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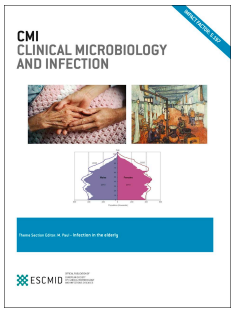

Impact of meningococcal ACWY conjugate vaccines on pharyngeal carriage in adolescents: evidence for herd protection from the UK MenACWY programme

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PII: S1198-743X(22)00368-8

DOI: https://doi.org/10.1016/j.cmi.2022.07.004

Reference: CMI 3011

To appear in: *Clinical Microbiology and Infection*

Received Date: 29 January 2022

Revised Date: 4 July 2022

Accepted Date: 6 July 2022

Please cite this article as: Carr JP, MacLennan JM, Plested E, Bratcher HB, Harrison OB, Aley PK, Bray JE, Camara S, Rodrigues CMC, Davis K, Bartolf A, Baxter D, Cameron JC, Cunningham R, Faust SN, Fidler K, Gowda R, Heath PT, Hughes S, Khajuria S, Orr D, Raman M, Smith A, Turner DP, Whittaker E, Williams CJ, Zipitis CS, Pollard AJ, Oliver J, Morales-Aza B, Lekshmi A, Clark SA, Borrow R, Christensen H, Trotter C, Finn A, Maiden MCJ, Snape MD, for theUKMenCar4 and 'Be on the TEAM' Study Collaborators, Impact of meningococcal ACWY conjugate vaccines on pharyngeal carriage in adolescents: evidence for herd protection from the UK MenACWY programme, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2022.07.004.

Impact of meningococcal ACWY conjugate vaccines on pharyngeal carriage in adolescents: evidence for herd protection from the UK MenACWY programme

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Abstract

Objectives Serogroup W and Y invasive meningococcal disease (IMD) increased globally from 2000 onwards. Responding to a rapid increase in serogroup W clonal complex 11 (W:cc11) IMD, the UK replaced an adolescent booster dose of meningococcal C conjugate vaccine with quadrivalent MenACWY conjugate vaccine in 2015. By 2018, vaccine coverage in the eligible school cohorts aged 14-19 years-old was 84%. We assessed the impact of the MenACWY vaccination programme on meningococcal carriage.

Methods An observational study of culture-defined oropharyngeal meningococcal carriage prevalence before and after the start of the MenACWY vaccination programme in UK school students, aged 15–19 years, using two cross-sectional studies: 2014–15 "UKMenCar4" and 2018 "Be on the TEAM" (ISRCTN75858406).

Results A total of 10625 participants pre-implementation and 13434 post-implementation were included. Carriage of genogroups C, W, and Y (combined) decreased from 2·03% to 0·71% (OR 0·34 [95% CI 0·27–0·44] p<0·001). Carriage of genogroup B meningococci did not change (1·26% vs 1·23% [95% CI 0.77–1.22] p=0·80) and genogroup C remained rare (n = 7/10625 vs 17/13488, p=0·135). The proportion of serogroup positive isolates, *i.e.,* those expressing capsule, decreased for genogroup W by 53.8% (95% CI -5.0%–79.8%, p=0·016) and for genogroup Y by 30·1% (95% CI 8·9%–46·3%, p=0·0025).

Conclusions The UK MenACWY vaccination programme reduced carriage acquisition of genogroup and serogroup Y and W meningococci and sustained low levels of genogroup C carriage. These data support the use of quadrivalent MenACWY conjugate vaccine for indirect (herd) protection.

