Clot twist – D-dimer analysis of healthy adults receiving heterologous or homologous booster COVID-19 vaccine after a single prime dose of Ad26.COV2.S in a phase II randomised open-label trial, BaSiS

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Background. Rapid COVID-19 vaccine development occurred during the pandemic and vaccine-related complications such as thrombosis with thrombocytopenia syndrome were discovered. Clinical trials and treating facilities included D-dimer testing in COVID-19 vaccine trials and COVID-19 disease-severity assessments, respectively. D-dimer testing and result interpretation is complex and its use in isolation is controversial.

Objectives. To evaluate D-dimer levels in healthy adult participants regardless of HIV status, prior to and 2 weeks after receipt of fractional and full-dose Ad26.COV2.S or Comirnaty booster COVID-19 vaccination, after a full dose Ad26.COV2.S prime, stratified by booster vaccination arm, age and HIV status.

Methods. BaSiS, a prospective open-label trial, enrolled 289 healthy adults. Participants with controlled comorbidities, HIV infection with no immunological or virological exclusions, and no prior thrombosis enrolled at four sites in South Africa (SA). Participants previously received a single Ad26.COV2.S prime vaccination through the Sisonke phase IIIB open-label implementation study or the COVID-19 vaccine programme in SA. Participants were randomised 1:1:1:1 to receive one of four boosters: full-dose Ad26.COV2.S, half-dose Ad26.COV2.S, full-dose Comirnaty or half-dose Comirnaty. D-dimer testing (INNOVANCE D-dimer assay), as a coagulopathy marker, was conducted before the booster (baseline) and 2 weeks after the booster. The primary objectives previously reported included safety and immunogenicity of booster vaccination and fractional dosing with Ad26.COV2.S or Comirnaty in Ad26.COV2.S-vaccinated participants. An exploratory objective evaluating clotting profiles, measured by D-dimers, is reported here.

Results. The median age among 285 evaluable participants included in this analysis was 42.2 (interquartile range (IQR): 35.5 - 48.7) years; 82.5% (235/285) were female and 94.4% (269/285) were black African. Of the 40.4% (115/285) of people living with HIV, 79.1% (91/115) were well controlled on antiretroviral therapy. At baseline, 39.3% (112/285) of participants had elevated D-dimer levels – all asymptomatic. Females and obese participants were significantly more likely to have elevated baseline D-dimer levels (adjusted odds ratio (aOR): 3.14, 95% confidence interval (CI): 1.32 - 7.48 and aOR: 2.20, 95% CI: 1.22 - 3.96, respectively). Of 276 participants with D-dimer results available at 2 weeks after the booster, 109 (39.5%) had elevated D-dimer levels. Those with elevated levels at baseline and female participants (aOR: 14.75, 95% CI: 7.64 - 28.48 and aOR: 3.24, 95% CI: 1.14 - 9.22, respectively) were significantly more likely to have elevated D-dimer levels at 2 weeks.

Conclusion. Elevated D-dimer levels in asymptomatic, low-risk adults were unexpectedly common and not associated with thromboembolism. This supports the rationale of including D-dimer testing in conjunction with other coagulopathy markers, only if clinically indicated in both COVID-19 vaccine clinical trials and the general population.

Keywords: COVID 19, D-dimer, thrombosis, heterologous, vaccine

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SARS-CoV-2, first identified in December 2019, caused a pandemic. Symptoms varied from asymptomatic to death. By April 2023, the World Health Organization (WHO) estimated that >765 million people worldwide had been infected with COVID-19 and >6.9 million people had died.[1] The rapid development, testing and roll-out of multiple COVID-19 vaccines contributed to limiting disease severity, especially in high-risk individuals,[2-6] but were surrounded by controversy. With the withdrawal of Vaxzevria (ChAdOx vaccine, AstraZeneca, UK) from the South African (SA) national COVID-19 vaccine roll-out in January 2021, alternatives were sought. The phase IIIB open-label implementation study, Sisonke (ClinicalTrials.gov number NCT048387950), implemented on 17 February 2021, was at the time SA's only access to COVID-19 vaccines. Via Sisonke, a single Janssen Ad26.COV2.S COVID-19 vaccine was provided exclusively to healthcare workers (HCWs). Subsequently, the SA National Department of Health (NDoH) vaccination programme broadly rolled out Ad26.COV2.S, and expanded to include the 2-dose Pfizer BNT162b2/Pfizer-BioNTech vaccine (Comirnaty, USA). Later, homologous and heterologous booster vaccinations were offered.

In April 2021, Ad26.COV2.S was linked to a thromboembolic syndrome, thrombosis with thrombocytopenia syndrome (TTS), usually seen in the first 2 weeks post vaccination. TTS is defined as thrombosis in an unusual location (i.e. cerebral vein, visceral artery or vein, extremity artery, central artery or vein) and new-onset thrombocytopenia (i.e. platelet count $<150 \times 10^9$/L) OR new-onset thrombocytopenia (i.e. platelet count $<150 \times 10^9$/L), thrombosis in an extremity vein or pulmonary artery in the absence of thrombosis at an unusual location, and a positive antiplatelet factor 4 (anti-PF4) antibody enzyme-linked immunosorbent assay (ELISA) test or functional heparin-induced thrombocytopenia (HIT) platelet test occurring any time after vaccination.[7] Globally, ~4 TTS cases per million vaccinations have been reported, mostly in females 30 - 49 years old (1 case per 100 000 vaccinations). Approximately 15% of TTS cases are fatal.[8] A similar incidence was seen in Sisonke, at 0.45 events per 100 000 people.[9] Despite the US Food and Drug Association (FDA)'s preference for mRNA vaccines, Ad26.COV2.S was still used, mainly in resource-limited settings, as it prevented severe SARS-CoV-2 infection.[10] Additionally, the risk-benefit ratio still favoured the use of Ad26.COV2.S when vaccine options were limited.[11]

