Check for updates

Received: 9 November 2022 | Accepted: 22 March 2023

DOI: 10.1111/hiv.13495

ORIGINAL ARTICLE

The propositive study: Immunogenicity and safety of a four-component recombinant protein-based vaccine against MenB and a quadrivalent conjugate MenACWY vaccine in people living with HIV

Catherine Isitt[1] | **Angela Bartolf**[1] | **Nick Andrews**[2] | **Shehnaz Athaide**[1] | **Richard Pryce-Williams**[3] | **Kelly Townsend-Payne**[3] | **Ray Borrow**[3] | **Shamez Ladhani**[2,4] | **Paul T. Heath**[1,4] | **Catherine A. Cosgrove**[1]

[1]Vaccine Institute, St. George's University of London & St George's University Hospital NHS Trust, London, UK

[2]United Kingdom Health Security Agency, Colindale, UK

[3]United Kingdom Health Security Agency, Vaccine Evaluation Unit, Manchester, UK

[4]Centre for Neonatal and Paediatric Infection, St. George's University of London, London, UK

Correspondence
Catherine Isitt,
Vaccine Institute, St. George's University of London & St George's University Hospital NHS Trust, London, UK.
Email: cisitt@sgul.ac.uk

Funding information
GlaxoSmithKline

Abstract

Background: People living with HIV have been shown to have an increased risk of invasive meningococcal disease. In some countries, meningococcal vaccines are now routinely recommended to all people living with HIV, but no study has yet assessed the immunogenicity and safety of a meningococcal serogroup B vaccine or the co-administration of a MenB and MenACWY vaccine in people living with HIV.

Methods: This phase IV open-label clinical trial investigated the immunogenicity and safety of two doses of a four-component recombinant protein-based MenB vaccine (4CMenB) and a quadrivalent conjugate polysaccharide MenACWY vaccine (MenACWY-CRM197) given 1 month apart in a population of people living with HIV. Immunogenicity analysis was performed before vaccination and 1 month after the second doses of 4CMenB and MenACWY. Primary outcome measures were serum bactericidal assay geometric mean titres against three MenB reference strains at baseline and 1 month post vaccination, the proportion of participants achieving a putative protective titre of ≥4, and the proportion of participants with a ≥4-fold rise in titre from baseline. Secondary outcome measures were serum bactericidal assay geometric mean titres against MenA, C, W, and Y reference strains at baseline and 1 month post vaccination, the proportion achieving a putative protective titre of ≥8, and the proportion with a ≥4-fold rise in titre from baseline. Safety outcomes were solicited and unsolicited adverse events in the 7 days following vaccination. The trial was registered with clinicaltrials.gov (NCT03682939).

Findings: In total, 55 participants aged 20–45 years were enrolled. All participants (100%; 95% confidence interval [CI] 93–100) achieved putative protective titres for two of the three MenB strains and for MenA, W, and Y. A total of

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2023 The Authors. *HIV Medicine* published by John Wiley & Sons Ltd on behalf of British HIV Association.

98% (95% CI 89–100) achieved a protective titre for the third MenB strain and 94% (95% CI 83–99) for MenC. No serious adverse events were reported.

Interpretation: 4CMenB and MenACWY were immunogenic and well-tolerated in a population of people living with HIV 1 month after two doses.

KEYWORDS

HIV, meningococcal disease, vaccines

INTRODUCTION

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, is responsible for significant morbidity and mortality worldwide [1]. *N. meningitidis* has 12 different capsular polysaccharide groups, six of which – A, B, C, W, X, and Y – are responsible for invasive disease [2].

Patterns of *N. meningitidis* infection have shifted over time throughout the world. In the UK, Europe, and other industrialized nations, a hypervirulent serogroup C (MenC) strain of *N. meningitidis* (ST-11) drove the majority of IMD in the 1990s. The introduction of a conjugated polysaccharide MenC vaccine in the UK in 1999 as part of a national vaccination programme, and its subsequent introduction in other countries, led to significant reductions in the number of MenC cases due to both the direct protection of those vaccinated and a herd immunity effect [3]. In the subsequent two decades, the largest proportion of IMD was due to serogroup B (MenB) infections [4].

Historically, the development of MenB vaccines was complicated by the similarity of the MenB capsular polysaccharide to human foetal neural adhesion molecules. This renders MenB polysaccharide-based vaccines poorly immunogenic [3]. In 2013, a four-component MenB vaccine (4CMenB; Bexsero, GSK), was licensed in Europe. This recombinant protein-based vaccine was the first of its kind and combines three subcapsular membrane proteins (Neisserial heparin binding antigen [NHBA], Factor H binding protein [fHbp], Neisserial adhesin A [NadA]) and the outer membrane vesicle Porin-A (PorA) antigen from a New Zealand outbreak strain of MenB [5]. A second recombinant protein-based MenB vaccine (Trumenba, Pfizer) was licensed by the European Medicines Agency in 2017 [6]. In addition to these MenB-specific vaccines, MenACWY-conjugate quadrivalent vaccines have been available for over a decade in Europe. MenACWY-CRM197 (MENVEO, GSK) conjugated to cross-reacting material 197 (CRM197) was first licensed in 2010 [5], followed by MenACWY-TT (Nimenrix, Pfizer), conjugated to a tetanus toxoid protein, which was licensed in 2013. More recently, MenQuadfi (Sanofi Pasteur), also a tetanus toxoid conjugate, was licensed in 2020 [7, 8]. Therefore, it is now possible to vaccinate against the five most prevalent meningococcal serogroups with a combination of two vaccines. In the UK, 4CMenB is given as a 2 + 1 schedule to infants at 2, 4, and 12 months of age. A single MenACWY–conjugate vaccine is given to teenagers at age 13 years. In addition to routine vaccination of children, certain risk groups are recommended to receive meningococcal vaccines. These include those with asplenia or splenectomy and those with inherited or induced complement deficiency [9].

