

ORIGINAL ARTICLE

Immune thrombocytopenia and COVID-19 vaccination: Outcomes and comparisons to prepandemic patients

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Abstract

Background: Immune thrombocytopenia (ITP) has been reported following COVID-19 vaccination. After index case fatalities, there was concern among patients both with and without a prior history of ITP in Australia.

Objectives: To describe treatment outcomes of ITP after COVID-19 vaccination and compare relapsed vs historical pre-COVID-19 ITP cohorts.

Methods: We collected ITP cases in Australia within 6 weeks of receiving any COVID-19 vaccination as part of primary vaccination (up to October 17, 2021). Second, we reviewed platelet charts in a historical ITP cohort to determine whether platelet variability was distinct from relapsed ITP after vaccination.

Results: We report on 50 patients (37 *de novo*, 13 relapsed ITP) vaccinated from March 22, 2021, to October 17, 2021. Although there was 1 fatality, bleeding was otherwise mostly minor: (70% WHO bleeding grade <2). *De novo* ITP was more likely after AstraZeneca ChAdOx1 nCoV-19 (89%) than Pfizer BNT162b2 (11%). Most patients responded quickly (median, 4 days; complete response, 40 of 45 [89%]). In the historical cohort, only 6 of 47 patients exhibited platelet variability (>50% decrease and platelets <100 × 10⁹/L), but median platelet nadir was significantly higher than vaccination relapse (27 vs 6 × 10⁹/L, *P* = .005).

Conclusion: ITP was more frequently reported after AstraZeneca ChAdOx1 nCoV-19 than Pfizer BNT162b2 vaccination. Standard ITP treatments remain highly effective for *de novo* and relapsed ITP (96%). Although thrombocytopenia can be severe after vaccination, bleeding is usually mild. Despite some sampling bias, our data do not support a change in treatment strategies for patients with ITP after vaccination.

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Immune Thrombocytopenia after COVID-19 Vaccination: Characteristics and Treatment Outcomes

Immune thrombocytopenia (ITP), a rare immune mediated platelet disorder, has been reported following COVID-19 vaccinations

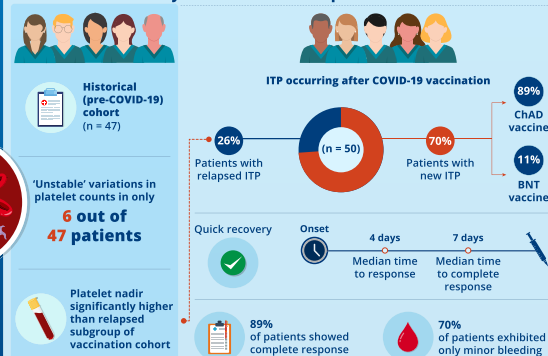


There is minimal information about ITP after COVID-19 vaccination, and this concerns patients with ITP

What are the presentations and treatment outcomes of ITP following COVID-19 vaccinations, and how does it differ from pre-COVID-19 historical cases?



Analysis of two cohorts of patient with ITP



Although risk of new or relapsed ITP after COVID-19 vaccination is low, recovery with treatment was rapid and most patients had no major bleeding

Immune thrombocytopenia and COVID-19 vaccination: comparisons between new onset, relapse and a historical cohort
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KEYWORDS

BNT162 vaccine, ChAdOx1 nCov-19, COVID-19 vaccines, immune thrombocytopenia, treatment outcome, vaccination

Essentials

- Immune thrombocytopenia (ITP) has been reported after COVID-19 vaccinations.
- Fifty cases of ITP after vaccination were reviewed for distinguishing features and treatment outcomes.
- Most cases (36 of 50) in our study presented after first-dose ChAdOx1 (AstraZeneca) vaccination.
- ITP after vaccination presents with infrequent bleeding and responds well to conventional treatments.

1 | INTRODUCTION

Rare immune-mediated complications have been reported following COVID-19 vaccination [1–4]. Immune thrombocytopenia (ITP) has also been described following COVID-19 and other vaccinations [5–8]. A Scottish National Registry study examined hospital-coded and general practice data to identify a small increased incidence of ITP diagnosis within 4 weeks of AstraZeneca ChAdOx1 nCoV-19 (ChAd) vaccination but published information on treatment outcomes is limited [9,10].

Rare thrombotic complications with thrombocytopenia after adenovirus-based COVID-19 vaccinations were well publicized and have led to a heightened scrutiny of platelet counts and cautious observation for symptoms of thrombosis and bleeding [11,12]. Against this backdrop, segments of the population expressed concern and anxiety with vaccination, particularly those with pre-existing conditions related to autoimmunity and thrombocytopenia.

To better understand the apparent emerging phenomenon and guide future management considerations, we established an online registry to collaboratively collect clinically relevant characteristics and treatment outcomes of patients diagnosed with ITP following COVID-19 vaccinations in Australia. The aim of this study was to contrast the

presentations of ITP in patients after vaccination (*de novo* vs relapse from prior diagnosis) with those in a pre-COVID-19 historical cohort, while also considering possible differences in outcomes between ChAd vs Pfizer BNT162b2 (BNT) vaccination.

2 | METHODS

2.1 | Post-COVID-19 cohort

We established a post-COVID-19 ITP registry and advertised it to all hematologists in Australia from May 12, 2021, through society networks targeting hemostasis experts via medical society websites, emails, social media, and word-of-mouth at conference meetings.

We aimed to collect data on any case of adult ITP diagnosed within 6 weeks of any COVID-19 vaccination received from the beginning of the national rollout to October 17, 2021. We elected to perform an interim analysis of available data by January 31, 2022, as the general Australian population had begun receiving COVID-19 vaccination third dose boosters.

Participating hematologists accessed a secure web-based software platform (REDCap electronic data capture tools hosted at ACT Health) and uploaded deidentified clinical data on adult patients aged 18 years and above, including patient demographics, platelet counts, bleeding assessments, and treatment outcomes for up to 3 months after presentation, from May 12, 2021, to January 31, 2022.

Hematologists did not register these cases as ITP if the clinical presentation suggested an alternative diagnosis, such as vaccine-induced immune-mediated thrombosis and thrombocytopenia (VITT) or thrombotic thrombocytopenia syndrome [13].

