Project Brief: BASIS

Full Title of Study/Programme	Phase II randomised open label trial of full and half dose J&J Ad26.CoV2.S and Pfizer BNT162b2 booster vaccinations after receiving the J&J Ad26.CoV2.S prime vaccine through the SISONKE phase IIIB implementation study
Technical Focus Area/Key Words	Research in Healthcare Workers
Rationale	1. Ad26.CoV2.S prime alone triggers lower titres of neutralizing antibodies than mRNA vaccines. 2. Other heterologous combinations of adenovirus vectored prime (ChAdOx) and RNA vaccine boosts (Pfizer BNT162b2) are highly immunogenic. 3. No data exists for J&J Ad26.COV2.S vaccine prime followed by an mRNA vaccine boost. 4. There is a scarcity of data regarding the immunogenicity of vaccines in PLHIV, who account for a significant proportion of South Africans. 5. People over the age of 55 years have a progressively weakened immune response to vaccines and may benefit from a homologous or a heterologous prime boost. 6. People living with HIV have compromised immune responses even if well controlled on ARVs and may benefit from a homologous or heterologous prime boost. 7. There is public health benefit, including cost and increased availability for greater numbers of people, in addition to potential reduction in local and systemic adverse effects, with fractional dosing for booster vaccines. Available data, although limited, demonstrates that fractional dosing results in robust immune responses. To boost the immunogenicity of the J&J Ad26.COV2.S vaccine already administered in the SISONKE phase IIIB implementation study, we propose to test a J&J Ad26.COV2.S /J&J Ad26.COV2.S homologous prime-boost vaccination design and a J&J Ad26.COV2.S/Pfizer BNT162b2 heterologous prime-boost vaccination design, which will include 4 arms: A. J&J Ad26.COV2.S/ J&J Ad26.COV2.S full dose homologous prime-boost vaccination B. J&J Ad26.COV2.S/ J&J Ad26.COV2.S half dose homologous prime-boost vaccination C. J&J Ad26.COV2.S/Pfizer BNT162b2 full dose heterologous prime-boost vaccination D. J&J Ad26.COV2.S/Pfizer BNT162b2 half dose heterologous prime-boost vaccination

	This design will determine if a boost of J&J Ad26.COV2.S or Pfizer BNT162b2 mRNA vaccine triggers high levels of nAbs and T cells, and determine whether the J&J Ad26.COV2.S and Pfizer BNT162b2 dosage can be reduced for cost effectiveness/vaccine sparing, and reduction in local and systemic adverse events post-vaccination. Immunogenicity will be quantified by measuring nucleocapsid binding antibodies (to assess prior infection) and neutralization capacity of blood plasma, a measure highly correlated to vaccine efficacy(12). Trial participants will be HCWs already vaccinated with one dose of J&J Ad26.COV2.S. Trial participants will be enrolled and have blood draws at baseline drawn immediately before vaccination, and then followed up at 2 weeks, 3 months and 6 months post vaccination to test peak immunogenicity and durability. Peripheral blood mononuclear cells will be isolated for evaluating T cell immune responses. Safety evaluations will be measured with the participant-administered diary card, recording local and systemic adverse reactions to the vaccine. Although one heterologous boost study reports an increase in reactogenicity compared to homologous boost, which may be a short-term disadvantage, these adverse events are likely short-lived and manageable particularly with the administration of agents such as paracetamol(35). It will be important to establish short- and longer-term adverse reactions with a J&J Ad26.COV2.S-Pfizer BNT162b2 prime-boost strategy, given that this information cannot be extrapolated from current clinical trials. Such information will assist with decision-making regarding prime-boost strategies in South African and sub-Saharan African countries where this strategy may be most likely given the currently available vaccines being offered in the rollout. Binding antibodies will be determined by ELISA to the nucleocapsid. Neutralization capacity will be determined independently by the laboratory of Penny Moore at NICD using a pseudovirus neutralization assay (PNA) and Alex Sigal at Africa Health Research Institute using a live virus neutralization assay (LVNA) by established protocols(39). SARS-CoV-2 variants to be neutralized will include the ancestral reference strain and the beta and delta variants for all samples, as well as other variants which may emerge for select samples. Assays will be completed once the effect of boost on neutralization at the tested significance level outlined in the analysis plan is determined. T cell responses to the ancestral, beta and delta strains will be measured by Wendy Burgers at the University of Cape Town, as described(40). Interim results will be made available after the 2 week and 3 months post-boost timepoints. Study follow up and evaluation will be extended through 6 months to assess durability of the booster immune response. Trial sites will be Wits RHI Shandukani and PHRU Kliptown in Johannesburg, the CAPRISA eThekwini Clinical Research Site in Durban and the Desmond Tutu Health Foundation site in Masiphumelele in Cape Town.
Primary Objectives	To evaluate the immunogenicity of a homologous vaccine boost with either a full (5x 10^{10} vp/ml, 0.25 ml) or a half dose (2.6x 10^{10} vp/ml, 0.13 ml) J&J Ad26.CoV2.S, or a heterologous boost, with either a full dose (30mcg, 0.3ml) or a half dose (15mcg, 0.15ml) Pfizer BNT162b2 vaccine, following

