MEETING REPORT — 9 June 2021

COVAX: MATERNAL IMMUNIZATION WORKING GROUP WEBINAR

EXPERT CONSULTATION ON POST-VACCINE THROMBOSIS THROMBOCYTOPENIA SYNDROME & IMPACT ON MATERNAL IMMUNIZATION

EXECUTIVE SUMMARY

On 9th June 2021, the COVAX Maternal Immunization Working Group, co-chaired by Ajoke Sobanjo ter-Meulen, MD and Flor Munoz, MD, held a virtual meeting on post-vaccine thrombosis thrombocytopenia syndrome (TTS) and the impact on maternal immunization.

OVERVIEW: SESSION 1

The first session focused on vaccine safety surveillance, the safety profiles of adenovirus-vectored vaccines, the theory of how TTS/vaccine-induced thrombosis and thrombocytopenia (VITT) develops, and an overview of thrombosis and thrombocytopenia in pregnancy. After an introduction by Dr Sobanjo-ter Meulen, Dr Kathryn Edwards, Professor of Pediatrics at Vanderbilt University School provided an overview of vaccine safety surveillance with a focus on the early experience from the US. She provided an overview of the four parts of the vaccine safety surveillance system in the US – v-safe, the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA) project. She provided data on the cases of cerebral venous sinus thrombosis (CVST) reported in the US after receipt of the Janssen vaccine, which were very similar in characteristics to those reported after AstraZeneca vaccination in Europe.

Dr David Kaslow, Chief Scientific Officer at PATH, then provided an overview of the safety profile of adenovirus-vectored vaccines, focusing on hAd5, hAd26, and ChAdY25 and platelets and coagulation factors associated with thrombosis and/or thrombocytopenia. Both adenoviruses and adenovirus vectors are associated with hematological effects including thrombocytopenia. Adenovirus vectors differ in genetic structure, with different deletions used in first and next generations vectors. There is extensive clinical experience to date with hAd5, hAd26, and ChAdOx1as vectors in other vaccines, including Ebola, HIV, MERS, RSV, influenza, Zika, malaria, and tuberculosis. There appears to be a route and dose-dependency to thrombocytopenia with the first generation adenovectors. Preclinical toxicology data from adenovirus type 5 and type 35 and chimpanzee type 3 vectored vaccines showed uniform decreases in platelet counts, elevated activated partial thromboplastin time (aTTT), shortened prothrombin time, and elevated fibrinogen which were judged extremely mild and not likely to be clinically significant. Unlike mRNA vaccines, adenovirus-vectored vaccines need to be transcribed in the nucleus. Multiple types of alternative splicing in nuclear pre-mRNA have been observed in vitro, and it could be that these aberrant spike proteins bind to a variety of tissues mediating an inflammatory response.

Professor Andreas Greinacher, Head of Transfusion Medicine at Greifswald University of Medicine provided an overview of the mechanism of VITT. VITT, like autoimmune heparin-induced thrombocytopenia, is mediated by platelet-activating anti-platelet factor 4 (PF4) antibodies. Professor Greinacher and his colleagues investigated vaccine, PF4, and VITT patient-derived anti-PF4 antibody interactions using dynamic light scattering, 3D-super-resolution microscopy, and electron microscopy. Mass spectrometry was used to analyze vaccine composition. They investigated the mechanism for early post-vaccine inflammatory reactions as potential co-stimulant for anti-PF4 immune response, and they evaluated VITT antibodies for inducing release of procoagulant DNA-containing neutrophil extracellular traps (NETs), and measured DNase activity in VITT patient serum. Biophysical analyses showed formation of complexes between PF4 and vaccine constituents, including virus proteins that were recognized by VITT antibodies. EDTA, a vaccine constituent, increased microvascular leakage in mice allowing for circulation of virus- and virus-producing

cell culture-derived proteins. Antibodies in normal sera cross-reacted with human proteins in the vaccine and likely contribute to commonly observed acute ChAdOx1 nCov-19 post-vaccination inflammatory reactions. Polyphosphates and DNA enhanced PF4-dependent platelet activation by VITT antibodies. In the presence of platelets, PF4 enhanced VITT antibody-driven procoagulant NETs formation, while DNase activity was reduced in VITT sera, with granulocyte-rich cerebral vein thrombosis observed in a VITT patient. They concluded that ChAdOx1 nCoV-19 vaccine constituents (i) form antigenic complexes with PF4, (ii) EDTA increases microvascular permeability, and (iii) vaccine components cause acute inflammatory reactions. Antigen formation in a proinflammatory milieu offers an explanation for anti-PF4 antibody production. High-titer anti-PF4 antibodies activate platelets and induce neutrophil activation and NETs formation, fueling the VITT prothrombotic response.

Dr Annemarie Fogerty, Director of Reproductive Hematology at Massachusetts General Hospital concluded the presentations for the first session with a discussion on the mechanisms which can lead to thrombosis or thrombocytopenia during pregnancy. Thrombocytopenia affects approximately 10% of pregnancies and etiologies can be quite varied: these can be pregnancy-specific, including gestational thrombocytopenia, pre-eclampsia/HELLP, or acute fatty liver disease of pregnancy; or pre-existing (e.g., lupus, immune thrombocytopenic purpura [ITP], liver disease, von Willebrand disease type 2B); or can be newly acquired during pregnancy. Normal pregnancies have an average decline in platelets of 10–13%. Dr Fogerty described the features of gestational thrombocytopenia and pre-eclampsia, which are the most common causes of thrombocytopenia in pregnancy. Thrombosis increases in pregnancy as estrogen promotes coagulation by increases in fibrinogen, vWF and factors II, VII, VIII, IX, and X, and decreases anticoagulant mechanisms leading to an increased resistance to activated protein C and decrease in protein S. Pregnancy is also a hypercoagulable state due to anatomical changes, thus the risk of venous thromboembolism is 6–10 fold higher in pregnancy compared with age-matched non-pregnant females. Heparin-induced thrombocytopenia (HIT) during pregnancy is extremely rare, possibly because heparin is not commonly used during pregnancy.

A panel discussion then followed focusing on the following questions:

1. **Can we reach a consensus on the mechanisms involved in post-vaccination TTS?**
2. **Is there an increased risk of TTS in pregnant women or women of child-bearing age?**

The key points from the discussion were:

- Ongoing studies show that high titers of responsive anti-PF4 antibodies occurring 5–10 days after vaccination are the key factor for VITT or TTS development. This doesn't exclude very rare cases where individuals have other antibodies but these will be very difficult to find in such small numbers of people.
- Thrombotic events are seen with other (non-adenovirus-vectored) vaccines but they have different clinical presentations.
- It should be noted that low avidity anti-PF4 antibodies are found in about 5–8% of recipients of other vaccines, as seen in healthy blood donors. Therefore, screening for presence of anti-PF4 antibodies using highly sensitive ELISAs will not be beneficial and likely not of clinical relevance.
- Anti-PF4 response is thought to be extremely rare in pregnancy and pregnant women are not at high-risk of developing these strong pro-thrombotic antibodies. It is not expected that rates of VITT would be higher than the general population.
- The greatest potential risk to the fetus is placental thrombosis from pro-thrombotic anti-phospholipid antibodies. However, there has been no reports of this to date.
- Data are needed on which host factors might amplify the route and dose-dependent effects of adenovirus, and what effects there are at the dose level in use for COVID-19 vaccines. While enough evidence exists to defensibly speculate that adenovectors can initiate and/or induce thrombocytopenia and/or thrombosis, an absence of data in humans leaves open whether there's an increased risk at the dose and by the route of administration for vaccine use cases. Therefore, including some obvious additional

biomarkers in safety studies in women of childbearing age and pregnancy would seem prudent to address this evidence gap, and could be applicable beyond COVID-19 vaccines.

- Pre-clinical data on adenovirus vectors has shown that biodistribution is generally limited to the injection site draining lymph nodes, and, for some adenoviruses (e.g., adenovirus 5), the liver.
- LMICs have limited diagnostic and treatment capabilities for VITT, and there is limited information on the risk of VITT or TTS in co-infections such as malaria.
- There are limited data available on pregnancy-associated COVID-19 risk in LMICs. Pregnant women may also not have access to healthcare providers with enough knowledge to advise them about the benefits of vaccination versus risk of COVID-19 or TTS risk.
- HIT is very rare in pregnancy, but it can't be assumed that pregnant women are protected against VITT. The rarity of HIT is influenced by the absence of heparin use in pregnancy.
- With HIT, there needs to be a triad of features: heparin plus activated platelets plus PF4 antibody development.
- WHO SAGE are currently updating pregnancy recommendations and discussing moving pregnant women higher up the priority-use group list (Stage 2 instead of Stage 3), given the increased risk of severe COVID-19 disease in pregnant women compared to non-pregnant women with similar COVID-19 risk factors.

OVERVIEW: SESSION 2

The second session focused on updates on pregnancy and TTS surveillance in the UK, Brazil, the US, the EMA, and India.

Dr Katherine Donegan, Pharmacoepidemiology Research and Intelligence Manager at the Medicines and Healthcare products Regulatory Agency (MHRA) provided an overview of the UK data. Up to 28th May 2021, 348 cases of TTS have been reported (330 after the first dose or unknown, 18 after the second). Of these 128 were CVST (28% fatal) and 220 were non-CVST (11% fatal). Overall incidence rate was 13.6 per 1,000,000 after the first dose and 2.4 per 1,000,000 after the second dose. Incidence rates were higher in people aged 18–49 years (18.0/1,000,000 first doses) compared with those aged 50+ (10.2/1,000,000 first doses). But there was not a statistically significant difference in incidence between women (19.9/1,000,000) and men (15.8/1,000,000). Vaccine surveillance in the UK includes a four-tiered approach from the MHRA which includes enhanced passive surveillance, targeted active surveillance (yellow card vaccine monitor), rapid cycle analysis in the clinical practice research datalink database, and epidemiology studies, including in pregnancy. No cases of TTS have been reported in pregnancy in the UK. One case has been reported 5 weeks post-delivery, and 2 cases of DVT and pulmonary embolism have been reported, but did not meet the case definition for TTS. There have been no signals of miscarriages or stillbirths.

Dr Cristiana Toscano, Professor at the Federal University of Goiás, Brazil provided an overview of the vaccine surveillance system findings in Brazil, including a case report of a pregnant woman and her fetus who died from TTS following vaccination. By mid-May 2021, the incidence of laboratory confirmed COVID-19 in pregnant women was 257.9 per 100,000, and mortality rates due to COVID-19 were 20.3 per 100,000 pregnant women. Evidence from the literature indicates that mortality rates among pregnant and postpartum women is high among those with COVID-19, particularly in regions where maternal mortality rates are already high. For this reason, Brazil expanded COVID-19 vaccination to all pregnant and postpartum women as of April 26th, 2021. Up to 6th June 2021, 126,185 doses of COVID-19 vaccines had been administered to pregnant and postpartum women, including 124,890 first doses and 1,295 second doses, and including Pfizer, AstraZeneca or Sinovac vaccines. When evaluating post-vaccination adverse events from the national surveillance system, a considerably higher rate of events overall, and severe events in particular, have been reported in pregnant women when compared to rates in the general population. On 14th May 2021, COVID-19 vaccination was suspended for pregnant women, except those

with other high-risk conditions, following the death of a 35-year-old pregnant women at 23 weeks gestation who presented with TTS. For those who received the first dose only and for high-risk pregnant women, the second dose should be administered in the post-partum period. Brazil has a strong passive vaccine safety surveillance system in place. However, sensitivity of the surveillance system and the capacity to investigate TTS suspected events is likely not homogeneous across the whole country. Additional challenges include quality of local investigational procedures, particularly in poorer, remote areas. An active prospective surveillance system including follow-up of pregnant women in pregnancy and postpartum period, and their offspring, is being implemented in the country in pilot sites.

