Meningococcal serogroup B strain coverage of the multicomponent 4CMenB vaccine with corresponding regional distribution and clinical characteristics in England, Wales, and Northern Ireland, 2007–08 and 2014–15: a qualitative and quantitative assessment

Sydel R Parikh, Lynne Newbold, Stephanie Slater, Maria Stella, Monica Moschioni, Jay Lucidarme, Rosita De Paola, Maria Giuliani, Laura Serino, Stephen J Gray, Stephen A Clark, Jamie Findlow, Mariagrazia Pizza, Mary E Ramsay, Shamez N Ladhani, Ray Borrow

Lancet Infect Dis 2017; 17: 754–62

Published Online March 30, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30170-6

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Immunisation Department, Public Health England, London, UK (S R Parikh MSc, M E Ramsay FFPHM, S N Ladhani MRCPCH); **Meningococcal Reference Unit, Public Health England, Manchester, UK** (L Newbold PhD, S Slater BSc, J Lucidarme PhD, S J Gray PhD, S A Clark BSc, J Findlow PhD, R Borrow FRCPath); **GlaxoSmithKline Vaccines, Siena, Italy** (M Stella PhD, R De Paola PhD, M Giuliani PhD, L Serino PhD, M Pizza PhD); **Médecins Sans Frontières, Nukus, Uzbekistan** (M Moschioni PhD); **and St George's University of London, London, UK** (S N Ladhani)

Correspondence to: Ms Sydel Parikh, Immunisation Department, Public Health England, London NW9 5EQ, UK **sydel.parikh@phe.gov.uk**

Summary

Background **The UK introduced 4CMenB—a multicomponent vaccine against serogroup B meningococcal disease—into the national infant immunisation programme in September, 2015. The Meningococcal Antigen Typing System (MATS) was used to estimate coverage by 4CMenB of invasive meningococcal group B isolates obtained during 2007–08 in England and Wales (MATS coverage). We aimed to repeat the MATS survey for invasive meningococcal group B isolates obtained during 2014–15, before 4CMenB introduction; compare strain coverage between 2007–08 and 2014–15; and investigate associations between MATS coverage, age, region, and disease outcomes.**

Methods **Invasive serogroup B meningococcal isolates from cases in England, Wales, and Northern Ireland during 2014–15 were assayed using MATS and compared with 2007–08 data. MATS coverage was assessed by geographical region and age group. Clinical characteristics, risk factors, and outcomes were assessed according to MATS coverage for 2014–15 English cases.**

Findings **In 2014–15, 165 of 251 (66%; 95% CI 52–80) meningococcal group B isolates were estimated by MATS to be covered by 4CMenB, compared with 391 of 535 (73%; 95% CI 57–87) in 2007–08. The proportion of MATS-positive isolates with one vaccine antigen increased from 23% (122 of 535) in 2007–08 to 31% (78 of 251) in 2014–15, whereas the proportion with more than one antigen fell from 50% (269 of 535) to 35% (87 of 251). This effect reflected changes in circulating strains, particularly ST-269 clonal complex strains. MATS coverage increased with age, varied by geographical region, and was associated with more severe disease.**

Interpretation **In 2014–15, two-thirds of meningococcal group B isolates were predicted to be covered by 4CMenB. Temporal changes in MATS coverage underscore the need for continued monitoring of antigen expression and diversity, particularly in countries with 4CMenB programmes.**

Funding **Public Health England, GlaxoSmithKline.**

Introduction

In September, 2015, the UK introduced a novel multicomponent vaccine (4CMenB; Bexsero, GlaxoSmithKline Vaccines, Siena, Italy) against serogroup B meningococcal disease into the nationally funded infant immunisation programme.[1] Similar to most European countries, group B is the main serogroup that causes invasive meningococcal disease in the UK, with the highest incidence in infants.[1] Currently licensed glycoconjugate vaccines that target the capsular polysaccharides of serogroups A, C, W, and Y meningococci do not provide any cross-protection against other meningococcal serogroups.[2] The development of polysaccharide-based vaccines against meningococcal group B disease has been hampered because of structural similarities to fetal neural tissue, rendering the polysaccharide poorly immunogenic.[2]

During development of the 4CMenB vaccine, relatively conserved and cross-protective meningococcal group B surface proteins were identified by reverse vaccinology. Three recombinant proteins—factor H binding protein (fHbp) variant 1.1, neisserial heparin-binding antigen (NHBA) peptide 2, and neisserial adhesin A (NadA) variant 3—were included in 4CMenB, along with outer membrane vesicles containing the porin PorA (P1.4) from the New Zealand outbreak strain. Unlike capsular polysaccharides, which tend to be expressed abundantly and are antigenically relatively uniform in invasive meningococci, surface proteins can be sparse and antigenically diverse. Poorly expressed surface proteins and antigenic variability resulting from different mechanisms (eg, mutation or recombination)[3] might result in the binding of insufficient antibodies to promote complement-mediated lysis. Therefore, the ability of 4CMenB to protect against serogroup B meningococcal strains and the breadth of protection depends on the degree of surface expression and the extent to which

Research in context

Evidence before this study

We searched PubMed with the terms "meningococcal B" and any combination of "vaccine", "coverage", "MATS", or "Meningococcal Antigen Typing System". Publication dates and languages were not limited. Initial studies using the Meningococcal Antigen Typing System (MATS) reported the assay to be reliable and reproducible, providing a conservative estimate of 4CMenB coverage. There is an association between the number of vaccine antigens predicted to be covered by MATS and the probability of being killed by immune serum in the serum bactericidal antibody assay. Strains covered by two or more antigens have a 96% probability of being killed compared with at least 80% of strains covered by one antigen. In a large European survey of more than 1000 clinical meningococcal group B isolates from the 2007–08 epidemiological year, MATS predicted that 78% (95% CI 63–90) of all meningococcal group B strains would be killed by post-vaccination sera, with half of all strains and 64% of MATS-positive strains covered by more than one vaccine antigen. Other countries have since reported coverage of meningococcal group B isolates by 4CMenB and, in a global review, coverage as predicted by MATS ranged from 66% in Canada to 91% in the USA. We found one study from Canada reporting regional variation and trends in coverage over time. Our search identified no studies assessing coverage of isolates by 4CMenB associated with clinical disease, severity, or outcome.

Added value of this study

In England, Wales, and Northern Ireland, coverage of meningococcal group B isolates by 4CMenB from patients with invasive meningococcal disease fell between 2007–08 and 2014–15, and coverage by more than one antigen also decreased. These declines were mainly attributable to changes in circulating strains, particularly the ST-269 clonal complex. Regional coverage of isolates as predicted by MATS varied widely and was lower in most regions in 2014–15 compared with 2007–08. By comparison with older children and adults, coverage of meningococcal group B isolates by 4CMenB was lower in infants, who are also less likely to benefit from the cross-protective effects of the vaccine. In England, MATS-positive meningococcal group B strains were more likely to cause invasive meningococcal disease in healthy individuals and more severe disease, in terms of intensive-care admission and death, than were MATS-negative strains.

Implications of all the evidence

Our findings emphasise the complexity of estimating 4CMenB strain coverage and highlight the importance of MATS when assessing vaccine impact on meningococcal group B disease in a population with fluctuating strain coverage. The association we identified between MATS-positive strains and increased severity of disease—although expected—is reassuring because it suggests that immunised infants might develop milder disease. The UK will be the first country to assess the usefulness of MATS for monitoring vaccine impact and to characterise the meningococci causing invasive disease in both vaccinated and unvaccinated cohorts.

vaccine-induced antibodies recognise and bind to these proteins.[4]

The Meningococcal Antigen Typing System (MATS) is a qualitative and quantitative ELISA that quantifies fHbp, NHBA, and NadA expression in combination with the ability of 4CMenB-induced antibodies to recognise these proteins on individual meningococcal isolates.[5] For an isolate to be deemed vaccine-preventable (MATS-positive), either the relative potency of one or more antigens must be greater than the respective positive bactericidal thresholds, which were assigned on the basis of killing using post-vaccination pooled sera from toddlers, or the isolate must possess homologous PorA (P1.4).[4]

The first application of MATS to a large-scale epidemiological survey entailed assaying 1052 sero-group B meningococcal isolates from five European countries obtained during 2007–08; all meningococcal group B isolates possessed at least one gene encoding a major vaccine antigen.[6] MATS predicted that 78% of meningococcal group B isolates from patients across Europe (including 73% in England and Wales) would be killed by post-vaccination serum samples (referred to herein as MATS coverage). Since this survey is now almost a decade old, we aimed to perform a second MATS survey of isolates from patients with invasive serogroup B meningococcal disease in England, Wales, and Northern Ireland during 2014–15, the last epidemiological year before 4CMenB introduction. We then aimed to compare MATS coverage and regional distribution with the corresponding 2007–08 data. We also aimed to assess age distribution, clinical characteristics, and outcomes of invasive meningococcal disease in patients with MATS-positive and MATS-negative meningococcal group B isolates.

Methods

Data collection

Public Health England conducts enhanced national surveillance of invasive meningococcal disease and provides a national reference service for confirmation of this disease and characterisation of invasive meningococci (both culture and non-culture).[7] Confirmed cases in England are followed up routinely with a short questionnaire sent to the patient's family doctor requesting information on comorbidities, clinical presentation, intensive-care admission, and outcomes. We obtained data for all patients in England, Wales, and Northern Ireland diagnosed with invasive serogroup B meningococcal

disease between July 1, 2014, and June 30, 2015. Data for meningococcal group B isolates obtained in 2007–08 have been published previously.[6]

For the **Meningitis Research Foundation's Meningococcus Genome Library** see http://www.meningitis.org/genome-library

Procedures

We characterised isolates genotypically by multilocus sequence typing[8] and each of the four main 4CMenB antigens. Genotypic characterisation of 2007–08 isolates was done using Sanger sequence analysis.[6] We did genotypic characterisation of 2014–15 isolates using the Illumina platform[7] and with data extracted from the Meningitis Research Foundation's Meningococcus Genome Library, which contains genome sequences for all English, Welsh, and Northern Irish invasive isolates received by the Public Health England Meningococcal Reference Unit since July, 2010, and is populated on an ongoing basis.[9]

We generated MATS data for both epidemiological years (2007–08 and 2014–15) using the same methods described previously.[4,10,11] We determined PorA subtypes by phenotyping,[7] Sanger sequencing, and genome sequencing.[12] We defined predicted strain coverage as the proportion of serogroup B meningococcal isolates with MATS relative potency greater than the positive bactericidal thresholds for one or more antigen or the presence of PorA (P1.4).

For 2007–08 isolates, we calculated log-normal approximation estimates of 95% CIs for all positive bactericidal thresholds and based them on overall assay reproducibility, as described in the MATS laboratory standardisation study.[10] We used new rabbit sera to manufacture fhbp MATS plates for the 2014–15 analysis, but these required reassignment of a new positive bactericidal threshold because they showed a lower affinity for genetically distant and middle-to-low fHbp-expressing strains. We set new specifications using previously described standardisation methods.[10] For 2014–15 isolates, the fHbp positive bactericidal threshold was 0·012 (95% CI 0·008–0·018) compared with 0·021 (0·014–0·031) in 2007–08, whereas NHBA and NadA positive bactericidal thresholds did not change from those set in 2007–08 (0·294 [0·169–0·511] for NHBA; 0·009 [0·004–0·019] for NadA).[13] We stratified the fHbp and NHBA peptides by their relative potencies and plotted them against the positive bactericidal thresholds in MATS. We assigned isolates with relative potency less than the lower limit of quantification (LLOQ) half of the LLOQ (0·0045 for 2007–08 fHbp isolates; 0·002 for 2007–08 NHBA isolates and for both antigens in 2014–15 isolates), and we did not include isolates with peptide frequencies less than 5 (either dataset).

Statistical analysis

We analysed data using Stata SE version 13.1; data are mainly descriptive. We described data that did not follow

	2007–08 (n=535)	2014–15 (n=251)
No antigens	144 (27%)	86 (34%)
One antigen	122 (23%)	78 (31%)
fHbp	78 (15%)	63 (25%)
NHBA	42 (8%)	14 (6%)
NadA	0	0
PorA	2 (<1%)	1 (<1%)
Two antigens	184 (34%)	64 (25%)
fHbp + NHBA	160 (30%)	44 (18%)
fHbp + NadA	0	5 (2%)
fHbp + PorA	17 (3%)	12 (5%)
PorA + NHBA	5 (1%)	3 (1%)
NHBA + NadA	2 (<1%)	0
Three antigens	85 (16%)	23 (9%)
fHbp + NHBA + PorA	84 (16%)	23 (9%)
fHbp + NHBA + NadA	1 (<1%)	0

Data are number of isolates (%). fHbp=factor H binding protein. NadA=neisserial adhesin A. NHBA=neisserial heparin-binding antigen. PorA=porin A.

Table 1: **4CMenB antigens affording protection among invasive meningococcal B isolates from England, Wales, and Northern Ireland during 2007–08 and 2014–15**

	2007–08		2014–15	
	MenB isolates (n=535)	MATS coverage (%)	MenB isolates (n=251)	MATS coverage (%)
cc269	176 (33%)	73%	60 (24%)	53%
cc41/44	169 (32%)	94%	82 (33%)	94%
cc213	52 (10%)	17%	26 (10%)	23%
Unassigned	35 (7%)	54%	22 (9%)	64%
cc32	31 (6%)	100%	23 (9%)	93%
cc461	12 (2%)	42%	10 (4%)	10%
cc60	11 (2%)	46%	3 (1%)	67%
cc162	10 (2%)	100%	8 (3%)	88%
cc18	9 (2%)	89%	1 (<1%)	100%
cc35	8 (1%)	38%	9 (4%)	33%
cc11	6 (1%)	100%	0	..
cc282	4 (1%)	50%	0	..
cc22	2 (<1%)	50%	0	..
cc254	2 (<1%)	100%	0	..
cc364	2 (<1%)	0%	1 (<1%)	0
cc8	1 (<1%)	100%	0	..
cc103	1 (<1%)	0%	1 (<1%)	0
cc174	1 (<1%)	0%	0	..
cc226	1 (<1%)	0%	0	..
cc865	1 (<1%)	100%	1 (<1%)	0
cc1157	1 (<1%)	100%	3 (1%)	33%
cc4821	0	..	1 (<1%)	0
Total covered	..	73%	..	66%

Data are number of isolates (%), unless otherwise stated. cc=clonal complex. MATS=Meningococcal Antigen Typing System. MenB=meningococcal serogroup B.

Table 2: **Clonal complex distribution among meningococcal group B isolates from England, Wales, and Northern Ireland in 2007–08 and 2014–15 and MATS coverage within each clonal complex**

	No antigen		fHbp		NHBA		NadA		PorA	
	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15
cc103	1 (100%)	1 (100%)	0	0	0	0	0	0	0	0
cc11	0	0	0	0	2 (33%)	0	0	0	0	0
cc1157	0	2 (67%)	1 (100%)	1 (33%)	0	0	0	0	0	0
cc162	0	1 (13%)	3 (30%)	2 (25%)	5 (50%)	3 (38%)	0	0	1 (10%)	0
cc174	1 (100%)	0	0	0	0	0	0	0	0	0
cc18	1 (11%)	0	8 (89%)	1 (100%)	0	0	0	0	0	0
cc213	43 (83%)	18 (75%)	5 (10%)	5 (21%)	3 (6%)	0	0	0	0	1 (4%)
cc22	1 (50%)	0	0	0	0	0	0	0	0	0
cc226	1 (100%)	0	0	0	0	0	0	0	0	0
cc254	0	0	0	0	1 (50%)	0	0	0	0	0
cc269	48 (27%)	26 (45%)	26 (15%)	25 (43%)	13 (7%)	1 (2%)	0	0	0	0
cc282	2 (50%)	0	0	0	0	0	0	0	0	0
cc32	0	3 (13%)	14 (45%)	12 (50%)	0	1 (4%)	0	0	0	0
cc35	4 (50%)	6 (67%)	1 (13%)	0	2 (25%)	3 (33%)	0	0	0	0
cc364	2 (100%)	1 (100%)	0	0	0	0	0	0	0	0
cc41/44	11 (7%)	5 (6%)	5 (3%)	3 (4%)	8 (5%)	6 (7%)	0	0	1 (1%)	1 (1%)
cc461	7 (58%)	9 (90%)	0	1 (10%)	3 (25%)	0	0	0	0	0
cc4821	0	1 (100%)	0	0	0	0	0	0	0	0
cc60	6 (55%)	1 (33%)	2 (18%)	2 (67%)	2 (18%)	0	0	0	0	0
cc8	0	0	0	0	0	0	0	0	0	0
cc865	0	1 (100%)	0	0	1 (100%)	0	0	0	0	0
Unassigned	16 (46%)	8 (38%)	13 (37%)	10 (48%)	2 (6%)	1 (5%)	0	0	0	0

Data are number of isolates (%). Denominators for each clonal complex by year are in table 2. cc=clonal complex. fHbp=factor H binding protein. NadA=neisserial adhesin A. NHBA=neisserial heparin-binding antigen. PorA=porin A.

Table 3: **Numbers of invasive meningococcal group B isolates from England, Wales, and Northern Ireland afforded protection by no or one antigen *vs* clonal complex: 2007–08 and 2014–15**

a normal distribution as median (IQR) and compared them using the Mann-Whitney *U* test. We compared proportions using the χ^2 test or Fisher's exact test, as appropriate. We based 95% CIs for MATS coverage on overall assay reproducibility using a log-normal scale to estimate 95% CIs around the positive bactericidal thresholds for the different antigens, then calculating the proportion of relative potencies falling within the upper and lower limits. We did the same analysis for both epidemiological years (2007–08 and 2014–15). We used logistic regression to assess any association between adverse outcomes (intensive-care admission or death) and MATS positivity (yes or no), after adjusting for age (<1 year, 1–2 years, 3–4 years, or ≥5 years), underlying comorbidity (present or absent), and clinical presentation (meningitis, septicaemia, both, or other).

Role of the funding source

Public Health England, which is an executive agency of the UK Department of Health, employs SRP, MER, SNL, LN, SS, JL, SJG, SAC, JF, and RB; GlaxoSmithKline Vaccines employs MS, RDP, MG, LS, and MP. The authors had sole responsibility for study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 1, 2014, and June 30, 2015, 764 cases of invasive meningococcal disease were confirmed in England, Wales, and Northern Ireland, including 440 (58%) cases of serogroup B meningococcal disease, of which 251 (57%) were culture-confirmed (appendix pp 7–16). By comparison, in 2007–08, 1289 cases of invasive meningococcal disease were confirmed in England, Wales, and Northern Ireland, with 1123 (87%) serogroup B of which 535 (48%) were confirmed by culture.

See Online for appendix

In 2014–15, 165 (66%; 95% CI 52–80) of 251 meningococcal group B isolates contained antigens that were covered by 4CMenB, compared with 391 (73%v; 57–87) of 535 in 2007–08 (table 1; appendix p 4). For both years, MATS-positivity was most frequently due to coverage by fHbp alone and in combination with NHBA. None of the MATS-positive isolates in either year were covered by all four vaccine antigens. The proportion of isolates covered by more than one vaccine antigen fell from 50% in 2007–08 to 35% in 2014–15, whereas the proportion covered by one antigen increased from 23% to 31%. This difference was mainly attributable to a shift in the

	fHbp + NHBA		fHbp + PorA		fHbp + NadA		NHBA + NadA		NHBA + PorA		fHbp + NHBA + NadA		fHbp + NHBA + PorA	
	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15
cc103	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc11	1 (17%)	0	0	0	0	0	2 (33%)	0	0	0	1 (17%)	0	0	0
cc1157	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc162	0	0	0	0	0	0	0	0	1 (10%)	2 (25%)	0	0	0	0
cc174	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc18	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc213	1 (2%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc22	1 (50%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc226	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc254	1 (50%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc269	85 (48%)	6 (10%)	0	0	0	0	0	0	1 (1%)	0	0	0	3 (2%)	0
cc282	0	0	2 (50%)	0	0	0	0	0	0	0	0	0	0	0
cc32	17 (55%)	4 (17%)	0	0	0	4 (17%)	0	0	0	0	0	0	0	0
cc35	1 (13%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc364	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc41/44	46 (27%)	32 (39%)	15 (9%)	11 (13%)	0	0	0	0	3 (2%)	1 (1%)	0	0	80 (47%)	23 (28%)
cc461	2 (17%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc4821	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc60	1 (9%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc8	1 (100%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc865	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unassigned	3 (9%)	1 (5%)	0	0	0	1 (5%)	0	0	0	0	0	0	1 (3%)	0

Data are number of isolates (%). Denominators for each clonal complex by year are in table 2. cc=clonal complex. fHbp=factor H binding protein. NadA=neisserial adhesin A. NHBA=neisserial heparin-binding antigen. PorA=porin A.

Table 4: **Numbers of invasive meningococcal group B isolates from England, Wales, and Northern Ireland afforded protection by two or more antigens *vs* clonal complex: 2007–08 and 2014–15**

proportion of isolates covered by both NHBA and fHbp in 2007–08 to a higher frequency of isolates covered by fHbp only in 2014–15.

The clonal complexes cc269, cc41/44, and cc213 accounted for more than two-thirds of meningococcal group B isolates during 2007–08 and 2014–15 (table 2; appendix p 1). The proportion of cc269 isolates decreased by 9%, from 33% in 2007–08 to 24% in 2014–15. MATS coverage of cc269 also decreased, from 73% to 53%, mainly through loss of coverage provided by NHBA, both individually (table 3; appendix p 6) and in combination with fHbp (table 4; appendix p 6). The clonal complex cc41/44 accounted for around a third of isolates and retained very high MATS coverage (94% in both 2007–08 and 2014–15; table 2). MATS coverage for cc213 increased by 6% (from 17% in 2007–08 to 23% in 2014–15) because of a proportional increase in isolates possessing protective fHbp variant 1 (table 3). cc32 representation in isolates increased by more than 3% between 2007–08 and 2014–15, but MATS coverage of this clonal complex declined by 7% (table 2).

The clonal complex cc269 is composed of two major clusters, centred around sequence types (ST)-269 and ST-275, respectively. A large proportion of unassigned isolates share four or more loci with ST-275 on multilocus sequence typing but fewer than four with the founder sequence type ST-269 and, thus, are unassigned to cc269. In 2007–08, this included 15 of 35 unassigned isolates, seven of which were MATS-positive. If these isolates had been included in the ST-275 cluster, the overall number of cc269 isolates would have increased from 176 to 191 (thus, MATS coverage 135 of 191 [71%, rather than 73%; table 2]). In 2014–15, five unassigned isolates could be treated as belonging to the ST-275 cluster, none of which were MATS-positive (thus, MATS coverage 32 of 65 [49%, rather than 53%; table 2]). ST-269 cluster isolates typically have NHBA peptide 21, which is more likely to have a relative potency greater than the positive bactericidal threshold, whereas ST-275 cluster isolates harbour NHBA peptide 17, which is less likely to have a relative potency greater than the positive bactericidal threshold (appendix p 2). Compared with 2007–08, the proportion of isolates with NHBA peptide 21 was lower in 2014–15, whereas those with NHBA peptide 17 remained stable (figure 1; appendix p 2). NHBA peptide 21 coverage decreased by 23% between 2007–08 and 2014–15 (86% [97 of 113] in 2007–08 to 63% [19 of 30] in 2014–15). Similar trends were observed with fHbp peptide subvariants 1·15 and 1·13 (figure 1; appendix p 3), which are associated with the ST-269 and ST-275 clusters, respectively. These

changes resulted in a decrease in MATS coverage of cc269 in 2014–15.

During 2014–15, 39% of isolates (99 of 251) had one or more proteins homologous to a vaccine antigen compared with 35% (189 of 535) during 2007–08. Coverage by each individual vaccine antigen declined between 2007–08 and 2014–15 (from 64% to 59% for fHbp; from 55% to 33% for NHBA; and from 20% to 16% for PorA), except NadA for which coverage increased (from 1% to 2%; figure 2).

During 2007–08, the fHbp gene was absent in only one (0·19%) of 535 isolates, and two other isolates (0·37%) had frameshift mutations. No deletions or frameshifts were noted among 2014–15 isolates. The overall distribution of fHbp variants remained the same between the two periods, with variant 1 being the most prevalent (70% in 2007–08 and 68% in 2014–15; appendix p 3). MATS coverage of fHbp decreased between 2007–08 and 2014–15, from 63% (333 of 532) to 59% (148 of 251). A 2% increase was recorded in the proportion of isolates with the vaccine-homologous fHbp subvariant 1.1. None of the isolates containing variant 2 or 3 was above the fHbp positive bactericidal threshold for either year (figure 1).

In 2007–08, 18% of meningococcal group B isolates (97 of 535) possessed NadA alleles, including all cc11 (n=6), cc32 (n=31), and cc1157 (n=1) isolates and a proportion of cc213 (47 of 52 [90%]), cc269 (four of 176 [2%]), cc364 (one of two [50%]), cc41/44 (one of 169 [1%]), and unassigned (six of 35 [17%]) isolates. Of the 97 isolates containing NadA alleles, 31 possessed alleles encoding intact peptide subvariants that would potentially be recognised by 4CMenB-induced antibody (NadA-1 and NadA-2/3). However, only three of 535 isolates (1% overall, all cc11) were above the NadA positive bactericidal threshold.

In 2014–15, 22% of meningococcal group B isolates (54 of 251) possessed NadA alleles, including all cc1157 isolates (n=3) and a proportion of cc32 (22 of 23 [96%]), cc213 (23 of 26 [88%]), cc269 (one of 60 [2%]), and unassigned (five of 22 [23%]) isolates. 37% of NadA alleles (20 of 54) encoded intact peptide subvariants that would potentially be recognised by 4CMenB-induced antibody, but only five of 251 isolates (2% overall, four cc32 and one unassigned) were above the NadA positive bactericidal threshold.

The PorA (P1.4) subtype was identified in 20% (107 of 535) and 16% (39 of 251) of isolates in 2007–08 and 2014–15, respectively. This difference was mainly attributable to a lower prevalence of P1.4 among cc41/44 isolates (appendix p 1). Among the remaining isolates, PorA variable region 2 was highly diverse in both periods, with 49 distinct variants belonging to 15 families in 2007–08 and ten families in 2014–15. PorA variable region 2 was deleted in one isolate (belonging to cc41/44) in 2007–08.

The vaccine-homologous NHBA peptide 2 was harboured by a quarter of meningococcal group B isolates for both periods, but MATS-coverage of NHBA

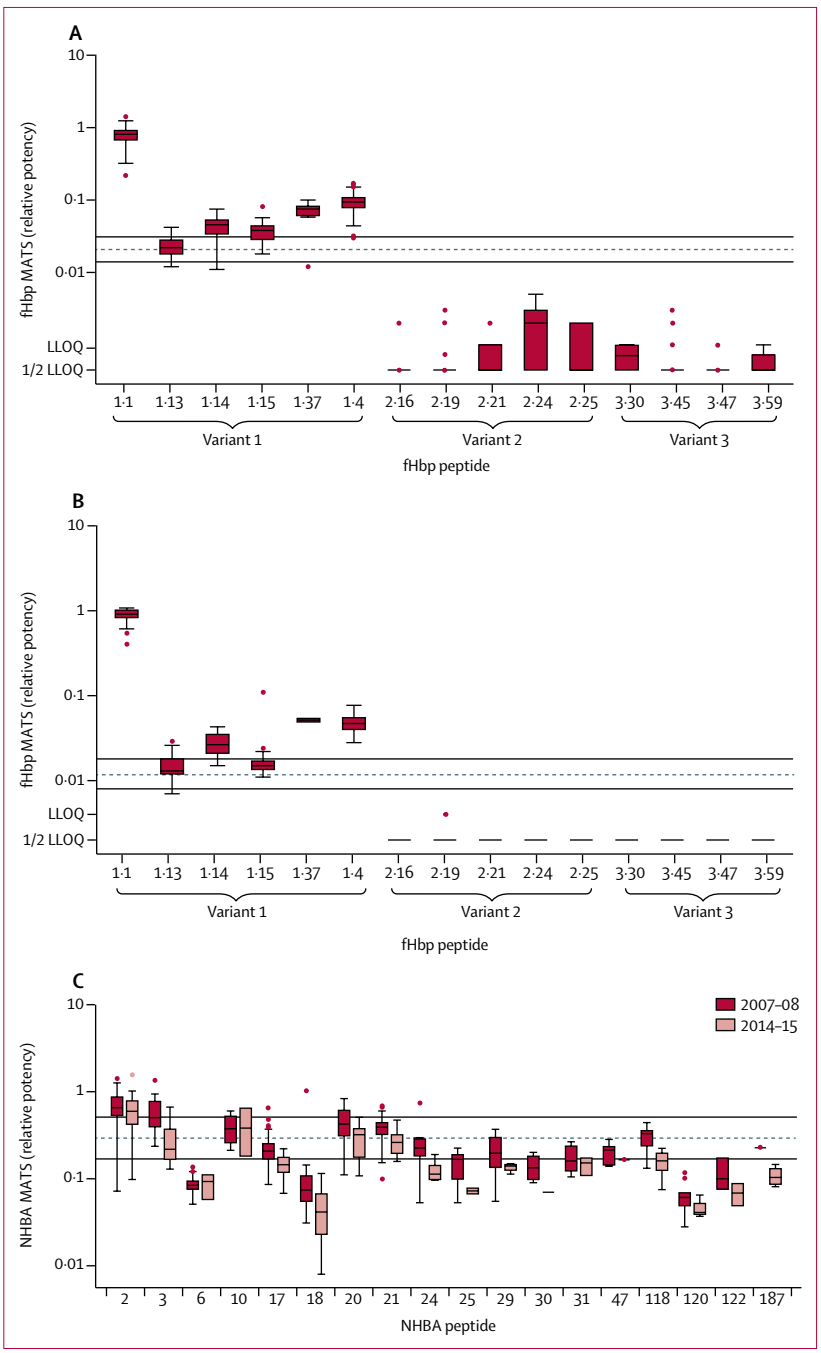

Figure 1: **Distribution of MATS relative potencies of fHbp and NHBA peptides in invasive meningococcal group B isolates in England, Wales, and Northern Ireland during 2007–08 and 2014–15**
(A) fHbp peptide subvariants in 2007–08 (n=442). (B) fHbp peptide subvariants in 2014–15 (n=226). (C) NHBA peptide in 2007–08 and 2014–15 (n=785). Groups accounting for fewer than five isolates are not included in the plots. Boxes represent the median and IQR for each distribution and whiskers signify the 75th percentile + 1·5 × IQR and the 25th percentile – 1·5 × IQR. The horizontal dashed line represents the respective PBT for each antigen and the two horizontal solid lines are the 95% CI. Dots signify individual outliers. LLOQ=0·009 for fHbp in 2007–08, and 0·004 for NHBA in 2007–08 and for both antigens in 2014–15. 1/2 LLOQ=0·0045 for fHbp in 2007–08, and 0·002 for NHBA in 2007–08 and for both antigens in 2014–15. fHbp=factor H binding protein. LLOQ=lower limit of quantification. MATS=Meningococcal Antigen Typing System. NHBA=neisserial heparin-binding antigen. PBT=positive bactericidal threshold.

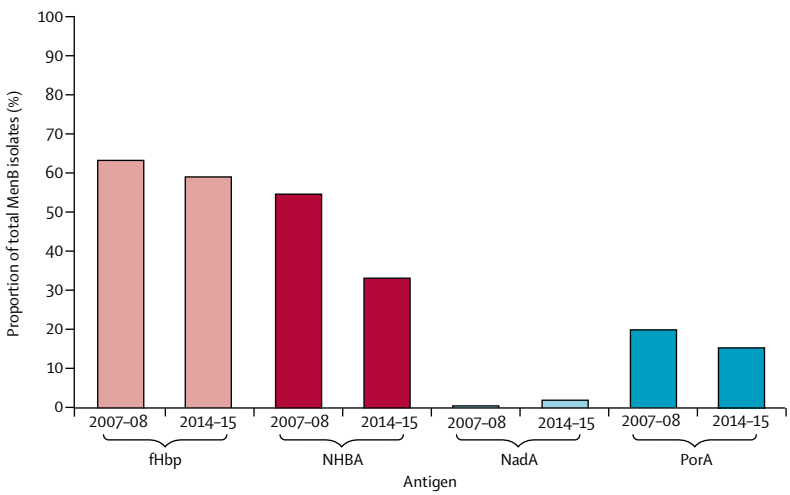

Figure 2: **Proportion of invasive meningococcal group B isolates from England, Wales, and Northern Ireland during 2007–08 and 2014–15 afforded protection by each vaccine antigen**
fHbp=factor H-binding protein. MenB=meningococcal serogroup B. NadA=neisserial adhesin A. NHBA=neisserial heparin-binding antigen. PorA=porin A.

	No antigens	One antigen	Two antigens	Three antigens
2007–08 (n=534*)				
Age <1 years (n=150)	50 (33%)	38 (25%)	45 (30%)	17 (11%)
Age 1–2 years (n=69)	20 (29%)	23 (33%)	14 (20%)	12 (17%)
Age 3–4 years (n=105)	26 (25%)	20 (19%)	40 (38%)	19 (18%)
Age ≥5 years (n=210)	49 (23%)	46 (22%)	80 (38%)	35 (17%)
2014–15 (n=232*)				
Age <1 years (n=70)	26 (37%)	21 (30%)	18 (26%)	5 (7%)
Age 1–2 years (n=55)	21 (38%)	13 (24%)	16 (29%)	5 (9%)
Age 3–4 years (n=15)	7 (47%)	1 (7%)	5 (33%)	2 (13%)
Age ≥5 years (n=92)	28 (30%)	35 (38%)	20 (22%)	9 (10%)

Data are number of isolates (% of age group). MATS=Meningococcal Antigen Typing System. *Age was not reported for one case in 2007–08 and 19 cases in 2014–15.

Table 5: **MATS coverage of invasive meningococcal group B isolates from England, Wales, and Northern Ireland in 2007–08 and 2014–15, stratified by age group**

peptide 2 isolates was 3% lower (from 97% in 2007–08 to 94% in 2014–15; figure 1). Three other peptides (21, 17, and 18) accounted for 42% (223 of 535) of the remaining NHBA peptides in 2007–08 and 37% (92 of 251) in 2014–15. The lower MATS coverage of NHBA in 2014–15 was attributable to small reductions across several peptides, most notably, peptide 21.

In 2007–08, 93 (17%) of 535 isolates had fHbp relative potency values less than or equal to the LLOQ compared with 21 (8%) of 251 isolates in 2014–15. Overall, the distribution of fHbp variant 1 was similar between the two periods, with most isolates having relative potencies above the positive bactericidal threshold (figure 1). NHBA peptides, on the other hand, were more variable between the two periods, with a high proportion of isolates falling within or below the 95% CI boundaries (figure 1).

MATS coverage was highest for individuals older than 5 years for both 2007–08 (77%) and 2014–15 (70%). In 2014–15, MATS coverage, and the number of antigens covered, were mostly lower across the age groups, compared with 2007–08 (table 5). In particular, in 2014–15, 37% (26 of 70) of meningococcal group B isolates in infants (age <1 years) were MATS-negative and a further 30% (21 of 70) were only covered by one vaccine antigen (table 5).

MATS coverage varied by UK region; during 2007–08 it was 53–79% and in 2014–15 it was 48–80%. MATS coverage fell in eight of 11 regions, with significant declines in the West Midlands and Yorkshire and Humber (appendix p 4). The increase in MATS coverage in two regions was not significant.

In 2014–15, 231 (92%) of 251 cases were from England. MATS-positivity was associated with a lower prevalence of underlying comorbidities (p=0·002) and, although not significant, intensive-care admissions (p=0·128) and deaths (p=0·874) were higher (appendix p 5). In a logistic regression model, MATS-positivity was associated with a 1·95-fold increased risk (95% CI 1·02–3·76; p=0·017) of severe invasive meningococcal disease (intensive-care admission, death, or both), independent of age, sex, underlying comorbidity, or clinical presentation.

Discussion

This study provides baseline data for MATS coverage of serogroup B meningococcal disease in England, Wales, and Northern Ireland before introduction of the 4CMenB (Bexsero) vaccine. Cases of serogroup B meningococcal disease more than halved between 2007–08 and 2014–15, from 1123 cases to 440 cases (61% decrease), MATS coverage declined from 73% to 66%, and the proportion of isolates covered by more than one antigen fell from 50% to 35%. In infants younger than 1 year, the age group targeted for vaccination, a third of isolates were MATS-negative and more than a third (37%) were only covered by one vaccine antigen. We found some evidence of more severe disease, in terms of lower comorbidity prevalence and increased risk of intensive-care admissions and death, associated with MATS-positive isolates.

MATS coverage in 2014–15 was lower than in 2007–08, mainly because cases attributable to cc269 (the most prevalent clonal complex in 2007–08) declined, whereas the proportion of the less well covered cc269 sub-population (the ST-275 cluster) increased, resulting in lower coverage attributable to NHBA. This change led to a higher proportion of isolates covered by one antigen (fHbp) only, which potentially could affect the protection offered by 4CMenB. In one study, 80% of strains with one vaccine antigen were killed by immune serum in the serum bactericidal antibody assay compared with 96% for strains with two or more antigens.[4] At the same time, the cross-protection offered by vaccine-induced antibodies is lower in infants compared with children and adults.[4,14–16]

MATS, however, provides a conservative estimate of protection offered by 4CMenB when compared with serum bactericidal antibody assays.[5] For example, some evidence suggests a synergistic effect, whereby antibodies that are not independently bactericidal can augment the killing effect in serum bactericidal antibody assays.[17] Antibodies against minor components of the outer membrane vesicle might also contribute to the killing.[17] Additionally, NadA coverage could be higher than predicted by MATS because NadA expression is repressed under in-vitro growth conditions.[18]

On the other hand, a third of 4CMenB-vaccinated adolescents in a recent US university outbreak had no bactericidal antibodies against the outbreak strain in a human serum bactericidal antibody assay, despite this strain being predicted by MATS to be covered by fHbp and NHBA. However, no additional cases have been reported since the start of the vaccination campaign.[19] In view of the uncertainties surrounding both MATS and serum bactericidal antibody for predicting clinical protection, the early UK data reporting high vaccine effectiveness and significant reductions in cases of serogroup B meningococcal disease among 4CMenB-eligible infants are reassuring.[20]

Previous study findings have shown that the clonal complex does not reliably predict MATS positivity or killing in the serum bactericidal antibody assay because of the dynamic antigenic expression within strains, within clonal complexes, or both.[6,21] The two main cc269 clusters, for example, show different genotypic and phenotypic profiles with respect to the genes encoding 4CMenB antigens and MATS coverage.[22] Furthermore, the diversification of isolates that cluster around ST-275 away from ST-269 underestimates the scale of both the ST-275 cluster and the overall clonal complex, making it difficult to accurately predict coverage of either clonal complex or cluster. Recent genotype-phenotype modeling has shown some promise, with one study estimating 66% coverage for meningococcal group B isolates in the UK and Ireland during 2010–14 using Bexsero Antigen Sequence Type (BAST) scheme.[23]

We assessed MATS coverage by region and found wide variation, even between neighbouring areas, and over time, similar to findings of a Canadian study.[24] This finding is important when interpreting coverage in countries with few cases of serogroup B meningococcal disease, particularly if MATS assessment is undertaken intermittently. MATS-positive strains were also associated with more severe disease, a finding that is, perhaps, not surprising since the selected vaccine antigens are important virulence factors. Immunised infants could, therefore, potentially develop milder disease; this possibility is being monitored after 4CMenB introduction. We did not find any association with clinical presentation, which suggests a more important role for host factors.

The limitations of MATS for predicting killing of specific meningococcal group B strains are well described.[4–6] By using the same laboratory to do MATS testing[6] we could compare regional and national variations in strain coverage over a 7-year interval, although we cannot comment on any trends between these two periods. Since MATS can only be done on cultured isolates, we cannot predict the effect of 4CMenB on culture-negative, PCR-confirmed cases of invasive meningococcal disease, although meningococcal group B isolates are likely to provide good overall genotypic representation of invasive serogroup B meningococcal strains.[25]

In England, a detailed multifaceted plan is in place for enhanced surveillance of invasive meningococcal disease.[26] This surveillance will provide invaluable data for the usefulness of MATS for monitoring vaccine effect and help to characterise the meningococci that cause invasive meningococcal disease in both vaccinated and unvaccinated cohorts.

Contributors

SRP, SNL, and RB did the literature search and wrote the first draft. SRP was responsible for the epidemiological surveillance data. LN, SS, MS, RDP, MG, MM, LS, and MP ran and oversaw all Meningococcal Antigen Typing System assays and collated the outputs for analysis. SRP did the data analysis and prepared the figures. JL prepared genomic data and contributed to their analyses. SRP, JL, JF, SAC, SJG, RB, LS, MER, and SNL contributed to data interpretation. All authors commented on drafts of the report and agreed with the final version.

Declaration of interests

RB, JF, SAC, SS, LN, and SJG perform contract research on behalf of Public Health England for GlaxoSmithKline, Pfizer, and Sanofi Pasteur. JF has also acted on behalf of Public Health England as a consultant and received travel assistance from GlaxoSmithKline and Pfizer. JL reports contract research from GlaxoSmithKline during the conduct of the study. SNL has received research funding on behalf of his institution from GlaxoSmithKline, Pfizer, and Sanofi Pasteur, outside the submitted work. MS, RDP, MG, LS, and MP are employees of GlaxoSmithKline. SRP, MM, and MER declare no competing interests.

Acknowledgments

The study was funded jointly by GlaxoSmithKline Vaccines and Public Health England. We thank all laboratory staff at Public Health England Meningococcal Reference Unit for their assistance with all work related to the Meningococcal Antigen Typing System and the enhanced surveillance of invasive meningococcal disease in the UK; and Kim Taylor, Tracey Smeulders, and Rehana Shivji for facilitating patient follow-up and data entry. For this study, we made use of the Neisseria Multi Locus Sequence Typing website (http://pubmlst.org/neisseria/) developed by Keith Jolley and sited at the University of Oxford; the development of this website has been funded by the Wellcome Trust and European Union. For this study, we also made use of the Meningitis Research Foundation's Meningococcus Genome Library (http://www.meningitis.org/research/genome) developed by Public Health England, the Wellcome Trust Sanger Institute, and the University of Oxford as a collaboration; that project is funded by the Meningitis Research Foundation.

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