Overview of COVID-19 vaccines and VITT/TTS (Thrombosis with thrombocytopenia syndrome), update March 2022

Introduction

After the conditional approval and introduction of COVID-19 vaccines a rare condition of thrombosis in combination with low platelet counts (below 150 /nL) caused by antibody formation against platelet factor-4 (PF4) was identified as a serious but rare adverse event following immunisation with the vector vaccines Vaxzevria and Janssen [1-3]. The condition is called 'vaccine-induced (immune) thrombotic thrombocytopenia' (VITT) by workers in the field or 'thrombosis with thrombocytopenia syndrome' (TTS) by regulatory agencies [4]. First cases of VITT/TTS were reported in literature in Germany in February 2021 [5].

Specific tests were developed quickly and many guidelines and case definitions how to diagnose and report VITT/TTS appeared. Common features of case definitions of VITT/TTS include 1) the onset of symptoms 5-30 (42) days post COVID-19 vaccination with a vector vaccine, 2) documented thrombosis or severe and persistent headache, 3) platelet count < 150 /nL, 4) fibrin D-dimer > 2000-4000 µg/L and 5) positive anti-PF4/heparin IgG ELISA [6]. In the Dutch guideline, VITT should be considered in every patient with thrombocytopenia with or without thrombosis within 28 days following any COVID-19 vaccine and a functional platelet activation test (HIPA) is promoted as confirmatory test next to the ELISA [7].

By the nature of spontaneous reporting, not all required diagnostics are available with reported cases. Therefore, we applied a more practical classification from the US Centers of Disease Control and Prevention (CDC) to determine confirmed or strongly suspected VITT/TTS cases following any COVID-19 vaccine. The first group concerns thrombosis at unusual locations and new onset of thrombocytopenia (<150 /nL) and further diagnostic tests are not obliged (tier 1). The second group concerns new onset of thrombocytopenia and more common venous thrombosis in extremities or pulmonary artery *and* a positive test result of the anti-platelet factor (PF)4 antibody ELISA test or the functional heparin-induced platelet activation test (HIPA), occurring any time after receipt of a COVID-19 vaccine (tier 2) [8]. The Dutch guideline further specify that with VITT/TTS thrombosis can occur as pulmonary embolism, deep vein thrombosis and *arterial thrombosis* or, in rare cases, without thrombosis [7]. If the ELISA and/or HIPA test is positive, TTS is confirmed. Locally used HIT screening tests in hospitals cannot confirm or rule out VITT/TTS [7]. Thrombocytopenia is defined as a platelet count <150 /nL [7], however in patients with a high baseline platelet count a reduction of > 50% could also indicate thrombocytopenia. [4]

This overview describes reported cases of VITT/TTS with COVID-19 vaccines in The Netherlands in the first year of the vaccination campaign. Up to 16th January 2022, 32.5 million vaccine doses were administered in more than 13 million people who received at least one vaccination dose of any brand.

Reports

Until January, 26th 2022 The Netherlands Pharmacovigilance Centre Lareb received a total of 75 spontaneous reports of a combination of thrombosis and thrombocytopenia from healthcare professionals and consumers. Among these, 26 were confirmed or strongly suspected for thrombosis with thrombocytopenia syndrome (VITT/TTS) with COVID-19 vaccines according to CDC case criteria and the Dutch guideline.

**Table 1: Characteristics of confirmed and strongly suspected reports of VITT/TTS with COVID 19 vaccines. ***One report can contain more than one site of thrombosis. Abbreviations: DIC = diffuse intravasal coagulation; CVST= cerebral venous sinus thrombosis.