Dr Christine Olson, co-lead of the v-safe pregnancy registry and Medical Officer at VAERS, the Immunization Safety Office (ISO), and the National Center for Emerging and Zoonotic Infections at the CDC presented an update on the TTS and pregnancy surveillance data in the US. She provided an overview of the four vaccine safety monitoring systems under the ISO (VAERS, CISA, VSD, and v-safe). As of 7th May 2021, 28 confirmed TTS cases were reported to VAERS, all after receipt of the Janssen vaccine. Of these cases, 22 occurred in females, median age was 40 years and median time from vaccination to symptom onset was 9 days. Nineteen of the cases had CVST. None were pregnant or postpartum (up to 12 weeks after delivery). To date, there have been no reports of TTS in the v-safe pregnancy registry.

Dr Kelly Plueschke, Scientific Administrator at the EMA provided an overview of TTS and pregnancy surveillance following COVID-19 vaccine receipt in European Economic Area (EEA) Member States. In a contextualization exercise which aimed at providing more specific recommendations to guide vaccination programs in Member States, the risk of TTS following AstraZeneca COVID-19 vaccine administration was put in the context of the benefit of the vaccine for different age groups, and the different rates of infection, with higher risks of TTS in younger people at low infection rates. Following the exercise, most Member States restricted the use of AstraZeneca COVID-19 vaccine in the younger population, with age cut-offs varying across countries. The EMA performs continuous characterization of the risk and re-evaluation as new evidence arises. This includes routine pharmacovigilance activities, monthly summary safety reports, and performance of prospective observational studies. The EMA is also performing and planning observational studies using real-world data, including the CONSIGN project and a two-year vaccine safety monitoring study assessing long-term effects of the vaccines.

Dr Narendra Kumar Arora, Executive Direction of the INCLEN Trust International provided an update on maternal immunization in India with COVID-19 vaccines. Given the high case and mortality rates experienced during the second COVID-19 wave in India, the COVID-19 working group of the National Technical Advisory Group on Immunization (NTAGI) and STSC now recommends pregnant women should not be excluded from vaccination, as exposure probability is very high. At the time of the workshop this vaccine policy recommendation had not yet been endorsed by the government. All lactating women are eligible to receive a COVID-19 vaccine any time after delivery, and COVID-19 vaccines can be given any time during pregnancy. 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 adenovirus-vectored vaccines e.g., thrombosis and thrombocytopenia may be developed. Studies will also be immediately put in place to monitor the safety of adenovirus-vectored COVID-19 vaccines in pregnant women.

A second panel discussion then followed.

The key points raised in the discussion were:

- Risk from COVID-19 is currently much higher than risk of TTS due to pregnancy and/or vaccination, but this is dependent on population infection risk
- Most countries do not have capacity to diagnose and treat TTS, particularly in LMICs who also experience limited supply and vaccine options. Even in high-income countries (HIC), VITT and TTS are difficult to diagnose and very rarely seen by healthcare professionals treating pregnant women. Enhanced diagnostic and treatment capacity, together with

routine training of healthcare professionals to consider TTS is important.

- Benefit/risk assessment should be performed within individual settings, and guidance should not differ between LMICs and HICs based on diagnostic and treatment capacities.
- A systematic and inter-institutional review of data from existing surveillance systems in pregnant women who have been vaccinated in countries which predominantly use adenovirus-vectored COVID-19 vaccines would help drive evidence-based decisions.
- Paradox that countries which are least able to treat TTS are likely to primarily receive adenovirus-vectored vaccines. Provision of alternative vaccines is preferred, where and when an option.
- From a regulatory perspective, no increased risk is perceived to pregnant versus non-pregnant women at present. If this changes, labelling can be updated accordingly. It is possible that TTS is occurring on a spectrum but only severe cases are reported, in which case, more data may provide evidence of this.
- There is no clear increased risk of TTS in pregnancy, and there may be a decreased risk.
- Currently no underlying risk factors for VITT have been identified, and risk factors for thrombosis (e.g., Factor V Leiden) were not associated with VITT. Synergy between multiple factors may play a role but no published cases had underlying thrombophilia.
- The underlying comorbidities (e.g., obesity) associated with reported VITT cases are very common, which would result in large screening campaigns for very few cases (which may be missed as the patient may not have the risk factor). Approximately half of all women are overweight or obese during pregnancy. Additionally, comorbidities such as obesity are already risk factors for severe COVID-19 so women at greatest risk of severe disease may be excluded.
- It is not feasible to screen everyone who presents with headaches, as it is an incredibly common symptom. However, healthcare providers should be educated to not dismiss headaches.
- In VITT, the antibodies are so pro-thrombotic and super-strongly platelet activating that they are the driving force – other pro-thrombotic risk factors are just minor players. They may slightly modulate outcome but don't drive immune response or outcome.
- Collaboration with reference laboratories would aid in sample processing and confirmatory tests, particularly in areas where facilities are not available.

KEY FINDINGS AND NEXT STEPS

Key findings from both sessions and next steps are summarized in the tables below.

Key Findings from the Webinar

- Benefit/risk assessment is key: hypothetical COVID-19 risk is higher than vaccine-associated risks in most epidemiologic settings with community transmission of SARS-CoV-2
- TTS is extremely rare and the phenotypes of people at risk is currently unknown
- COVID-19 severity in some countries is high, particularly in pregnancy
- No data indicating increased TTS risk in pregnancy. Unlikely that there is a synergy of pro-thrombotic factors specific for outcomes post-vaccination in pregnancy
- Post vaccination safety data are scarce in pregnant women from LMICs: this needs to be addressed with studies, including active surveillance studies
- From the TTS/VITT perspective, it is important that early diagnostic algorithms and diagnostic tests be made available, which are suitable for LMIC settings, so that if such TTS/VITT cases occur, they will be suspected, diagnosed, and treated properly
- Pathogenesis studies should take into consideration comorbidities typical of LMIC, such as malaria
- Decision-makers may be shifting risk-benefit equation due to risk of being unable to detect or treat TTS, particularly in areas where no alternative vaccines are available

Next Steps

- Collect further data on the prevalence of COVID-19 cases and pregnancy outcomes, particularly in LMICs
- Gather information on which resources are needed to aid in diagnosis and treatment of TTS in countries/regions lacking facilities, and whether partnerships with other organizations (e.g., labs) can aid in this
- Further examine existing pregnancy surveillance data available in countries where adenovirus-vectored vaccines have been administered to pregnant women
- Enhance training of healthcare professionals in risks of COVID-19, benefits of vaccination, consideration of TTS, and identification of TTS symptoms
- Expand supply of different vaccines to LMICs/COVAX recipients
- No regulatory change at this point but may be considered in future if evidence of increased risk in pregnancy
- Harmonize pregnancy vaccine policy guidance globally

MEETING SUMMARY

TIME (PDT)	SESSION	SPEAKER
7:00 am	Workshop Introduction	Ajoke Sobanjo-ter Meulen Flor Munoz
7:05 am	**Session 1**	*Moderator:* Flor Munoz
7:05 am	Vaccine safety surveillance	Kathryn Edwards
7:15 am	Safety profile of adenovirus vectored vaccines	David Kaslow
7:30 am	Theory of TTS/VITT mechanism	Andreas Greinacher
7:40 am	Thrombosis/thrombocytopenia in pregnancy	Annemarie Fogerty
9:00 am	**Panel Discussion 1**	
	Panelists: 1. Hanna Nohynek 2. Annemarie Fogarty 3. David Kaslow 4. Asma Khalil 5. Arnaud Marchant	*Moderator:* Paul Henri Lambert
8:20 am	Break (5 min)	
8:25 am	**Session 2**	*Moderator*: Ajoke Sobanjo-ter Meulen
8:30 am	TTS/pregnancy surveillance update UK	Katherine Donegan
8:40 am	TTS/pregnancy surveillance update Brazil	Cristiana Toscano
8:50 am	TTS/pregnancy surveillance update US	Christine Olson
9:00 am	TTS/pregnancy surveillance update EMA	Kelly Plueschke
9:10 am	TTS/pregnancy surveillance update India	Narendra Arora
9:20 am	**Expert Roundtable**	
	Panelists: 1. Jeff Roberts 2. Daniel Brasseur 3. Cristiana Toscano 4. Laura Riley 5. Narendra Arora	*Moderators:* Ruth Karron and Mark Turrentine
10:00 am	Concluding remarks	Ajoke Sobanjo-ter Meulen Flor Munoz

WELCOME AND INTRODUCTION TO THE WEBINAR

Dr Ajoke Sobanjo-ter Meulen (co-chair of the COVAX Maternal Immunization Working Group) welcomed everyone to the webinar. She outlined the objectives of this expert review workshop:

- To characterize the state of the science of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with adenovirus-vectored COVID-19 vaccines, and how TTS might affect pregnant women
- To provide expert review and information to inform evidence-based COVID-19 vaccine policy making for pregnant women in low- and middle-income countries (LMICs), taking into account the risks of:
  - TTS following administration of adenovirus-vectored vaccines in pregnancy
  - COVID-19 infection and disease
  - Availability of other COVID-19 vaccines

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)***

Currently, in many parts of the world, COVID-19 vaccination is not recommended or no clear position statements have been made, which leads to substantial uncertainty both for healthcare providers and pregnant women themselves. Additionally, availability of vaccines and availability of choice are important factors in decision-making, as many women in LMICs either do not currently have access to vaccination or do not have a choice of which vaccine they can receive.

References

1. Unicef COVID-19 vaccine market dashboard. Available from: https://www.unicef.org/supply/covid-19-vaccine-market-dashboard

SESSION 1

Dr Flor Munoz (co-chair of the COVAX MIWG working group) chaired the first session of the workshop which focused on COVID-19 vaccine surveillance, mechanisms of TTS, and data on thrombosis in pregnancy.

VACCINE SAFETY SURVEILLANCE

Dr Kathryn Edwards, Professor of Pediatrics at Vanderbilt University School provided an overview of vaccine safety surveillance with a focus on the early experience from the US. In early April 2021, two publications describing cases of thrombotic thrombocytopenia (also termed vaccine-induced immune thrombotic thrombocytopenia; VITT) in patients in Europe who had received the AstraZeneca vaccine were published in New England Journal of Medicine.[1,2] The cases occurred in otherwise healthy individuals approximately 6–10 days after receipt of the vaccine and many cases were associated with platelet-activating antibodies directed against platelet factor 4 (PF4). One week later, a similar case of central venous sinus thrombosis (CVST) and thrombocytopenia was reported in the US following the Janssen vaccine.[3]

In the US, the vaccine safety system includes v-safe, the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA) project. A new element of safety surveillance introduced during the COVID-19 pandemic was a phone app linked to the v-safe system (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html. The system provides text messages from the CDC every day for the first week after vaccination, weekly for 6 weeks, and then at 3, 6, and 12 months asking participants to complete a web survey. Any clinically important events are followed-up via a call center, and recipients who check that they are pregnant can also choose to enroll in the v-safe pregnancy registry. An analysis of ~4000 women enrolled in the v-safe pregnancy registry in April 2021 who received mRNA vaccines showed that rates of systemic reactions were similar to non-pregnant women, although rates of pain were slightly higher and rates of other systemic reactions were slightly lower.[4] Pregnancy loss and neonatal outcomes were similar to published figures.

