NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

VACCINE BENEFIT RISK EXPERT WORKING GROUP

Title of paper: COVID-19 Vaccines and the potential risk of immune thrombocytopenia

Type of paper: For advice

Active(s) rINN	Pfizer/BioNTech COVID-19 vaccine BNT162b2 AstraZeneca COVID-19 vaccine Moderna COVID-19 vaccine BNT162b2
Product name(s)	
Marketing Authorisation Holder(s)	Pfizer/BioNTech AstraZeneca Moderna
Legal status	Prescription only medicines
Therapeutic classification (ATC code)	
Previous assessments	
Assessor(s)	Name: [redacted] (Scientific Assessor) Email: [redacted] Name: [redacted] (Scientific Assessor) Email: [redacted] Name: [redacted] (Senior Medical Assessor) Email: [redacted]

1. Introduction

The Pfizer/BioNTech COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 2 December 2020. It is estimated that over 10 million doses have been administered in the UK as of 21 February 2021. The AstraZeneca COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 30 December 2020, and over 8.4 million doses have been administered in the UK as of 21 February 2021.

Immune thrombocytopenia is an adverse event of special interest with the COVID-19 vaccines and has been kept under close review by the MHRA since the start of the UK vaccination programme. The MHRA has received several reports of immune thrombocytopenia following administration of both the Pfizer/BioNTech and AstraZeneca COVID-19 vaccines, including some cases reporting serious bleeding events and fatal outcomes. There have also been international reports of immune thrombocytopenia with the Pfizer/BioNTech COVID-19 vaccine, including a fatal case in the USA[1].

This paper provides a summary of the data available to date regarding the potential risk of immune thrombocytopenia with the COVID-19 vaccines and seeks the EWGs advice on what, if any, action is required based on this data.

2. Immune thrombocytopenia, COVID-19 infection and vaccines

Immune thrombocytopenia (ITP) is an auto-immune condition characterised by low platelet count (thrombocytopenia) and is associated with an increase risk in bleeding which often presents as bruising or petechia/purpura. ITP may also be associated with nosebleeds, bleeding from the gums and women with ITP may experience heavier than normal menstrual bleeding. Rarely, severe bleeding in the brain can occur with ITP which is life threatening. The prevalence of ITP is estimated to be 50 in 100,000 of the UK population, which in adults increases with age and is higher in women compared to men[2]. ITP is also associated with other autoimmune conditions such as rheumatoid arthritis, lupus and Sjogren's syndrome. The number of ITP cases being identified is rising as more routine blood tests are carried out which can detect low platelet count[3].

ITP has been associated with infections by several viruses such as varicella zoster virus and the hepatitis C/B viruses. There is also evidence that it may also be associated with COVID-19 infection[4]. In a review of ITP cases post- COVID-19 infection, the majority of ITP cases were in the elderly (71%) and had moderate-severe COVID-19 (75%). ITP onset was variable after onset of COVID-19 symptoms with the highest proportion of cases occurring 8-14 days post symptoms (36%), followed by 15-21 days (23%), >21 days (20.5%) and <7 days (20.5%). Severe life-threatening bleeding was uncommon. The association between ITP and viral infection can be attributed to underlying immune dysregulation, susceptibility mutations in suppressor of cytokine signaling 1 (SOCS 1), and other mechanisms, including molecular mimicry, cryptic antigen expression, and epitope spreading.

ITP has also been associated with the live MMR vaccine, and typically occur within 6 weeks of vaccination with the highest incidence in the period 15-28 days post vaccination[5]. The risk of ITP with the MMR vaccine is low, with an estimated attributable risk of 1 in 25,000 vaccines and is much lower

[1] https://www.nytimes.com/2021/01/12/health/covid-vaccine-death.html
[2] https://pubmed.ncbi.nlm.nih.gov/22139790/
[3] https://www.nhlbi.nih.gov/health-topics/immune-thrombocytopenia
[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7501509/
[5] https://adc.bmj.com/content/84/3/227

than the risk of developing thrombocytopenia with infection of measles, mumps or rubella[6]. ITP has also been reported to occur after vaccination against pneumococcus, *Haemophilus influenzae B*, varicella zoster virus, and hepatitis B. The biological mechanism may be similar to that of infection, with molecular mimicry causing immune complex formations on the platelet surface leading to clearance of the platelets[4].