Introduction

During the first two decades of the 21st century, serogroup W invasive meningococcal disease (IMD) increased globally. Previously confined to small local outbreaks, serogroup W expanded from 2% to 40% of IMD in the UK between 2008 and 2015 (Figure 1).[1] Serogroup Y IMD also increased, albeit with lower prevalence than serogroup W IMD and predominantly affecting the elderly.[2] These changes led to some countries introducing the quadrivalent protein-conjugate (MenACWY) vaccine.[1,2] The licenced MenACWY conjugate vaccines were anticipated, but not robustly demonstrated, to induce herd protection. Large-scale carriage studies accompanying the introduction of the monovalent Meningococcal C conjugate (MCC, 1999) and the serogroup A conjugate (MenAfriVac®, 2011) vaccines demonstrated strong herd protective effect by reducing carriage acquisition of the targeted serogroup.[3-5] However, in early studies MenACWY immunogenicity against serogroup C was reduced when compared with the monovalent MCC.[6] A recent systematic review concluded that there was a lack of evidence supporting herd protective effects from multivalent MenACWY vaccines.[7]

The absence of large-scale carriage studies represented an important evidence gap and this uncertainty affected the immunisation programmes introduced. For example, Chile introduced an infant-only programme providing direct protection to the age group at highest risk of IMD,[8] whereas the United Kingdom targeted adolescents as the age-group with both a 'peak' in IMD incidence and the highest asymptomatic pharyngeal carriage rates. This strategy aimed to interrupt transmission and provide protection to unvaccinated age groups.[9]

The UK MenACWY programme was implemented in 2015 using MenACWY-TT (Nimenrix®, Pfizer) and MenACWY-CRM_{197} (Menveo®, GSK) vaccines (figure 1) to replace

the MCC school booster given at 13–14 years of age.[10] In England, there was a phased roll-out over three years, with a school based catch-up programme and a General Practitioner-based programme up to 25 years of age. In Scotland, vaccination was delivered in schools within one-year. In Wales, the catch-up programme was delivered in school and primary care over two years. By mid-2018, MenACWY vaccine school-based coverage in England, Wales, and Scotland, was 84%, ranging from 71-86% in each year cohort between 14 to 19 years of age.[11,12] Vaccination coverage in the cohort aged 20 – 25 years was significantly lower; for example, in England it was 35% to 39%. The MenACWY vaccine was not introduced for any other age group. An infant-only '2 + 1' schedule of 4CMenB (Bexsero®, GSK) commenced in September 2015,[13] which was not anticipated to impact on meningococcal carriage.[14]

The UK Meningococcal Carriage (UKMenCar1-4) surveys demonstrated the impact of herd protection from the MCC vaccine, and highlighted behaviours that increase the risk of meningococcal carriage and transmission.[4,15,16] UKMenCar4 was conducted in 2014-2015 just prior to the introduction of the MenACWY vaccination programme. The subsequent 'Be on the TEAM (Teenagers Against Meningitis)' study (ISRCTN75858406) commenced in 2018 using compatible methods. We report the impact of the MenACWY campaign on meningococcal carriage in adolescents using these two studies.

Methods

Study Design and Sample Population

We compared two cross-sectional oropharyngeal carriage surveys of adolescents, taken before (UKMenCar4: September 2014 – March 2015)[15] and after ('Be on the TEAM', March – November 2018)[17] MenACWY vaccine introduction. Participants were aged 15–19 years

attending their penultimate year of school or college. Both studies were done by the same research network with participants recruited in schools across multiple sites in England, Wales, and Scotland. Characteristics of included schools reflected the diversity of educational settings across the community.[15] The 2018 cohort was eligible for MenACWY vaccination two to three years prior,[18] while those sampled in 2014–15 were eligible for the adolescent MCC vaccine. This study was approved by the NHS Research Ethics Committee (UKMenCar4 reference 14/SC/1163, Be on the TEAM reference 18/SC/0055). The study protocols have been previously published[17,19] and the 'Be on the TEAM' protocol is publicly available at www.beontheteam.uk.