D-dimer is a degradation product produced after fibrinolysis of blood clots. D-dimer testing can be used to diagnose TTS and other thrombotic events. Such tests are sensitive but specificity for thromboembolism is poor. D-dimer levels may be elevated for many reasons including inflammation, pregnancy, infections, cancer, HIV at the seroconversion stage and chronic diseases, and also increases physiologically with age.[12-14] In COVID-19-infected individuals, D-dimer testing may serve as a marker of COVID-19 severity, prognosis and mortality.[15] Thromboembolism is not uncommon, and the risks increase with age – comorbidities such as cardiovascular disease and metabolic syndromes, lifestyle factors and living with HIV.[16]

The **B**ooster **A**fter **Si**sonke **S**tudy (BaSiS)'s primary objectives were evaluation of safety and immunogenicity of the four booster vaccination regimens, stratified by age and HIV status.[17] In this article, we report results of an exploratory analysis evaluating the clotting profiles of participants by booster vaccination arm, age and HIV status, measuring D-dimer levels at baseline (pre-booster) and at the 2-week post-booster vaccination.

Methods

Study design

BaSiS was a phase II randomised open-label trial with the primary objective to evaluate safety and compare the cellular and humoral responses of four SARS-CoV-2 booster vaccine regimens in participants who originally received a single dose of the Ad26.COV2.S vaccine through the Sisonke phase IIIB implementation study or via the SA NDoH roll-out.[18] The four booster vaccination regimens were full-dose Ad26.COV2.S (5×10^{10} vp/mL, 0.25 mL), half-dose Ad26.COV2.S (2.6×10^{10} vp/mL, 0.13 mL), full-dose Comirnaty vaccine (30 µg) and half-dose Comirnaty vaccine (15 µg). BaSiS was conducted at four SA clinical research sites: Wits RHI Shandukani Research Centre and the Perinatal HIV Research Unit (PHRU) in Johannesburg, Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekwini Clinical Research Site in Durban and Desmond Tutu Health Foundation Masiphumelele Clinical Research Site in Cape Town.

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (ref. no. 211001B), University of KwaZulu-Natal Biomedical Research Ethics Committee (ref. no. BREC/00003487/2021), University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (ref. no. 680/2021) and the SA Health Products Regulatory Authority (ref. no. 20210423). The study has been registered to the South African National Clinical Trials Registry (SANCTR) (ref. no. DOH-27-012022-7841).

All participants signed written informed consent forms for study participation. Trial safety monitoring was overseen by the Sisonke Protocol Safety Review Team (PSRT), and monitoring was performed by the Hutchinson Centre Research Institute of SA (HCRISA).

Participants

Initially, HCWs >30 years of age, who received a Sisonke single prime Ad26.COV2.S dose, and who had no or well-controlled comorbidities, and people living with HIV (PLHIV) on antiretroviral therapy (ART), regardless of immunological or virological control, were enrolled. A protocol amendment implemented in April 2022 adjusted eligibility criteria to include participants ≥18 years of age, and those who received the single prime dose of Ad26.COV2.S through the SA NDoH roll-out. Women of childbearing potential did not require contraception use; however, a negative pregnancy test was required at vaccination. Those with previous SARS-CoV-2 infection >28 days prior to enrolment were included if clinically well. A history of previous severe allergic reaction and any thromboembolic disease was exclusionary. Body mass index (BMI) measurements were recorded but did not affect eligibility.

Procedures

Enrolment took place between 8 December 2021 and 28 July 2022. Participants were vaccinated at enrolment (baseline) and had follow-up visits at 2 weeks, 3 months and 6 months post booster vaccination. Each visit included clinical enquiry for intercurrent illness and targeted clinical examinations where necessary. Full blood count (FBC) and D-dimer levels were tested at baseline (pre-vaccination) and at week 2 post vaccination. Interim visits were conducted for safety-related concerns including abnormal blood results.

All D-dimer samples were tested at the Bio Analytical Research Corporation SA (BARC-SA) using the INNOVANCE D-dimer assay, a particle-enhanced immunoturbidimetric (immune-based) assay.[19,20] This assay was previously compared with a highly validated ELISA assay, VIDAS D-dimer Exclusion (bioMerieux Inc., USA), and demonstrated strong correlation and good consistency between assays. Since D-dimer levels increase physiologically with age, an American College of Emergency Physicians age-related adjustment was used in individuals >50 years of age. The formula: age in years × 10 µg/L (converted as age in years × 0.01 µg/mL based on the units used in our study) was used for interpreting D-dimer levels and

determining elevations (i.e. D-dimer levels higher than the age-adjusted value were considered to be elevated).[21] Participants with raised D-dimer levels were monitored more frequently. They were discussed with the Haematology Department at Charlotte Maxeke Johannesburg Academic Hospital and on weekly patient safety and risk teams (PSRT) meetings with medical specialists (internal medicine, infectious diseases, haematology and pulmonology), as well as members of the Sisonke protocol and safety teams.