	Total	AstraZeneca	Janssen	Pfizer	Moderna
Reports	26	19 (73.1%)	5 (19.2%)	1 (3.8%)	1 (3.8%)
- Dose 1	23 (88.5%)	17 (89.5%)	5 (100%)	1 (100%)	0
- Dose 2	2 (7.7%)	2 (10.5%)	na	0	0
- Dose 3	1 (3.8%)	0	na	0	1 (100%)
Case definition					
- Tier 1 (unusual)	15 (57.7%)	11 (57.8%)	2 (40%)	1 (100%)	1 (100%)
- Tier 2 (common, test)	6 (23.1%)	5 (26.3%)	1 (20%)	0	0
- Dutch guidelines (other)	5 (19.2%)	3 (15.8%)	2 (40%)	0	0
Sex					
- male	8 (30.8%)	6 (31.6%)	2 (40%)	0	0
- female	18 (69.2%)	13 (68.4%)	3 (60%)	1 (100%)	1 (100%)
Age (mean; range)	53.2 (27-83)	54.7 (27-72)	30.6 (27-53)	75	83
Diagnosis*					
- CVST	5 (19.2%)	3 (15.8%)	2 (40%)		
- Abdominal veins	6 (23.1%)	5 (26.3%)		1 (100%)	
- Pulmonary embolism	7 (26.9%)	6 (31.6%)			1 (100%)
- Deep vein thrombosis limb	2 (7.7%)	1 (5.3%)	1 (20%)		
- Arterial thrombosis	3 (11.5%)	3 (15.8%)			
- Cerebral arterial thrombosis	3 (11.5%)	3 (15.8%)			
- DIC	2 (7.7%)	1 (5.3%)	1 (20%)		
- No thrombosis	1 (3.8%)		1 (20%)		
Platelet count (nadir) (mean, range; /nl)	55 (9-156)	56 (9-156)	59 (40-62)	unk	20
Time to onset after vaccination (mean, range; days)	14.1 (1-41)	13.5 (4-41)	14.4 (1-35)	22	15
Outcome					
- Recovered/recovering	13 (50.0%)	9 (47.4%)	4 (80%)	0	0
- Fatal	3 (11.5%)	3 (15.8%)	0	0	0
- Not recovered/ unknown	10 (38.5%)	7 (36.8%)	1 (20%)	1 (100%)	1 (100%)

Reporting rate

The number of administered vaccines of AstraZeneca was 1,271,409 (first dose) and 1,202,594 (second dose); Pfizer 21,851,974 (all doses), Moderna 5,858,606 (all doses), Janssen 876,500 (all doses) [9].

The reporting rate of VITT/TTS with the AstraZeneca vaccine is *7.7 per million vaccinations in total*, with *13.4 per million people who received the first dose* and 1.7 per million people who received the second dose. The reporting rates for Janssen, Pfizer and Moderna are 5.7, 0.05 and 0.2 per million vaccinations in total, respectively.

Classification

Reports with thrombosis at unusual sites were classified in tier 1, with positive tests or based on clinical patterns if tests were not available. For tier 2, venous thrombosis at more common sites, and confirmatory test results were required. Five reports did not meet CDC criteria but were based on Dutch guidelines. These concern reports of cerebral infarction (2), without specific thrombosis (1), with disseminated intravascular coagulation (1) and CVST without thrombocytopenia (156 /nL).

Tests

In 22 reports one or more specific diagnostic tests were performed, such as a local HIT screening test and confirmation tests performed by Sanquin, such as antibody PF4/HIT ELISA or functional HIPA tests.

The type of HIT test was not always clear in the reports: ‘HIT’ test was mentioned 14 times and ‘ELISA’ or ‘PF4’ was mentioned 6 times, of which 8 and 4 were positive, respectively. A functional HIPA test was done in 20 reports, of which 17 were positive.

In three reports VITT/TTS was strongly suspected based on clinical judgement despite negative (HIPA) confirmation tests (PF4/ELISA not performed in these cases). In one of these cases the negative test results were not reliable since blood samples for HIPA test were taken after treatment with IVIG.

VITT/TTS reports with mRNA vaccines
VITT/TTS is labelled as an adverse effect following immunisation with the COVID 19 adenovector vaccines of AstraZeneca and Janssen [1, 2]. VITT/TTS has not been associated with mRNA vaccines. However, Lareb received a few reports of VITT/TTS with the mRNA vaccines of Pfizer and Moderna.

One report concerns a female aged 70 years and older developing thrombosis with thrombocytopenia syndrome based on portal vein thrombosis and thrombocytopenia, 23 days following the first immunisation with the COVID-19 Pfizer vaccine, treated with apixaban and immunoglobulins. Unspecified HIT and VITT tests as well as regular blood tests and CT scan were performed, but results are not specified.

The second report concerns a female aged 70 years and older developing large pulmonary embolisms and thrombocytopenia (nadir 20 /nl) in 13 days following the third (booster) vaccination with Moderna whereas the first two vaccinations were Pfizer. Specific VITT PF4 ELISA and HIPA were positive and platelet counts were only recovering after immunoglobulin treatment. Of note, first treatment started with LMWH heparin (one dose) which was switched to danaparoid. However, HIT was considered as unlikely since specified tests for HIT were negative and she never had heparin exposure nor surgery in her life before.