3. Pfizer/BioNTech COVID-19 vaccine

Yellow Card Data

Up to and including 22 February 2021, the MHRA has received 5 reports of immune thrombocytopenia and 12 reports of thrombocytopenia, across a total of 16 cases. There are also 3 reported events of platelet count decreased, 24 reports of petechiae and 8 reports of purpura.

A summary of the 5 reports of ITP is provided below:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Additionally, there has been one report of gastrointestinal hemorrhage in [redacted]

Of the 12 reports of thrombocytopenia, one is included in the reports above. The further 11 reports are summarized below.

- One fatal case of thrombocytopenia in [redacted]
- [redacted]

6 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884189/#:~:text=The%20risk%20of%20ITP%20occurring,in%2025%20000%20vaccinated%20children.

[redacted]

Of the three reports of platelet count decreased, one is discussed above, and one reports platelet count decreased in [redacted] The third case is of [redacted]

Three of the petechia reports are discussed above, and of the remaining 21 reports, 16 report an onset time of 3 days or less, one is a sparse case with no onset time reported and one has an improbable onset time of 378 days. None of the patients reported a history of thrombocytopenia. In the remaining 5 cases, onset times range from 13-44 days and ages range from 5 (improbable) to 92 years and are reported in three females and one male. One reports concurrent lower respiratory tract infection. None of these cases report other bleeding events. There is one case with [redacted]

Of the 8 purpura cases, one also reported petechia and is discussed above. Of the remaining 7, four have an onset time of 1 day and one of 2 days. [redacted]

A review was also conducted of non-serious hemorrhage events that had >3 events reported to us, those with <3 but indicate serious or life-threatening event and excluding vaccination site reactions.

Epistaxis was also included as a potential indicator of thrombocytopenia (Table 1). This overview indicates that the majority of events are non-serious and occur less than 7 days post vaccination; this gives an indication to be unlikely related to an autoimmune reaction as antibody peaks typically occur 7-14 days post vaccination, although this makes significant assumptions that hemorrhagic events occurring less than 7 days post vaccination are not vaccine associated. The number of fatal cases reported remains low.

Table 1. Summary of Pfizer/BioNTech COVID-19 vaccine Yellow Card reports for frequently reported and serious hemorrhagic event terms, as of 22 February 2021.*

Reaction (PT)	Number events reported**	Onset >7 days (n)	Fatal (n)	Hospitalised*** (n)	Age range (average)
Conjunctival haemorrhage	11	0	0	0	25-87 (59)
Gastric haemorrhage	2	1	1	0	74-87 (81)
Anal haemorrhage	4	1	0	0	28-78 (46)
Rectal haemorrhage	14	2	0	3	24-93 (60)
Small intestinal haemorrhage	1	0	0	0	[redacted]
Gastrointestinal haemorrhage	3	0	0	1	49–78 (61)
Upper gastrointestinal haemorrhage	2	0	0	2	80-82 (81)
Cerebral haemorrhage	9	2	3	3	49-94 (71)
Haemorrhage intracranial	2	1	1	0	82-84 (83)
Subarachnoid haemorrhage	2	0	1	0	70-83 (77)
Haemorrhage urinary tract	4	1	0	0	22-76 (52)
Vaginal haemorrhage	35	8	2	0	16-81 (38)
Epistaxis	149	18	1	3	3-93 (53)

**This includes non-serious hemorrhage events where had >3 events reported to us, those with <3 reports but indicate serious or life-threatening event and excluding vaccination site reactions.*

*** more than one of these events may be reported in a single case and therefore the sum of these numbers does not equate to the total number of cases reporting the PTs of interest*

**** hospitalisation is not always accurately reported*

Clinical Trial Data

There are no reports of ITP in the unblinded safety data with a cut off 14 November 2020. In the Phase 2/3 data to the cutoff date, there was one report of thrombocytopenia in active arm and two in placebo, with the two placebo events being considered serious. There were no reports of petechia, purpura or platelet count decreases.