Sample size

The main study was powered to detect at least a 6 - 7.7-fold increase in antibody-mediated neutralisation after receiving the half-dose Comirnaty vaccine, with 90% probability. The study aimed to enrol up to 300 participants, with at least 10% being >55 years old and at least a third being PLHIV. This exploratory coagulopathy analysis included all eligible participants from the main study. Power and sample size calculations were not performed for the exploratory analysis; all participants from the main study with eligible data were included.

Randomisation

In the main study, participants were individually randomised in a 1:1:1:1 ratio to one of four booster regimens. Randomisation was performed in masked block sizes of 4 - 16, stratified by study site and HIV status, with a 2:1 ratio of HIV-uninfected people to PLHIV in each arm. Randomisation lists were uploaded to the study Research Electronic Data Capture (REDCap) database by the data manager for electronic implementation; once the study site investigator entered the HIV status of the participant into the REDCap demographic form, REDCap applied the random allocation table and assigned a participant to a study arm.

Statistical analysis

All data were collected using an assigned participant number, with no identifying data included in data capture or analysis. The REDCap application[22] was used for randomisation of participants to their study arms, data entry and as the data management system for the study. Analysis was carried out using Stata 15.1 (Stata Corp., USA). Medians and interquartile ranges (IQRs) were calculated for continuous data with a non-normal distribution. Categorical variables were described using proportions. An elevated D-dimer level was defined as a result of >0.5 µg/mL for persons ≤50 years of age,[21] and age-related cut-offs were used for persons >50 years old, as previously described. The proportion of participants with elevated D-dimer levels was determined by the number of participants with elevated D-dimer levels divided by the total number with D-dimer results at baseline and 2 weeks after booster vaccination. Univariate and multivariable logistic regression was used to explore the association between demographic and clinical factors, and elevated D-dimer levels at baseline and 2 weeks after booster vaccination. For multivariable models, variables with significant associations to the outcome in univariate stepwise analyses, as well as factors considered clinically important according to the available literature (sex, age, hypertension, obesity and living with HIV) and by the study site, were retained in the base model. For the remaining variables, a reverse stepwise selection was carried out using a significance cut-off of 25%. Unadjusted and adjusted odds ratios (ORs), as well as associated 95% confidence intervals (CIs), were computed.

A case series, depicting relevant clinical characteristics of participants that had a normal D-dimer level at baseline and a raised level thereafter, was also described.

Results

Of the 289 participants enrolled into the study, 285 were included in this baseline coagulopathy analysis (exclusions included 1 participant with an undisclosed history of thrombosis and 3 participants without baseline D-dimer levels) and 276/285 (96.8%) in the 2-week post-vaccine follow-up coagulopathy analysis (Fig. 1). At baseline, the median age was 42.2 (IQR: 35.5 - 48.7) years; 235 (82.5%) were female and 269 (94.4%) were of black African ethnicity. PLHIV comprised 40.4%, of whom 20.9% either had a low CD4 count (<350 cells/µL) or an elevated HIV viral load (VL) (>40 copies/mL) (appendix Table S1; http://coding.samedical.org/file/2366). Of the 235 female participants, 14 (6.0%) were on oestrogen-containing contraception, 50 (21.3%) were on a non-oestrogen-containing contraceptive and 171 (72.8%) were not taking a hormonal contraceptive. Almost two-thirds of participants (173/285, 60.7%) were obese (BMI ≥30 kg/m^2) and 80 (28.1%) had a history of hypertension or an elevated blood pressure at baseline (Table 1).

At baseline, 112/285 (39.3%) participants had elevated D-dimer levels, ranging between 0.50 µg/mL and 12.82 µg/mL, with females and obese participants significantly more likely to have elevated D-dimer levels (adjusted odds ratio (aOR): 3.14, 95% CI 1.32 - 7.48 and aOR: 2.20, 95% CI: 1.22 - 3.96, respectively). We found no associations with elevated D-dimer levels at baseline by age, ethnicity, hypertension, hormonal contraceptive use, menopausal status, previous reported COVID-19 infection, HIV status and poor HIV control defined as CD4 <350 cells/µL or HIV VL >40 copies/mL (appendix Table S2; http://coding.samedical.org/file/2367).

Of the 112 participants with elevated D-dimer levels at baseline, 4 had a baseline platelet count <150 × 10^9/L and 3 of the 4 had associated increased baseline D-dimer levels. Two of the 3 maintained the thrombocytopenia and increased D-dimer levels at week 2; neither was symptomatic for TTS.

At the 2-week post-booster visit, 276 participants had D-dimer results available, of which 109 (39.5%) were elevated. Of the 112 participants with elevated D-dimer levels at baseline, 80 (71.4%) remained elevated 2 weeks post booster, while 27 (24.1%) reduced to normal levels, and 5 (4.5%) did not have D-dimer level tests done at the 2-week post-booster visit (Fig. 2). Among the 173 participants with normal D-dimer levels at baseline, 29 (16.8%) had elevated levels 2 weeks post booster. Of the 29 participants with a new onset of elevated D-dimer levels at the 2-week post-booster visit, 13 were PLHIV, 3 of whom had poorly controlled HIV. None had a history of thrombocytopenia. Four participants had D-dimer levels >1.0 µg/mL and 2 others experienced a doubling of D-dimer levels when compared with baseline. These 6 participants had interim visits to repeat D-dimer levels; 2 remained elevated and 4 reduced to <0.5 µg/mL. None of the 285 participants presented with clinical evidence of thrombosis throughout the study period.

