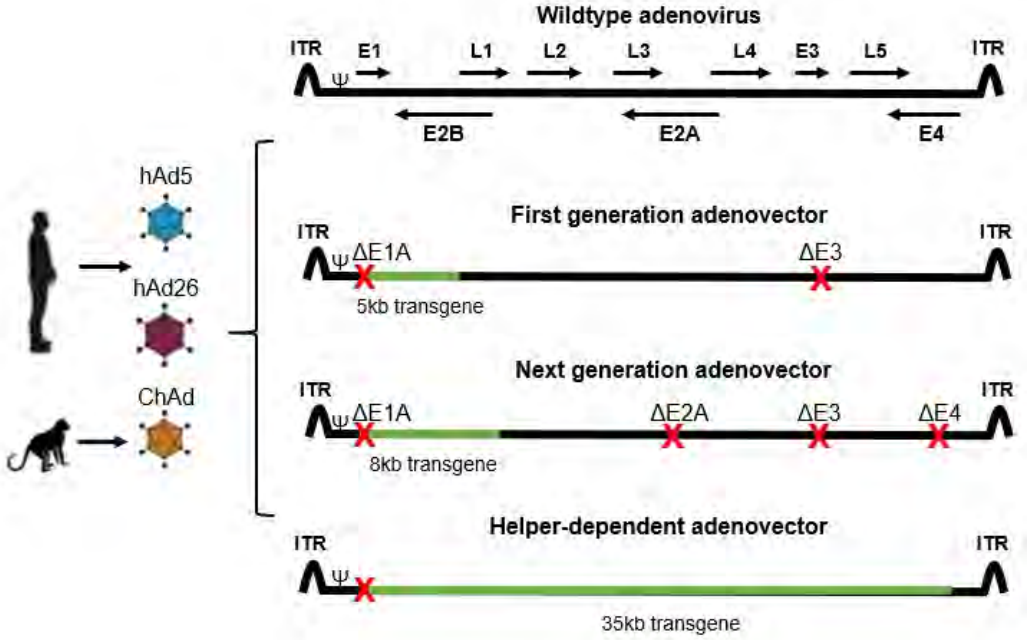


Fig. 2. Phylogenetic analysis of ChAd. The phylogenetic tree showing the different human adenovirus species (A to F) was obtained by aligning the adenovirus hexon sequences. Human adenovirus (hAd) representative of each species and chimpanzee adenoviruses [ChAd from chimpanzees (*P. troglodytes*) and PanAd from paniscus (*P. paniscus*)] were included in the analysis.

Source: *Sci Trans Med* 4:115ra2 (2012) https://doi.org/10.1126/scitranslmed.3002925
* aka ChAdOx1

[1]*Sci Rep* 5:16756 (2015) https://doi.org/10.1038/srep16756
[2]*Sci Adv* 5:eaax3567 (2019) https://doi.org/10.1126/sciadv.aax3567
[3]*Sci Trans Med* 4:115ra2 (2012) https://doi.org/10.1126/scitranslmed.3002925
[4]*PLoS ONE* 7:e40385 (2012) https://doi.org/10.1371/journal.pone.0040385

Adenovirus and vector genetic structure



Adapted from: https://www.researchgate.net/figure/Adenovirus-structure-and-vector-design-a-Structure-of-adenovirus-virion-showing-linear_fig2_320006566 https://doi.org/10.1002/bit.26461

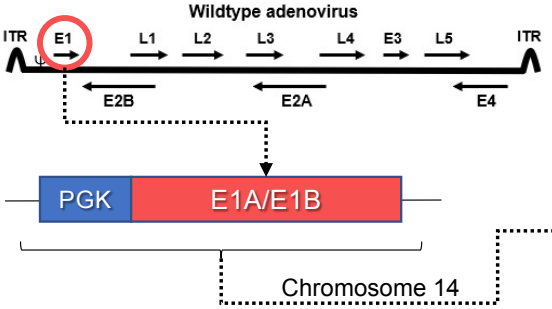
Adenovector platforms: COVID-19 vaccines

		E1	E2	E3	E4	Spike
ФНИЦ эпидемиологии и микробиологии имени Н.Ф. Гамалеи	hAd5/26[1]	Δ	?	?	?	FL PPS?
Johnson & Johnson	hAd26[2]	Δ	wt	Δ	hAd5 orf6	FL PPS
AstraZeneca / University of Oxford	ChAdOx1[3]	Δ	wt	Δ	hybrid[3]	FL

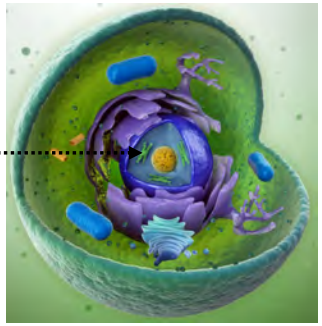
Δ = deleted; WT = wildtype; FL = Full length; PPS = pre-fusion stabilized

[1] No technical reference publicly available
[2] EMA Public Assessment Report (EPAR) https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-janssen-epar-public-assessment-report_en.pdf
[3] *PLoS ONE* 7: e40385 (2012) https://doi.org/10.1371/journal.pone.0040385 hAd5 *E4Orf4*, *6,* and *6/7*; ChAd25Y *E4Orf1*, *2* and *3*

E1-complementing cell lines required

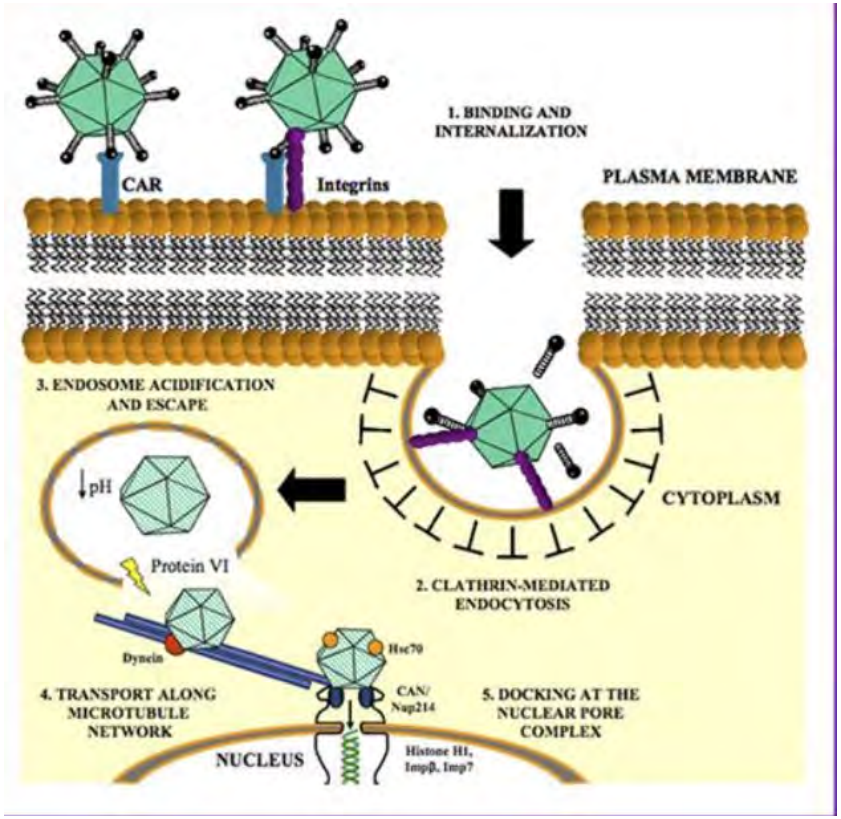


PER.C6™
(**P**GK-**E**1 **R**etina.**C**lone **6**)



Graphic credit:
https://www.medicalsciencenavigator.com/wp-content/uploads/2012/03/Mammalian-Cell-Model.jpg

Vaccine adenovectors require nuclear transcription, mRNA-based vaccines don't

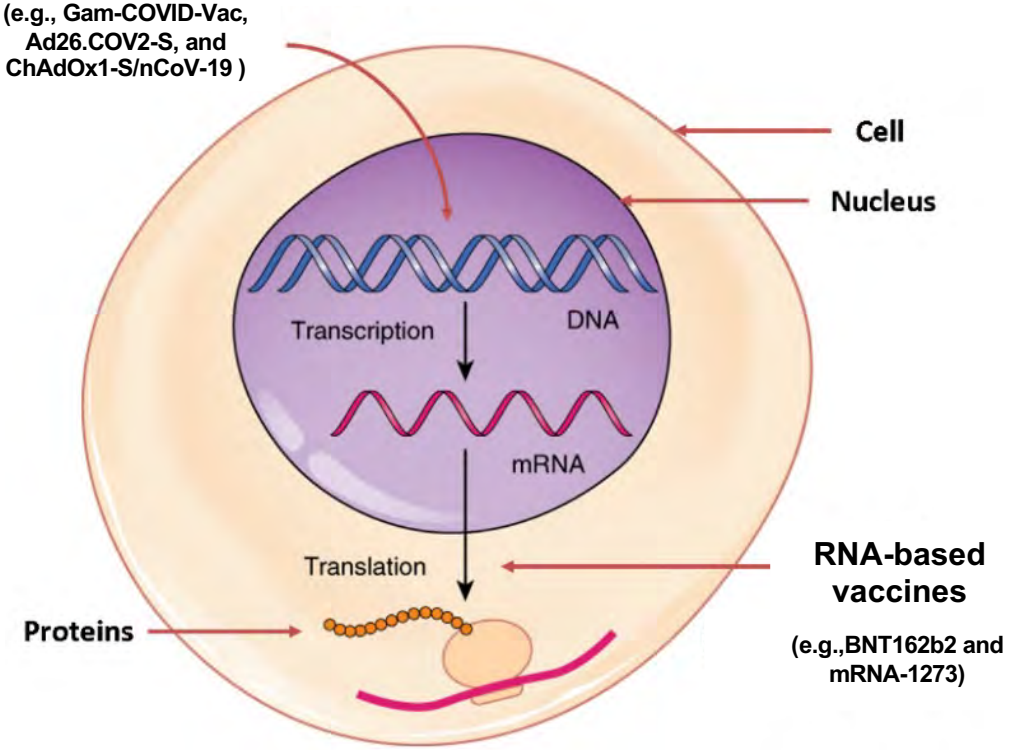


N.B. Adenovirus replication and expression: episomal rather than chromosomal

Source: https://mol-biol4masters.masters.grkraj.org/html/Genetic_Engineering2B-Molecular_Tools-Expression_Vectors_files/image017.jpg

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)

Adapted from: https://medium.com/microbial-instincts/platelet-disorders-and-genetic-vaccines-might-have-a-biological-link-but-its-negligible-2da695521d66

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

hAd5 +/-[1]	hAd26[2]	ChAdOx1[3]
• **Ebola virus:** GamEvac-Combi, heterologous VSV | Ad5-vectored • **MERS:** BVRS-GamVac-Combi • **Flu:** GamFluVac **hAd5 by others**[4] • HIV, TB, Flu, Malaria, RSV, Ebola virus, Norovirus…	• **Ebola virus**: Ad26.ZEBOV • **HIV:** Ad26.Mos.HIV, Ad26.Mos4.HIV, and Ad26.ENVA.01 • **Malaria:** Ad26.CS.01 • **RSV:** Ad26.RSV.FA2 and Ad26.RSV.preF • **Filovirus:** Ad26.Filo • **Zika:** Ad26.ZIKV.001 • **HPV:** Ad26.HPV16 and Ad26.HPV18	• **Malaria:**ChAdOx1 LS2 • **MERS:** ChAdOx1 MERS • **TB:** ChAdOx1 85A (+ MVA) • **Flu:** ChAdOx1 NP+M1 • **Chikungunya:** ChAdOx1 Chik • **Zika:** ChAdOx1 Zika

[1] *Hum Vaccin Immunother* 13:613 (2017) https://dx.doi.org/10.1080%2F21645515.2016.1238535; *Acta Naturae* 11:38 (2019) http://actanaturae.ru/2075-8251/article/view/10302/106; NCT04034290

[2] *Vaccine* 39:3081 (2021) https://doi.org/10.1016/j.vaccine.2020.09.018

[3] Source: clinicaltrials.gov and PubMed

[4] Source: clinicaltrials.gov

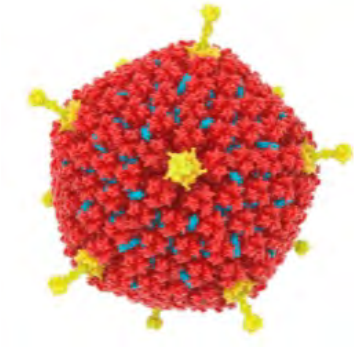
Background on Ad5, Ad26, & ChAdOx1

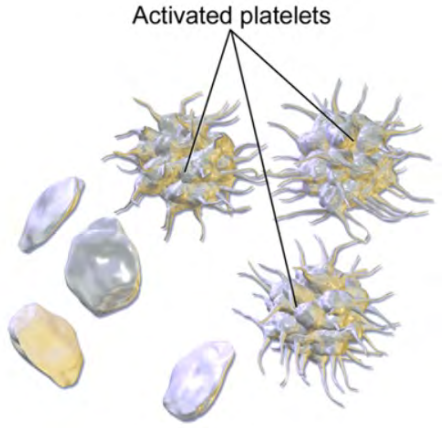
Platelets & Ad vectors

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	Sialic gylcans	Thrombi	↓ Platelet
hAd5	✓	?	✓	✓
hAd26	?	?	?	?
ChAdY25	?	?	?	?

- 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)

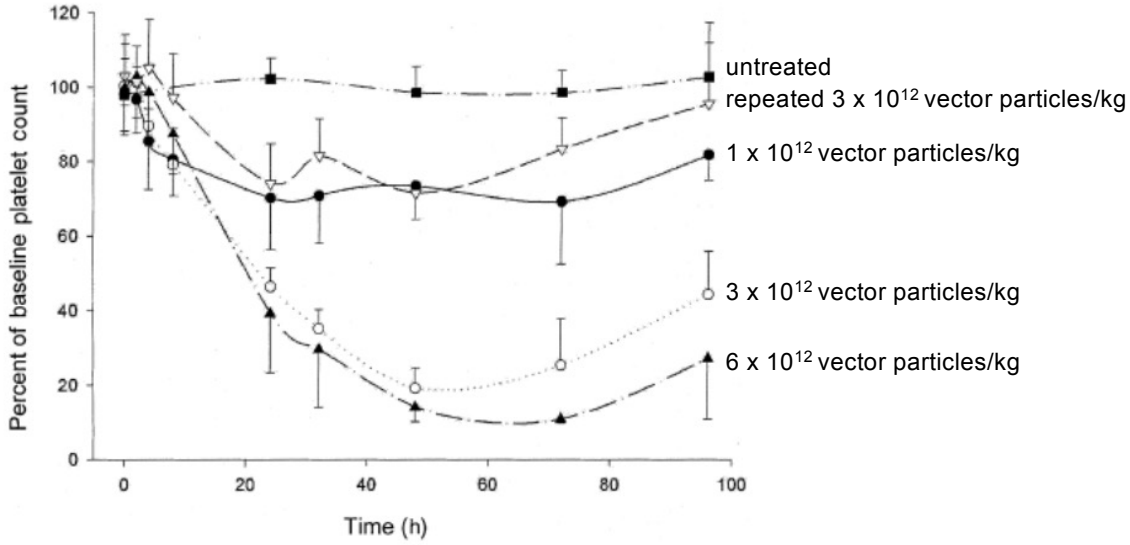
[1]*Blood* 109:2832 (2007) https://doi.org/10.1182/blood-2006-06-032524;
[2]*J Virol* 70:4502 (1996) https://doi.org/10.1186/1743-422X-7-148; *J Virol* 79:12125 (2005) https://doi.org/10.1128/jvi.79.19.12125-12131.2005
[3]*Virol J* 6:25 (2009) https://doi.org/10.1186/1743-422x-6-25
[4] *Hum Gene Ther.* 27:193 (2016) https://doi.org/10.1089/hum.2015.154
[5] *Virol J* 8:456 (2011) https://doi.org/10.1186/1743-422x-8-456
[6]*J Clin Med* 10:1661 (2019) 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
**Dispute presence of CAR on platelets: Ref 3 above

Graphic credits:
Adenovirus by Ramon Andrade uploaded on 3dciencia/science Photo Library 17 Sep 2018
Platelets https://s3-ap-southeast-1.amazonaws.com/subscriber.images/biology/2017/10/21111030/Blood-Platelets.png

Adenovector-associated thrombocytopenia

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



Br J Haematol 123:903 (2003)

Product	Dose
hAd5/26[1]	1 × 10^{11} virus particles/each
hAd26[2]	2.5 × 10^{10} viral particles*
ChAdOx1[3]	2.5 × 10^{10} viral particles**

*Reported as 8.92 log10 (8.3 × 10^8) infectious units (from EPAR)
**Reported as 2.5 × 10^8 infectious units (from EPAR)

[1] *Hum Gene Ther* 13:163 (2002). https://doi.org/10.1089/10430340152712719; *Mol Genet Metab* 80:148 (2003) https://doi.org/10.1016/j.ymgme.2003.08.016 *Mol Ther* 3:708 (2001) https://doi.org/10.1006/mthe.2001.0330
[2] *Hum Gene Ther* 10:1239 (1999) https://doi.org/10.1089/10430349950018229 ; *Gene Ther* 16:376 (2009) https://doi.org/10.1038/gt.2008.179 *Mol Ther* 4:182 (2001) https://doi.org/10.1006/mthe.2001.0444
[3] *Mol Ther* 18:609 (2010) https://doi.org/10.1038/mt.2009.279; *Br J Haematol* 123:903 (2003) https://doi.org/10.1046/j.1365-2141.2003.04719.x *J Gene Med* 1:360 (1999) https://doi.org/10.1002/(sici)1521-2254(199909/10)1:5%3C360::aid-jgm54%3E3.0.co;2-q
[4] see slide 14
[5] limited data

Vaccine adenovectors and platelets: *Preclinical tox data I*

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

Rebecca L. Sheets, Judith Stein, Robert T. Bailer, Richard A. Koup, Charla Andrews, Martha Nason, Bin He, Edward Koo, Holly Trotter, Chris Duffy, T. Manetz & Phillip Gomez

J Immunotox 5:315 (2008) https://doi.org/10.1080/15376510802312464

TABLE 1
Products Tested.

Product	Study	Virus	Genes	Adenovirus type	Vector characteristics	Manufacturer
14	A, D	HIV-1	Clade B gag-pol, Clade A env, Clade B env, Clade C env	5	ΔE1, E3, E4	GenVec
18	B, E	Ebola	Sudan/Gulu glycoprotein (GP) with point mut., Zaire GP with point mut.	5	ΔE1, E3	Crucell
21	F	Marburg	Marburg GP	5	ΔE1, E3	Crucell
22	E	Ebola	Sudan/Gulu . WT GP, Zaire WT GP	5	ΔE1, E3	Crucell
25	F	Marburg	Marburg GP	DNA plasmid	CMV/R promoter	Althea
27	C, G	HIV-1	Clade A env	35	ΔE1	GenVec

"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"

	HEMATOLOGIES					Treated		Controls[a]	
Parameter	Study	Product	Timepoint	Gender	Direction	Mean	S.D.[b]	Mean	S.D.
Platelets[i]	D	14	SD3	F	↓	303	104.75	425	128.03
		9, 14	SD86	M	↓	232	17.16	354	67
				F	↓	172	46.64	356	101.49
	E	18	SD3	M	↓	224.67	154.19	394	95.96
				F	↓	201.3	89.58	480.8	123.48
		22		M	↓	261.67	138.01	394	95.96
				F	↓	272.56	114.52	480.8	123.48
	F	25, 21	SD90	M	↑	991.8	138.03	473.9	66.57
				F	↑	1037.6	164.13	495.22	127.88
	G	27	SD45	F	↓	618.7	149.08	809.9	155.31

Cells highlighted in light gray represent mean values that fall outside the historical reference range.