2.2 | Historical cohort

A cohort drawn from a historical platelet diseases registry of patients diagnosed with ITP at The Canberra Hospital from August 16, 2017, to December 31, 2019, was used as a pre-pandemic comparator. From a total registry of 75 patients, 28 cases were excluded because of alternative diagnoses, ITP diagnosis from 2020 onward, or insufficient platelet count results (4 values) available for comparison. The remaining 47 patients were all managed at an Australian tertiary referral hospital experienced at treating patients consistently with local and international guidelines [14–16].

2.3 | ITP definition and severity

All ITP cases were diagnosed and verified by their treating hematologist with responses recorded using standard international consensus definitions (response [R], $\geq 30 \times 10^9/L$ and at least double baseline without bleeding; complete response [CR], $\geq 100 \times 10^9/L$ without bleeding; failure: loss of response and/or need for additional ITP-therapy), ITP-BAT (skin/mucosa/organ involvement with severity graded 0–4), and WHO criteria for bleeding (graded 0–4) [17–19]. Only patients presenting within 6 weeks of any COVID-19 vaccination were included in this analysis in line with other studies of post-vaccination ITP [20].

2.4 | Population vaccination statistics

Population vaccination statistics (number of vaccines administered; doses: first or second) for the period (March 22 to October 17, 2021) during which ITP cases were collected for the present study were obtained from the Therapeutic Goods Administration (TGA) [21], along with general population statistics from the Australian Bureau of Statistics for September 2021 (released March 17, 2022) [22]. From a population of 20.0 million eligible vaccine recipients in Australia aged 18 years and above, 32.7 million COVID-19 vaccination doses had been administered by October 17, 2021: 19.6 million BNT, 12.6 million ChAd, and 397,000 Moderna mRNA-1273 [21]. At that time, 18.3 million of these were first doses (56.0%) and 14.4 million were

second doses (44.0%). The Australian public health authority (TGA) acknowledged receipt of 85 cases of suspected ITP in relation to COVID-19 vaccination by this same date. However, their clinical features, treatment outcomes, and confirmation of diagnosis were unknown.

2.5 | Case number estimation

Total number of estimated cases of ITP was calculated as follows:

vaccination recipients \times annualized incidence \times temporal exposure to risk.

As a temporal relationship to COVID-19 vaccination was defined by presentation with thrombocytopenia within 6 weeks of either dose, the total exposure to risk varied from a maximum of 84 days after 2 consecutive ChAd vaccinations to only 63 days after 2 BNT vaccinations, as the recommended dosing interval was only 3 weeks for BNT (overlapping risk period of 3 weeks after second BNT vaccination—see [Supplementary Figure 1](#)). For our calculations, we assumed patients completed their primary vaccination sequence with no switching from BNT to ChAd vaccinations as available evidence suggests that this occurred rarely in this phase of the pandemic. Although there was also an accelerated program to shorten the primary ChAd vaccination sequence to 4 weeks (70 days exposure risk) during the Delta outbreak in certain jurisdictions with the highest risk, there were no data available to estimate how many individuals this affected [23]. Based on the annualized incidence estimates from French insurance-based literature (2.9 per 100,000) [24], the pre-pandemic estimated case number of ITP among ChAd recipients was as follows:

$$\frac{12,600,000}{2 \text{ doses}} \times \frac{2.9}{100,000} \times \frac{84}{365.25} = 42 \text{ cases}$$

Following BNT vaccination,

$$\frac{19,600,000}{2 \text{ doses}} \times \frac{2.9}{100,000} \times \frac{63}{365.25} = 49 \text{ cases}$$

Thus, we estimated a total of 91 *de novo* cases of ITP among vaccination recipients based on pre-pandemic estimates.

2.6 | Statistical analyses

Analyses were conducted in GraphPad Prism version 9.3.1 for macOS (GraphPad Software). Missing data were censored from analysis. Group differences were assessed using Mann–Whitney U-test for continuous variables and Fisher’s exact for categorical variables. Differences in paired platelet counts over time were assessed with Repeated Measures ANOVA. Relative risk estimations between groups were computed with logistic regression. Significance was set at $P \leq .05$ (2-tailed).

We probed for differences in outcomes between vaccination types (ChAd vs BNT) and *de novo* vs relapse in patients with a prior history of ITP. Subanalyses were also performed to identify differences in outcomes based on number of vaccines received, severity of thrombocytopenia at presentation, antecedent influenza vaccination (within 1 month), and onset in days between vaccination and presentation.

In addition, possible similarities between patients with relapsed ITP after COVID-19 vaccination and “unstable” ITP patients with pre-pandemic data were explored. To provide a basis for comparison with patients who relapsed after COVID-19 vaccination, we defined “unstable” ITP patients in the historical cohort as those with evidence of a decrease in their platelet by >50% and to a count $<100 \times 10^9/L$ within their 4 most recent consecutive historical values. A schematic of cohort and group selection is presented in [Figure 1](#).

2.7 | Ethical approval

Approval to collect deidentified information from medical records in the post-COVID-19 cohort was obtained from the ACT Health Human Research Ethics committee (ACT-HREC; 2021/ETH00723). Approval for the historical cohort data registry had been previously obtained from the ACT-HREC; 2017/ETH.2.17.029.

3 | OBJECTIVES

To describe treatment outcomes of ITP diagnosed after COVID-19 vaccination and compare presenting features with a historical ITP cohort before COVID-19.

4 | RESULTS

During the period of our data collection (April 1, 2021, to January 31, 2022), we received and analyzed 50 ITP cases following COVID-19 vaccinations meeting criteria for inclusion (37 *de novo* and 13 relapses of a prior history of ITP) vaccinated between March 22, 2021, and October 17 ([Figure 1](#)). The TGA acknowledged the receipt of 85 case reports of ITP following COVID-19 vaccination during this same period of time [21], and thus, our cohort represents 59% of all suspected (but not confirmed by consensus clinical criteria) cases in Australia at that time.

The patients were 56% female with a median age of 63.5 years. The median time from vaccination to presentation with thrombocytopenia was 15 days, and the average time between presentation with thrombocytopenia and enrolment onto the study was 110 days. Demographics are presented in [Table 1](#). Forty patients were diagnosed after ChAd and 10 after BNT. This equates to incident reporting rates of 3.2 cases/million ChAd doses and 0.5 cases/million BNT doses.

