Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
SARS-CoV-2 Vaccination and Immune Thrombocytopenia in de novo and pre-existing ITP patients

Tracking no: BLD-2021-013411R1

Eun-Ju Lee (Weill Cornell Medical Center, United States) Marina Beltrami Moreira (NewYork-Presbyterian Hospital, United States) Hanny Al-Samkari (Massachusetts General Hospital, Harvard Medical School, United States) Adam Cuker (University of Pennsylvania, United States) Jennifer DiRaimo (Platelet Disorder Support Association, United States) Terry Gernsheimer (University of Washington, United States) Alexandra Kruse (Platelet Disorder Support Association, United States) Caroline Kruse (Platelet Disorder Support Association (PDSA), United States) Andrew Leavitt (University of California San Francisco, United States) Alfred Lee (Yale University School of Medicine, United States) Howard Liebman (University of Southern California, United States) Adrian Newland (The Royal London Hospital, United Kingdom) Ashley Ray (Weill Cornell Medical Center, United States) Michael Tarantino (University of Illinois College of Medicine-Peoria, United States) Jecko Thachil (Manchester University Hospitals, United Kingdom) David Kuter (Massachusetts General Hospital, United States) Douglas Cines (Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States) James Bussel (Department of Pediatrics, Division of Hematology/Oncology, Weill Cornell Medicine, United States) C.Kruse. has not personally received any payment but report that PDSA received grants, honorarium and/or consultancy fees from: Amgen, Argenx, CSL Behring, Novartis, Pfizer, Principia, Rigel and UCB. A.D.L. receives research funding to his institution from BioMarin, Sangamo, Pfizer, is a consultant for Merck, and is on the Advisory Board of BioMarin, Dova, CSL, Catalyst, and HEMA Biologics A.I.L. has no

Abstract:
Cases of de novo immune thrombocytopenia (ITP) – including a fatality – following SARS-CoV-2 vaccination in previously healthy recipients led to studying its impact in pre-existing ITP.

In this study, four data sources were analyzed: the Vaccine Adverse Events Reporting System (VAERS) for cases of de novo ITP; a ten-center retrospective study of adults with pre-existing ITP receiving SARS-CoV-2 vaccination; and surveys distributed by the Platelet Disorder Support Association (PDSA, United States) and the United Kingdom (UK) ITP Support Association. Seventy-seven de novo ITP cases were identified in VAERS, presenting with median platelet count of 3 [1–9] x10^9/L approximately 1-week post-vaccination. Of 28 patients with available data, 26 responded to treatment with corticosteroids and/or intravenous immunoglobulin (IVIG), and/or platelet transfusions. Among 103 patients with pre-existing ITP who received a SARS-CoV-2 vaccine, 19 experienced an ITP exacerbation (any of: 250% decline in platelet count, nadir platelet count <30x10^9/L with >20% decrease from baseline, and/or use of rescue therapy) following the first dose and 14 of 70 after a second dose. Splenectomized persons and those who received 5 or more prior lines of therapy were at highest risk of ITP exacerbation. Fifteen patients received and responded to rescue treatment. In surveys of both 57 PDSA and 43 UK ITP patients, prior splenectomy was associated with worsened thrombocytopenia. ITP may worsen in pre-existing ITP or be identified de novo post-SARS-CoV2-vaccination; both situations responded well to treatment. Proactive monitoring of patients with known ITP, especially those post-splenectomy and with more refractory disease, is indicated.

Conflict of interest: COI declared - see note

COI notes: E.L. is a consultant for Principia Biopharma Inc. M.B.M. spouse is employed at Kadmon, Inc and previously at Jounce Therapeutics. H.A. receives research funding to his institution from Agios, Dova and Agen and is a consultant for Agios, Dova, Argenx, Sobi, Novartis, Moderna, and Rigel. A.C. has served as a consultant for Synergy; has received authorship royalties from UpToDate; and his institution has received research support on his behalf from Alexion, Bayer, Novartis, Novo Nordisk, Pfizer, Sanofi, Spark, and Takeda. J.D. has not personally received any payment but report that PDSA received grants, honorarium and/or consultancy fees from: Amgen, Argenx, CSL Behring, Novartis, Pfizer, Principia, Rigel and UCB. T.G. receives research funding from Rigel Corporation and Principia, is a consultant for Amgen, Dova, Novartis, Principia and Cellphire, had travel/accommodations and expenses paid by Amgen, Dova and Cellphire, and received honoraria from Amgen, Novartis, Sanofi and Dova. A.K. has not personally received any payment but report that PDSA received grants, honorarium and/or consultancy fees from: Amgen, Argenx, CSL Behring, Novartis, Pfizer, Principia, Rigel and UCB. C. Kessler has received research funding from Octapharma, Genentech, Takeda and Bayer, and has is part of the board of director or advisory committees for Octapharma, Genentech, Takeda, Bayer, Novo Nordisk, Pfizer and CSL Behring. C.Kruse. has not personally received any payment but report that PDSA received grants, honorarium and/or consultancy fees from: Amgen, Argenx, CSL Behring, Novartis, Pfizer, Principia, Rigel and UCB. A.D.L. receives research funding to his institution from BioMarin, Sangamo, Pfizer, is a consultant for Merck, and is on the Advisory Board of BioMarin, Dova, CSL, Catalyst, and HEMA Biologics A.I.L. has no
disclosures. H.A.L. receives research support from Sanofi/Genzyme, Novartis, and Argenx, and consulting fees from Novartis, Dova, Amgen, and Pfizer. A.C.N. is a consultant for Amgen, Angle, argenx, Dova, Grifols, Novartis, Pfizer, and Shionogi; received funding from Amgen, Novartis, and Rigel; received honoraria directly from Amgen, Angle, argenx, Dova, Novartis, Rigel, and Shionogi; and paid expert testimony from argenx and Rigel A.R. R. has no disclosures. M.D.T. receives research support from Grifols, Novo Nordisk, Pfizer, Principia, Spark Therapeutics, Takeda, UCB; speaker bureau from Amgen, Dova, Grifols, Octapharma, Sobi, Takeda, UCB; he is a consultant/Advisory Board consultant for Amgen, BioMarin, Dova, Genentech, Octapharma, Principia, Sobi, Spark Therapeutics, Takeda and UCB. J.T. received speaker honoraria from Amgen and Novartis. D.J.K. receives research funding to institution from Actelion (Syntimmune), Agios, Alnylam, Amgen, Argenx, Bristol Myers Squibb (BMS), Immunovant, Kezar, Principia, Protalix, Rigel, Takeda (Bioverativ), UCB. He serves as a consultant for Actelion (Syntimmune), Agios, Alnylam, Amgen, Argenx, BioCryst, Bristol Myers Squibb (BMS), Caremark, CRICO, Daiichi Sankyo, Dova, Genzyme, Immunovant, Incyte, Kyowa-Kirin, Merck Sharp Dohme, Momenta, Novartis, Pfizer, Platelet Disorder Support Association, Principia, Protalix, Protalix, Rigel, Sanofi, Genzyme, Shionogi, Shire, Takeda (Bioverativ), UCB, UpToDate, Zafgen. D.B.C. has received relevant research support from Alexion and Aplagon, served as a consultant or as a member of a data safety monitoring board for Rigel, Dova, CSL Behring, Principia and Arch Oncology. J.B.B. is a consultant and is on advisory boards of Amgen, Novartis, Dova, Rigel, UCB, Argenx, Janssens, Regeneron, RallyBio, Sanofi, Pfizer, and has received honoraria from UpToDate.