Vaccine adenovectors and platelets: *Preclinical tox data II*

RESEARCH ARTICLE

Journal of Applied Toxicology WILEY

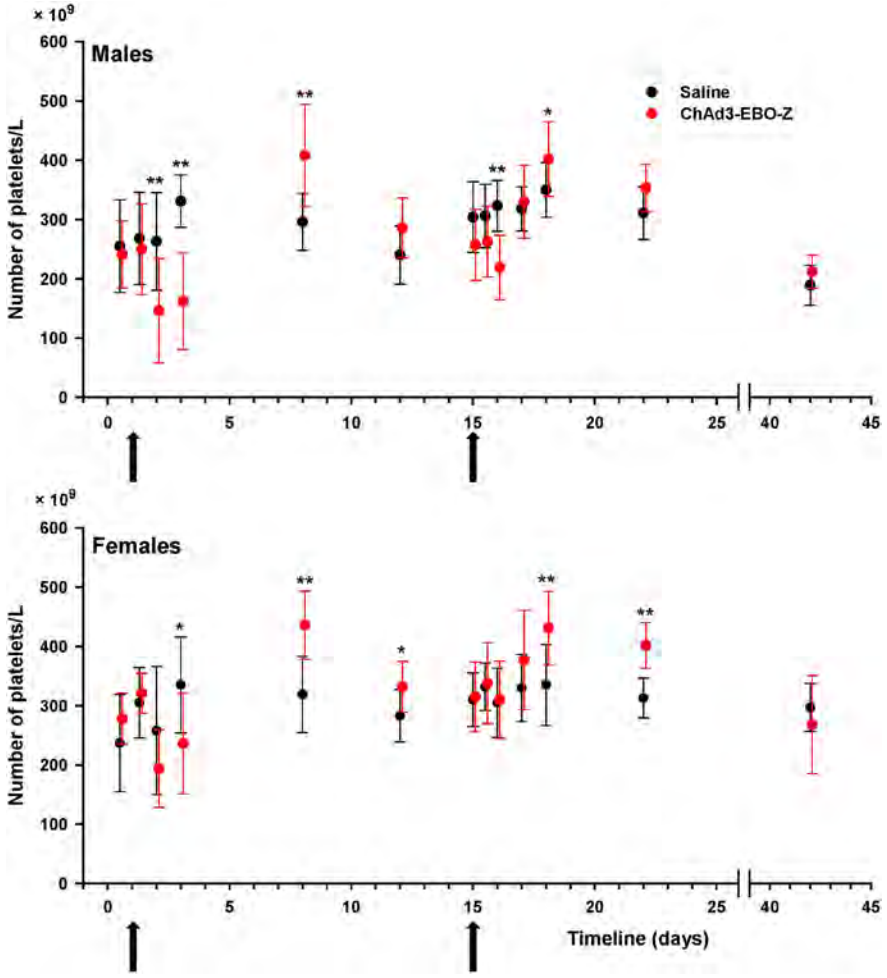
Nonclinical safety assessment of repeated administration and biodistribution of ChAd3-EBO-Z Ebola candidate vaccine

Camille Planty[1] | Guillaume Chevalier[2] | Marie-Ève Duclos[2] | Clémentine Chalmey[2] | Catherine Thirion-Delalande[2] | Cécile Sobry[2] | Ann-Muriel Steff[3] | Eric Destexhe[1]

"in line with earlier observations made in rabbit after IM administration of adenovirus vectors (Sheets et al., 2008)"

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



Source: Journal of Applied Toxicology, Volume: 40, Issue: 6, Pages: 748-762, First published: 21 January 2020, DOI:10.1002/jat.3941

Vaccine adenovectors and platelets: *Clinical data*

Non-COVID vaccine trials reporting thrombocytopenia

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

Ad 5 and other C type	Ad26	ChAdOX1
• rAd5-EnvA/rAd35-EnvA (HIV) https://doi.org/10.1371/journal.pone.0166393 • Ad5 (Ebola) https://doi.org/10.1016/j.vaccine.2010.10.037 • ChAd3-EBO-Z https://doi.org/10.1016/s1473-3099(15)00362-x https://doi.org/10.1016/s1473-3099(20)30016-5 https://doi.org/10.1016/s1473-3099(20)30019-0 https://doi.org/10.1016/S1473-3099(15)00486-7 https://doi.org/10.1056/NEJMoa1411627	• Ad26.ZEBOV https://doi.org/10.1093/infdis/jiz071	• ChAdOx1 85A https://doi.org/10.1016/j.vaccine.2019.10.102

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])

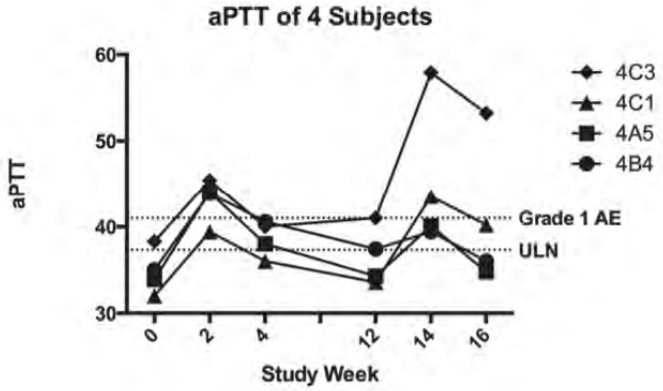
PLOS ONE

RESEARCH ARTICLE

Safety and Immunogenicity of a rAd35-EnvA Prototype HIV-1 Vaccine in Combination with rAd5-EnvA in Healthy Adults (VRC 012)

Michelle C. Crank[1], Eleanor M. P. Wilson[1☯], Laura Novik[1], Mary E. Enama[1], Cynthia S. Hendel[1], Wenjuan Gu[3], Martha C. Nason[2], Robert T. Bailer[1], Gary J. Nabel[1☯], Adrian B. McDermott[1], John R. Mascola[1], Richard A. Koup[1], Julie E. Ledgerwood[1], Barney S. Graham[1]*, VRC012 Study Team[¶]

Group 4A N=5	Group 4B N=5	Group 4C N=5
rAd35-EnvA at 10^{10} rAd5-EnvA at 10^{10}	rAd5-EnvA at 10^{10} rAd35-EnvA at 10^{10}	rAd35-EnvA at 10^{11} rAd5-EnvA at 10^{10}



Time course of abnormal activated Partial Thromboplastin Time (aPTT) in four subjects; abnormalities peaked around two weeks post-prime and boost and began to return to normal two weeks later.

	Product	Dose
ФНИЦ эпидемиологии и микробиологии имени Н.Ф. Гамалеи	hAd5/26[1]	1×10^{11} virus particles/each
Johnson & Johnson	hAd26[2]	2.5×10^{10} viral particles*
AstraZeneca / University of Oxford	ChAdOx1[3]	2.5×10^{10} viral particles**

*Reported as 8.92 log10 (8.3×10^8) infectious units (from EPAR)
**Reported as 2.5×10^8 infectious units (from EPAR)

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

[1] *Hum Gene Ther* 13:163 (2002). https://doi.org/10.1089/10430340152712719; *Mol Genet Metab* 80:148 (2003) https://doi.org/10.1016/j.ymgme.2003.08.016 *Mol Ther* 3:708 (2001) https://doi.org/10.1006/mthe.2001.0330
[2] *Urology* 66:830 (2005) https://doi.org/10.1016/j.urology.2005.04.041
[3] *Mol Ther* 18:609 (2010) https://doi.org/10.1038/mt.2009.279; *Br J Haematol* 123:903 (2003) https://doi.org/10.1046/j.1365-2141.2003.04719.x *J Gene Med* 1:360 (1999) https://doi.org/10.1002/(sici)1521-2254(199909/10)1:5%3C360::aid-jgm54%3E3.0.co;2-q
[4] *PLoS One* 11:e0166393 (2016) https://doi.org/10.1371/journal.pone.0166393
[5] limited data

Vaccine adenovectors and coagulation factors: *Preclinical tox data I*

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

Rebecca L. Sheets, Judith Stein, Robert T. Bailer, Richard A. Koup, Charla Andrews, Martha Nason, Bin He, Edward Koo, Holly Trotter, Chris Duffy, T. Manetz & Phillip Gomez

J Immunotox 5:315 (2008) https://doi.org/10.1080/15376510802312464

COAGULATION						Treated		Controls[a]	
Parameter	Study	Product	Timepoint	Gender	Direction	Mean	S.D.[b]	*Mean*	S.D.
Activated Partial Thromboplastin Time[k]	D	14	SD24	F	↑	83.71	7.65	73.35	10.95
		9, 14	SD86	F	↑	86.66	9.41	75	11.97
	E	18	SD3	M	↑	105.96	27.18	54.02	10.85
				F	↑	119.27	15.85	85.93	19.77
		22		M	↑	114.06	17.65	54.02	10.85
				F	↑	117.5	6.52	85.93	19.77
		18	SD24	F	↑	107.19	12.35	84.32	14.21
			SD45	M	↑	108.11	7.65	81.11	14.94
				F	↑	104.88	19.47	85.15	15.44
		22		M	↑	105.47	14.17	81.11	14.94
				F	↑	103.81	8.87	85.15	15.44
	F	25, 21	SD90	M	↑	135.1	17.4	86.51	8.13
				F	↑	132.5	15.83	93.69	17.85
			SD108	M	↑	100.72	10.29	81.76	9.18
	G	27	Pre-dose	F	↓	79.02	10.35	87.37	6.76
			SD30	F	↑	112.9	15.21	96.93	16.31
			SD45	M	↑	117.6	12.58	96.48	8.1

COAGULATION						Treated		Controls[a]	
Parameter	Study	Product	Timepoint	Gender	Direction	Mean	S.D.[b]	*Mean*	S.D.
Prothrombin Time[l]	D	14	SD3	M	↓	8.69	0.8	8.93	0.9
				F	↓	8.64	0.8	8.93	0.7
			SD24	M	↓	8.96	0.12	9.17	0.12
				F	↓	9.02	0.1	9.27	0.14
	E	18	SD3	M	↓	5.88	0.03	6.17	0.09
				F	↓	5.88	0.06	6.23	0.11
		22	SD3	M	↓	5.87	0.05	6.17	0.09
				F	↓	5.9	0.06	6.23	0.11
		18	SD24	M	↓	6.02	0.09	6.5	0.12
				F	↓	6.02	0.09	6.57	0.24
		22		M	↓	6.05	0.12	6.5	0.12
				F	↓	6.05	0.14	6.57	0.24
		18	SD45	M	↓	6.27	0.14	6.56	0.12
				F	↓	6.26	0.16	6.62	0.25
		22		M	↓	6.3	0.12	6.56	0.12
				F	↓	6.33	0.09	6.62	0.25
	F	25, 21	SD90	F	↓	6.74	0.18	6.98	0.18
			SD108	M	↓	6.57	0.07	6.99	0.08
				F	↓	6.54	0.08	7.05	0.21
	G	27	SD57	F	↓	6.45	0.11	6.99	0.17
Fibrinogen[m]	F	25, 21	SD90	M	↑	725.7	84.62	335.1	70.08
				F	↑	653.2	81.96	273	65.69
			SD108	M	↑	665.8	78.7	347.8	28.53
				F	↑	559.6	77.32	262.5	40.9
	G	27	SD4	M	↑	472	77.46	361.6	29.47
				F	↑	359.1	47.83	294.1	48.54
			SD30	M	↑	407.3	95.76	307.5	49.2
				F	↑	353.8	144.62	247	21.58
			SD45	M	↑	620.8	41.91	339.8	50.42
				F	↑	569.6	91.1	269.8	17.92
			SD57	F	↑	297.8	42.58	238	14.92

Vaccine adenovectors and coagulation factors: *Preclinical tox data II*

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

Rebecca L. Sheets, Judith Stein, Robert T. Bailer, Richard A. Koup, Charla Andrews, Martha Nason, Bin He, Edward Koo, Holly Trotter, Chris Duffy, T. Manetz & Phillip Gomez

J Immunotox 5:315 (2008) https://doi.org/10.1080/15376510802312464

TABLE 1
Products Tested.

Product	Study	Virus	Genes	Adenovirus type	Vector characteristics	Manufacturer
14	A, D	HIV-1	Clade B gag-pol, Clade A env, Clade B env, Clade C env	5	ΔE1, E3, E4	GenVec
18	B, E	Ebola	Sudan/Gulu glycoprotein (GP) with point mut., Zaire GP with point mut.	5	ΔE1, E3	Crucell
21	F	Marburg	Marburg GP	5	ΔE1, E3	Crucell
22	E	Ebola	Sudan/Gulu . WT GP, Zaire WT GP	5	ΔE1, E3	Crucell
25	F	Marburg	Marburg GP	DNA plasmid	CMV/R promoter	Althea
27	C, G	HIV-1	Clade A env	35	ΔE1	GenVec

- *"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."

Vaccine adenovectors and coagulation factors: *Preclinical tox data II*

RESEARCH ARTICLE

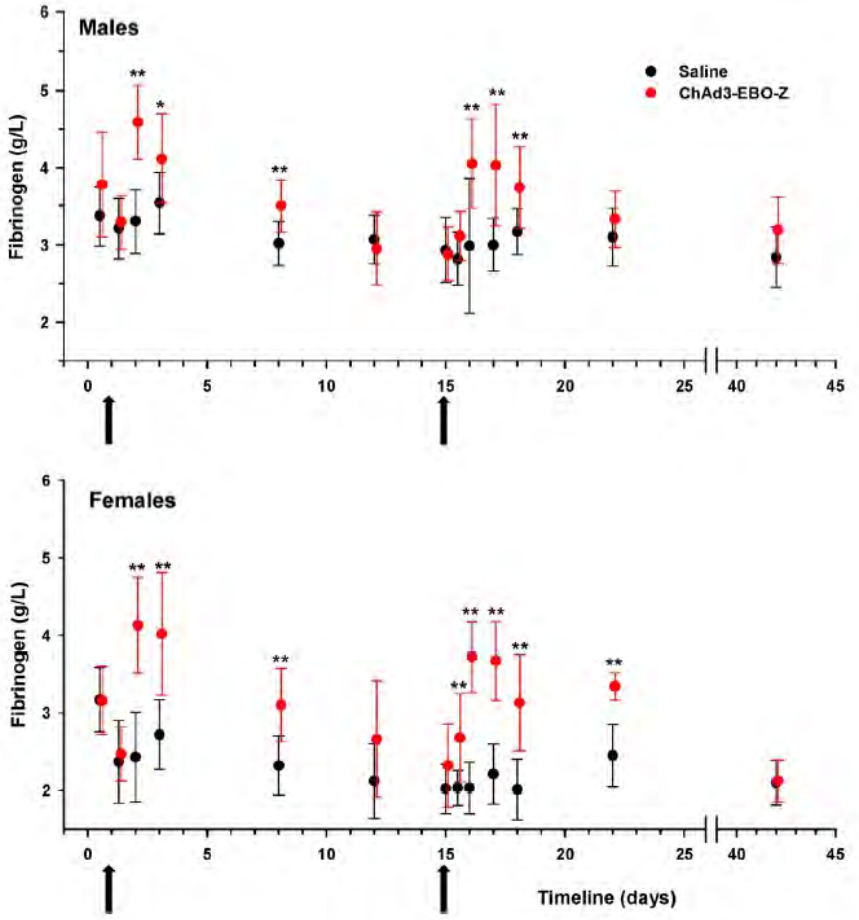
Journal of Applied Toxicology WILEY

Nonclinical safety assessment of repeated administration and biodistribution of ChAd3-EBO-Z Ebola candidate vaccine

Camille Planty[1] | Guillaume Chevalier[2] | Marie-Ève Duclos[2] | Clémentine Chalmey[2] | Catherine Thirion-Delalande[2] | Cécile Sobry[2] | Ann-Muriel Steff[3] | Eric Destexhe[1]

- *"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"*

Fibrinogen



Source: Journal of Applied Toxicology, Volume: 40, Issue: 6, Pages: 748-762, First published: 21 January 2020, DOI:10.1002/jat.3941

Vaccine adenovectors and coagulation factors: *Preclinical data II*

RESEARCH ARTICLE

Journal of Applied Toxicology WILEY

Nonclinical safety assessment of repeated administration and biodistribution of ChAd3-EBO-Z Ebola candidate vaccine

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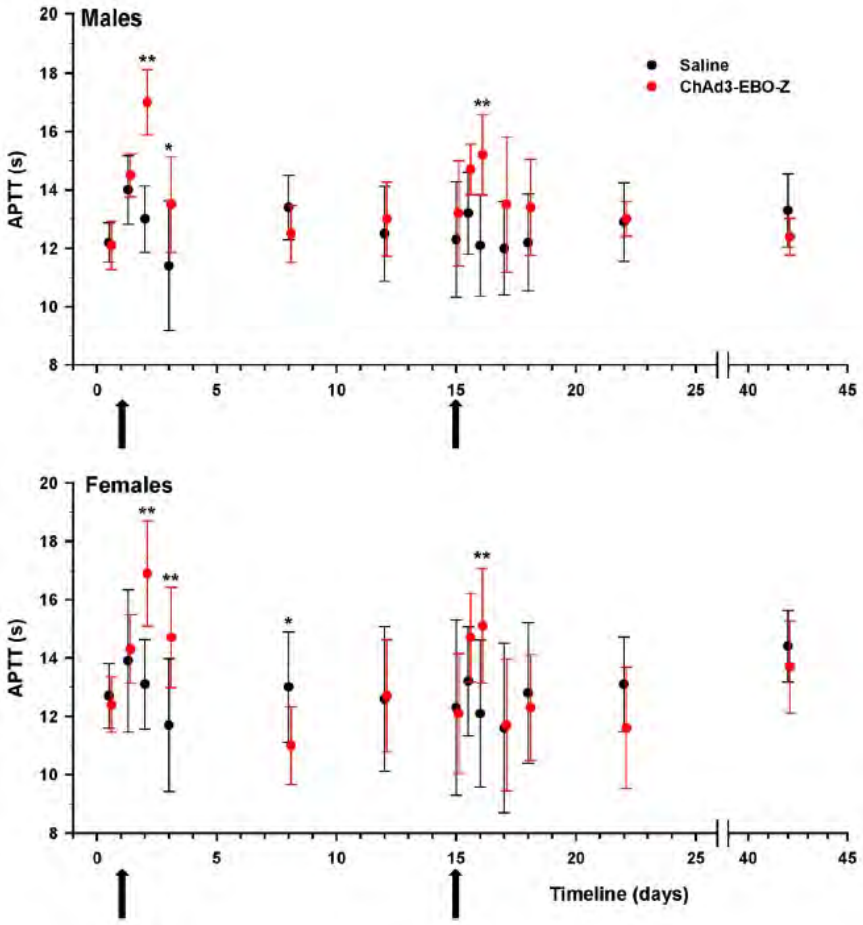
- *"Statistically significant prolongation of APTT was noted 24 hours after both injections and 48 hours after the first injection in males and females treated with ChAd3-EBO-Z candidate vaccine"*

Activated Partial Thromboplastin Time



Source: Journal of Applied Toxicology, Volume: 40, Issue: 6, Pages: 748-762, First published: 21 January 2020, DOI:10.1002/jat.3941

Vaccine adenovectors and platelets: *Clinical data*

Non-COVID vaccine trials reporting coagulopathies

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

Ad 5 and other C type	Ad26	ChAdOX1
• rAd5-EnvA/rAd35-EnvA (HIV) https://doi.org/10.1371/journal.pone.0166393 • Ad5 (Ebola) https://doi.org/10.1016/j.vaccine.2010.10.037 • ChAd3-EBO-Z https://doi.org/10.1016/s1473-3099(15)00362-x https://doi.org/10.1016/S1473-3099(15)00486-7 https://doi.org/10.1056/NEJMoa1411627	---	---

Access and/or assessment bias?

