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SARS-CoV-2 vaccine and thrombosis: Expert opinions

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Abstract:
Historically, the vaccination strategies developed in the second half of the 20th century have permitted to eradicate infectious diseases. From the onset of COVID-19 pandemic to March 2021, more than 141 million cases and 3 million deaths were documented worldwide with disruption of the economic and social activity, devastating material, physical and psychological consequences. Reports of unusual and severe thrombotic events, including cerebral and splanchnic venous thrombosis and other autoimmune adverse reactions such as immune thrombocytopenia or thrombotic microangiopathies (TMA) in connection with some of the SARS-CoV-2 vaccine have caused a great deal of concern within the population and the medical community. This report is intended to provide practical answers following an overview of our knowledge on these thrombotic events that are extremely rare but have serious consequences. Vaccine hesitancy threatens to reverse the progress made in controlling vaccine-preventable diseases. These adverse events must be put into perspective with an objective analysis of the facts and the issues of the vaccination strategy during this SARS-Cov-2 pandemic. Healthcare professionals remain the most pertinent advisors and influencers regarding vaccination decisions; they have to be supported in order to provide reliable and credible information on vaccines. We need to inform, reassure and support our patients when the prescription is made. Facing these challenges and these observations, a panel of experts express their insights and propose a tracking algorithm for vaccinated patients based on a10-point guideline for decision-making on what to do and not to do.

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SARS-CoV-2 vaccine and thrombosis: An Expert Consensus on Vaccine-induced Immune Thrombotic Thrombocytopenia

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Abstract

Historically, the vaccination strategies developed in the second half of the 20th century have permitted to eradicate infectious diseases. From the onset of COVID-19 pandemic to **the end of April 2021, more than 150 million cases** and 3 million deaths were documented

worldwide with disruption of the economic and social activity, devastating material, physical and psychological consequences. Reports of unusual and severe thrombotic events, including cerebral and splanchnic venous thrombosis and other autoimmune adverse reactions such as immune thrombocytopenia or thrombotic microangiopathies in connection with some of the SARS-CoV-2 vaccine have caused a great deal of concern within the population and the medical community. This report is intended to provide practical answers following an overview of our knowledge on these thrombotic events that are extremely rare but have serious consequences. Vaccine hesitancy threatens to reverse the progress made in controlling vaccine-preventable diseases. These adverse events must be put into perspective with an objective analysis of the facts and the issues of the vaccination strategy during this SARS-Cov-2 pandemic. Healthcare professionals remain the most pertinent advisors and influencers regarding vaccination decisions; they have to be supported in order to provide reliable and credible information on vaccines. We need to inform, reassure and support our patients when the prescription is made. Facing these challenges and these observations, a panel of experts express their insights and propose a tracking algorithm for vaccinated patients based on a10-point guideline for decision-making on what to do and not to do.

Keywords : SARS-CoV-2, Vaccination, Thrombosis, VITT,

After SARS-CoV-2 vaccination campaign initiation, European reports of rare, unusual and severe thrombotic events, such as cerebral venous sinus thrombosis (CVST) and splanchnic venous thrombosis (SVT), and other autoimmune adverse reactions such as immune thrombocytopenia or thrombotic microangiopathies in connection with some of the SARS-

CoV-2 vaccines have caused a lot of worry and even a panic turmoil within the population and the medical community. These events must be put into perspective with an objective analysis of the facts and the issues of the vaccination strategy during this pandemic. Among its many facets, COVID-19 is associated with an increased risk of vascular disease with often life-threatening thrombotic manifestations. After an overview of our knowledge on these extremely rare but extremely serious thrombotic events, this manuscript intends to provide practical answers and attitudes. Of course, many points still need to be clarified through cooperative, multinational, prospective studies. Meantime, we must learn to better cope with the consequences of these rare, albeit worrisome complications through continuous pharmacovigilance and appropriate management.

1. Different types of SARS-CoV-2 vaccines: facts and implications

Historically, the vaccination strategies developed in the second half of the 20th century have permitted to eradicate infectious diseases such as poliomyelitis, diphtheria and smallpox, and have considerably reduced the incidence of childhood illnesses, notably measles, mumps and rubella. The battle, however, has never been completely won. For example, there has been a 30% increase in measles cases worldwide, and in England the number of cases of measles and mumps has doubled in recent years. The reasons that people choose to not be vaccinated are complex. The World Health Organization (WHO) recently listed vaccine hesitancy as one of the ten greatest threats to global health (1). It identified the main reasons for hesitancy as the difficulties of access to vaccines and the lack of confidence (2). Healthcare professionals remain the most pertinent advisors and influencers regarding vaccination decisions; they need to be supported in order to provide reliable and credible information on vaccines. Vaccine hesitancy – the reluctance or refusal

to be vaccinated despite the availability of vaccines – threatens to reverse the progress made in controlling vaccine-preventable diseases. Vaccination is one of the most cost-effective ways of preventing disease. It currently prevents 2 to 3 million deaths per year, and an additional 1.5 million could be avoided with improvement of global vaccination coverage. (2)