In a third report of abdominal aortic and arterial thromboses with thrombocytopenia (25 /nL) in 23-26 days following the second dose of the COVID-19 Pfizer vaccine, a positive functional HIPA test was mentioned. However, this 70 years and older male also had used heparin for endovascular aortic aneurysm repair for 11 days. The HIT tests were unable to distinguish HIT from VITT. Thus, this report is not considered a VITT/TTS case.

Reports of thrombosis with thrombocytopenia not meeting VITT/TTS criteria
Lareb received 49 reports with COVID-19 vaccines (AstraZeneca 21, Janssen 3, Pfizer 19 and Moderna 6) of various forms of thrombosis and a low platelet count that could not be classified as VITT/TTS cases. In these reports criteria for VITT/TTS were not met by various reasons:

- In four reports there was another cause that was considered more likely (e.g. pre-existing thrombocytopenia, antiphospholipid syndrome and HIT).
- In ten reports VITT diagnostic tests were negative and in some of them other risk factors for thrombosis were present (e.g. COVID-19 infection, malignancies, familial risk factor, previous thrombo-embolic event).
- In twelve reports test results could not be interpreted due to lack of information (e.g. test name was mentioned without a result)
- In 23 reports no HIT or VITT tests were done. Note that in 8 early reports no guidelines were available yet (until 20-4-2021) and in another 8 reports tests and guidelines were developed over time (until 27-5-2021).

Fatal outcome

In total, six patients died following thrombosis and thrombocytopenia. In three reports, VITT/TTS diagnose following AstraZeneca vaccination was confirmed. These concern two women and one man, aged between 63 and 72, with pulmonary embolism (1) and cardiac thrombosis with cerebral infarction (1) and cerebral arterial thrombosis (1).
In the other three reports (2 AstraZeneca and 1 Pfizer), the criteria for VITT/TTS were not met. It concerned three women, aged between 45 and 69, with pulmonary embolisms. All had other risk factors for thromboembolic events, such as cardiac failure, obesity or concomitant use of medication with prothrombotic effects such as oral contraceptives and oral corticosteroids. In these three reports no specific VITT/TTS tests were performed, although in one report a HIT screening test was negative.

Discussion
Spontaneous reporting
Underreporting is a common feature of spontaneous reporting systems. However, it is assumed that the majority of confirmed or strongly suspected cases of VITT/TTS has been reported to Lareb, since there has been a lot of media attention and internists were encouraged to report cases in their guidelines [7].
On the other hand, VITT/TTS was a new entity without a clear diagnosis at the beginning and some cases could have been missed in the diagnostic process. First reports were also limited in diagnostic

documentation and specific tests were not available. All cases had to be diagnosed by Lareb in retrospect based on information provided by reporters, for which experts in the field were called in. By means of progressive insight, it has become clear that VITT/TTS presentation is heterogeneous and may present without thrombosis and varying severity of decreased platelet counts [10, 11]. For clinicians, it may not always be evident when to perform specific diagnostics for VITT/TTS, which is shown in our 23 reports where VITT diagnostics were absent; in at least eight early reports tests and guidelines were not available. Unfamiliarity with the presentation of the disorder may also have contributed to underdiagnosis and subsequent underreporting.

The incidence of VITT/TTS is not exactly known, since reported risks vary between countries and between vaccinated populations with AstraZeneca and Janssen vaccine. Until 30th September 2021 1809 cases were reported to European pharmacovigilance centres, resulting in reporting rates of 14 per million first doses and less than 2 per million second doses of the AstraZeneca vaccine [12].
In the US a study in VAERS calculated a reporting rate of TTS of 3.8 per million vaccinations for Janssen (54 reported cases) and 0.00085 per million for mRNA vaccines (3 reported cases with Moderna) [13]. The reporting rates in The Netherlands for VITT/TTS with AstraZeneca and Janssen are much in line with calculated reporting rates in Europe and the US, respectively.
In pharmacovigilance databases true VITT/TTS reports were difficult to retrieve, since not all reports that combined thrombosis and low platelet counts appeared to be caused by VITT/TTS. Only since December 2021, it became possible to use MedDRA coding for thrombosis with thrombocytopenia syndrome.