Preprint server: No;

Author contributions and disclosures: Contributed to the design of the study: E.L., J.D., E.I., C.K., A.C.N., J.B.B. Participated in patient enrollment and treatment, data collection, and assembly of data; and performed the research: E.L., M.B.M, H.A., A.C., J.D., T.G., E.I., C.K., A.D.L., A.I.L., H.A.L., A.C.N., A.R., M.D.T., J.T., D.J.K., E.C., J.B.B. Analyzed data and wrote the manuscript: E.L., M.B.M., J.B.B. Participated in manuscript writing: All authors provided their reviews and feedback during the development of the manuscript and provided final approval for the manuscript prior to submission.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: For access to de-identified individual subject data of any of the datasets, please contact eu17001@med.cornell.edu.

Clinical trial registration information (if any):
SARS-CoV-2 Vaccination and Immune Thrombocytopenia in de novo and pre-existing ITP patients

Running title: SARS-CoV-2 Vaccination and Immune Thrombocytopenia

Eun-Ju Lee,1 Marina Beltrami-Moreira,1 Hanny Al-Samkari,2 Adam Cuker,3 Jennifer DiRaimo,4 Terry Gernsheimer,5 Alexandra Kruse,4 Craig Kessler,6 Caroline Kruse,4 Andrew D. Leavitt,7 Alfred I. Lee,8 Howard A. Liebman,9 Adrian C. Newland,10 Ashley E. Ray,1 Michael D. Tarantino,11 Jecko Thachil,12 David J. Kuter,2 Douglas B. Cines,3 and James B. Bussel.13

1Division of Hematology/Oncology, New York Presbyterian Hospital – Weill Cornell Medicine, New York, NY

2Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

3Department of Medicine and Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

4Platelet Disorder Support Association, Cleveland, OH

5Division of Hematology, University of Washington, Seattle, WA
Division of Hematology/Oncology, Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, DC

Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA

Division of Hematology, Yale School of Medicine, New Haven, CT

Jane Anne Nohl Division of Hematology, Department of Medicine, University of Southern California, Los Angeles, CA

Department of Haematology, Centre for Haematology, Barts and the London School of Medicine and Dentistry The Royal London Hospital, London, UK

The Bleeding and Clotting Disorders Institute, Peoria, IL; Department of Medicine, University of Illinois College of Medicine-Peoria, Peoria, IL

Department of Haematology, Manchester University Hospitals, Manchester, UK.

Division of Pediatric Hematology/Oncology, New York Presbyterian Hospital – Weill Cornell Medicine, New York, NY

Corresponding Author:

Eun-Ju Lee, Department of Medicine, Division of Hematology – New York Presbyterian Hospital/Weill Cornell Medicine, 525 East 68th Street, P695, New York, NY 10065, USA; email: eul7001@med.cornell.edu.

Scientific Category: Platelets and Thrombopoiesis; Clinical Trials and Observations
KEY POINTS

- SARS-CoV-2 vaccines are generally safe in patients with pre-existing ITP but thrombocytopenia exacerbation may occur and requires monitoring
- Splenectomy and past use of 5 or more therapies predict higher risk of worsening thrombocytopenia in ITP patients post-SARS-CoV-2 vaccine
ABSTRACT

Cases of de novo immune thrombocytopenia (ITP) – including a fatality – following SARS-CoV-2 vaccination in previously healthy recipients led to studying its impact in pre-existing ITP.

In this study, four data sources were analyzed: the Vaccine Adverse Events Reporting System (VAERS) for cases of de novo ITP; a ten-center retrospective study of adults with pre-existing ITP receiving SARS-CoV-2 vaccination; and surveys distributed by the Platelet Disorder Support Association (PDSA, United States) and the United Kingdom (UK) ITP Support Association. Seventy-seven de novo ITP cases were identified in VAERS, presenting with median platelet count of 3 [1—9] x10⁹/L approximately 1-week post-vaccination. Of 28 patients with available data, 26 responded to treatment with corticosteroids and/or intravenous immunoglobulin (IVIG), and/or platelet transfusions. Among 109 patients with pre-existing ITP who received a SARS-CoV-2 vaccine, 19 experienced an ITP exacerbation (any of: ≥50% decline in platelet count, nadir platelet count <30x10⁹/L with >20% decrease from baseline, and/or use of rescue therapy) following the first dose and 14 of 70 after a second dose. Splenectomized persons and those who received 5 or more prior lines of therapy were at highest risk of ITP exacerbation. Fifteen patients received and responded to rescue treatment. In surveys of both 57 PDSA and 43 UK ITP patients, prior splenectomy was associated with worsened thrombocytopenia. ITP may worsen in pre-existing ITP or be identified de novo post-SARS-CoV2-vaccination; both situations responded well to treatment. Proactive monitoring of patients with known ITP, especially those post-splenectomy and with more refractory disease, is indicated.
INTRODUCTION

The COVID19 pandemic led to urgent development and widespread use of SARS-CoV-2 vaccines\textsuperscript{1,2}. In January 2021, USA Today and the New York Times reported an otherwise-well 56-year-old physician diagnosed with de novo immune thrombocytopenia (ITP) 3 days after receiving the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine who died 13 days later from intracranial hemorrhage refractory to administered treatments\textsuperscript{3,4}. This widely-publicized case led to interrogating the Vaccine Adverse Events Reporting System (VAERS) for other potential cases of de novo ITP\textsuperscript{5,6}.

Discovery of additional cases of de novo ITP following SARS-CoV-2 vaccination generated considerable concern among patients with pre-existing ITP and their healthcare providers. The desire for potentially life-saving vaccination was tempered by fear of ITP exacerbation and life-threatening bleeding. This report describes both additional discovery of de novo ITP cases and three independent series each describing outcomes of patients with pre-existing ITP following SARS-CoV-2 vaccination.

METHODS

VAERS was reviewed to identify potential cases of de novo ITP following SARS-CoV-2 vaccination using search terms: immune thrombocytopenia, thrombocytopenia, decreased platelet count, immunoglobulin (IVIG) therapy, and platelet transfusion \textit{(last VAERS access Mar 19, 2021)}. Duplicate entries, reports lacking platelet counts and details of treatments, platelet nadirs >50
x10^9/L, presence of other active conditions including hematologic conditions, IVIG given for other indications, and mislabeled records were excluded. ITP was the presumptive diagnosis in cases of isolated thrombocytopenia <50 x10^9/L refractory to platelet transfusion in the absence of alternative causes. Eight patients with de novo ITP contacted one author (JBB) and provided additional information; some of these patients may have been entered in VAERS. These patients were included to illustrate management of refractory ITP.