From the onset of COVID-19 pandemic to **April 2021, more than 150 million** cases and 3 million deaths were documented worldwide with disruption of the economic and social activity, devastating material, physical and psychological consequences (3,4). Unfortunately, a large proportion of the public is still hesitant to accept the dangers associated with SARS-CoV-2, comparing it with influenza epidemics from the past, ignoring the fact that the death toll continues to rise globally despite strict hygiene measures and lock-downs. The rapid availability of an effective vaccine for limiting viral transmission and serious forms of the disease has emerged as the only real solution for controlling this pandemic (5) (Figure 1). The development of antibodies directed against one part of the spike protein (the protein that enables SARS-CoV-2 to bind to the membrane receptor for angiotensin-converting enzyme-2 and thus promote viral invasion) is the strategy chosen by most vaccine developers. It is necessary to keep in mind that these vaccines also promote development of cellular immunity via the action on dendritic cells and T cells such as cytotoxic T and T-helper lymphocytes (6,7).

To date, 240 vaccine candidates have been registered by WHO: 63 in the clinical evaluation phase, 177 in the pre-clinical phase and 11 that are authorized in at least one country.

2. Thrombosis and vaccines: very rare events

An association between the AstraZeneca vaccine (Vaxzevria/ChAdOx1 nCoV-19/AZD1222) and rare cases of thrombosis have been recently reported **in United Kingdom (UK) and Europe (8-11).** In contrast to adenoviral vaccines (AstraZeneca and Johnson & Johnson/Janssen), no CVST and splanchnic thrombosis cases have been linked to mRNA-vaccines (Comirnaty/BioNTech/Pfizer and mRNA-1273/Moderna) (10). In UK, Germany, Austria and Norway, thrombosis in unusual locations, such as cerebral venous sinus, splanchnic vein or pulmonary thrombosis, have been reported in the days following vaccination (within 4 to 24 days) (12-14). The authors have proposed grouping them under the acronym "VITT" (vaccine-induced immune thrombotic thrombocytopenia). Indeed, these episodes of venous thrombosis were associated with low platelet levels and a strong increase in D-dimers with normal or low fibrinogen levels. Of the 11 reported cases in Germany and Austria, 10 were cerebral venous thrombosis (CVST) that occurred in young women (9/11, aged 22 to 49 years) (13). These CVST cases were associated with other forms of thrombosis, including pulmonary emboli (3 cases), splanchnic vein thrombosis (3 cases) and other unusual thromboses (4 cases). Six of the patients died. Two of the women had autoimmune disease (13). The Norwegian authors reported the occurrence of five cases of CVST with severe thrombocytopenia in healthcare professionals (14); three patients died. They were mainly young women (4/5, aged 32 to 54 years) (14). These thrombotic episodes occurred 7 to 10 days after injection of the AstraZeneca vaccine. At that time, close to 133,000 people had received a single dose of this vaccine in Norway (14). In the largest cohort reported in UK with 23 cases, they were 14 women (22 to 71 years old) and 9 men (21 to 77 years old) (12). 13 thrombotic episodes were related to CVST, 6 cases to PE and 4 cases to splanchnic vein thrombosis (12). Seven patients died. It is not known whether these

patients had other risk factors of thrombosis (e.g. use of birth control pills, comorbidity, acquired or inherited thrombophilia, overweight or obesity).

On 4 April 2021, with more than 40 million vaccinated individuals, 169 cases of CVST and 53 cases of splanchnic vein thrombosis were reported on the European EudraVigilance database. (15-17). On 17 April 2021, data from the UK pharmacovigilance, the Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card Scheme, reported 168 severe thrombotic events (including 77 CVST) among 22 million people who received the first dose of AstraZeneca vaccine (8). The overall incidence is around 8 per one million doses (8). These events occurred in 93 women and 75 men aged from 18 to 93 years and the overall case fatality rate was 19% with 32 deaths (8). On 23 April 2021, the Vaccine Adverse Event Reporting System (VAERS) database in the United States recorded 161 classical thrombotic events during COVID-19 vaccination campaign with 5 CVST without thrombocytopenia among 125 million Moderna vaccinated individuals and 154 million doses of BioNTech/Pfizer vaccine administered (18). In last update, on 15 April 2021, the French Agency reported a total of 27 cases of severe thrombosis (24 CVST, 2 SVT and 1 pulmonary embolism with disseminated intravascular coagulopathy) in around 3 300 000 people who received a first injection of AstraZeneca vaccine (19). The sex-ratio was around 1 (13 women/14 men) and the mean age was 63 years old (19). No such a severe thrombotic case was reported among 12 million doses of BioNTech/Pfizer vaccine and 1.5 million doses of Moderna vaccine to date (19). The incidence of these severe venous thrombotic events therefore appears particularly low, about 1/100,000 (9). These types of incidents have not been reported in India thus far, despite a particularly high use of the AstraZeneca vaccine. Some cases of unrelated acute myocardial infarction episodes were reported but a review is conducted by

