

## **FREQUENTLY ASKED QUESTIONS (FAQ) on Thrombosis with Thrombocytopenia Syndrome (TTS) and WHO Emergency Use Listed (EUL) Adenovirus-Vectored COVID-19 Vaccines During Pregnancy**

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Thrombosis with Thrombocytopenia Syndrome (TTS) is a condition characterized by thrombosis, particularly at unusual sites including cerebral sinus venous thrombosis (CVST), in combination with thrombocytopenia (platelet levels  $<150,000/\mu\text{L}$ ). TTS has been identified as an adverse event following immunization (AEFI) with adenovirus-vector COVID-19 vaccines manufactured by AstraZeneca and Janssen.<sup>1-4</sup> Recipients experiencing TTS following immunization have been predominantly female and younger than 50 years of age, mostly without pre-existing risk factors for development of either thrombosis or thrombocytopenia.<sup>2,5,6</sup> Following the initial case reports, many countries, mostly in Europe, temporarily suspended use of the AstraZeneca COVID-19 vaccine, and subsequently the Janssen COVID-19 vaccine, while TTS cases were assessed.<sup>7,8</sup> In most of these countries, immunization with these products has since resumed, although often restricted to older age groups.

Adenovirus-vector COVID-19 vaccines play an important role in immunization campaigns worldwide. While many high-income countries (HICs) have access to COVID-19 vaccines from different platforms, adenovirus-vector vaccines make up a significant proportion of the COVID-19 vaccine supply currently available to low- and middle-income countries (LMICs).<sup>9</sup> Clear, consistent, evidence-based guidance is required to enable countries, vaccine providers, and vaccine recipients, to assess the risk-benefit profiles of available COVID-19 vaccines and its use in specific population groups, based on their specific epidemiological situation.

Guidelines for immunization of pregnant women with COVID-19 vaccines vary globally and at a national level.<sup>10</sup> A number of resources that provide approaches to the clinical evaluation and management of TTS, and specific considerations for COVID-19 immunization during pregnancy, are available through professional societies and the Centers for Disease Control and Prevention (CDC).<sup>11-14</sup> Given the increased risk of both thrombotic and/or thrombocytopenic events associated with pregnancy, this Frequently Asked Question (FAQ) resource aims to clarify the current state of knowledge regarding the risk of TTS following adenovirus-vector COVID-19 vaccine immunization during pregnancy.

## 1. Does the WHO currently prioritize immunization of pregnant women with WHO Emergency Use Listed COVID-19 vaccines?

The WHO currently prioritizes immunization of pregnant women in vaccine supply stage II (stage I: very limited availability, 1–10% of population; stage II: limited availability, 11–20% of population; stage III: moderate availability, 20–50% of population) within all epidemiological scenarios (Scenario A: community transmission; Scenario B: sporadic/clusters of cases; and Scenario C: no cases) as groups with comorbidities or health states that put them at significantly higher risk of severe disease or death.<sup>15</sup> This corresponds to recommending immunization of pregnant women even when there is limited vaccine availability (11–20% of the national population).

Pregnant women and women of childbearing age make up a significant proportion of the frontline healthcare workforce, particularly in LMICs, and are also often employed in other occupations at high risk of exposure to SARS-CoV-2. Pregnant women have been shown to be at increased risk of severe COVID-19 disease and death compared with non-pregnant women with similar COVID-19 risk factors.<sup>16,17</sup> In an ongoing living review, pregnant women with COVID-19 were more likely to be admitted to the intensive care unit (ICU; odds ratio: 2.13 [95% confidence interval 1.53 to 2.95]), need invasive ventilation (odds ratio: 2.59 [2.28 to 2.94]), or extracorporeal membrane oxygenation (odds ratio: 2.02 [1.22 to 3.34]) compared with non-pregnant women of a similar age with COVID-19.<sup>16</sup> In a matched cohort study, pregnant women with COVID-19 had a higher odds of death (odds ratio: 1.84), pneumonia, and ICU admission (both odds ratio: 1.86) than matched non-pregnant women.<sup>18</sup> Poorer outcomes have also been seen in pregnant women with symptomatic SARS-CoV-2 infections, compared with those who were not infected. In a multi-national, cohort study from March to October 2020, pregnant women with laboratory confirmed COVID-19 had substantially higher risk of severe infection (relative risk [RR]: 3.38 [1.63 to 7.01]), intensive care unit admission (RR: 5.04 [3.13 to 8.10]), mortality (RR: 22.3 [2.88 to 172]), severe neonatal morbidity index (RR: 2.66 [1.69 to 4.18]), and preterm birth (RR: 1.59 [1.30 to 1.94]), compared with women without a diagnosis of COVID-19.<sup>19</sup>

