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ORIGINAL ARTICLE

Propositive follow-up: Long-term immune responses to the 4CMenB and MenACWY vaccines in people living with HIV

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Abstract

Background: People living with HIV have an increased risk of meningococcal disease. The Propositive trial evaluated co-administration 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 people with HIV. The follow-up trial assessed the immunogenicity of these vaccines at 1.5 and 2.5 years after primary vaccination.

Methods: Participants who completed the parent Propositive trial were invited to the follow-up study. Immunogenicity analysis was performed at 18 and 30 months after primary vaccination. Primary outcome measures were serum bactericidal antibody (SBA) geometric mean titres (GMTs) against three MenB reference strains and the proportion of participants maintaining a protective SBA titre of ≥4 at 18 and 30 months. Secondary outcome measures were SBA GMTs against MenA, C, W, and Y serogroups and the proportion of participants maintaining a protective SBA titre of ≥8 at 18 and 30 months. The trial is registered with Clinicaltrials.gov (NCT042394300).

Results: A total of 40 participants aged 22–47 years were enrolled. Geometric mean titres waned by 18 and 30 months but remained higher than pre-vaccination for all MenB strains and MenA, C, W, and Y. In total, 75%–85% of participants retained protective SBA titres by 30 months against individual MenB strains, whereas 68.8% of patients retained protective antibody titres against all three MenB strains. Antibodies against MenC waned more rapidly than did those against MenA, W, and Y. The proportion of participants with protective titres against MenC at 30 months was also lower (46.9%) than that with protective titres against MenA (87.5%), W (78.1%), and Y (87.5%).

Conclusions: Immune responses against MenB in our cohort of people living with HIV at 2.5 years of follow-up were reassuring, with 68.8% of participants

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retaining protection against all three reference strains. However, responses against MenC were lower than those against MenA, W, and Y serogroups.

KEYWORDS

HIV, long-term immunogenicity, meningococcal disease, meningococcal vaccination, vaccines

INTRODUCTION

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, presents clinically as septicaemia when bacteria enter the bloodstream and meningitis if the blood–brain barrier is breached. It is a devastating disease that has a case fatality rate of around 10% and can leave survivors with serious permanent sequelae [1]. Of the 12 serogroups that have been described, six (serogroups A, B, C, W, X, and Y) are responsible for most IMD cases worldwide. In the UK, IMD is rare because of an extensive national meningococcal immunization programme, which includes MenB vaccination (4CMenB, *Bexsero*®) for infants, MenC conjugate vaccination for toddlers and MenACWY conjugate vaccination for adolescents [2, 3].

4CMenB is a protein-based, multi-component vaccine against MenB that contains three recombinant protein antigens—Neisseria heparin-binding antigen (NHBA), factor H-binding protein (fHbp), and Neisseria adhesin A (NadA)—as well as the outer membrane vesicle (OMV) from *N. meningitidis* strain NZ98/254, expressing PorA P1.4 [4]. The vaccine has been shown to be highly protective against MenB disease in young children [5, 6] and adolescents [7, 8], and may also protect against other meningococcal serogroups with cross-reactive surface antigens [9]. 4CMenB has no impact on MenB carriage and, therefore, cannot induce indirect (herd) protection [10]. Thus, individual protection relies on direct protection achieved through vaccination.

In contrast, the MenACWY conjugate vaccines prevent carriage acquisition and can, therefore, induce indirect protection in addition to direct protection when offered to older adolescents, who are the main nasopharyngeal carriers of meningococci [11]. Although *N. meningitidis* typically targets previously healthy children and adults, a number of underlying conditions can increase the risk of IMD, namely asplenia, splenic dysfunction, complement deficiency, and HIV. We have previously shown that people living with HIV, including those receiving effective antiretroviral therapy (ART), have an increased risk of IMD compared with the general population [12]. Similarly, a recent systematic review and meta-analysis of risk factors for IMD showed an increased risk in people living with HIV (PLHIV) versus those without HIV, which was nearly three-fold higher in adults aged 25–44 years [13]. In the USA and several European countries, PLHIV are included in the increased high-risk groups for IMD for which vaccination against meningococcus is recommended [14, 15]. However, in the UK, PLHIV are not routinely recommended to receive meningococcal vaccination outside the routine immunization schedule [16, 17]. Furthermore, there are limited data on the safety, reactogenicity, immunogenicity, or antibody persistence of meningococcal vaccines in PLHIV, especially with the novel protein-based MenB vaccines. A previous study reported reduced responses after MenC conjugate vaccination in children with HIV [18], whereas another study of MenACWY conjugate vaccine found better immunogenicity after two doses than after a single dose in young people with HIV [19].