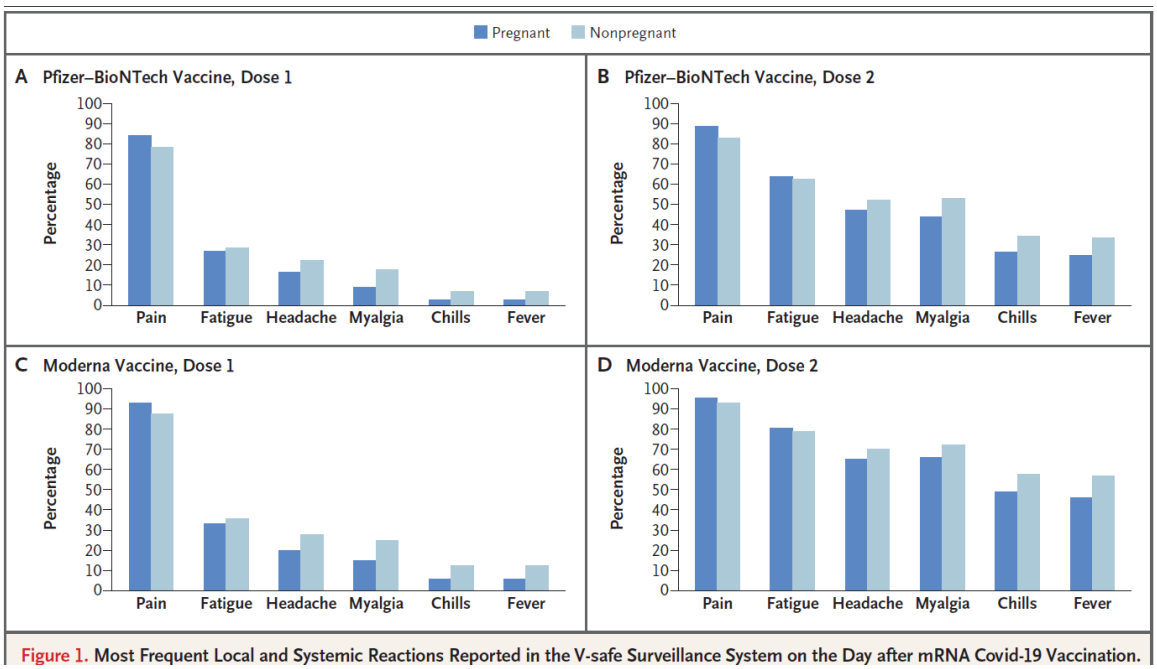


Figure 1. Most Frequent Local and Systemic Reactions Reported in the V-safe Surveillance System on the Day after mRNA Covid-19 Vaccination.

VAERS (https://vaers.hhs.gov/) is a system for reporting adverse events which has the benefits of being able to rapidly detect safety signals and rare adverse events, but with the caveat of not being designed to assess causality. VAERS accepts all reports from everyone regardless of the plausibility of the vaccine causing the event or the clinical seriousness.

VSD (https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html) includes a large linked health maintenance organization (HMO) with nine participating healthcare organizations with data on ~12 million persons per year. Immunization records are linked to other medical data such as hospitalizations, outpatient visits, demographics etc. Preliminary results of the VSD sequential vaccinated concurrent comparator analysis did not identify any safety signals as of Feb 2021 but only included mRNA vaccines.

CISA is a 24/7 on-call system where physicians can call in and seek advice about an adverse event (https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html).

By mid-April, there were six reports of CVST with thrombocytopenia out of 6.86 million doses of the Janssen vaccine administered, which is a reporting rate of around 0.87 cases per million. No cases were reported after receipt of the Pfizer vaccine (97.9 million doses administered) and three cases were seen after the Moderna vaccine (84.7 million doses administered) but all of the cases had normal platelet counts. Of the Janssen cases, characteristics were very similar to those reported in Europe after the AstraZeneca vaccine. Median age was 33, all were white females, none were pregnant, and many had pre-existing conditions. Twelve additional cases have since been identified, with similar characteristics.[5] In April, a warning was issued and the vaccine was temporarily put on hold. On April 23, the ACIP concluded that the benefits of resuming the Janssen COVID-19 vaccine outweighed the risk but a warning for rare clotting events among women aged 18–49 years was recommended to be included.[6] The European Medicines Agency (EMA) issued similar warnings for the AstraZeneca COVID-19 vaccines.[7]

References

1. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med*. 2021 Jun 3;384(22):2092-2101.
2. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, Wiedmann M, Aamodt AH, Skattør TH, Tjønnfjord GE, Holme PA. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med.* 2021 Jun 3;384(22):2124-2130.
3. Costello A, Pandita A, Devitt J. Case Report: Thrombotic Thrombocytopenia after COVID-19 Janssen Vaccination. *Am Fam Physician.* 2021 Jun 1;103(11):646-647.
4. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, Marquez PL, Olson CK, Liu R, Chang KT, Ellington SR, Burkel VK, Smoots AN, Green CJ, Licata C, Zhang BC, Alimchandani M, Mba-Jonas A, Martin SW, Gee JM, Meaney-Delman DM; CDC v-safe COVID-19 Pregnancy Registry Team. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med.* 2021 Apr 21:NEJMoa2104983.
5. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, Streiff MB, Rao AK, Wheeler AP, Beavers SF, Durbin AP, Edwards K, Miller E, Harrington TA, Mba-Jonas A, Nair N, Nguyen DT, Talaat KR, Urrutia VC, Walker SC, Creech CB, Clark TA, DeStefano F, Broder KR. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. *JAMA.* 2021 Apr 30:e217517.
6. MacNeil JR, Su JR, Broder KR, Guh AY, Gargano JW, Wallace M, Hadler SC, Scobie HM, Blain AE, Moulia D, Daley MF, McNally VV, Romero JR, Talbot HK, Lee GM, Bell BP, Oliver SE. 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. *MMWR Morb Mortal Wkly Rep.* 2021 Apr 30;70(17):651-656.
7. European Medicines Agency. COVID-19 vaccine safety update: Vaxzevria. 21 May 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca

SAFETY PROFILE OF ADENOVIRUS-VECTORED VACCINES

Dr David Kaslow, Chief Scientific Officer at PATH, then provided an overview of the safety profile of adenovirus-vectored vaccines, focusing on hAd5, hAd26, and ChAdY25 and platelets and coagulation factors associated with thrombosis and/or thrombocytopenia. He began by discussing the phylogenetic relationships between the adenovirus vector backbones, which are important because there may be differences in tropism, pre-existing adenovirus immunity, or immune responses directed at the vector which contribute to the safety profile.[1-4] Adenovirus vectors differ in genetic structure, with different deletions used in first and next generations vectors. For E4, some elements have been added back in to the non-Ad5 vectors so that they are replication competent in the

production cell line. There is extensive clinical experience to date with hAd5, hAd26, and ChAdOx1as vectors in other vaccines, including Ebola, HIV, MERS, RSV, influenza, Zika, malaria, and tuberculosis.[5-7]

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

Wildtype adenovirus are known to bind platelets, presumably through the coxsackie adenovirus receptor (CAR) but also through other receptors including sialic acid-bearing glycans.[8-10] Binding is associated with activation, thrombosis, and thrombocytopenia. As platelets are a-nucleated, it should be noted that the effects seen are due to adenovirus binding with platelets, rather than any replication. When adenovirus vectors are considered, there does appear to be a route and dose-dependency to thrombocytopenia with the first generation adenovectors. Preclinical toxicology data showed uniform decreases in platelet counts which was judged extremely mild and not likely to be clinically significant.[11-12] In non-COVID-19 adenovirus-vectored vaccine trials, thrombocytopenia reported was infrequent, transient, and mostly mild without clinical consequences, although not all data may be available in the published literature.

As with thrombocytopenia, adenovirus vectors have also shown a route and dose-dependent association with coagulation and coagulopathies. Preclinical toxicology showed elevated activated partial thromboplastin time (aTTT), shortened prothrombin time, and elevated fibrinogen.[11] These were also considered not clinically significant, and potentially associated with a transient rise in anti-phospholipid antibodies. For ChAd3, elevated fibrinogen levels were correlated with increased neutrophil counts and thought to be associated with the inflammatory reaction following vaccination.[12] The only reports of coagulopathies from non-COVID-19 adenovirus-vectored vaccines are from Ad5 and other C type adenovirus, with no reports from Ad26 or ChAdOx1.

An additional consideration is that unlike mRNA vaccines, adenovirus-vectored vaccines need to be transcribed in the nucleus. Multiple types of alternative splicing in nuclear pre-mRNA have been observed in vitro,[13] and it could be that these aberrant spike proteins bind to a variety of tissues mediating an inflammatory response.

References

1. Dicks MD, Spencer AJ, Coughlan L, Bauza K, Gilbert SC, Hill AV, Cottingham MG. Differential immunogenicity between HAdV-5 and chimpanzee adenovirus vector ChAdOx1 is independent of fiber and penton RGD loop sequences in mice. Sci Rep. 2015 Nov 18;5:16756.
2. Baker AT, Mundy RM, Davies JA, Rizkallah PJ, Parker AL. Human adenovirus type 26 uses sialic acid-bearing glycans as a primary cell entry receptor. *Sci Adv.* 2019 Sep 4;5(9):eaax3567.