	J&J Ad26.CoV2.S vaccine administered through the SISONKE phase IIIB implementation study by comparing antibody and T cell responses before and after boosting. To evaluate safety and reactogenicity after a half or full dose J&J Ad26.CoV2.S or Pfizer BNT162b2 vaccine booster dose.
Secondary Objectives	To assess whether length of time between prime and booster dose impacts immunogenicity. To assess differences in immunogenicity by age and by HIV status. To evaluate boosted antibody responses against ancestral and novel SARS-CoV-2 strains including D614G, beta, delta, and other variants of concern (VOCs) compared to baseline. To evaluate the capacity of boosted T cell responses against ancestral and novel SARS-CoV-2 strains including D614G, beta, delta, and other relevant VOCs as they emerge compared to baseline.
Exploratory Objectives	To evaluate whether clotting profiles in participants at baseline and 2 weeks differ by booster arm, HIV status and age.
Study Design (R)	This is a phase II randomised open label clinical trial in health care workers, age ≥30 years, who have previously received one dose of the J&J Ad26.CoV2.S vaccine through the SISONKE phase IIIB implementation study. PLWH and HIV-uninfected participants will be enrolled. We will aim to enrol at least 10% of participants ≥55 years and participants who may have known, well controlled comorbidities. Previous SARS-CoV-2 infection, prior to or after the J&J Ad26.CoV2.S vaccine, will not result in exclusion but study results will be stratified according to evidence of previous infection. Participants will be recruited from 4 clinical trial sites in South Africa over a 4-month period. They will be recruited from 4 months after receiving the prime J&J Ad26.CoV2.S vaccine. Participants will be randomised 1:1:1:1 to group A, B, C and D. Group A will receive the Ad26.CoV2.S prime plus full dose Ad26.CoV2.S booster at a dose of $5x\ 10^{10}$ vp/ml (0.25 ml); Group B will receive the Ad26.CoV2.S prime plus half dose Ad26.CoV2.S booster at a dose of $2.6x\ 10^{10}$ vp/ml (0.13 ml); Group C will receive Ad26.CoV2.S prime plus full dose BNT162b2 booster at a dose of 30 mcg (0.3ml); and Group D will receive Ad26.CoV2.S prime plus half dose BNT162b2 booster at a dose of 15 mcg (0.15ml). Participants will be followed up for 6 months on study after randomisation.