(i.e., absence of effect or absence of data)

Background on Ad5, Ad26, & ChAdOx1

Platelets & Ad vectors

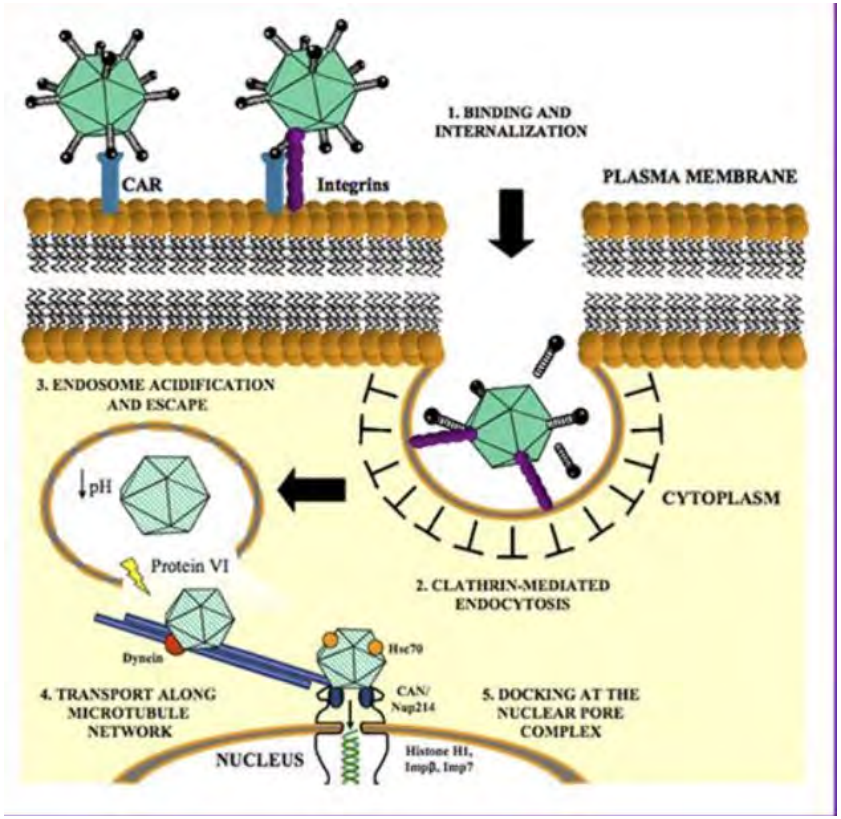
Coagulation factors & Ad vectors

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

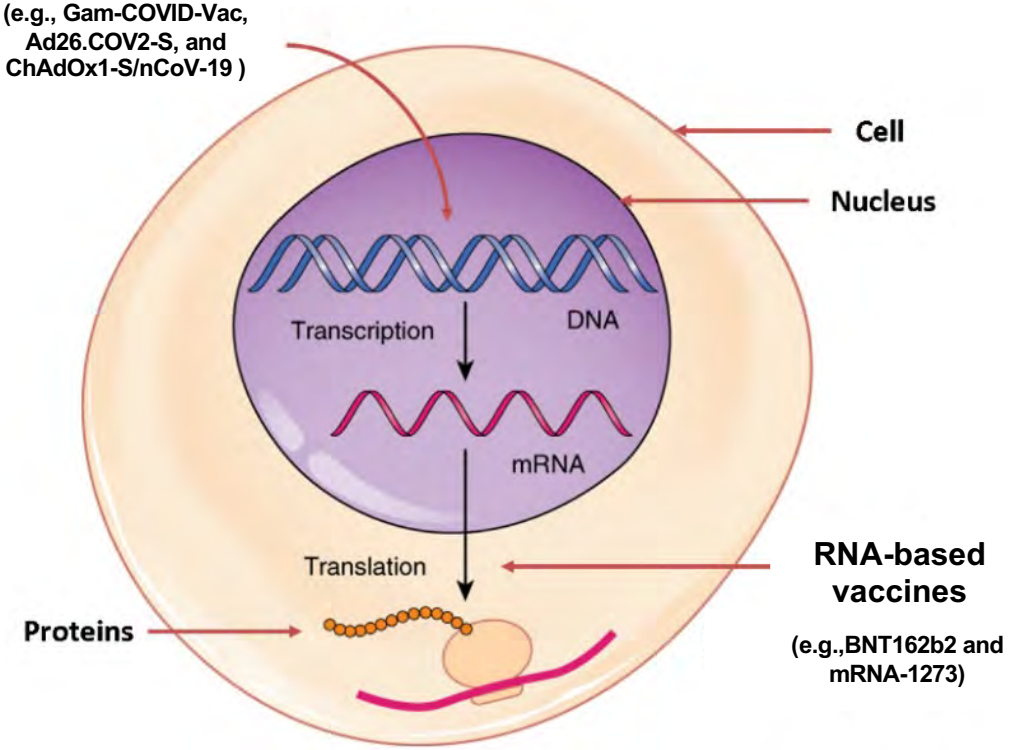
Adeno-vectored vaccines require nuclear transcription, mRNA vaccines don't



Source: https://mol-biol4masters.masters.grkraj.org/html/Genetic_Engineering2B-Molecular_Tools-Expression_Vectors_files/image017.jpg

DNA-based vaccines

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

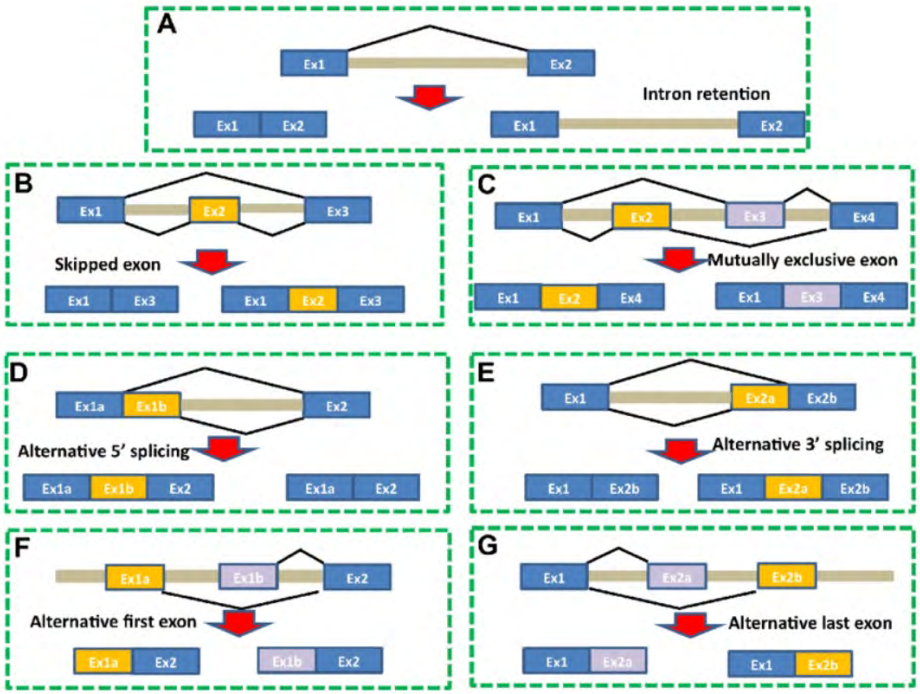


RNA-based vaccines

(e.g.,BNT162b2 and mRNA-1273)

Adapted from: https://medium.com/microbial-instincts/platelet-disorders-and-genetic-vaccines-might-have-a-biological-link-but-its-negligible-2da695521d66

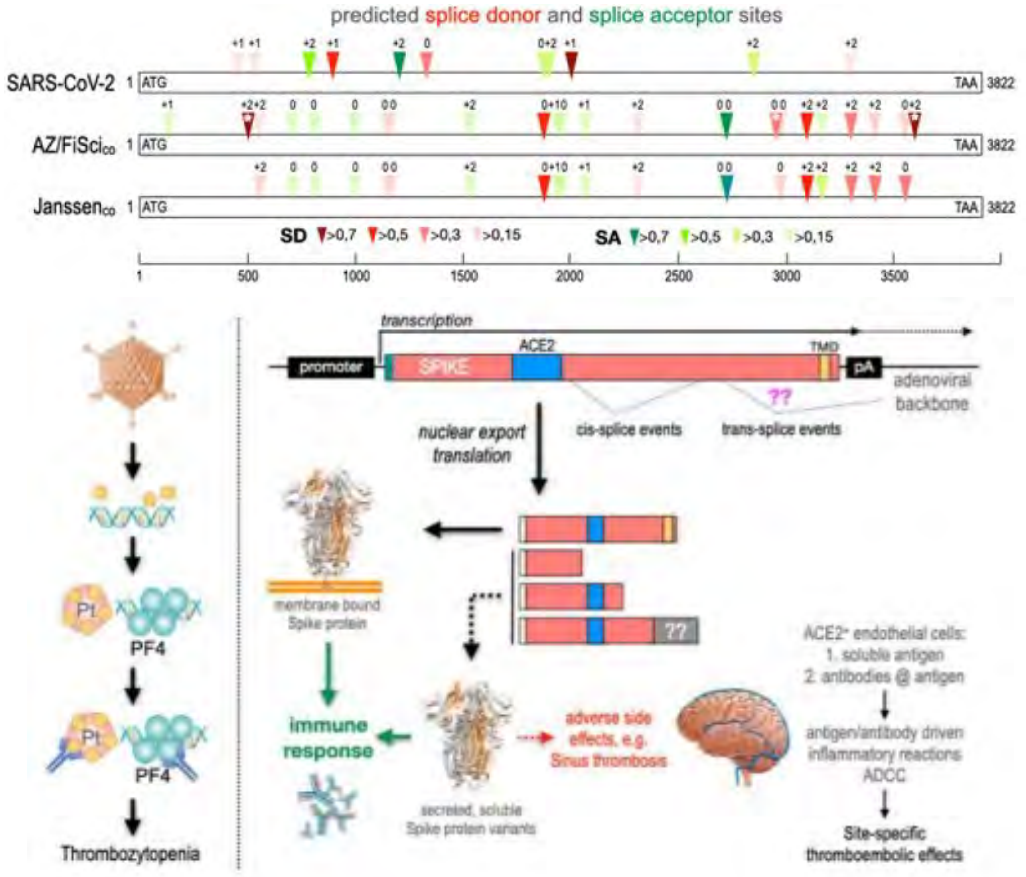
Multiple types of alternative splicing in nuclear pre-mRNA processing



N.B. Pre-mRNA splicing initially described in hAd2 late mRNA processing[1]

Source: *BMB Reports* 46:439 (2013) https://doi.org/10.5483/bmbrep.2013.46.9.161
[1] *Cell* 12:1 (1977) https://doi.org/10.1016/0092-8674(77)90180-5 ; *PNAS* 74:3171 (1977) https://doi.org/10.1073/pnas.74.8.3171

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

Prof. Dr. med. Andreas Greinacher

Universitätsmedizin Greifswald

Sauerbruchstraße

Theory of TTS/VITT mechanism

Annemarie E. Fogerty, MD.

Director, Reproductive Hematology

Massachusetts General Hospital

Boston, MA USA

Thrombosis/thrombocytopenia in pregnancy

A Teaching Affiliate
of Harvard Medical School

COVAX Maternal Immunization Working Group Webinar

Thrombosis/Thrombocytopenia in Pregnancy

Annemarie E. Fogerty, M.D.

MASSACHUSETTS
GENERAL HOSPITAL
CANCER CENTER

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

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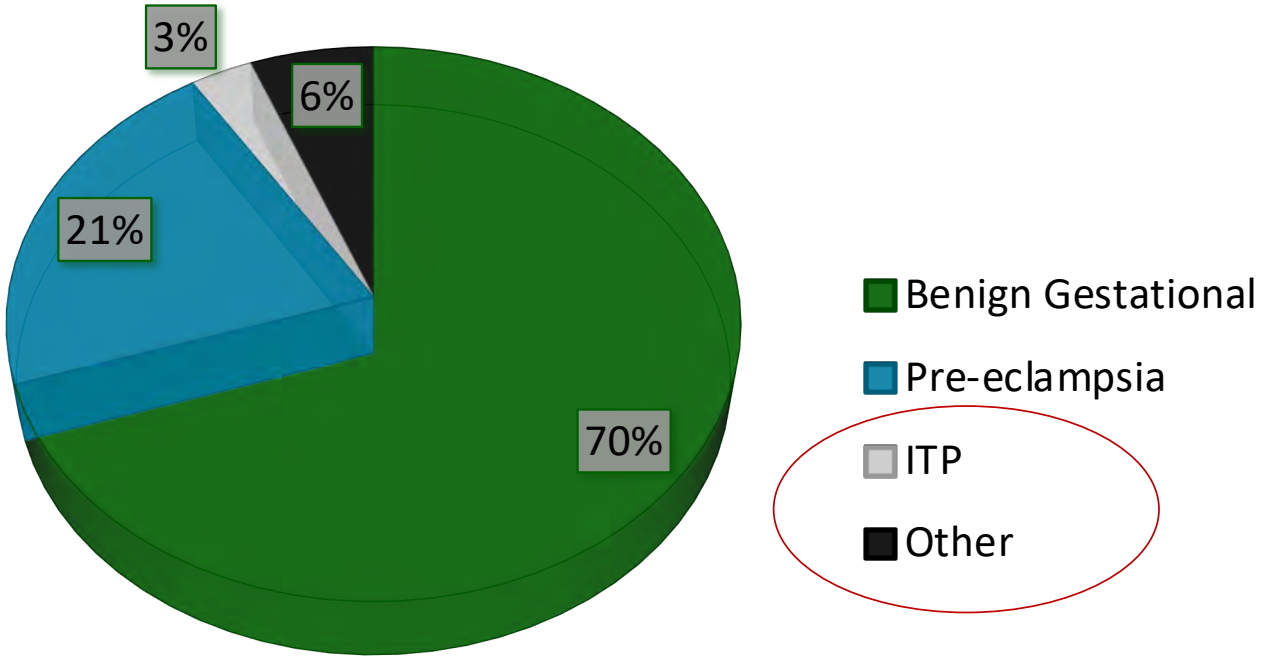
Maternal thrombocytopenia: Most Common Causes



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Features that may contribute to thrombocytopenia development in normal pregnancies

- Published reviews reveal an average decline of platelets by 10-13% in pregnancy [1,2]
- Minor increase in thrombopoietin (TPO), which can be insufficient in disease states[3]
- ADAMTS13 activity level declines[4]
- Increased vWF production and prolongation of the vWF half life[5]
- Increasing mean platelet volume (MPV) as pregnancy progresses likely reflects progressive increase in platelet turnover [6]

1. Reese JA. Am J Hematol. 2017.
2. Reese JA. N Engl J Med. 2018.
3. Zhang X, Zhao Y, Li X, et al. Oncotarget 2016
4. Sanchez-Luceros A. Thromb Haemost. 2004
5. Drury-Stewart DN. PLoS ONE 2014
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 [1-2]
- 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]

1. McCrae KR. Blood. 1992.
2. Crowther MA. Blood Rev. 1996.
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 [1]
  - Fetal intracranial hemorrhage: 1.5% [1]

1. Provan D. Blood. 2010.

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%)

L Grimaldi-Bensouda et al. Blood 2012;120:4938-4944.

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Covid data from Vaccine Adverse Events Reporting System (VAERS)

DOI: 10.1002/ajh.26132

COMMENTARY

AJH WILEY

Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination

Eun-Ju Lee[1] | Douglas B. Cines[2] | Terry Gernsheimer[3] | Craig Kessler[4] | Marc Michel[5] | Michael D. Tarantino[6] | John W. Semple[7] | Donald M. Arnold[8] | Bertrand Godeau[5] | Michele P. Lambert[9,10] | James B. Bussel[11]

- 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

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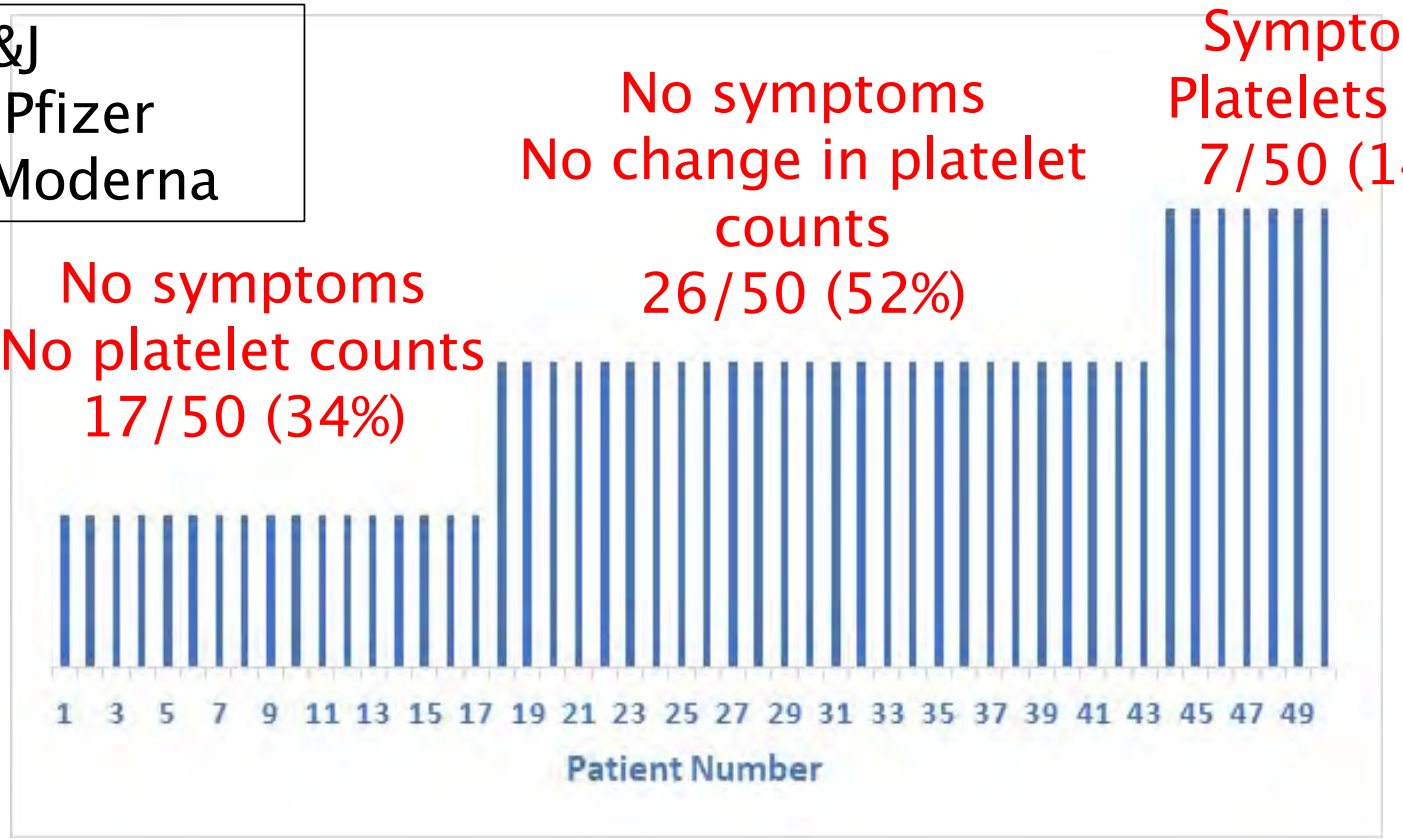
MGH COVID Vaccination Experience in 50 patients with pre-existing ITP diagnosis

8%: J&J
46%: Pfizer
46% Moderna



*3/7 admitted to hospital, all 7 had increased ITP treatment, all recovered in 3-35 days

Kuter DK. BJH. 2021.