Multiple studies have shown that people living with HIV are at increased risk of IMD but this group are not routinely offered vaccination against meningococcal disease in the UK [10]. In one UK study, people living with HIV had an overall relative risk of IMD 4.5 times that of people without HIV. Specifically, for adults with HIV aged 16–24 years, the risk of IMD with capsular groups C, W, and Y was increased 22.7-fold compared with adults without HIV, irrespective of CD4 count or treatment with antiretroviral therapy [11]. A study from the USA found a 10-fold increased risk of IMD in people living with HIV [12], and a study from South Africa reported that people living with HIV had an 11.3-fold increased risk of IMD [13]. In the UK, an estimated 106 890 people were living with HIV in 2020, with 45% of new diagnoses among gay and bisexual men [14]. Multiple outbreaks of IMD among men who have sex with men (MSM) have been reported globally, emphasizing the increased risk faced by this group [15].

Small studies have previously investigated the immunogenicity and safety of meningococcal vaccines in people living with HIV. These studies suggested reduced immunogenicity of a single dose of MenC-conjugate vaccine in children and adolescents with HIV [16]. An investigation of MenACWY-conjugate vaccine use in adolescents with HIV found better responses in those with higher CD4 counts and a better response after two doses [17]. People living with HIV are known to have reduced immune responses to certain other vaccines, including hepatitis B recombinant DNA surface antigen vaccines [10]. To date, no study has assessed the safety and immunogenicity of MenB vaccination in people living with HIV.

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

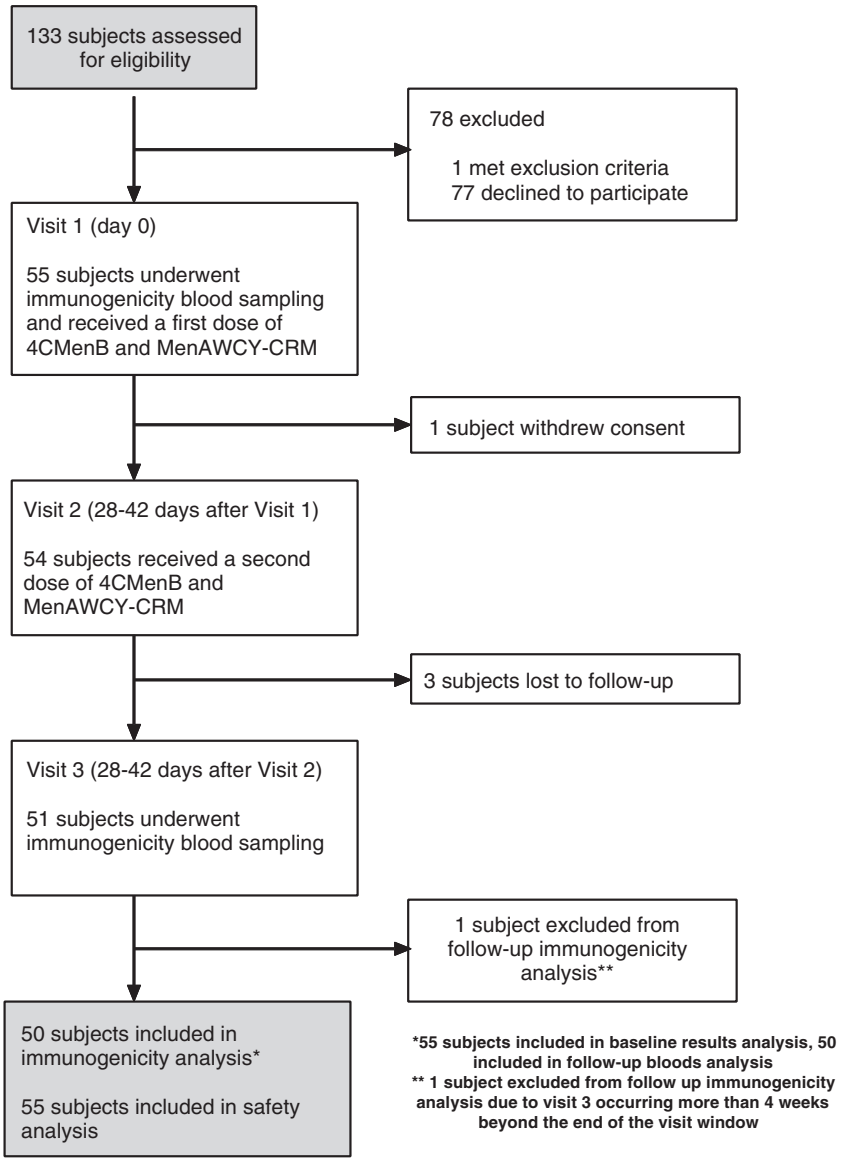

FIGURE 1 Participant flow chart.

We present the results of a phase IV open-label vaccine clinical trial designed to investigate the safety and immunogenicity of two doses each of 4CMenB and a MenACWY-conjugate vaccine in people living with HIV.

METHODS

Study population and schedule

Any person aged 10–45 years living with HIV, where they or their legal guardian were able to sign a consent form, was able to enrol in this study. Exclusion criteria were pregnancy, history of vaccination with both 4CMenB and a MenACWY-conjugate vaccine in the previous 2 years (receipt of a single vaccine was not an exclusion criterion), latex allergy, receipt of non-live vaccines in the 2 weeks or live vaccines in the 4 weeks before visit 1, active malignancy, hypersensitivity to the vaccine components, bleeding disorder, acute or chronic illness judged by the investigator as being a contraindication to vaccination, participation in another clinical trial of an investigational medicinal product within 60 days, and children in care.

4CMenB (Bexsero, GSK; lot no. ABX6E3BZ and ABX712AC) and MenACWY-CRM197 (MENVEO, GSK; lot no. AMVA062A) were administered intramuscularly in opposite deltoid muscles at visit 1 (day 0) and visit 2 (days 28–42). 4CMenB was administered into the non-dominant arm and MenACWY-CRM197 into the dominant arm. 4CMenB was supplied in a 0.5 mL pre-filled syringe for injection. MenACWY-CRM197 was supplied

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

as a lyophilised MenA component that was mixed with a liquid MenC, W, Y component, reconstituted to a total 0.5 mL prior to administration. Blood samples were taken at visit 1, before vaccination, and at visit 3 (28–42 days after visit 2) (Figure 1). Vaccination was deferred in the case of fever ≥38°C or acute illness on the day of intended vaccination or if the participant had received a dose of non-study vaccine within 2 weeks in the case of non-live, or 4 weeks in the case of live, vaccines. After each study vaccine administration, participants were provided with a diary card to complete daily for 7 days to note local and systemic solicited and unsolicited reactions. Participants also received a 24/7 emergency contact number for a telephone held by a study investigator.