Sampling Collection & Laboratory Methods

Methods were compatible between the two surveys. After standard informed consent, participants completed a meningococcal carriage risk factor questionnaire.[15,17] Oropharyngeal swab samples were taken using a standardised collection technique. Swab samples were either directly plated (in some sites in 2014/15) or placed in STGG (skim milk, tryptone, glucose, glycerol) broth and frozen at -80ºC within 4 hours of collection.[15] After rethawing, swab samples were incubated on GC-VCAT (vancomycin, colistin amphotericin B, trimethoprim; ThermoFisher Scientific, Basingstoke, UK) at 37ºC with 5% CO_2 for up to 48 hours. Putative *Neisseria* isolates (oxidase-positive gram-negative colonies) were serogrouped by an in-house dot-blot ELISA method to identify serogroups B, C, W, and Y (UK Health Security Agency Meningococcal Reference Unit).[17] Following short-read whole genome sequencing (llumina HiSeq or NovaSeq6000 platform, Wellcome Trust Oxford Genomics Centre), genomes were assembled, characterised, and uploaded on the https://pubMLST.org/neisseria database, as described in the study protocols.[15,17,19]

Statistical Methods

The survey sample sizes were pre-determined by a subset of the two cross-sectional studies: all Year 12 students (or S5 in Scotland) from the 2014–15 MenCar4 study (n=10625) and all Year 12 (S5) students recruited in 2018 at the time of a planned interim analysis of the 'Be on the TEAM' study (n=13341). In 2014–15, the carriage prevalence of genogroup W was 0·34%, genogroup Y 1·60%, and genogroup C 0·07%. The sample size was estimated to provide a detectable effect size of a 24% reduction in the carriage prevalence of genogroups C, W, and Y combined at 80% power and alpha of 0·05. The primary analysis used logistic regression to compare the difference in carriage prevalence between the pre- and post-implementation surveys, adjusting for study site. Several secondary analyses were done to assess the robustness of our findings including: (i) clustering at the school level; (ii) restricting analysis to sites that were included at both time points only; and (iii) multivariable logistic regression to adjust for risk factors for any meningococcal carriage. Risk-factors included on the questionnaire were chosen based on significance from prior carriage studies.[15] These included: age; gender; self-reported ethnicity; smoking and vaping status; household-smokers; current sore throat; current or recent use of antibiotics; attendances at clubs, pubs or parties in the last week; number of people kissed in the last week; relationship status and regular partner smoking status. Risk factors with p values of < 0·20 in the univariable models were included in the multivariable regression model and retained in the full model if the p < 0·05. Carriage prevalence was reported as odds ratios with 95% confidence intervals (Clopper-Pearson). Carriage prevalence reduction was derived from the odds ratio using the formula ((1 – OR) x 100). Missing data was not imputed and assumed to be missing at random. Statistical analyses were performed using Stata version 17.

Results

In total 24062 oropharyngeal swab samples were included: 10624 from the pre-implementation survey (2014–15) and 13438 from the post-implementation survey (2018). The cohorts were demographically similar, with minor reductions in carriage risk factors consistent with previously reported trends (Table 1).[15] In 2014-2015, 5·80% of participants were carriers of any meningococcus compared with 4·49% in 2018 (Table 2). There was a significant decrease in combined genogroup C, W, and Y meningococcal carriage from 2·03% to 0·71% (OR 0·34 [95% CI 0·27–0·44] p<0·001) (Table 2). Genogroup W carriage decreased from 0·34% to 0·09% (OR 0·27 [95% CI 0·14–0·51] p<0·001) and genogroup Y carriage decreased from 1·60% to 0·50% (OR 0·31 [95% CI 0·23–0·41] p<0·001). Genogroup C remained rare, with no evidence of a difference in carriage prevalence between the time points, 0·07% (n=7/10625) to 0·13% (n=17/13488) (OR 1·96 [95% CI 0·81–4·73] p=0·135). There was no evidence of a change in the carriage prevalence of genogroup B (1.26% vs 1.24%, OR 0·97 [95% CI 0·77–1·22] p=0·81), other genogroups (OR 1·01 [95% CI 0·87–1·39] p=0·45), or capsule null (*cnl*) meningococci (OR 0·90 [95% CI 0·72–1·12] p=0·36).

