SYNTHESIS

COVID-19 Viral Vector Vaccines and Rare Blood Clots – Vaccine Safety Surveillance In Action

Date: 06/1/2021

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). Synthesis documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19. All synthesis documents are reviewed by PHO subject-matter experts before public release.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the posting date.

Key Findings

- Rare blood clots (venous or arterial thrombosis or thromboembolism) at unusual sites following viral vector COVID-19 vaccination accompanied by thrombocytopenia (low platelet count) are referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) (also called Vaccine-Induced Prothrombotic Immune Thrombocytopenia [VIPIT] or Thrombosis with Thrombocytopenia Syndrome [TTS]). The mechanism appears to be immune-mediated, related to platelet activation. Following enhanced surveillance, no specific risk factors have been identified for VITT.

- With early recognition and intervention, VITT is treatable. The blood clots seen in VITT cases are not the same as the more commonly observed blood clots associated with strokes, pulmonary embolism (PE) or deep vein thrombosis (DVT).

- VITT is a very rare event with reported incidence following the first dose of AstraZeneca/Oxford University ChAdOx1-S COVID-19 (referred to herein as AstraZeneca) vaccine occurring between 1 in 26,500 and 1 in 127,300. Early evidence estimates the risk of VITT following a second dose of AstraZeneca to be approximately 1 in 600,000. As of May 29, 2021, the rate of VITT in Ontario was 1 in 61,000 in.

- Following reported cases of VITT and TTS, some jurisdictions have limited the AstraZeneca and COVID-19 Johnson & Johnson/Janssen (referred to herein as J&J/Janssen) vaccines to particular age groups, while some have continued their use but recommend available alternatives, while others have suspended use. As of mid-May 2021, all Canadian provinces had paused administering first doses of the AstraZeneca COVID-19 vaccine.

- Early evidence suggests combining a first dose viral vector vaccine with a second dose mRNA vaccine is safe and can elicit a strong immune response.
Post-marketing vaccine safety surveillance is crucial for the early detection and timely response to vaccine safety signals. The identification of VITT illustrates that vaccine safety surveillance is able to identify safety signals that require further investigation and actions to mitigate risk.

Background

The AstraZeneca and COVISHIELD (manufactured by the Serum Institute of India and distributed by Verity Pharmaceuticals in Canada) COVID-19 vaccines were authorized for use in Canada for individuals 18 years of age and older on February 26, 2021. The J&J/Janssen COVID-19 vaccine was authorized for use in Canada for individuals 18 years of age and older on March 5, 2021, but as of June 1, 2021, it has not yet been distributed for use in Canada. The AstraZeneca and J&J/Janssen COVID-19 vaccines both use non-replicating viral-vector (adenovirus) vaccine technology. Vaccines undergo rigorous clinical trials demonstrating efficacy, safety, and being of high quality before approval, and through post-marketing surveillance after their approval for use. When vaccine safety surveillance detects a safety signal, an investigation is initiated. A safety signal was identified initially in Europe following the use of the AstraZeneca COVID-19 vaccine, followed by a safety signal for the J&J/Janssen COVID-19 vaccine in the United States (US). The safety signal for both vaccines involves cases with both thrombosis and thrombocytopenia.

The purpose of this synthesis is to describe literature related to a vaccine safety signal identified following administration of COVID-19 viral vector vaccines, including the Ontario context.

Methods

PHO Library Services conducted a search of peer-reviewed literature and pre-prints on the AstraZeneca COVID-19 vaccine and VITT on April 4 and 5, 2021 in National Institutes of Health COVID-19 Portfolio (pre-prints), and Ovid MEDLINE, respectively. On April 13, 2021, the same databases were searched for literature on J&J/Janssen, TTS, and VITT.

To identify grey literature on the AstraZeneca COVID-19 vaccine and VITT, records were obtained by PHO Library Services on April 7, 2021 through online searches using Google Custom Search Engines for Canadian health departments and agencies, US government websites, and international public health agencies and resources. To augment the library search, further records were obtained through online hand searches conducted between April 5 and April 27, 2021 of recent policies, media articles, government websites, and official press releases.