In participants with elevated compared with non-elevated D-dimer levels 2 weeks post booster, females had higher odds of elevated levels at week 2 (OR: 4.74, 95% CI: 2.04 - 11.02), along with participants who were obese (OR: 2.25, 95% CI: 1.34 - 3.79) and those who had elevated D-dimer levels at baseline (OR: 14.30, 95% CI: 7.92 - 25.85) on univariate analysis (appendix Table S3; http://coding.samedical.org/file/2368). We found no significant differences by site, age, HIV status or control, hypertension, hormonal contraceptive use, prior SARS-CoV-2 infection and time between prime and booster vaccination (Table 3). On multivariable analysis, female participants (aOR: 3.24, 95% CI: 1.14 - 9.22) and those with elevated D-dimer levels at baseline (aOR: 14.75, 95% CI: 7.64 - 28.48) had a significantly higher odds of having elevated levels at week 2, while participants with hypertension had lower

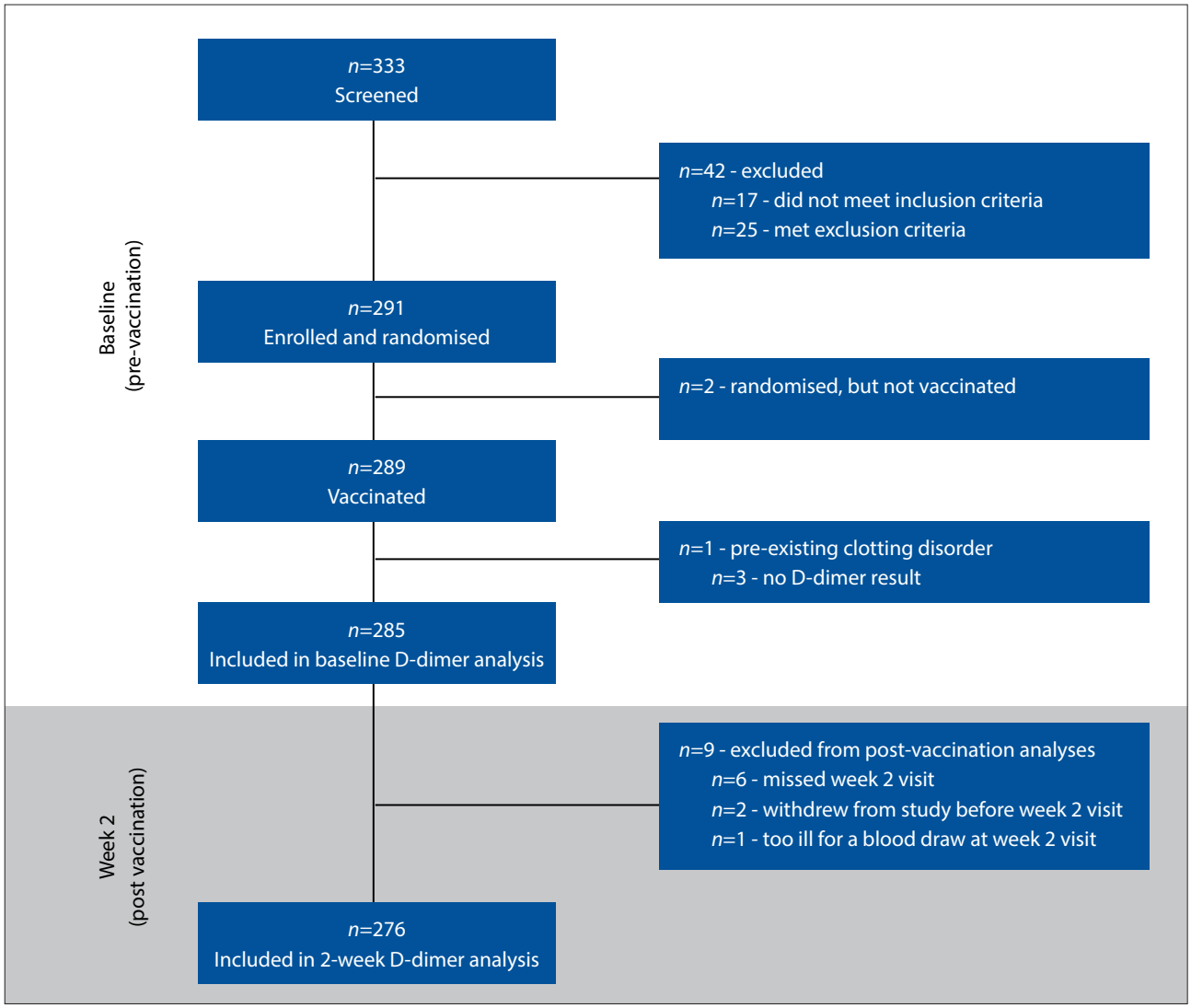

*Fig. 1. BaSiS (**B**ooster **A**fter **Si**sonke **S**tudy) cohort CONSORT diagram.*

odds of having elevated D-dimer levels at week 2 (aOR: 0.47, 95% CI: 0.23 - 0.94). Participant age, ethnicity, vaccine dose and type, recent SARS-CoV-2 infection, obesity and HIV status were not associated with elevated D-dimer levels at the 2-week post-booster visit in the multivariable analysis (Table 3).