Most patients responded quickly and completely (median time to response [TTR], 4 days [IQR, 2-7]; median time to complete response [TTCR], 7 days [IQR, 4-19]; overall R, 45 of 47 [96%]; and CR of 40 of

45 [89%]). First-line treatment used included 25 prednisolone/IVIg (2 with methylprednisolone loading), 7 prednisolone only, 7 dexamethasone/IVIg, 5 dexamethasone only, 1 IVIg only, and 6 observation only. One patient was started with prednisolone/mycophenolate combination upfront. Sex, age, antecedent influenza vaccination, and severity of thrombocytopenia had no significant impact on bleeding at presentation, response rates, relapse rates, time to response, or need for ongoing treatments at day 90 ([Table 2](#)). Bleeding was mostly minor, with 35 of 50 (70%) having WHO bleeding grade <2, but there was 1 notable fatality (see below). Platelet counts were not significantly lower in patients with WHO bleeding grade ≥ 2 compared with those with only WHO bleeding grade 0 to 1 (5 vs $8 \times 10^9/L$, $P = .08$).

A 61-year-old woman presented on day 17 after her first ChAd vaccination with WHO bleeding grade 4, ITP-BAT S3M4O4. Her platelet count at presentation was $5 \times 10^9/L$, and despite treatment with pulse dexamethasone 40 mg and IVIg 1 g/kg on days 1 and 2, she developed catastrophic posterior fossa and cerebellar intracranial hemorrhage resulting in tentorial herniation within 24 hours of admission. Platelet transfusions and neurosurgical evacuation were attempted, but brainstem reflexes were lost and she died on day 4 of presentation.

Despite high response rates, 18 patients (39%) needed additional therapy. The most commonly used second-line therapy was 7 eltrombopag. Other options used included 5 rituximab, 3 romiplostim, 3 mycophenolate mofetil, 2 azathioprine, 1 vincristine, and 1 IVIg. A noticeable minority of patients (13%) experienced refractory disease requiring >2 lines of therapy. Overall, 10 patients (20%) required thrombopoietin receptor agonist therapy, and such immune-sparing approaches were preferred over rituximab or splenectomy.

Routine anti-platelet factor 4 (PF4) ELISA was not recommended by local guidelines for isolated thrombocytopenia. No patients presented with thrombosis. PF4 ELISA was positive in only 1 of 18 cases after ChAd (functional testing in this case was negative).

Community transmission of COVID-19 was very low in Australia at the time of the COVID-19 vaccine roll out, and none of the cases in this analysis was complicated by a prior history of COVID-19 infection.

4.1 | Predictors of response

The following predictors of response were explored: time from vaccination to presentation, severity of thrombocytopenia at presentation, use of prednisolone vs dexamethasone, IVIg vs no IVIg, first-dose vs second-dose vaccination, sex, severity of bleeding, and concomitant or antecedent influenza vaccinations.

A shorter time from vaccination to presentation (<14 days vs ≥ 14 days) was associated with lower platelet count by day 30 (73 vs $138 \times 10^9/L$, $P = .03$), but this difference was not sustained ([Figure 2](#)).

Patients treated initially with dexamethasone (with or without IVIg) had lower platelet counts at day 30 than those treated with prednisolone (with or without IVIg) (median, 36 vs $149 \times 10^9/L$, $P < .001$), but 24 of 25 patients were still on prednisolone at that time compared with only 5 of 11 dexamethasone patients on any ongoing

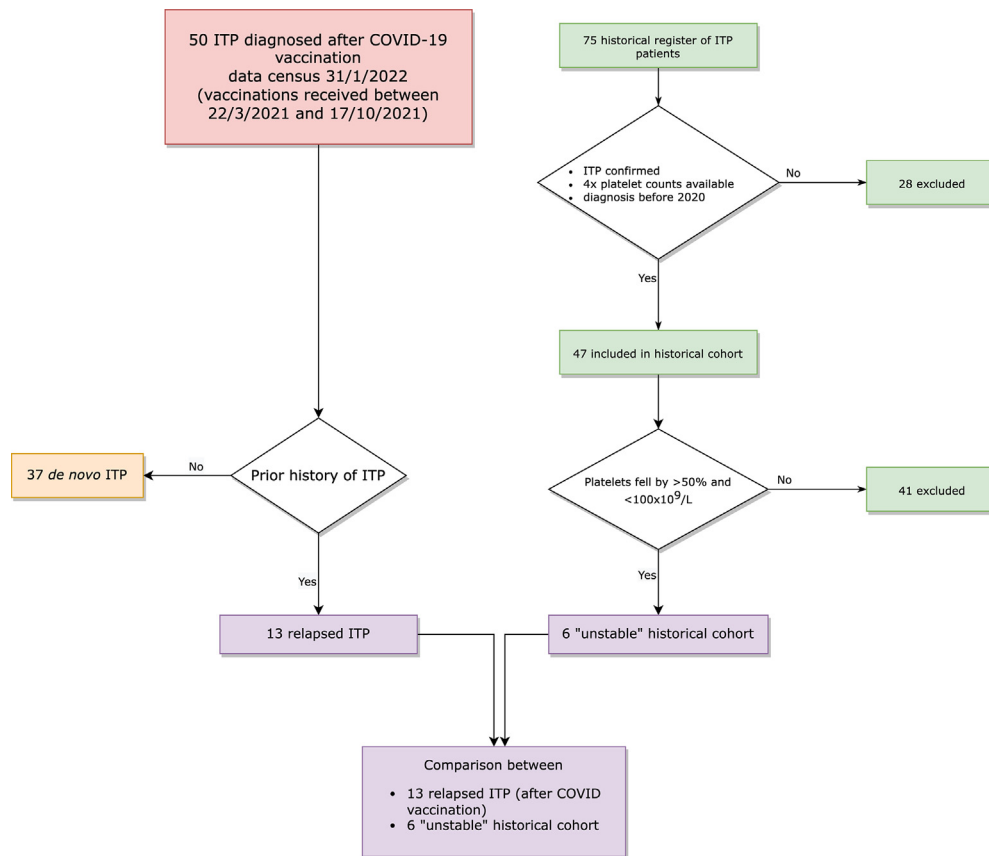


FIGURE 1 Flow diagram of recruitment, classification, and comparison with historical cohort. ITP, immune thrombocytopenia.

therapy. TTCR was shorter for dexamethasone recipients at 3 vs 7 days for prednisolone ($P = .03$), but not TTR at 2.5 vs 3.5 days ($P = .21$).