For the secondary analysis including meningococcal carriage risk factors, the final multivariable logistic regression model included smoking status, party/club/pub attendances, gender, recent antibiotic use, self-reported ethnicity, vaping, regular partner, partner smoking status. Whilst key carriage risk factors such as smoking decreased between 2014–15 and 2018, inclusion of carriage risk factors in the model did not substantially change the outcome measurements (supplemental figure 1). Outcome was also unaffected by adjustment of clustering in schools, or inclusion of only sites in both pre- and post-implementation surveys

(supplemental figure 1). Carriage showed between-site variation, as seen in previous studies (supplemental table 1).[15,16]

The odds ratio for serogroup W carriage in 2018 was 0·16 (95% CI 0·06–0·40, p<0·001) and 0·22 (95% CI 0·15–0·32, p < 0·001) for serogroup Y (Table 2). Capsule expression, defined by serogroup positive isolates, decreased as a proportion of all genogroup W isolates from 72·2% to 33·3% (relative difference in proportions 53.8% [95% CI -5·0%–79·8%] p=0·016) and for genogroup Y, from 69·4% to 48·5% (relative difference in proportions 30·1% [95% CI 8·9%–46·3%] p=0·0025) (figure 2). In 2014–15, one of seven genogroup C isolates expressed capsule compared with none of the 17 genogroup C meningococci in 2018. There was no significant change in the proportion of genogroup B that were expressing capsules (relative difference in proportions 16.6% [95% CI -4.8%– 33.5%] p=0.120).

The change in the carriage of the major ccs reflected the serogroup-specific vaccine effects (Figure 3): there were decreases in cc11 and cc22, associated with genogroups W, and cc-23, cc-167 and cc-174, associated with genogroup Y. However the proportion of clonal complexes associated with genogroups W, Y, and C remained similar (table 3). The carriage of W:cc-11 in 2014–15 was 0·22%, despite its high disease burden, in contrast to Y:cc23 (1·34%), which has a lower IMD incidence but was carried more commonly.

Discussion

Three years after the introduction of the UK MenACWY vaccination programme, cross-sectional oropharyngeal carriage surveys showed: (i) a sustained low carriage of genogroup C meningococci; (ii) a 73% reduction in carriage of genogroup W meningococci; and (iii) a 69% reduction of genogroup Y meningococci. There was no change in genogroup B meningococcal

158 carriage. Reductions of carriage were observed at both genogroup level, *i.e.*, those
159 meningococci with *cps* regions encoding these capsules, and to a greater extent the serogroup
160 level, *i.e.*, those meningococci expressing the capsule. These results were consistent with
161 studies of monovalent meningococcal conjugate polysaccharide vaccines, notably in the
162 UKMenCar1-3 and MenAfriCar Studies. [3,4] Am impact of MenACWY on carriage was aso
163 seen in observational studies conducted in Polish soldiers, and an individually randomised
164 controlled trial in UK university students.[5,20,21] In this RCT, MenACWY-$_{CRM}$ vaccinated
165 participants had relative genogroup B C, W and Y carriage reduction of 27·1% (95% CI 6·9 –
166 42·9%) at any timepoint between 2 – 12 months after vaccination compared with controls. In
167 this present population-level study, the magnitude of the reduction in carriage was greater, and
168 was commensurate with the impact of both the monovalent MCC and serogroup A vaccines.[3,4]
169 A 2020 systematic review reported an absence of evidence supporting carriage effects of
170 MenACWY conjugate vaccines.[7] However, this review included only the primary outcome at
171 1-month after vaccination for the UK student RCT, which did not differ between control and
172 vaccine groups.[22] The other negative studies reviewed were in university populations in the
173 USA and the UK. In the USA MenACWY studies, meningococcal Y and W carriage rates were
174 so low that any inference about the impact of vaccination on carriage could not be considered
175 definitive with respect to these serogroups.[23-25] By contrast, in the UK student populations
176 analysed, carriage prevalence of genogroup W increased during the surveillance period after
177 MenACWY vaccination. This was likely due to an inadequate time interval between
178 vaccination and the commencement of the university year, where the maximum frequency of
179 transmission occurs.[5,26] An observational carriage study in Norwegian teenagers did not
180 demonstrate any impact of individual MenACWY vaccination status on serogroup-specific
181 carriage, although vaccination coverage in the cohort was less than 30%.[27]