Information about the solicited adverse events (AEs) pain, redness, and swelling at the injection site, headache, fatigue, nausea, myalgia, abdominal pain, and fever was collected in the 7 days post-vaccination. Serious AEs (SAEs) and AEs leading to study withdrawal were recorded for the duration of the subject's participation in the study. AEs were graded 1–4 according to the Division of AIDS (DAIDs) criteria for grading the severity of adult and paediatric AEs [18]. AEs and SAEs were judged by a study investigator as either definitely related, probably related, possibly related, or unrelated to the study vaccine. The proportion of participants who reported solicited AEs at each grade of severity during the 7 days of active follow-up was also recorded. Each AE was graded according to the highest grade of severity reported in the participant diary card within the follow-up period. Where an AE was reported to have resolved and then restarted within the 7-day period, this was counted as two separate AEs for the same participant for the purposes of a total count of episodes, but when determining the proportion of participants with an AE this was only counted once. All other AEs were reported in the same way, with the grade reported from 1 to 4 as per the DAIDs criteria.

This study was carried out in accordance with the principles of the declaration of Helsinki and followed good clinical practice. Ethical approval was obtained before the study start, and all subjects gave written informed consent before any study procedures were carried out. The study was registered at clinicaltrials.gov with the identifier NCT03682939.

Outcomes

The primary outcomes in this study were serum bactericidal antibody (SBA) assay using a human complement source (hSBA) geometric mean titres (GMT), against three MenB reference strains chosen to express each of three of the 4CMenB vaccine components, at baseline (visit 1) and 1 month after the second dose of the study vaccines (visit 3); the proportion of subjects who achieved putative protective hSBA titres of ≥4 against the three MenB reference strains 1 month after administration of the second dose of the study vaccines (visit 3); and the proportion of subjects with at least a 4-fold increase in hSBA GMTs from baseline (visit 1) to 1 month after the second doses of the study vaccines (visit 3).

The secondary outcomes were SBA assays performed with baby rabbit complement (rSBA) GMTs against MenA, C, W, and Y reference strains at baseline (visit 1) and 1 month after administration of the second dose of the study vaccines (visit 3); the proportion of patients achieving putative protective rSBA titres ≥8 against MenA, C, W, and Y reference strains at baseline and visit 3, and the proportion of patients achieving a ≥4-fold increase in GMT from baseline to visit 3.

Safety outcomes were the incidence of solicited local and systemic AEs up to 7 days after each vaccination visit, the incidence of unsolicited AEs up to 7 days after each vaccination visit and the incidence of SAEs or AEs leading to study withdrawal throughout the subject's entire study period.

Serology

Serology was performed at the Vaccine Evaluation Unit at the UK Health Security Agency (UKHSA), formerly Public Health England, Manchester, UK. For 4CMenB, immunogenicity was assessed by hSBA using three reference strains for MenB to assess response to three MenB antigens (44/76-SL for fHbp, 5/99 for NadA, and NZ98/254 for PorA). rSBA was used for immunogenicity studies of the MenACWY vaccine with reference strains for serogroups A, C, W, and Y [19]. Reference strain details are presented in Table 1.

Statistical analyses

Analysis was performed on a modified intention-to-treat basis, with all individuals with a measured antibody level taken no more than 4 weeks beyond the end of the visit window included. GMTs with 95% confidence intervals (CIs) were calculated, as were the proportions of subjects who achieved >4-fold increase in titres and a protective hSBA titre of ≥4 for MenB and rSBA titre of ≥8 for MenA, C, W, and Y with 95% CIs.

For SBA titres, values below the limit of detection were set at half the limit of detection for all analyses. Analysis was performed using STATA. The planned sample size was 55 participants with a 10% withdrawal rate

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Meningococcal strains used in serum bactericidal assays.

		fHbp		NadA			PorA		MLST	
Sero group	Isolate	Variant	Peptide	Variant	Peptide	NHBA peptide	VR1	VR2	ST	Clonal complex
B	44/76-SL	1	1	n/a	0	3	7	16	32	ST-32 complex
B	NZ 98/254	1	14	n/a	0	2	7–2	4	42	ST-41/44 complex
B	5/99	2	23	NadA-2/3	3	20	5	2	1349	ST-8 complex
C	L94 5016	2	22	NadA-2/3	8	357	7–1	1	345	Unassigned
A	M99 243 594	1	5	NadA-2/3	8	27	20	9	5	ST-5 complex
W	M01 240 070	2	16	n/a	0	20	18–1	3	184	ST-22 complex
Y	M03 241 125	2	22	NadA-2/3	3	29	5	2	11 149	ST-11 complex

Abbreviations: fHbp, Factor H binding protein; MLST, multi-locus sequence type; n/a, not applicable; NadA, Neisserial adhesin A; NHBA, Neisserial heparin binding antigen; PorA, Porin-A; VR1/2, variable region 1/2.

accounted for to give a 95% CI for GMTs with a ± width of approximately 1.5-fold around the point estimate based on the expected variance of antibody responses.

Exploratory analyses were planned using logistic regression to investigate associations between achieving a 4-fold increase in titre or achieving a protective titre after vaccination, and age, gender, smoking status, CD4 count, viral load, presence of co-morbidities, or alcohol intake. Post-vaccination data were log transformed, and regression was performed for each variable of interest. A p-value < 0.01 was used to identify variables of interest given the large number of variables.