To identify grey literature on the J&J/Janssen COVID-19 vaccine and VITT, records were obtained by PHO Library Services on April 14, 2021 through online searches using Google Custom Search Engines for Canadian health departments and agencies, US government websites, and international public health resources. To augment this library search, additional online hand searches were conducted between April 13 and 27, 2021, to identify recent policies, media articles, government websites, and official press releases. On April 27, 2021, May 20, 2021, and June 1, 2021, information obtained from government department and agency websites was updated to reflect the most recent statements regarding the use of the AstraZeneca and J&J/Janssen COVID-19 vaccines.

English-language peer-reviewed and non-peer-reviewed records that discussed thrombocytopenia, blood clots, or bleeding and the AstraZeneca or J&J/Janssen COVID-19 vaccines were included. Content experts also identified relevant articles and reports from ongoing scans and hand searches of recent published articles, official press releases, reports, and briefs.
Findings
The findings below describe what VITT is, its risk of occurrence and who is at risk for it, and how the
syndrome was recognized. We also describe how and why guidance on viral vector vaccine use changed
so quickly in such a brief period in Canada, as well as the global response to the issue. Lastly, we briefly
summarize the latest evidence regarding mixed vaccine product schedules, and the vaccine safety
surveillance process in Ontario, Canada.

What is Thrombosis with Thrombocytopenia Syndrome (TTS) and
Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)?

- **TTS** is a condition characterized by the presence of acute venous or arterial thrombosis with
  new onset thrombocytopenia, and no known recent exposure to heparin. A case finding
definition proposed by the Brighton Collaboration is being used to support the investigation of
this new clinical syndrome by identifying individuals who present with TTS following COVID-19
vaccination. VITT refers to the clinical syndrome of TTS, in addition to laboratory tests that
confirm platelet activation (i.e., anti-platelet 4 antibodies [PF4]). VITT is characterized by
thrombocytopenia (<150 x 10⁶ per mL) and primarily venous thrombosis (blood clots) at unusual
sites such as the brain (cerebral sinus venous thrombosis [CVST]) or abdomen (portal, hepatic
splanchnic vein thrombosis [SVT]). VITT cases commonly exhibit elevated D-dimer levels (>4000
mcg/L) and low fibrinogen levels. Clinically, VITT resembles “atypical” or “autoimmune”
heparin-induced thrombocytopenia (HIT), which develops in the presence of known exposure to
heparin, and is caused by platelet-activating antibodies. However, VITT does not appear to be
triggered by heparin.

- The blood clots seen in VITT cases are not the same as the more commonly observed blood clots
  associated with strokes, DVT or PE. Serological investigation of VITT cases identified high levels
  of antibodies to PF4, which can induce massive platelet activation, stimulating the formation of
  blood clots, and lowering of the platelet count with resulting thrombosis. This is not the
  same mechanism responsible for the more common blood clots associated with strokes, PEs and
  DVTs.

- Cases of VITT have been reported to occur 4 to 28 days following vaccination with the
  AstraZeneca COVID-19 vaccine, and 6 to 15 days following the J&J/Janssen COVID-19
  vaccine. Symptons of VITT include: a sudden onset of severe or persistent worsening headache;
  confusion or seizures; difficulty moving part of the body; acute onset of blurry vision that does
  not go away; difficulty speaking; focal neurological symptoms (e.g., weakness, tingling);
  dizziness; shortness of breath; chest pain; persistent abdominal pain; acute onset of arm or leg
  swelling, pain, pallor or colour change; or easy skin bruising (beyond the site of vaccination) or
  petechiae/skin rash. Recipients of the AstraZeneca or J&J/Janssen COVID-19 vaccines should be advised by healthcare
  providers administering the vaccine to seek immediate medical attention should they develop any

- The case fatality of VITT is between 25 to 40%, although the high case fatality is expected to
decrease with early diagnosis and appropriate treatment. VITT is treatable and treatment success increases with prompt diagnosis. There are diagnosis and treatment guidelines for
healthcare professionals.
symptoms of VITT following immunization. Healthcare professionals have also been advised as to how to identify, diagnose and manage clinical symptoms and signs consistent with VITT.49,63,64

Who is at risk for VITT/TTS?