In a blinded review of the clinical database as of 19 January 2021 there were 3 reports of thrombocytopenia, none with a diagnosis of ITP, all serious and all assessed as non-related. Of these, one event was associated with cirrhosis, one with cellulitis and one had a four-month history of rectal bleeding.

Pfizer/BioNTech Signal Review

The company has conducted a review of ITP post-authorization cases received up to 30 January 2021, which retrieved 15 unique, relevant cases under the search for thrombocytopenia (n=6) and ITP (n=7). Of these 4 were from the UK, 6 from the US, 2 from France and one from [redacted] Two of the UK cases have already been discussed as part of the Yellow Card and will not be repeated here.

Of the 6 remaining cases reporting ITP, a summary is provided below:

- US: [redacted]
- US: [redacted]
- France: [redacted]
- US: [redacted]
- US: [redacted]
- Switzerland: [redacted]

Of the 5 cases reporting thrombocytopenia:

- [redacted]
- UK: [redacted]
- US: [redacted]
- UK: [redacted]
- US: [redacted]

Pfizer/BioNTech also conducted an observed vs expected analysis and based on an estimate of nearly 34 million BNT162b2 vaccine administrations as of 30 January 2021, and equating to 1,456,409.8 person years of total follow up, and an assumed background rate of 3.3 incident events of immune thrombocytopenia per 100,000 person years. The crude ratio of the count of observed cases (n=1) to expected cases was determined using person time accrued during the 3-, 7-, and 21-day risk windows

after vaccination resulting in ratios of 11.71 (95% CI: 0.96 – 2.82, $n_{expected}$ = 8.8), 0.80 (95% CI: 0.45 – 1.32, $n_{expected}$ = 18.7) and 0.38 (95% CI: 0.21 – 0.62, $n_{expected}$ = 39.9).

Although the O/E ratio exceeds 1 under the 3-day risk window assumption, the lower limit of the 95% CI does not exceed 1 for any of the risk windows, indicating that the observed count is not higher than expected. Regardless of the risk window all 15 cases were included in the numerator, however of the 13 cases for which time to onset was reported, 5 occurred within 3 days, 1 between 4 and 7 days and 7 between 8 and 21 days. Therefore, the number of events in the risk windows does not exceed that expected based on the background incidence rate.

Summary

Of the Yellow Card reports received and international data available from Pfizer/BioNTech, there are 11 reports of ITP and 17 reports of thrombocytopenia. There are several of these cases reporting pre-existing ITP or risk factors such as rheumatoid arthritis and CMV/EBV infection. These are likely to be confounding factors, and these patients may be undergoing routine monitoring and therefore are more likely to have changes in platelet count picked up, although it should also be considered whether these existing conditions may predispose the patients to potential effect from the vaccine.

Five fatal cases were reported across the spontaneous data from the UK and internationally, reporting fatal events of intracranial bleed (n=2), renal failure (n=1), pulmonary embolism (N=1) and a sparse case with limited details of the events. The time to onset varies across these cases and potential confounding factors are reported in several cases including previous heart bypass and anticoagulant therapy, pre-existing essential thrombocytosis and other comorbidities. There are also 5 cases reporting serious bleeding events in association with thrombocytopenia, including stroke, hospitalization due to unspecified hemorrhage and gastrointestinal hemorrhage.

The number of events reported remains fairly low considering the high usage of the vaccine globally. The company's observed expected analysis using global data also did not indicate a reporting rate higher than that expected based on the estimated background incidence rate.

Limited conclusions can be drawn on the clinical trial data as most cases are blinded; it is noted that all events were considered non-related by the investigator. The unblinded data does provide some reassurance of no increased risk of ITP and thrombocytopenia, however this size of study and duration of follow up may not be sufficient to detect an effect.

4. Moderna

As no doses of the Moderna COVID-19 vaccine have been administered in the UK to date, data has been evaluated from the post-authorisation data from the summary PSUR, non-UK reports submitted to the MHRA's database, a report issued by the CDC in January 2021 and clinical trial data.

Monthly simplified PSUR

During the reporting period (18 Dec 2020 to 17 Jan 2021), a total of 28,608,700 doses have been distributed worldwide with 27,615,600 doses distributed within the US. Estimates of post authorization patient exposure are based on the number of doses distributed by country.