Upfront IVIg recipients had lower platelet counts at presentation as expected (5 vs $12 \times 10^9/L$, $P = .02$), but by day 30, their platelet counts were higher 135 vs $75 \times 10^9/L$, $P = .02$. Even though TTR was shorter (3 vs 4.5 days, $P = .007$), there was no reduction in the need for second-line therapy, which was still required in 14 of 33 (42%) IVIg recipients compared with 3 of 17 (18%) patients who did not receive IVIg. In addition, 12 of 15 (80%) patients with WHO bleeding grade ≥ 2 received IVIg upfront compared with 21 of 35 (60%) with lesser grades of bleeding.

4.2 | Subgroup analyses

Key summary differences in presentation and outcomes based on vaccination received and *de novo* vs relapsed ITP are presented in Tables 3 and 4, respectively.

4.2.1 | ChAd vs BNT

Forty cases presented after ChAd vaccination (36 first dose and 4 second dose) and 10 after BNT (6 first dose and 4 second dose). Compared with ITP diagnosed after BNT, ChAd-associated ITP

presented (40 of 50) more frequently after the first dose than after the second dose (36 of 40 vs 4 of 40; OR, 6.0; 95% CI, 1.4-26; $P = .04$), with *de novo* cases more often than relapsed ITP (33 of 40 vs 7 of 40; OR, 7.1; 95% CI, 1.7-26; $P = .01$) (see Figure 3). However, there was no difference between ChAd and BNT in time from vaccination to ITP presentation, thrombocytopenia severity at presentation, ITP-BAT bleeding, TTR or TTCR, or ongoing platelet responses at days 30, 60, and 90 (see Supplementary Figure S2).

However, patients with ITP after BNT seemed to have disease that was easier to treat: only 1 of 10 (10%) patients needed second-line treatments compared with 16 of 40 (40%) after ChAd (OR, 0.17; 95% CI, 0.014-1.1; $P = .13$), and only 1 of 10 (10%) presented with WHO bleeding grade >1 compared with 14 of 40 (35%) after ChAd (OR, 0.21; 95% CI, 0.018-1.3; ns) (see Supplemental Figures S3-5).

4.2.2 | De novo vs relapsed ITP

Compared with relapsed ITP (13 of 50), *de novo* cases (37 of 50) were more likely to follow ChAd (33 of 37) vaccination than BNT (4 of 37) (OR, 19; 95% CI, 3.6-83; $P < .001$), were more likely to require second-line therapy (14 of 17 vs 3 of 17; OR, 5.5; 95% CI, 1.4-20; $P = .02$), and presented after a longer time from vaccination (median, 17 vs 4 days; $P = .03$), but there was no difference in age, thrombocytopenia severity

TABLE 1 Demographics and presenting features of patients diagnosed with ITP within 6 weeks of COVID-19 vaccination.

Characteristics	No. (%)	Range [IQR]
Female	28 (56)	
Age in median, y	63.5	20-97 [51.8-77.0]
ChAd	40 (80)	
Prior history of ITP	13 (26)	
Time from vaccination to presentation in median, d	15	1-41 [8.3-23.8]
Platelet count at presentation ($\times 10^9/L$)	7	0-87 [4.0-13.0]
Platelet nadir ($\times 10^9/L$)	5	0-50 [1.0-12.8]
WHO bleeding grade		
	0	8 (16)
	1	27 (54)
	2	9 (18)
	3	3 (6)
	4	2 (4)
	5	1 (2)
ITP-BAT skin (n = 35)		
	0	8 (23)
	1	15 (43)
	2	6 (17)
	3	6 (17)
	4	0
	5	0
ITP-BAT mucosa (n = 35)		
	0	21 (60)
	1	8 (23)
	2	3 (9)
	3	1 (3)
	4	3 (9)
	5	0
ITP-BAT organ (n = 35)		
	0	25 (71)
	1	5 (14)
	2	1 (3)
	3	3 (9)
	4	1 (3)
	5	1 (3)

BAT, Bleeding Assessment Tool; ITP, immune thrombocytopenia.

at presentation, ITP-BAT bleeding scores, TTR or TTCR, or ongoing platelet responses at days 30, 60, and 90 (see [Supplementary Figure S6](#)). Almost all cases (93%) with WHO bleeding scores of ≥ 2

had *de novo* ITP. Platelet counts in relapsed ITP after vaccination returned to pre-COVID-19 vaccination levels as soon as day 30 ([Figure 4](#)), with median platelet counts at day 30 of $77 \times 10^9/L$ (IQR, 44.5-224.5) vs baseline platelets prevaccination of $94 \times 10^9/L$ (IQR, 65.5-208.5) (Repeated Measures One-Way ANOVA of platelet counts from baseline, to presentation, then day 30, $P < .0001$).

4.2.3 | *De novo* case reporting compared with case number estimation

There was no observed increase in the number of ITP cases reported after COVID-19 vaccination compared with prepandemic estimates of incident ITP. There were 37 new cases on our database compared with an estimated case number of 91. Although the reported number of cases after ChAd was 33 and was closer to the estimated number of 42, the reported number after BNT was only 4 in contrast to the estimated 49 cases.

Compared with a prepandemic estimate of annualized incident ITP of 2.9 per 100,000, the reporting incidence ITP was 1.13 (based on adult population statistics) and 1.41 per 100,000 (based on vaccination receipts). Specifically, after ChAd vaccination, the incidence was 2.72 per 100,000, but it was only 0.28 per 100,000 after BNT vaccination.

4.2.4 | Background variability vs relapse of ITP after vaccination—cohort study

The historical prepandemic cohort ($n = 47$) comprised 25 women (53%) with a median age of 58.6 years (IQR, 35.0-74.2), with 13 receiving ongoing TPO-RA therapy (28%), 4 splenectomized (8.5%), with a median prior lines of therapy of 2 (IQR 1-3.5), and with 22 of them being treatment-free (47%) for the preceding 3 months.