We have recently reported on the Propositive study, which evaluated the immunogenicity and reactogenicity after 4CMenB and MenACWY conjugate vaccines given together, two doses 1 month apart, in PLHIV aged 18–45 years. Both vaccines were found to be safe, and nearly all participants achieved protective thresholds against three MenB indicator strains and the other four meningococcal serogroups [20]. The Propositive follow-up study was set up to evaluate long-term immunogenicity of the 4CMenB and MenACWY conjugate vaccines in PLHIV. Here, we report on antibody persistence and waning of immunity in the same Propositive cohort of PLHIV at 18 and 30 months after completing their two-dose 4CMenB and MenACWY conjugate vaccine schedule.

METHODS

The parent Propositive study (NCT03682939), including the detailed methodology and post-vaccination immunogenicity, has already been published [20]. Propositive follow-up is a phase IV, single site, observational study that was conducted at St George's University of London. The current study is an extension of the parent study and is registered in ClinicalTrials.Gov (NCT042394300).

Briefly, Propositive recruited 55 people living with HIV aged 20–45 years (median 36), of whom 54 received two doses each of 4CMenB (BEXSERO, GSK, lot no.

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ABX6E3BZ and ABX712AC) and MenACWY-CRM197 (MenACWY conjugate, MENVEO, GSK, lot no. AMVA062A) with an interval of 1 month between doses, and 51 attended for their follow-up blood test at 1 month after the second dose.

For the current study, participants in Propositive were contacted to take part in the follow-up study at 18 months after completion of primary vaccination. Written informed consent was obtained from participants prior to enrolment. Inclusion criteria included receipt of two doses of both vaccines and provision of informed consent. Unwillingness to take part in the trial was the only exclusion criterion.

Objectives

The primary objective was to evaluate the persistence of immune response to 4CMenB vaccine at 18 and 30 months after completion of a two-dose schedule. The primary immunogenicity outcomes were serum bactericidal antibody (SBA) assay using an exogenous human complement (hSBA) geometric mean titres (GMTs) and proportions with titres ≥4, against relevant meningococcal serogroup B strains, at 18 and 30 months post completion of vaccination.

The secondary objective was to evaluate the persistence of the immune response to the MenACWY conjugate vaccine at 18 and 30 months after completion of a two-dose schedule. The secondary outcomes were SBA using an exogenous source of baby rabbit complement (rSBA), GMTs and proportions with titres ≥8, against meningococcal A, C, W, and Y serogroups, at 18 and 30 months post completion of primary vaccination.

Immunogenicity assessments

Participants had blood samples collected at two time points: 18 and 30 months after the second dose of 4MenB and MenACWY conjugate vaccines. Sera from the original Propositive study and the current follow-up study were analysed at UK Health Security Agency (UKHSA) Vaccine Evaluation Unit, Manchester, UK, using previously validated methodology [21]. hSBA were performed to measure antibodies against three strains of *N. meningitidis* serogroup B: 44/76-SL for fHbp-1, 5/99 for NadA, and NZ98/254 for Porin A (PorA). hSBA titres of ≥4 are considered protective against MenB [22]. In addition, rSBA were performed to measure antibody production against four *N. meningitidis* serogroups: A, C, W, and Y. rSBA titres of ≥8 are considered protective against MenC [22].

Statistical analysis

Sample size calculations were performed for the original Propositive study, with planned recruitment of 55 participants to accommodate a 10% dropout rate and give a 95% confidence interval (CI) for GMTs with a ± width of approximately 1.5-fold around the point estimate based on the expected variance of antibody responses [20]. For the current study, all vaccinated Propositive participants were invited to take part in the follow-up.

Participant demographics and characteristics at the 18-month follow-up visit are described using descriptive statistics. Immunogenicity data at baseline and 1 month after second vaccination from the parent study are included for comparison.

For primary and secondary immunogenicity outcomes in the current follow-up study, GMTs were calculated with 95% CIs for the three MenB reference strains as well as MenA, C, W, and Y. Geometric mean ratios (GMRs) with 95% CIs were also calculated to assess declines from the peak at 1 month post vaccination using the paired data in individuals with results at each time point. For SBA titres, values below the limit of detection were set at half the limit of detection for all analyses. Additionally, the proportions of participants with hSBA titres ≥4 against MenB strains and rSBA titres ≥8 against MenACWY strains with associated two-sided 95% CIs were calculated.

Exploratory analyses were performed to evaluate the relationship between antigen-specific antibody levels at 18 and 30 months with the following clinical variables: age, sex, ethnicity, body mass index, presence of comorbidities, route of transmission, smoking, alcohol intake, CD4 count, detectable viral load, and years since HIV diagnosis. Univariable normal errors regression analysis on logged vaccination titres at 18 and 30 months was performed initially. Subsequently, a multivariable linear regression model using logged vaccination titres at 18 and 30 months for all antigens was performed using the following variables: CD4 count (continuous variable), detectable viral load (yes/no), age (continuous variable), sex (male/female), and ethnicity (white/non-white). Geometric mean fold ratios were estimated by anti-logging the model estimates. Finally, logistic regression on proportions of participants with titres ≥4 for MenB and ≥8 for MenA, C, W, and Y at 18 and 30 months was performed using the same variables. Because of multiple comparisons, a p-value of <0.01 in the univariable and multivariable analyses was considered statistically significant.