India's National Committee for Adverse Event Following Immunization. With the estimation that the EMA gave, India should have had 320 cases for the 80 million doses already been given (20).

The North American Food and Drug Administration (FDA) has just suspended injections of the adenoviral Johnson and Johnson/Janssen vaccine after having identified eight cases of CVST with severe thrombocytopenia among close to 7.5 million vaccinated subjects (21-23). In their last update of 21 April, the FDA reported a total of 12 CVST cases that occurred between 6 to 15 days after Janssen vaccine injection. It would be important to know whether the additional 5 cases were also associated with thrombocytopenia such as VITT cases. All these cases were in young women with a median age of 37 years (18 to 59 years old) among 8 million administered doses (18).

It should be remembered that in the general population, and independent of any vaccination, the annual incidence of venous thrombosis is 1 to 2 per 1000 people and that of cerebral venous thrombosis is from 1 to 2 per 100,000 (4). In France, apart from any pandemic, there are around 350 venous thrombotic episodes per day. The absolute risk of having venous thrombosis after an airplane flight longer than 4 hours was estimated at 1 per 4600 , which therefore appears to be well above (50 to 100 times) that of having CVST after a SARS-CoV-2 vaccination (25,26). Along with the other agencies, it highlights the very significant clinical benefit of vaccination and the very low potential thrombotic risk.

The potential of severe adverse reactions needs also be weighed against the alternative not to vaccinate. In France, there are currently over 500 people per day admitted to intensive care units with severe or serious forms of COVID-19 and approximately 30% will die within the following two weeks. Despite systematic thromboprophylaxis during hospitalization of patients with COVID-19, the incidence of thrombosis ranges from 7–8% in

traditional hospitalization to 25–30% in intensive care (27-29). We must also take into account the potential sequelae described in so called “long COVID” after the hospitalization (30).

All these data highlight that during infection with SARS-CoV-2 and its related disease (COVID-19), thrombosis occurs at least hundred-fold more often without vaccination than after it. Furthermore, politicians, authorities, media and the public should be reminded that thrombotic risks have been willingly accepted in modern lifestyles. Apart from the already discussed risk from long-distance flights, millions of women use birth control pills which increase the risk of thrombotic events considerably (3 to 5 times). In fact, vaccination does not appear to induce a higher risk of thrombosis than that reported for combined oral contraceptives. A recent Danish study also notes that the number of cases of thrombosis reported after SARS-CoV-2 vaccine remains below the expected number in the general population, which was estimated from the incidence rate of “classical” venous thrombosis in the entire Danish population before introduction of the vaccination programme (91 venous thrombotic episodes per week in individuals from 18 to 64 years, or 169 episodes per week in individuals from 18 to 99 years) (31). However, we must be careful to compare the thrombotic risks from flying and contraceptive pill intake with the risks of these severe CVST. Clearly the morbi-mortality is different from classical deep venous thrombosis with a high mortality rate reaching around 40% in VITT. This fatality rate is particularly high because usually the prognosis of classical CVST is less severe with a mortality rate around 5-10% (32). The Pharmacovigilance Risk Assessment Committee (PRAC) uses O/E ratios as the first level of evaluation of safety signals and these have clearly shown an increase for CVST and splanchnic vein thrombosis in specific age categories.

In countries that have rapidly applied a wide-scale effective vaccination program (Israel, UK and USA) the COVID-19-related morbidity and mortality have been dramatically reduced, saving at least hundreds of lives per day. This spectacular achievement should be weighed against the extremely low risk of thrombotic events post-vaccination.

3. Haemorrhage and Thrombocytopenia: rare events

Another point to be incorporated in the thrombotic risk analysis is the risk of haemorrhagic accidents. Out of more than 30 million vaccinated people, the MHRA reported 267 haemorrhagic events (including 6 fatal) with the AstraZeneca vaccine and 220 events (9 fatal) with the BioNTech/Pfizer vaccine. In the VAERS database in the United States, out of more than 110 million vaccinated people, 439 haemorrhagic episodes were recorded with the BioNTech/Pfizer and Moderna vaccines (18). With regard to thrombocytopenia, approximately 60 cases (including 2 fatal) were reported in the United Kingdom with the AstraZeneca vaccine and 34 cases (1 fatal) with the BioNTech/Pfizer vaccine, whereas in the United States only 105 cases of thrombocytopenia were reported with the BioNTech/Pfizer and Moderna vaccines. Immune thrombocytopenic purpura (ITP) is of course possible, as after any vaccine.