RESULTS

The study was conducted between March 2019 and January 2020 at St George's University of London and St George's University Hospitals NHS Foundation Trust. A total of 55 subjects aged 20–45 years (median 36) were included in the study. Although we aimed to include subjects from the age of 10 years, most of the paediatric and adolescent population with HIV who were regularly seen in the paediatric HIV clinic had already been vaccinated either as part of the national vaccination programme or because they were at risk through travel to endemic areas and thus were not eligible. In total, 54 subjects received both planned doses of 4CMenB and MenACWY-CRM197. A total of 51 subjects attended for their follow-up blood tests at visit 3. One subject withdrew from the study after visit 1, and a further three participants were lost to follow-up after visit 2. One subject was excluded from the immunogenicity analysis as they attended for their visit 3 more than 4 weeks after the end of the visit window (Figure 1). The majority of subjects were male (76.4%), and the most common route of transmission of HIV was sex between men (MSM) (65.5%). Transmission via heterosexual sex accounted for 20% of participants. White ethnicity was the most common (56.4%), followed by Black ethnicity (25.5%). A total 83.6% of subjects had an undetectable viral load at their most recent clinic visit, and the median CD4 count at most recent clinic visit was 551 cells/mm^3 (range 151–1488); 9.1% of subjects had a most recent CD4 count <250 and 45.5% had a nadir CD4 count <250. In total, 63.6% of subjects reported one or more co-morbidity (Table 2).

GMT and the proportion of subjects achieving protective titres

At baseline, the proportion of subjects who had a protective hSBA titre of ≥4 was 53%, 73%, and 64% for the reference strains 5/99 (NadA), 44/76-SL (fHbp), and NZ98/254 (PorA), respectively. A clear increase in GMT from baseline to visit 3 (28–42 days post second-dose vaccination) was seen for all MenB reference strains (Figure 2). At visit 3, 100% (95% CI 93–100) of subjects had a protective titre for 5/99 and NZ98/254, and 98% (95% CI 89–100) had a protective titre for 44/76-SL (Figure 2). A 4-fold increase in titres was seen in 80% (95% CI 66–90), 72% (95% CI 58–84), and 74% (95% CI 60–85) of subjects for 5/99, 44/76-SL, and NZ98/254, respectively (Table 3).

For the MenA, C, W, and Y reference strains, an increase was seen in rSBA GMTs from baseline to visit 3 for all four strains (Figure 2). The proportion of subjects with a protective titre of ≥8 increased from 51% (95% CI 37–65), 35% (95% CI 22–49), 45% (95% CI 32–59), and 47% (95% CI 34–61) to 100% (95% CI 93–100), 94% (95% CI 83–99), 100% (95% CI 93–100), and 100% (95% CI 93–100) for MenA, C, W, and Y reference strains, respectively. Four-fold or greater increases in titres were seen in 78% (95% CI 64–88) for MenA, 86% (95% CI 73–94) for

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 Participant characteristics.

Gender	N (%)	Years lived in UK	N (%)	Route of transmission	N (%)	Alcohol consumption (units/week)	N (%)	Ethnicity	N (%)
Male (%)	42 (76.4)	Since birth	17 (30.9)	MSM	36 (65.5)	0	25 (45.5)	White British	14 (25.5)
Female (%)	13 (23.6)	<5	7 (12.7)	Heterosexual sex	11 (20.0)	1–5	22 (40.0)	White Irish	1 (1.8)
		5–9	7 (12.7)	Vertical transmission	7 (12.7)	6–10	7 (12.7)	White Other	16 (29.1)
Age (range)	36 (20–45)	10–14	10 (18.2)	Unknown	1 (1.8)	11–15	1 (1.8)	Black or Black British African	9 (16.4)
		15–19	8 (14.6)	Latest viral load and CD4				Black or Black British Carribbean	5 (9.1)
BMI (range)	23.4 (18.4–38.3)	20–24	4 (7.3)	Undetectable, N (%)	46 (83.6)	Smoking status	N (%)	Asian or Asian British Indian	1 (1.8)
		>25	2 (3.6)	Detectable, N (%)	9 (16.4)	Never smoker	33 (60)	Asian or Asian British Pakistani	3 (5.5)
		Co-morbidity		Latest CD4 count (range)	551 (151–1488)	Current smoker	10 (18.2)	Other Asian	3 (5.5)
		No	20 (36.4)	Nadir CD4 (range)	250 (3–600)	Ex-smoker	12 (21.8)	Other	3 (5.5)
		Yes	35 (63.6)	Years since dx (IQR)	7 (3–20)				

Abbreviations: BMI, body mass index; dx, diagnosis; IQR, interquartile range; MSM, men who have sex with men.

MenC, 94% (95% CI 83–99) for MenW, and 90% (95% CI 78–97) for MenY (Table 4).

Safety

The most frequently reported AE was pain at the injection site after 4CMenB injection (83.6% dose 1; 75.9% dose 2) (Table 5), of which 9.1% and 11.1% were grade 3 reactions. All other reactions were grade 1 and 2. Injection site pain was reported much less frequently after MenACWY-CRM197 injection (36.4% dose 1; 33.3% dose 2), with only 1.8% reporting a grade 3 reaction after dose 1. Other reactions were all grade 1 or 2 (Figure 3).

The most frequently reported systemic AEs were fatigue (52.7% dose 1; 59.3% dose 2) and headache (43.6% dose 1; 42.6% dose 2) (Table 6). Grade 3 fatigue events were reported by 1.8% and 1.9% after doses 1 and 2, and grade 3 headache events by 3.6% and 1.9% after doses 1 and 2. A single grade 4 reaction for fever (1.9%) was reported after dose 2. No other grade 4 events were reported (Figure 4).

The unsolicited AEs reported were mostly deemed unrelated to the study vaccines. One case of dizziness immediately after vaccination with dose 1 was judged to be a pre-syncopal event and did not re-occur after dose 2. Drowsiness judged to be a grade 2 AE was reported in the same participant after doses 1 and 2, although this spontaneously resolved within 24 hours. One case of grade 1 itch at the 4CMenB injection site was reported. No SAEs were reported within the study period, and no AEs led to participant withdrawal.

Exploratory analysis

In the exploratory analysis of factors associated with ≥4-fold rises, follow-up titres were log-transformed and regression performed for each variable of interest. No variable achieved a significance $p < 0.01$, so a multivariable regression was not performed. Given the high proportion of subjects achieving a protective titre, regression was not performed for this outcome.