Only 6 of 47 patients (13%) had platelet counts that fluctuated sufficiently to be classified as “unstable.” These historically “unstable” patients with ITP had nadir platelet counts that were significantly higher than the presenting thrombocytopenia of relapsed ITP after COVID-19 vaccination (median, 27 vs $6 \times 10^9/L$; $P = .005$), even though platelet counts before decrease and after recovery were similar between the 2 cohorts ([Figure 5](#)). Demographics of the “unstable” historical cohort are compared with the relapsed ITP subset in [Table 5](#).

5 | DISCUSSION

We report a higher number of ITP cases diagnosed within 6 weeks of ChAd vs BNT vaccination (3.2 cases/million doses vs 0.5 cases/million doses). Although there was a longer time window in which exposure to risk after ChAd could be assessed (12 weeks vs 9 weeks for BNT because of a shorter primary vaccination sequence of only 3 weeks—see [Supplementary Figure 1](#)), only 4 patients were diagnosed with ITP

TABLE 2 Outcomes and subgroup comparisons; significant results in red.

Outcomes	n	R (%)	TTR, median [IQR]	CR (%)	TTCR, median [IQR]	Second line needed (%)	Treatment at day 90 (%)	Platelets, 10 × 10 ⁹ / L [IQR]		
								At diagnosis	Day 30	Day 90
Overall	50	45/47 (96)	4 [2-6]	40/45 (89)	7 [4-15.8]	17/50 (34)	14/30 (47)	7 [4-13]	111 [44-175]	175 [62-218]
ChAd	40	35/37 (95)	3.5 [2-6.8]	31/36 (86)	6.5 [4-22.8]	16/40 (40)	11/25 (44)	7.5 [3.3-14.5]	108 [42.5-177]	131.5 [60.3-215]
BNT	10	10/10 (100)	4 [2-5.8]	9/9 (100)	7 [5-14]	1/10 (10)	3/5 (60)	5 [3.3-9]	122.5 [41-157]	202 [115-246.5]
De novo	37	32/34	4 [2-11]	30/33	7.5 [4-28.3]	14/37	12/24	7 [3-15]	116 [40-171.3]	175 [67-214]
Relapsed	13	13/13	4 [2-4]	10/12	5 [4-6.3]	3/13	2/6	6 [4.5-11.5]	77 [44.5-224.5]	82 [47.5-205.5]
First dose	42	37/39	4 [2-8]	32/37	6.5 [4-19]	13/42	11/26	7.5 [3-16]	123 [63-176]	175 [67-214]
Second dose	8	8/8	3 [2.3-4.8]	8/8	7 [4.5-20]	4/8	3/4	5 [4-8]	40 [22-170]	164 [51-288]
Flu vaccine	5	5/5	18 [2.5-59]	5/5	23 [6.5-59]	3/5	1/3	5 [1.5-38]	144 [46-168]	163 [90-282]
No flu vaccine	45	40/42	4 [2-5.5]	35/40	6 [4-15]	14/45	13/27	7 [4-13]	110 [43-175]	175 [55-218]
Plt <10x10 ⁹ /L at presentation	35	31/33	4 [2-6]	27/32	6.5 [4-15]	15/35	12/21	3 [1-5]	121 [32-175]	180 [55-220]
Plt ≥10x10 ⁹ /L	15	14/14	4 [2-12]	13/13	7 [4.8-30]	2/15	2/9	15 [12-27]	108 [74-170]	110 [71-204]
Presentation from vaccination										
<7 d	12	12/12	3 [2-4.8]	10/12	6 [3.8-9.3]	5/12	6/7	7 [5-8]	53 [34-138]	82 [49-181]
≥7 d	38	33/35	4 [2-7.3]	30/33	7 [4-22]	12/38	8/23	7 [3-14]	125 [73-178]	178 [74-232]
<14 d	23	23/23	4 [3-8]	18/22	7 [5-37]	8/23	8/14	5 [3-8]	73 [26-151]	146 [54-207]
≥14 d	37	22/24	3 [2-5]	22/23	6 [4-18]	9/27	6/16	10 [4-17]	138 [104-178]	175 [65-227]
Treatment										
Prednisone	31	28/29	3.5 [2-5.8]	27/28	7 [5-15]	11/31	10/17	5 [3-13]	149 [93-206]	180 [82-220]
Dexamethasone	12	11/12	2.5 [2-4]	10/12	3 [3-41]	6/12	4/9	5 [3.3-10]	36 [19-91]	85 [33-211]
IVIg used	33	31/32	3 [2-5]	30/32	7 [4-12]	14/33	11/20	5 [3-11]	135 [48-178]	178 [60-219]
No IVIg	17	14/15	4.5 [4-27]	10/13	18 [4.5-45]	3/17	3/10	12 [5-27]	75 [20-110]	112 [71-230]

CR, complete response; IVIg, intravenous immunoglobulin; TTCR, time to complete response; TTR, time to response.

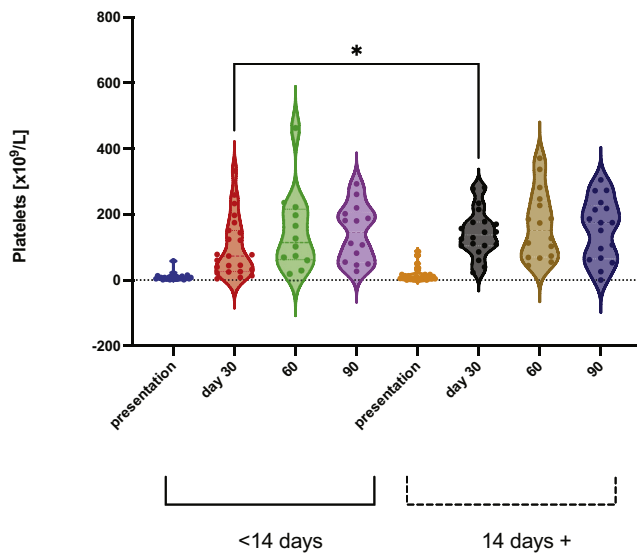


FIGURE 2 Platelet responses were higher in patients who presented with ITP later after vaccination (14 days or more), than those presenting earlier (<14 days) (median 73 vs 138 $\times 10^9/L$, $P = .03^*$). ITP, immune thrombocytopenia.

after second-dose ChAd (at days 6, 10, 19, and 29). Thus, despite the wider period of recruitment for ChAd compared with BNT, only relatively few cases of ITP were diagnosed late after second-dose ChAd.