The main problem is that there are no trustworthy denominators stratified for age and for sex (8,9). Studies are underway to try to better identify the profile of at-risk individuals and to better manage these risks. The collection method for these adverse events is also important since it may be based on spontaneous reporting (with a risk of under-reporting) or on more systematic prospective analyses. This continuous and rigorous pharmacovigilance

remains crucial for post-marketing (phase 4) vaccination studies. In this health emergency, it should enable us to reinforce the trust established during phase 3 randomised clinical trials and to combat drug mistrust with more extensive experience.

4. VITT: A pathophysiological approach to thrombosis following SARS-CoV-2 vaccine

The clinical and biological profile that is characteristic of the events described by the German and Norwegian authors and that associates significant thrombocytopenia with major hypercoagulability suggests an immunological mechanism, such as those described during catastrophic antiphospholipid syndrome or heparin-induced thrombocytopenia (HIT). As these patients vaccinated for SARS-CoV-2 had not received heparin, it could be a form of autoimmune HIT or "spontaneous" HIT (33,34). A new syndrome was proposed, vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), which has now been changed to vaccine-induced immune thrombotic thrombocytopenia (VITT) (13). The German authors, by studying the serum of 9 of the 11 patients, were able to demonstrate very high levels of heparin-Platelet-Factor 4 (PF4) antibodies in some of them and the ability of these antibodies to activate the platelets of control subjects with or without added PF4 (13). Furthermore no addition of heparin was required to activate platelets which distinguishes VITT of classical HIT. This platelet-activating ability was neutralised in the presence of high heparin concentrations, as in HIT. It was also blocked by the use of monoclonal antibodies binding on the platelet membrane FcγRIIa receptor (CD32a), which induces signalling and platelet aggregation/secretion, platelet-neutrophil- and monocyte complex formation, and thrombin generation. Use of high concentrations of polyclonal immunoglobulins can also interrupt the platelet-activating effects of these **autoreactive anti-PF4 antibodies** thus

confirming immunological hyperactivation of platelets through CD32a (35). This profile was also reported in the Norwegian and English cohorts (12,14).. The appearance of these autoantibodies in cases of exaggerated inflammatory response probably by the adenoviral vector, which triggers the release of PF4 contained in the platelets, could be responsible for multicellular activation with massive generation of thrombin, platelet consumption and severe thrombogenicity (36).The inflammatory reaction can cause “NETosis” or “immunothrombosis” with the release of leukocytic DNA, which supports the formation of microthrombi (37-39). Disproportionate post-vaccination inflammation can also increase endothelial adhesiveness and the release of tissue factor, a real trigger of the generation of thrombin, a key enzyme in coagulation (33,36). An important point is that this thrombotic and thrombocytopenic symptomatology occurred after the first vaccine injection, with intervals to detection ranging from 4 to 28 days (40). The cause and effect relationship has not been clearly established given that post-vaccination seroconversion has not been proven and that this type of anti-PF4 antibody can exist prior to the vaccination. Indeed, 5 to 7% of blood donors have detectable anti-PF4/heparin antibodies (41).

Of note, particular care should be taken to ensure that these reported cases of thrombosis are not related to a SARS-CoV-2 infection concomitant with the vaccination. Not all the reported patients were tested for other immune and systemic conditions that might be responsible for complement pathway activation, inflammation and coagulation in order to explain an idiosyncratic reaction (36). All UK patients had a negative SARS-Cov-2 polymerase chain reaction at their admission and no recent asymptomatic SARS-CoV-2 infection that may have caused the excessive autoimmune response was reported (12). The possibility of catastrophic antiphospholipid syndrome can also not be ruled out, although post-infectious antiphospholipid antibodies are generally less thrombogenic and transient.

5. Principle of protection

As rightfully claimed, “abstention is not a solution!”. All scientific societies and thrombosis experts stress the value of continuing vaccination programmes to protect patients against serious forms of COVID-19 and to slow viral circulation, particularly of the variants.