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

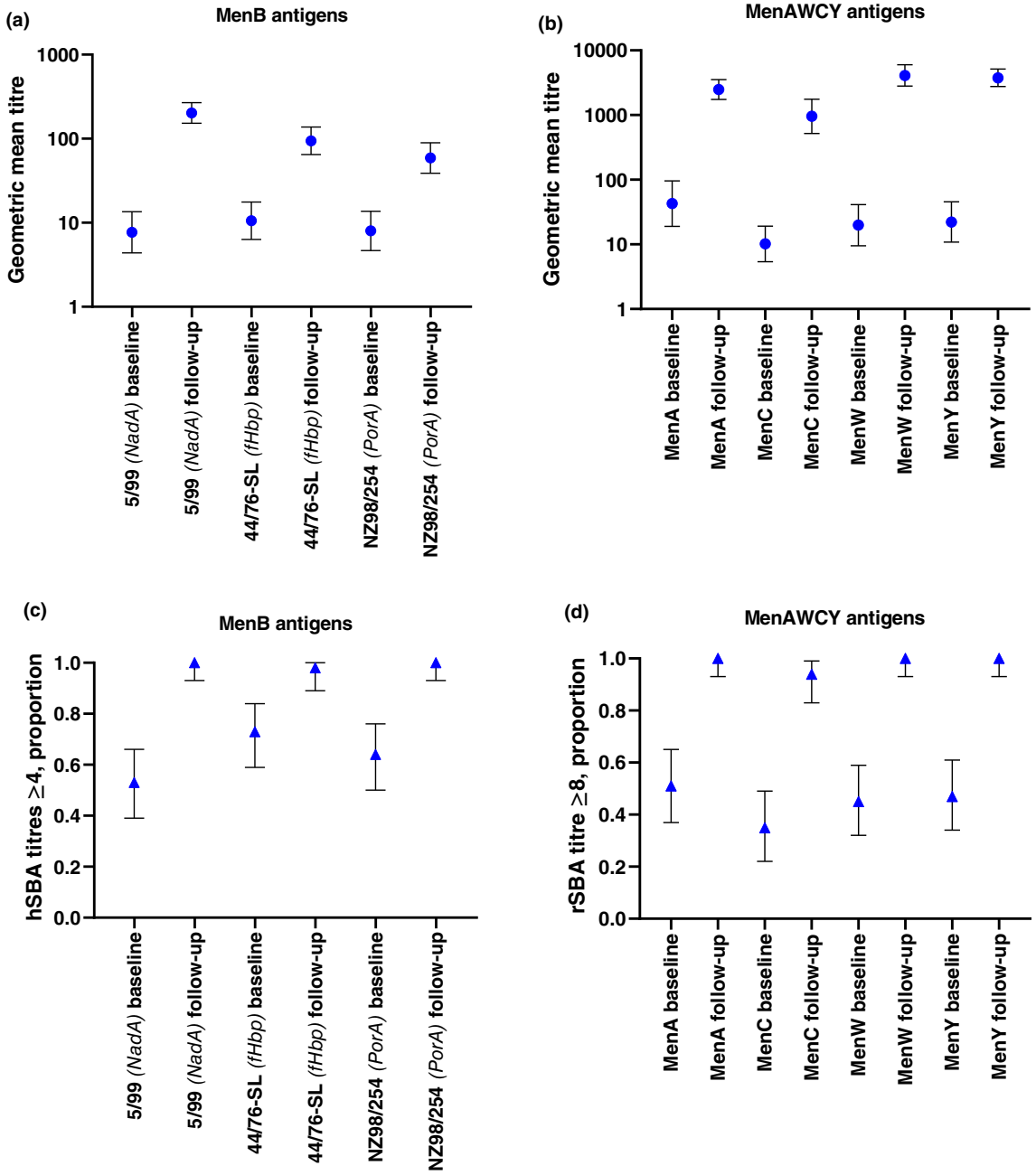

FIGURE 2 (a) Geometric mean titres pre-vaccination (baseline) and 1 month after two doses (follow-up) against three MenB reference strains. (b) Geometric mean titres pre-vaccination (baseline) and 1 month after two doses (follow-up) against MenA, C, W, and Y reference strains. (c) Proportion of participants who achieved a protective titre of ≥4 against three MenB reference strains pre and post-vaccination. (d) Proportion of participants who achieved a protective titre of ≥8 against Men A, C, W, and Y reference strains, pre and post vaccination. fHbp = Factor H binding protein; hSBA = serum bactericidal antibody assay with human complement source; NadA = Neisserial adhesin A; PorA = Porin-A; rSBA = serum bactericidal antibody assay with baby rabbit complement.

DISCUSSION

To our knowledge, this is the first study to assess the safety and efficacy of vaccination with 4CMenB and MenACWY-CRM197 in people living with HIV. In our study, 100% of participants achieved a protective titre for the MenB reference strains 5/99 and NZ98/254. In addition, 100% of subjects achieved protective titres for the MenA, W, and Y reference strains, 98% of participants achieved a protective titre for the 44/76-SL MenB reference strain, and 94% of participants achieved a protective titre for the MenC reference strain. The high proportion of subjects achieving protective titres suggests that both 4CMenB and MenACWY-CRM197

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Immunogenicity of 4CMenB components.

		5/99 (*NadA*)	44/76-SL (*fHbp*)	NZ98/254 (*PorA*)
Geometric mean titre (95% CI)	Baseline	7.7 (4.4–13.5)	10.6 (6.3–17.6)	8.0 (4.7–13.7)
	Follow-up	202.3 (152.4–268.4)	94.4 (64.8–137.4)	58.9 (38.7–89.5)
Proportion with protective (≥4) titre (95% CI)	Baseline	0.53 (0.39–0.66)	0.73 (0.59–0.84)	0.64 (0.5–0.76)
	Follow-up	1.00 (0.93–1.00)	0.98 (0.89–1.00)	1.00 (0.93–1.00)
Proportion achieving four-fold rise (95% CI)		0.80 (0.66–0.90)	0.72 (0.58–0.84)	0.74 (0.60–0.85)
Geometric mean fold increase in titre (95% CI)		29.0 (15.8–53.5)	8.5 (5.4–13.1)	7.5 (5.0–11.1)

Abbreviations: CI, confidence interval; fHBP, Factor H binding protein; NadA, Neisserial adhesin A.