Most *de novo* cases presented after the first dose of vaccination (33 of 37). However, 12 of 29 patients diagnosed with ITP after first dose ChAd presented between days 22 and 38 after vaccination

(median, 26.5 days). Seven of these patients might have presented within 1 week of second-dose vaccination if ChAd was administered on the same 3-week schedule as BNT. Therefore, the dosing schedule of BNT may have underestimated the number of ITP cases after the first dose and inflated that after the second dose, which may explain the greater proportion of ITP cases observed after the second dose of vaccination.

With public concern surrounding VITT after ChAd, ascertainment bias cannot be excluded because of increased blood testing and scrutiny after ChAd. Patients with VITT and pre-VITT [25] were unlikely to be mistaken for patients with ITP in our case series as no patients presented with thrombosis or headaches, none had gross elevations of D-dimer levels, and ELISA for anti-PF4 antibodies was negative in nearly all cases tested (17 of 18).

Despite the heightened awareness of platelet disorders after vaccination, the total number reported in our database of Australian cases was lower than predicted after extrapolating from annualized French incidence data (37 new cases vs 91 predicted) [24,26]. Public health measures to ameliorate the pandemic may have inadvertently impacted the presentation of ITP. Social distancing, working from home, and mask wearing may have reduced the seasonal effect of environmental triggers, such as pollen, and the transmission of viruses previously implicated in observed cyclical fluctuations of ITP incidence throughout the calendar year [27–29]. In Australia, flu activity was at historically low levels in 2021, adding further uncertainty to comparisons with pre-pandemic epidemiology on the incidence of ITP [30]. These pre-pandemic seasonal variations in the presentation of ITP may somewhat cloud the interpretation of surveys that compare data in epochs of <12 continuous months such as the self-controlled case

TABLE 3 Subgroup analysis of ChAd vs BNT demographics and outcomes. BNT patients were younger, but this was expected because the vaccination policy median age was 35 vs 68 ($P < .001$).

	ChAd	BNT	OR (95% CI)	P
Demographics				
Male	20	2	4.0 (0.74-20)	.15
Female	20	8		
<i>De novo</i>	33	4	7.1 (1.7-26)	.01
Prior ITP	7	6		
First dose	36	6	6.0 (1.4-26)	.04
Second dose	4	4		
Time from vaccination to presentation, median, d [IQR]	17.0 [10.0–25.25]	7.5 [2.0–19.25]	(Mann-Whitney U-test)	.11
Outcomes				
WHO bleeding 0–1	26	9	0.21 (0.018 to 1.3)	.25
WHO bleeding ≥ 2	14	1		
Need for second-line therapy	16	1	6.0 (0.95 to 69)	.13
No need for second-line therapy	24	9		
On treatment at day 90	12	4	0.56 (0.13 to 2.5)	.68
Off treatment at day 90	16	3		

ITP, immune thrombocytopenia.

TABLE 4 Subgroup analysis of ChAd vs BNT demographics and outcomes between *de novo* vs relapsed ITP.

	<i>De novo</i>	Relapsed	OR (95% CI)	P
Demographics				
Male	19	4	2.4 (0.66-7.8)	.33
Female	18	9		
ChAd	4	9	19 (3.6-83)	<.001
BNT	33	4		
First dose	33	9	3.7 (0.89-14)	.18
Second dose	4	4		
Time from vaccination to presentation, median, d [IQR]	17 [10-24.5]	4 [2-25]	(Mann-Whitney U-test)	.03
Outcomes				
WHO bleeding 0-1	23	12	0.14 (0.012-1.0)	.08
WHO bleeding ≥ 2	14	1		
Need for second-line therapy	23	3	5.5 (1.4-20)	.02
No need for second-line therapy	14	10		
On treatment at day 90	14	2	1.9 (0.36-11)	.67
Off treatment at day 90	15	4		

series analysis of the Scottish registry [9,24]. Additionally, patients may have been discouraged from visiting their doctor or presenting for routine blood testing during COVID-19 lockdowns, further diminishing opportunities for diagnosing milder, more transient forms of ITP.

We received 59% of the total number of suspected ITP cases notified to the TGA. Although the diagnosis of cases reported to public health authorities may not have been confirmed by a hematologist, selection bias by our participating clinicians may have enriched our report with more difficult memorable cases requiring lengthier treatment interactions and hospitalization. Our collaborators work across the major tertiary referral centers in the country, and we believe that most serious cases requiring hospitalization during the collection period have been included in this registry, whereas many milder cases of ITP (platelets $50\text{-}100 \times 10^9/\text{L}$) otherwise meeting diagnostic criteria for ITP are less likely to have been included in our analysis even though they may have been notified to the TGA. Only 3 of 50 (6%) cases in our dataset had a platelet count of $>50 \times 10^9/\text{L}$. Despite this risk of bias toward more severe disease, standard first-line treatments for ITP were highly effective (RR, 96%), even though as many as 34% eventually required second-line therapies.

Our study also has other important limitations, including selection bias by participating clinicians, incomplete data collection because of the observational nature of the study including data on ethnicity or race, and the small number of “unstable” patients with ITP from the historical cohort. Moreover, a greater scrutiny of platelet counts after vaccination due to initial clinical reports from the United States, heightened population concerns, and extensive media interest may

have led to some ascertainment bias. However, this effect is likely to have been minimized by the design of this registry, which appealed to specialist clinicians who diagnosed these cases as ITP at the exclusion of other causes of thrombocytopenia.

Despite these limitations, our data reaffirm the safety of vaccinating patients with pre-existing ITP, as even in the rare instance of relapse, bleeding is mild (92% WHO bleeding grade <2) and platelets respond quickly (TTCR, 5 days). In contrast to poor outcomes described in our previous brief analysis [31], concomitant influenza vaccination had no significant impact on key outcomes such as bleeding at presentation, response rates, relapse rates, time to response, and need for ongoing treatments at day 90. Likewise, age, sex, and severity of thrombocytopenia at presentation had no impact on outcomes. Patients with severe disease appear to be receiving IVIg in first-line: lower platelet count at presentation (5 vs $12 \times 10^9/\text{L}$; $P = .02$), 80% of patients with WHO bleeding grade ≥ 2 , and 14 of 17 (82%) patients who will eventually require second-line therapies.