Data for patients with pre-existing ITP were obtained via a ten-center retrospective study of adults with ITP who received a SARS-CoV-2 vaccine between December 2020 and March 2021 and who had a post-vaccination platelet count; all but one center was in the United States. ITP was defined per American Society of Hematology and International Consensus guidelines\(^7,^8\). De-identified clinical data were collected from electronic medical records, including patient demographics, duration of ITP, treatment history including past use of rituximab and/or splenectomy, SARS-CoV-2 vaccine type, bleeding symptoms, and platelet counts; all patients with post-vaccination platelet counts were included. The data cut-off for both de novo and existing cases of ITP occurred prior to published reports of vaccine-induced thrombosis-thrombocytopenia syndrome (VITT-TTS)\(^9\) following adenoviral vaccines. Therefore testing for anti-platelet factor 4 antibodies had not been performed. The study was approved by the Institutional Review Board (IRB) of New-York-Presbyterian-Hospital Weill-Cornell-Medicine with waiver of informed consent.

A second source of ITP patient data was obtained from the Platelet Disorder Support Association’s (PDSA) IRB-approved ITP Natural History Registry;
(https://pdsa.org/images/COVID-19-survey-results.pdf). A third source came from the United Kingdom ITP Support Association which performed a similar survey. Both surveys were posted online and all responses were tabulated.

Continuous variables are described as means and standard deviations or medians and interquartile ranges (IQR), and categorical variables as proportions. Groups were compared using t-test, Mann-Whitney test, chi-squared or Fisher exact test as applicable. Relative risk (RR) and 95% confidence intervals (CI) were calculated to assess strength of association. No multivariate analyses were performed. Missing information was handled by pairwise deletion; in certain cases, platelet counts were “adequate/normal” and thus could not be used for numerical analyses.

The lowest or highest post-vaccination platelet count was used to characterize post-vaccine change. A ‘stable platelet count’ was defined as a post-vaccination platelet count within 20% of the pre-vaccination level. An “exacerbation of ITP” was defined as development of any one or more of the following: a) ≥50% decline in platelet count from pre-vaccination baseline; b) >20% decline from pre-vaccination baseline and platelet nadir <30x10^9/L; and/or c) receipt of rescue therapy for ITP. No distinction was made among patients meeting 1, 2 or 3 criteria for the composite endpoint.

Data sharing statement

For access to de-identified individual subject data of any of the datasets, please contact eul7001@med.cornell.edu.
RESULTS

*De novo* ITP: VAERS data

A total of 93 records in VAERS included a platelet count, or 'severe' or 'low' platelets and platelet-specific interventions. Of these, 16 were excluded (pre-existing thrombocytopenia (n=5), pre-existing ITP (n=10), thrombocytopenia resolved with platelet transfusion only (n=1)), leaving 77 reports (Table 1). All received either the Pfizer-BioNTech (BNT162b2) (n=37) or Moderna (mRNA-1273) (n=40) vaccine. The mean age was 63±20 years with 60% female. Premorbid autoimmune disease was reported in 32%.

Of the 66 reports that specified first or second dose, 51 (77%) developed thrombocytopenia following dose #1 of a SARS-CoV-2 vaccine and 15 (23%) following dose #2. Median platelet count was 3 [1—9]x10^9/L at a median of 8 [3—13] days following vaccination (n=73). Seventy-four percent of patients presented with skin or oral mucosa bleeding. Six patients presented with genitourinary (GU) bleeding, 5 gastrointestinal (GI) bleeding and 1 presented with central nervous system (CNS) bleeding. Additional information regarding bleeding was not available; however, the only death noted was the widely-reported “index” patient who developed CNS bleeding. No thrombotic events were reported in these patients.

There was no significant difference in time to symptom onset (Figure 1) or platelet count at presentation (data not shown) between those who received the Moderna versus the Pfizer-BioNTech SARS-CoV-2 vaccine.
Among 46 records specifying treatment, all patients received IVIG and/or corticosteroids and/or platelet transfusions and 5 received additional agents: thrombopoietin receptor agonists (TPO-RA), rituximab, or vincristine (Table 1). An increase in the platelet count to >30x10^9/L was reported in 26 (93%) of 28 records with a follow-up platelet count. The 2 non-responders included the “index” patient and a 63-year-old man with platelet count of 1x10^9/L 11 days following Pfizer-BioNTech dose #1 with no response to ‘typical ITP therapies’ by day 4 (outcome unknown).

Additional information was available in 8 patients who contacted one of the authors (JBB) because they were difficult to manage. It is unclear how many of these patients were reported to VAERS. Each case followed dose #1 of the Pfizer-BioNTech or Moderna SARS-CoV-2 vaccine and were distinguished by minimal response to platelet transfusion, corticosteroids, IVIG, and, in 7 of 8, rituximab. Initiation of additional treatment ranged from 3-13 days after diagnosis of ITP. Seven patients received romiplostim (3-7 micrograms/kg) and 1 eltrombopag (75 mg daily). Other agents included vincristine (1.5 mg IV push) in 6 patients, mycophenolate mofetil, dapsone, and cyclosporine (1 patient each). All 8 patients responded with improvement in platelet count. An 80-year-old woman on warfarin for antiphospholipid syndrome developed subarachnoid and subdural hemorrhages; corticosteroids, IVIG, platelet transfusion, and romiplostim increased her platelet count.

Pre-existing ITP Cohort: Platelet Counts Before and After Vaccination

Between December 2020 and March 2021, 117 patients with pre-existing ITP from 10 centers were vaccinated for SARS-CoV-2 and had post-vaccine platelet counts. The mean age was 63
±17 years, 62% were female, there was a median 12 [4—23] years since diagnosis of ITP, and patients had received a median of 3[2—4] prior medical treatments. Sixty-nine patients were receiving ITP treatment at the time of vaccination, 58 (84%) a TPO-RA. Twenty-seven had undergone splenectomy. Sixteen of 48 off-treatment patients had platelet counts ≥ 150x10^9/L (Table 2).

**Platelet count following dose #1**

The median baseline platelet count in 109 patients was 101 [60–199]x10^9/L assessed 14 [4—34] days prior to vaccination, and the median platelet count was unchanged at follow-up: 100 [50–195]x10^9/L at 6 [4–9] days post-vaccination (Table 3). Platelet counts rose in 32 (29%), remained stable (within 20% variation from baseline) in 43 (39%), and decreased in 34 patients (31%) (Figure 2A). Nineteen (17%) developed an exacerbation of ITP (Table 4) with 7 patients receiving rescue therapy. Rescue treatments included corticosteroids (n=2), TPO-RA (n=3), IVIG (n=1), and a combination of IVIG, steroids, rituximab and cyclosporine (n=1) as well as increased dosing of ongoing ITP treatment (Supplemental figure S1). All responded to treatment with platelets > 30x10^9/L or return to pre-vaccination ranges within 2 to 4 weeks without major bleeding (Supplemental Figure S1).

**Platelet count following dose #2**

The median platelet count prior to the second vaccination was 101 [60 – 186]x10^9/L (n=70) assessed 12 [3—30] days prior to vaccination. At a median of 5 [3 – 8] days post-vaccination the median platelet count was 106 [53—202]x10^9/L (Table 3). Platelets rose in 24 (34%), remained
stable in 25 (36%), and declined in 21 (30%) (Figure 2A). Fourteen (20%) patients developed an exacerbation of ITP. The 9 patients receiving rescue treatment responded with platelets >30x10^9/L or return to pre-vaccination ranges (Supplemental Figure S1).