During the reporting period, Moderna states no cases relating to autoimmune terms or thrombocytopenia were reported.

A caveat is that due to a high volume of adverse event reporting to date, Moderna has experienced a backlog in processing cases. Moderna issued correspondence to regulators dated 10 February 2021,

explaining the backlog had increased between 21 January and 28 January 2021. Remedial action has been undertaken to address the issue, aiming for a resolution date of 15 March 2021, and the manufacturer has confirmed that the backlog does not include any serious cases.

Non-UK ADR reports

The MHRA database was searched for individual case safety report originating from outside the UK. Cumulatively to the 19th of February 2021, there were 2 reports of immune thrombocytopenia and 11 reports of thrombocytopenia or decreased platelet count amongst a total of 830 reports.

The two immune thrombocytopenia cases occurred with onset times of 9 and 23 days. The first, in a [redacted] Both report significant thrombocytopenia, however, no bleeding events were reported in either case.

Notable cases of thrombocytopenia include a fatal cerebral haemorrhage in a [redacted] A further two cases, also describing bleeding events, [redacted]

Although these cases include supportive factors including a plausible time to onset and response to treatment, immune thrombocytopenia is challenging to diagnose given the need to exclude other potential causes of thrombocytopenia (including malignancy, myelofibrosis, exposure to medication that may cause thrombocytopenia) and to establish information on whether other cell lines or coagulation pathways may have been affected, which may suggest other causes. There is currently insufficient information available in these cases to fully determine this, and as these are non-UK cases, follow-up is not available. Two cases would at least meet Brighton Collaboration criteria level 2 (platelet count less than $150\times10^{9}/L$) with 3 possibly meeting level 1 criteria (platelet count less than $150\times10^{9}/L$ with bleeding event or confirmed by smear).

There were also two reports of decreased platelets occurring in individuals with a known diagnosis of ITP. In one report [redacted] In the second report the event occurred [redacted]

In the remaining 6 cases, the event occurred within a short timeframe for antibody mediated event (1 to 3 days), occurred concurrently with other events which may have had a contributing effect (sepsis) or there was very limited information regarding the event.

Seventeen other reports mention events of haemorrhage without reporting thrombocytopenia. These describe a mixture of events and systems including cerebral, gastrointestinal, ocular and vaginal bleeds, some included alternative reasons for the bleeding event including anticoagulation or trauma.

In summary, the current reports are not considered to provide sufficient evidence for further action at this stage, however, this will continue to be monitored closely as an Adverse Event of Special Interest.

Clinical trial data

From Phase 3 clinical trials, no reports of autoimmune/ immune thrombocytopenia were noted. In the safety set, there were 2 reports of thrombocytopenia occurring in the vaccine arm (N=15185), compared to no reports from the placebo arm (N=15166).

Summary

Data at present does not suggest a signal with the Moderna COVID-19 vaccine. However, until the case processing backlog is cleared it is possible the full extent of any adverse events occurring with the Moderna vaccine will not be fully known.

5. CDC Report on mRNA vaccines

The CDC COVID-19 vaccine safety update issued by the Advisory Committee on Immunization Practices (ACIP) dated January 27 2021 provided data on adverse events monitored via the Vaccine Safety Datalink Rapid Cycle Analysis. The Vaccine Safety Datalink includes data from 9 participating integrated healthcare organizations across the USA and has data on over 12 million persons per year. No signal was detected for either immune thrombocytopenia or thrombotic thrombocytopenic purpura. It is noted this is now approximately 1 month out of date, however new data is not yet available from the CDC.

6. AstraZeneca

Yellow Card data

Up to and including 22 February 2021, the MHRA has received 17 reports of immune thrombocytopenia (1 of these cases also reports thrombocytopenic purpura) and 5 reports of thrombocytopenia. There are also 5 reported events of platelet count decreased (one of which also reports thrombocytopenia and another reports immune thrombocytopenia), 13 reports of petechiae (1 case co-reported with platelet count decreased and immune thrombocytopenia, another 2 co-report ITP), 6 reports of purpura (1 co-reported with petechiae) and one report of Henoch-Schonlein purpura.