3. Colloca S, Barnes E, Folgori A, Ammendola V, Capone S, Cirillo A, Siani L, Naddeo M, Grazioli F, Esposito ML, Ambrosio M, Sparacino A, Bartiromo M, Meola A, Smith K, Kurioka A, O'Hara GA, Ewer KJ, Anagnostou N, Bliss C, Hill AV, Traboni C, Klenerman P, Cortese R, Nicosia A. Vaccine vectors derived from a large collection of simian adenoviruses induce potent cellular immunity across multiple species. *Sci Transl Med.* 2012 Jan 4;4(115):115ra2.
4. Dicks MD, Spencer AJ, Edwards NJ, Wadell G, Bojang K, Gilbert SC, Hill AV, Cottingham MG. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. *PLoS One.* 2012;7(7):e40385.
5. Dolzhikova IV, Zubkova OV, Tukhvatulin AI, Dzharullaeva AS, Tukhvatulina NM, Shcheblyakov DV, Shmarov MM, Tokarskaya EA, Simakova YV, Egorova DA, Scherbinin DN, Tutykhina IL, Lysenko AA, Kostarnoy AV, Gancheva PG, Ozharovskaya TA, Belugin BV, Kolobukhina LV, Pantyukhov VB, Syromyatnikova SI, Shatokhina IV, Sizikova TV, Rumyantseva IG, Andrus AF, Boyarskaya NV, Voytyuk AN, Babira VF, Volchikhina SV, Kutaev DA, Bel'skih AN, Zhdanov KV, Zakharenko SM, Borisevich SV, Logunov DY, Naroditsky BS, Gintsburg AL. Safety and immunogenicity of GamEvac-Combi, a heterologous VSV- and Ad5-vectored Ebola vaccine: An open phase I/II trial in healthy adults in Russia. *Hum Vaccin Immunother.* 2017 Mar 4;13(3):613-620.
6. Ozharovskaia TA, Zubkova OV, Dolzhikova IV, Gromova AS, Grousova DM, Tukhvatulin AI, Popova O, Shcheblyakov DV, Scherbinin DN, Dzharullaeva AS, Erokhova AS, Shmarov MM, Loginova SY, Borisevich SV, Naroditsky BS, Logunov DY, Gintsburg AL. Immunogenicity of Different Forms of Middle East Respiratory Syndrome S Glycoprotein. *Acta Naturae.* 2019 Jan-Mar;11(1):38-47.
7. Custers J, Kim D, Leyssen M, Gurwith M, Tomaka F, Robertson J, Heijnen E, Condit R, Shukarev G, Heerwegh D, van Heesbeen R, Schuitemaker H, Douoguih M, Evans E, Smith ER, Chen RT; Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG). Vaccines based on replication incompetent Ad26 viral vectors: Standardized template with key considerations for a risk/benefit assessment. *Vaccine.* 2021 May 21;39(22):3081-3101.
8. Othman M, Labelle A, Mazzetti I, Elbatarny HS, Lillicrap D. Adenovirus-induced thrombocytopenia: the role of von Willebrand factor and P-selectin in mediating accelerated platelet clearance. *Blood.* 2007 Apr 1;109(7):2832-9.
9. Lyle C, McCormick F. Integrin alphavbeta5 is a primary receptor for adenovirus in CAR-negative cells. *Virol J.* 2010 Jul 8;7:148.
10. Shimony N, Elkin G, Kolodkin-Gal D, Krasny L, Urieli-Shoval S, Haviv YS. Analysis of adenoviral attachment to human platelets. *Virol* J. 2009 Feb 17;6:25.
11. Sheets RL, Stein J, Bailer RT, Koup RA, Andrews C, Nason M, He B, Koo E, Trotter H, Duffy C, Manetz TS, Gomez P. Biodistribution and toxicological safety of adenovirus type 5 and type 35 vectored vaccines against human immunodeficiency virus-1 (HIV-1), Ebola, or Marburg are similar despite differing adenovirus serotype vector, manufacturer's construct, or gene inserts. *J Immunotoxicol.* 2008 Jul;5(3):315-35.
12. Planty C, Chevalier G, Duclos MÈ, Chalmey C, Thirion-Delalande C, Sobry C, Steff AM, Destexhe E. Nonclinical safety assessment of repeated administration and biodistribution of ChAd3-EBO-Z Ebola candidate vaccine. *J Appl Toxicol.* 2020 Jun;40(6):748-762
13. E Z, Wang L, Zhou J. Splicing and alternative splicing in rice and humans. *BMB Rep.* 2013 Sep;46(9):439-47.

THEORY OF VITT MECHANISMS

Professor Andreas Greinacher, Head of Transfusion Medicine at Greifswald University of Medicine provided an overview of the mechanism of VITT. He began with a description of the patterns of VITT observed to date with adenovirus-vectored COVID-19 vaccines, with thrombocytopenia and thrombosis appearing 4–20 days after vaccination, with strongly positive PF4/heparin IgG ELISA findings and confirmatory Fc-~ receptor-mediated platelet activation in the presence of PF4. In previous research, the magnitude of the immune response to PF4 strongly depends on a co-inflammatory signals, with B cells producing anti-PF4/heparin antibodies requiring a co-signal (the "danger signal", which may have important consequences for VITT.[1]

Research data indicates that VITT pathogenesis is structured into two parts; the first occurs within 1–2 days after vaccination and includes antigen formation and the pro-inflammatory danger signal, and the second occurs 5–14 days after vaccination, where high titers of antibodies are present, resulting in a prothrombotic state and thrombosis.[2] Dynamic light scattering (DLS) measuring particle size showed ChAdOx1 particles are about 90nm in size, which is approximately the same size as the adenovirus. Size increased when PF4 was added and then again when monoclonal anti-PF4 antibodies or anti-PF4 antibodies purified from VITT patient serum were added. Large increases of the complexes were observed when DNA was added. These increases were charge-related. Super-resolution microscopy staining showed binding of PF4 to particles containing adenovirus hexon proteins. Electron microscopy also confirmed these findings.

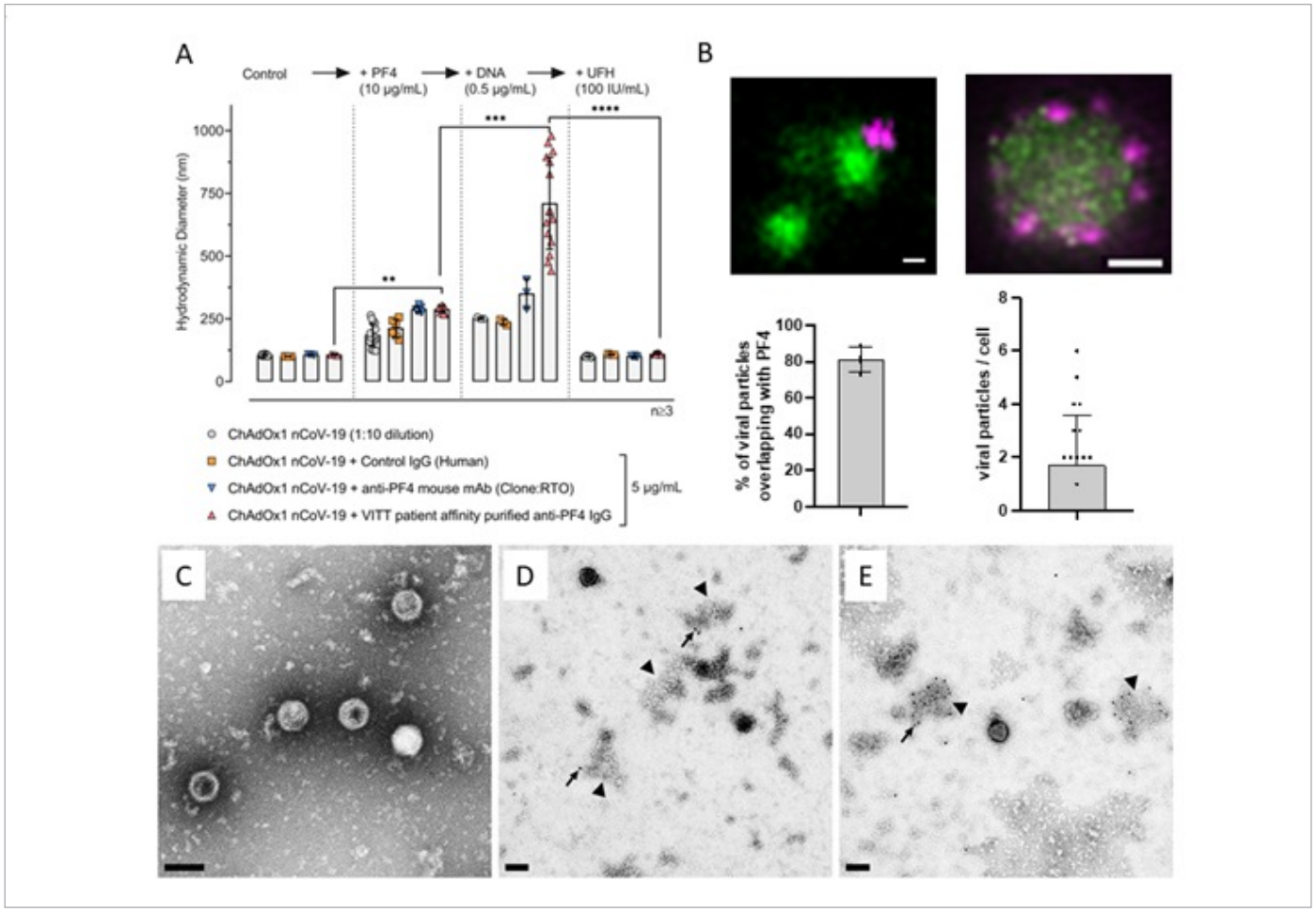


Figure 1. Interaction of PF4 with the vaccine. A) Hydrodynamic diameter of ChAdOx1 nCoV-19 vaccine (1:10 dilution in 0.9% NaCl, 0.4 mg/mL saccharose) was increased by the addition of PF4 (10 µg/mL). Addition of an anti-PF4 monoclonal antibody (Clone RTO) or affinity-purified anti-PF4 IgG from VITT patient sera further increased hydrodynamic diameters of vaccine components. The largest complexes were formed in the presence of DNA. Addition of heparin (100 IU/mL) dissociated formed complexes. Each data point represents 12 runs of n≥3 individual measurements. Statistical assessment by ordinary one-way ANOVA with Sidak's multiple comparisons test. **P < 0.01, ***P < 0.001, ****P < 0.0001. B) 3D-super-resolution microscopy shows binding of PF4 (green) to clusters of proteins of the ChAdOx1 virus (purple; upper left). Particle-/PF4 interaction was analyzed in 8005 aggregates of 4 individual images; 80.6% of particles stained positive for PF4. Upper right, adenoviral protein positive particles (purple) bound to platelets (green). Mean viral density of 1.7 stained particles per platelet. Platelets were incubated with 10 µg/mL PF4 or 1:10 diluted ChAdOx1 nCoV-19 vaccine. Scale: 1 µm. (Further details are given in supplementary material) C) -E) Electron micrograph of aggregates in the vaccine after addition of PF4 (Further details are given in supplementary material). C) vaccine without added PF4 shows no major aggregates but many amorphous small structures; D) aggregates (arrowhead) formed in the vaccine after addition of PF4. The adenovirus capsid protein is labelled. E) aggregates (arrowhead) formed in the vaccine after addition of PF4. Now the biotinylated PF4 is labelled with 10 nm gold particles (arrow):, Bars: 100 nm

Dr Greinacher and colleagues also measured the impact of EDTA in the vaccine. In mice, injection of EDTA leads to leakage of the micro-vasculature. Thirty minutes after vaccination of the vaccine in mice, they found infiltration of the vaccine into many body tissues, which may potentially explain some of the inflammatory symptoms which have been seen in vaccine recipients resembling serum sickness disease.

The second stage, the prothrombotic stage, occurs around one week after vaccination. In VITT patients, autoantibodies to PF4 activate platelets. Activated platelets recruit granulocytes and induce DNA released from granulocytes. The DNA from granulocytes binds PF4, which allows further binding of anti-PF4 antibodies and formation of immune complexes. These immune complexes then activate platelets, granulocytes and presumably also monocytes causing massive thromboin

generation. VITT patients also show increased levels of cell free DNA and myeloperoxidase (MPO) compared with controls (ex vivo signal for intravascular activation of granulocytes). Staining of cerebral veins from affected patients show high levels of released DNA from granulocytes, indicating that the findings from the in vitro experiments are reflected in pathological findings.