Risk factors for ITP exacerbation

Patients with prior splenectomy had a significantly higher risk of exacerbation after dose #1 (12/25, 48%) compared to non-splenectomized patients (7/86, 8%, RR 1.8 [1.3—2.8]) (Table 4). After dose #2, 7/19 (37%) splenectomized patients developed an exacerbation compared to 7/51 (14%) non-splenectomized patients (RR 1.4 [1.02-2.2]). Patients treated with ≥5 prior lines of therapy also had a significantly higher risk of exacerbation after dose #1 (9/16, 56%) compared to patients with 0-4 prior lines of therapy (3/54, 6%, RR 2.2 [1.4—4.1]). After dose #2, 5/12 (42%) individuals who received ≥5 lines of therapy developed an ITP exacerbation, whereas for 0-4 lines of therapy, only 7/43 (16%) patients developed ITP exacerbation (RR 1.4 [0.9-2.6]).

Prior use of ≥5 lines of medical treatment was more common among splenectomized patients (59% vs 11% in non-splenectomized group). The incidence of ITP exacerbation after dose #1 was highest among splenectomized patients with ≥5 lines of therapy (6/10, 60%) compared to 1/47 (2%) who had not undergone splenectomy and had received ≤4 prior treatments (Table 5).

There was no difference in age, gender, vaccine type (data not shown), or history of autoimmune disease (Table 4) between those who did and did not develop an ITP exacerbation.

Comparison of platelet responses following dose #1 and dose #2
Sixty-three patients had platelet counts available after both doses of a SARS-CoV-2 vaccine. We investigated if the response to dose #1 could predict the effect of dose #2 on platelet count. Of the patients who had stable or increased platelet counts after dose #1, 80% percent had stable or increased counts after dose #2. Among patients whose platelets decreased by > 20% after dose #1, the effect of dose #2 was less consistent: only 44% had again a decrease >20% in platelet counts (Figure 2B and Supplemental Figure S2). Of 5 patients who received rescue treatment following dose #1, 4 did not receive rescue after dose #2.

**PDSA Natural History Registry Survey of ITP patients**

Of 122 individuals with pre-existing ITP who completed the PDSA survey, 57 received a SARS-CoV-2 vaccine and had post-vaccination platelet counts. The survey did not differentiate between first and second vaccine doses. Forty-four of 57 (75%) respondents were women (mean age 51 years). Vaccine type was Moderna (29), Pfizer-BioNTech (23), Oxford-AstraZeneca (ChAdOx1 nCoV-19) (4), and Janssen (1). Nineteen individuals (33%) reported decreased post-vaccination platelet counts, including 2 with platelets <10x10^9/L, one with mucocutaneous bleeding (Supplemental Table S1). Participants who were post-splenectomy had a higher risk of a post-vaccination platelet decline >100x10^9/L (RR 1.8 [1.3—3.4]). Participants in remission had a lower incidence of platelet count decline >100x10^9/L (RR 0.7 [0.5—0.9]) compared to those with active ITP.

**United Kingdom ITP Support Association Survey**
Of 311 participants only 43 (32 female) reported post-vaccination platelet counts of which 11 were higher, 18 were stable and 14 were lower than before vaccination. Vaccine type was Pfizer-BioNTech (24) and Oxford-AstraZeneca (19). Among the 14 participants reporting decreased platelets, the pre-vaccine median platelet count was 78 [58-173]\times10^9/L falling to 12 [10-68]\times10^9/L post-vaccine; 13 decreased by ≥ 50%, and 10 reached platelet nadirs <30\times10^9/L (7 Oxford-AstraZeneca, 3 Pfizer-BioNTech). Splenectomy was again associated with higher risk of a ≥50% decrease in platelet count post-vaccination (RR 2.3 [1.1—7.9]).

**DISCUSSION**

This report describes the effects of SARS-CoV-2 vaccination on platelet counts of patients without known (*de novo*) and with pre-existing ITP. The study does not include patients with VITT-TTS, nor does it include patients with inherited thrombocytopenia. This is the largest report to date both of patients with apparent *de novo* ITP identified in VAERS and also of post-vaccination platelet counts in patients with pre-existing ITP. We report findings of ITP development or exacerbation secondary to the first large scale administration of mRNA vaccines.

In *de novo* ITP patients identified from VAERS, the median time to presentation was 8 days, similar to a recent report of thrombocytopenia after the Oxford-AstraZeneca vaccine. While there is evidence dating back to the 1960’s, primarily in children, that attenuated live viral vaccines cause ITP perhaps via direct effect on megakaryocytes, *In contrast, the best study of*
killed vaccines in adults did not identify an increased incidence of ITP post-vaccination, substantial evidence that killed vaccines cause ITP is lacking. While mRNA vaccines are novel, they are thought to represent a new form of “killed” vaccines; there is no reason to suspect they directly impact megakaryocytes. A recent report of a national registry from Scotland suggested that the Pfizer-BioNTech vaccine did not result in an increased incidence of ITP, while results with the Oxford-AstraZeneca vaccine were equivocal. Pre-existing undiagnosed asymptomatic ITP with post-vaccination exacerbation could be one explanation for development of ITP within days post-vaccination. This would also be consistent with the failure to demonstrate an increased post-vaccination incidence of ITP since these cases were evolving at the time of vaccination. Other etiologies for occurrence of de novo ITP include molecular mimicry and underlying predisposition to autoimmunity; these might represent cases not presenting until at least 1 week post-vaccination. No data is available on the etiology or incidence of de novo ITP in this report. This study also did not identify predictive factors for de novo ITP; although, 32% of cases had pre-existing autoimmune disease, which may be higher than expected in the adult US population. Long-term outcomes of post-vaccine cases of ITP could not be assessed.

It is encouraging to note that among VAERS reports with available information, almost 90% of patients responded to first-line ITP treatment: steroids and/or IVIG and/or platelet transfusions. In 8 patients who were difficult to treat, addition of a TPO-RA and single-dose vincristine led to good responses. Vincristine appeared to accelerate response compared with the expected 7-14 days with TPO–RAs. Reasons not to use anti-CD20 treatment (eg rituximab) for suspected post-
vaccination ITP include a 1–8-week time to response, negation of the recent vaccination, and inability to effectively revaccinate for months\textsuperscript{17,18}.

Details regarding the 8 patients unresponsive to first-line therapy were sent to one of the authors featured in a publication of one of these cases in the lay press\textsuperscript{19}. As such, these refractory cases likely represent a small fraction of \textit{de novo} cases of ITP rather than an influx of refractory cases post-vaccination. Exactly why certain \textit{de novo} cases of ITP, either post-vaccination or idiopathic, are refractory is not well understood.

The findings of \textit{de novo} ITP post-vaccination led to examination of vaccine effects in patients with pre-existing ITP. Surprisingly, post-vaccination changes in platelet counts in this group were approximately evenly divided among those that increased, remained stable, or decreased in all 3 data sources analyzed. We do not have a parallel comparison group for the vaccinated ITP patients, but the post-vaccination platelet fluctuations were prominent in both directions with changes far exceeding those seen in the placebo arms of numerous ITP studies\textsuperscript{20-23}.

In the multicenter cohort of ITP patients, approximately 1 in 5 developed an ITP exacerbation after vaccination. Rescue treatment – whether increased dosing of ongoing treatment and/or addition of new ITP treatment – was universally effective. No major bleeding occurred.