To evaluate antibody weaning, antibody half-lives and 95% CIs for each serogroup/antigen were estimated using the individual-level data with a multilevel linear

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random slope model on the logged titres. The half-life was calculated using the model slope via the following equation: $T_{1/2} = \log_{10}(0.5)/\text{slope}$. Statistical analysis was performed using STATA (V.17).

RESULTS

The study was conducted at St George's University of London and St George's University Hospital NHS Trust (both located at the same site) between November 2020 and August 2022. A total of 51 patients who had completed the parent study were contacted to be recruited for the follow-up study. Of those, 40 participants aged 22–47 years (median 37) signed informed consent and were enrolled. In total, 38 participants attended the first follow-up visit at 18 months after the second 4CMenB and MenACWY vaccination within the study visit window (±2 months). Subsequently, 32 subjects attended the second follow-up visit at 30 months (±2 months) post vaccination, and eight were lost to follow-up. Figure 1 shows the flow diagram for the parent Propositive and the follow-up trial.

The majority of participants in the follow-up study were male (31/40 [77.5%]) and white (26/40 [65%]). The most common route for HIV transmission was sex between men (24/40 [70%]). Median CD4 count from their most recent clinic appointment was 592 cells/mm^3 (range 28–1438). All patients were taking antiretroviral medication, and 34 of 40 (85%) participants had an undetectable viral load throughout the duration of the study. A total of 35 of 40 (87.5%) participants reported good compliance with antiretroviral medication, defined as missing less than one dose over a 3-month period. Full participant characteristics are shown in Table 1.

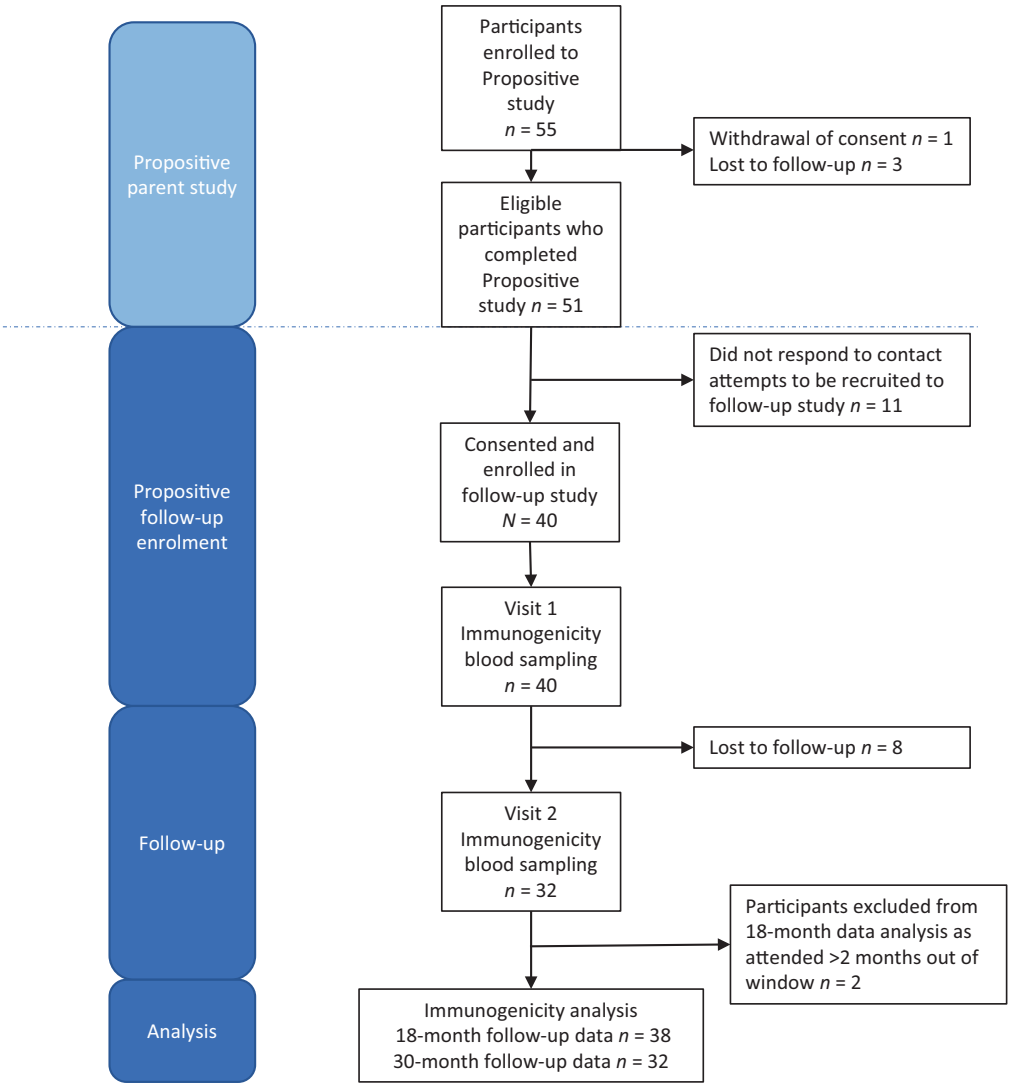

FIGURE 1 Study flow diagram.