On the basis of previous experience with other vaccines used during pregnancy, the effectiveness of COVID-19 vaccines in pregnant women is expected to be comparable to that observed in non-pregnant women of the same age and health status.<sup>15</sup>

## 2. Is there evidence of an increased risk of TTS following immunization with WHO Emergency Use Listed adenovirus-vectored COVID-19 vaccines (i.e., AstraZeneca and Janssen COVID-19 vaccines) in pregnant compared to non-pregnant women with similar COVID-19 risk factors?

The evidence available to date does not suggest that pregnant women are at higher/greater risk of TTS following receipt of an adenovirus-vectored COVID-19 vaccine than non-pregnant women with similar COVID-19 risk factors.<sup>15</sup>

The biological mechanism for development of TTS following COVID-19 immunization is still unclear and being investigated, but may be a platform-specific response to adenovirus-vectored vaccines. Current research data suggest that vaccine-induced TTS is mediated by platelet-activating anti-platelet factor 4 (PF4) antibodies, resulting in a thrombin burst and thrombosis.<sup>20</sup> While thrombotic events have been observed following receipt of mRNA COVID-19 vaccines, the clinical presentation differs from TTS. Data from the UK, where the AstraZeneca COVID-19 vaccine has been used extensively, indicate that the risk of TTS in the general population following immunization is between 1 in 50,000 and 1 in 100,000 vaccinated individuals.<sup>21</sup> Analysis by the European Medicines Agency (EMA) based on EudraVigilance data showed the highest risk of TTS following receipt of the vaccine in people under 50 years of age.<sup>22</sup> The risk of TTS after the first dose vaccine is 1.9 per 100,000 in 20–29 year-olds, 1.8 per 100,000 in 30–39 year-olds, and 2.1 per 100,000 in 40–49 year-olds. The risk of TTS was lower in older age groups (from 1.1 per 100,000 in 50–59 year-olds down to 0.4 per 100,000 in 80+). Initial case reports also indicated a higher risk in women, and analysis of data up to 30 April 2021 indicates very low incidence after the second

vaccine dose.<sup>21,23</sup> No additional specific risk factors have been identified for development of vaccine-induced TTS, and standard venous thromboembolism risk factors seem not to be associated with an increased risk of TTS.

To July 2021, national surveillance schemes have not identified an increased risk of vaccine-induced TTS during pregnancy.<sup>24</sup> In the UK, no cases of TTS have as yet been reported during pregnancy in women who received the AstraZeneca vaccine.<sup>21</sup> In total, 51,724 pregnant women in the UK had received at least one dose of COVID-19 vaccines by 22nd July 2021, although data are not available for individual vaccines.<sup>25</sup> Similarly, in the US, as of 26th July 2021, 39 cases of TTS reported to the Vaccine Adverse Event Reporting System (VAERS) have been confirmed out of more than 13 million doses of Janssen COVID-19 vaccine administered. None of the cases were in pregnant.<sup>26,27</sup> In Brazil, immunization of pregnant women without other risk factors was paused following the reported death of a pregnant women from a probable TTS event following AstraZeneca vaccine immunization.<sup>28</sup> After risk-benefit evaluation, vaccination of all pregnant women, both with and without additional risk factors resumes but using only either inactivated or mRNA vaccines.<sup>10</sup> Overall, the mortality risk from COVID-19 during pregnancy remains substantially higher than the risk from rare AEFIs, including TTS.<sup>15</sup>

### **3. Is there evidence that the risk or severity of pregnancy-associated thrombocytopenia and/or thrombosis increases following immunization with AstraZeneca and Janssen COVID-19 vaccines?**

**Analysis of pregnancy outcomes data from the V-safe pregnancy registry has not identified any evidence to date that the risk or severity of pregnancy-associated thrombocytopenia or thrombosis is increased following immunization with adenovirus-vectored COVID-19 vaccines.**

Approximately 10% of pregnancies are affected by thrombocytopenia, the majority of which are categorized as benign gestational thrombocytopenia, or pre-eclampsia. In a normal pregnancy, platelet levels decline on average by 10–13%.<sup>29,30</sup> Features contributing to this reduction include minor increases in thrombopoietin, reduced ADAMTS13 activity, increased von Willebrand (vWF) factor production and half-life, and increasing mean platelet volume as pregnancy progresses.<sup>31-33</sup>