An increased risk of developing ITP exacerbation in splenectomized patients was independently seen in each of the 3 data sources. Whether having undergone splenectomy, even if successful, represents more refractory ITP or if the absence of the spleen in some way influences (worsens)
the vaccination effect on the platelet count is unclear. In the multicenter cohort, a significantly higher proportion of patients developing ITP exacerbation were post-splenectomy, had a longer duration of ITP, and/or had received \( \geq 5 \) treatments for ITP. These categories overlap considerably albeit not completely; all suggest that the worse the ITP, the more likely there is to be a thrombocytopenic effect of vaccination. No patient with normal platelet counts off-treatment and who had not undergone splenectomy developed an exacerbation of ITP. Furthermore, only 1 patient who had a past history of neither splenectomy nor having received \( \geq 5 \) treatments had an exacerbation. Thus the patient at greatest risk of a substantial decrease in platelets post-vaccination seems to be one whose treatment history has demonstrated the need for more aggressive ITP therapies.

A critical question was whether platelet response to the first vaccine dose predicted platelet response to the second dose (for 2-dose immunization schedules). Most patients who did not develop ITP exacerbation after the first vaccine dose also did well with the second dose. Over half of those who experienced a decrease in their platelet counts after the first dose had stable or increased platelet counts after the second dose; only 1 patient received ITP-directed therapy after both vaccine doses. This suggests that ITP patients who are eligible to receive additional vaccine doses, especially if they tolerated the first dose well, may safely do so. A decrease in platelet count with a prior vaccine dose does not guarantee the same effect with a subsequent dose. No major bleeding was seen in any patient. Whether this is also the case after booster doses will require further study.
Limitations of this study include its retrospective design and reliance on information of undefined completeness from diverse sources. Since participation in VAERS and the PDSA and UK surveys was voluntary, there might have been an increased number of adverse events and/or poor outcomes driving the choice to report. Since asymptomatic ITP patients may have chosen not to obtain pre- and post-vaccination platelet counts, the exclusion of these patients may have resulted in an over-estimation of platelet decrease post-vaccination. The majority of patients received the Moderna and Pfizer-BioNTech vaccines, limiting ability to assess potential differences in changes with platelet counts following the adenoviral-based Janssen and Oxford-AstraZeneca SARS-CoV-2 vaccines. Incomplete data resulted in different numbers of patients available for different analyses. In a few patients with pre-existing ITP, the pre-vaccination platelet count was obtained months prior to vaccination; however, 75% of pre-vaccination counts were within 1 month of vaccination. Although the timing and number of post-vaccine counts was not fixed, most patients obtained counts 5-7 days after vaccination. As data was de-identified, there may have been overlap between the multicenter and PDSA survey cases. Despite these limitations, overall there was consistency across each of the 3 ITP cohorts, including similar percentages with increased, stable, and decreased post-vaccination platelet counts as well as the adverse influence of previous splenectomy.

Our data support and expand upon a recent reports of post-vaccination ITP, that the incidence of severe thrombocytopenia and bleeding is low and patients can be managed with standard, and occasionally, intensified approaches to therapy. These data strongly support the safety of the SARS-CoV-2 vaccines, both acutely in the rare patients developing ITP de novo and in patients with pre-existing ITP. Therapy was effective in essentially all who developed
clinically-meaningful thrombocytopenia. Obtaining pre-vaccination counts followed by weekly monitoring of the platelet count in consultation with a hematologist after each vaccination may be warranted in most ITP patients, especially those post-splenectomy or who had received 5 or more prior treatment regimens.

In summary, this report provides a factual basis to encourage SARS-CoV-2 vaccination for patients with ITP by describing the relatively infrequent adverse outcomes and their reversibility with treatment. It also encourages receipt of both doses of 2-dose vaccines which appears to be particularly important as SARS-CoV-2 variants emerge.

AUTHORSHIP

Contributions: Contributed to the design of the study: E.L., J.D., E.I., C.K., A.C.N., J.B.B. Participated in patient enrollment and treatment, data collection, and assembly of data; and performed the research: E.L., M.B.M, H.A., A.C., J.D., T.G., E.I., C.K., C.K., A.D.L., A.I.L., H.A.L., A.C.N., A.R., M.D.T., J.T., D.J.K., E.C., J.B.B. Analyzed data and wrote the manuscript: E.L., M.B.M., D.B.C., J.B.B. Participated in manuscript writing: All authors provided their reviews and feedback with editing during the development of the manuscript and provided final approval for the manuscript prior to submission.

Conflict-of-interest disclosures: E.L. is a consultant for Principia Biopharma Inc. M.B.M. spouse is employed at Kadmon, Inc and previously at Jounce Therapeutics. H.A. receives research funding to his institution from Agios, Dova and Amgen and is a consultant for Agios, Dova,
Argenx, Sobi, Novartis, Moderna, and Rigel. A.C. has served as a consultant for Synergy; has received authorship royalties from UpToDate; and his institution has received research support on his behalf from Alexion, Bayer, Novartis, Novo Nordisk, Pfizer, Sanofi, Spark, and Takeda. J.D. has not personally received any payment but report that PDSA received grants, honorarium and/or consultancy fees from: Amgen, Argenx, CSL Behring, Novartis, Pfizer, Principia, Rigel and UCB. T.G. receives research funding from Rigel Corporation and Principia, is a consultant for Amgen, Dova, Novartis, Principia and Cellphire, had travel/accommodations and expenses paid by Amgen, Dova and Cellphire, and received honoraria from Amgen, Novartis, Sanofi and Dova. A.K. has not personally received any payment but report that PDSA received grants, honorarium and/or consultancy fees from: Amgen, Argenx, CSL Behring, Novartis, Pfizer, Principia, Rigel and UCB. C. Kessler has received research funding from Octapharma, Genentech, Takeda and Bayer, and has is part of the board of director or advisory committees for Octapharma, Genentech, Takeda, Bayer, Novo Nordisk, Pfizer and CSL Behring. C.Kruse. has not personally received any payment but report that PDSA received grants, honorarium and/or consultancy fees from: Amgen, Argenx, CSL Behring, Novartis, Pfizer, Principia, Rigel and UCB. A.D.L. receives research funding to his institution from BioMarin, Sangamo, Pfizer, is a consultant for Merck, and is on the Advisory Board of BioMarin, Dova, CSL, Catalyst, and HEMA Biologics. A.I.L. has no disclosures. H.A.L. receives research support from Sanofi/Genzyme, Novartis, and Argenx, and consulting fees from Novartis, Dova, Amgen, and Pfizer. A.C.N. is a consultant for Amgen, Angle, argenx, Dova, Grifols, Novartis, Pfizer, and Shionogi. received funding from Amgen, Novartis, and Rigel; received honoraria directly from Amgen, Angle, argenx, Dova, Novartis, Pfizer, and Shionogi; and paid expert testimony from Argenx and Rigel A.E. R. has no disclosures. M.D.T.
receives research support from Grifols, Novo Nordisk, Pfizer, Principia, Spark Therapeutics, Takeda, UCB; speaker bureau from Amgen, Dova, Grifols, Octapharma, Sobi, Takeda, UCB; he is a consultant/Advisory Board consultant for Amgen, BioMarin, Dova, Genentech, Octapharma, Principia, Sobi, Spark Therapeutics, Takeda and UCB. J.T. received speaker honoraria from Amgen and Novartis. D.J.K. receives research funding to institution from Actelion (Syntimmune), Agios, Alnylam, Amgen, Argenx, Bristol Myers Squibb (BMS), Immunovant, Kezar, Principia, Protalex, Rigel, Takeda (Bioverativ), UCB. He serves as a consultant for Actelion (Syntimmune), Agios, Alnylam, Amgen, Argenx, BioCryst, Bristol Myers Squibb (BMS), Caremark, CRICO, Daiichi Sankyo, Dova, Genzyme, Immunovant, Incyte, Kyowa-Kirin, Merck Sharp Dohme, Momenta, Novartis, Pfizer, Platelet Disorder Support Association, Principia, Protalex, Protalix, Rigel, Sanofi, Genzyme, Shionogi, Shire, Takeda (Bioverativ), UCB, UpToDate, Zafgen. D.B.C. has received relevant research support from Alexion and Aplagon, served as a consultant or as a member of a data safety monitoring board for Rigel, Dova, CSL Behring, Principia and Arch Oncology. J.B.B. is a consultant and is on advisory boards of Amgen, Novartis, Dova, Rigel, UCB, Argenx, Janssens, Regeneron, RallyBio, Sanofi, Pfizer, and has received honoraria from UpToDate.