<table>
<tr><td>Study arms (R)</td><td>
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<tr><th>Group</th><th>Number</th><th>Time after J&J Ad26.CoV2.S prime</th><th>Objectives</th><th>Vaccination</th><th>Vaccine Schedule</th></tr>
<tr><td>A N= 75</td><td>50 HIV Uninfected 25 PLHIV</td><td>≥ 4 months</td><td>Immunogenicity and safety</td><td>J&J Ad26.CoV2.S 5x 10^{10} vp/ ml</td><td>One dose (0.25 ml)</td></tr>
<tr><td>B N=75</td><td>50 HIV Uninfected 25 PLHIV</td><td>≥ 4 months</td><td>Immunogenicity and safety</td><td>J&J Ad26.CoV2.S 2.6x 10^{10} vp/ ml (dose for rounded off volume)</td><td>One dose (0.13 ml – rounded off for ease of correct dosing)</td></tr>
<tr><td>C N=75</td><td>50 HIV uninfected 25 PLHIV</td><td>≥ 4 months</td><td>Immunogenicity and safety</td><td>Pfizer BNT162b2 30 mcg IMI</td><td>One dose (0.3 ml)</td></tr>
<tr><td>D N=75</td><td>50 HIV uninfected 25 PLHIV</td><td>≥ 4 months</td><td>Immunogenicity and safety</td><td>Pfizer BNT162b2 15 mcg IMI</td><td>One dose (0.15ml)</td></tr>
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<tr><td>Study population (R)</td><td>Study participants will be ≥ 30 years, aiming to recruit at least 10% ≥ 55 years, 1/3 PLHIV and 2/3 HIV-uninfected. Participants may enrol if they have no or well controlled comorbidities and have had 1 dose of the J&J Ad26.CoV2.S vaccine through the SISONKE phase IIIB implementation study. Participants will not be screened for previous SARS-CoV-2 infection prior to enrolment but will have nasopharyngeal PCR testing on the day of enrolment. Participants will also have nucleocapsid antibody testing at enrolment to identify those previously infected with SARS-CoV-2, but these results will not be available prior to vaccination and will be noted when analysing response results. Participants will be recruited ≥4 months after receiving the J&J Ad26.CoV2.S prime</td></tr>
<tr><td>Study sample size (R)</td><td>300 participants, approximately 75 at each site will be enrolled</td></tr>
<tr><td>Follow up/duration</td><td>Study enrolment will be conducted over 4 months. Follow-up visits will take place 2 weeks, 3 months and 6 months (study exit) from the enrolment date. Interim visits may be arranged for any solicited adverse events (AEs) beyond 7 days post vaccination, or unsolicited AEs throughout the study post vaccination if they are grade 3 or higher. Additional study visits will be conducted for participants who develop symptoms of SARS-CoV-2 infection or test positive for SARS-CoV-2 infection with a nasopharyngeal swab polymerase chain reaction test or rapid antigen test while on the BaSiS study</td></tr>
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Study/Programme sites	Wits RHI Shandukani Research Centre (SRC) CAPRISA PHRU Desmond Tutu
Intervention (R)	• **Group A** = 75 Ad26.CoV2.S prime plus full dose Ad26.CoV2.S booster (50 HIV-, 25 HIV+) at a dose of 5x 10^{10} vp/ ml (0.25 ml) • **Group B**= 75 Ad26.CoV2.S prime plus half dose Ad26.CoV2.S booster (50 HIV-, 25 HIV+) at a dose of 2.6x 10^{10} vp/ ml (0.13 ml) • **Group C**= 75 Ad26.CoV2.S prime plus full dose BNT162b2 booster (50 HIV-, 25 HIV+) at a dose of 30mcg (0.3ml) • **Group D**= 75 Ad26.CoV2.S prime plus half dose BNT162b2 booster (50 HIV-, 25 HIV+) at a dose of 15mcg (0.15ml)
Operations	Study specific
Investigators	**Dr Faeezah Patel, Principal Investigator** **Prof. Lee Fairlie** **Dr Elizea Horne, Sub Investigator** **Dr Mrinmayee Dhar** **Tiffany Seef** **Othusitse Segalo** **Dr Jeanne Coetzee**
Other Partners & Collaborators	• Texas Children's Hospital • University of California, UC San Diego • Lurie Children's Hospital of Chicago • Pediatric Perinatal HIV Clinical Trials Unit • Boston Medical Center Pediatric HIV Program • Jacobi Medical Center • Seattle Children's Research Institute • San Juan City Hospital • SUNY Stony Brook • Emory University School of Medicine • The University of Southern California- LA • University of Florida- Jacksonville • South Florida CDTC Ft. Lauderdale • Rush University Cook County Hospital • University of Colorado- Denver • Johns Hopkins University • David Geffen School of Medicine at UCLA • St. Jude Children's Research Hospital • Bronx-Lebanon Hospital Center • University of Puerto Rico Pediatric HIV/AIDS Research Program

• **Sponsors /Donors**	• SA MRC
Linked Sub Studies and post grad projects	
Publications/key presentations to date	None as yet
Progress Update as at Dec-2023	Screened:115 Enrolled:101 Withdrawal:04 LTF:02 Extension Study Enrolled 59 Withdrawal 01 Completed extension study 49
Frequency of donor narrative report	Monthly
Overall Study/Project Contact	Dr Lee Fairlie Hermien Gous
Briefing owner and date	Dr Hermien Gous and Dr Faeezah Patel Dec-2023