The reduction in IMD incidence in the UK in both immunised and unimmunised cohorts following the introduction of the MenACWY programme[28] was consistent with the maintenance of direct and herd protection against serogroup C IMD, and the introduction of direct and herd protection against serogroup W and serogroup Y IMD. The number of lives under five-years of age saved by herd protection against serogroup W in England and Wales was estimated to be between 114 to 899 over four years.[28] Infant 4CMenB immunisation may have provided some direct protection against serogroup W:cc11 IMD.[28] Serogroup W IMD, which had been rising rapidly until 2015, plateaued and fell (figure 1). Whilst there is natural fluctuations in meningococcal carriage, in our study the interval between pre and post-intervention was short and the carriage impact was shown to be specific to the dominant vaccine capsular targets genogroups Y and W and was demonstrated across multiple clonal complexes associated with these genogroups. In contrast, genogroup B carriage was unchanged.

The strengths of the present study included large scale, consistent methodology, and the use of age and school year-level matched cohorts. The culture-defined endpoint of meningococcal carriage permitted high-resolution phenotypic and genotypic isolate characterisation, strengthening the evidence that the trends in UK IMD are due to a capsule-specific vaccine impact, rather than secular changes in meningococcal epidemiology. The existence of a national immunisation program precluded a cluster-randomised approach and the study remains observational. The timing of sampling of each survey differed for pragmatic reasons, with more sampling during winter months in the pre-implementation study. Meningococcal carriage, unlike IMD, has not been shown to exhibit seasonal variation and even if present, it would not disproportionally affect specific carriage of genogroup W and Y. The absence of

sampling from Northern Ireland was unlikely to have biased the results, given the similarity between the populations in these countries. Whilst vaccine roll-out was more rapid in Scotland than in England or Wales, Scotland was only in the pre-implementation survey, hence these differences in roll-out did not impact on the post-implementation carriage results. Finally, while small changes in risk factors for meningococcal carriage reach statistical significance, this is a factor of the study sample size, and the magnitude of differences is clinically small. Inclusion of risks fact in the secondary analysis did not change the vaccine impact. It is unlikely that these differences between groups would effect carriage of genogroups W and Y and not B.

We have demonstrated that the UK meningococcal ACWY conjugate vaccine programme maintained low carriage of genogroup C meningococci, and reduced carriage of serogroup and genogroup W and Y meningococci. This herd protection effect reduced IMD in all age groups, affirming the UK Joint Committee on Vaccines and Immunisation strategy of deploying meningococcal conjugate vaccines in age groups with high meningococcal transmission.[13] As with monovalent meningococcal serogroup C and A conjugate vaccines, public health interventions that leverage herd protection from MenACWY vaccines will result in greater reductions in IMD across all age-cohorts, more rapid impact, and favourable cost-effectiveness. By contrast, there remains no evidence of indirect protection from outer membrane protein vaccines designed for group B meningococci, thus carriage studies are essential to complement IMD surveillance and inform meningococcal vaccine policy.