Correspondence: Eun-Ju Lee, Department of Medicine, Division of Hematology – New York Presbyterian Hospital/Weill Cornell Medicine, 1305 York Avenue, 7th floor, New York, NY 10065, USA; email: eul7001@med.cornell.edu.

REFERENCES
1. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403-416. (In eng). DOI: 10.1056/NEJMoa2035389.

2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603-2615. (In eng). DOI: 10.1056/NEJMoa2034577.

3. Weintrab K. Death of Florida doctor after receiving COVID-19 vaccine under investigation. USA Today. Published January 6, 2021.

4. Grady D MP. Doctor’s Death After Covid Vaccine Is Being Investigated. The New York Times. Published January 12, 2021.

5. Lee EJ, Cines DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. American journal of hematology 2021;96(5):534-537. (In eng). DOI: 10.1002/ajh.26132.

6. Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2021 (In eng). DOI: 10.1016/j.vaccine.2021.04.054.

7. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113(11):2386-93. (In eng). DOI: 10.1182/blood-2008-07-162503.

8. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood advances 2019;3(22):3780-3817. (In eng). DOI: 10.1182/bloodadvances.2019000812.

9. Scully M, Singh D, Lown R, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021 (In eng). DOI: 10.1056/NEJMa2105385.

10. Hippisley-Cox J, Patone M, Mei XW, et al. Risk of thrombocytopenia and thromboembolism after COVID-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ 2021;374:n1931. DOI: 10.1136/bmj.n1931.

11. Oski FA, Naiman JL. Effect of live measles vaccine on the platelet count. N Engl J Med 1966;275(7):352-6. (In eng). DOI: 10.1056/nejm196608182750703.

12. Grimaldi-Bensouda L, Michel M, Aubrun E, et al. A case-control study to assess the risk of immune thrombocytopenia associated with vaccines. Blood 2012;120(25):4938-44. DOI: 10.1182/blood-2012-05-431098.

13. Simpson CR, Shi T, Vasileiou E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and trombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nature medicine 2021;27(7):1290-1297. (In eng). DOI: 10.1038/s41591-021-01408-4.

14. Zhang W, Nardi MA, Borkowsky W, Li Z, Karpatkin S. Role of molecular mimicry of hepatitis C virus protein with platelet GPIIIa in hepatitis C-related immunologic thrombocytopenia. Blood 2009;113(17):4086-93. (In eng). DOI: 10.1182/blood-2008-09-181073.

15. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997;84(3):223-43. DOI: 10.1006/clin.1997.4412.
16. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. Endocrine 2012;42(2):252-65. DOI: 10.1007/s12020-012-9703-2.

17. Cooper N, Stasi R, Cunningham-Rundles S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. Br J Haematol 2004;125(2):232-9. (In eng). DOI: 10.1111/j.1365-2141.2004.04889.x.

18. Nazi I, Kelton JG, Larché M, et al. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. Blood 2013;122(11):1946-53. (In eng). DOI: 10.1182/blood-2013-04-494096.

19. Grady D. A Few Covid Vaccine Recipients Developed a Rare Blood Disorder. New York Times. New York, NYPublished February 8th, 2021.

20. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet (London, England) 2008;371(9610):395-403. (In eng). DOI: 10.1016/s0140-6736(08)60203-2.

21. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 2007;357(22):2237-47. (In eng). DOI: 10.1056/NEJMo073275.

22. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2009;373(9664):641-8. (In eng). DOI: 10.1016/s0140-6736(09)60402-5.

23. Bussel J, Arnold DM, Grossbard E, et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials. Am J Hematol 2018;93(7):921-930. (In eng). DOI: 10.1002/ajh.25125.

24. Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. Br J Haematol 2021 (In eng). DOI: 10.1111/bjh.17645.

25. Crickx E, Moulis G, Ebbo M, et al. Safety of anti-SARS-CoV-2 vaccination for patients with immune thrombocytopenia. British Journal of Haematology;n/a(n/a). DOI: https://doi.org/10.1111/bjh.17813.
### APPENDIX

Table 1. Demographic and clinical characteristics of 77 individuals identified in VAERS without reported platelet disorders with suspected *de novo* ITP following SARS-CoV-2 immunization

| Characteristic                                      | Mean ±SD, Median [IQR], or n (%) | Number available for analysis |
|-----------------------------------------------------|----------------------------------|-------------------------------|
| Age                                                 | 63 ±19.7                         | 76                            |
| Gender                                              |                                  |                               |
| ≤50 years old                                       | 3 (15%)                          | 20                            |
| Men                                                  | 17 (85%)                         |                               |
| Women                                               | 28 (50%)                         | 56                            |
| >50 years old                                       | 28 (50%)                         |                               |
| Vaccine type                                         |                                  |                               |
| Moderna                                              | 37 (48%)                         | 77                            |
| Pfizer-BioNTech                                      | 40 (52%)                         |                               |
| Number of doses received prior to presentation      |                                  |                               |
| 1                                                   | 51 (77.3%)                       | 66                            |
| 2                                                   | 15 (22.7%)                       |                               |
| Days to symptom onset                                | 8 [3.2—13]                       | 74                            |
| Range 0—38                                          |                                  |                               |
| Symptoms at presentation*                            |                                  |                               |
| Mucocutaneous bleeding                              | 42 (73.7%)                       | 57                            |
| Genitourinary bleeding                              | 6 (10.5%)                        |                               |
| Gastrointestinal bleeding                            | 5 (6.9%)                         |                               |
| Central Nervous System bleeding                      | 1 (1.8%)                         |                               |
| Bleeding reported but not specified                 | 2 (3.5%)                         |                               |
| No bleeding or skin findings reported               | 6 (10.5%)                        |                               |
| Platelet count at presentation                      | 3 [1—9]                          | 73                            |
| Range 0—47                                          |                                  |                               |
| ≤10 x10⁹ /L                                         | 58 (79.4%)                       |                               |
| History of autoimmune disease other than ITP       |                                  |                               |
| Any autoimmune disease                              | 22 (31.9%)                       | 69                            |
| Hypothyroidism†                                      | 13 (18.8%)                       |                               |
| Rheumatologic                                       | 4 (5.8%)                         |                               |
| Dermatologic                                        | 2 (2.9%)                         |                               |
| Gastrointestinal                                    | 1 (1.4%)                         |                               |
| Antiphospholipid syndrome†                           | 1 (1.4%)                         |                               |
| Multiple sclerosis‡                                   | 1 (1.4%)                         |                               |
| Treatment                                                                 | Count (Percentage) | Total |
|--------------------------------------------------------------------------|--------------------|-------|
| Any combination of steroids, IVIG, and platelet transfusion              | 21 (44.7%)         | 46    |
| Steroids only                                                            | 16 (34%)           |       |
| Platelet transfusion only                                                | 3 (8.5%)           |       |
| IVIG only                                                                | 1 (2.1%)           |       |
| TPO-RA, IVIG, +/- platelet transfusion, steroid                          | 3 (6.4%)           |       |
| Rituximab, steroids, IVIG, platelet transfusion                         | 1 (2.1%)           |       |
| Vincristine, IVIG, rituximab, TPO-RA, +/- platelet transfusion, steroid  | 1 (2.1%)           |       |