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Primary outcome

The primary objective was to evaluate the long-term immunogenicity of two doses of 4CMenB at 18 and 30 months. Table 2 shows the hSBA GMTs and the proportion of participants with protective titres ≥1:4 against three MenB reference strains (5/99 [NadA], 44/76-SL [fHbp], and NZ98/254 [PorA]) at four time points: baseline and 1, 18, and 30 months. GMTs peaked at 1 month after vaccination, then dropped during the follow-up visits but remained higher at 18 and 30 months than at baseline for all MenB strains (Figure 2). For NadA, antibody levels dropped 13.6-fold (GMR 18 m/1 m = 0.07 [95% CI 0.04–0.13]) by 18 months compared with the peak at 1 month post vaccination and remained stable at 30 months (GMR 30 m/1 m = 0.08 [95% CI 0.08–0.15]). Antibody waning over time was less marked for fHbp: 3.9-fold by 18 months compared with 1 month (GMR 18 m/1 m = 0.26 [95% CI 0.19–0.35]), with similar values at 30 months (GMR 30 m/1 m = 0.26 [95% CI 0.17–0.38]). For PorA, there was a 3.7-fold drop at 18 months (GMR 18 m/1 m = 0.27 [95% CI 0.18–0.42]) and similar values at 30 months (GMR 30 m/1 m = 0.25 [95% CI 0.15–0.41]). Estimated half-lives for NadA were shorter than for fHbp or PorA (212 [95% CI 174–271], 395 [95% CI 320–514], and 430 [95% CI 327–630] days, respectively).

The proportion of subjects with protective titres ≥1:4 against NadA, fHbp, and PorA antigens was 68.4% (95% CI 51.3–82.5), 92.1% (95% CI 78.6–98.3), and 76.3% (95% CI 59.8–88.6) at 18 months and 87.5% (95% CI 71–96.5), 87.5% (95% CI 71–96.5), and 75% (95% CI 56.6–88.5) at 30 months, respectively. At 30 months, 22/32 (68.8%) patients retained protective antibody titres against all three MenB strains, 6/32 (18.8%) against two MenB strains, 2/32 (6.3%) against one strain, and 2/32 (6.3%) had no protection against any strain (Table 2).

Secondary outcome

The secondary objective was to evaluate the long-term immunogenicity of two doses of MenACWY conjugate vaccine at 18 and 30 months. Table 3 shows the rSBA GMT with 95% CI and the proportion of participants with protective titres ≥1:8 against MenA, C, W, and Y at four time points: baseline and 1, 18, and 30 months. GMT peaked at 1 month post vaccination: MenC had significantly lower GMTs than did MenW and MenY. GMT dropped from 1 month post vaccination to the 18- and 30-month visits and was significantly lower at 18 months for MenC serogroup than for MenA, W, and Y serogroups (Table 3 and Figure 3).

Antibodies waned 27.2- and 66.8-fold for MenC at 18 and 30 months compared with levels at 1 month (GMR 18 m/1 m, 0.04 [95% CI 0.03–0.07] and 30 m/1 m, 0.01 [95% CI 0.01–0.03]). The rate of antibody decline was lower for the other serogroups: 6.0- and 10.6-fold for

TABLE 1 Summary of participant characteristics.

Characteristic	Participants ($N = 40$)
Age	36 (22–47)
Male	31 (77.5)
Female	9 (22.5)
Body mass index	24.36 (18.4–38.3)
Most recent CD4	592 (28–1438)
Nadir CD4	250 (11–600)
Detectable VL	6 (15)
Undetectable VL	34 (85)
Self-reported compliance with ARV treatment	35 (87.5)
Route of transmission	
Men who have sex with men	28 (70)
Heterosexual sex	9 (22.5)
Vertical transmission	2 (5)
Unknown	1 (2.5)
Comorbidities (any chronic condition or history of previous AIDS-defining illness)	
Yes	33 (82.5)
No	7 (17.5)
Receiving immunosuppressive medication (%)	1 (2.5)
Smoking status	
Never smoker	10 (25)
Current smoker	10 (25)
Ex-smoker	20 (50)
Alcohol consumption (units/week)	
0	8 (20)
1–5	24 (60)
6–10	8 (20)
Received at least one dose of COVID-19 vaccine	34 (85)
Ethnicity	
White British	9 (22.5)
White other	15 (37.5)
Black or Black British African	4 (10)
Black or Black British Caribbean	3 (7.5)
Asian or Asian British Indian	1 (2.5)
Asian or Asian British Pakistani	3 (7.5)
Other Asian	2 (5)
Other	3 (7.5)

Note: Data are n (%) or median (range).
Abbreviations: AIDS = Acquired Immune Deficiency Syndrome; ARV = antiretroviral; VL = viral load.