Discussion

In this exploratory coagulopathy analysis in the BaSiS study, we found a high proportion (39.3%) of participants with elevated D-dimer levels at baseline, prior to receipt of their allocated randomised booster vaccination. Female participants and those with obesity (BMI ≥30 kg/m^2) had a significantly higher odds of elevated D-dimer levels at baseline (aOR: 3.14, 95% CI: 1.32 - 7.48 and aOR: 2.20, 95% CI: 1.22 - 3.96, respectively). In addition, 39.5% of participants had elevated D-dimer levels 2 weeks post booster vaccination, including those with elevations at baseline and new elevations at the 2-week post-booster visit. None had symptoms of thrombosis pre- or post-booster vaccination, and no TTS was diagnosed. Those with elevated D-dimer levels at baseline and female participants (aOR: 14.75, 95% CI: 7.64 - 28.48 and aOR: 3.24, 95% CI: 1.14 - 9.22, respectively) had a significantly higher odds of having elevated D-dimer levels 2 weeks after booster vaccination, while participants with hypertension had a lower odds of having elevated D-dimer levels at the 2-week post-booster visit (aOR: 0.47, 95% CI: 0.23 - 0.94).

On univariate and multivariate analysis, we found an association between female gender and obesity with elevated baseline D-dimer levels. The female predominance in the cohort may present a selection bias but is reflective of the population of HCWs in SA, who are predominantly female.[23] The high proportion of obese participants (60.7%) is reflective of the obesity rates in the general SA female population (67%) and was expected, given the study's female predominance.[24] We found no further associations on multivariate analysis between age, ethnicity, booster vaccine type and dose, prior COVID-19 infection, hormonal contraception use, obesity and HIV infection with D-dimer elevations 2 weeks after booster vaccination. The interpretation of elevated baseline D-dimer levels is challenging, as there are few data available globally on D-dimer levels within a clinically well population – especially not in resource-limited settings such as SA.

D-dimer tests supplement diagnoses of deep vein thrombosis and pulmonary embolism when clinical signs and symptoms are present, alongside radiological and sonar imaging. D-dimer use is limited when thromboembolism is not suspected. Its use as a stand-alone diagnostic test is diminished, as several conditions increase D-dimer levels in the absence of thromboembolism and increases occur physiologically with age.[25-27]

Table 1. Baseline demographic and clinical characteristics of participants included in the coagulopathy analysis*

Demographic and clinical characteristics		All participants, *n* (%)† (*N*=285)
Study site		
	Wits RHI	101 (35.4)
	CAPRISA	27 (9.5)
	PHRU	54 (19)
	Desmond Tutu	103 (36.1)
Age		
	Median (IQR), years	42.2 (35.5 - 48.7)
	18 - 29	22 (7.7)
	30 - 39	101 (35.4)
	40 - 49	100 (35.1)
	50 - 59	44 (15.4)
	60 - 75	18 (6.3)
Gender		
	Male	50 (17.5)
	Female	235 (82.5)
Ethnicity		
	Black African	269 (94.4)
	Other/undisclosed‡	16 (5.6)
Vaccine administered		
	J & J Ad26.COV2.S – full dose	73 (25.6)
	J & J Ad26.COV2.S – half dose	68 (23.9)
	Pfizer BNT162b2 – full dose	72 (25.3)
	Pfizer BNT162b2 – half dose	72 (25.3)
Time between prime and BaSiS booster, months		
	<9	152 (53.3)
	9 - <12	112 (39.3)
	12 - 16	21 (7.4)
Prior history of SARS-CoV-2 infection		
	No	205 (71.9)
	Yes	80 (28.1)
SARS-CoV-2 infection in last 90 days		
	No	260 (91.2)
	Yes	25 (8.8)
Hypertension (prior known or raised BP at screening)		
	No	205 (71.9)
	Yes	80 (28.1)
Obese (BMI ≥30 kg/m^2)		
	No	112 (39.3)
	Yes	173 (60.7)
Thrombocytopenia (<150 cells/μl)		
	No	280 (98.2)
	Yes	4 (1.4)
Hormonal contraception		*n*=235
	None	171 (72.8)
	Oestrogen containing	14 (6.0)
	Non-oestrogen containing	50 (21.3)
Post-menopausal		*n*=235
	No	198 (84.3)
	Yes	37 (15.7)
HIV status		
	Uninfected	170 (59.6)
	Infected	115 (40.4)
CD4 count <350 cells/μL or VL >40 copies/mL		*n*=115
	No	91 (79.1)
	Yes	24 (20.9)

CAPRISA = Centre for the AIDS Programme of Research in South Africa; PHRU = Perinatal HIV Research Unit; IQR = interquartile range; J & J = Johnson and Johnson; BaSiS = Booster After Sisonke Study; BP = blood pressure; BMI = body mass index; VL = viral load.
*Full table available as appendix Table S1.
†Three participants did not have baseline D-dimer results available; 2 insufficient blood samples, 1 sample not taken in error.
‡Ethnicity for smaller groups (*n*≤5) were collapsed to maintain confidentiality; includes 5 with undisclosed ethnicity.