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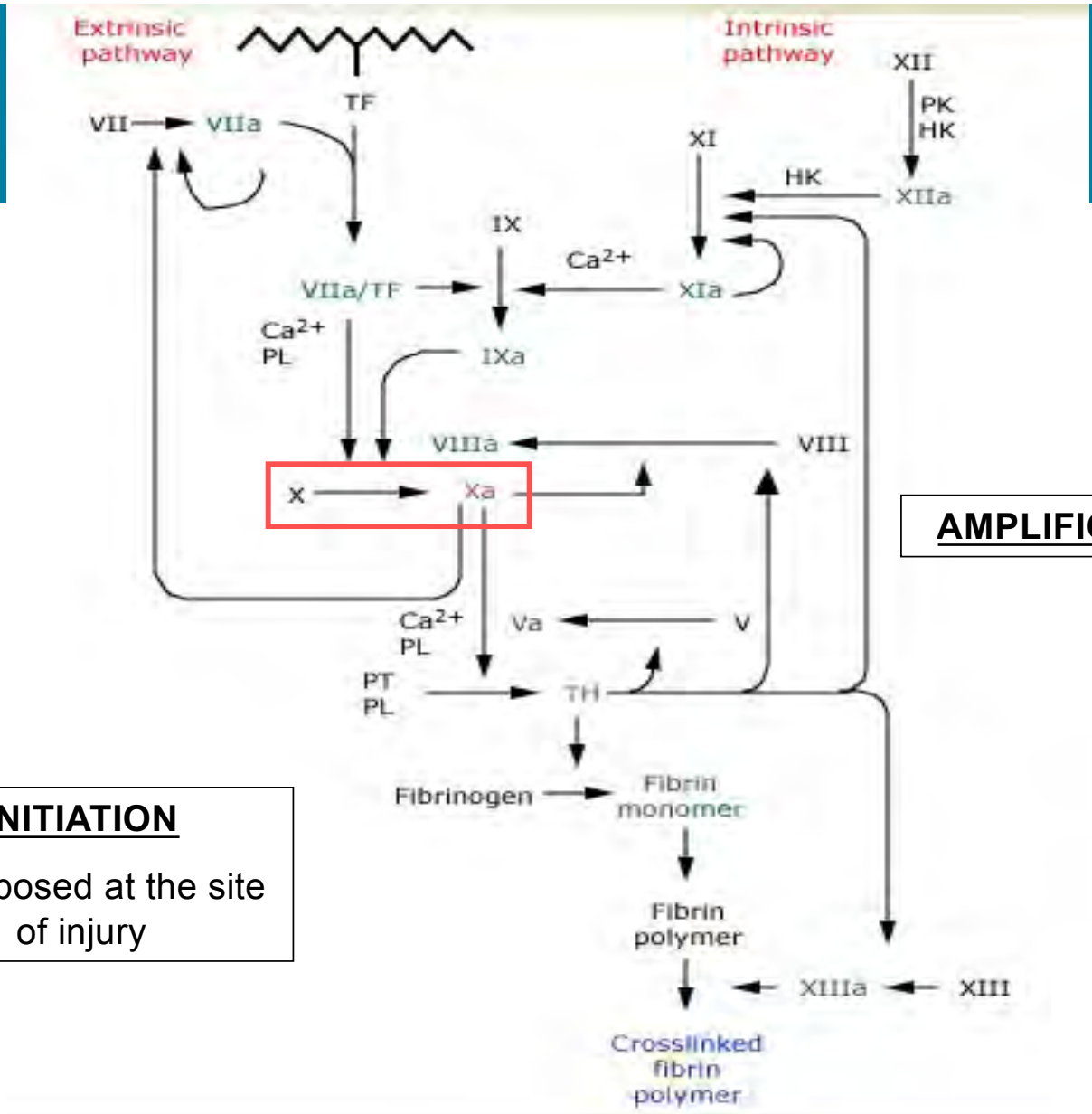
Thrombosis in Pregnancy
Estrogen induces a hypercoagulable state

- 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



AMPLIFICATION

INITIATION

TF exposed at the site of injury

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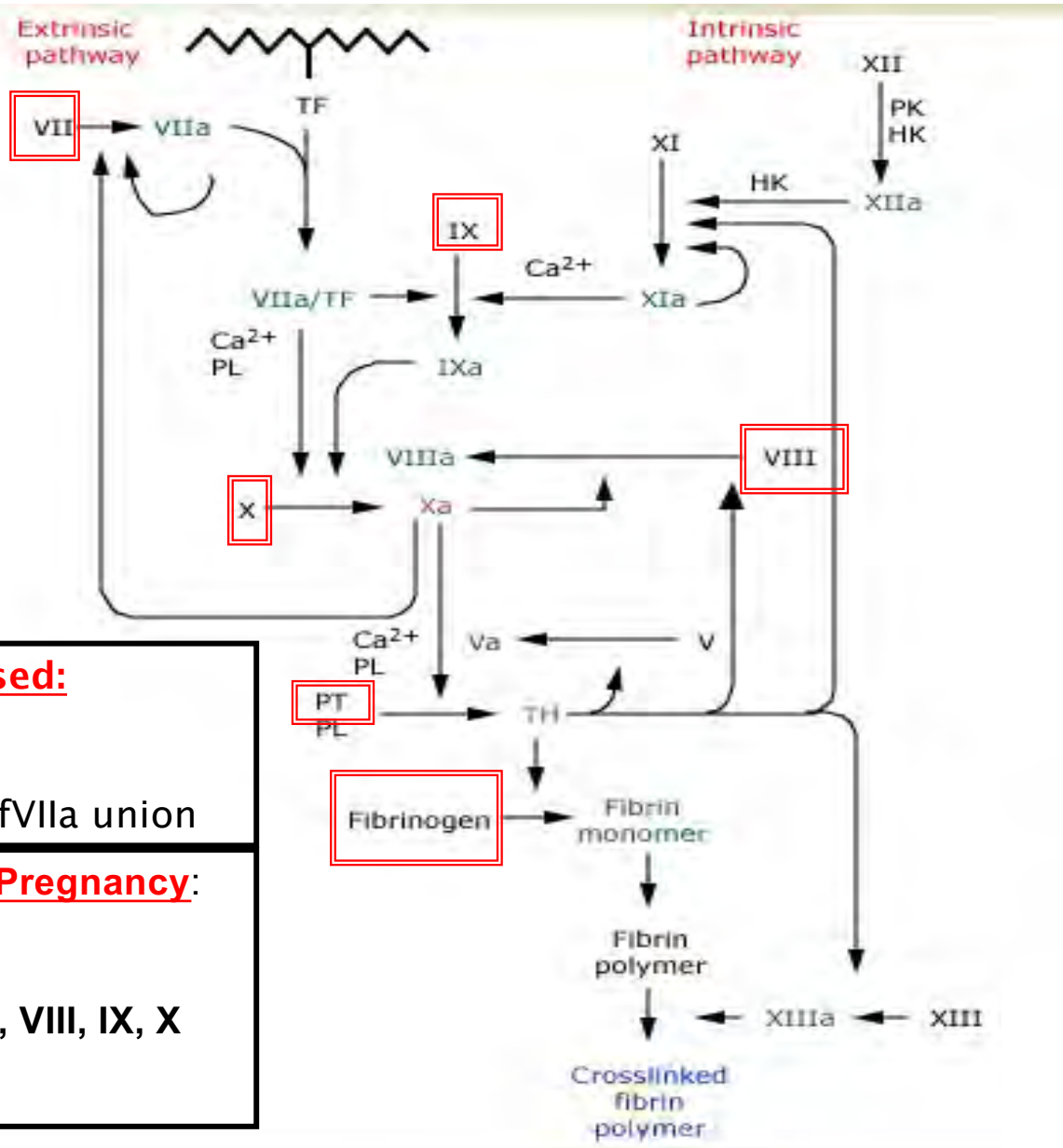

TFPI decreased:

- Inhibits fX
- Inhibits TF/fVIIa union

Increased in Pregnancy:

Fibrinogen

Factors II, VII, VIII, IX, X

VWF

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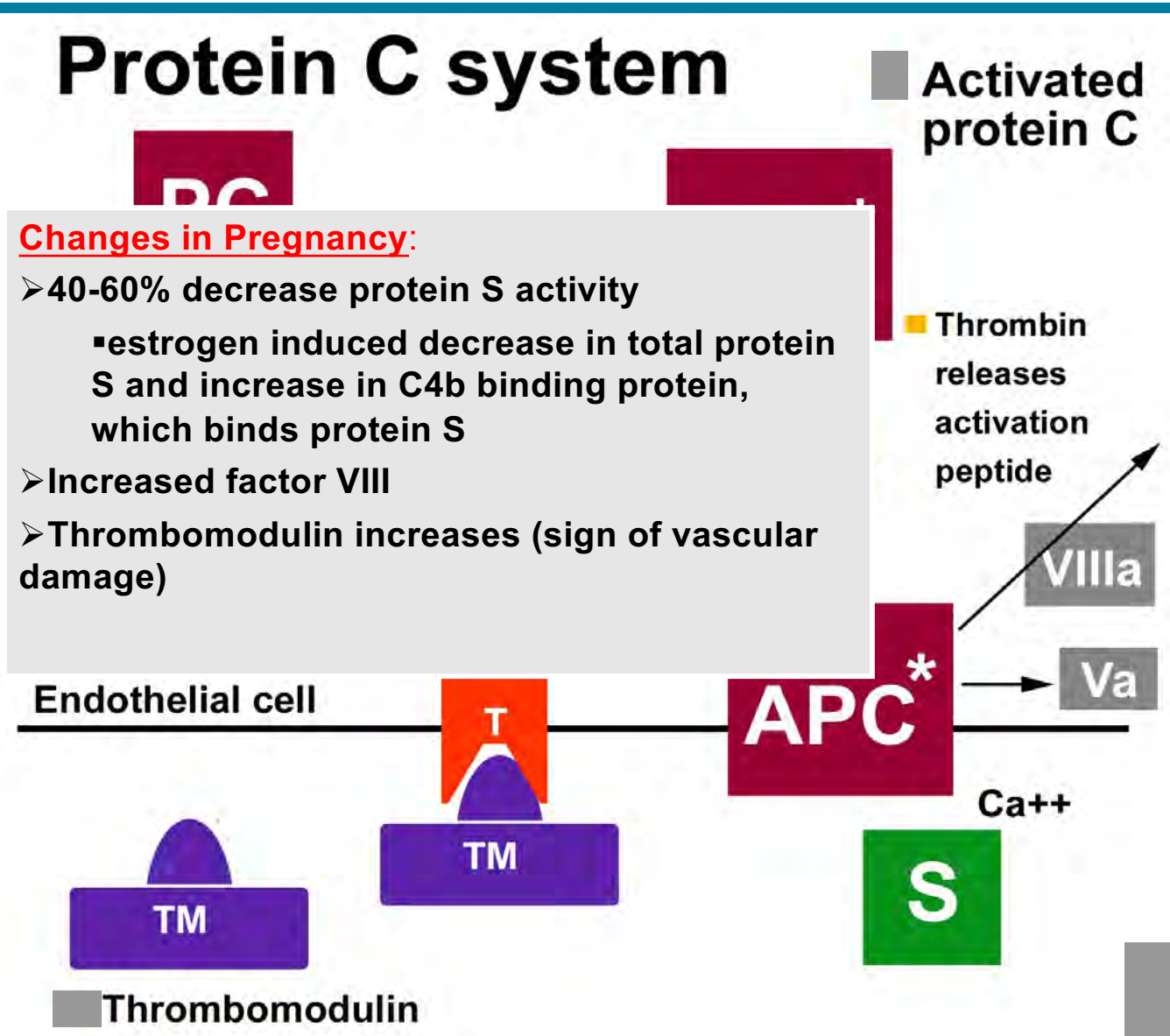
Protein C system



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)**

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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

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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)

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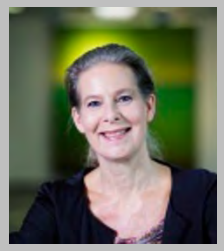
Panel discussion

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

TTS / pregnancy surveillance update UK

Dr Katherine Donegan

UK AZ vaccine deployment

- First AZ doses deployed 30th December 2020
- Up to 28th May, 24.3 million 1st AZ doses and 13.4 million 2nd 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

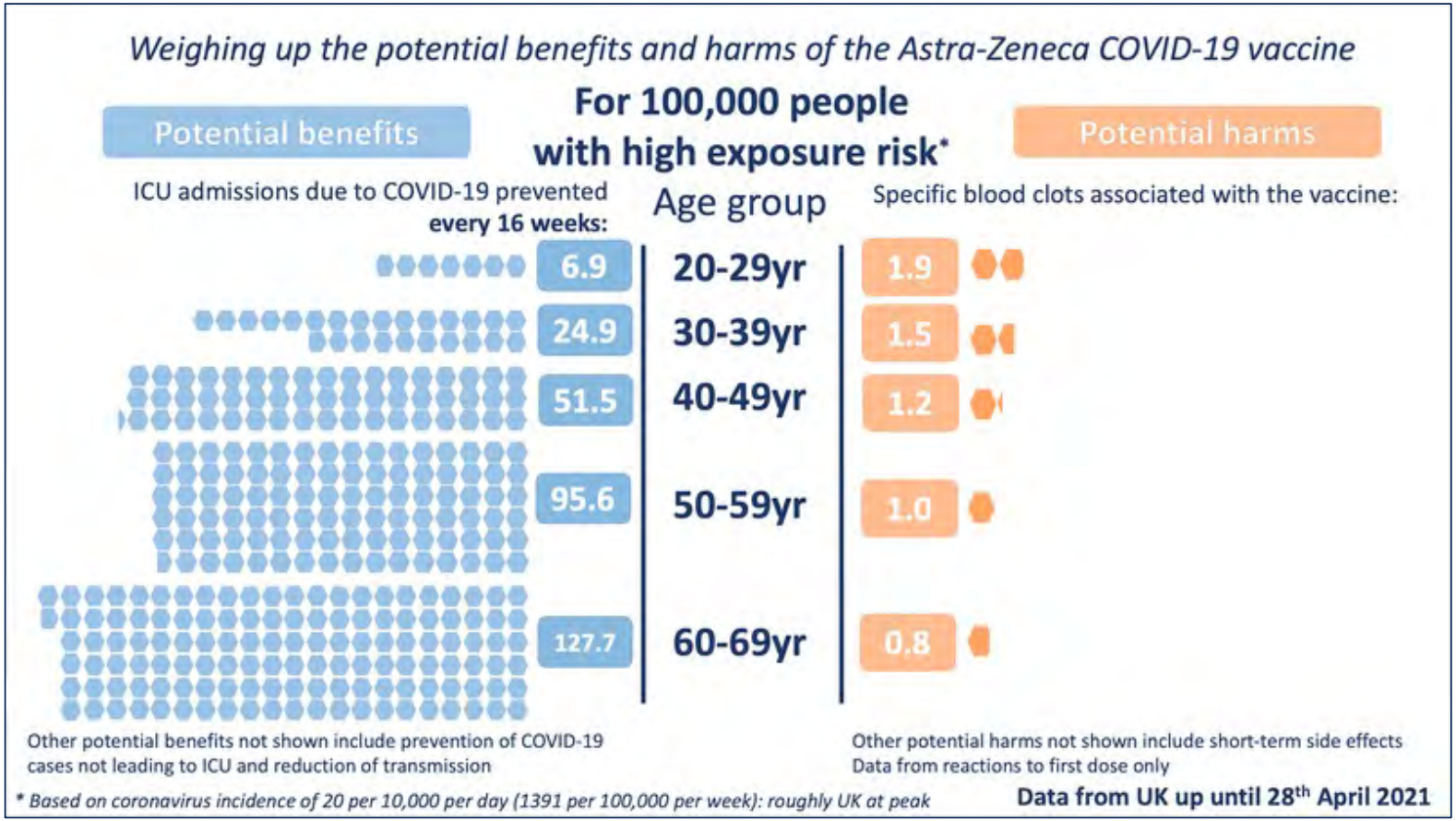
- https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