TABLE 4 Immunogenicity of MenACWY-CRM197 components.

		MenA	*MenC*	*MenW*	*MenY*
Geometric mean titre (95% CI)	Baseline	42.8 (19.0–96.0)	10.2 (5.4–19.2)	19.8 (9.5–41.4)	22.2 (10.9–45.4)
	Follow-up	2486.7 (1745.6–3542.3)	955.4 (518.2–1761.4)	4096 (2802.1–5987.4)	3769.1 (2757.6–5151.5)
Proportion with protective (≥8) titre (95% CI)	Baseline	0.51 (0.37–0.65)	0.35 (0.22–0.49)	0.45 (0.32–0.59)	0.47 (0.34–0.61)
	Follow-up	1.00 (0.93–1.00)	0.94 (0.83–0.99)	1.00 (0.93–1.00)	1.00 (0.93–1.00)
Proportion achieving 4-fold rise (95% CI)		0.78 (0.64–0.88)	0.86 (0.73–0.94)	0.94 (0.83–0.99)	0.90 (0.78–0.97)
Geometric mean fold increase in titre (95% CI)		66.7 (28.1–158.2)	95.7 (46.0–198.9)	194.0 (88.7–424.5)	168.9 (71.7–397.7)

TABLE 5 Solicited local adverse events within 7 days of vaccination after doses 1 and 2.

	Vaccine dose 1 N (%)	Vaccine dose 2 N (%)
Pain at injection site 4CMenB	46 (83.6)	41 (75.9)
Pain at injection site MenACWY-CRM	20 (36.4)	18 (33.3)
Swelling at injection site 4CMenB	10 (18.2)	13 (24.1)
Swelling at injection site MenACWY-CRM	1 (1.8)	1 (1.9)
Redness at injection site 4CMenB	3 (5.5)	6 (11.1)
Redness at injection site MenACWY-CRM	0 (0)	1 (1.9)

induce a robust immune response in people living with HIV.

Studies conducted in laboratory workers aged 18–55 years without HIV produced similar immune responses after two doses of 4CMenB, as measured by the proportion of subjects achieving a protective SBA titre [20], suggesting that the efficacy of vaccination with 4CMenB is unaffected by the recipient's HIV status.

Furthermore, vaccination was generally well tolerated and acceptable to the study population, with no SAEs reported and no participants withdrawing from the study due to AEs. Pain at the injection site after administration with 4CMenB is a well-documented side effect of this vaccine. Other studies in adults have documented injection site pain in over 90% of participants [20]. In contrast to 4CMenB vaccination in infants, fever was not a commonly reported AE [21].

We note that the level of pre-existing immunity to the meningococcal reference strains (as evidenced by pre-vaccination SBA assays) was higher in this study than has been observed in studies performed in infants [21]. This is expected and likely reflects natural immunity from meningococcal nasopharyngeal carriage, which is most common during adolescence [22].

The follow-up period of 1-month post vaccination used in this study gives an indication of the immediate effect of vaccination in people living with HIV. However, longer-term immunogenicity has not yet been assessed in

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

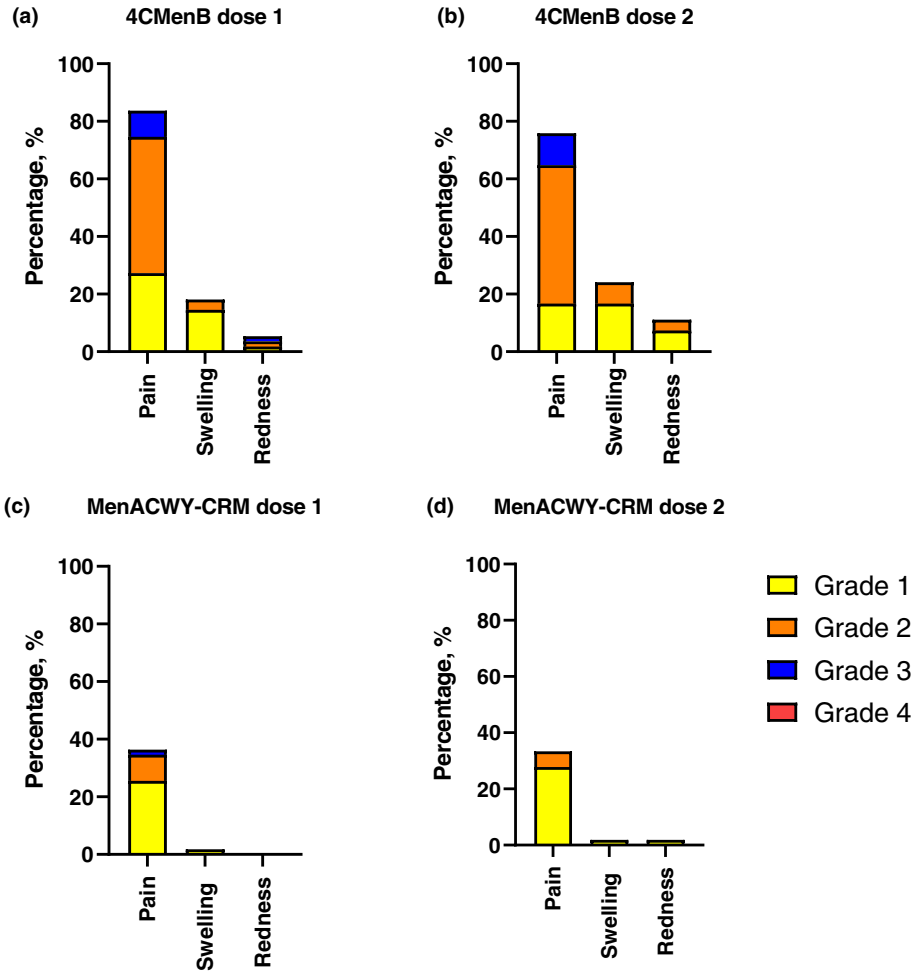

FIGURE 3 Solicited local adverse events within 7 days after (a) 4CMenB dose 1 and (b) 4CMenB dose 2 and after (c) MenACWY-CRM197 dose 1 and (d) MenACWY-CRM197 dose 2.