Table 2. Demographic and clinical characteristics associated with elevated D-dimer levels at baseline*

Demographic and clinical characteristics		All participants, *n* (*N*=285)†	Elevated D-dimer level at baseline, *n* (%) (*n*=112 (39.3))	Univariate analyses, unadjusted OR (95% CI)	Multivariable analyses, adjusted OR (95% CI)
Study site					
	Wits RHI	101	36 (35.6)	1 (base)	1 (base)
	CAPRISA	27	14 (51.9)	1.94 (0.82 - 4.58)	3.15 (1.18 - 8.40)
	PHRU	54	14 (25.9)	0.63 (0.30 - 1.31)	0.76 (0.33 - 1.75)
	Desmond Tutu	103	48 (46.6)	1.58 (0.90 - 2.76)	1.76 (0.94 - 3.30)
Age groups, years					
	18 - 29	22	7 (31.8)	1 (base)	1 (base)
	30 - 39	101	48 (47.5)	1.94 (0.73 - 5.16)	2.27 (0.75 - 6.88)
	40 - 49	100	36 (36.0)	1.21 (0.45 - 3.23)	1.70 (0.54 - 5.35)
	50 - 59	44	13 (29.6)	0.90 (0.30 - 2.72)	1.08 (0.30 - 3.90)
	60 - 75	18	8 (44.4)	1.71 (0.47 - 6.24)	3.18 (0.72 - 14.07)
Gender					
	Male	50	8 (16.0)	1 (base)	1 (base)
	Female	235	104 (44.3)	4.17 (1.88 - 9.26)	3.14 (1.32 - 7.48)
Obese (BMI ≥30 kg/m^2)					
	No	112	29 (25.9)	1 (base)	1 (base)
	Yes	173	83 (48.0)	2.64 (1.57 - 4.43)	2.20 (1.22 - 3.96)
HIV status					
	Uninfected	170	69 (40.6)	1 (base)	1 (base)
	Infected	115	43 (37.4)	0.87 (0.54 - 1.42)	0.74 (0.41 - 1.31)
CD4 count <350 cells/μL or VL >40 copies/mL		115			
	No	91	31 (34.1)	1 (base)	-
	Yes	24	12 (50.0)	(0.78 - 4.81)	-

OR = odds ratio; CI = confidence interval; CAPRISA = Centre for the AIDS Programme of Research in South Africa; PHRU = Perinatal HIV Research Unit; BMI = body mass index; VL = viral load.
*Full table available as appendix Table S2.
†Three participants did not have baseline D-dimer results available; 2 insufficient blood samples, 1 sample not taken in error.

D-dimer tests have different sensitivities, specificities, cut-off values and reporting units.[13,28] Sample collection and processing, lack of standardisation across assay types, differences in thresholds for age and comorbid conditions can affect D-dimer results and there is no international reference standard. Sample collection and processing, lack of standardisation across assay types, lack of international reference standards, differences in thresholds for age and comorbid conditions can all affect the interpretation of D-dimer results.[13,29] Gender differences have been noted, with females being more likely to have elevated D-dimer levels above the upper-limit cut-off, consistent with our findings. Currently, there is no gender-specific D-dimer reference range.[30]

Among PLHIV, data from resource-rich and resource-poor settings have demonstrated raised D-dimer levels during the acute seroconversion phase and with chronic HIV infection.[27,31] ART initiation with subsequent virological and immunological control results in a reduction of D-dimer levels;[32-35] however, despite viral suppression, higher D-dimer levels may persist in PLHIV.[36,37] To our knowledge there is no available published evidence on the effect of HIV on D-dimer levels after COVID-19 vaccination. As SA remains one of the highest HIV-burden countries globally, with almost 8 million PLHIV,[38] having elevated D-dimer levels could place many of these individuals at higher risk of thromboembolism.

Increased risk of clotting after Ad26.COV2.S vaccination and the usefulness of raised D-dimer levels in predicting COVID-19 illness severity and associated thromboembolism, have remained key questions[39,40] to which our analysis is able to contribute evidence. A similar prospective observational study in Croatia (*n*=171) compared D-dimer levels between participants receiving Comirnaty (*n*=87) and those receiving Ad26.COV2.S (*n*=84) vaccines pre dose and at multiple time points post dose. This study had a similarly high proportion of female participants, with 59% and 48% in the Comirnaty and Ad26.COV2.S groups, respectively. Using the INNOVANCE D-dimer assay, they reported a statistically significant (*p*=0.004) rise in D-dimer levels post vaccination in both groups, without clinical evidence of thromboembolism. No further subgroup analyses were performed to elucidate differences in sex and HIV status.[41] The TREASURE study (*N*=368) compared 4 COVID-19 vaccines (Vaxzevria, Ad26.COV2.S, Comirnaty and Spikevax/Moderna) head-to-head, and their impact on platelet activation, coagulation and inflammation, using a percentage change from baseline (T0) to vaccination (T1). The percentage change from baseline across all participants and all vaccines was 13% (8.8, 17.4), with no difference by vaccination type (viral vaccine compared with mRNA vaccine), although with lower numbers of participants receiving Ad26.COV2.S (*n*=19) and Comirnaty (*n*=169) in the study.[42] A Norwegian study compared healthcare personnel who received Vaxzevria (*n*=521) with a control group who received no SARS-CoV-2 vaccination and had no prior history of COVID-19 infection (*n*=102).[43] In this study, 76% of the Vaxzevria group and 50% of controls were females. Interestingly, the control group had higher mean D-dimer levels post vaccination (227 ng/mL, 95% CI: 206, 248) than the Vaxzevria recipients (214 ng/mL, 95% CI: 205, 224).