- VITT is not thought to occur more commonly in people who have had previous blood clots, with a family history of blood clots, with thrombocytosis (i.e., increased number of platelets), women on oral contraception, or pregnant women. This is because VITT is immune-mediated and does not develop through the same process as more common causes of thrombocytopenia and/or coagulation disorders.2
- **AstraZeneca COVID-19 vaccine:** Initial cases of VITT were mostly women under the age of 55 years; however, this observation may have been due to women under 55 years being overrepresented in the initial vaccine roll out in some settings.2,48,59,65 After the identification of additional events following enhanced surveillance, a strong relationship with sex and age is no longer observed for the AstraZeneca COVID-19 vaccine and VITT.1,5-11,17 In a statement on April 14, 2021, Health Canada concluded that “based on the review of available data from Europe and from the United Kingdom (UK) and AstraZeneca, no specific risk factors have been identified.”12
- **J&J/JANSSEN COVID-19 vaccine:** In a May 12, 2021 presentation, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) reported that most cases of TTS following J&J COVID-19 vaccination were in women, with most aged 18-49 years old.66
- At the time of writing, no vaccine safety surveillance signals for thrombosis with thrombocytopenia and platelet activating antibodies had been identified for either of the two mRNA COVID-19 vaccines authorized for use in Canada (i.e., Pfizer-BioNTech and Moderna).

How common is VITT/TTS?

Since VITT was only recently identified and is very rare, it is difficult to accurately estimate its true incidence.

- **AstraZeneca COVID-19 vaccine:** Estimates of the risk of VITT from countries with moderate to high data quality following a first dose of the AstraZeneca vaccine range from 1 in 26,500 to 1 in 127,300.14-16,67 Early evidence estimates the risk of VITT following a second dose of AstraZeneca to be approximately 1 in 600,000, although information on the risk of VITT following a second dose is evolving.17-19
- On April 13, 2021, the first Canadian case of VITT following vaccination with the AstraZeneca/COVISHIELD vaccine was reported in Quebec, Canada, and the case later died.68,69 As of May 8, 2021, the risk of VITT in Canada was estimated to be approximately 1 in 55,000 doses, but several presumptive cases were still under investigation.67 Up to May 29, 2021, Ontario had 17 reports of TTS after receipt of AstraZeneca/COVISHIELD vaccine. Of these, 14 were VITT, which translates to a rate of 1 in 61,000.20
- **J&J/JANSSEN COVID-19 vaccine:** The US has the most experience with the J&J COVID-19 vaccine, having administered more than 8 million doses. As of May 7, 2021, the US reported 28 confirmed cases of thrombosis with thrombocytopenia out of 8,739,657 doses of J&J/Janssen COVID-19 vaccine administered, which translates to a rate of approximately 1 in 310,000.66
How was the issue identified?

The first cases of very rare blood clots in combination with low platelets were initially identified in Austria, Norway and Germany in February 2021. In response to these reports, several European Union (EU) countries suspended their use of the AstraZeneca COVID-19 vaccine pending investigation of these events.57,70 By March 10, 2021, 30 cases of thromboembolic events (predominantly venous) had been reported among approximately 5 million AstraZeneca COVID-19 vaccine recipients in the European Economic Area.71 Clinical and laboratory analyses of cases from Austria and Germany shifted the focus of the vaccine safety signal from thromboembolic events to more specifically thrombosis with thrombocytopenia, and disseminated intravascular coagulation (DIC).1,72 The authors of the study suggested the rare syndrome be named vaccine-induced prothrombotic immune thrombocytopenia (VIPIT),1 which is now referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT).1 There was no evidence that a manufacturing or product quality issue with the batches of AstraZeneca COVID-19 vaccine administered in Europe was responsible for the cases of VITT.59

Timeline of the use of the AstraZeneca/COVISHIELD COVID-19 vaccine in Canada and reasons for the changes

In Canada, post-marketing surveillance is a shared responsibility between Health Canada, vaccine manufacturers, the Public Health Agency of Canada (PHAC), provinces and territories, as well as local public health authorities.73 Following the approval of a new vaccine, post-marketing surveillance is initiated to ensure the ongoing monitoring of safety on a larger scale, throughout implementation of a vaccine program. Individual reports of Adverse Events Following Immunization (AEFI) represent an important source of data because they have the potential to identify previously unrecognized or rare AEFIs or an increase in frequency or severity of known AEFIs, which can be further evaluated.