- 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



Reported incidence of TTS – 1st vs 2nd dose

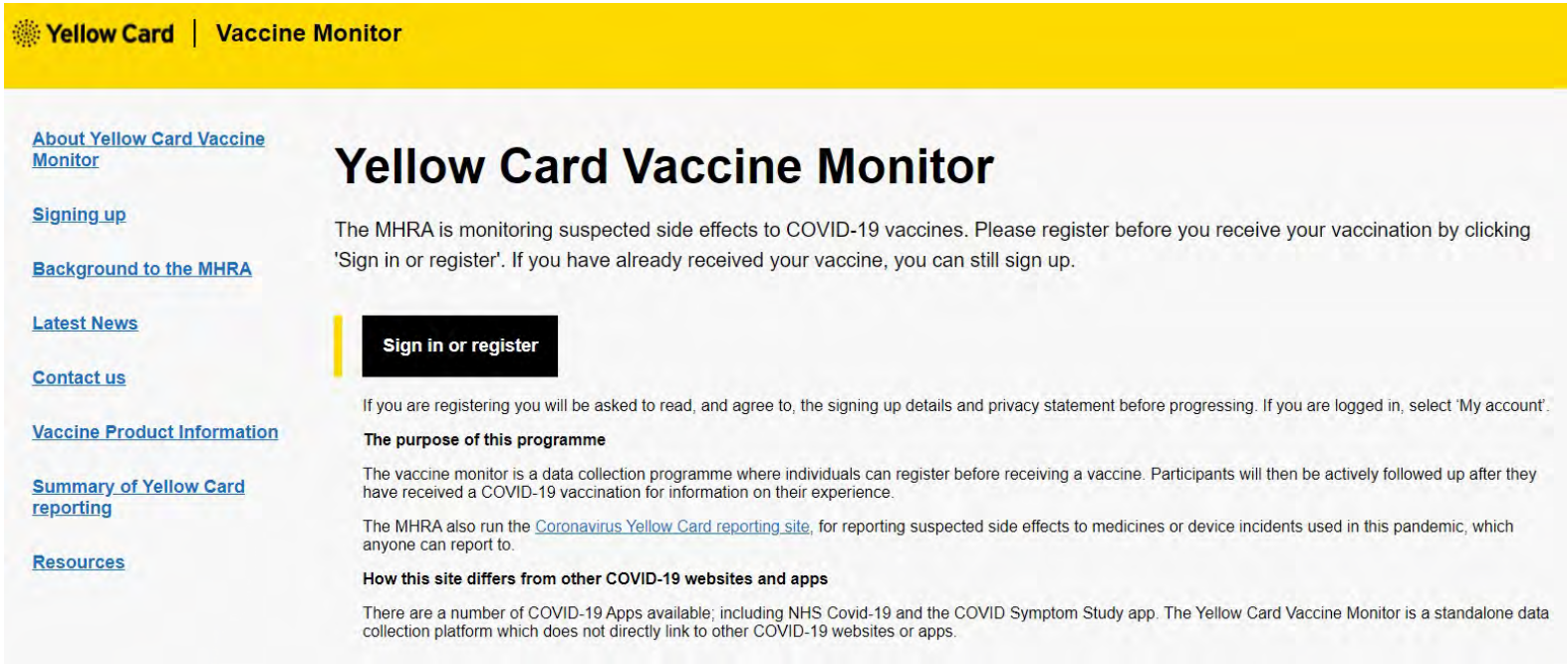
Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases (exc. unlikely cases)	Case incidence rate (per 1 million doses)	Estimated number of second doses in UK (1,000,000s)	Total number of cases (exc. unlikely cases)	Case incidence rate (per 1 million doses)
18-49 yrs	8.4	151	18.0 (15.3, 21.1)	2.7	0	0 (0, 1.4)
50+ yrs	15.9	163	10.2 (8.7, 11.9)	10.7	15	1.4 (0.8, 2.3)
Total	24.3	330*	13.6 (12.2, 15.1)	13.4	18**	1.3 (0.8, 2.1)

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

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TTS/Pregnancy Surveillance in Brazil

Expert Consultation on Post-Vaccine TTS & Impact on Maternal Immunizaton

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 recomendations

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

[1]Nota Técnica 467/2021 - CGPNI/DEIDT/SVS/MS
[2]Nota 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**

	Número	Incidência/100 mil habitantes
Casos SRAG	6.880	276,52
Casos de SRAG por covid-19	4.442	178,53
Óbitos por SRAG	541	21,74
Óbitos de SRAG por covid-19	514	20,75

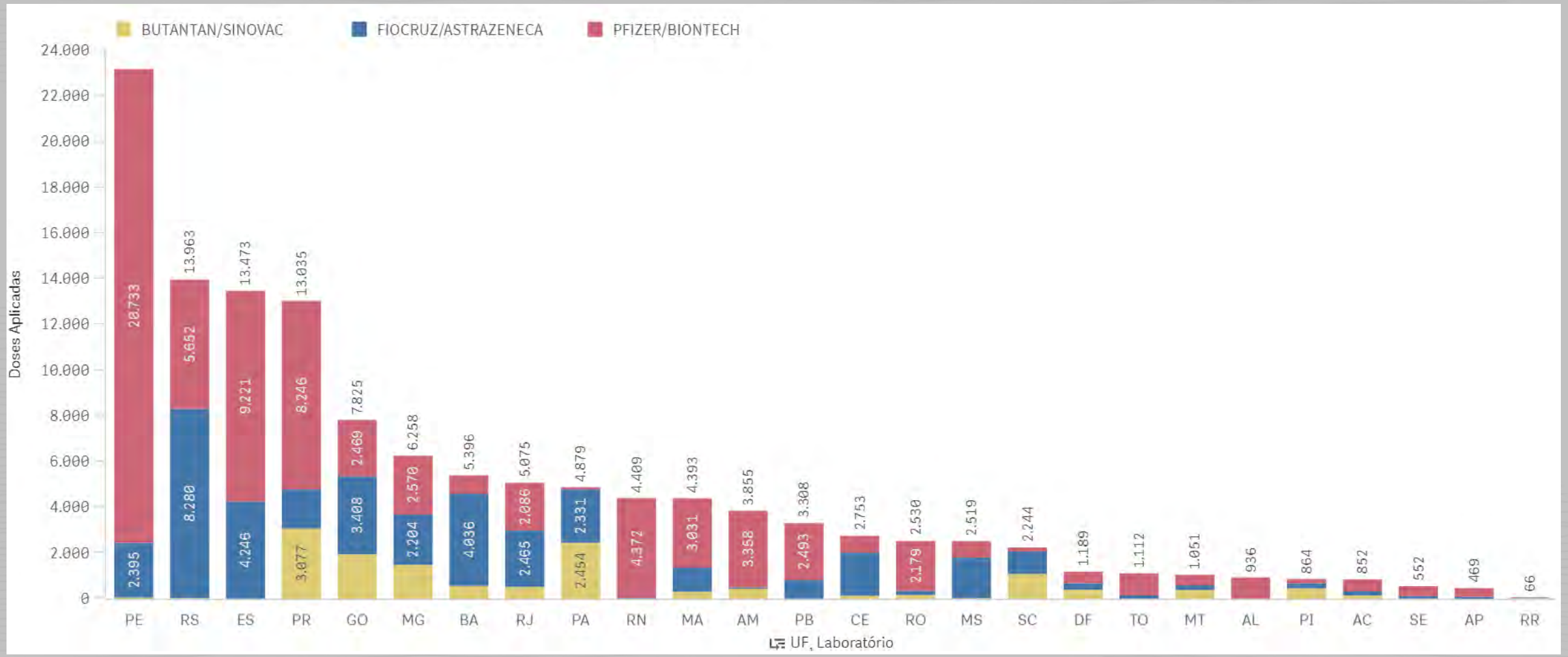
Fonte: SIVEP-Gripe, atualizado em 17/05/2021, dados sujeito a alterações

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

Total: 126.185	Dose 1: 124.890 (99%)	Dose 2: 1.295 (1%)
Pfizer: 73,4K(58%)	AstraZeneca: 39,1 K (31%)	Sinovac: 13,8 K(11%)

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, disponível 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

Total eventsl: 773
(612,6/100 K doses)

Severe events: 41
(32,5/100 K doses)

Deaths: 4
(3,2/100 K doses)

By vaccine	Cumulative incidence /100K doses administered
• 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

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

Manufacturer	Abortion	Premature labor	Fetal Death	TTS/death	Others
Fiocruz/AstraZeneca	7	4	3	1	13
Coronavac/Butantan	13	1	0	0	5
Pfizer	1	0	1	0	2
Total	21	5	4	1	20

Fonte: eSUS Notifica/CGPNI/DEIDT/SVS/MS. Dados preliminares, sujeitos a alterações
[1]Síndrome Trombótica com trombocitopenia
[2]Outras complicações da gravidez não relacionadas às vacinações

DISQUE SAÚDE 136

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)

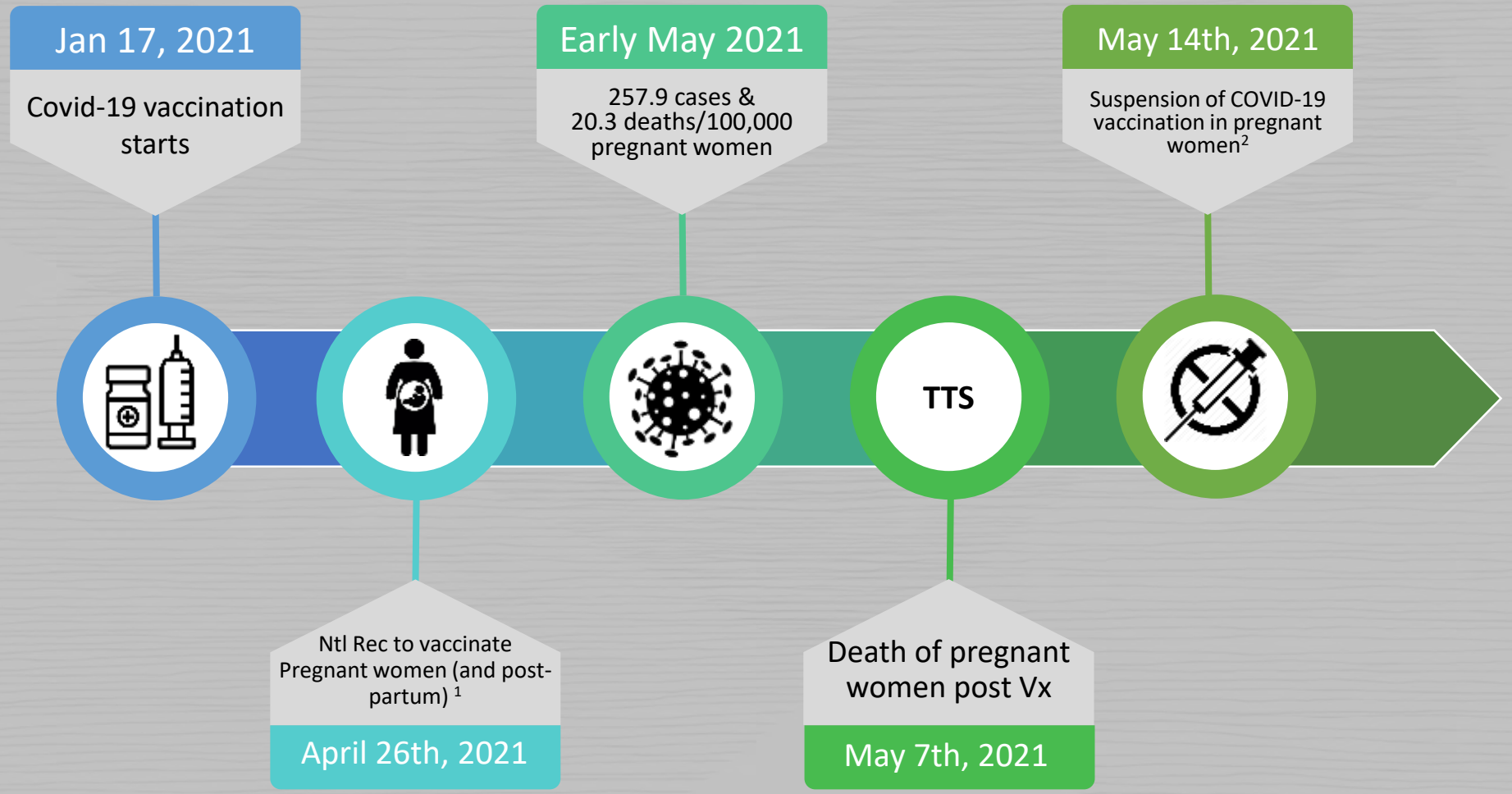
Pfizer/Wyeth

-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

SUS | MINISTÉRIO DA SAÚDE | PÁTRIA AMADA BRASIL GOVERNO FEDERAL

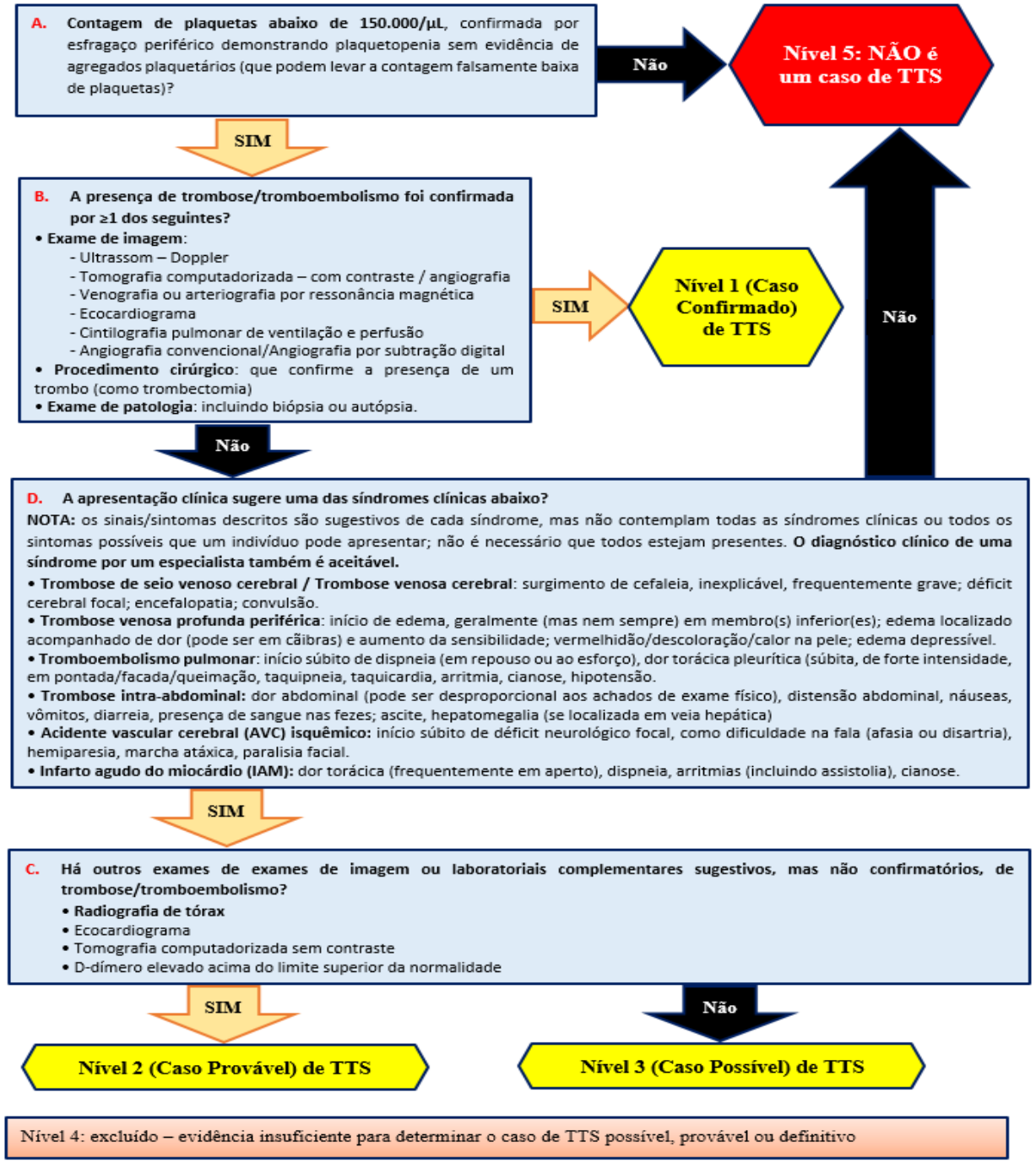
COVID-19 vaccination in pregnancy, Brazil



[1]Nota Técnica 467/2021 - CGPNI/DEIDT/SVS/MS
[2]Nota Técnica 627/2021 - CGPNI/DEIDT/SVS/MS

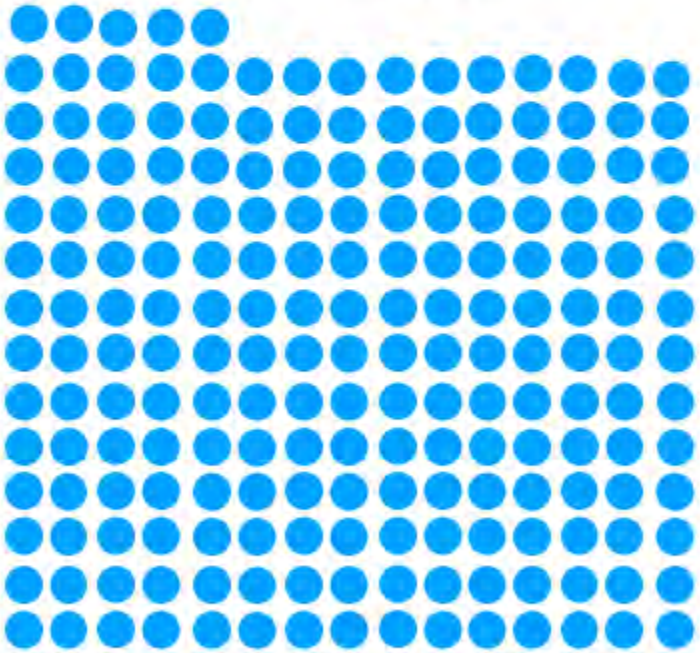
Alghoritm for identification and diagnosis of TTS events,

Brazil 2021



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

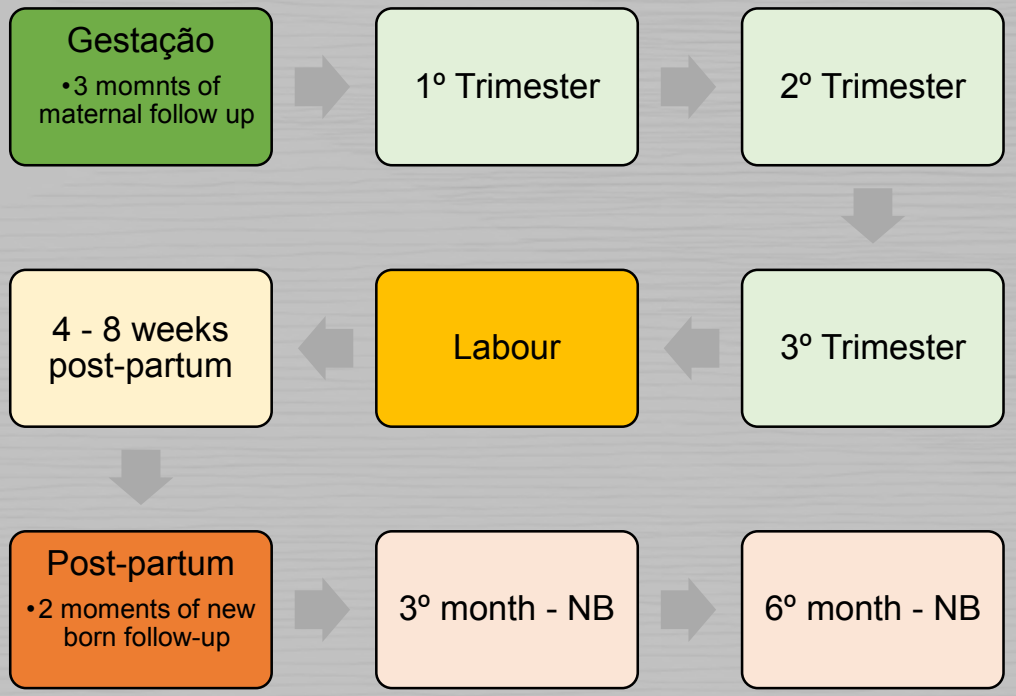
TTS post-COVID-19 vaccination with AstraZeneca/Oxford

~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 investiation 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



Pilot project, PAHO/CLAP, in 5 states of the county:

- RO, PE, DF, SP e RS
- Start date: 15/06

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Thank you!!!!!