Collaborators

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Transparency Declaration

JPC GlaxoSmithKline grant to institution, Monash Health, for meningococcal vaccine study, no individual payment or inducements. JEB receives financial support from a Wellcome Trust Biomedical Resources Grant (218205/Z/19/Z). SNF NIHR payments only to institution; Pfizer, Sanofi, GlaxoSmithKline, J&J, Merck, AstraZeneca, Valneva, Moderna – Clinical trial investigator on behalf of institution, no personal payments of any kind; Novavax, Moderna, Pfizer – fees for symposium session participation paid to INSTITUTION, not a personal fee; AstraZeneca, MedImmune, Sanofi, Pfizer, Seqirus, Sandoz, Merck, J&J – fees for advisory board participation paid to INSTITUTION, not a personal fee; Chair of UK NICE Sepsis (2014-16) and Lyme Disease (2016-18) Guidelines (adults and children) expenses paid in line with NICE financial regulations. MR payments to the R&D University Hospitals Plymouth NHS Trust. CW Oxford Vaccine Group and Health & Care Research Wales, funding to institution for study conduct as part of the research grant. AL, SAC, and RB: Be on the Team & UKMenCar4 Projects funding for carriage study, work performed as part of UK Health Security Agency; GSK, Pfizer, Sanofi Pasteur - perform contract research on behalf of UK

Health Security Agency. AJP institutional support from NIHR Oxford Biomedical Research Centre; Funding from the Meningitis Research Foundation to Institution, University of Oxford; Patent for a meningococcal B vaccine (all rights waived); Chair, Joint Committee of Vaccines and Immunisation reporting to the Department of Health and Social Care; Member, WHO SAGE; Institution, Oxford University, has entered into a partnership with AstraZeneca for development of a Covid-19 vaccine. HC Department of Health and Social Care, 2017, grant, "Evaluating the effect of immunisation with group B meningococcal vaccines on meningococcal carriage", co-applicant; NIHR HPRU in Behavioural Science and Evaluation, (i) 2021, grant "Hold the door open: involving older adults from diverse backgrounds in health research", co-principal investigator (ii) 2019, grant, co-investigator; NIHR Career Development Fellowship, 2018, grant, principal investigator, Career Development Fellowship; UK Research and Innovation, 2020, grant, "Joint UNIversities Pandemic and Epidemiological Research, co-investigator; Elizabeth Blackwell Institute University of Bristol, 2020, grant "Social contacts and mixing patterns under COVID19 social distancing measures, principal investigator; European Centre for Disease Control, 2020, grant "Estimating national prevalence of chronic hepatitis B Virus Infection in EU/EEA countries, co-investigator; GSK, 2019, grant "Investigating the potential impact of Bexsero vaccination against Neisseria gonorrhoeae, co-principal investigator; Department of Health and Social Care, 2017, grant "Evaluation of patient access to medical test results services in General Practice", principal investigator; Meningitis Research Foundation, Member of the Scientific Advisory Panel. AF UK government Department of Health via Univeristy of Oxford, funding to employers to support conduct of study; Sanofi, funding to me eployers for my time and for costs of conducting a clinical trial of a Meningococcal vaccine in young children; Member, Joint Committee on Vaccination and Immunisation (Independent UK government advisory

committee); Chair, WHO Euro Technical Advisory Group of Experts on Immunisation. MCJM Wellcome Trust & NIHR, grant funding to the University of Oxford; Pfizer, preparation and remote delivery of a presentation in conjunction with the ESPID 2021 Meningococcal Vaccines Symposium project. The sole purpose of such project was to provide up-to-date information related to the current epidemiology of Meningococcal disease worldwide; consultancy via Oxford University Innovation. MDS NIHR payments to institution; Pfizer donation of vaccine; GlaxoSmithKline, grants to University of Oxford for RSV and meningococcal vaccines; Pfizer, grants and vaccines supplied to University of Oxford for research on pneumococcal and meningococcal disease; Janssen, grants to University of Oxford for RSV vaccine study; MCM Vaccines, grants to University of Oxford for clinical research on multivalent infant vaccine; MedImmune, grants to Oxford University Hospitals NHS trust for study of RSV monoclonal antibodies; AstraZeneca, grants paid to University of Oxford for COVID-19 vaccine studies; Novavax, vaccine supply for COMCOV2 and COMCOV3 COVID-19 vaccine studies; Meningitis Research Foundation, member of medical advisory board. JM EP, HBB, PTH, OBH, PA, SC, CMCR, KD, AB, DB, JCC, RC, KF, RG, SH, SK, DO, AS, DT, EW, CZ, BMA, and CT declare no conflicts.