When the AstraZeneca COVID-19 vaccine was first added to NACI’s Recommendations on The Use of COVID-19 Vaccines on March 1, 2021, NACI made a preferential recommendation for mRNA COVID-19 vaccines based on higher vaccine efficacy.74 NACI made a discretionary recommendation that the AstraZeneca COVID-19 vaccine may be offered to individuals 18 to 64 years of age if: (1) The advantages of earlier vaccination outweigh the limitations of vaccinating with a less efficacious vaccine; (2) The ease of transport, storage and handling of the AstraZeneca COVID-19 vaccine facilitates access to vaccination which may otherwise be challenging; and (3) Informed consent includes a discussion about current vaccine options and the timing of future vaccine options.

On March 16, 2021, NACI revised its guidance on the AstraZeneca COVID-19 vaccine to include use in individuals ≥ 65 years of age.75 This update was based on observational studies of vaccine effectiveness from the UK that were released after NACI’s previous recommendations for the use of the vaccine in those 18 to 64 years of age.

In response to the discovery of VITT, on March 24, 2021, Health Canada updated the AstraZeneca and COVISHIELD product monographs to include information on very rare reports of blood clots associated with low levels of blood platelets following immunization with the AstraZeneca vaccine.76

On March 29, 2021, following population-based analyses of VITT and risk of COVID-19 disease by age and considering the availability of alternative vaccines, NACI concluded that as a precautionary measure, the AstraZeneca COVID-19 vaccine should not be used in adults under 55 years of age while Health Canada continued to analyze the emerging data.54 NACI recommended that adults 55 years of age and older still be offered the AstraZeneca COVID-19 vaccine with informed consent, based on the increased
risk of hospitalization and death due to COVID-19 disease in that population and since VITT appeared to be an even rarer event in that age group.

On **April 14, 2021**, Health Canada released a statement that their analyses had concluded that these very rare blood clot events may be linked to use of the AstraZeneca COVID-19 vaccine with no specific identified risk factors and therefore, Health Canada would not restrict the use of the AstraZeneca COVID-19 vaccine by age or sex (beyond the manufacturer’s recommendations).12

On **April 23, 2021**, Health Canada updated the AstraZeneca, COVISHIELD, and Janssen COVID-19 vaccine product monographs to include the risk of thrombosis with thrombocytopenia.77-79

In response to new evidence on VITT, NACI conducted an age-based benefit-risk analysis to determine if the benefit of earlier vaccination with an authorized viral vector COVID-19 vaccine (instead of waiting for an mRNA vaccine) outweighed potential harms. Possible benefits were hospitalizations and deaths due to COVID-19 that could be prevented with the use of a viral vector COVID-19 vaccine instead of waiting for a later mRNA vaccine, and the potential harm was the development of VITT events post COVID-19 vaccination requiring intensive care unit admission and/or resulting in death. Based on their analyses on **April 23, 2021** (updated May 3, 2021 and May 21, 2021), NACI released updated COVID-19 vaccine recommendations:80-83

- NACI maintained its recommendation that a complete series with an mRNA COVID-19 vaccine (e.g., Pfizer-BioNTech or Moderna) should be preferentially offered to individuals in the authorized age group.81
- NACI made a discretionary recommendation that a complete series with a viral vector COVID-19 vaccine may be offered to individuals 30 years of age and older without contraindications if the individual does not wish to wait for an mRNA vaccine and if the following conditions are met: (1) Benefit-risk analysis determines that the benefit of earlier vaccination with a viral vector vaccine outweighs the risk of the individual getting COVID-19 while waiting for an mRNA COVID-19 vaccine; (2) The individual provides informed consent once the benefits and risks of VITT compared to COVID-19 are outlined, including how long the individual will have to wait for an mRNA vaccine and what public health measures they can take to minimize their exposure to the COVID-19 virus; and (3) The individual will have to wait a long time in order to get an mRNA vaccine.80
- NACI noted that the assessment of whether individuals should be offered the AstraZeneca or J&J/Janssen COVID-19 vaccines may vary between jurisdictions depending on: local COVID-19 epidemiology, local vaccine supply, risk of severe illness and death, risk of exposure, and vaccine logistical considerations.81

On **May 11, 2021**, Ontario paused the roll out and administration of first doses of the AstraZeneca/COVISHIELD vaccine, out of an abundance of caution due to an observed increase in the frequency of VITT linked to the AstraZeneca COVID-19 vaccine.40 Shortly after, all Canadian provinces paused administering first doses of the AstraZeneca COVID-19 vaccine.32-40 On **May 21, 2021**, the Ontario government announced that it would proceed with second dose administration of the AstraZeneca COVID-19 vaccine with informed consent.34,85 On **June 1, 2021**, in response to the latest evidence on interchangeability of COVID-19 vaccines, NACI recommended that individuals who received a first dose of the AstraZeneca/COVISHIELD vaccine may receive either the AstraZeneca/COVISHIELD vaccine or an mRNA vaccine (Pfizer-BioNTech or Moderna) for their second dose, unless contraindicated.86,87
What has been the response globally?