Proteomics showed that the vaccines contained approximately 50% of proteins derived from the human embryonic kidney (HEK) cell lines. In the veterinary field, there is at least one example of severe thrombocytopenia derived from feto-maternal incompatibility induced by alloantibodies created by polymorphic proteins associated with vaccination.3 Proteins in humans are polymorphic and it should be investigated whether an immune response to the HEK cell proteins is induced in vaccinated individuals. Such a theoretically possible (but up to now not shown) immune response to these proteins may potentially play a role in future feto-maternal incompatibility.

Professor Greinacher concluded that human and free virus proteins together with EDTA in the vaccine likely contribute to triggering the immune response to PF4. Anti-PF4 autoantibodies, which are formed approximately one week after vaccination, activate platelets, which in turn recruit granulocytes. These release DNA which acts as a co-factor for antibodies to bind and form immune complexes, resulting in a thrombin burst. This induces thrombosis.

References

1. Lubenow N, Hinz P, Thomaschewski S, Lietz T, Vogler M, Ladwig A, Jünger M, Nauck M, Schellong S, Wander K, Engel G, Ekkernkamp A, Greinacher A. The severity of trauma determines the immune response to PF4/heparin and the frequency of heparin-induced thrombocytopenia. *Blood.* 2010 Mar 4;115(9):1797-803.
2. Greinacher A, Selleng K, Wesche K, Handtke S, Palankar R, Aurich K, Lalk M, Methling K, Voelker U, Hentschker C, Michalik S, Steil L, Schoenborn L, Beer M, Franzke K, Rangaswamy C, Mailer RK, Thiele T, Kochanek S, Krutzke L, Siegerist F, Endlich N, Warkentin TE, Renne T. Towards Understanting ChAdOx1 nCov-19 Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). 2021. *Research Square preprint* doi: 10.21203/rs.3.rs-440461/v1
3. Bastian M, Holsteg M, Hanke-Robinson H, Duchow K, Cussler K. Bovine Neonatal Pancytopenia: is this alloimmune syndrome caused by vaccine-induced alloreactive antibodies? *Vaccine.* 2011 Jul 18;29(32):5267-75.

THROMBOSIS AND THROMBOCYTOPENIA IN PREGNANCY

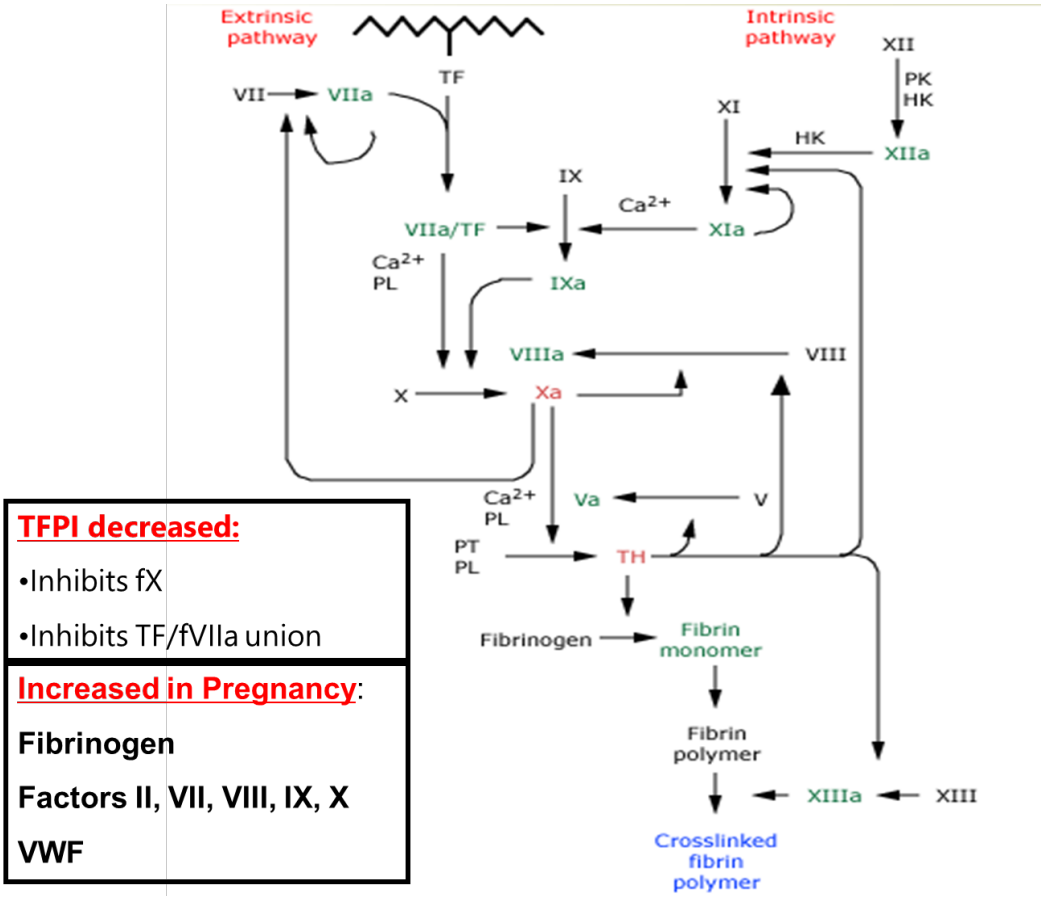
Dr Annemarie Fogerty, Director of Reproductive Hematology at Massachusetts General Hospital concluded the presentations for the first session with a discussion on the mechanisms which can lead to thrombosis or thrombocytopenia during pregnancy. Thrombocytopenia is defined as platelet count <150,000. It affects approximately 10% of pregnancies and etiologies can be quite varied: these can be pregnancy-specific, including gestational thrombocytopenia, pre-eclampsia/HELLP, or acute fatty liver disease of pregnancy; or pre-existing (e.g., lupus, immune thrombocytopenic purpura [ITP], liver disease, von Willebrand disease type 2B); or can be newly acquired during pregnancy (e.g., ITP, thrombotic microangiopathies, various infections, antiphospholipid antibody syndrome, aplasia etc). Most cases of thrombocytopenia in pregnancy are benign gestational (GT) (70%) or pre-eclampsia (21%).

Normal pregnancies have average decline in platelets of 10–13%.[1,2] Features that contribute to thrombocytopenia development in normal pregnancies include a minor increase in thrombopoietin by the liver during pregnancy,[3] a decline in ADAMTS13 activity from Week 6 through to delivery,[4] increased von Willebrand factor (vWF) production and prolongation of half-life,[5] and increasing mean platelet volume (MPV) as pregnancy progresses, likely reflecting progressive increase in platelet turnover.[6] Benign GT generally occurs in late gestation (mid-second to third trimester), with platelet counts >70,000 to 80,000, and 10% of cases experiencing platelets <100,000.[7,8] Features of GT are: no increased risk of newborn thrombocytopenia, no treatment requirements, epidural anesthesia is not contraindicated, and rapid return to normal levels after delivery. GT recurs in future pregnancies and an exaggerated increase in MPV occurs compared with normal pregnancies.[6] Pre-eclampsia accounts for approximately 20–25% of thrombocytopenia cases in pregnancy, and is defined as hypertension and proteinuria occurring after 20 weeks, with clinical presentation of headaches, rapid weight gain, and limb

edema. It is responsible for about a third of pregnancy related deaths, with around 40% of these deaths being attributed to cerebrovascular events. It is thought to originate at the beginning of pregnancy with failure of embryonic trophoblasts to adequately invade the uterus and spiral arteries, leading to placental ischemia from a number of factors.

While immune thrombocytopenic purpura (ITP) only accounts for 3% of cases of thrombocytopenia in pregnancy, it is the most common cause in the first/early second trimesters. This is also most the likely pathophysiology to be impacted by COVID-19 vaccination. ITP is generally diagnosed by exclusion of other diagnoses. It can result in fetal thrombocytopenia where autoantibodies readily cross the placenta. Fetal thrombocytopenia is reported in 8.7–14.7% of cases, with fetal intracranial hemorrhage rates of 1.5%.[9] There has been no evidence to date of vaccinations causing ITP in adults.[10] Data from VAERS showed similar rates of ITP in Pfizer and Moderna COVID-19 vaccine recipients as background population rates.[11] In patients with existing ITP, 14% experienced symptoms and platelet reductions after receipt of a COVID-19 vaccine.[12]

Thrombosis increases in pregnancy as estrogen promotes coagulation by increases in fibrinogen, vWF and factors II, VII, VIII, IX, and X, and decreases anticoagulant mechanisms leading to an increased resistance to activated protein C and decrease in protein S. Additionally, fibrinolysis is inhibited by increased levels and activity of fibrinolytic inhibitors. Dr Fogerty explained the pathways involved, with tissue factor leading to production of thrombin, which is then rapidly amplified in a thrombin burst:



TFPI decreased:

- Inhibits fX
- Inhibits TF/fVIIa union

Increased in Pregnancy:

Fibrinogen

Factors II, VII, VIII, IX, X

VWF

Thrombin also binds to thrombomodulin which activates protein C and turns off factors VIII and V in the presence of protein S. In pregnancy, there is a 40–60% decrease in protein S activity both due to an estrogen-induced decrease in production and increase in C4b binding protein which binds protein S.

Pregnancy is also a hypercoagulable state due to anatomical changes including decreased rate of venous return from the legs due to hormonal changes that decrease venous tone in the legs, venous obstruction by the gravid uterus, and endothelial damage to pelvic veins at the time of delivery due to venous hypertension. Thus the risk of venous thromboembolism (VTE) in pregnancy is increased 6–10 fold compared with age-matched non-pregnant females.13 The estimated incidence is 0.76–1.72 per 1000 pregnancies. Death from pulmonary embolism is about 1.1–1.5 per 100,000 deliveries in the US and Europe, and two-thirds of deep vein thrombosis occur antepartum, and are evenly distributed across trimesters. Around half the pulmonary embolism cases occur postpartum, and 50% of women with pregnancy-associated thrombosis will be diagnoses with primary thrombophilia. Heparin-induced thrombocytopenia (HIT) during pregnancy is extremely rare, possibly because heparin is not commonly used during pregnancy. VITT is quite rare but most common in women of reproductive age, and autoimmune flares have been observed in COVID-19 vaccines, which should be taken into consideration when vaccinating pregnant women.