Smaller studies conducted in Singapore (*n*=18) and Italy (*n*=30) compared pre- and post-booster vaccination D-dimer levels using different assays in participants vaccinated with two doses of Comirnaty.[44,45] Median baseline D-dimer levels in the predominantly young (median age 35 years; IQR: 31 - 44) female (78%) Singaporean

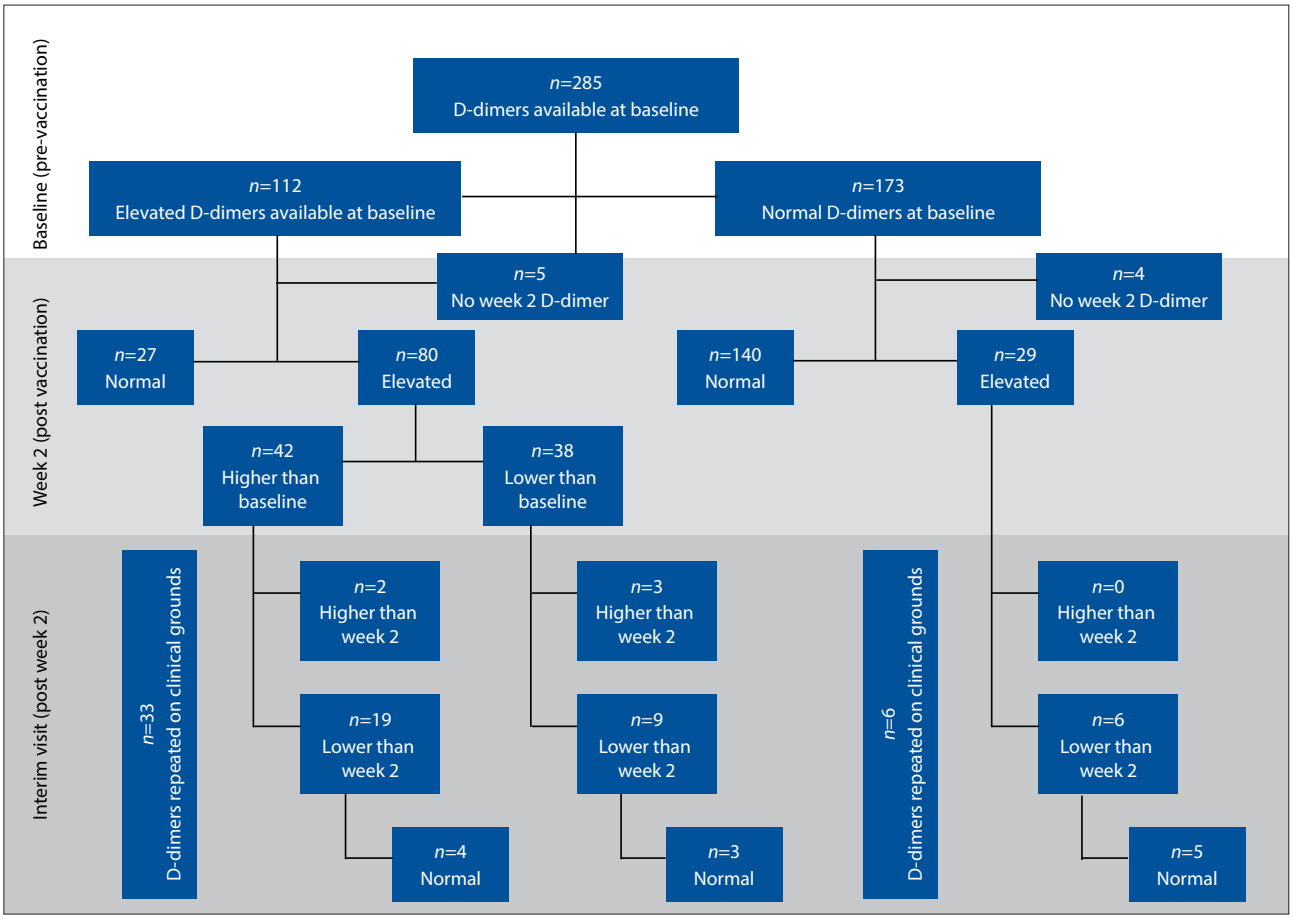

*Fig. 2. BaSiS (**B**ooster **A**fter **Si**sonke **S**tudy) cohort D-dimer level profile among 285 participants, reflecting D-dimer levels at baseline, 2 weeks after booster vaccination and up to 4 weeks after booster vaccination.*

cohort was 0.32 µg/mL (IQR: 0.22 - 0.38), with similar results after the first (0.21 µg/mL, IQR: 0.14 - 0.35) and second vaccine doses (0.29 µg/mL, IQR: 0.24 - 0.34) (p=0.35). The Italian study, with no age or gender disaggregation, reported a median baseline D-dimer level of 273 ng/mL (IQR: 175 - 360), noting 1 ng/mL is equivalent to 0.001 µg/mL. The median D-dimer level was 214 ng/mL (IQR: 144 - 431) after the first dose and 286 ng/mL (IQR: 160 - 514) after the second dose (p=0.633 baseline compared with 14 days post second dose). Their preliminary data concluded that administration of Comirnaty vaccines did not result in a hypercoagulable state. Neither study provided descriptive data about the BMI or HIV status of the participants. Contrary to our results, 30 majority female (64.7%) Sudanese participants, previously vaccinated with Ad26.COV2.S, who received an Ad26.COV2.S booster, had a statistically significant increase in mean D-dimer levels (mean (standard deviation) 0.17 (0.03) v. 0.37 (0.08), $p \leq 0.05$) noted post-booster vaccination. No symptoms of thrombosis and no difference in mean D-dimer levels post vaccination between females and males were noted.[46]

Our study enrolled PLHIV (40%), well and poorly controlled, and found no significant differences in elevated D-dimer levels compared with HIV-uninfected participants, neither at baseline nor at 2 weeks after booster vaccination.