Immune thrombocytopenia

Of the 17 reports of immune thrombocytopenia, 8 report an onset time of 7 days or more (which is more plausible for a vaccine associated ITP) and of those 8, 4 cases have additional features supporting ITP diagnosis (no other confounders, platelets only cell line affected, considered ITP by a haematologist, responding to treatment with IVIg/ steroids). 1 fatal case has an onset of more than 7 days, but features supporting causality have not been confirmed.

8 cases have short onset times or have confounding factors:

- 4 with onset times of 1-4 days,
- 1 case with a feasible onset time but with a PMH of non-Hodgkin's lymphoma,
- 1 case was being treated for previous sinus thrombosis more information on the PMH in this case is needed.
- 1 case was previously investigated for myelodysplasia although diagnosis was never confirmed
- 1 patient was concurrently treated with clozapine, which can cause thrombocytopenia

4 cases report an ITP flare in a patient with previously diagnosed ITP, 1 of these cases was fatal. The onset times are short (within 1- 5 days), however, 3 of the cases state that the patient's condition and

platelet counts had been stable prior to receiving the vaccine. While these onset times are very short for a causal association with the vaccine, it could be possible that the pre-existing condition makes a more rapid reaction feasible in these patients.

Summaries of the ITP cases can be found in annex 3.

Overall, for cases reporting ITP, there are 4 strong cases, which have a plausible onset time for association with the vaccine as well as sufficient detail on the diagnosis of ITP. There is one additional possible case, which requires further information. As well as this, there are 4 cases which describe ITP flares in patients with pre-existing ITP. The onset times in these cases are short which may indicate that these are chance findings in patients with underlying ITP who receive regular blood tests. Alternatively, it could be associated to vaccination if the underlying condition somehow primed them for a rapid onset of these autoimmune events.

Thrombocytopenia

5 cases reporting thrombocytopenia were assessed as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The report regarding the [redacted]

There is also 1 case reported [redacted]

Platelet count decreased

1 case is discussed above in the fatal case of [redacted] Of the remaining cases:

- [redacted]

Petechiae

3 cases are previously discussed as co-reported with ITP or thrombocytopenia

7 cases report rapid onset times, within 1-4 days, 1 case in [redacted]

Purpura

1 case is co-reported with petechiae. 3 cases have rapid onset times of 1-2 days, one is additionally confounded by treatment with ibrutinib for CLL. One case in [redacted]

The last case is fatal and while ITP was not reported as a reaction, it is stated that the working diagnosis was of ITP. This was in [redacted]

This case is plausible for an association with vaccination, with an onset time of 7 days and features supportive of an ITP diagnosis.

Henoch-Schonlein purpura

The case reporting Henoch-Schonlein purpura fits more with a reactogenicity reaction [redacted]

Haemorrhage cases

1 case reporting a haemorrhage was of particular note:

[redacted] The diagnosis of Venous Sinus Thrombosis was confirmed with a CT angiography. [redacted]

This case is being followed up to find out if any malignancy was found. Otherwise, it is possible that this could be a case of ITP, although further diagnostic details would be required.

Other haemorrhage cases are reviewed in table 2. As was seen for the review of Pfizer cases reporting haemorrhage, the majority of cases do not have onset times consistent with ITP associated with vaccination and serous and fatal cases are low. Many of the fatal cases reported below are discussed elsewhere in this paper as they co-report terms reviewed above.

Table 2. Summary of AstraZeneca COVID-19 vaccine Yellow Card reports for frequently reported and serious hemorrhagic event terms, as of 22 February 2021*

Reaction (PT)	Number events reported**	Onset >7 days (n)	Fatal (n)	Hospitalised*** (n)	Age range (average)
Eye haemorrhage	2	0	0	1	67-72 (70)
Rectal haemorrhage	8	1	0	1	24-81 (60)
Small intestinal haemorrhage	6	0	0	0	41-53 (47)
Gastrointestinal haemorrhage	2	0	1	0	66-70 (68)
Subdural haemorrhage	1	0	0	0	[redacted]
Cerebral haemorrhage	8	1	3	3	32-86 (66)
Haemorrhage intracranial	4	0	1	2	19-87 (39)
Subarachnoid haemorrhage	1	0	0	1	[redacted]
Vaginal haemorrhage	34	2	0	0	22-73 (41)
Pulmonary haemorrhage	1	0	1	0	[redacted]
Haemorrhage	17	1	1	1	31-87 (55)
Epistaxis	175	7	1	7	18-99 (55)