Although median platelet counts at day 30 seem substantially higher for prednisolone recipients vs dexamethasone recipients (36 vs $149 \times 10^9/\text{L}$; $P < .001$), this is probably a reflection of ongoing corticosteroid exposure, with nearly all patients still receiving prednisone at this time (96%) compared with dexamethasone recipients, of whom 6 of 11 (55%) are treatment-free.

Uncertainty remains as to whether these cases represent coincident ITP unrelated to vaccination, susceptibility to ITP unmasked by vaccination (as occurs after viral illness), or whether there is a cohort of secondary ITP truly induced by COVID-19 vaccination with novel culprits already described, such as spike-dependent platelet-activating antibodies [32]. Assuming underreporting of ITP cases onto our database because of

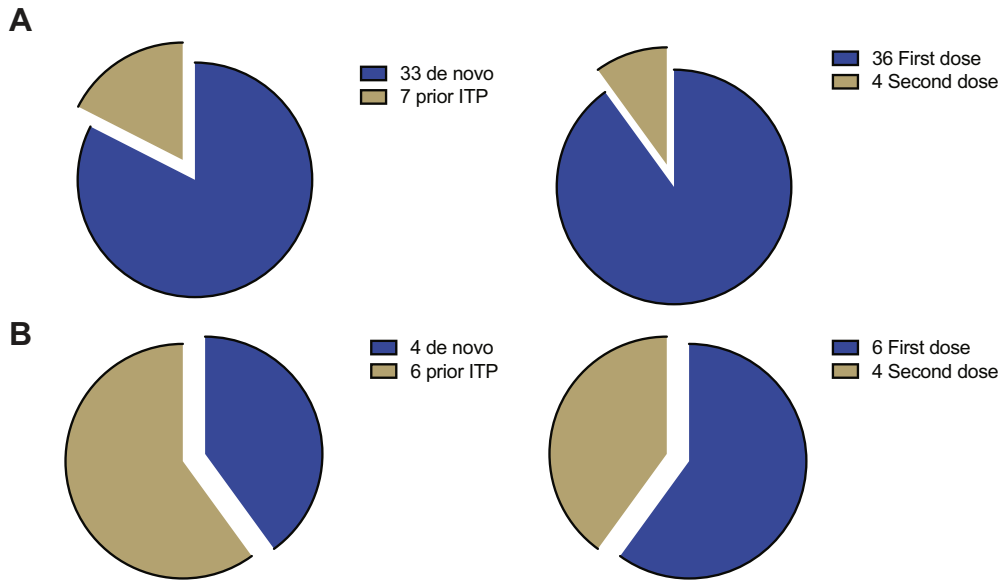


FIGURE 3 (A) ITP after ChAd vaccinations were more commonly associated with *de novo* presentations (OR 7.1, 95% CI: 1.7 to 26, $p = 0.01^*$) and first dose vaccinations (OR 6.0, 95% CI: 1.4-26, $P = .04^*$) compared with (B) ITP after BNT vaccinations. ITP, immune thrombocytopenia.

our study design (only 4 cases after BNT vs 41 estimated by prepandemic incidence), the large difference between the annualized incidence of new ITP after ChAd vs BNT (2.72 vs 0.28 per 100,000 vaccination recipients) strongly suggests either a unique reporting bias based on patient or

medical fears surrounding ChAd, a protective effect of BNT vaccination against ITP, or a pathologic impact of ChAd vaccination not observed with BNT. There is a strong relationship between increasing age and incidence of ITP [24], and the vaccination program in Australia encouraged older

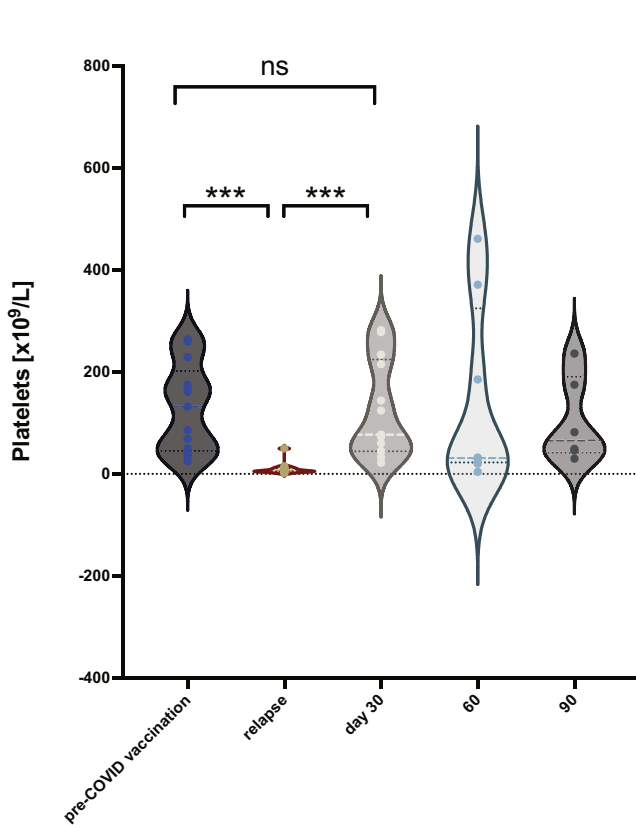


FIGURE 4 Platelet counts for patients whose ITP relapsed after vaccination: platelets returned to pre-COVID-19 vaccination levels. ITP, immune thrombocytopenia.