ctoscano@ufg.br

Christine K. Olson MD, MPH

Captain, United States Public Health Service
Co-lead, v-safe pregnancy registry

Medical Officer, VAERS/ISO/DHQP/NCEZID

Centers for Disease Control and Prevention

TTS/pregnancy surveillance update US

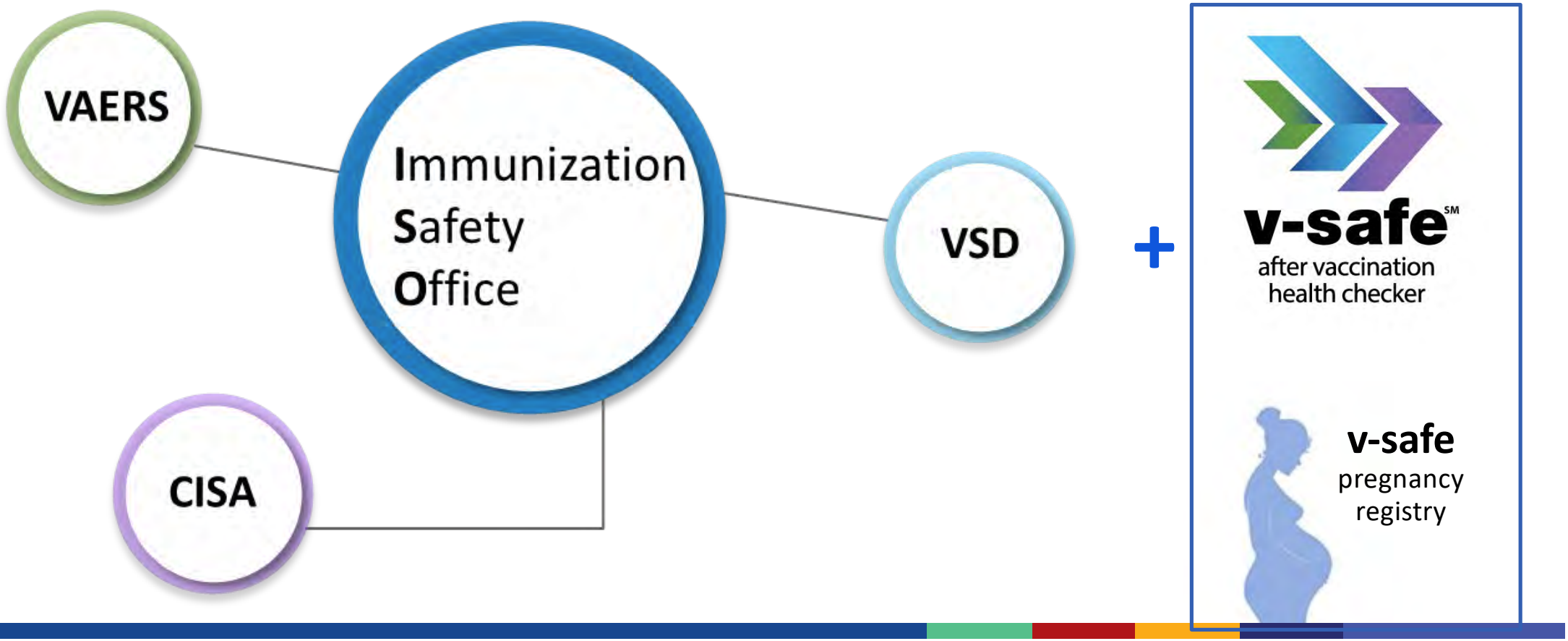
TTS/pregnancy surveillance update: United States

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



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

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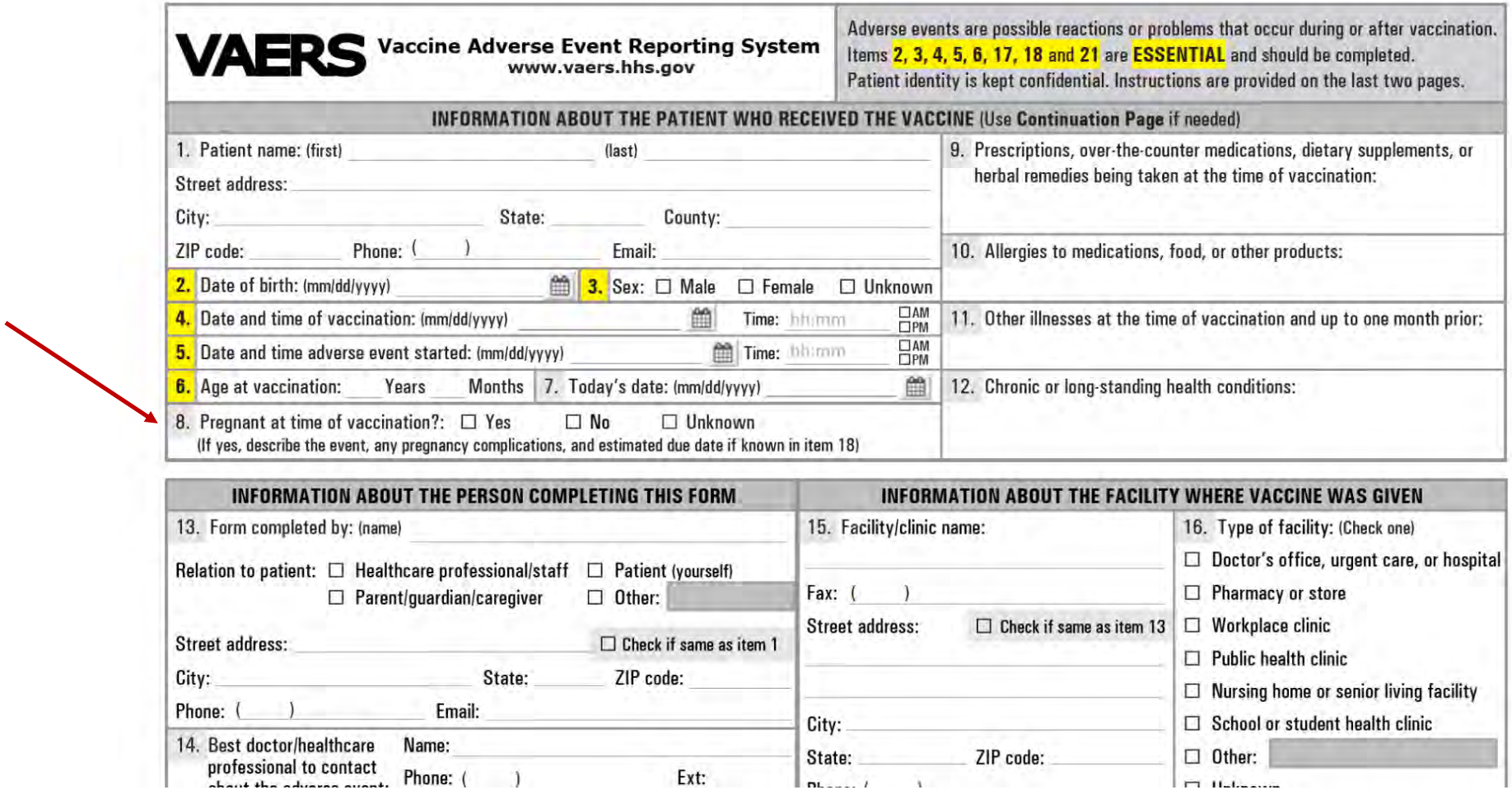
VAERS pregnancy identification



VAERS Vaccine Adverse Event Reporting System
www.vaers.hhs.gov

Adverse events are possible reactions or problems that occur during or after vaccination. Items **2, 3, 4, 5, 6, 17, 18** and **21** are **ESSENTIAL** and should be completed. Patient identity is kept confidential. Instructions are provided on the last two pages.

INFORMATION ABOUT THE PATIENT WHO RECEIVED THE VACCINE (Use **Continuation Page** if needed)

1. Patient name: (first) _____ (last) _____
Street address: _____
City: _____ State: _____ County: _____
ZIP code: _____ Phone: ( ) _____ Email: _____
2. Date of birth: (mm/dd/yyyy) _____ 3. Sex: ☐ Male ☐ Female ☐ Unknown
4. Date and time of vaccination: (mm/dd/yyyy) _____ Time: hh:mm ☐AM ☐PM
5. Date and time adverse event started: (mm/dd/yyyy) _____ Time: hh:mm ☐AM ☐PM
6. Age at vaccination: ___ Years ___ Months 7. Today's date: (mm/dd/yyyy) _____
8. Pregnant at time of vaccination?: ☐ Yes ☐ No ☐ Unknown
(If yes, describe the event, any pregnancy complications, and estimated due date if known in item 18)

9. Prescriptions, over-the-counter medications, dietary supplements, or herbal remedies being taken at the time of vaccination:

10. Allergies to medications, food, or other products:

11. Other illnesses at the time of vaccination and up to one month prior:

12. Chronic or long-standing health conditions:

INFORMATION ABOUT THE PERSON COMPLETING THIS FORM

13. Form completed by: (name) _____
Relation to patient: ☐ Healthcare professional/staff ☐ Patient (yourself) ☐ Parent/guardian/caregiver ☐ Other: _____
Street address: _____ ☐ Check if same as item 1
City: _____ State: _____ ZIP code: _____
Phone: ( ) _____ Email: _____
14. Best doctor/healthcare professional to contact about the adverse event: Name: _____ Phone: ( ) _____ Ext: _____

INFORMATION ABOUT THE FACILITY WHERE VACCINE WAS GIVEN

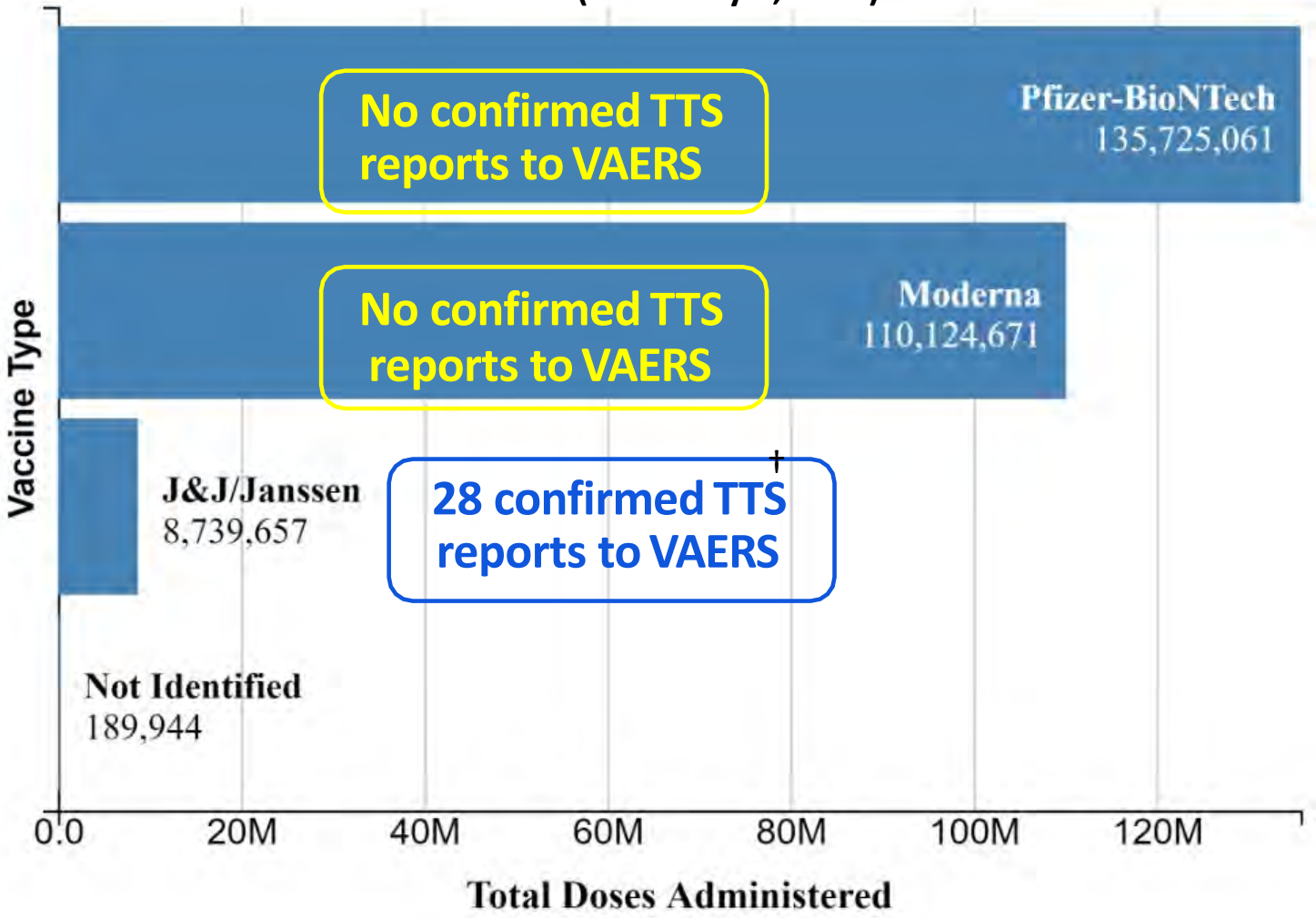
15. Facility/clinic name: _____
Fax: ( ) _____
Street address: ☐ Check if same as item 13 _____
City: _____
State: _____ ZIP code: _____

16. Type of facility: (Check one)
☐ Doctor's office, urgent care, or hospital
☐ Pharmacy or store
☐ Workplace clinic
☐ Public health clinic
☐ Nursing home or senior living facility
☐ School or student health clinic
☐ Other: _____

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)*



* Data source: 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

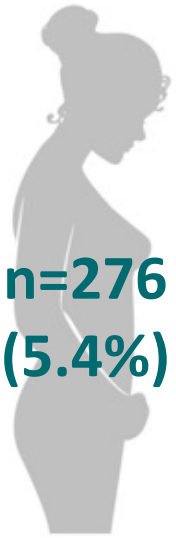
- **V-safe** participants who report pregnancy following COVID-19 vaccination are actively contacted to enroll in pregnancy registry*
- Outcomes of interest include miscarriage and still birth, pregnancy complications, maternal intensive care unit admission, adverse birth outcomes, neonatal death, infant 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

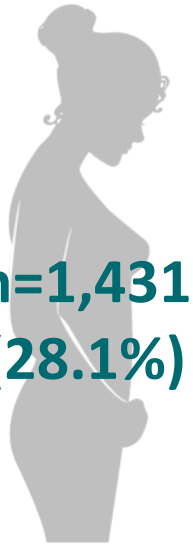
Timing of first eligible COVID-19 dose among v-safe pregnancy registry participants as of June 7, 2021

Among 5,095 pregnancies



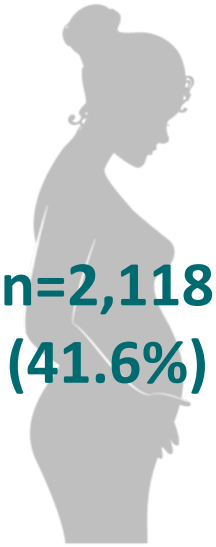
n=276 (5.4%)

Peri-conceptional



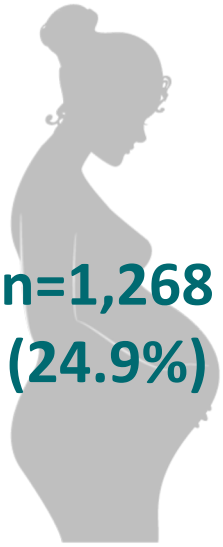
n=1,431 (28.1%)

First Trimester



n=2,118 (41.6%)

Second Trimester



n=1,268 (24.9%)

Third Trimester

Updated v-safe pregnancy registry participants as of June 7, 2021

Pfizer-BioNTech	Moderna	J&J Janssen	Total
N (%)	N (%)	N (%)	N (%)
2,585 (50.7)	2,234 (43.8)	276 (5.4)	5,095 (100)

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafepregnancyregistry.html

Resources

- CDC COVID Data Tracker https://covid.cdc.gov/covid-data-tracker/#vaccinations
- Vaccine Pregnancy Registry | CDC https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafepregnancyregistry.html
- V-safe https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html
- VAERS https://vaers.hhs.gov/
- VSD https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html
- CISA https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html
- Update: Thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination Advisory Committee on Immunization Practices (ACIP) May 12, 2021 https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf

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)
TTY: 1-888-232-6348 www.cdc.gov

Kelly Plueschke

Scientific Administrator

Data Analytics and Methods Task Force

European Medicines Agency

TTS/pregnancy surveillance update EMA

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)

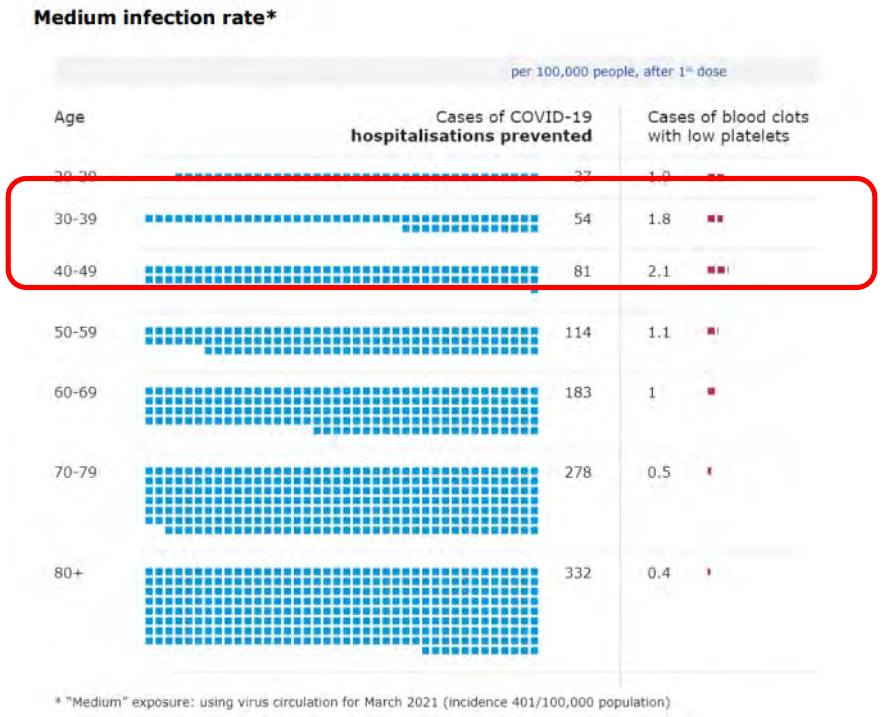
Vaxzevria: further advice to HCP on blood clots and low blood platelets – EMA 21/05/2021