**ASTRAZENECA COVID-19 VACCINE**

Following reported cases of VITT and statements from regulatory agencies about the AstraZeneca COVID-19 vaccine, jurisdictions have varied in their decisions related to use of the AstraZeneca COVID-19 vaccine. Some jurisdictions have limited the AstraZeneca COVID-19 vaccine to particular age groups (e.g., France, Spain, Italy, Netherlands, Ireland), the UK and Australia have continued its use but recommend available alternatives be offered unless certain risk criteria are met, and Germany has removed its age restrictions for the AstraZeneca COVID-19 vaccine (offering it to all adults over the age of 18) and plans to expand eligibility to 12 to 18 year olds by the end of August 2021. There are also some jurisdictions that have suspended the use of the AstraZeneca COVID-19 vaccine entirely (e.g., Denmark). Please see Appendix A for a list of select jurisdictions and their current use of the AstraZeneca COVID-19 vaccine.

**J&J/JANSSEN COVID-19 VACCINE**

In late April 2021, the US CDC and Food and Drug Administration (FDA) recommended the resumed use of the J&J/Janssen COVID-19 vaccine following a temporary pause, noting that after a review of all available data, the vaccine’s known and potential benefits outweigh the risks. On March 11, 2021, the J&J/Janssen COVID-19 vaccine was authorized for use in the EU; however, there have been delays in the rollout of this vaccine across Europe in light of the reported cases of TTS in the US and the subsequent decisions made by the CDC and FDA. On April 20, 2021, J&J/Janssen announced they would resume rollout in the EU following the European Medicines Agency (EMA’s) most recent review. However, some jurisdictions decided that their vaccination program would continue without the J&J/Janssen vaccine.

On May 19, 2021, the WHO Global Advisory Committee on Vaccine Safety (GACVS) stated that the benefits of the J&J/Janssen COVID-19 vaccine continue to outweigh the risks of TTS, and because it is the only single dose vaccine approved for use, it may be an important tool for accessing difficult-to-reach populations, thus playing a key role in preventing COVID-19 infections and reducing deaths across the world. Please see Appendix B for a list of select jurisdictions and their current responses.

What’s Next: What is known about mixed COVID-19 vaccine product schedules?

Combining similar vaccines from different manufacturers is not a new concept. This has been done when vaccine supply or public health programs change e.g., influenza, hepatitis A. At the time of writing, there were several trials and real-world studies underway to investigate possible combinations of first and second dose COVID-19 vaccine products. As of May 20, 2021, data from the UK Com-COV study reported more mild and moderate side effects when individuals received a first dose of AstraZeneca and a second dose of Pfizer-BioNTech and vice versa, compared to standard same dose 1 and 2 vaccination schedules. The side effects were short-lived and there were no other safety concerns. The Com-COV immunogenicity data are expected in June 2021. Data from Spain’s CombivacS trial has reported that a first dose of the AstraZeneca COVID-19 vaccine followed by a second dose of mRNA vaccine (Pfizer-BioNTech) boosts the immune response, which is the purpose of a second dose of vaccine. On June 1, 2021, in response to the evidence from Com-COV and CombivacS, NACI recommended that individuals who received a first dose of the AstraZeneca/COVISHIELD vaccine may receive either the AstraZeneca/COVISHIELD vaccine or an mRNA vaccine (Pfizer-BioNTech or Moderna)
for their second dose, unless contraindicated.\textsuperscript{86,87} MOSAIC (Mix and match of the second COVID-19 vaccine dose for Safety and Immunogenicity) is a study from the Canadian Immunization Research Network (CIRN) that will be examining mixed vaccine dose interchangeability between Canada’s currently authorized COVID-19 vaccines (Pfizer-BioNTech, Moderna, AstraZeneca) with dose 1 and 2 administered 16 weeks apart.\textsuperscript{97}