TABLE 6 Solicited systemic adverse events within 7 days after doses 1 and 2.

	Vaccine dose 1 (%)	Vaccine dose 2 (%)
Headache	24 (43.6)	23 (42.6)
Fatigue	29 (52.7)	32 (59.3)
Nausea	4 (7.3)	3 (5.6)
Myalgia	19 (34.5)	15 (27.8)
Abdominal pain	5 (9.1)	5 (9.3)
Fever	4 (7.3)	4 (7.4)

this group. Since 4CMenB vaccination was only licensed in 2013, was first incorporated into a routine vaccination programme in 2015 (in the UK), and is predominantly used in infants, the longer-term immunogenicity effects are not known, even in the primary target population. Studies in children that performed SBA assays 24–36 months after completion of the vaccination course found decreases in GMTs and protective titres across all vaccine antigens. However, booster doses elicited antibody responses that were better than responses to primary vaccination in age-matched cohorts [23]. A study in adults similarly found reductions in the percentage of vaccine recipients with protective titres for both reference and non-reference strains after 4–6 months [24]. A follow-up study conducted with the participants in this study will assess the longer-term immunogenicity of 4CMenB vaccination in people living with HIV.

Evidence is emerging that 4CMenB may give additional protection against non-serogroup B strains, including a recent hypervirulent MenW outbreak strain [25–27]. Other evidence is also emerging of some cross-protection against *Neisseria gonorrhoea* infections [28, 29]. Future studies should also examine this potential cross-protection in the context of people living with HIV.

The USA and Australia currently recommend meningococcal vaccines to all people living with HIV [30]; however, the UK British HIV association guidelines recommend only MenACWY vaccination for those

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

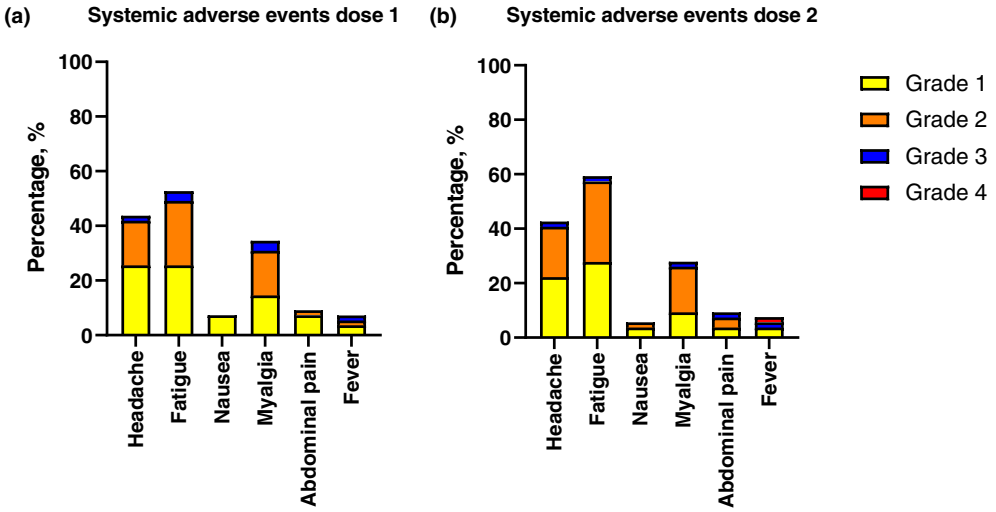

FIGURE 4 Solicited systemic adverse events in the 7 days after (a) the first dose of 4CMenB and MenACWY-CRM197 and (b) the second dose of 4CMenB and MenACWY-CRM197.

travelling to endemic areas and do not recommend vaccination against MenB [10]. Within the EU/EEA, Ireland, Italy, and Luxembourg already recommend routine meningococcal vaccination for people living with HIV, and Norway recommends meningococcal vaccination to MSM [31].

Given the increased risk of IMD in people living with HIV, the promising immunogenicity outcomes and tolerability reported in this study, and the abovementioned potential for cross-protection, we suggest that consideration is given to the inclusion of routine vaccination against IMD in the UK guidelines for the vaccination of people living with HIV.

AUTHOR CONTRIBUTIONS

CC, PH, SL, and AB conceived the study. CC, CI and AB initiated study design and SL and PH assisted with implementation. RB provided expert scientific advice for vaccine evaluation and KTP and RPW performed the SBAs. NA and CI performed data analysis and statistical analysis of results. CI and SA performed all study visits and data collection and participant follow-up. CI wrote the manuscript. All authors approved the final manuscript.

ACKNOWLEDGEMENTS

The authors acknowledge the study participants and the staff of the Courtyard Clinic at St George's Hospital for accommodating the study and their invaluable assistance.

FUNDING INFORMATION

This study was funded by GlaxoSmithKline. The investigators and representatives of the study sponsor (St George's, University of London) designed and performed the study. Investigators collected and analyzed data with statistical analysis support from UKHSA (N.A.). The study authors are responsible for the data interpretation and manuscript presentation. The funder had no role in protocol or study design, completion of the study, preparation of the final study report, or the decision to publish.

CONFLICT OF INTEREST STATEMENT

RB, KT-P, RP-W perform contract research for UKHSA on behalf of GSK, Pfizer, and Sanofi Pasteur. CI has previously received a research grant from Pfizer.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

1. Parikh SR, Campbell H, Bettinger JA, et al. The everchanging epidemiology of meningococcal disease worldwide and the potential for prevention through vaccination. *J Infect*. 2020; 81(4):483-498.
2. Harrison OB, Claus H, Jiang Y, et al. Description and nomenclature of Neisseria meningitidis capsule locus. *Emerg Infect Dis*. 2013;19(4):566-573.
3. Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. Enter B and W: two new meningococcal vaccine programmes launched. *Arch Dis Child*. 2016;101(1):91-95.
4. Whittaker R, Dias JG, Ramliden M, et al. The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004-2014. *Vaccine*. 2017;35(16):2034-2041.
5. Isitt C, Cosgrove CA, Ramsay ME, Ladhani SN. Success of 4CMenB in preventing meningococcal disease: evidence from real-world experience. *Arch Dis Child*. 2020;105(8):784-790.