References

1. Reese JA, Peck JD, McIntosh JJ, Vesely SK, George JN. Platelet counts in women with normal pregnancies: A systematic review. *Am J Hematol.* 2017 Nov;92(11):1224-1232.
2. Reese JA, Peck JD, Deschamps DR, McIntosh JJ, Knudtson EJ, Terrell DR, Vesely SK, George JN. Platelet Counts during Pregnancy. *N Engl J Med.* 2018 Jul 5;379(1):32-43.
3. Zhang X, Zhao Y, Li X, Han P, Jing F, Kong Z, Zhou H, Qiu J, Li L, Peng J, Hou M. Thrombopoietin: a potential diagnostic indicator of immune thrombocytopenia in pregnancy. *Oncotarget.* 2016 Feb 16;7(7):7489-96.
4. Sánchez-Luceros A, Farías CE, Amaral MM, Kempfer AC, Votta R, Marchese C, Salviú MJ, Woods AI, Meschengieser SS, Lazzari MA. von Willebrand factor-cleaving protease (ADAMTS13) activity in normal non-pregnant women, pregnant and post-delivery women. *Thromb Haemost.* 2004 Dec;92(6):1320-6.
5. Drury-Stewart DN, Lannert KW, Chung DW, Teramura GT, Zimring JC, Konkle BA, Gammill HS, Johnsen JM. Complex changes in von Willebrand factor-associated parameters are acquired during uncomplicated pregnancy. *PLoS One.* 2014 Nov 19;9(11):e112935.
6. Fogerty AE, Dzik W. Gestational thrombocytopenia: a case-control study of over 3,500 pregnancies. *Br J Haematol.* 2021 Jun 9. doi: 10.1111/bjh.17611. Epub ahead of print.
7. Crowther MA, Burrows RF, Ginsberg J, Kelton JG. Thrombocytopenia in pregnancy: diagnosis, pathogenesis and management. *Blood Rev.* 1996 Mar;10(1):8-16.
8. McCrae KR, Samuels P, Schreiber AD. Pregnancy-associated thrombocytopenia: pathogenesis and management. *Blood.* 1992 Dec 1;80(11):2697-714.
9. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, Chong BH, Cines DB, Gernsheimer TB, Godeau B, Grainger J, Greer I, Hunt BJ, Imbach PA, Lyons G, McMillan R, Rodeghiero F, Sanz MA, Tarantino M, Watson S, Young J, Kuter DJ. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood.* 2010 Jan 14;115(2):168-86.
10. Grimaldi-Bensouda L, Michel M, Aubrun E, Leighton P, Viallard JF, Adoue D, Magy-Bertrand N, Tisserand G, Khellaf M, Durand JM, Quittet P, Fain O, Bonnotte B, Morin AS, Limal N, Costedoat-Chalumeau N, Morel N, Pan-Petesch B, Decaux O, Mahevas M, Ruel M, Sacre K, Lefrere F, Abenhaim L, Godeau B; PGRx Immune Thrombocytopenia Study Group. A case-control study to assess the risk of immune thrombocytopenia associated with vaccines. *Blood.* 2012 Dec 13;120(25):4938-44.
11. Lee EJ, Cines DB, Gernsheimer T, Kessler C, Michel M, Tarantino MD, Semple JW, Arnold DM, Godeau B, Lambert MP, Bussel JB. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol.* 2021 May 1;96(5):534-537.
12. Kuter DJ. Exacerbation of immune thrombocytopenia following Covid-19 vaccination. *Br J Haematol.* 2021 Jun 1. doi: 10.1111/bjh.17645. Epub ahead of print.
13. Fogerty AE. Management of Venous Thromboembolism in Pregnancy. *Curr Treat Options Cardiovasc Med.* 2018 Jul 23;20(8):69..

PANEL DISCUSSION

A panel discussion moderated by Dr Paul-Henri Lambert (Professor at University of Geneva) then followed. Panelists were Dr Hanna Nohynek (Chief Physician at the Finnish Institute for Health and Welfare), Dr Annemarie Fogarty (Director of Reproductive Hematology at Massachusetts General Hospital), Dr David Kaslow (Chief Scientific Officer at PATH), Dr Asma Khalil (Professor of Obstetrics and Maternal Fetal Medicine at St George's Hospital, University of London), and Dr Arnaud Marchant (Director of the Institute for Medical Immunology, Université Libre de Bruxelles).

The panel discussion focused on the following questions:

1. **Can we reach a consensus on the mechanisms involved in post-vaccination TTS?**
2. **Is there an increased risk of TTS in pregnant women or women of child-bearing age?**

The key points from the discussion were:

- SOngoing studies show that high titers of responsive anti-PF4 antibodies occurring 5–10 days after vaccination are the key factor for VITT or TTS development. This doesn't exclude very rare cases where individuals have other antibodies but these will be very difficult to find in such small numbers of people.
- Thrombotic events are seen with other (non-adenovirus-vectored) vaccines but they have different clinical presentations.
- It should be noted that low avidity anti-PF4 antibodies are found in about 5–8% of recipients of other vaccines, as seen in healthy blood donors. Therefore, screening for presence of antibodies using highly sensitive ELISAs will not be beneficial and likely not of clinical relevance.
- Anti-PF4 response thought to be extremely rare in pregnancy and pregnant women are not at high-risk of developing these strong pro-thrombotic antibodies. It is not expected that rates of VITT would be higher than the general population.
- The greatest potential risk to the fetus is placental thrombosis from pro-thrombotic anti-phospholipid antibodies. However, there has been no reports of this to date.
- Data are needed on which host factors might amplify the route and dose-dependent effects of adenovirus, and what effects there are at the dose level in use for COVID-19 vaccines. While enough evidence exists to defensibly speculate that adenovectors can initiate and/or induce thrombocytopenia and/or thrombosis, an absence of data in humans leaves open whether there's an increased risk at the dose and by the route of administration for vaccine use cases. Therefore, including some obvious additional biomarkers in safety studies in women of childbearing age and pregnancy would seem prudent to address this evidence gap, and could be applicable beyond COVID-19 vaccines.
- Pre-clinical data on adenovirus vectors has shown that biodistribution is generally limited to the injection site draining lymph nodes, and, for some adenoviruses (e.g., adenovirus 5), the liver.
- LMICs have limited diagnostic and treatment capabilities for VITT, and there is limited information on the risk of VITT or TTS in co-infections such as malaria.
- There are limited data available on pregnancy-associated COVID-19 risk in LMICs. Pregnant women may also not have access to healthcare providers with enough knowledge to advise them about the benefits of vaccination versus risk of COVID-19 or TTS risk.
- HIT is very rare in pregnancy, but it can't be assumed that pregnant women are protected against VITT. The rarity of HIT is influenced by the absence of heparin use in pregnancy.
- With HIT, there needs to be a triad of features: heparin plus activated platelets plus PF4 antibody development.
- WHO SAGE are currently updating pregnancy recommendations and discussing moving pregnant women higher up the priority-use group list (Stage 2 instead of Stage 3), given the increased risk of severe COVID-19 disease in pregnant women compared to non-pregnant women with similar COVID-19 risk factors.
- Antiphospholipid antibody syndrome also involves antibodies, platelet activation, and T-cell responses. The experience of diagnosing and treating this condition in pregnancy may be helpful for TTS and VITT.

SESSION 2

The second part of the meeting focused on updates on pregnancy and TTS surveillance in the UK, Brazil, the US, the EMA, and India.

TTS/PREGNANCY SURVEILLANCE UPDATE: UK

Dr Katherine Donegan, Pharmacoepidemiology Research and Intelligence Manager at the Medicines and Healthcare products Regulatory Agency (MHRA) provided an overview UK data.

The UK was the first country to start deployment of the AstraZeneca vaccine on 30th December 2020. Up to 28th May 2021, 24.3 million first doses and 13.4 million second doses of the AstraZeneca vaccine have been administered, mostly to older people. So far, 13.1 million first doses and 1.4 million second doses have been administered to individuals under 40 years of age. In the UK, roll-out was prioritized based on age, exposure risk, and risk of severe disease (based on medical history). Pregnant women at risk of severe COVID-19 were eligible but not prioritized separately. From May 2021, alternative vaccines (mRNA vaccines) are now being offered to people under 40s years of age, including pregnant women within that age group.

Up to 28th May 2021, 348 cases of TTS have been reported (330 after the first dose or unknown, 18 after the second). Of these 128 were CVST (28% fatal) and 220 were non-CVST (11% fatal). Overall incidence rate was 13.6 per 1,000,000 after the first dose and 2.4 per 1,000,000 after the second dose.1 Incidence rates were higher in people aged 18–49 years (18.0/1,000,000 first doses) compared with those aged 50+ (10.2/1,000,000 first doses).[1] But there was not a statistically significant difference in incidence between women (19.9/1,000,000) and men (15.8/1,000,000). Within this, CVST rates were higher in women than in men, but not for overall TTS. No cases of TTS have been reported after the second dose in people under 50 years of age, and those reported in older people show a different phenotype to the TTS cases reported post-first dose and often just report low platelet counts.

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)

At high exposure risk levels, the potential population and individual level benefits in terms of reduced ICU admissions outweigh blood clot risks across age groups.

Vaccine surveillance in the UK includes a four-tiered approach from the MHRA which includes:

- Enhanced passive surveillance: spontaneous reporting of cases from patients or healthcare providers)
- Targeted active surveillance: yellow card vaccine monitor which actively targets pregnant women and follows up for additional data. Currently 935 women have registered, of whom 319 (34%) have reported an adverse drug reaction (ADR)
- Rapid cycle analysis in the clinical practice research datalink database
- Epidemiology studies, including in pregnancy

Public Health England are also leading the Vaccination in Pregnancy study which contains reports of inadvertent exposures in pregnancy. These data are being linked with those reported to UK obstetrics and teratology programs and are likely to give the earliest indications for findings in pregnant women.

Additionally, collaborative epidemiological studies are being performed including mandatory pregnancy data collected at point of care and pregnancy specific adverse events of special interest (AESIs).

She concluded the talk with data from the yellow card reporting system in pregnant women. Up to 12th May 2021, there were 278 exposures from women who had received the AstraZeneca vaccine during pregnancy reported to the yellow card system, and a provisional estimate of ~4000 women receiving any COVID-19 vaccine nationwide. No cases of TTS have been reported in pregnancy in the UK. One case has been reported 5 weeks post-delivery, and 2 cases of DVT and pulmonary embolism have been reported, but did not meet the case definition for TTS. There have been no signals of miscarriages or stillbirths.