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TABLE 2 Immunogenicity outcomes for MenB antigens: fHbp, NadA, and PorA.

		Propositive study [20]		Follow-up study	
Meningococcal serogroup	**Estimate**	**Baseline (*N* = 55)**	**1 month (*N* = 50)**	**18 months (*N* = 38)**	**30 months (*N* = 32)**
44/76 L (fHbp)	GMT	10.6 (6.3–17.6)	94.4 (64.8–137.4)	25.7 (15.9–41.7)	25.2 (14.4–44.1)
	% with titres ≥1:4	72.7 (59–83.9)	98 (89.4–99.9)	92.1 (78.6–98.3)	87.5 (71–96.5)
5/99 (NadA)	GMT	7.7 (4.4–13.5)	202.3 (152.4–268.4)	14.6 (8–26.6)	13.5 (7.9–23.1)
	% with titres ≥1:4	52.7 (38.8–66.3)	100 (92.9–100)	68.4 (51.3–82.5)	87.5 (71–96.5)
NZ98/254 (PorA)	GMT	8 (4.7–13.7)	58.9 (38.7–89.5)	14.6 (7.7–27.5)	15.3 (8–29.3)
	% with titres ≥1:4	63.6 (49.6–76.2)	100 (92.9–100)	76.3 (59.8–88.6)	75 (56.6–88.5)
Not protected against any MenB strain		13/55 (23.6)	0/50 (0)	1/38 (2.6)	2/32 (6.3)
		8/30[a] (25)	0/30[a] (0)	1/30[a] (3.1)	2/30[a] (6.3)
Protected against one MenB strain		6/55 (10.9)	0/50 (0)	6/38 (15.8)	2/32 (6.3)
		2/30[a] (9.4)	0/30[a] (0)	4/30[a] (12.5)	2/30[a] (6.3)
Protected against two MenB strains		10/55 (18.2)	1/50 (2)	9/38 (23.7)	6/32 (18.8)
		7/30[a] (21.9)	1/30[a] (3.1)	7/30[a] (21.9)	6/30[a] (18.8)
Protected against all MenB strains		26/55 (47.3)	49/50 (98)	22/38 (57.9)	22/32 (68.8)
		13/30[a] (43.8)	29/30[a] (96.9)	18/30[a] (56.3)	20/30[a] (68.8)

Note: Data are GMT (95% confidence interval), % (95% confidence interval), or *n/N* (%). The color shading represents each of the clinical studies.
Abbreviations: fHbp = factor H-binding protein 1; GMT = geometric mean titres; NadA = Neisseria adhesin A; PorA = Porin A.
[a]Participants who completed the study with data available for all time points.

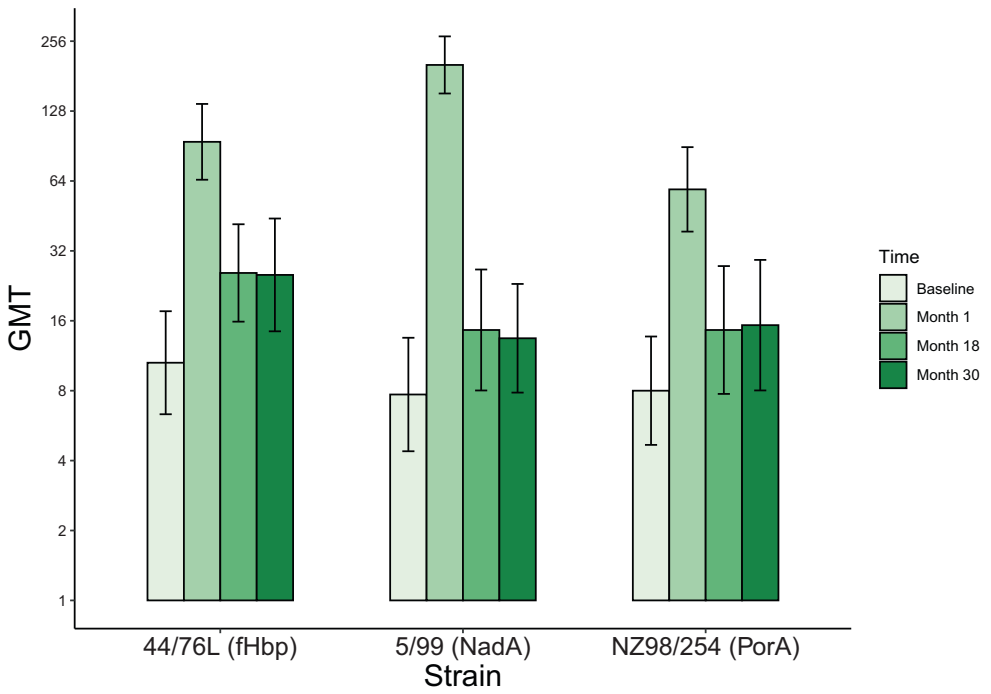

FIGURE 2 Human complement serum bactericidal antibody (hSBA) geometric mean titres (GMTs) and 95% confidence intervals for MenB reference strains factor H-binding protein (fHbp), Neisseria adhesin A (NadA), and Porin A (PorA).