Without vaccination, patients are exposed to contracting SARS-CoV-2 with far greater inflammatory and immune stimuli and potentially more devastating consequences than those of the vaccine (42). They therefore need to be protected from COVID-19, a disease with particular vascular tropism, through vaccination and subsequent monitoring (43,44). In England, the health authorities and the Joint Committee on Vaccination and Immunisation (JCVI) maintained the second injection programmes with the same vaccine for all patients who had received their first AstraZeneca injection with no particular concerns (8). In contrast, authorities restrict the use of AstraZeneca now to patients older than 60 years in Germany, 55 years in France, 40 years in Canada or 30 years in UK and even recommend using non-AstraZeneca alternatives as booster for younger patients initiated on AstraZeneca (15). This recommendation is bare of any evidence (both for efficacy and safety of such an approach) and demonstrates the turmoil caused by the rare thrombotic side effects of the vaccine.

Rapid protection needs to be afforded to patients under 60 years of age with comorbidities (cancer, cardiovascular disease, kidney or liver impairment, immunosuppressant use, obese, diabetes…). This should also be the case for patients on long term anticoagulant treatment for antiphospholipid syndrome or other reasons. It is very instructive to look at changes in the curves comparing the number of new cases of COVID-19 before and after vaccination implementation in the healthcare personnel of Paris Public

Hospitals (AP-HP) (more than 50% vaccinated) versus the general population in the greater Paris region (12% vaccination rate). It shows a very clear drop in infections of AP-HP personnel during the third wave of infection, whereas the curves were completely identical in the autumn of 2020 during the second wave (Figure 2). Repeated and appropriate vaccination will likely be the best solution for combatting this pandemic and its variants. More information on potential risk factors and better understanding with a high level of concern on how the vaccine induces these platelet-activating antibodies are needed but larger and quicker population protection is required (45).

6. Principle of education

In a recent English report on accidents, the annual risk of death from road accidents was estimated at 110 out of 1,000,000 individuals at the age of 25 years, and 180 out of 1,000,000 at the age of 55 years (46). As a comparison, the risk of having a serious event in relation to SARS-CoV-2 vaccination was estimated at 11 out of 1,000,000 individuals at the age of 25 years, and 4 out of 1,000,000 at the age of 55 years (46). Heparin-Induced Thrombocytopenia (HIT) is a paradoxical prothrombotic syndrome with life-threatening consequences (47). Concerning the incidence of HIT in heparinized patients, this varies according to the clinical context and ranges from 0.1% in medicine with **low- molecular-weight heparin** to over 3% in cardiac surgery with unfractionated heparin (47). Given its proven clinical benefit, the use of heparin is not prohibited, but patients and their platelet counts are closely monitored to limit these risks.

We must observe, analyse and make decisions on the basis of our experience and data from real-world prescribing conditions (apart from clinical trials). Medicine is based on scientific evidence and clinical examination. After the reporting and description of

thrombosis cases, we were able to have an etiopathogenic lead within several days. The aim is to provide a practical approach to limit the potential risks of vaccination within the general population. The expected benefits of vaccination are far superior to the risks involved (Tables 1 A and 1B) (48). The benefits of SARS-CoV-2 vaccination remain acknowledged worldwide, especially for avoiding the serious forms, significantly limiting the number of hospitalisations, reducing viral transmission and providing herd immunity.

There should be more about the approach to those not yet vaccinated, to mass media and to other opinion leaders (teachers, supervisors at large workplaces, religious leaders) regarding reassurance and promotion of vaccination and to primary care and emergency physicians and nurses that may come in contact with people vaccinated and reporting suspicious symptoms how to identify and appropriately manage VITT. Various guidance is thus proposed by experts and scientific societies for both clinicians and patients (39,49,50). This understandable information must be vulgarized and shared as much as possible to make everyone aware but not scared. Therefore **widespread,** comprehensive and simplified information should be proposed such as it was done for stroke recognition for example with "BEFAST" acronym:

- B - Balance: Watch for a sudden loss of balance with severe headache or dizziness
- E - Eyes: Double vision or blurred vision that doesn't go away when you blink your eyes
- F - Fainting : or loss of consciousness
- A – Abdominal pain: severe and persistent pain, diarrhea, nausea, vomiting, bloody or tarry stools
- S - Swelling: oedema of an arm or a leg with or without colour change, shortness of breath with chest pain

- T - Time: these symptoms appear between 4 and 28 days after vaccination. They can be associated with Thrombosis and Thrombocytopenia

Combining this clinical suspicion with a more rapid identification and an adapted treatment implementation would help to re-establish the confidence in the vaccination strategy and to reduce the risk of dying from this rare VITT syndrome.