Reference

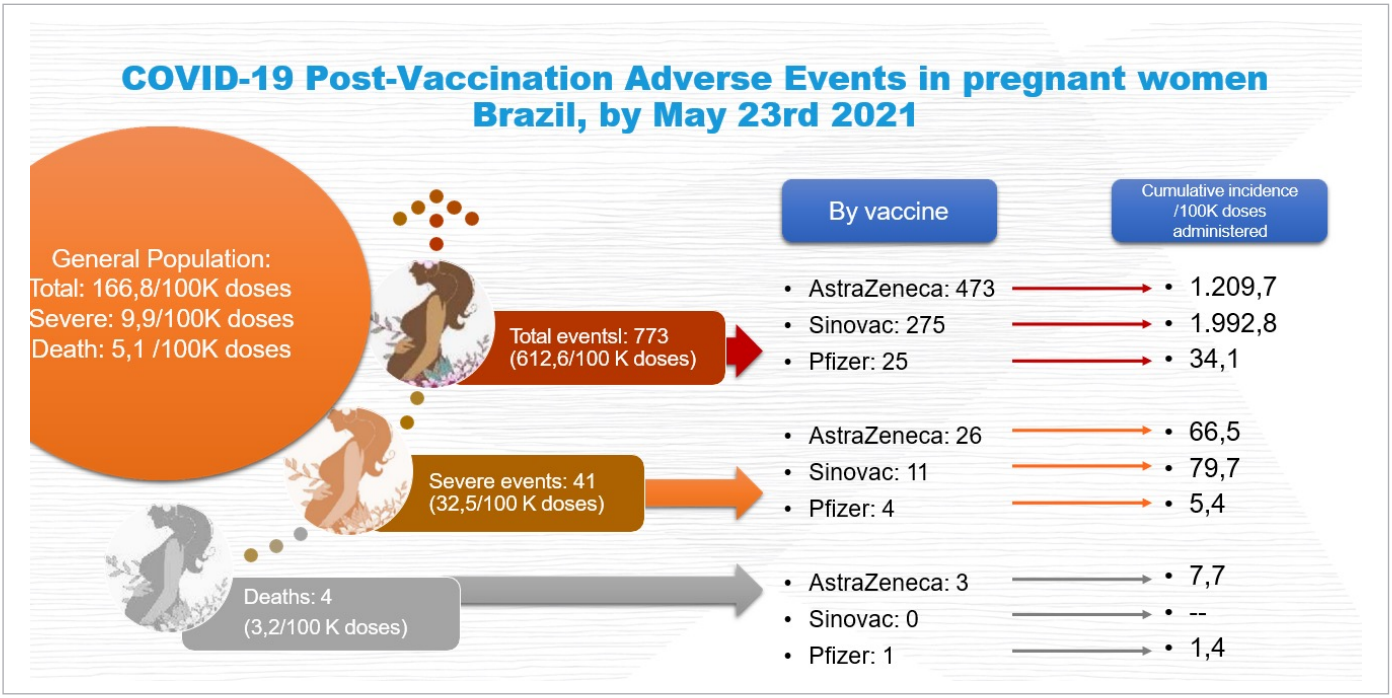
1. Medicines & Healthcare products Regulatory Agency (MHRA). Coronavirus vaccine – weekly summary of Yellow card reporting. Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting.

TTS/PREGNANCY SURVEILLANCE UPDATE: BRAZIL

Dr Cristiana Toscano, Professor at the Federal University of Goiás, Brazil provided an overview of the vaccine surveillance system findings in Brazil, including a case report of a pregnant woman who died from TTS following vaccination. Data presented were provided by Ministry of Health/National Imunization Program, Pan-American Health Organization/country office in Brazil, and Biomanguinho/Fiocruz, in Brazil.

COVID-19 vaccination began in mid-January with AstraZeneca and Sinovac vaccines. By the end of April, vaccination was extended to all pregnant and post-partum women due to the high risk and high levels of morbidity and mortality observed in Brazil. In Brazil, there are an estimated 2,488,052 pregnant women. By mid-May 2021, the incidence of laboratory confirmed COVID-19 in pregnant women was 257.9 per 100,000, and mortality rates due to COVID-19 were 20.3 per 100,000 pregnant women. Mortality rates among pregnant and post-partum women is high among those with COVID-19, particularly in regions where maternal mortality rates are already high. Up to 6th June 2021, 126,185 doses of COVID-19 vaccines had been administered to pregnant women in Brazil, 99% of which were first doses. Of the vaccines administered by then, 58% were Pfizer, 31% AstraZeneca, and 11% Sinovac.[1] Within Brazilian states, there is wide variation in the number of doses and the type of vaccine administered.

In pregnant women, a considerably higher rate of events and severe events have been reported compared with the general population:



Source: figure provided by PAHO, data from the Brazilian vaccine safety surveillance system

These data are events reported, and are not necessarily related to the vaccine. In data up to June 7th assessing severe events by vaccine, 7 abortions, 4 premature labors, 3 fetal deaths, and 1 TTS death were reported in pregnant women receiving the AstraZeneca vaccine. Thirteen abortions and 1 premature labor were reported in Sinovac vaccine recipients, and 1 abortion and 1 fetal death in Pfizer vaccine recipients. On 14th May 2021, COVID-19 vaccination was suspended for pregnant women, except those with other high risk conditions, following the death of one women from TTS. Women who had received the first dose also had to wait until the postpartum period to receive the second dose.

Dr Toscano then provided case details of the 35-year-old pregnant woman at the 23rd week of gestation who had died from TTS following receipt of the AstraZeneca vaccine. Based on the algorithm used in Brazil for identification and diagnosis of TTS event, this was defined as a Level 2 "Probable" TTS event. Despite risk-benefit analysis showing that the risk of TTS after receipt of the AstraZeneca vaccine is very rare, while the risk of deaths due to COVID-19 in pregnant women in Brazil were ~20/100,000 and hospitalizations ~200/100,000, clearly demonstrating that the benefits of the vaccine outweigh the potential risks, vaccination of pregnant women was suspended as it was unclear whether pregnant women were at a higher risk of TTS than the general population.

She concluded by reiterating that Brazil has a strong passive vaccine safety surveillance system in place. However, sensitivity of the surveillance system and the capacity to investigate TTS suspected events is likely not homogeneous in the whole country. Additional challenges include quality of local investigational procedures, particularly in poorer, remote areas. An active prospective surveillance system including follow-up of pregnant women in pregnancy and postpartum period, and their offspring, is being implemented in the country in pilot sites. The Pan American Health Organization (PAHO) and the Ministry of Health will be implementing an active surveillance system based on regional protocol for monitoring, evaluation, and classification of adverse events in pregnant women and newborns during the first six months of life.

References

1. Brazil Ministry of Health. Information on the National Vaccination Campaign against COVID-19. Available from: https://localizasus.saude.gov.br/

TTS/PREGNANCY SURVEILLANCE UPDATE: US

Dr Christine Olson, co-lead of the v-safe pregnancy registry and Medical Officer at VAERS, the Immunization Safety Office (ISO), and the National Center for Emerging and Zoonotic Infections at the CDC presented an update on the TTS and pregnancy surveillance data in the US. She provided an overview of the four vaccine safety monitoring systems under the ISO (VAERS, CISA, VSD, and v-safe). VAERS was implemented in 1990 and received spontaneous reports of adverse events following vaccination, and the data are monitored in real-time to detect new unusual or rare vaccine adverse events, and increases in known adverse events. Among the demographics and characteristics collected in the report form is pregnancy status. Strengths of the system include the broad, national scope, the ability to rapidly detect and evaluate adverse events, including rare events, and enabling focused investigative efforts based on findings. Limitations include under or over-reporting, biased reporting, inconsistency in quality of completeness of reports, lack of a denominator, no causality assessments, and no data on the number of vaccines administered, therefore it is not possible to calculate incidence or prevalence estimates. Publicity around events can lead to over-reporting (e.g., spontaneous abortions in the A/H1N1 pandemic in 2009). Signs and symptoms of adverse events are coded by preferred terms, which allows for systematic review of submitted individual reports.

CISA was established in 2001 to address unmet vaccine safety clinical research needs. It is a national network of vaccine safety experts from the ISO, 7 research centers, and other partners which provides a comprehensive vaccine safety and public health service. The group is important in reviewing individual cases of reported adverse events, and works closely with VAERS.

VSD is a collaborative project between the ISO and nine healthcare organizations. It monitors the safety of vaccines and conducts studies on rare and serious adverse events following vaccination by using electronic health data from each participating site, including data on vaccines received and medical illnesses diagnosed during clinician or hospital visits. VSD data covers approximately 3% of the US population, including approximately 125,000 pregnant women per year, and has a validated pregnancy algorithm for monitoring pregnancy dates and outcomes.

The final surveillance system, v-safe, was specifically designed for the COVID-19 vaccination program. People who enroll with v-safe receive text reminders to complete surveys post-vaccination, including details of local and systemic reactions, impacts on daily life (e.g., absenteeism), pregnancy status, and medical care. People who report requiring medical care are encouraged to complete a VAERS report. The v-safe pregnancy registry collects additional information from patients who report being pregnant at the time of vaccination or become pregnant post-vaccination (30 days before last menstrual period [LMP] through to 14 days after LMP). People who enroll in the registry are contacted several times by phone to answer questions about their pregnancy and medical history, through to three months post-partum. Data are analyzed weekly and compared with published background rates and estimates seen in other safety monitoring systems.

When TTS was recognized, the CDC embarked upon additional case finding to characterize and understand TTS as rapidly as possible. Steps included directly contacting healthcare providers about potential TTS cases, screening of incoming VAERS reports to identify possible cases, assessment of medical records for all potential TTS cases, and review of cases reports by CDC, FDA, and CISA experts. CDC has a working case definition of TTS following COVID-19 vaccination:

CDC working case definition for TTS following COVID-19 vaccination

- Tier 1 TTS case
  - Thrombosis in an unusual location, including cerebral venous sinuses, portal vein, splenic vein, and other rare venous and arterial thromboses
    - May also concurrently have thrombosis in more common locations (e.g., venous thromboembolism, axillary vein thrombosis, deep vein thrombosis, pulmonary embolism)
  - Platelet count <150,000 per microliter
  - Positive (+) heparin-PF4 ELISA HIT antibody* result is supportive, but not required
- Tier 2 TTS case
  - Thrombosis in a common location only (e.g., venous thromboembolism, axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, etc.)
    - Excludes isolated acute myocardial infarction or ischemic stroke
  - Platelet count <150,000 per microliter
  - Positive (+) heparin-PF4 ELISA HIT antibody* result is required

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

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

As of 7th May 2021, 28 confirmed TTS cases were reported to VAERS, all after receipt of the Janssen vaccine (https://covid.cdc.gov/covid-data-tracker). Of these cases, the majority occurred in females (n=22), median age was 40 years and median time from vaccination to symptom onset was 9 days. Nineteen of the cases had CVST. None were pregnant or postpartum (up to 12 weeks after delivery). Data from VSD following 7 million doses of mRNA vaccines reported a total of 17 coded CVST diagnoses. Of these, 3 are still pending review, and 8 were ruled out as incident cases. None of the 6 remaining cases were associated with thrombocytopenia.

To date, there have been no reports of TTS in the v-safe pregnancy registry. Within the v-safe pregnancy registry, as of June 7, 2021, 5.4% of women enrolled received their first vaccine dose peri-conceptionally, 28.1% in the first trimester, 41.6% in the second trimester, and 24.9% in the third trimester. In total, 50.7% received the Pfizer vaccine, 43.8% Moderna, and 5.4% Janssen. Most of the women enrolled are in the 25–34 year age group.

TTS/PREGNANCY SURVEILLANCE UPDATE: EMA

Dr Kelly Plueschke, Scientific Administrator at the EMA provided an overview of TTS and pregnancy surveillance following COVID-19 vaccine receipt in EEA Member States. Following the reports of 22 cases of thromboembolic events that evolved into investigation of very rare blood clots with unusual features (low numbers of platelets) and locations (CVST, splanchnic vein thrombosis), the EMA Pharmacovigilance and Risk Assessment Committee (PRAC) recommended that benefits of COVID-19 vaccine continue to outweigh the risks in adults of all age. Risk minimization measures included updating product information, updating the risk management plan, and direct communication with healthcare professionals. Healthcare professionals were advised on 21st May 2021 that AstraZeneca vaccine must not be given to anyone who has had

blood clots with low blood platelets (thrombosis with thrombocytopenia syndrome, TTS) after receiving the vaccine. Checks for signs of blood clots should be performed in patients who has had low blood platelets within 3 weeks of vaccination, and vice versa, and patients with blood clots and low platelets should receive specialist care. Similar advice was also given for the Janssen vaccine in April 2021.