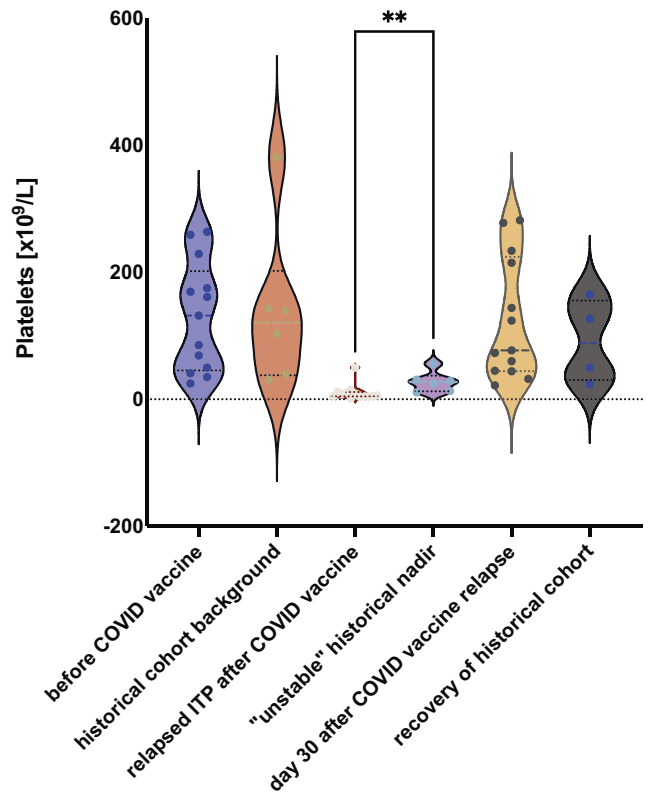


FIGURE 5 Platelet nadirs in ITP relapse after COVID-19 vaccination were significantly lower than nadirs in “unstable” chronic ITP patients in the historical cohort (median 27 vs $6 \times 10^9/L$, $P = .005^{**}$). ITP, immune thrombocytopenia.

TABLE 5 Demographic comparison of “unstable” ITP drawn from historical cohort vs relapsed ITP after COVID-19 vaccination.

	“Unstable” historical cohort (n = 6)	Relapsed ITP after COVID-19 vaccination (n = 13)	P
Sex (female, %)	3 (50)	9 (69)	
Age (median, y)	71	64	
Splenectomy (%)	2 (33)	1 (8)	
Stable off treatment (%)	–	11 (85)	.001
TPO-RA (%)	5 (83)	2 (15)	.01
Baseline platelets (median, $\times 10^9/L$)	122 [IQR 38-203]	132 [IQR 46-202]	
Nadir platelets (median, $\times 10^9/L$)	27 [IQR 13-37]	6 [IQR 4.5-12]	.005
Postnadir platelets (median, $\times 10^9/L$)	77 [IQR 45-225]	89 [IQR 31-156]	

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

patients onto ChAd over BNT, possibly accounting for some of the observed differences in incidence.

The Scottish-linked database analysis identified a small increased risk of ITP after ChAd (but not BNT) corresponding to an estimated incidence of 11.3/million doses after identifying 22 cases from a study population of 2.53 million [9]. However, this study had numerous limitations, including reliance on accurate hospital coding in lieu of confirmation by a specialist diagnosis, inability to discriminate between *de novo* and relapsed ITP cases, 48% of identified patients had concurrent prescriptions of medications associated with thrombocytopenia or drug-induced thrombocytopenia, and no follow-up data were available on the clinical response to immunomodulatory therapies such as corticosteroids and intravenous immunoglobulins, which often help confirm suspicion of immune-mediated thrombocytopenia.

Smaller clinician-guided studies consistently demonstrate a small subset of patients with chronic ITP (10%-15%) who experience a significant decrease in platelet counts after any COVID-19 vaccination (mRNA or adenovirus vector based), with similarly swift platelet recovery and infrequent bleeding events (<3%) [8,10,33,34]. However, the incidence of the reported platelet variability is within the limits of our own observed “unstable” historical cohort, where 6 of 47 (12.7%) also experienced significant random fluctuations in their platelet counts (pre-2020). Our subsequent comparison with relapsed ITP cases suggests that this fluctuation may be deeper after vaccination (lower platelet nadir media, 6 vs $27 \times 10^9/L$; $P = .005$) but with a similarly early platelet response and minimal bleeding in a potentially overlapping predisposed subset of “unstable” chronic ITP.

Compelling evidence linking other rare outcomes from COVID-19 vaccination, such as VITT, has only been established by the sensitivity of anti-PF4 antibody immunoassays and PF4-enhanced functional tests [1,35]. Direct evidence of ITP causation by COVID-19 vaccines (either *de novo* or relapse) remains beyond the scope of this paper. Without analogous tools to confirm the diagnosis of ITP or elucidate a mechanism behind vaccine-associated ITP, the rarity of these events could be lost within seasonal variance and the impact of COVID-19 pandemic measures on health outcomes generally.

However, viral infections induce interferon responses that may exacerbate thrombocytopenia through well-described inhibitory

effects on terminal megakaryocyte development and platelet production [36,37]. Vaccinations that mimic viral infection likely contribute to transient interferon-mediated thrombocytopenia often seen in clinical practice, but many other mechanisms of enhanced platelet destruction have also been proposed [38,39]. Ultimately, any reduction in the pool of circulating platelets may diminish platelet-derived TGF- β immunoregulation of previously balanced autoimmunity against platelet glycoproteins in susceptible individuals leading to the development or relapse of ITP [40].

New challenges will emerge as we advise patients on updated vaccinations for rapidly evolving variants and the safety of booster doses. Many patients with ITP after COVID-19 vaccination received some form of immunosuppression which may impair their vaccination efficiency.

Ongoing surveillance is critical as we begin to vaccinate younger populations, and collaborative networks need to be developed to better identify rare, emergent safety signals before future iterations of population-wide vaccination campaigns.

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AUTHOR CONTRIBUTIONS

P.C. and R.B. conceived the study, collected data, and prepared the manuscript. N.C. provided expert epidemiologic advice and prepared the manuscript. All other authors (D.H., H.A.T., C.W.T., A.E., V.M.Y.C.,

E.M., A.Y., J.S., J.C., and D.P.) contributed to the design of the study, data collection, and manuscript preparation. P.C. prepared the first draft, data analysis, and final submission.

RELATIONSHIP DISCLOSURE

P.C. has received speaking fees from Novartis, is a consultant with Sobi and Sanofi, and is on the advisory board for Janssen. R.B. has received speaking fees from Amgen and Novartis, is on the advisory board for Amgen and Novartis, and is a consultant with Sobi. D.H. has received speaking fees from Amgen and Novartis and is a consultant with Sobi. D.P. has provided consultancy with Sanofi. All other authors—H.A.T., C.W.T., A.E., V.M.Y.C., A.Y., E.M., J.S., E.G., N.C., and J.C.—do not have any conflicts of interest to declare.

INFORMED PATIENT CONSENT

Human Rights Ethics Committee approval waived the need for informed patient consent to collect, analyse and disseminate this data.

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SUPPLEMENTARY MATERIAL

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