As of 18th February 2021, analysis of data from 4218 pregnant women in the V-safe pregnancy registry have not shown any evidence of increased risk or severity of thrombocytopenia and thrombosis after immunization with any of the WHO Emergency Use Listed COVID-19 vaccines, although it should be noted that the vast majority of pregnant women received an mRNA vaccine (~94%).<sup>34,35</sup> In general, analysis of pregnancy outcomes and complications in pregnant women in the V-safe pregnancy registry indicates that the rates observed in vaccinated pregnant women are similar to population background rates.<sup>36</sup> Analysis of pregnancy outcomes following receipt of the AstraZeneca vaccine has not yet been performed.

### **4. Should AstraZeneca and Janssen COVID-19 vaccine recommendations differ for pregnant women compared with non-pregnant women with similar COVID-19 risk factors?**

**Based on current evidence of the risk of vaccine-induced TTS during pregnancy, recommendations for receipt of AstraZeneca and Janssen COVID-19 vaccines during pregnancy should be the same as for non-pregnant women with similar COVID-19 risk factors.**

As outlined above, there is no evidence to date of an increased risk of vaccine-induced TTS in pregnant women versus non-pregnant women with similar COVID-19 risk factors, following immunization with any of the WHO Emergency Use Listed COVID-19 vaccines, including the AstraZeneca and Janssen COVID-19 vaccines. Similarly, there is no evidence to date of an increased risk of adverse pregnancy outcomes in pregnant women who have received any of these COVID-19 vaccine compared with non-vaccinated pregnant women. COVID-19 during pregnancy has been estimated to result in a ~22-fold increase in risk of mortality, compared with non-infected

pregnant women,<sup>19</sup> therefore immunization of pregnant women should be prioritized even when there is no choice of COVID-19 vaccine available.<sup>15,37-39</sup>

Where vaccine options are available, preferential recommendations for certain types of COVID-19 vaccines (e.g. mRNA vaccines) for certain risk groups may be implemented. For example, based on risk-benefit analysis across different age groups, the UK has restricted use of AstraZeneca vaccine to people over 40 years,<sup>40</sup> and many other European countries have restricted use of both vaccines to older individuals (e.g., over 55 years,<sup>41</sup> over 60 years,<sup>42,43</sup> or over 65 years<sup>44</sup>). In the US, use of the Janssen vaccine was temporarily paused but was restarted in April 2021 with a warning about the potential for rare clotting events in women aged 18–49 years.<sup>45</sup> Similar warnings were also issued by the EMA.<sup>37,46</sup>

Countries should perform individual risk-benefit assessments based on local epidemiology, target age groups for immunization, and availability of COVID-19 vaccines, including doses and vaccine products.

As already noted, the WHO recommends that pregnant women should be included in stage II of COVID-19 vaccine prioritization, as a priority-use group "with comorbidities or health states determined to be at significantly higher risk of severe disease or death."<sup>15</sup>

## **5. What data are needed to assess risk-benefit profile of adenovirus-vectored COVID-19 immunization of pregnant women within individual countries?**

**The risk-benefit profile of adenovirus-vectored COVID-19 vaccines during pregnancy within individual countries may vary based on the COVID-19 burden, risk data for available COVID-19 vaccines, availability of other vaccine products, and country- and local-level epidemiological data.**<sup>47,48</sup>

The WHO roadmap on vaccine prioritization in the context of limited vaccine supply advises that immunization should be offered to pregnant women particularly under the epidemiological scenarios of community transmission (a) or sporadic/clusters of cases (b).<sup>15</sup> Country-level epidemiological data will aid with the assessment of the potential hospitalizations and deaths avoided by COVID-19 immunization versus the risks of rare clotting events such as TTS in otherwise healthy individuals.

Based on epidemiological modelling, at a population incidence of approximately 2 cases per 10,000 (low exposure risk) the benefit of COVID-19 vaccine in terms of preventing ICU admissions due to COVID-19 prevented far exceeds the potential serious vaccine harms in all age groups  $\geq$  30 years, in persons without high-risk comorbidities. At higher exposure risk, the potential vaccine benefits outweighed the potential vaccine harms across all age groups  $\geq$  20 years (data were not available for under 20s).<sup>49</sup> Unfortunately, no modelling has been specifically performed in pregnant women.

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