**This includes non-serious hemorrhage events where had >3 events reported to us, those with <3 reports but indicate serious or life-threatening event and excluding vaccination site reactions.*

*** more than one of these events may be reported in a single case and therefore the sum of these numbers does not equate to the total number of cases reporting the PTs of interest*

**** hospitalisation is not always accurately reported*

Clinical trial data

There were no cases of ITP, thrombocytopenia or purpura reported in either arm of AZ clinical trials. There was one case of petechiae reported in the control arm.

Discussion

Overall, there are 6 cases which are considered strong for a diagnosis of ITP and the onset times are plausible in the context of an autoimmune reaction to vaccination. 1 further case reporting a haemorrhage could be considered possible, but this requires further information on a diagnosis of ITP and to rule out an underlying malignancy as a cause. 4 of the reports had fatal outcome. An association with vaccination is possible, in terms of the onset times to the reaction, in 2 of these fatal cases. No evidence of ITP or thrombocytopenia was seen in AstraZeneca clinical trials.

While there are 6 cases in which an association with vaccination is possible, this association is based solely on onset times to reactions and with so few events with plausible onset times, in the context of 8.4 million doses given, it is difficult to establish causality

7. Epidemiological analysis

As part of the safety surveillance strategy for COVID-19 vaccines, MHRA are undertaking enhanced passive surveillance, which compares the observed number of case reports with the expected given the underlying age-specific background risk and size of the vaccinated population. We are also conducting rapid cycle analyses, which rely on primary care data available through the Clinical Practice Research Datalink and compare the incidence rate of cases within a risk window post vaccination to historical background rates.

For the Observed vs Expected analyses, expected rates are based on background risks calculated prior to the pandemic using linked Hospital Episode Statistic and primary care data captured in the Clinical Practice Research Datalink (CPRD) for the period 2015-2019. The analyses presented here are based on UK cases reported up to 22nd Feb 2021 i.e. 5 cases of immune thrombocytopenia and 1 case of reported fatal thrombocytopenia where ITP was a likely diagnosis for the Pfizer/BioNTech vaccine and 20 cases of immune thrombocytopenia for the AstraZeneca vaccine. No signals of increased risk are seen for ITP within 42 days of the first dose of the Pfizer vaccine in any age group and under any level of under-reporting investigated. For the AstraZeneca vaccine, the log likelihood of the Observed vs Expected ratio has crossed the signal threshold in patients aged <50 years, assuming 100% reporting, and in patients aged 50-64 years under the assumption of 50% reporting. No such signal is seen for older patients.

Rapid cycle analyses are based on data in the CPRD up to 21st Feb 2021. For the Pfizer vaccine, rapid cycle analyses show the observed number of recorded cases of ITP within 42 days of the first dose (6) to be consistent with the expected (6.7) based on over 80,000 patient years of follow up adjusting for delays in recording of cases in primary care records. For the AstraZeneca vaccine, 7 cases of ITP have been recorded within 42 days of a first dose. This compares to an expected 3 cases based on approximately 35,000 patient years of follow up adjusting for delays in recording of cases in primary care records. The 7 cases are seen in patients of different ages, 2 in patients aged <50 years, 3 in ages 70-79, and 2 in patients aged 80+ years. This has just crossed the threshold for signalling an increased rate of ITP compared to the background rate. These analyses are conducted

on a weekly basis and this is the first week such a signal has been observed so should be treated with caution. This signal is only seen when we allow the null hypothesis to be excluded based on small numbers of cases. This approach increases the risk of spurious early signals which again highlights the need for caution.