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TABLE 3 Immunogenicity outcomes for MenA, C, W, and Y serogroups.

		Propositive study [20]		Follow-up study	
Meningococcal serogroup	**Estimate**	**Baseline ($N = 55$)**	**1 month ($N = 50$)**	**18 months ($N = 38$)**	**30 months ($N = 32$)**
MenA	GMT	42.8 (19–96)	2486.7 (1745.6–3542.3)	382.4 (179.9–812.8)	250.5 (117.1–535.9)
	% with titres ≥1:8	50.9 (37.1–64.6)	100 (92.9–100)	86.8 (71.9–95.6)	87.5 (71–96.5)
MenC	GMT	10.2 (5.4–19.2)	955.4 (518.2–1761.4)	33.8 (14.3–79.8)	18.6 (7.6–45.7)
	% with titres ≥1:8	34.5 (22.2–48.6)	94 (83.5–98.7)	57.9 (40.8–73.7)	46.9 (29.1–65.3)
MenW	GMT	19.8 (9.5–41.4)	4096 (2802.1–5987.4)	285.6 (117.1–696.8)	220 (83–583)
	% with titres ≥1:8	45.5 (32–59.4)	100 (92.9–100)	81.6 (65.7–92.3)	78.1 (60–90.7)
MenY	GMT	22.2 (10.9–45.4)	3769.1 (2757.6–5151.5)	318.6 (143.7–706.7)	273.2 (125.4–595)
	% with titres ≥1:8	47.3 (33.7–61.2)	100 (92.9–100)	84.2 (68.7–94)	87.5 (71–96.5)

Note: Data are GMT (95% confidence interval) or % (95% confidence interval). The color shading represents each of the clinical studies.
Abbreviation: GMT, geometric mean titres.

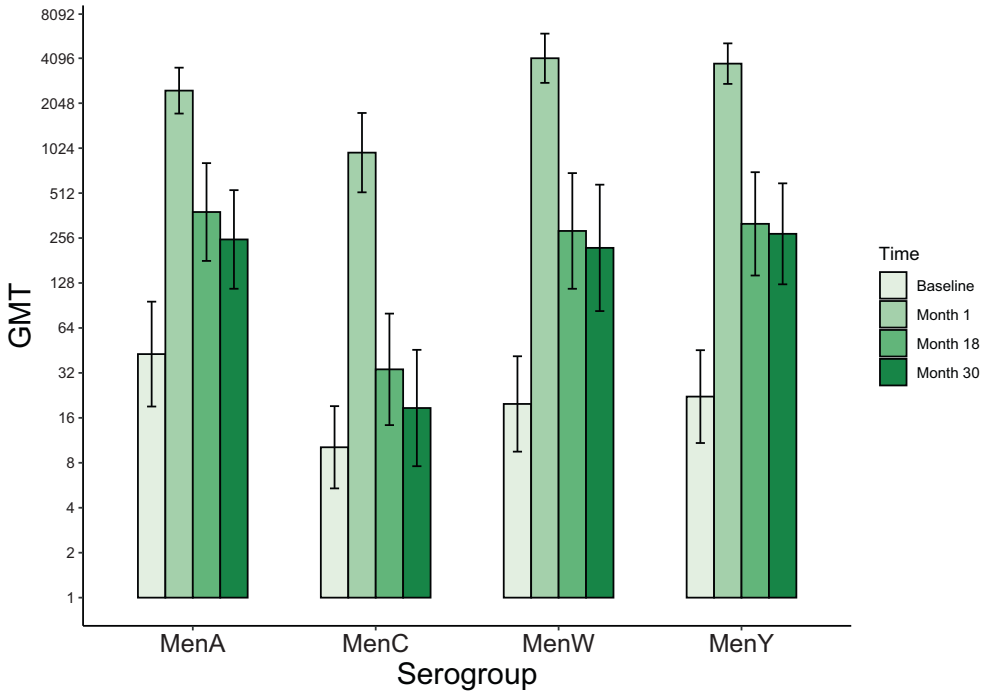

FIGURE 3 Rabbit complement serum bactericidal antibody (rSBA) geometric mean titres (GMTs) and 95% confidence intervals for Men A, C, W, and Y serogroups.