7. Principle of vigilance

Do all SARS-CoV-2 vaccines carry a risk of thrombosis? Dozens of COVID-19 vaccine candidates of various types are under development, including inactivated, live attenuated, viral vector and nucleic acid-based forms. It appears that the methods of vaccination using adenoviruses and containing genetic material from the spike protein are the most likely to result in an inflammatory reaction and systemic stimulation with general symptoms : pain and tenderness at the injection site, headache, tiredness, muscle pain, general feeling of being unwell, chills, fever, joint pain and nausea (8,9) (Table 2). Vigilance should be maintained regarding large-scale injections of vaccines, which are also based on the use of various adenoviral vectors. No information on any thrombotic risk with the Sputnik V vaccine using different adenoviruses in each injection (Ad26 and Ad5 CoV2-S) has been published so far. The question is raised as to whether single-strand messenger RNA vaccines, which form antibodies against the spike protein, are more targeted and with fewer vascular side effects. In fact, rare cases of thrombosis have also been reported in patients vaccinated with these mRNA vaccines. There is no “zero risk”, and it is essential that we maintain oversight of all patients regardless of the vaccine used. In France, the French General Medical Council (CNOM) obtained important safeguards for protecting physicians in their decision-making to offer the vaccine to their patients (51). Article L.3131-15 of the French Public Health Code

offers both vaccinated individuals and healthcare professionals the same legal safeguards as those provided for in the context of compulsory vaccinations (52). Full compensation for any accidents attributable to the vaccination campaign will therefore be assured by the Office National d'Indemnisation des Accidents Médicaux (French National Office of Medical Workers Compensation) in the name of national solidarity.

8. Principle of precaution

We need to inform, reassure and support our patients when the prescription is made. Based on these observations, we propose a tracking algorithm for vaccinated patients. It uses a 10-point guideline for safe decision-making.

1. Intramuscular injection should be done correctly in the deltoid muscle and not intravascularly by using the right technique and applying the injection at the appropriate lower site of the muscle (53,54). **Injection itself can cause injuries as it is not as harmless as one commonly thinks.**

2. Check that there is not an extensive ecchymotic or purpuric local reaction that is particularly painful.

3. Be aware of the possibility of minimal systemic signs, low-grade fever or muscular pain, which relate to the expected inflammatory response and to stimulation of the immune system, and which varies from one subject to another. It is advisable for the patient to drink a lot of fluids and take paracetamol in case of flu-like symptoms and to discuss it with their doctor. These signs should decrease in 48 to 72 hours.

4. Patients should consult with their doctors urgently or go to the hospital in the event of emerging and persistent clinical manifestations more than 4 days after the vaccination, including intense and persistent headaches, dizziness, visual disorders, impaired speech,

acute pain or worsening muscular pain, oedema of a limb suggestive of phlebitis, significant changes in the temperature of a limb (heat or cold), difficulty breathing, sudden heart rate acceleration. The same awareness should be given to unusual bleeding signs, especially petechiaes. For effective workup, patients presenting with suggestive symptoms should be admitted with a low threshold to allow for an immediate and thorough workup.

5. Start laboratory investigations after physical examination: complete blood count with platelet count, D-dimers (>1000 ng/ml) and schistocytes to rule out a hypercoagulable state with platelet consumption (Plts < 120 G/L) or disseminated intravascular coagulation with a decrease in fibrinogen (<2 g/L) (depending on the clinical profile, additional tests may be ordered such as C-reactive protein, antiphospholipid antibodies (anticardiolipin, anti-betaGP1), screening for lupus anticoagulant, antinuclear antibodies, ADAMTS13…).

6. Detect thrombosis through imaging in various sites (venous ultrasound, MRI, CT angiography).

7. Investigation for HIT in case of thrombocytopenia (platelets < 120 G/L) through screening for heparin-PF4 antibodies with ELISA assay (Lifecodes PF4 IgG (Immucor) or **Asserachrom HPIA – IgG (Stago)).** Assess the ability of these antibodies to activate platelets through a rapid functional test in presence of PF4 (Heparin-induced multi-electrode aggregometry method (HIMEA) or adapted Flow Cytometry specialised test by expert centre) (55-57).

8. Implement without delay an effective non-heparin antithrombotic treatment by injectable anticoagulant (fondaparinux, danaparoid, argatroban) based on availability, experience and the possibilities of close biological monitoring of the treatment. Depending on the clinical context and evolution, the switch to direct oral anticoagulant (dabigatran, rivaroxaban, apixaban) can be proposed.

9. In the event of major thrombotic events, infuse immunoglobulins (1g/kg) in combination with antithrombotics for 48 hours (to occupy the CD32 membrane sites of autoantibody cell docking and thus limit multicellular excitability leading to this generalised prothrombotic event). Steroids or plasma exchange are also options to reduce these incendiary auto-antibodies. Interestingly, inhibitors of Bruton tyrosine kinase (Btk), pleiotropically targeting multiple pathways downstream of CD32 activation and approved for B-cell malignancies (e.g. ibrutinib), are proposed as another potential therapeutic option in VITT (36).