Discussion

For Pfizer/BioNTech, there is a low number of ITP and thrombocytopenia cases that report serious bleeding events or fatal outcomes, and of these, several have short time to onset from vaccination or report concomitant conditions such as infections which may present alternative explanations for the thrombocytopenia. Of the haemorrhagic events reported overall with the Pfizer/BioNTech vaccine there are a small number of fatal cases considering the usage and the comorbidities in the populations prioritised for vaccination so far. Additionally, many of these cases reported short times to onset following vaccination and may have been coincidental.

There are a number of cases of ITP and related events reported with an onset time of 2-6 weeks post-vaccination where an autoimmune reaction to be plausible. This is based on when an antibody response is expected post vaccination (from about 7 days) and the time course for ITP following MMR vaccination typically being 2-6 weeks post vaccination. However, considering the large population currently vaccinated there is potential for these cases to be coincidental, particularly in patients which may be undergoing routine blood screening due to pre-existing conditions or medicines they may be on, and this alone does not indicate a causal association. The number of ITP events reported for Pfizer/BioNTech in the UK remains within that expected according to the RCA and observed expected analysis, and similar results are found based on global observed expected analysis by the company.

For the Moderna COVID-19 vaccine, there is no indication of a signal based on the non-UK reports available and clinical trial data, however, the number of unprocessed reports for Moderna means there may be unidentified reports which may be of relevance. These events will continue to be monitored as this backlog of cases is processed.

The data from the US CDC does not indicate a signal for the Pfizer/BioNTech and Moderna COVID-19 vaccines based on the Rapid Cycle Analysis, however this data is over a month old now and this may not represent the current situation.

For the AstraZeneca COVID-19 vaccine, many of the cases reporting terms relevant to immune thrombocytopenia are seen with onset times that would not be consistent with an autoimmune reaction to the vaccine. After analysis of the cases, there is a handful of cases with thorough diagnoses and plausible onset times, however this is a very small number in the context of vaccine usage. Some signals have been seen in observed/expected and rapid cycle analysis however these only just cross signal thresholds and caution is advised in interpretation.

There are limitations to the conclusions that can be drawn on Yellow Card reports where data confirming the course of events and or to support the diagnoses of reactions is incomplete. A series of questions have been drafted to support gathering more information on these cases. These are included in Annex 1of this paper.

It is also to be considered whether the current case definitions used for the epidemiological analysis of observed vs expected and rapid cycle analysis should be broadened to include additional terms. The code lists used for the analyses to identify cases recorded using ICD-10 codes in hospital discharge data from Hospital Episode Statistics and SNOMED codes in CPRD primary care data are included in Annex 2 of this paper. While test results, including platelet counts, are available in CPRD these are

not consistently coded and hence available for extraction and use in analyses therefore cases should be preferentially identified using clinical diagnosis codes.

8. Conclusions

For the Moderna COVID-19 vaccine there is insufficient evidence to raise a signal. However, this is a rapidly evolving picture as more cases are processed and these events will be kept under close review.

For the Pfizer/BioNTech COVID-19 vaccine, there are several cases of ITP and thrombocytopenia from both the Yellow Card data and company's international data which report a plausible time to onset and serious or fatal outcomes. While the RCA and observed expected analysis do not currently suggest a higher reported incidence than expected, these plausible serious and fatal cases are considered potential cause for concern and require consideration from the EWG.

Similarly for the AstraZeneca COVID-19 vaccine there are serious and fatal cases with plausible onset times, as well as some signalling from observed/expected and rapid cycle analyses. While in the context of usage it is difficult to establish causality, these cases require EWG consideration.

9. Advice sought from the EWG

1. Does the EWG agree with the conclusion drawn for the Moderna COVID-19 vaccine?

2. Does the EWG consider that a signal should be raised for the Pfizer/BioNTech COVID-19 vaccine? If so, what additional action should be taken?

3. Does the EWG consider that a signal should be raised for the AstraZeneca COVID-19 vaccine? If so, what additional action should be taken?
4. Does the EWG consider there a mechanism by which shorter onset reactions could be seen in patients with pre-existing ITP? If so, is this likely to be a vaccine-specific effect or an effect that could be seen with any vaccine (including non-COVID-19 vaccines)?

5. Should the MHRA broaden criteria the case criteria used for the observed expected and RCA reviews? If so, what additional event terms should it cover, such as thrombocytopenia?