**Surveillance process in Ontario and Canada**

Although clinical trials of COVID-19 vaccines have enrolled tens of thousands of individuals, even very large studies of this size will not have sufficient numbers of participants to identify very rare adverse events, such as VITT. Very rare adverse events typically require post-marketing surveillance to be identified, when a larger and more diverse population is exposed with hundreds of thousands, or more, individuals vaccinated. Vaccine safety surveillance functions to ensure that a vaccine continues to have a favourable benefit-risk profile, and allows for identification of risk factors that may place individuals, or groups at higher risk of an adverse event following immunization. The identification of VITT demonstrates that COVID-19 vaccine safety surveillance is working and will allow for ongoing monitoring and characterization of these events.

In Ontario, passive vaccine safety surveillance relies on reporting of all adverse events following immunization (AEFIs) by health care providers, vaccine recipients or their caregivers to their local public health unit.\textsuperscript{73} Reporting of AEFIs is mandated for health care providers under the *Health Protection and Promotion Act*.\textsuperscript{98} AEFI reports received by PHUs are investigated, assessed and documented in the provincial surveillance system which is managed by PHO. AEFI reports are then submitted to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), which is overseen by the Public Health Agency of Canada (PHAC). In Canada, PHAC and Health Canada work jointly to monitor vaccine safety, in collaboration with provincial and territorial vaccine safety partners. Any AEFI reports received by vaccine manufacturers must be submitted to Health Canada under federal legislation.

**All AEFIs, including suspected or confirmed TTS/VITT events should be reported to local public health using the** [provincial AEFI form].\textsuperscript{73,99}
## Appendix A: Administration of AstraZeneca COVID-19 Vaccine in Select Jurisdictions