MenA (GMR 18 m/1 m, 0.15 [95% CI 0.09–0.32] and 30 m/1 m, 0.09 [95% CI 0.05–0.48]), 14.1- and 21.2-fold for MenW (GMR 18 m/1 m, 0.07 [95% CI 0.03–0.15] and 30 m/1 m, 0.05 [95% CI 0.02–0.11]), and 11.5- and 14.7-fold for MenY (GMR 18 m/1 m, 0.09 [95% CI 0.04–0.18] and 30 m/1 m, 0.07 [95% CI 0.03–0.14]). Estimated half-lives for antibodies against MenC were 145 days (95% CI 125–171) compared with 249 (95% CI 192–352), 180 (95% CI 142–248), and 196 (95% CI 153–272) days for MenA, W, and Y, respectively.

The proportion of subjects with protective titres ≥1:8 against MenA, C, W, and Y was 86.8% (95% CI 71.9–95.6), 57.9% (95% CI 40.8–73.7), 81.6% (95% CI 65.7–92.3), and 84.2% (95% CI 68.7–94), respectively at

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18 months. By 30 months, 46.9% (95% CI 29.1–65.3) of participants retained protective antibodies against MenC, which was lower than for MenW (78.1% [95% CI 60–90.7]) and significantly lower than for MenA (87.5% [95% CI 71–96.5]) and MenY (87.5% [95% CI 71–96.5]).

Risk factors for low antibodies

For MenB antigens, univariable linear regression analysis on logged vaccination titres at 18 and 30 months showed an association between male sex and higher antibody titres against fHbp at 18 months (fold ratio 4.17 [95% CI 1.52–11.48] $p = 0.006$), fHbp at 30 months (fold ratio 6.35 [95% CI 2.03–19.95] $p = 0.002$), PorA at 18 months (fold ratio 9.04 [95% CI 2.53–32.28] $p = 0.001$) and 30 months (fold ratio 8.16 [95% CI 2.15–30.91] $p = 0.002$) but not for other antigens. No other variables were associated with MenB antibody titres, and no significant associations were found for MenA, C, W, and Y serogroups at 18 or 30 months in the univariable analyses.

In the multivariable linear regression model, male sex remained independently associated with higher antibody titres against fHbp at 30 months (fold ratio 7.65 [95% CI 1.76–33.17] $p = 0.007$) but not for other antigens or timepoints. No significant associations were found for the MenA, C, W, and Y serogroups at 18 or 30 months.

A logistic regression analysis of proportions with titres ≥4 for MenB antigens and titres ≥8 for MenA, C, W, and Y serogroups for the same variables did not identify any significant independent variables.

DISCUSSION

As expected, we found that, in our cohort of PLHIV who received two doses of 4CMenB and MenACWY conjugate vaccine given 1 month apart, antibody levels at 18 and 30 months had waned for all antigens but still remained above pre-vaccination levels. At 30 months following vaccination, 87.5% of participants retained a protective titre against MenB antigens NadA and fHbp, whereas 75% were protected against PorA. Reassuringly, 68.8% of participants retained protection against all three MenB antigens. With respect to MenA, C, W, and Y, titres waned for all serogroups at 18 and 30 months, more markedly for MenC than for MenA, W, or Y. By 30 months, only 46.9% of participants retained protection against MenC compared with 78.1% for MenW and 87.5% for MenA and Y.

HIV infection confers a modest increased risk of IMD compared with other conditions such as complement deficiency asplenia/splenic dysfunction [15]. Recent studies have identified this increased risk even in well-controlled HIV [13]. Consequently, meningococcal vaccines are recommended for PLHIV in some countries such as the USA, Ireland, Italy, Australia, and Luxembourg [14, 15]. However, the UK British HIV association guidelines do not yet recommend vaccination against MenB, and MenACWY is recommended only in the context of international travel [16]. 4CMenB is a protein-based vaccine that has been shown to be effective in protecting against MenB disease and may also protect against other serogroups due to serogroup cross-reactivity [9, 23].

PLHIV respond poorly to some vaccines, including MenC vaccines [16, 18], so the duration of protection could be lower than in people without HIV. It is therefore important to assess waning of immunity in this population at increased risk. In our study, antibody responses waned for all tested MenB antigens; however, 68.8% of participants retained titres above the protective threshold against three reference strains, and 6.3% had no protection against any strain at 2.5 years. Unlike serogroup-specific protection achieved through protective antibodies against a polysaccharide capsule, the protection conferred by 4CMenB against target-specific protein surface antigens is difficult to interpret. Its protection will depend on the number and quantity of antigens expressed on the meningococcal membrane surface, cross-protection against any related surface antigens, and the additional broad-spectrum provided by the proteins in the OMV. For these reasons, real-world data on 4CMenB protection against MenB disease were critical when the vaccines were first licensed [24].