10. Report the proven and documented serious event to pharmacovigilance authorities.

After seeing what still needs to be accomplished, let's have a look at what not to do:

1. Systematic management of vaccination with thromboprophylaxis (low-molecular-weight heparin or direct oral anticoagulant) or aspirin
2. Systematic screening for thrombophilia before vaccination.
3. Systematic measure of anti-PF4 antibodies after vaccination
4. Systematic monitoring of changes in D-dimers before and after vaccination.
5. Systematic use of a venous ultrasound exam before and after vaccination.
6. Contraindicating SARS-CoV-2 vaccination in case of history of thrombosis.
7. Contraindicating SARS-CoV-2 vaccination in case of autoimmune disease.
8. Contraindicating SARS-CoV-2 vaccination in case of history of HIT but due to potential "genetic susceptibility" choosing mRNA vaccine is preferable
9. Systematically contraindicating SARS-CoV-2 vaccination in case of history of allergy. Of course this is not the case of allergy after first dose of any vaccine.

10. Contraindicating SARS-CoV-2 vaccination in case of immune thrombocytopenia (ITP).

Conclusion

The scientific evaluation of the European Medicines Agency concluded to the safe and effective use of COVID-19 vaccines and that the most recent data do not change the recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC). Use of the vaccine during national vaccination campaigns must take into account the pandemic situation and the availability of the vaccine in each member state. All vaccines must be administered under close supervision with appropriate medical treatment available (15). Most international medical scientific societies, including the International Society on Thrombosis and Haemostasis (ISTH) and the World health Organisation (WHO), have issued statements to encourage populations of countries where the AstraZeneca vaccine was available to continue using it (40,49,50,58). The vaccination has clear and accessible health, economic and societal objectives. The role of any preventive medicine is to offer safe protection and control of potential adverse events, although the latter is part of the risk of medical decision-making. Abstinence is not an option since it results in failure to provide assistance to a large population that remains in danger. Action with increased vigilance and a broader understanding is the best solution in our public health mission.

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Figure 1: SARS-COV2 vaccination objectives *(based on 5)*.

Among multiple objected benefits of SARS-CoV-2 vaccination, significant prevention of thrombosis must also be taken into account.

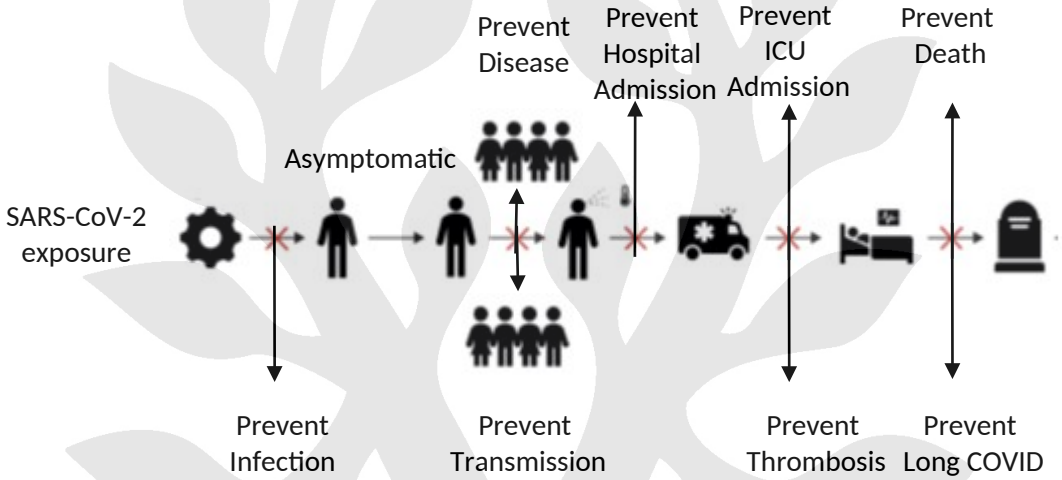

Figure 2. Profile of changes in COVID-19 cases in the greater Paris region and in AP-HP hospital personnel.

Comparing the infection rate between the two populations, the effectiveness of vaccination campaign of AP-HP health workers in hospitals is obvious. After a perfect overlap of both populations curves during the previous wave, a significant gap is observed. This is probably related to vaccination campaign acceleration involving more health workers with more than 50% effectively vaccinated compared to only 12% in the general Parisian population.