Mechanism
VITT/TTS is an autoimmune response in which IgG anti-PF4 antibodies bind to platelet FcγRIIA (Fc gamma IIA receptor) directly activating platelets and triggering the formation of blood clots [3]. How adenovirus vectors trigger this response is not well understood [3, 15]. It is suggested that adenoviral proteins bind to PF4 to form a complex that is recognized as antigen and along with a systemic inflammatory response anti-PF4 antibodies are produced [16].
VITT resembles HIT in the way that heparin can bind to PF4 forming a complex that can be seen as an antigen which is recognized by antibodies [17]. Fc fragments of antibodies against PF4/heparin bind to FcγRIIA on platelets causing aggregation and degranulation with release of more PF4 and particles activating the coagulation cascade. In contrast to HIT, VITT is not induced by heparin exposure [16].

Anti-PF4 antibodies produced in B cells can be present in patients affected by tissue trauma and inflammation, even in the absence of heparin. Thiele et al. showed the presence of antibodies against PF4 in 6.8% of healthy people vaccinated with AstraZeneca and in 5.6% vaccinated with Pfizer. None had a positive platelet activating assay however [18]. The presence of anti-PF4 antibodies alone is not enough evidence and should be confirmed with an ELISA immunoassay or a HIPA in the presence of PF4 to confirm VITT/TTS.

TTS with mRNA vaccines
In literature few articles describe the occurrence of VITT/TTS with mRNA vaccines: one literature review, one database study and three individual case-reports.
Hafeez et al. performed a systematic review including published papers until July 2021, collecting five possible cases with mRNA vaccines with reference to WHO case definition of VITT/TTS [19]. However, a short screening of the cases involved reveals that 4 out of
es do not meet the CDC case definition nor Dutch guidelines.
In the US, three cases of VITT/TTS were reported with the Moderna mRNA vaccine to VAERS database, summarized by See et al. [14]. One of these cases concerns the fifth case mentioned by Hafeez and is also published as a case-report by Sangli [20]. The three published case-reports concern two men (65 and 70 years) and one women (34 years) with pulmonary embolisms and CVST, multiple cerebral infarctions and no specific thrombosis, respectively. All had decreased platelet counts and positive anti-PF4/heparin IgG ELISA tests but none describe a functional HIPA test for additional confirmation [20-22]. Furthermore, in all cases other patient related conditions may have contributed to the development of thrombosis and thrombocytopenia. In an editorial by Pishko on the case published by Sangli, it is argued that this case should be interpreted with caution, since elevated HIT antibodies in part of asymptomatic patients is also low but not zero and autoimmune subtypes of spontaneous HIT is described in patients with orthopaedic surgery and in medical patients with infections [18, 23]. See et al. suggested that the cases reported with mRNA vaccines might reflect

background incidence since patient characteristics were different from the cases with Janssen. In VAERS, TTS cases with mRNA vaccines, two out of three were male and mean age was higher (> 50 years) and at least two had cardiovascular risk factors [14].

Based on published case-reports and the spontaneous reports of possible VITT/TTS with mRNA vaccines, it is too early to draw firm conclusions on a causal relationship.

Other causes of thrombosis with low platelet counts
Before the COVID-19 pandemic, it was estimated that 14% of patients with VTE had low platelet counts [24]. Causes for concurrent thrombosis and thrombocytopenia may also be vaccination related or may have a different aetiology. Both a transient thrombocytopenia and immune thrombocytopenia (ITP) have been observed with COVID-19 vector vaccines [1,2]. Other causes for thrombocytopenia are infections, medications and ITP [16, 25]. General risk factors for venous thrombosis are cancer, pregnancy, oral contraceptives and other estrogen containing medications, surgery, immobilisation, acquired and inherited thrombophilic disorders and COVID-19 [16]. Venous thrombosis is labelled as adverse event for the Janssen vaccine [2]. Finally, part of the platelets is used in the formation of blood clots, resulting in a decrease of the platelet count as well [26]. Classical venous and arterial thrombosis following COVID 19 vaccines are described separately.

Conclusion

During the first year of the COVID-19 vaccination campaign, The Netherlands Pharmacovigilance Centre Lareb received 26 confirmed or strongly suspected cases of VITT/TTS. This very rare adverse event has been acknowledged as a side effect with the COVID-19 vector vaccines of AstraZeneca and Janssen. The reporting rate of VITT/TTS with AstraZeneca in The Netherlands is comparable to other countries. It is unclear whether VITT/TTS is also an extremely rare adverse event of mRNA vaccines, or whether there is a rare and not well-defined background incidence of this condition.

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This signal has been raised on April 28, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl