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Antibody persistence and booster responses 24–36 months after different 4CMenB vaccination schedules in infants and children: A randomised trial

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Abbreviations: AE, adverse event; CI, confidence interval; FAS, full analysis set; fHbp, factor H-binding protein; GMT, geometric mean titre; hSBA, serum bactericidal activity assay using human complement; IMD, invasive meningococcal disease; MenACWY-CRM, quadrivalent serogroups A, C, W and Y conjugated to the diphtheria toxin mutant CRM197; MenB, meningococcal serogroup B; 4CMenB, meningococcal serogroup B vaccine; NadA, Neisserial adhesin A; NHBA, neisserial heparin-binding antigen; PorA, porin A protein; rLP2086, multicomponent vaccine against serogroup B; SAE, serious adverse event; UK, United Kingdom.

Clinical Trial Registration: NCT01894919.

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Abstract *Objectives:* This phase IIIb, open-label, multicentre, extension study (NCT01894919) evaluated long-term antibody persistence and booster responses in participants who received a reduced 2 + 1 or licensed 3 + 1 meningococcal serogroup B vaccine (4CMenB)-schedule (infants), or 2-dose catch-up schedule (2–10-year-olds) in parent study NCT01339923.
Materials and methods: Children aged 35 months to 12 years (N = 851) were enrolled. Follow-on participants (N = 646) were randomised 2:1 to vaccination and non-vaccination subsets; vaccination subsets received an additional 4CMenB dose. Newly enrolled vaccine-naïve participants (N = 205) received 2 catch-up doses, 1 month apart (accelerated schedule). Antibody levels were determined using human serum bactericidal assay (hSBA) against MenB indicator strains for fHbp, NadA, PorA and NHBA. Safety was also evaluated.
Results: Antibody levels declined across follow-on groups at 24–36 months versus 1 month post-vaccination. Antibody persistence and booster responses were similar between infants receiving the reduced or licensed 4CMenB-schedule. An additional dose in follow-on participants induced higher hSBA titres than a first dose in vaccine-naïve children. Two catch-up doses in vaccine-naïve participants induced robust antibody responses. No safety concerns were identified.
Conclusion: Antibody persistence, booster responses, and safety profiles were similar with either 2 + 1 or 3 + 1 vaccination schedules. The accelerated schedule in vaccine-naïve children induced robust antibody responses.

Introduction

Invasive meningococcal disease (IMD) is a serious bacterial infection caused by *Neisseria meningitidis* with more than 1.2 million cases reported annually[1] and a fatality rate ranging from 10% to 40%.[2] Disease progression is often very rapid. Survivors may suffer from long-term complications such as hearing impairment, seizures, amputations, and visual or cognitive dysfunctions.[2,3] The disease poses both a short- and long-term clinical and financial burden and reduces the quality of life of patients and their family members providing medical care. To lower the global clinical and economic burden, vaccination has been deemed the most effective strategy.[2] Although 12 disease-causing serogroups exist worldwide, serogroups A, B, C, W, X and Y account for almost all IMD cases.[1,4] Meningococcal serogroup B (MenB) causes a significant proportion of IMD cases, with the highest incidence in infants under 1 year of age, followed by 1–4-year-olds and adolescents and recent outbreaks in various settings (at university campuses, schools, child care institutions and family clusters) in the United States and Europe have been attributed to MenB.[5–15] While meningococcal conjugate vaccines against serogroups A, C, W and Y have been available for years, the development of a vaccine against serogroup B has been more challenging due to the poor immunogenicity and antigenic variability of the surface antigens.[16] The first vaccines against this serogroup were outer membrane vesicle vaccines, which were only effective against homologous serogroup B strains. Subsequently, two multicomponent vaccines against serogroup B (4CMenB [*Bexsero*, GSK] and rLP2086 [*Trumenba*, Pfizer]) have been developed, each using a different approach to identify surface antigens.[16,17]

Previous studies have shown that 4CMenB vaccine is immunogenic with a clinically acceptable safety profile when administered as 3 doses during infancy with a booster dose in the second year of life.[18–22] This schedule has been approved in several countries.[23] In 2015, a reduced 2 + 1 dose schedule (2, 4 and 12 months of age) was implemented in the infant immunisation programme in the United Kingdom (UK)[24,25] based on the preliminary results from a clinical trial evaluating a 2 + 1-dose 4CMenB-schedule.[26] This reduced 4CMenB-schedule was shown to be 82.9% effective after 2 doses in the eligible cohort within 10 months of 4CMenB implementation and, national surveillance is ongoing to evaluate the long-term impact.[26]

Here, we present the results of an extension study, which included children who received 4CMenB according to various immunisation schedules in the parent study.[27] The parent study showed that the immune response to a reduced 2 + 1 dose infant vaccination schedule with 4CMenB was similar to the response to a 3 + 1 dose schedule, and that a 2-dose catch-up series was immunogenic in children aged 2–10 years.[27] As for meningococcal conjugate vaccines, antibody waning has been observed following administration of 4CMenB in infants and young children.[22,28–31] However, up to this date, persistence data for a reduced 2 + 1 schedule are not available. This study assessed the antibody persistence up to 3 years after the completion of the different vaccination schedules (3 + 1, 2 + 1 and catch-up) in the parent study as well as the safety and tolerability of an additional 4CMenB dose. Moreover, the immune response to a 2-dose accelerated catch-up schedule of 4CMenB was evaluated in vaccine-naïve children.

Materials and methods

Study design and participants

This phase IIIb, open-label, randomised, multicentre extension study (clinicaltrials.gov: NCT01894919) was conducted in 9 centres in Hungary and 8 centres in Spain between June

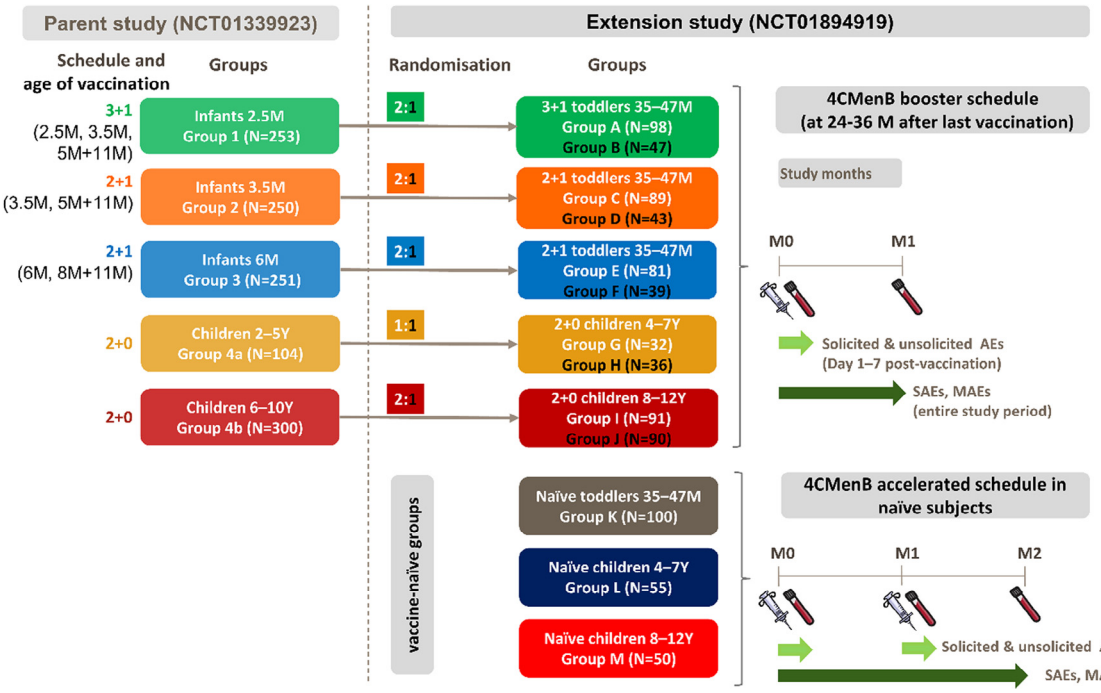

Fig. 1. Study design. 3 + 1, 3 primary doses and a booster of 4CMenB; 2 + 1, 2 primary doses and a booster of 4CMenB; 2 + 0, 2 primary doses of 4CMenB; Groups A, C, E, and G, I, follow-on vaccination groups who received an additional 4CMenB dose at month 0, 24–36 months after the last vaccination in the parent study and had blood draws at months 0 and 1; Groups B, D, F, H, and J, follow-on non-vaccination groups who did not receive any vaccination in the extension study and only had blood draw at month 0; Groups K–M, newly enrolled vaccine-naïve children who received 2 doses of 4CMenB 1 month apart (accelerated schedule) and had blood draws at months 0, 1 and 2; the syringe indicates 4CMenB vaccination and the blood tube blood sampling; N, number of participants enrolled per group; M, month(s); Y, years; AE, adverse event; SAE, serious AE; MAE, medically attended AE.

2013 and November 2015, in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki and all applicable regulatory requirements. The study protocol and its amendments were approved by local ethics committees and regulatory authorities. Written informed consent was obtained from the parents or legal guardians of each child before enrolment. In addition, written informed assent was obtained from each study participant eligible for informed assent per local policies.

Healthy children aged 35–47 months to 12 years who had completed different 4CMenB vaccination schedules in the parent study (clinicaltrials.gov: NCT01339923) were enrolled as "follow-on" participants in this extension study 24–36 months after vaccination completion (Fig. 1).

Follow-on participants who had received (i) 3 + 1 doses of 4CMenB at 2½, 3½, 5 and 11 months of age (Group 1), (ii) 2 + 1 doses of 4CMenB at 3½, 5 and 11 months of age (Group 2), or (iii) 2 + 1 doses of 4CMenB at 6, 8 and 11 months of age (Group 3) were randomised (2:1) to vaccinated (Groups A, C, and E, respectively) and unvaccinated (Groups B, D and F, respectively) subsets. Follow-on participants who had received 2 catch-up doses of 4CMenB 2 months apart at 2–5 years of age (Group 4a) or 6–10 years of age (Group 4b) were randomised (1:1 and 2:1 ratio, respectively) to vaccinated (Groups G and I, respectively) and unvaccinated (Groups H and J, respectively) subsets. Participants were randomised using an electronic randomisation system.

In addition, new vaccine-naïve participants were enrolled in this study. They received 2 catch-up doses of 4CMenB given 1 month apart (accelerated schedule). These participants were of similar age as follow-on participants from Groups A to F: 35–47-month-olds were enrolled in Group K, 4–7-year-olds in group L, and 8–12-year-olds in Group M. Detailed inclusion and exclusion criteria are presented in Supplementary Text S1. The vaccine[5] was administered intramuscularly into deltoid area of the non-dominant arm or in the thigh for 2 participants.

Objectives

The primary immunogenicity objective of this extension study was to evaluate the antibody persistence in children 24–36 months after 4CMenB vaccination in the parent study.

The secondary immunogenicity objectives were to evaluate (i) the immune response to an additional dose of 4CMenB administered 24–36 months after vaccination in the parent study; and (ii) the immune response to 2 catch-up doses of 4CMenB administered 1 month apart (accelerated schedule) to healthy vaccine-naïve children. Safety objectives were (i) to assess the safety and tolerability of 4CMenB when given as an additional dose 24–36 months after vaccination in the parent study, and (ii) to determine the safety and tolerability of 2 catch-up doses of 4CMenB administered 1 month apart to healthy vaccine-naïve children.

Immunogenicity assessment

For the follow-on participants, immune responses were evaluated at the start of the extension study (Groups A–J) and at

1 month post-booster in the vaccinated subset (Groups A, C, E, G and I). For the vaccine-naïve participants (Groups K–M), immune responses were evaluated at baseline (pre-vaccination) and at 1 month after each dose of the 2-dose catch-up schedule. Blood samples were collected at pre-specified time points (Fig. 1) and were tested at GSK Clinical Laboratory Sciences, Marburg, Germany (Neisseria heparin-binding antigen, NHBA) or Public Health England Laboratory, Manchester, UK (factor H-binding protein, fHbp; Neisserial adhesin A, NadA; Porin A protein, PorA).

Serum bactericidal activity assays using human complement (hSBA) were used to measure the induction of functional antibodies directed against 4 indicator strains of *N. meningitidis* serogroup B: H44/76 for fHbp, 5/99 for NadA, NZ98/254 for PorA and M10713 for NHBA.[1]

Safety assessment

Within Day 1–7 after each vaccination, solicited local and systemic adverse events (AEs), other solicited data and all unsolicited AEs were reported in participants from the vaccinated subset (Groups A, C, E, G, I) and vaccine-naïve participants (Groups K, L, M) on diary cards. During the entire study period, serious unsolicited AEs, medically attended AEs and AEs leading to withdrawal from the study were collected. All unsolicited AEs were monitored throughout the study in participants included in the unvaccinated subset. The severity of AEs and the possible relationship to study vaccination were determined by the investigator.

Statistical analysis

Descriptive statistics were used for immunogenicity and safety analyses and no statistical hypotheses testing were performed. The immunogenicity analyses were based on the 3 full analysis sets (FAS) for persistence, booster or catch-up and the safety analyses on the safety set (Supplementary Text S2).

For immunogenicity endpoints, percentages of participants with hSBA titres ≥4[32] and associated 2-sided Clopper–Pearson 95% confidence intervals (CIs) were computed by vaccine group for each *N. meningitidis* serogroup B indicator strain. Geometric mean titres (GMTs) and associated 2-sided 95% CIs were computed by exponentiating ($base_{10}$) the corresponding least square means of the log_{10}-transformed titres and associated 95% CIs were obtained from a 2-way analysis of variance model having factors for vaccine group and study centre.

All statistical analyses were performed using SAS version 9.2.

Results

Demographic characteristics

Out of 851 enrolled participants, 391 were assigned to the follow-on vaccination subset, 255 to the follow-on unvaccinated subset, and 205 were vaccine-naïve participants. Eight individuals terminated the study prematurely (Supplementary Fig. S1). Demographic characteristics were similar across groups (Supplementary Tables S1 and S2).

Immunogenicity

Long-term antibody persistence

At 24–36 months post-last vaccination in the parent study, hSBA GMTs declined and percentages of children with hSBA titres ≥4 decreased in all follow-on age groups compared to 1 month post-last vaccination (Table 1). In the follow-on groups aged 35–47 months (Groups A–F), percentages of participants with hSBA titres ≥4 ranged from 51%–61% for fHbp, 84%–93% for NadA, 38%–56% for PorA and 36%–45% for NHBA (Table 1 and Supplementary Fig. S2A). The hSBA GMTs in these follow-on groups were similar with overlapping CI against each given strain. The percentages of children aged 4–7 years and 8–12 years in the follow-on groups (Groups G–J) with hSBA titres ≥4 ranged from 52%–58% for fHbp, 79%–85% for NadA, 29%–50% for PorA, and 42%–66% for NHBA at 24–36 months post-last vaccination in the parent study (Table 1 and Supplementary Fig. S2B).

In all age groups, both percentages of children with hSBA titres ≥4 and GMT levels tended to be higher than baseline percentages in the age-matched vaccine-naïve groups for fHbp, NadA and PorA, but remained similar for NHBA (Table 1 and 2 and Supplementary Fig. S2).

Immunogenicity of an additional dose

The response to an additional 4CMenB dose against all indicator strains was comparable between participants who had received a reduced 2 + 1 (Groups C and E) or the licensed 3 + 1 dose schedule of 4CMenB vaccine (Group A), except for NHBA, for which the immune response was higher in Group E than Group A (Table 2 and Supplementary Fig. S3). An additional4CMenB dose following 2 catch-up doses in the parent study (Groups G and I) induced robust booster responses (Table 2). Across all age-matched groups, the percentages of participants with hSBA antibody titres ≥4 and hSBA GMTs tended to be higher in the follow-on groups at 1 month post-booster (Groups A, C, E, G, I) than in vaccine-naïve groups (Groups K–M) at 1 month post-dose 1 (Table 2).

Immunogenicity of a 2-dose catch-up

Across all vaccine-naïve groups (Groups K–M), the percentages of participants with hSBA titres ≥4 increased substantially between baseline and 1 month post-dose 1 for fHbp (80%–95%), NadA (80%–93%) and PorA (70%–85%). Percentages of participants with hSBA titres ≥4 against NHBA were lower and ranged between 50% and 69% at 1 month post-dose 1. At 1 month post-dose 2, 98%–100% of participants achieved hSBA titres ≥4 against fHbp, all participants against NadA and PorA, and 75%–80% against NHBA (Table 2 and Supplementary Fig. S4). In the FAS for catch-up, all vaccine-naïve participants demonstrated robust increases in hSBA GMTs for fHbp, NadA and PorA, ranging from 34–46-fold for fHbp, 242–558-fold for NadA, 27–30-fold for PorA and from 2.20–3.86 for NHBA at 1 month post-dose 2.

Reactogenicity

Solicited AEs

During the 7-day follow-up period post-booster, at least 1 solicited AE was reported for 94%–97% of children in follow-on

Table 1 Percentage of participants with hSBA titres ≥4 and geometric mean titres for antigens fHbp, NadA, PorA and NHBA at 1 month and 24–36 months post-vaccination in the parent study (FAS cohort for Persistence).

Antigen	Estimate	Timing	35–47 M						4–7 Y		8–12 Y	
			Groups A + B		Groups C + D		Groups E + F		Groups G + H		Groups I + J	
			N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)
fHbp	% ≥ 4	T1	137	100 (97.3–100.0)	129	100 (97.2–100.0)	118	100 (96.9–100.0)	67	100 (94.6–100.0)	173	99 (95.9–99.9)
		T2	140	51 (42.8–60.0)	131	53 (43.8–61.5)	119	61 (52.0–70.1)	67	52 (39.7–64.6)	178	58 (50.3–65.2)
	GMT	T1	137	144 (120–171)	129	207 (172–250)	118	188 (155–229)	67	143 (112–182)	173	135 (115–158)
		T2	140	4.17 (3.40–5.13)	131	4.48 (3.60–5.57)	119	5.62 (4.48–7.04)	67	3.97 (2.99–5.28)	178	5.75 (4.78–6.91)
NadA	% ≥ 4	T1	136	100 (97.3–100.0)	130	100 (97.2–100.0)	118	100 (96.9–100.0)	66	98 (91.8–100.0)	176	99 (96.9–100.0)
		T2	140	84 (77.2–89.9)	131	88 (80.9–92.9)	119	93 (87.2–97.1)	67	79 (67.4–88.1)	179	85 (79.4–90.3)
	GMT	T1	136	1898 (1571–2292)	130	1670 (1368–2040)	118	1518 (1235–1865)	66	475 (366–616)	176	441 (373–523)
		T2	140	44 (32–60)	131	52 (37–72)	119	83 (58–117)	67	21 (14–33)	179	21 (16–28)
PorA	% ≥ 4	T1	136	100 (97.3–100.0)	129	99 (95.8–100.0)	116	100 (96.9–100.0)	68	99 (92.1–100.0)	174	99 (96.8–100.0)
		T2	140	45 (36.6–53.6)	131	38 (29.8–47.1)	119	56 (46.9–65.4)	68	29 (19.0–41.7)	179	50 (42.2–57.3)
	GMT	T1	136	58 (47–72)	129	79 (63–99)	116	71 (56–90)	68	46 (35–62)	174	48 (39–58)
		T2	140	3.48 (2.78–4.36)	131	2.98 (2.35–3.78)	119	4.86 (3.80–6.22)	68	2.81 (2.07–3.82)	179	4.57 (3.74–5.59)
NHBA	% ≥ 4	T1	105	86 (77.5–91.8)	84	89 (80.6–95.0)	78	88 (79.2–94.6)	61	90 (79.8–96.3)	160	96 (91.2–98.2)
		T2	127	36 (27.9–45.2)	111	38 (28.8–47.5)	109	45 (35.4–54.8)	65	42 (29.4–54.4)	173	66 (58.9–73.5)
	GMT	T1	105	14 (11–18)	84	18 (13–24)	78	17 (12–23)	61	22 (15–30)	160	35 (28–44)
		T2	127	2.77 (2.06–3.71)	111	3.03 (2.20–4.16)	109	3.17 (2.30–4.38)	65	3.53 (2.38–5.25)	173	7.82 (6.04–10)

Groups A + B, children who received 3 + 1 doses of 4CMenB in the parent study at age 2.5, 3.5, 5 and 11 months; Groups C + D, children who received 2 + 1 doses of 4CMenB at age 3.5, 5 and 11 months; Groups E + F, children who received 2 + 1 doses of 4CMenB at age 6, 8 and 11 months; Groups G + H, children who received 2 catch-up doses of 4CMenB at 2–5 years of age; Groups I + J; children who received 2 catch-up doses of 4CMenB at 6–10 years of age; T1, 1 month after last vaccination in the parent study; T2, 24–36 months after last vaccination in the parent study; FAS, full analysis set; CI, confidence interval; N, number of participants in each group with available results; M, months; Y, years; hSBA, serum bactericidal activity assay using human complement; GMT, geometric mean titre; fHbp, factor H binding protein; NadA, neisserial adhesin A; PorA, porin A protein; NHBA, neisserial heparin binding antigen.

Table 2 Percentage of participants with hSBA titres ≥4 and geometric mean titres for antigens fHbp, NadA, PorA and NHBA at 24–36 months post-vaccination in the parent study and at 1 month post-booster for follow-on participants and at baseline and post-catch-up dose 1 (FAS cohort booster) and 2 for vaccine-naïve participants (FAS cohort for catch-up).

			Follow-on participants				Vaccine-naïve participants		
				35–47 M		4–7 Y	8–12 Y	35–47 M	4–7 Y	8–12 Y
			Group A	Group C	Group E	Group G	Group I	Group K	Group L	Group M
Antigen	Estimate	Timing	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N
fHbp	% ≥ 4	T1	48 (37.3–58.5) 92	51 (40.1–62.1) 86	64 (52.1–74.8) 75	39 (21.8–57.8) 31	59 (48.5–69.5) 91	39 (28.8–49.0) 96	27 (16.1–41.0) 55	20 (10.0–33.7) 50
		T2	99 (94.3–99.97) 96	100 (95.8–100.0) 86	100 (95.2–100.0) 75	97 (83.8–99.9) 32	99 (94.0–99.97) 91	95 (88.3–98.3) 96	91 (80.0–97.0) 55	80 (66.3–90.0) 50
		T3	-	-	-	-	-	100 (96.3–100.0) 98	98 (90.1–99.95) 54	100 (92.7–100.0) 49
	GMT	T1	3.91 (3.01–5.08) 92	4.84 (3.66–6.41) 86	6.21 (4.65–8.31) 75	3.14 (2.08–4.75) 31	6.15 (4.77–7.93) 90	2.82 (2.26–3.50) 96	2.33 (1.77–3.07) 55	1.93 (1.39–2.68) 50
		T2	158 (116–215) 96	205 (147–287) 86	288 (204–408) 75	155 (95–252) 32	258 (190––349) 91	14 (11–17) 96	16 (12–23) 55	13 (8.67–20) 50
		T3	-	-	-	-	-	107 (84–135) 98	74 (56–99) 54	63 (47–85) 49
NadA	% ≥ 4	T1	84 (74.5–90.6) 92	91 (82.7–95.9) 87	95 (87.1–98.5) 76	74 (55.4–88.1) 31	86 (76.8–92.2) 91	3 (0.6–8.9) 96	4 (0.44–12.5) 55	8 (2.2–19.2) 50
		T2	99 (94.3–99.97) 96	99 (93.8–99.97) 87	97 (90.8–99.68) 76	100 (89.1–100.0) 32	100 (96.0–100.0) 91	88 (79.2–93.4) 96	93 (82.4–98.0) 55	80 (66.3–90.0) 50
		T3	-	-	-	-	-	100 (96.3–100.0) 98	100 (93.4–100.0) 54	100 (92.7–100.0) 49
	GMT	T1	39 (26–58) 92	53 (35–82) 87	89 (57–139) 76	19 (9.92–35) 31	22 (15–32) 91	1.15 (1.02–1.29) 96	1.20 (0.96–1.51) 55	1.38 (1.10–1.73) 50
		T2	2908 (2059–4107) 96	3593 (2474–5218) 87	3677 (2495–5419) 76	3205 (1860–5526) 32	2921 (2079–4104) 91	38 (28–54) 96	27 (18–40) 55	20 (12–33) 50
		T3	-	-	-	-	-	631 (503–792) 98	421 (319–555) 54	317 (238–423) 49
PorA	% ≥ 4	T1	45 (34.2–55.3) 92	42 (31.3–53.0) 86	52 (40.2–63.7) 75	25 (11.5–43.4) 32	47 (36.7–58.0) 91	2 (0.25–7.3) 96	7 (2.1–17.9) 54	6 (1.3–16.5) 50
		T2	99 (94.3–99.97) 96	100 (95.8–100.0) 86	100 (95.2–100.0) 75	100 (89.1–100.0) 32	100 (96.0–100.0) 91	78 (68.5–85.9) 96	85 (72.9–93.4) 54	70 (55.4–82.1) 50
		T3	-	-	-	-	-	100 (96.3–100.0) 98	100 (93.4–100.0) 54	100 (92.6–100.0) 48
	GMT	T1	3.41 (2.57–4.54) 92	3.17 (2.34–4.31) 86	4.86 (3.54–6.67) 75	2.99 (1.92–4.65) 32	4.49 (3.40–5.92) 91	1.14 (1.06–1.23) 96	1.35 (1.15–1.59) 54	1.22 (1.06–1.41) 50
		T2	92 (70–122) 96	91 (68–123) 86	133 (97–181) 75	71 (46–110) 32	82 (63–108) 91	6.94 (5.60–8.59) 96	13 (8.88–19) 54	8.56 (5.51––13) 50
		T3	-	-	-	-	-	34 (27–42) 98	37 (28–49) 54	34 (26–46) 48

(*continued*)

Table 2 (*continued*)

			Follow-on participants					Vaccine-naïve participants		
				35–47 M		4–7 Y	8–12 Y	35–47 M	4–7 Y	8–12 Y
			Group A	Group C	Group E	Group G	Group I	Group K	Group L	Group M
Antigen	Estimate	Timing	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N	Value (95% CI) N
NHBA	% ≥ 4	T1	38 (27.7–50.2) 78	37 (25.4–49.3) 68	49 (36.6–61.9) 65	28 (12.7–47.2) 29	69 (58.1–78.5) 87	44 (33.2–55.3) 84	45 (30.7–59.8) 49	63 (47.5–76.8) 46
		T2	75 (64.6–83.6) 88	84 (73.5–90.9) 79	97 (89.6–99.64) 67	93 (77.9–99.2) 30	96 (88.9–98.8) 89	50 (39.1–60.9) 88	69 (54.1–80.9) 51	68 (52.9–80.9) 47
		T3	-	-	-	-	-	77 (66.9–85.1) 91	75 (61.1–86.0) 52	80 (65.7–89.8) 49
	GMT	T1	3.05 (2.08–4.46) 78	3.10 (2.05–4.68) 68	3.58 (2.35–5.45) 65	2.31 (1.29–4.13) 29	7.83 (5.52–11) 87	3.53 (2.64–4.71) 84	4.80 (2.86–8.06) 49	7.70 (4.55–13) 46
		T2	13 (9.15–18) 88	18 (13–26) 79	40 (27–59) 67	32 (19–54) 30	53 (38–73) 89	4.92 (3.39–7.13) 88	9.44 (5.84–15) 51	12 (6.61–21) 47
		T3	-	-	-	-	-	12 (7.57–18) 91	11 (6.87–19) 52	14 (8.34–24) 49

Group A, children who received 3 + 1 doses of 4CMenB in the parent study at age 2.5, 3.5, 5 and 11 months; Group C, children who received 2 + 1 doses of 4CMenB at age 3.5, 5 and 11 months; Group E, children who received 2 + 1 doses of 4CMenB at age 6, 8 and 11 months; Group G, children who received 2 catch-up doses of 4CMenB at 2–5 years of age; Group I, children who received 2 catch-up doses of 4CMenB at 6–10 years of age; T1, 24–36 months after last vaccination in the parent study (Groups A, C, E, G, I) or baseline (Groups K–M); T2, 1 month post-booster (Groups A, C, E, G, I) or 1 month post-catch-up dose 1 (Groups K–M); T3, 1 month post-catch-up dose 2 (Groups K–M); FAS, full analysis set; CI, confidence interval; N, number of participants in each group with available results; M, months; Y, years; hSBA, serum bactericidal activity assay using human complement; GMT, geometric mean titre; fHbp, factor H binding protein; NadA, neisserial adhesin A; PorA, porin A protein; NHBA, neisserial heparin binding antigen.

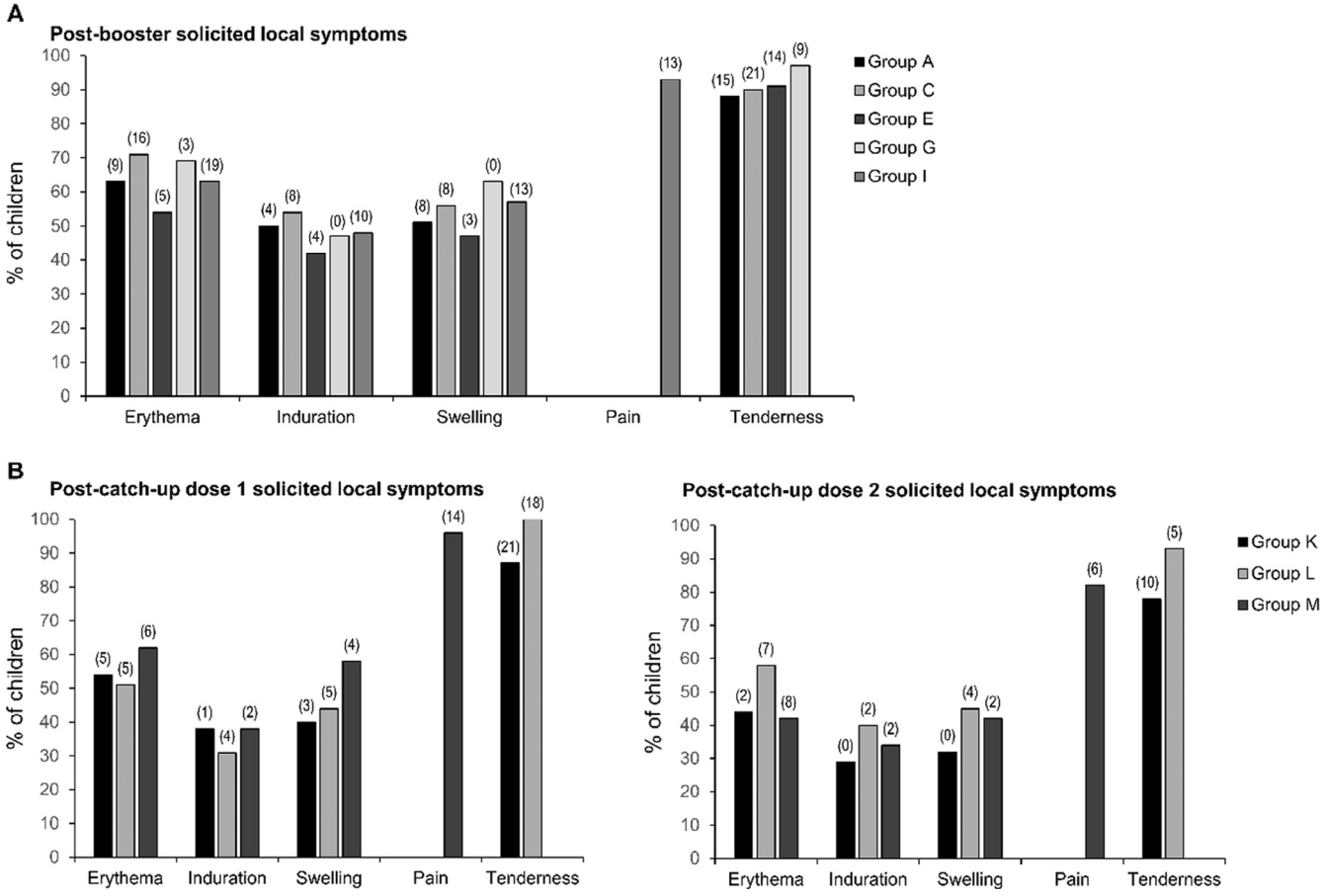

Fig. 2. Solicited local reactions after 4CMenB booster vaccination for follow-on participants (A), and after dose 1 (left panel) and after dose 2 (right panel) for vaccine-naïve participants (B). Group A, children 35–47 months of age who received 3 + 1 doses of 4CMenB in the parent study; Groups C and E, children 35–47 months of age who received 2+1 doses of 4CMenB in the parent study; Group G, children 4–7 years of age who received 2 catch-up doses of 4CMenB in the parent study; Group I, children 8–12 years of age who received 2 catch-up doses of 4CMenB in the parent study; Group K, naïve children 35–47 months of age; Group L, naïve children 4–7 years of age; Group M, naïve children 8–12 years of age.

groups. In vaccine-naïve groups, the percentage of participants experiencing at least 1 solicited AE tended to decrease post-dose 2 compared to post-dose 1. From day 1 to day 7 post-dose 1 and 2, at least 1 solicited AE was reported for 93% and 82% of participants in Group K, all participants and 93% in Group L, and 98% and 90% of participants in Group M, respectively. The most commonly reported local reactions after any vaccination were injection-site pain in Groups I and M, and tenderness in Groups A, C, E, G, K and L (Fig. 2). The most frequent systemic reaction was irritability in Groups A, C, E, G, K, and L. Malaise and headache were the most common systemic reactions in Group I, and headache in Group M (Fig. 3).

Unsolicited AEs

Across the follow-on Groups, unsolicited AEs post-booster were reported for 15% to 33% of participants. Out of these, 8% to 19% were considered at least possibly related to vaccination by the investigator. In the vaccine-naïve Groups K and M, 15% and 12% (post-dose 1) and, 12% and 8% (post-dose 2) of participants reported unsolicited AEs; in Group L this was 13% post-dose 1 and 2. Out of these, 5%–11% post-dose 1 and 6%–9% post-dose 2 were possibly related to vaccination. Across all groups, the most commonly reported unsolicited AEs as per system organ class were "infections and infestations" and "general disorders and administration site conditions".

The majority of unsolicited AEs at least possibly related to vaccination were solicited local and systemic AEs that continued beyond day 7 after vaccination. There were no serious AEs and deaths reported in this study.

Discussion

Our novel data show that a reduced 2 + 1 4CMenB vaccination series in infants produces protective antibody levels similar to the licensed 3 + 1 schedule. These results suggest that the schedule (2 + 1 or 3 + 1) does not impact the antibody persistence 24–36 months post-vaccination in young infants. This is also the first study presenting data on antibody persistence 24–36 months following a 2-dose catch-up vaccination series, with similar bactericidal antibody levels against each given strain in children who had received 2 catch-up doses at 2–5 years and 6–10 years in the parent study. The GMTs and the percentages of participants with

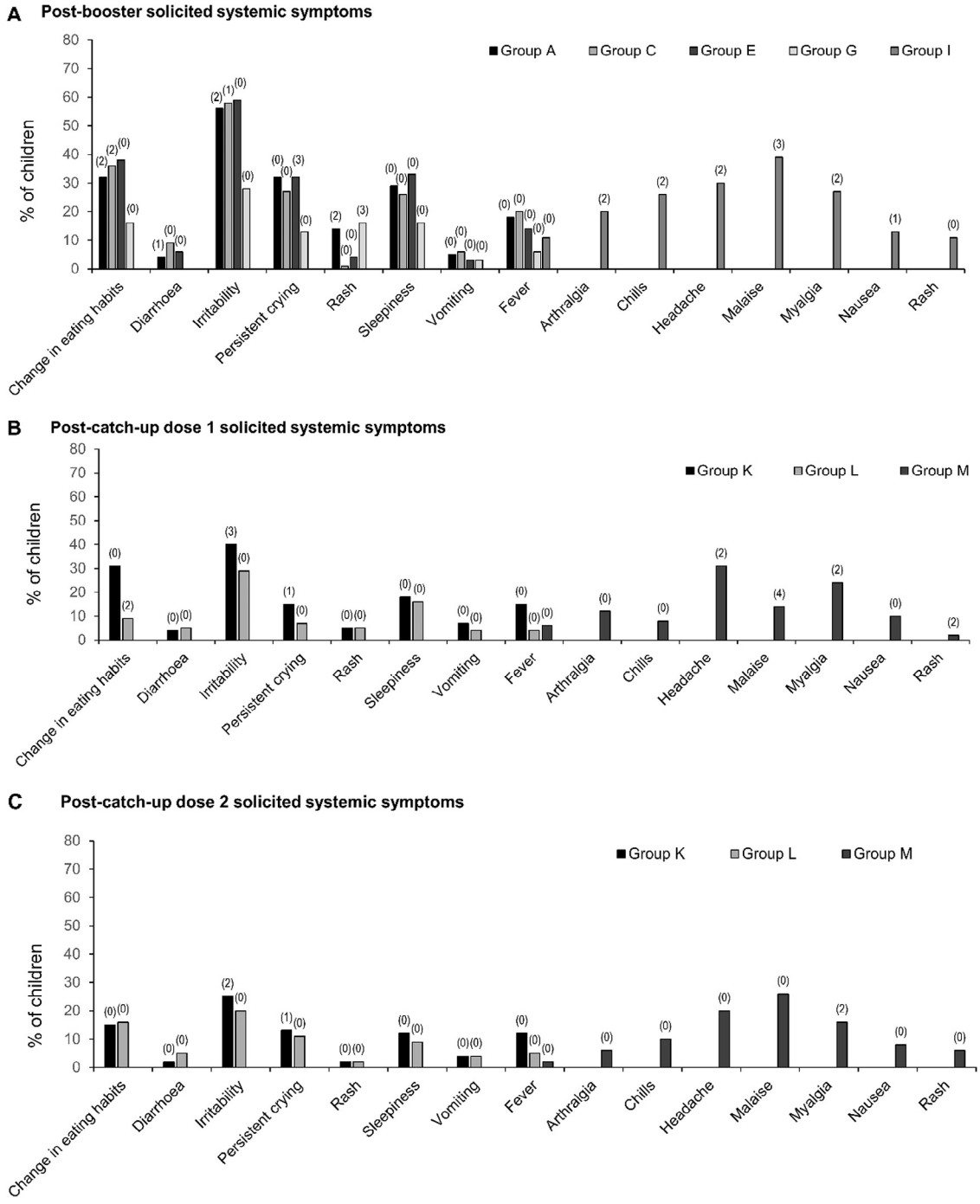

Fig. 3. Solicited systemic reactions after 4CMenB booster vaccination for follow-on participants (A), and after dose 1 (B) and after dose 2 (C) for vaccine-naïve participants. Group A, children 35–47 months of age who received 3 + 1 doses of 4CMenB in the parent study; Groups C and E, children 35–47 months of age who received 2+1 doses of 4CMenB in the parent study; Group G, children 4–7 years of age who received 2 catch-up doses of 4CMenB in the parent study; Group I, children 8–12 years of age who received 2 catch-up doses of 4CMenB in the parent study; Group K, naïve children 35–47 months of age; Group L, naïve children 4–7 years of age; Group M, naïve children 8–12 years of age.

hSBA titres ≥4 were generally higher among follow-on participants at 24–36 months post-vaccination as compared to the baseline antibody levels in vaccine-naïve children (except for NHBA).

The presence of functional circulating antibodies measured by hSBA is a main factor contributing to the duration of protection against IMD. It is particularly important to ensure protection of children under 5 years, who are the most susceptible for IMD.[33] Waning antibody titres following immunisation with 4CMenB have been observed in other clinical studies.[22,28–31] Whether the observed decline in antibodies translates in reduced vaccine effectiveness is not clear. The first vaccine effectiveness data after 4CMenB implementation in the UK was recently reported to be 82.9%

after 2-dose priming.[26] In Canada, 4CMenB has been used in a mass immunisation campaign in individuals between 2 months and 20 years of age to control a regional outbreak of serogroup B disease in the Saguenay–Lac-Saint-Jean region.[34] Two years after the start of this campaign, no IMD cases due to serogroup B occurred in the vaccinated and unvaccinated target population, and multivariate analysis showed a statistically significant decrease in MenB IMD rate in the region.[34] Longer follow-up data will become available as the vaccine is introduced in other countries.

Persistence data regarding the other licensed protein-based serogroup B vaccine, rLP2086, have so far only been reported for one study performed in a different age group (adolescents aged 11–18 years): up to 4 years after a 3-dose schedule, protective hSBA titres were elicited in at least 50% of adolescents against 3 of 4 meningococcal serogroup B test strains.[35] The antibody persistence data following meningococcal serogroup B protein-based vaccines seem to follow a similar pattern to that of quadrivalent meningococcal conjugate vaccines or meningococcal C conjugate vaccines.[36–38]

At 24–36 months after last vaccination in the parent study, the administration of an additional 4CMenB dose in previously primed participants (follow-on groups) showed a stronger immune response with a higher increase of hSBA titres, as compared to a first dose of 4CMenB in age-matched vaccine-naïve participants (except for NHBA). This robust immune response triggered by administration of an additional 4CMenB dose indicated that initial vaccination in the parent study had resulted in successful immune memory. Anamnestic responses to a booster dose of 4CMenB vaccine (fifth dose) have also been described in another clinical study.[28]

While the hSBA assay offers information on the immunity of individuals, it fails to provide a comprehensive population-wide overview because other factors such as immune memory, herd immunity and bacterial carriage also impact long-term protection. For instance, in the UK, waning antibody titres have been reported for meningococcal serogroup C vaccination but catch-up campaigns among children, teenagers and young adults resulted in herd immunity, which vigorously contributed to the effectiveness of the immunisation programme.[39] The influence of 4CMenB vaccination on nasopharyngeal carriage and its ability to induce herd immunity is currently not well-known. One randomised clinical study found that 4CMenB, as well as the quadrivalent meningococcal conjugate vaccine MenACWY-CRM, modestly reduced meningococcal carriage in UK university students from 3 to 12 months post-vaccination, but found no correlation between post-vaccination hSBA titres and carriage.[40,41] Active surveillance will be key to ascertain the clinical impact of antibody persistence and real-life effectiveness data will help to formulate the most efficient disease control.

This study is the first evaluation of an accelerated 2-dose catch-up schedule with 4CMenB (given 1 month apart) in vaccine-naïve participants at either 35–47 months of age, 4–7 years of age or 8–12 years of age. Robust antibody responses were induced against all strains (except for a lower response against NHBA), with an early response after the first dose. This accelerated schedule may be used as a measure to control disease outbreaks or for people that face imminent exposure such as travellers to risk areas and emergency responders in disaster zones. Vaccination with 4CMenB has already been used in response to MenB outbreaks at university campuses in the United States[14,15] and in Quebec (Canada) following increased MenB incidences.[34] The use of an accelerated 2-dose schedule inducing robust immune responses allows for a rapid intervention with the promise to confer protection.

The lower performance of NHBA might result from high pre-vaccination titres as observed in previous studies.[28,31] Many vaccine-naïve children had baseline hSBA titres ≥1:4 against NHBA, suggesting that M10713 is particularly sensitive to killing within the assay.[31]

The tolerability profile of 4CMenB vaccine was acceptable, similar to previous studies, and no major safety concerns were identified after an additional4CMenB dose in follow-on participants or after 2 catch-up doses in vaccine-naïve children. Similar percentages of participants reported local and systemic reactions after vaccination. The majority of unsolicited reactions were mild in nature, most of them were solicited AEs persisting beyond day 7 post-vaccination. While in a different study systemic reactogenicity was lowest in vaccine-naïve two-year-olds, followed by infants and toddlers, local reactogenicity was common in all groups.[29] In 5-year-old children, a fifth dose of 4CMenB was well tolerated, although injection-site pain was noteworthy.[30] In line with these results, real-life experience with 4CMenB in the UK or Canada has been reassuring in terms of safety data and no new safety concerns have been identified.[16] Ongoing post-licensure surveillance after widespread use of 4CMenB will be important to identify any possible safety signals.

As a drawback of the study, the low number of participants, due to loss of follow-up from the parent study, might limit interpretation. However, the design of the extension study further allows elaborating on the immunogenicity of a booster response in children who received different 4CMenB vaccination schedules.

Conclusions

A reduced 2 + 1 4CMenB primary vaccination schedule resulted in similar antibody persistence compared to the licensed 3 + 1 schedule, and no safety concern was observed for either schedules. Both vaccination schedules triggered a comparably strong booster response. Two catch-up doses of 4CMenB at an accelerated schedule in vaccine-naïve participants induced robust antibody responses.

Authors contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and commented critically on drafts of the manuscript for important intellectual content and gave final approval to submit for publication. HW, CB and DT were involved in the conception or the design of the study/project. All authors participated in the collection or generation of the study/project data. FMT, RS, PIM, JLA, JACG, PR, HW, CB and DT performed the study/project. ACM, RS, PIM, JACG, HW and CB contributed to materials/analysis/reagent tools. FMT, ACM, RS, PIM, HW, CB and DT were involved in the analyses or interpretation of the data.

Trademarks

Bexsero is a trademark owned by the GSK group of companies.

Trumenba is a trademark of Wyeth LLC (marketed by Pfizer Inc.).

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Conflict of interest

The institution of FMT received clinical trial fees from Novartis Vaccines (on 2 March 2015 Novartis non-influenza Vaccines Business was acquired by the GSK group of companies) for the conduct of this study, and he received personal fees/non-financial support/grants/other from Pfizer, SPMSD and/or from the GSK group of companies, outside the submitted work. FMT research time and activities have been supported by grants from Consellería de Sanidade, Xunta de Galicia (RHI07/2-intensificación actividad investigadora, PS09749 and 10PXIB918184PR), Instituto de Salud Carlos III (Intensificación de la actividad investigadora 2007–2017), Fondo de Investigación Sanitaria (FIS; PI070069/PI1000540/PI1601569) del plan nacional de I + D + I and "fondos FEDER" and 2016-PG071 Consolidación e Estructuración REDES 2016GI-1344 G3VIP (Grupo Gallego de Genética Vacunas Infecciones y Pediatría, ED341D R2016/021). ACM received a grant from Novartis during the conduct of the study. RS received personal fees from Novartis during the conduct of the study as national coordinator of this trial in Hungary and personal fees from the GSK group of companies for a lecture on Meningitis prevention, outside the submitted work. FGS has participated as principal investigator in clinical trials sponsored by the GSK groups of companies and has received grants for participation in conferences. HW, CB and DT are employed by the GSK group of companies. JLA received clinical trial fees from Novartis Vaccines and the GSK group of companies, personal fees from Pfizer for clinical trials, from SPMSD and AstraZeneca for conferences. DT holds shares in the GSK group of companies as part of her employee remuneration. PIM, JLA, JACG, EK and PR declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jinf.2017.12.005.

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