Several studies have reported antibody persistence in immunocompetent adults after two 4CMenB doses: 85%–97% of those aged 18–24 years maintained hSBA titres ≥4 against MenB strains after 11 months in one study, 9%–64% of those aged 10–25 years after 2 years in other, and 9%–75% at 4 years and 29%–84% at 7 years in another study [10, 25, 26]. In our cohort, 75%–85% of participants retained protective antibodies at 2.5 years, indicating that persistence in PLHIV was at least as good as in their counterparts without HIV. 4CMenB may also provide up to 30%–40% protection against *Neisseria gonorrhoeae* [24, 27], which would be of additional benefit in people living with HIV given their high risk of recurrent gonorrhoea, especially among men who have sex with men [28]. This requires separate studies.

In contrast to the protein-based MenB vaccines, more data are available for conjugate polysaccharide vaccines, including MenACWY-CRM197. Such vaccines are highly effective in preventing disease and preventing carriage, therefore inducing herd immunity. Two doses are recommended for immunocompromised children and adults as they may not mount an adequate response to a single

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dose [17]. A review of antibody persistence data for MenACWY-CRM197 in immunocompetent adolescents aged 11–18 years showed overall good retention of protective titres for all serogroups in two studies; another study reported lower proportions of participants maintaining protective titers against MenA (32%) than against MenC (59%), W (82%), and Y (64%) at 5 years [29]. In contrast, we have shown lower proportions for MenC (46.9%) than for MenA (87.5%), W (78.1%), and Y (87.5%) at 2.5 years.

This is the first study to provide data on antibody persistence in PLHIV. The high antibody levels alongside the proportion achieving seroprotective thresholds after two doses, as demonstrated in the parent study, is reassuring. Although antibodies against MenA, W, and Y declined modestly, there was a significant reduction in MenC antibodies over time, such that more than half of our cohort had levels below the protective threshold. However, whether this result is associated with increased susceptibility to MenC disease remains unknown because the protective thresholds were developed originally based on antibodies induced by natural infection and not for vaccine responses against conjugate vaccines, which induce both humoral and cell-mediated immune responses [22]. The low MenC response is concerning, especially for travellers to endemic countries, since most MenC cases reported in the UK are in adults who acquired infection abroad [30]. Our findings highlight the importance of vaccinating travellers to endemic areas, especially people living with HIV.

Other tetanus-conjugated MenACWY vaccines, such as MenACWY-TT (MenQuadfi) or MenACWY-TT (Nimenrix), are available [31, 32]. Further studies may reveal whether these vaccines can provide longer-lasting immune protection in this high-risk population.

We found an association between male sex and fHbp antibody levels at 30 months in the regression analysis, which seems of small clinical relevance given that the association was not found for other 4CMenB antigens or time points. More importantly, antibody levels were not associated with CD4 count or detectable viral load. Other studies have shown better responses in those with higher CD4 counts. It is possible that our population was overall healthier, with access to better care and established on ART.

Our cohort was derived from a single centre and had detailed clinical data available with 2.5 years of follow-up time. Sample size was small because of the highly specialized cohort. A proportion of patients were lost to follow-up, which may have made our study underpowered; however, it is unlikely that this would substantially affect the antibody decline rates observed.

CONCLUSIONS

Immune responses against MenB antigens at 2.5 years of follow-up in our cohort of PLHIV were reassuring: 68.8% of participants retained protection against all three reference strains. However, responses against MenC were lower than for those against MenA, W, and Y serogroups; only 46.8% of participants maintained MenC protective titres at 2.5 years. Future studies are required in this population to the inform the need for and timing of booster doses beyond 3 years.

AUTHOR CONTRIBUTIONS

Catherine A. Cosgrove, Paul T. Heath, and Catherine Isitt conceived the study. Ray Borrow provided expert scientific advice for vaccine evaluation, and Jennifer Louth, Ann Holland, and Kelly Townsend-Payne performed the SBAs. Alberto San Francisco Ramos and Shehnaz Athaide performed follow-up visits and data collection. Alberto San Francisco Ramos performed the data analysis, supported by Nicholas J. Andrews and Shamez N. Ladhani. Alberto San Francisco Ramos and Shamez N. Ladhani wrote the manuscript, and all authors approved the final version.

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CONFLICT OF INTEREST STATEMENT

Ray Borrow, Jennifer Louth, Ann Holland, and Kelly Townsend-Payne perform contract research for UKHSA on behalf of GSK, Pfizer, and Sanofi Pasteur. Catherine Isitt has previously received a research grant from Pfizer.

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Paul T. Heath and Catherine A. Cosgrove coordinate vaccinology research on behalf of St George's University of London, which is funded by vaccine manufacturers (Pfizer, Novavax, Moderna, Valneva, Janssen). Paul T. Heath is a member of the UK Joint Committee on Vaccination and Immunization.

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.

ETHICS STATEMENT

This study was performed in line with the principles of the Declaration of Helsinki and followed good clinical practice guidelines. Ethical approval was obtained from the NHS Health Research Authority and Research Ethics Committee before the study started.

PATIENT CONSENT STATEMENT

All subjects provided written informed consent before any study procedures were performed.

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