This exploratory analysis had a few limitations. The study was powered to evaluate the primary endpoints related to response to booster vaccination rather than to evaluate the differences in D-dimer levels. However, the sample size of this coagulopathy analysis is higher than that of most studies evaluating D-dimer levels pre- and post-prime vaccination, as well as booster vaccination, and are delineated by factors such as gender, age, HIV status and obesity. This is possibly the largest cohort of its kind, describing D-dimer levels among those who received an Ad26.COV2.S prime vaccination followed by a homologous or heterologous booster vaccination. TTS diagnosis requires antiplatelet factor 4 (PF4) testing, which was not evaluated in our study, although none of our participants had symptoms of thrombosis during the study. Despite these limitations, the data represented here contribute to the limited research published and strengthens the advocacy for more conservative use of D-dimer level testing in healthy asymptomatic patients in the context of COVID-19 vaccination.

Conclusion

In the BaSiS study, a cohort consisting mostly of females with a BMI ≥30 kg/m^2, who received heterologous or homologous full-dose or fractional COVID-19 booster vaccines, a high proportion (39.3%) had elevated baseline D-dimer levels and almost 40% had increased D-dimer levels 2 weeks after booster vaccination. We found no association between booster vaccine type or dose in participants with raised D-dimer levels post-booster vaccination.

This exploratory analysis supports the rationale that D-dimer testing should be done together with other coagulopathy markers, such as anti-PF4 antibody, and only if clinically indicated, in clinical trial participants. The results and significance of raised D-dimer levels may also be difficult to interpret in the context of elevated D-dimer levels in the general population.

Table 3. Demographic and clinical characteristics associated with elevated D-dimer level 2-week post-booster vaccination*

Demographic and clinical characteristics		All participants, *n* (*N*=276)†	Elevated D-dimer level, 2-week post-booster vaccination, *n* (%) (*n*=109 (39.5))	Univariate analyses, unadjusted OR (95% CI)	Multivariable analyses, adjusted OR (95% CI)
Gender					
	Male	48	7 (14.6)	1 (base)	1 (base)
	Female	228	102 (44.7)	4.74 (2.04 - 11.02)	3.24 (1.14 - 9.22)
D-dimer levels at baseline					
	Normal	169	29 (17.2)	1 (base)	1 (base)
	Elevated	107	80 (74.8)	14.30 (7.92 - 25.85)	14.75 (7.64 - 28.48)
Booster vaccine type and dose administered					
	J & J Ad26.COV2.S – full dose	73	27 (37)	1 (base)	1 (base)
	J & J Ad26.COV2.S – half dose	65	22 (33.9)	0.87 (0.43 - 1.75)	0.54 (0.22 - 1.32)
	Pfizer BNT162b2 – full dose	71	27 (38.0)	1.05 (0.53 - 2.05)	0.76 (0.31 - 1.84)
	Pfizer BNT162b2 – half dose	67	33 (49.3)	1.65 (0.84 - 3.25)	1.59 (0.67 - 3.79)
Booster vaccine type administered					
	J & J Ad26.COV2.S	138	49 (35.5)	1 (base)	
	Pfizer BNT162b2	138	60 (43.5)	1.40 (0.86 - 2.27)	
Time between prime and BaSiS booster vaccination, months					
	<9	145	56 (38.6)	1 (base)	
	9 - <12	111	44 (39.6)	1.04 (0.63 - 1.73)	
	12 - 16	20	9 (45.0)	1.30 (0.51 - 3.34)	
Hypertension (prior known or raised BP at screening)					
	No	197	84 (42.6)	1 (base)	1 (base)
	Yes	79	25 (31.7)	0.62 (0.36 - 1.08)	0.47 (0.23 - 0.94)
Obese (BMI ≥30 kg/m^2)					
	No	107	30 (28.0)	1 (base)	1 (base)
	Yes	169	79 (46.8)	2.25 (1.34 - 3.79)	1.17 (0.58 - 2.33)
Thrombocytopenia (<150 × 10^9 cells/L)					
	No	271	107 (39.5)	1 (base)	
	Yes	4	2 (50.0)	1.53 (0.21 - 11.05)	
HIV status					
	Uninfected	166	64 (38.6)	1 (base)	1 (base)
	Infected	110	45 (40.9)	1.10 (0.67 - 1.80)	1.26 (0.67 - 2.37)
CD4 count <350 cells/μL or VL >40 copies/mL		*n*=110			
	No	88	32 (36.4)	1 (base)	
	Yes	22	13 (59.1)	2.53 (0.97 - 6.57)	

OR = odds ratio; CI = confidence interval; J & J = Johnson and Johnson; BaSiS = Booster After Sisonke Study; BP = blood pressure; BMI = body mass index; VL = viral load.
*Full table available as appendix Table S3.
†9/285 with D-dimer results available at enrolment; did not have 2-week D-dimer level data – therefore excluded from this table; 6 missed week 2 visits, 2 early withdrawals, 1 participant too ill for blood draw.

Data availability. All relevant data are in the manuscript and in the appendix tables.

Declaration. None.

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