6. Does the EWG have any comments or additions to the questions for gathering further information on Yellow Card reports?

Annex 1

Proposed questions to gather additional information on immune thrombocytopenia Yellow Card reports

General

- Age, gender, ethnicity
- Please specify how long after vaccination the event of thrombocytopenia occurred? Was this with the first or second dose of the vaccine?

Clinical details regarding thrombocytopenia

- Could you please confirm if an overarching diagnosis which contributed to the event of thrombocytopenia was confirmed? Was this confirmed following haematology review?
- Could you please confirm if there was involvement of any other cell lines, or if platelets were the only cell line affected?
- Please provide information on any other potential causes of thrombocytopenia excluded eg: infectious causes (including SARS-CoV-2, HIV, hepatitis C, hepatitis B, herpes zoster, cytomegalovirus), malignancy including metastatic disease, leukaemia, myelofibrosis, lymphoproliferative disorders, thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation(DIC), heparin induced thrombocytopenia and thrombotic syndrome (HITT)
- Was there a known history or new diagnosis of autoimmune/ inflammatory disease eg: SLE, antiphospholipid syndrome?
- Were any medications with a potential thrombocytopenic effect to be taken concomitantly prior to the event eg: heparin, alemtuzumab, sodium valproate.
- Was any anticoagulation used? If yes, please specify anticoagulation and when this was started/ stopped.
- Please provide information about response to treatment used for treatment eg: IvIG/ steroids.
- Please provide details of any other vaccines administered recently, including the type of vaccine administered and date of administration.
- Were there any other concurrent events that may have contributed to thrombocytopenia?
- Please let us know about the outcome of the event eg: recovering, not resolved, ongoing? If resolved, please provide date of resolution.

Relevant investigations

- Please provide the blood film/ blood smear report if available.
- Please provide nadir platelet counts and relevant blood results where available. If sequential blood results are available, please provide this.
- Please provide results of any additional examinations performed(e.g., bone marrow cytology/histology, anti-platelet antibodies, serum cytokine levels)

Relevant history

- Was there any relevant medical history (including prior history of thrombocytopenia, malignancy, autoimmune/ inflammatory disorder, myelofibrosis)?
- Was there a previous history of adverse events occurring with previous vaccinations, including thrombocytopenia?

For cases reporting concurrent thrombosis:

- Could you please confirm if an if a diagnosis which contributed to the event of thrombosis was confirmed?
- Was a unifying diagnosis for both thrombosis and thrombocytopenia confirmed? Was this confirmed following haematology review?
- Please provide information on any other potential risk factors for thrombosis eg: active malignancy, imalignancy, infection, significant dehydration, immobility, previous DVT, protein C and S deficiency, systemic inflammatory diseases, recent CNS trauma/ surgical intervention, acquired prothrombotic states (including nephrotic syndrome)

Annex 2

Secondary care – ICD-10

[redacted]

Annex 3

Summary of AstraZeneca ITP cases

1. [redacted]
2. Purpura non thrombocytopenic. [redacted]
3. [redacted] immune thrombocytopaenic purpura. [redacted]
4. [redacted] cerebral haemorrhage. [redacted]
5. [redacted] Platelets low [redacted]
6. [redacted] L.
7. [redacted] Haemorrhage intracranial (Recovering/resolving). [redacted] cerebral venous sinus thrombosis, immune thrombocytopenia and intracranial bleeding.
8. Possible duplicate of above case. [redacted] persistent headaches [redacted] cerebral venous sinus thrombosis, immune thrombocytopenia and intracranial bleeding. [redacted]
9. [redacted] haematemesis, treated as ITP, [redacted]
10. [redacted] petechial rash [redacted]

11. [redacted] atal case. [redacted] severe headache, vomiting, left-sided hemiplegia, [redacted]
12. [redacted] developed bruising, petechiae, epistaxis, mouth blood blisters - platelet count 4. [redacted]
13. [redacted]

Previous ITP flare up (reported as ITP/ thrombocytopenia)

14. [redacted] petechial rash. [redacted]
15. [redacted]

16. [redacted]

17. [redacted]