### Table 1. Jurisdictions that have continued or resumed or discontinued use of the AstraZeneca COVID-19 Vaccine

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Status of the use of the AstraZeneca COVID-19 Vaccine</th>
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<tbody>
<tr>
<td>Australia</td>
<td>Currently administering AstraZeneca vaccine. On April 8, 2021, the Australian Technical Advisory Group on Immunisation (ATAGI) released a statement indicating that the COVID-19 vaccine by Pfizer-BioNTech (licensed under the brand name Comirnaty) is preferred over the AstraZeneca vaccine in adults aged under 50 years of age. AstraZeneca can be used in adults under the age of 50 where benefits are likely to outweigh the risks, and when the individual has made an informed decision based on an understanding of the risks and benefits. ATAGI notes that individuals who have had their first dose without any serious side effects can be confident in getting their second dose.</td>
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<td>Denmark</td>
<td>Originally suspended use on March 11, 2021. On March 25, 2021, after a two-week suspension in use of the AstraZeneca vaccine, the Danish Health Authority extended the suspension by three weeks pending further investigations. On April 14, 2021, the Danish Health Authority announced it would remove the AstraZeneca vaccine from its vaccination program but that the vaccine would remain authorized for use.</td>
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<td>European Medicines Agency (EMA)</td>
<td>On April 23, 2021, the EMA released a statement concluding that benefits of Vaxzevria (formerly called the AstraZeneca COVID-19 vaccine) outweigh its risks in adults of all age groups; however, very rare cases of blood clots with low blood platelets have occurred following vaccination. The EMA reported that, after considering available data, Vaxzevria is effective at preventing hospitalizations, intensive care unit admissions and deaths due to SARS-CoV-2 infections. The EMA’s Human Medicines Committee (CHMP) recommended to continue administering a second dose of Vaxzevria between four and 12 weeks after giving the first dose (in line with the product monograph information). The EMA also stated that there has not been enough exposure and follow-up time to determine whether the risk of blood clots with low blood platelets after a second dose will differ from the risk after the first dose (presently, there are no or limited data to change current recommendations). The CHMP conducted a further analysis of available data to contextualize the risk of very rare blood clots with low platelets for different age groups and monthly rates of infection. The CHMP analyzed Vaxzevria’s benefits and the risk of unusual blood clots in different age groups in the context of monthly infection rates. As the monthly infection rate and age increase, the magnitude of benefits of Vaxzevria (preventing hospitalization, preventing ICU admissions, preventing deaths due to SARS-CoV-2 infection) can be contextualized in the context of monthly infection rates.</td>
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<tr>
<td>Jurisdiction</td>
<td>Status of the use of the AstraZeneca COVID-19 Vaccine</td>
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<tr>
<td>France</td>
<td>• Currently administering AstraZeneca vaccine. Resumed use of the AstraZeneca vaccine on March 19, 2021, but only for individuals age 55 and older.</td>
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<td>Germany</td>
<td>• Currently administering AstraZeneca vaccine. Temporarily suspended use on March 15, 2021 (based on Paul Ehrlich Institute’s recommendation), but resumed vaccinations on March 19, 2021 due to insufficient vaccine supply to contain a third wave of COVID-19, and the Paul Ehrlich Institute’s agreement with the positive safety assessment by the EMA. On March 31, 2021, it was announced that its use would be limited to individuals age 60 and older.</td>
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<tr>
<td>Ireland</td>
<td>• Currently administering AstraZeneca vaccine. Use suspended on March 14, 2021, but resumed use on March 20, 2021. In April 2021, AstraZeneca was not recommended for people under the age of 60 in Ireland.</td>
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<td>Italy</td>
<td>• Currently administering AstraZeneca vaccine. Resumed use of the vaccine on March 19, 2021. Individuals who decline to receive AstraZeneca will be given an alternative later on. Starting on April 7, 2021, Italy began recommending the AstraZeneca vaccine only for individuals age 60 and older.</td>
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<tr>
<td>Netherlands</td>
<td>• Currently administering AstraZeneca vaccine. Resumed use the week of March 18, 2021, for individuals age 60 and older.</td>
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<tr>
<td>Spain</td>
<td>• Currently administering AstraZeneca vaccine. As of April 8, 2021, AstraZeneca will only be used in Spain for individuals age 60 and older. In May 2021, Spain’s Health Minister announced that people under age 60 who have received a first dose of the AstraZeneca COVID-19 vaccine (prior to the implementation of age restrictions) can receive their second inoculation either with the AstraZeneca or Pfizer-BioNTech vaccines. Until this decision, those who received their first dose of the AstraZeneca vaccine were unable to receive a second dose of AstraZeneca because the government suspended its use for people under 60, due to blood-clot concerns.</td>
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<td>United Kingdom (UK)</td>
<td>• Currently administering AstraZeneca vaccine. On May 7, 2021, the UK government confirmed that adults under the age of 40 (increased from 30 years of age in April 2021) are to be offered an alternative COVID-19 vaccine, if to COVID-19) continue to outweigh the risk of blood clots with low platelets.</td>
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<td>Jurisdiction</td>
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<td>available, at which point they may make an informed choice to receive the AstraZeneca vaccine.111</td>
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<td>• On April 7, 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) stated there was evidence of a possible link between blood clots with low platelets and the AstraZeneca COVID-19 vaccine. However, these blood clots are extremely rare and unlikely to occur, and that the benefits of the AstraZeneca COVID-19 vaccine outweigh any risks. MHRA advised careful consideration be given to people who are at higher risk of specific types of blood clots because of their medical condition.65</td>
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<td>• On April 7, 2021, the Joint Committee on Vaccination and Immunization (JCVI) advised that for individuals over the age of 30 and for those who have underlying health conditions which put them at higher risk of severe COVID-19 disease, the benefits of prompt vaccination with the AstraZeneca COVID-19 vaccine far outweigh the risk of adverse events. According to the JCVI statement on April 7, 2021, it is preferable for adults under the age 30 years (without underlying health conditions that put them at higher risk of severe COVID-19 disease) to be offered an alternative to the AstraZeneca COVID-19 vaccine, if available, at which point they may make an informed choice to receive the AstraZeneca COVID-19 vaccine. JCVI stated due to rare reporting of VITT following receipt of the second dose of the AstraZeneca COVID-19 vaccine, all those who received a first dose of the AstraZeneca COVID-19 vaccine and did not experience VITT should be offered a second dose of AstraZeneca COVID-19 vaccine, irrespective of age.112</td>
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<td>• On May 7, 2021, JCVI issued an update advising that “unvaccinated adults aged 30 to 39 years who are not in a clinical priority group at higher risk of severe COVID-19 disease, should be preferentially offered an alternative to the AstraZeneca COVID-19 vaccine, where possible and only where no substantial delay or barrier in access to vaccination would arise.”28 The JCVI stated that if there were issues with supply of the alternate vaccines, challenges with the vaccine program, or an increase in the incidence of COVID-19, then the vaccination of adults aged 30 to 39 years with any of the UK-authorised vaccines is always better than no vaccination (except where there are specific contraindications).28</td>
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<td>• On May 7, 2021, in response to the latest JCVI advice, the MHRA released a statement regarding the use of the AstraZeneca COVID-19 vaccine, saying that: “The balance of benefits and risks is very favourable for older people but is more finely balanced for younger people and we advise that this evolving evidence should be taken into account when considering the use of the vaccine, as JCVI has done.”113</td>
</tr>
<tr>
<td>World Health Organization (WHO)</td>
<td>• On April 7, 2021, WHO released an interim statement from the COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) on AstraZeneca COVID-19 vaccine.114 They concluded that: “Based on current information, a causal relationship between the vaccine and the occurrence of blood clots with low platelets is considered plausible but is not confirmed” and that further research is needed to fully understand the potential relationship between vaccination and possible risk factors.115 WHO</td>
</tr>
<tr>
<td>Jurisdiction</td>
<td>Status of the use of the AstraZeneca COVID-19 Vaccine</td>
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<td>GACVS noted that while the events are concerning, they are very rare, with low numbers reported among the nearly 200 million individuals who have received the AstraZeneca COVID-19 vaccine worldwide.</td>
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<td>• On April 16, 2021, GACVS released a statement on their analysis of the most recent VITT evidence. In terms of a biological mechanism, they stated that, “a ‘platform specific’ mechanism related to the adenovirus-vector vaccines is not certain but cannot be excluded.”</td>
</tr>
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115
### Table 2. Jurisdictions that have continued or resumed or discontinued use of the J&J/Janssen COVID-19 Vaccine