| Response to therapy           | Count (Percentage) | Total |
|-------------------------------|--------------------|-------|
| Yes                           | 26 (92.9%)         | 28    |
| No                            | 2 (7.1%)           |       |

| Best known response           | Count (Percentage) | Total |
|-------------------------------|--------------------|-------|
| 30 to 50 x10^9/L              | 3 (11.5%)          | 26    |
| 50 to 100 x10^9/L             | 7 (26.9%)          |       |
| 100 to 150 x10^9/L            | 3 (11.5%)          |       |
| Normalization §               | 6 (23.1%)          |       |
| Improvement ¶                 | 7 (26.9%)          |       |

| Time to platelet count >30 x10^9 cells/l | Count (Percentage) | Total |
|-----------------------------------------|--------------------|-------|
| < 3 days of treatment                   | 9 (81.8%)          | 11    |

SD indicates standard deviation; IQR, interquartile range; IVIG, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist.

*More than 1 site of bleeding reported in some cases, excludes one patient with CNS bleeding whose thrombocytopenia resolved with platelet transfusion only and the patient who developed an intracranial hemorrhage 13 after presentation with thrombocytopenia
†Includes one person with “anti-thyroglobulin antibody”
‡Antiphospholipid Syndrome in the same patient with other rheumatologic conditions
§Platelet count ≥150 x10^9/L or described as “platelets normalized”
¶No platelet count provided but described as “improved” or “resolved”
Table 2. Demographic and clinical characteristics of 117 patients with pre-existing ITP who received at least 1 dose of a SARS-CoV-2 vaccine

| Characteristic                                      | Mean ±SD, Median [IQR], or n (%) | Number available for analysis |
|-----------------------------------------------------|----------------------------------|------------------------------|
| **Age**                                             | 62.5 ±16.9                       | 116                          |
| **Gender**                                          |                                  |                              |
| Male                                                | 43 (37.8%)                       | 117                          |
| Female                                              | 74 (62.2%)                       |                              |
| **Duration of ITP diagnosis (years)**                | 12 [4–23]                        | 97                           |
| **Number of previous ITP treatments**               |                                  |                              |
| None                                                | 6 (8.1%)                         | 74                           |
| Medical treatments*  
  *Includes only patients previously treated, includes rituximab | 3 [2–4]                         | 75                           |
| Rituximab                                           | 41 (40.6%)                       | 101                          |
| Splenectomy                                         | 25 (20.7%)                       | 117                          |
| **Current ITP treatment**                           |                                  |                              |
| TPO-RA only                                         | 47 (40.2%)                       | 117                          |
| corticosteroid only                                 | 4 (3.4%)                         |                              |
| Other single-agent therapies†  
  †Fostamatinib (n=2), azathioprine (n=1), dapsone (n=1), and cyclosporine (n=1) | 5 (4.3%)                         |                              |
| TPO-RA + corticosteroid                             | 5 (4.3%)                         |                              |
| TPO-RA + IVIG + mycophenolate                       | 3 (2.6%)                         |                              |
| TPO-RA + ibrutinib                                  | 2 (1.7%)                         |                              |
| corticosteroid + mycophenolate                      | 2 (1.7%)                         |                              |
| TPO-RA + corticosteroid + mycophenolate             | 1 (0.8%)                         |                              |
| No current treatment and platelets <150 x10^9/l     | 32 (27.4%)                       |                              |
| No current treatment and platelets ≥150 x10^9/l     | 16 (13.7%)                       |                              |
| **Comorbidities**                                   |                                  |                              |
| Autoimmune hemolytic anemia                         | 10 (11.6%)                       | 86                           |
| Other autoimmune disease                            | 31 (36%)                         |                              |
| **Vaccine manufacturer**                            |                                  |                              |
| Moderna                                             | 48 (42.1%)                       | 114                          |
| Pfizer-BioNTech                                     | 53 (46.5%)                       |                              |
| Janssen                                             | 4 (3.5%)                         |                              |
| Oxford-AstraZeneca                                   | 9 (7.9%)                         |                              |

ITP indicates immune thrombocytopenia; SD, standard deviation; IQR, interquartile range; IVIG, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist.

*Includes only patients previously treated, includes rituximab

†Fostamatinib (n=2), azathioprine (n=1), dapsone (n=1), and cyclosporine (n=1)
Table 3. Pre- and post-vaccine platelet counts in patients with pre-existing ITP following dose 1 and dose 2 of a SARS-CoV-2 vaccine

| Dose #1                          | Median [IQR], or n (%) | N  |
|----------------------------------|------------------------|----|
| **Platelet count pre-vaccine (x10^9/L)** | 101 [60 –199]         | 109|
| **Timing of pre-vaccine assessment (days prior to first vaccine dose)** | 14 [4.5—34]           | 93 |
| **Platelet count at first post-vaccine assessment (x10^9/L) * | 100 [50.5–195]         | 109|
| **Timing of first post-vaccine assessment (days)** | 6 [4–9]               | 99 |
| **Timing of platelet nadir† (days)** | 6 [4.8–9.3]           | 30 |
| **Platelet count nadir† (x10^9/L)** | 46.8 [27.8–93.3]       | 34 |
| 11—29 x10^9/L                     | 7 (20.6%)              | 34 |
| 11—30 x10^9/L                     | 5 (22.7%)              | 21 |
| 11—30 x10^9/L                     | 5 (23.8%)              | 21 |

| Dose #2                          | Median [IQR], or n (%) | N  |
|----------------------------------|------------------------|----|
| **Platelet count pre-vaccine (x10^9/L)** | 101 [59.8—186]        | 70 |
| **Timing of pre-vaccine assessment (days prior to first vaccine dose)** | 11.5 [3—30]           | 64 |
| **Platelet count at first post-vaccine assessment (x10^9/L)** | 105.5 [52.8—202]      | 70 |
| **Timing of first post-vaccine assessment (days)** | 5 [3—7.5]             | 69 |
| **Timing of platelet nadir† (days)** | 5 [2.5–8.5]           | 21 |
| **Platelet count nadir† (x10^9/L)** | 34 [10.5–116]         | 21 |
| 11—29 x10^9/L                     | 5 (22.7%)              | 21 |
| 11—30 x10^9/L                     | 5 (23.8%)              | 21 |