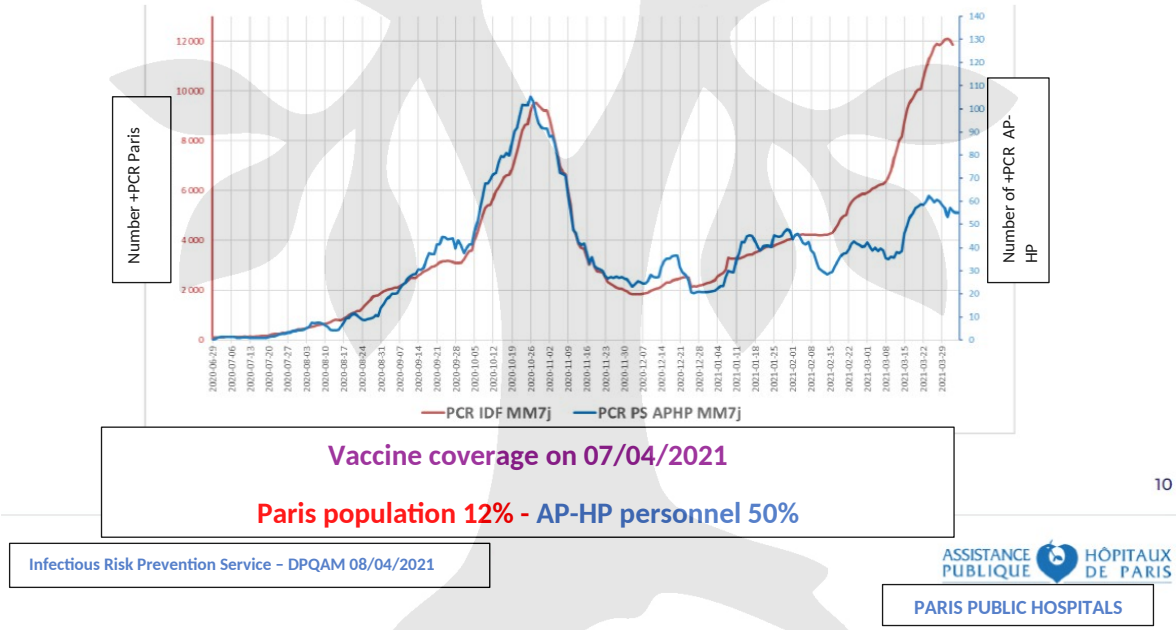

Table 1: Modelling of the risk/benefit ratio of the AstraZeneca vaccine per 100,000 people based on age and infectious risk of exposure *(based on Winton Centre@maths.cam.ac.uk, University of Cambridge, 48)*

ICU: intensive care units

Numbers of cases balancing the risk between potential severe vaccine-related side effects and vaccine-related benefit avoiding ICU admissions **(A) and COVID-19-related Death (B)** in correlation with the age and the importance of SARS-CoV-2 infection exposure.

Table 1.(A)

Potential risk of severe thrombotic thrombocytopenia n/100,000	Age (years)	Potential benefit ICU admissions avoided based on Sars-Cov-2 infection rate		
		Low 55/100,000	Medium 400/100,000	High 900/100,000
1.9	20-29	0	3	6
1.8	30-39	0	5	8
2.1	40-49	1	10	15
1.1	50-59	1	15	28
1.0	60-69	3	28	50
0.5	70-79	6	39	78
0.4	+80	13	29	110

Table 1 (B)

Potential risk of severe thrombotic thrombocytopenia n/100,000	Age (years)	Potential benefit COVID-19 Deaths prevented based on Sars-Cov-2 infection rate		
		Low 55/100,000	Medium 400/100,000	High 900/100,000
1.9	20-29	0	0	0
1.8	30-39	0	2	3
2.1	40-49	1	7	10
1.1	50-59	1	8	14
1.0	60-69	3	25	45
0.5	70-79	14	87	172
0.4	+80	90	197	733

Table 2. The different types of vaccines used in Europe: classical side effects (based on 9,10)

TYPE OF VACCINE	1/10 vaccinated patients	1/100 vaccinated patients	Allergic reactions
BioNTech/Pfizer (mRNA)	Local pain, swelling, fatigue, headache, muscular pain, joint pain,	Pain to extremities, local adenopathy, poor	11/1,000,000 vaccinated patients Rare cases of anaphylactic

	fever	general wellbeing	reaction
Moderna Therapeutics (mRNA)	Local pain, oedema, local adenopathy, fatigue, headache, muscular pain, nausea, fever	Redness at injection site, vesicular lesions	2.5/1,000,000 vaccinated patients rare anaphylactic reaction
Oxford/AstraZeneca ChAdOx1-S	Local pain, swelling, fatigue, muscular pain, joint pain, poor general wellbeing, nausea, fever	Dizziness, sweating, abdominal pain, skin rash	10/1,000,000 vaccinated patients rare anaphylactic reaction
Janssen Ad26.COV2-S	Local pain, headache, fatigue, muscular pain, joint pain, poor general wellbeing, nausea, fever	Cough, joint pain, fever, erythema, oedema, chills	Rare anaphylactic reaction, hypersensitivity, hives