In a contextualization exercise which aimed at providing more specific recommendations to guide vaccination programs in Member States,[1] the risk of TTS following AstraZeneca vaccination was put in the context of the benefit of the vaccine for different age groups, and the different rates of infection, with higher risk of TTS in younger people at low infection rates. Following the exercise, most Member States restricted the use of AstraZeneca COVID-19 vaccine in the younger population, with age cut-offs varying across countries.

Regarding risk management of TTS in pregnant women, the EMA performs continuous characterization of the risk and re-evaluation as new evidence arises. This includes routine pharmacovigilance activities, monthly summary safety reports, and performance of prospective observational studies. While pregnant women were not included in initial clinical trials of the vaccines, Pfizer, Moderna, AstraZeneca, and Janssen are now planning or in the process of conducting studies in pregnant women. The EMA is also performing observational studies using real-world data, including the CONSIGN project outlined below:

CONSIGN project – July 2020 to July 2022

Covid-19 infectiON and medicineS In pregnancy

C NSIGN

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

A two-year vaccine safety monitoring study assessing long-term effects of the vaccines will also include pregnant women enrolled across Member States. EMA is also part of the International Coalition of Medicines Regulatory Authorities, which promotes collaboration and exchange of information/expertise between regulators through its various subgroups, including the ones on COVID-19 in pregnancy research, and vaccine pharmacovigilance. Dr Plueschke particularly highlighted the need to collect safety and efficacy data in pregnancy pre-approval y enrolling pregnant women in clinical trials to allow improved benefit-risk analysis of medicines in this population.

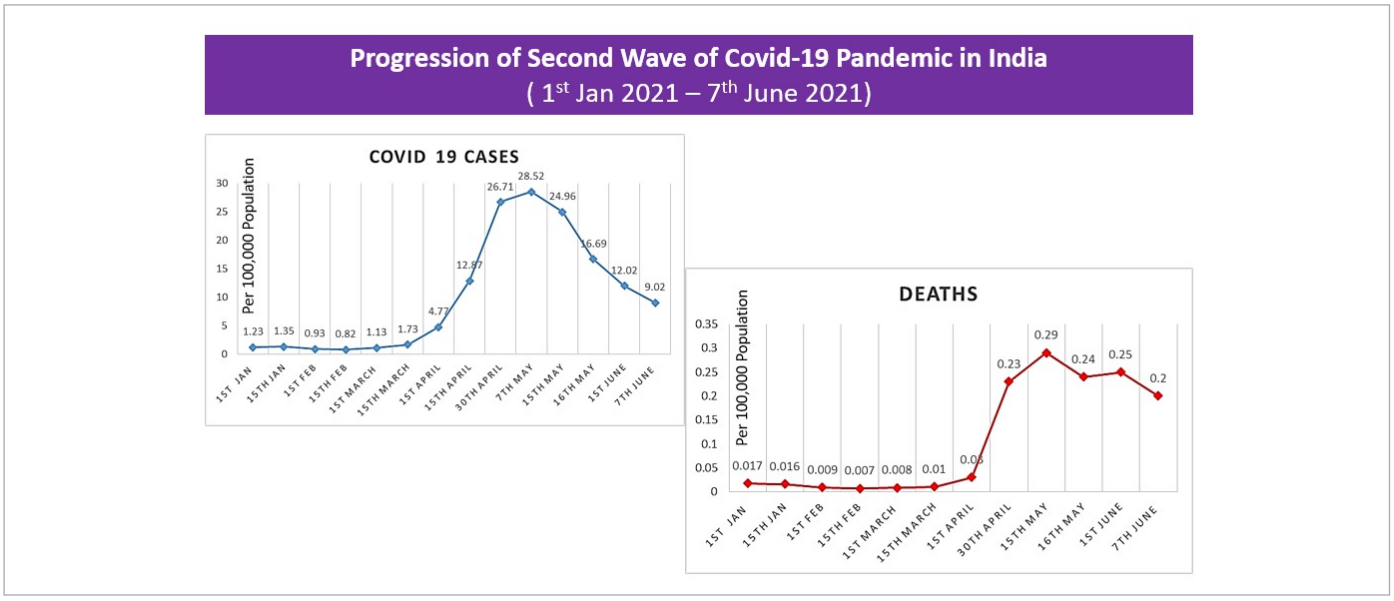
References

1. European Medicines Agency. AstraZeneca's COVID-19 vaccine: benefits and risks in context. Available from: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-benefits-risks-context

TTS/PREGNANCY SURVEILLANCE UPDATE: INDIA

Dr Narendra Kumar Arora, Executive Direction of the INCLEN Trust International provided an update on maternal immunization in India with COVID-19 vaccines. He provided information on the COVID-19 working group of the National Technical Advisory Group on Immunization (NTAGI). The group provide evidence-based recommendations on the use of COVID-19 vaccines in India, as well as evaluate vaccines and vaccine candidates, track capacity and supply potential, identify development cycle or implementation gaps, evaluate disease surveillance data for identifying high risk groups, identify the platform for vaccine delivery, recommend post-licensure surveillance, and advise on studies necessary to fill any evidence gaps. The group regularly meet, and have had 24 meetings since 24th August 2020.

Dr Arora provided a brief overview of the timelines of the second COVID-19 wave in in the country as a whole, with cases per 100,000 reaching a peak of 28.52 around 7th May 2021, and death rates peaking at 0.29 per 100,000 a week later. Case rates are now falling but death rates remain high.



COVID-19 vaccine eligibility for pregnant women is based on UK modelling showing the risks based on age groups and exposure risks. At high exposure risk, as India was experiencing at the height of the second COVID-19 wave, potential benefits in reduced ICU admissions outweighed potential harms of specific blood clots associated with the vaccine across all age groups. However, Dr Arora highlighted the case of a pregnant women in Brazil who died after receipt of the AstraZeneca vaccine.

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. While initial experiences from mRNA vaccines are encouraging, there have been thrombosis-thrombocytopenia related complication with adenovirus-vectored vaccines (Brazil, Belgium, USA). Given the current situation, WG & STSC recommended pregnant women should not be excluded from vaccination, as exposure probability is very high. Prior to 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. A mandatory 30 minute in-hospital observation period after vaccination is recommended. All lactating women are eligible to receive a COVID-19 vaccine any time after delivery, and COVID-19 vaccines can be given any time during pregnancy. 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 adenovirus-vectored vaccines e.g., thrombosis and thrombocytopenia may be developed. Studies will also be immediately put in place to monitor the safety of adenovirus-vectored COVID-19 vaccines in pregnant women.

PANEL DISCUSSION

Dr Ruth Karron, Professor at Johns Hopkins University and Dr Mark Turrentine, Professor at Baylor College of Medicine chaired the panel discussion at the end of Session 2. Panelists were Dr Laura Riley, Chair of Obstetrics and Gynecologist-in-chief at Weill Cornell Medicine, Dr Jeffery Roberts, Associate Director for Scientific Affairs at the Office of Vaccines Research and Review at Center for Biologics Evaluation and Research (CBER) at the FDA, Dr Daniel Brasseur, Consultant at CEPI, Dr Cristiana Toscano, and Dr Narendra Kumar Arora.

The key points raised in the discussion were:

- Risk from COVID-19 is currently much higher than risk of TTS due to pregnancy and/or vaccination, but this is dependent on population infection risk
- Most countries do not have capacity to diagnose and treat TTS, particularly in LMICs who also experience limited supply and vaccine options. Even in high-income countries (HIC), VITT and TTS are difficult to diagnose and very rarely seen by healthcare professionals treating pregnant women. Enhanced diagnostic and treatment capacity, together with routine training of healthcare professionals to consider TTS is important.
- Benefit/risk assessment should be performed within individual settings, and guidance should not differ between LMICs and HICs based on diagnostic and treatment capacities.
- A systematic and inter-institutional review of data from existing surveillance systems in pregnant women who have been vaccinated in countries which predominantly use adenovirus-vectored COVID-19 vaccines would help drive evidence-based decisions.
- Paradox that countries which are least able to treat TTS are likely to primarily receive adenovirus-vectored vaccines. Provision of alternative vaccines is preferred, where and when an option.
- From a regulatory perspective, no increased risk is perceived to pregnant versus non-pregnant women at present. If this changes, labelling can be updated accordingly. It is possible that TTS is occurring on a spectrum but only severe cases are reported, in which case, more data may provide evidence of this.
- There is no clear increased risk of TTS in pregnancy, and there may be a decreased risk.
- Currently no underlying risk factors for VITT have been identified, and risk factors for thrombosis (e.g., Factor V Leiden) were not associated with VITT. Synergy between multiple factors may play a role but no published cases had underlying thrombophilia.
- The underlying comorbidities (e.g., obesity) associated with reported VITT cases are very common, which would result in large screening campaigns for very few cases (which may be missed as the patient may not have the risk factor). Approximately half of all women are overweight or obese during pregnancy. Additionally, comorbidities such as obesity are already risk factors for severe COVID-19 so women at greatest risk of severe disease may be excluded.
- It is not feasible to screen everyone who presents with headaches, as it is an incredibly common symptom. However, healthcare providers should be educated to not dismiss headaches.
- In VITT, the antibodies are so pro-thrombotic and super-strongly platelet activating that they are the driving force – other pro-thrombotic risk factors are just minor players. They may slightly modulate outcome but don't drive immune response or outcome.
- Collaboration with reference laboratories would aid in sample processing and confirmatory tests, particularly in areas where facilities are not available.

CONCLUDING REMARKS

Flor and Ajoke thanked all the presenters and attendees and summarized the main conclusions and next steps:

Conclusions

- Benefit/risk assessment is key: hypothetical COVID-19 risk is higher than vaccine-associated risks in most epidemiologic settings with community transmission of SARS-CoV-2
- TTS is extremely rare and the phenotypes of people at risk is currently unknown
- COVID-19 severity in some countries is high, particularly in pregnancy
- No data indicating increased TTS risk in pregnancy. Unlikely that there is a synergy of pro-thrombotic factors specific for outcomes post-vaccination in pregnancy
- Post vaccination safety data is scarce on pregnant women from LMICs: this needs to be addressed with studies, including active surveillance studies
- From the TTS/VITT perspective, it is important that early diagnostic algorithms and diagnostic tests be made available, which are suitable for LMIC settings, so that if such TTS/VITT cases occur, they will be suspected, diagnosed, and treated properly
- Pathogenesis studies should take into consideration comorbidities typical of LMIC, such as malaria
- Decision-makers may be shifting risk-benefit equation due to risk of being unable to detect or treat TTS, particularly in areas where no alternative vaccines are available

Next Steps

- Collect further data on the prevalence of COVID-19 cases and pregnancy outcomes, particularly in LMICs
- Gather information on which resources are needed to aid in diagnosis and treatment of TTS in countries/regions lacking facilities, and whether partnerships with other organizations (e.g., labs) can aid in this
- Further examine existing pregnancy surveillance data available in countries where adenovirus-vectored vaccines have been administered to pregnant women
- Enhance training of healthcare professionals in risks of COVID-19, benefits of vaccination, consideration of TTS, and identification of TTS symptoms
- Expand supply of different vaccines to LMICs/COVAX recipients
- No regulatory change at this point but may be considered in future if evidence of increased risk in pregnancy
- Harmonize pregnancy vaccine policy guidance globally