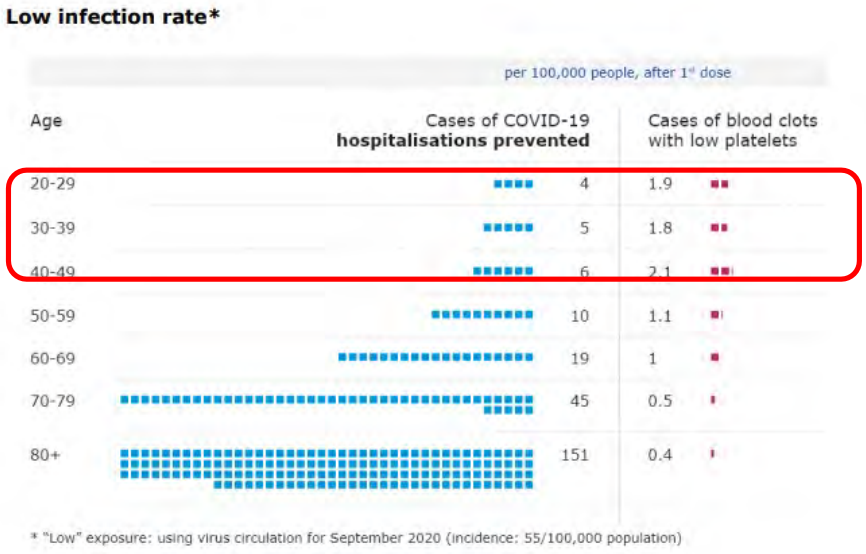
- Must not give Vaxzevria to anyone who has had blood clots with low blood platelets (thrombosis with thrombocytopenia syndrome, TTS) after receiving the vaccine.
- Should check for signs of blood clots in any person who has low blood platelets within 3 weeks of vaccination.
- Should check for signs 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

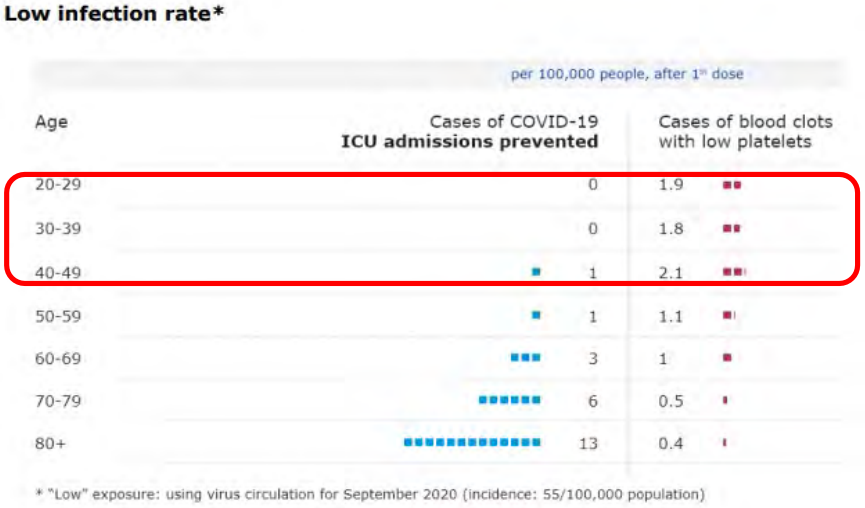
Contextualisation exercise

- 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)

Visuals benefit risk contextualisation







Benefits depending on age, infection rate and parameter of interest

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):

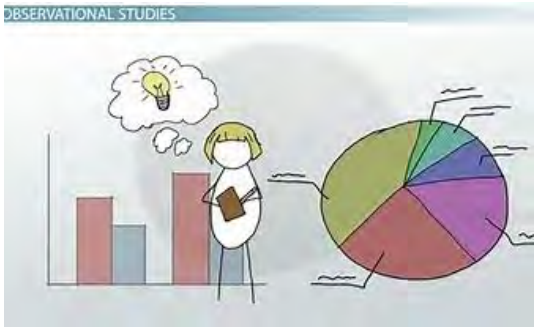
- Routine Pharmacovigilance activities
- Enhanced:
  - ❑ Monthly Summary Safety Reports including reports received during pregnancy
  - ❑ Prospective observational studies

Vaccines	vaccine	placebo	Total
Comirnaty – remained in trial, total	**7**	**8**	**15**
Spontaneous pregnancy loss	0	1	1
Withdrawn from trial	4	4	8
Moderna – no pregnancy-related trial withdrawals	**6**	**7**	**13**
Vaxzevria, total	**10**	**7**	**17**
Spontaneous loss	1	1	2
Elective termination of pregnancy	1	2	3
COVID-19 Vaccine Janssen, total	**4**	**4**	**8**
Spontaneous abortion and ectopic pregnancy	1 + 1	0	2
TOPs and incomplete abortion	0	2 + 1	3
Exposed during breastfeeding	128	157	285
Total included in trials	**27**	**26**	**53**

Vaccines	Post-authorisation studies
Comirnaty	• **Phase 2/3, Placebo-Controlled, Randomized**, 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 • **4000 healthy pregnant** women followed up until end of pregnancy and 6 months infants age
Moderna	• **Prospective observational pregnancy outcome study (IQVIA)** to evaluate impact of exposure on pregnancy complications and birth outcomes • **600 pregnant women** followed up until end of pregnancy and 12 months infants age
Vaxzevria	• **Phase IV Enhanced Active Surveillance Study including pregnancy sub-cohort and Prospective observational pregnancy registry (C-VIPER)** to estimate the risk of obstetric outcomes and infants outcomes among vaccinated pregnant women relative to non-vaccinated pregnant women • Pregnancy registry: **500 pregnant women** followed up until end of pregnancy and 12 months infants age
COVID-19 Vaccine Janssen	• **Open-label, Phase 2 Study** to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26.COV2.S in Healthy Pregnant Participants - HORIZON 1 • **400 pregnant women** followed up until end of pregnancy and 12 months

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 ne**onatal 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
Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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Back up slides - CONSIGN

Contributing organizations

- University Medical Center Utrecht, Utrecht, the Netherlands (UMCU)
- UKOSS, NPEU, University of Oxford, ITOSS, 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 (FICF)
- 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

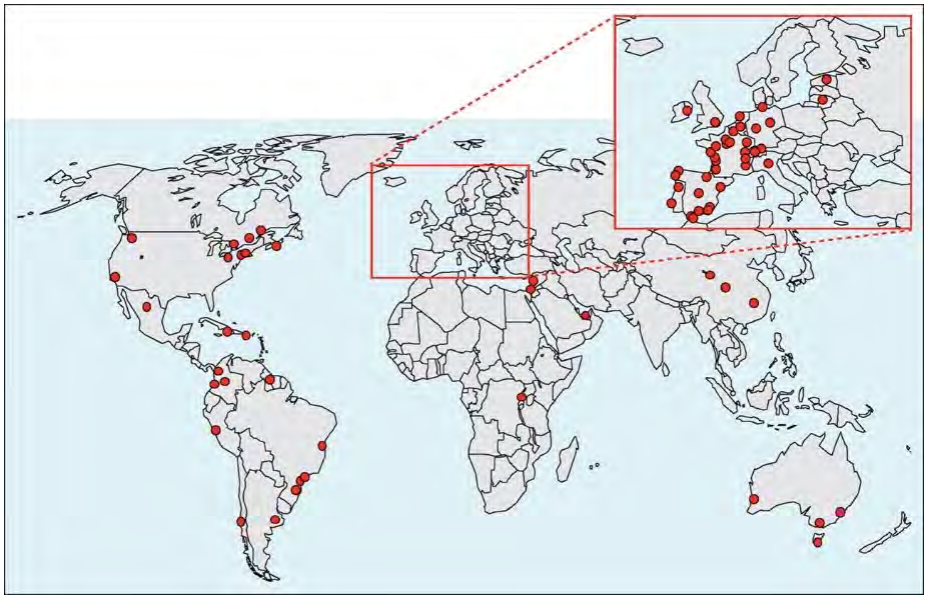
- **International collaboration to increase study power: discussions with ICMRA technical WG on feasibility to implement the CONSIGN protocol in their region (e.g. FDA-Sentinel)**

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

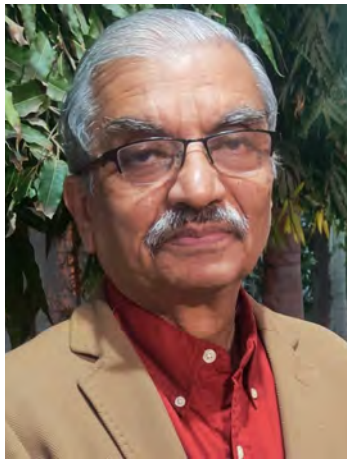
CONSIGN project

- **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

TTS/pregnancy surveillance update India

Maternal Immunization in India
Decision to Include Pregnant Women for COVID 19 Vaccines (COVISHIELD & COVAXIN)

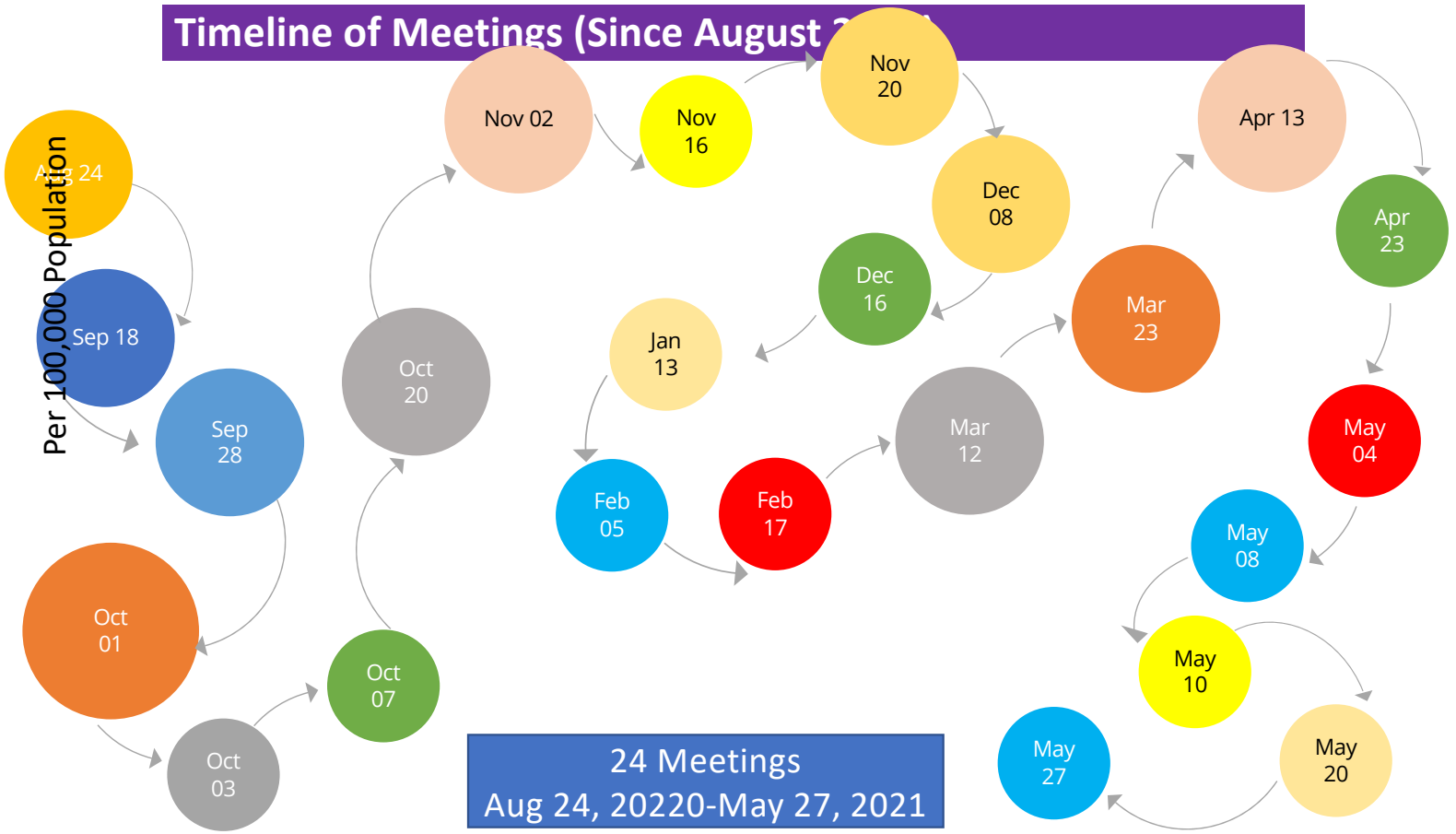
Narendra Arora

COVAX Working Group

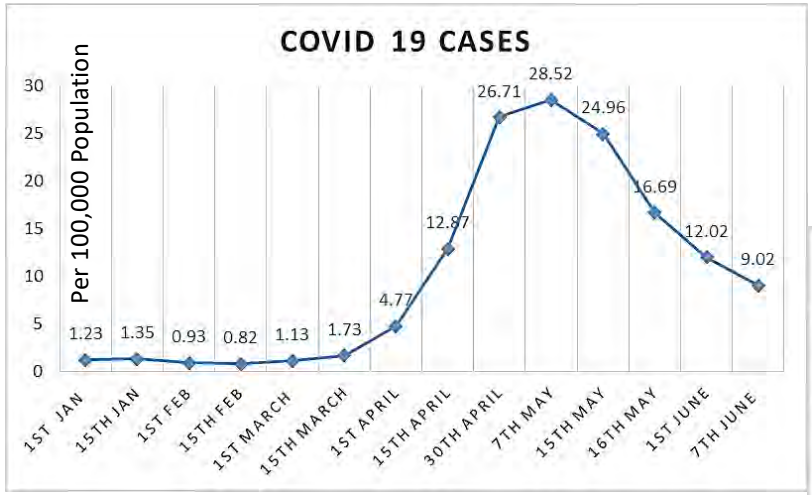
Wednesday, 9th June, 2021

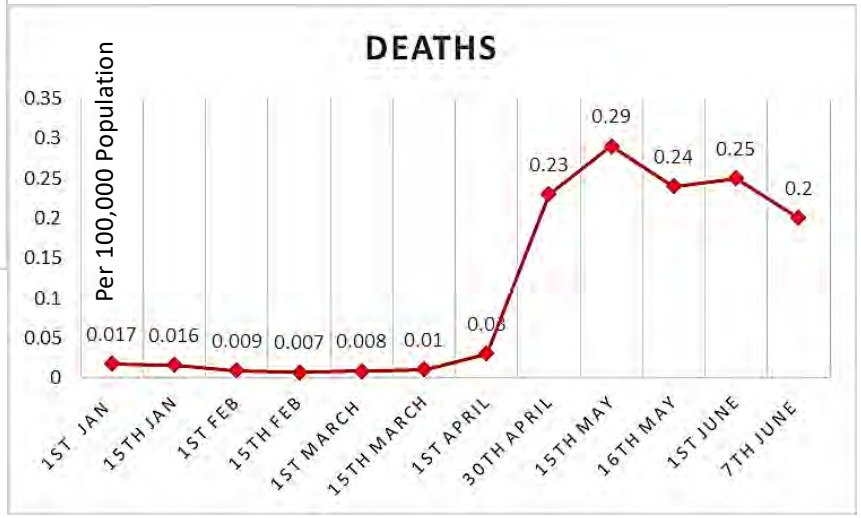
COVID 19 Working Group of NTAGI

- **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
Per 100,000 Population
Aug 24
Sep 18
Sep 28
Oct 01
Oct 03
Oct 07
Oct 20
Nov 02
Nov 16
Nov 20
Dec 08
Dec 16
Jan 13
Feb 05
Feb 17
Mar 12
Mar 23
Apr 13
Apr 23
May 04
May 08
May 10
May 20
May 27
24 Meetings
Aug 24, 20220-May 27, 2021

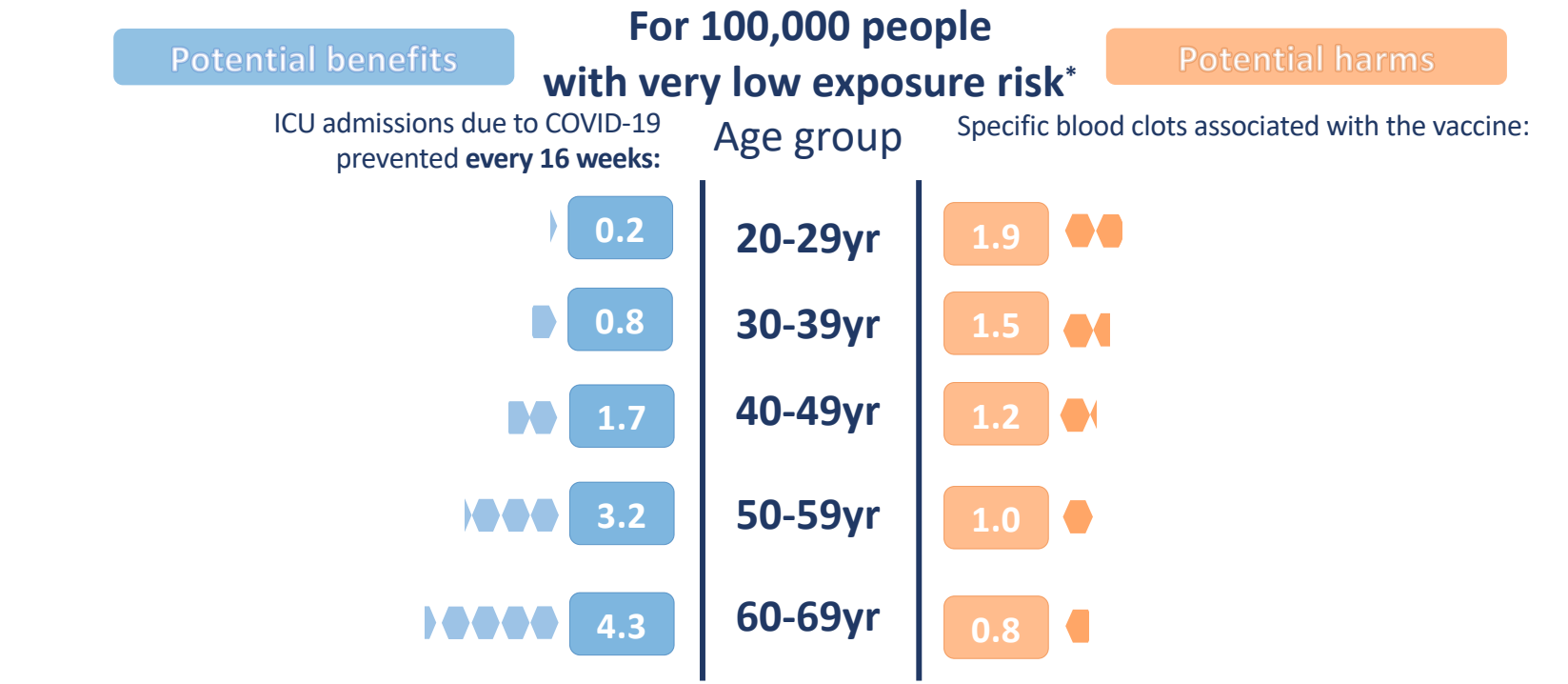
Progression of Second Wave of Covid-19 Pandemic in India
(1st Jan 2021 – 7th June 2021)