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

6. Findlow J, Nuttens C, Kriz P. Introduction of a second MenB vaccine into Europe – needs and opportunities for public health. *Expert Rev Vaccines*. 2019;18(3):225-239.
7. Berti F, Romano MR, Micoli F, Adamo R. Carbohydrate based meningococcal vaccines: past and present overview. *Glycoconj J*. 2021;38(4):401-409.
8. Martinón-Torres F, Bertrand-Gerentes I, Oster P. A novel vaccine to prevent meningococcal disease beyond the first year of life: an early review of MenACYW-TT. *Expert Rev Vaccines*. 2021;20(9):1123-1146.
9. UKHSA. The routine immunisation schedule from February 2022. 2022.
10. Geretti AM, Brook G, Cameron C, et al. British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. *HIV Med*. 2016;17(August):s2-s81.
11. Simmons RD, Kirwan P, Beebeejaun K, et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. *BMC Med*. 2015; 13:297.
12. Miller L, Arakaki L, Ramautar A, et al. Elevated risk for invasive meningococcal disease among persons with HIV. *Ann Intern Med*. 2014;160(1):30-37.
13. Cohen C, Singh E, Wu HM, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. *Aids*. 2010; 24(9):1351-1360.
14. Martin VSA, Mackay N, Lester J, et al. HIV testing, new HIV diagnoses, outcomes and quality of care for people accessing HIV services: 2021 report. The annual official statistics data release (data to end of December 2020). In: Agency UHS, ed.; 2021.
15. Folaranmi TA, Kretz CB, Kamiya H, et al. Increased risk for meningococcal disease among men who have sex with men in the United States, 2012-2015. *Clin Infect Dis*. 2017;65(5): 756-763.
16. Frota AC, Milagres LG, Harrison LH, et al. Immunogenicity and safety of meningococcal C conjugate vaccine in children and adolescents infected and uninfected with HIV in Rio de Janeiro. *Brazil Pediatr Infect Dis J*. 2015;34(5):e113-e118.
17. Lujan-Zilbermann J, Warshaw MG, Williams PL, et al. Immunogenicity and safety of 1 vs 2 doses of quadrivalent meningococcal conjugate vaccine in youth infected with human immunodeficiency virus. *J Pediatr*. 2012;161(4):676–681.
18. U.S. Department of Health and Human Services NIoH, National Institute of Allergy and Infectious Diseases, Division of AIDS. *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1*. [July 2017]. National Institue of Allergy and Infectious Diseases; 2017.
19. Lucidarme J, Louth J, Townsend-Payne K, Borrow R. Meningococcal Serogroup a, B, C, W, X, and Y serum bactericidal antibody assays. *Methods Mol Biol*. 2019;1969:169-179.
20. Findlow J, Bai X, Findlow H, et al. Safety and immunogenicity of a four-component meningococcal group B vaccine (4CMenB) and a quadrivalent meningococcal group ACWY conjugate vaccine administered concomitantly in healthy laboratory workers. *Vaccine*. 2015;33(29):3322-3330.
21. Vesikari T, Esposito S, Prymula R, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. *Lancet*. 2013;381(9869): 825-835.
22. McMillan M, Walters L, Sullivan T, et al. Impact of meningococcal B (4CMenB) vaccine on pharyngeal Neisseria meningitidis carriage density and persistence in adolescents. *Clin Infect Dis*. 2021;73(1):e99-e106.
23. Martinon-Torres F, Carmona Martinez A, Simko R, et al. Antibody persistence and booster responses 24-36 months after different 4CMenB vaccination schedules in infants and children: a randomised trial. *J Infect*. 2018;76(3):258-269.
24. Giuntini S, Lujan E, Gibani MM, et al. Serum bactericidal antibody responses of adults immunized with the MenB-4C vaccine against genetically diverse Serogroup B Meningococci. *Clin Vaccine Immunol*. 2017;24(1):1-12.
25. Ladhani SN, Campbell H, Andrews N, et al. First real-world evidence of meningococcal group B vaccine, 4CMenB, protection against meningococcal group W disease: prospective enhanced National Surveillance. *Engl Clin Infect Dis*. 2021; 73(7):e1661-e1668.
26. Ladhani SN, Giuliani MM, Biolchi A, et al. Effectiveness of meningococcal B vaccine against endemic Hypervirulent Neisseria meningitidis W strain. *Engl Emerg Infect Dis*. 2016;22(2): 309-311.
27. Biolchi A, Tomei S, Brunelli B, et al. 4CMenB immunization induces serum bactericidal antibodies against non-Serogroup B meningococcal strains in adolescents. *Infect Dis Ther*. 2021; 10(1):307-316.
28. Longtin J, Dion R, Simard M, et al. Possible impact of wide-scale vaccination against Serogroup B Neisseria Meningitidis on gonorrhea incidence rates in one region of Quebec, Canada. Open forum. *Infect Dis*. 2017;4(suppl_1):S734-S735.
29. Ladhani SN, Borrow R, Ramsay ME. Killing 2 cocci with 1 vaccine: unleashing the full potential of an adolescent meningococcal B immunization program. *Clin Infect Dis*. 2021;73(1):e238-e240.
30. Chang L, Lim BCW, Flaherty GT, Torresi J. Travel vaccination recommendations and infection risk in HIV-positive travellers. *J Travel Med*. 2019;26(6):1-18.
31. European Centre for Disease Prevention and Control. *Expert Opinion on the Introduction of the Meningococcal B (4CMenB) Vaccine in the EU/EEA2017*:1-38. European Center for Disease Prevention and Control; 2017.

How to cite this article: Isitt C, Bartolf A, Andrews N, et al. The propositive study: Immunogenicity and safety of a four-component recombinant protein-based vaccine against MenB and a quadrivalent conjugate MenACWY vaccine in people living with HIV. *HIV Med*. 2023;1-11. doi:10.1111/hiv.13495

14681293, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hiv.13495 by St George'S University Of London, Wiley Online Library on [09/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License