*Does not include 2 patients with ‘normal’ platelet count
†Includes only patients with decrease >20% in platelet count
Table 4. Patient characteristics and incidence of ITP exacerbation following SARS-CoV-2 vaccination

|                     | First vaccine dose |                |                | Second vaccine dose |                |                |
|---------------------|--------------------|----------------|----------------|---------------------|----------------|----------------|
|                     | N                  | Platelet count decrease ≥50% | Platelet count decrease >20% and nadir <30x10^9/L | Use of rescue therapy | ITP exacerbation* | N                  | Platelet count decrease ≥50% | Platelet count decrease >20% and nadir <30x10^9/L | Use of rescue therapy | ITP exacerbation* |
| All patients        | 111                | 16 (14.4%)     | 10 (9%)        | 7 (6.3%)            | 19 (17.1%)     | 70                | 14 (20%)         | 10 (14.3%)        | 9 (12.9%)          | 14 (20%)          |
| Splenectomy         | 25                 | 11 (44%)       | 8 (32%)        | 6 (24%)             | 12 (48%)       | 19                | 7 (36.8%)        | 4 (21%)           | 4 (21%)            | 7 (36.8%)         |
| No splenectomy      | 86                 | 5 (5.8%)       | 2 (2.3%)       | 1 (1.2%)            | 7 (8.1%)       | 51                | 7 (13.7%)        | 6 (11.8%)         | 5 (9.8%)           | 7 (13.7%)         |
| Relative Risk       |                    |                |                |                     | 1.8 [1.3—2.8]  |                    |                | 1.4 [1.02—2.2]    |                     | 1.4 [0.9—2.6]     |
| 0—4 prior medical therapies | 54 | 2 (3.7%)       | 2 (3.7%)      | 3 (5.6%)            | 3 (5.6%)       | 43                | 7 (16.3%)        | 6 (14%)           | 6 (14%)            | 7 (16.3%)         |
| ≥5 prior medical therapies | 16 | 8 (50%)        | 4 (25%)       | 3 (18.8%)           | 9 (56.3%)      | 12                | 5 (41.7%)        | 2 (16.7%)         | 1 (8.3%)           | 5 (41.7%)         |
| Relative Risk       |                    |                |                |                     | 2.2 [1.4—4.1]  |                    |                | 1.4 [0.9—2.6]     |                     | 1.4 [0.9—2.6]     |
| Prior rituximab use† | 39                | 9 (23.1%)      | 4 (10.3%)      | 3 (7.7%)            | 10 (25.6%)     | 26                | 9 (34.6%)        | 5 (19.2%)         | 5 (19.2%)          | 9 (34.6%)         |
| No prior rituximab use† | 56              | 4 (7.1%)       | 4 (7.1%)       | 4 (7.1%)            | 6 (10.7%)      | 34                | 5 (14.7%)        | 5 (14.7%)         | 4 (11.8%)          | 5 (14.7%)         |
| Relative Risk       |                    |                |                |                     | 1.2            |                    |                | 1.3               |                     | 1.3               |
|                                | [95% CI] | [0.9—1.6] | [0.9—1.9] |
|--------------------------------|----------|------------|-----------|
| On current therapy for ITP     | 67 (16.4%) | 14 (20.9%) | 11 (27.5%) |
| No current therapy, pre-vaccine platelet count <150x10⁹/L | 30 (13.3%) | 4 (13.3%) | 16 | 0 |
| No current therapy, pre-vaccine platelet count ≥150x10⁹/L | 14 (7.1%) | 1 (7.1%) | 7 | 1 (12.5%) |
| Any concurrent auto-immune disease | 34 (14.7%) | 6 (17.6%) | 25 | 5 (20%) |
| No concurrent auto-immune disease | 47 (8.5%) | 6 (12.8%) | 30 | 6 (20%) |
| Relative Risk [95% CI]         | 1.06 [0.8—1.4] | 1 [0.7—1.4] |          |

*Defined as development of any one or more of the following: a) ≥50% decline in platelet count from pre-vaccination baseline; b) > 20% decline from pre-vaccination baseline and platelet nadir < 30x10⁹/L; and/or c) receipt of rescue therapy for ITP.
†Prior rituximab use was specifically solicited in the data collection form as opposed to all prior treatment history, which was volunteered by some centers.
Table 5. Incidence of ITP exacerbation* after sample stratification by history of splenectomy and number of prior medical therapies or history of rituximab use

|                                | First vaccine dose | Second vaccine dose |
|--------------------------------|--------------------|---------------------|
|                                | N (n)              | ITP exacerbation (%)| N (n)              | ITP exacerbation (%)|
| Splenectomy, 0-4 prior therapies | 7 2               | 28.6%               | 6 1               | 16.7%               |
| Splenectomy, ≥5 prior therapies  | 10 6              | 60%                 | 9 4               | 44.4%               |
| No splenectomy, 0-4 prior therapies | 47 1             | 2.1%                | 37 6              | 16.2%               |
| No splenectomy, ≥5 prior therapies | 6 3               | 50%                 | 3 1               | 33.3%               |
| Splenectomy, no prior rituximab  | 6 3               | 50%                 | 5 2               | 40%                 |
| Splenectomy, + prior rituximab   | 17 8              | 47.1%               | 13 5              | 38.5%               |
| No splenectomy, no prior rituximab | 50 3             | 6%                  | 28 3              | 10.7%               |
| No splenectomy, + prior rituximab | 22 2             | 9.1%                | 14 4              | 28.6%               |

*Defined as development of any one or more of the following: a) ≥50% decline in platelet count from pre-vaccination baseline; b) > 20% decline from pre-vaccination baseline and platelet nadir < 30x10^9/L; and/or c) receipt of rescue therapy for ITP.
Figure legends:

Figure 1: Time to presentation after most recent vaccine dose. Day from vaccine dosing to presentation according to vaccine type (Pfizer-BioNTech (n=39) and Moderna (n=37)) in persons without reported pre-existing platelet disorders per VAERS database

Figure 2: Relative change in platelet counts pre and post SARS-CoV-2 vaccination in patients with pre-existing ITP. A: Relative change in platelet count from pre-vaccine levels following dose #1 and #2 of a SARS-CoV-2 vaccine. B: Effect of dose #2 in platelet count according to effect observed after dose #1.
Figure 1

Cumulative incidence of thrombocytopenia (%) vs Days from most recent vaccine dose.

- Red circles: Moderna
- Blue squares: Pfizer-BioNTech
Figure 2

A Relative change from baseline

First dose (N=109)

Proportion (%)

11.9%
17.4%
39.4%
15.6%
15.6%

Second dose (N=70)

Proportion (%)

8.6%
25.7%
35.7%
10%
20%

Legend:
- Increase ≥50%
- Increase 20-50%
- Stable ± 20%
- Decrease 20-50%
- Decrease ≥50%

B Dose #2 effect on platelet count according to effect of dose #1

Platelet count stable or increased after dose #1 (n=45)

Proportion (%)

80%
20%

Platelet count decreased by >20% after dose #1 (n=18)

Proportion (%)

56%
44%

Legend:
- Stable or increased after dose #2
- Decreased by >20% after dose #2