COVID 19 Vaccine Eligibility for Pregnant Women

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



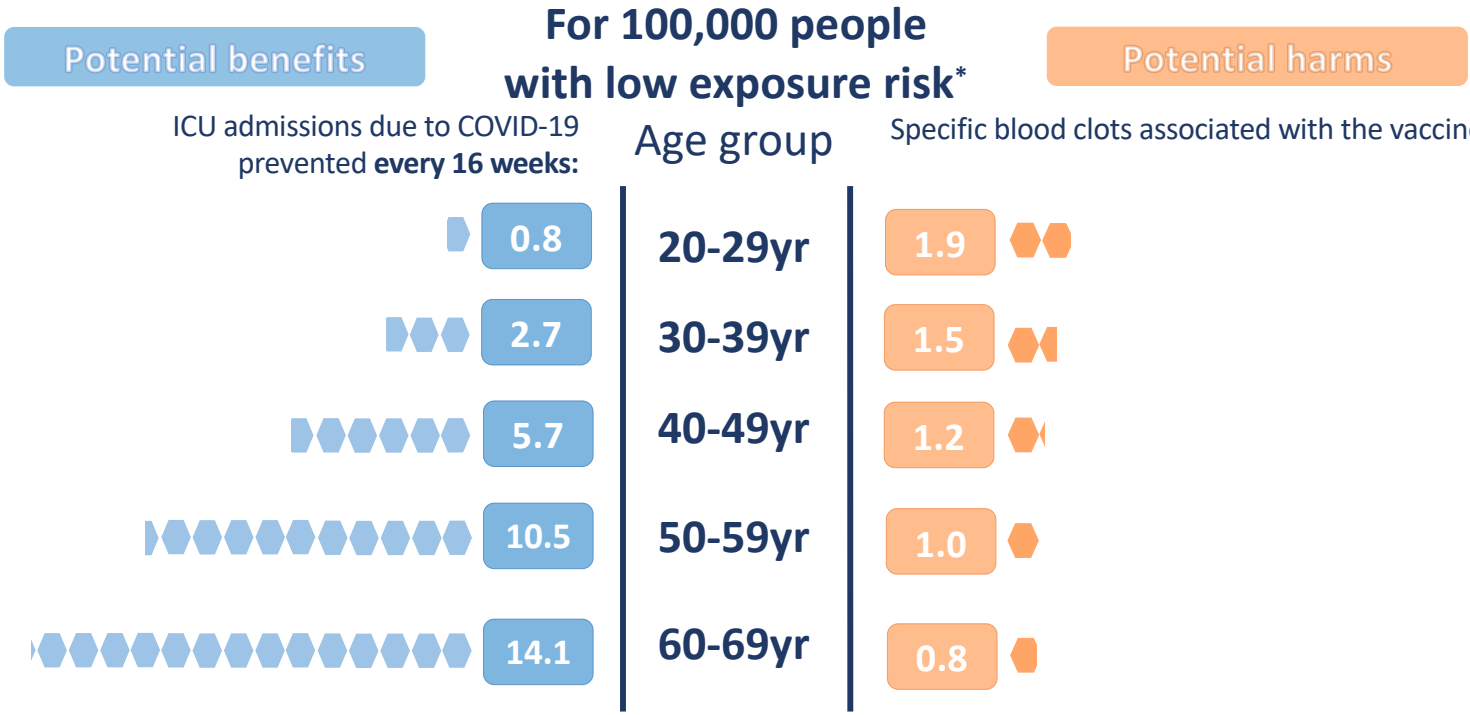
Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission

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 0.6 per 10,000 per day (42 per 100,000 per week): roughly UK in April 2021***

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



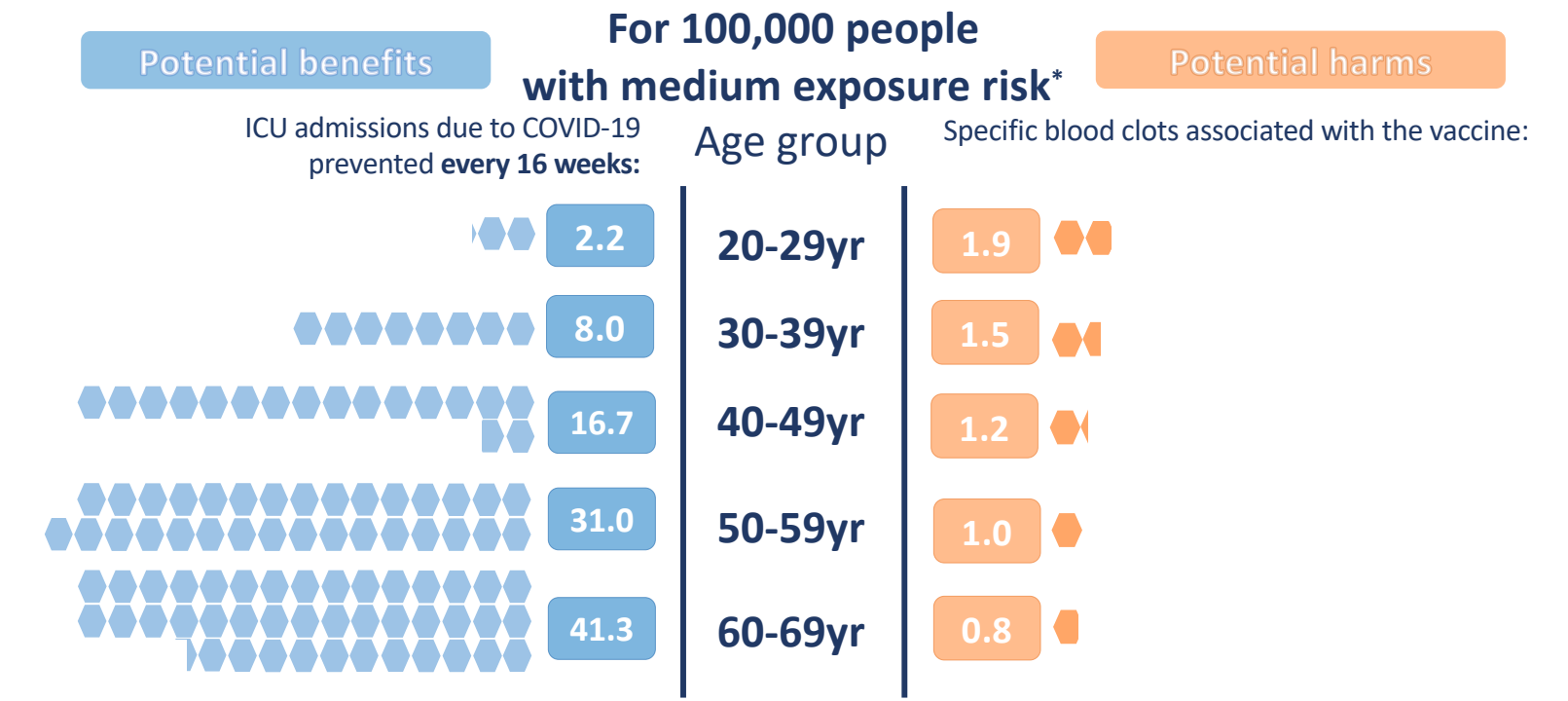
Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission

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 2 per 10,000 per day (140 per 100,000 per week): roughly UK in March 2021***

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



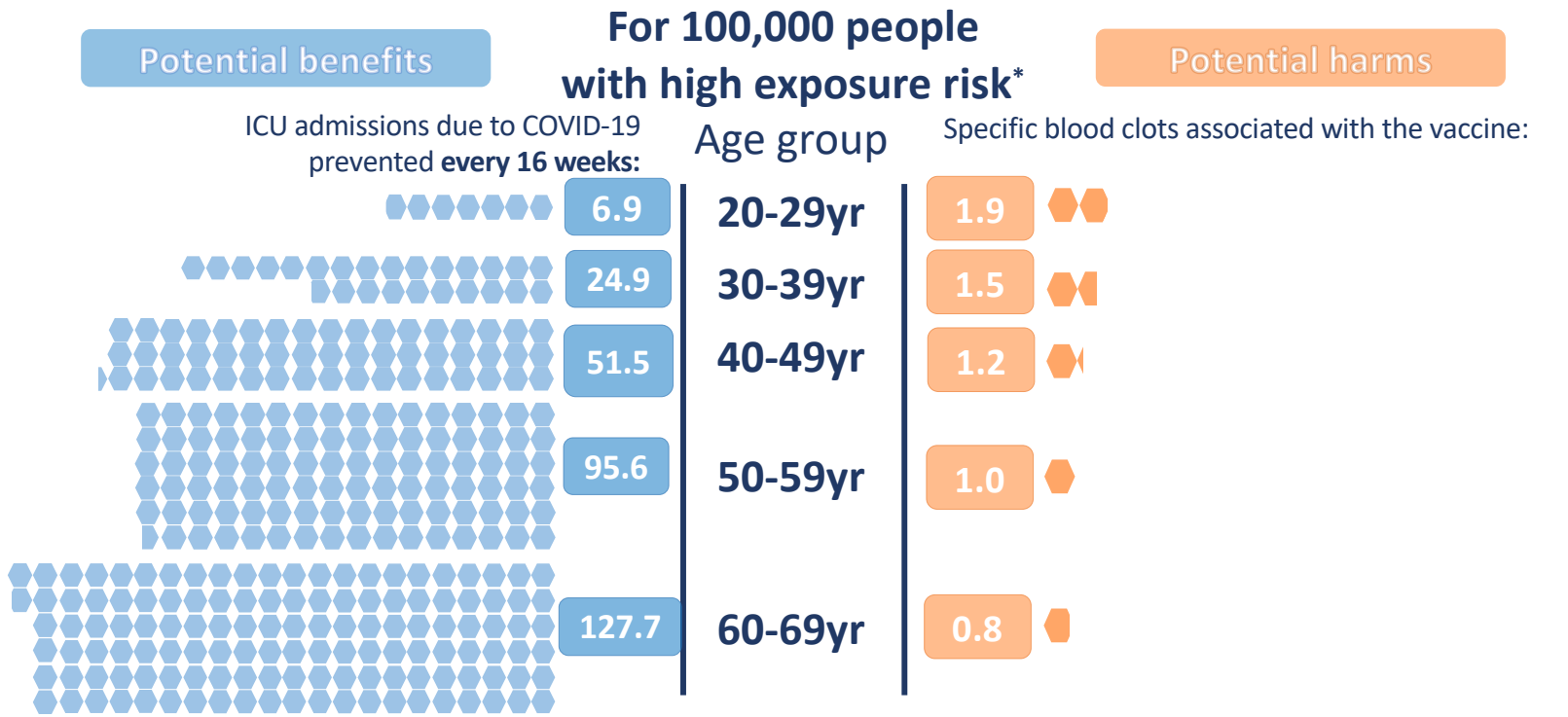
Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission

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 6 per 10,000 per day (419 per 100,000 per week): roughly UK in February 2021***

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



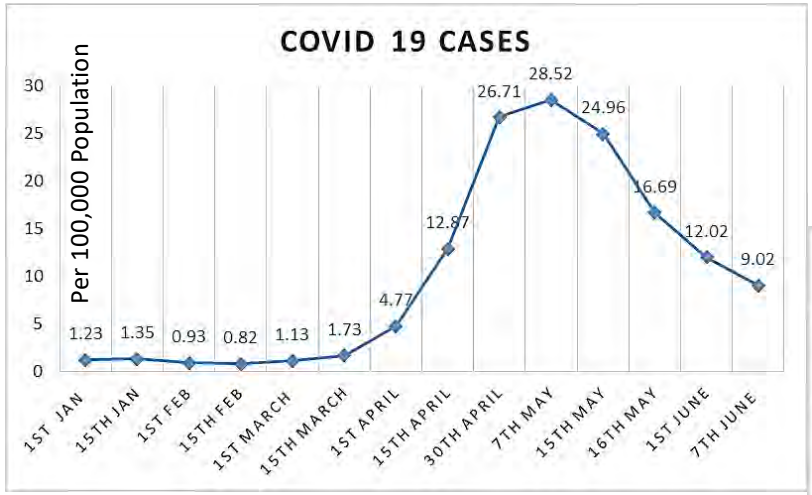
Other potential benefits not shown include prevention of COVID-19 cases not leading to ICU and reduction of transmission

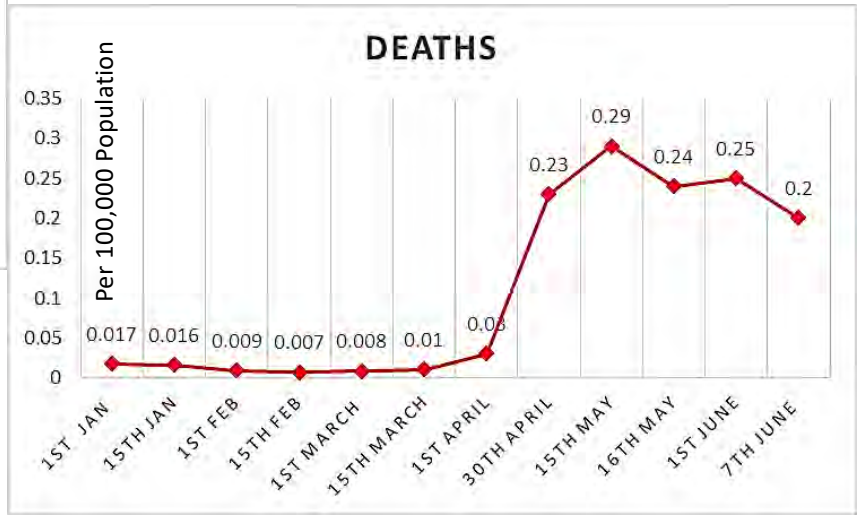
Other potential harms not shown include short-term side effects
Data from reactions to first dose only

Data from UK up until 28th April 2021

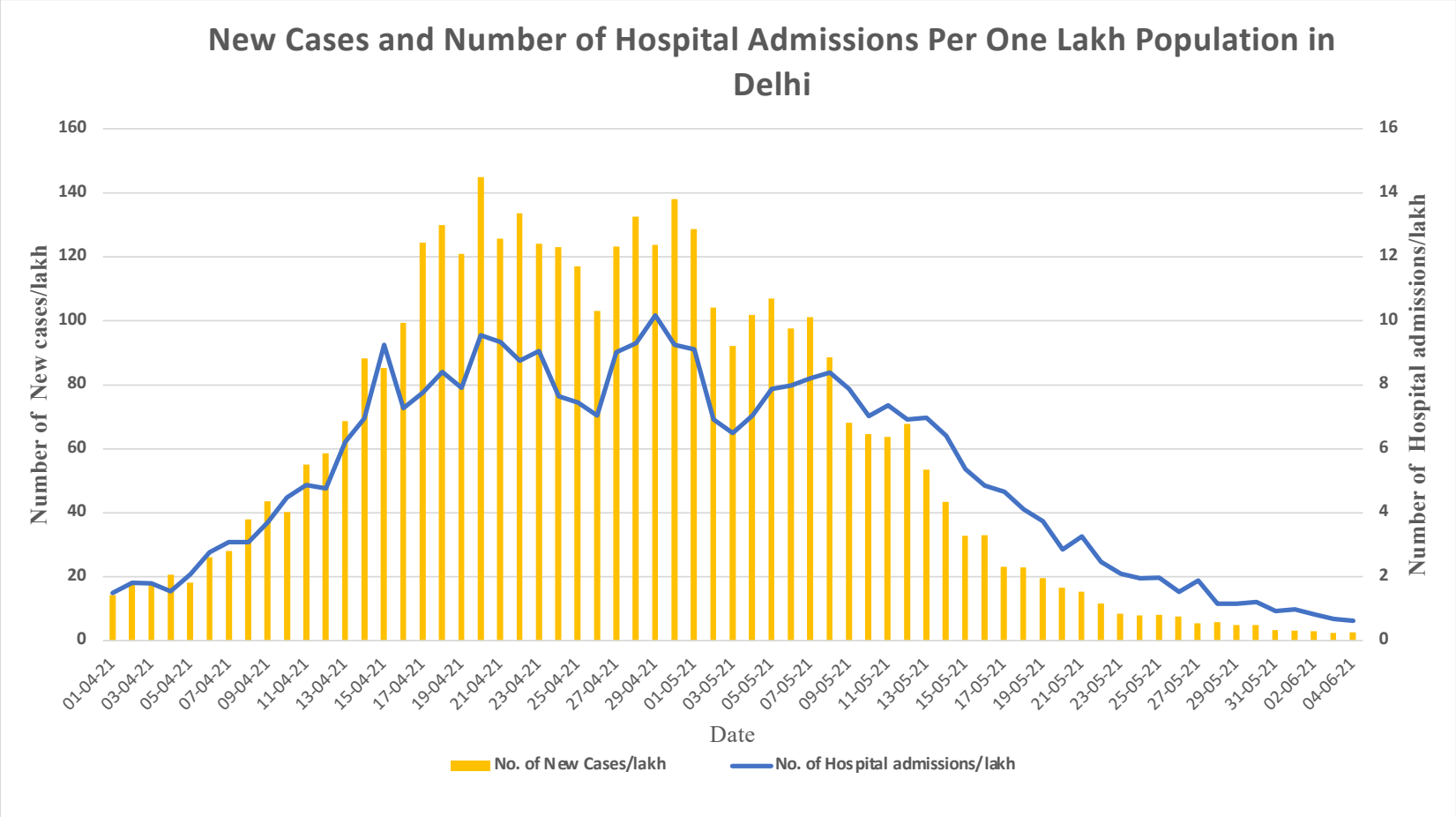
**** Based on coronavirus incidence of 20 per 10,000 per day (1391 per 100,000 per week): roughly UK at peak***

Progression of Second Wave of Covid-19 Pandemic in India
(1st Jan 2021 – 7th June 2021)





Delhi COVID 19 Cases & Hospitalization (1st April to 4th June 2021)



COVISHIELD in Pregnant Women

May 12, 2021
6:42 PM IST

Healthcare & Pharmaceuticals

Brazil suspends use of AstraZeneca vaccine in pregnant women nationally after death

3 minute read

Pedro Fonseca, Ricardo Brito

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.

SUMMARY

- 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
  - Intial 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)

SUMMARY

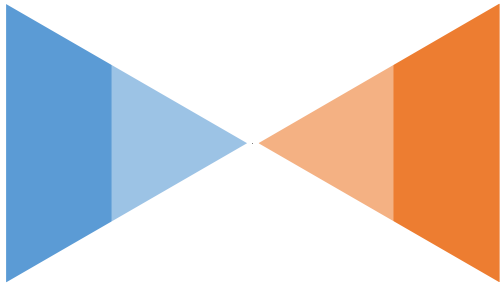
- Considering the current situation of the pandemic, WG & STSC recommended pregnant women should not be excluded from vaccination.
  - Exposure probability is very high: benefit>>risk
  - Before vaccination, pregnant women should be fully informed that the long-term adverse reactions are unknown and 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 Haldar

DBT

- Dr Alka Sharma
- Dr Jyoti Logani

ICMR

- Dr Samiran Panda
- Dr Nivedita Gupta

Immunization Division, MoHFW

- Dr M K Aggarwal
- Dr Veena Dhawan

NTAGI Secretariat

- Dr Dinesh Paul
- Dr Awnish Kumar Singh

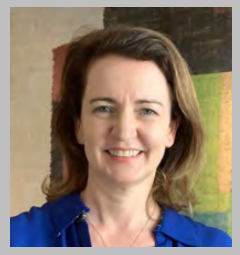
Thank You

Experts' roundtable

Members

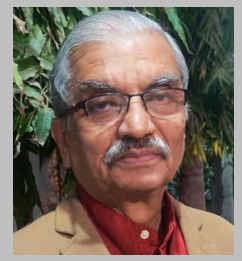
Jeff Roberts

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

Ajoke Sobanjo-ter Meulen

Flor Munoz

Concluding remarks

Maternal Immunization Working Group

Clinical Development & Operations SWAT Teams