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Status of the use of the J&amp;J/Janssen COVID-19 Vaccine</th>
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<tbody>
<tr>
<td>Denmark</td>
<td>On May 3, 2021, the Danish Health Authority announced their vaccination program would continue without the J&amp;J/Janssen COVID-19 vaccine.</td>
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<tr>
<td>European Medicines Agency (EMA)</td>
<td>J&amp;J/Janssen was initially authorized for use in the EU on March 11, 2021. On April 20 and 22, 2021, the EMA released statements outlining that their Pharmacovigilance Risk Assessment Committee (PRAC) reviewed a safety signal to assess reports of thromboembolic events in people who received the J&amp;J/Janssen vaccine in the US. They concluded that a warning about unusual blood clots with low blood platelets should be added to the product information and that these events should be listed as very rare side effects of the vaccine. They also concluded that the overall benefits of the J&amp;J/Janssen vaccine in preventing COVID-19 outweigh the risks of side effects.</td>
</tr>
<tr>
<td>United States of America (US)</td>
<td>On April 23, 2021, the CDC Advisory Committee on Immunization Practices (ACIP) concluded that the benefits of resuming J&amp;J/Janssen COVID-19 vaccination (after a brief pause instituted by the FDA and CDC) among individuals aged 18 years and older outweighed the risks and reaffirmed its interim recommendation under FDA’s Emergency Use Authorization. The recommendation is intended to support flexibility, choice and improved access to authorized vaccine products. ACIP members agreed that provider and patient education regarding the risk for VITT/TTS among women ages 18 to 49, and awareness of other COVID-19 vaccine options were critical to resuming use of the J&amp;J/Janssen COVID-19 vaccine. On April 25, 2021, the CDC and FDA released a joint statement recommending that the use of the J&amp;J/Janssen COVID-19 vaccine resume in the US, following a temporary pause. The joint statement notes that after a review of all available data, the J&amp;J/Janssen COVID-19 vaccine’s known and potential benefits outweigh its known and potential risks.</td>
</tr>
<tr>
<td>WHO</td>
<td>On May 19, 2021, the WHO GACVS released a statement on the safety of the J&amp;J/Janssen COVID-19 vaccine, concluding that the benefits of the J&amp;J/Janssen COVID-19 vaccine continue to outweigh the risks of TTS. WHO GACVS also note that as the only single dose COVID-19 vaccine approved for use, this vaccine may be an important tool for accessing difficult-to-reach populations, thus playing a key role in preventing COVID-19 infections and reducing deaths across the world.</td>
</tr>
</tbody>
</table>
References


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