Funding

This study was funded by the Wellcome Trust and the National Institute for Health Research (NIHR) Policy Research Programme (PR-ST-0915-10015 and PR-R18-0117-21001). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. MenB-fHbp for the ‘Be on the TEAM’ study donated by Pfizer. The study funders had no role in the study design or in the collection, analysis or interpretation of data, manuscript preparation, or the decision to submit for publication.

Acknowledgements

NIHR Oxford Biomedical Research Centre. Children's Research team, Nottingham University Hospitals NHS Trust. Women's & Children's Research team, University Hospitals Bristol and Weston NHS Foundation Trust. The 'Be on the TEAM' Scientific Advisory Board; Chair - Prof Sir Brian Greenwood; Deputy Chair - James Stuart, Simon Nadel, Helen Marshall, Helen Bedford, Nick Andrews. James Adamson, Public Health Wales. Andrew Walker & Lloyd Walsh, UKHSA Meningococcal Reference Unit. Melanie Carr; Yama Farooq, Simon Kerridge, Annabel Giddings and Hannah Robinson, Oxford Vaccine Group. Helen Watson, Heather Murdoch, Laura Walsh & Laura Macdonald, Public Health Scotland. Karen Duffy, NHS Greater Glasgow and Clyde Clinical Research Unit. NHS Greater Glasgow and Clyde Public Health Department. Thomas Bower, Stephen Saich, Alasdair Munro, Robert Dorey, Louise Haskell, Jane Martin, Helen Gale, Anne Magee & Anna Hardy, NIHR Southampton Clinical Research Facility. Margaret Varga, University of Oxford. Clarendon Scholarship Fund, University of Oxford (JPC). We thank the study team from all sites for recruitment, data and sampling, the UKHSA Meningococcal Reference Unit (Manchester UK) and the Maiden Lab (University of Oxford UK) for microbiological and genomics expertise. We acknowledge the Meningitis Research Foundation and Meningitis Now for their input into the Be on the TEAM study. The schools, staff and participating students for their enthusiasm and support of this research.

Contribution

'UKMenCar4' conceptual design by JMM, CT, AJP, RB, SNL, and MCJM. 'Be on the TEAM' study conceptual design and management committee: MDS, AF, MCJM, CT, HC, RB, SG,

JMM, PH, SF, KD, SC, PA, EP, JPC. Study sites – investigators, local management, recruitment, microbiology processing and data handling MDS, JC, SC, EP, AL, RB, AF, JO, SNF, PH, DPJT, EW, MR, SH, AS, JPC, MW, SR, CC, ASm, DO, DB, CW, RG, CSZ, PTH, AB, AV, MDS, RS, RC, KP, DS, NP, JMM, HBB, KF and OBH. Bioinformatics and genomic analysis by HBB, JMM, CMCR, OH, KAJ, JEB. Data reviewed by JC HC, CT and MCJM with primary statistical analysis by JPC, JMM, HC, CT, MCJM, MDS. Preparation of original draft manuscript, figures and literature search by JPC, with conceptual design, original input and initial revisions by MCJM, MDS, JMM, CT, HC. All listed authors have reviewed, revised and approved the manuscript.

Access to Data

UKMenCar4: All genomes and metadata for the UKMenCar4 study are available open access through PubMLST, with short-read sequence data available from the European Nucleotide Archive (reference PRJEB14319) with European Nucleotide Archive accession run identifiers accessible on Pub MLST. Corresponding data from the Be on the TEAM study will be added after publication of the final results.

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Table 1 Participant demographics & risk factors for meningococcal carriage

	Pre-Implementation Survey 2014-15	Post Implementation Survey 2018	Difference between groups % (95% CI) unless stated
Sample Size	10624	13438	
Sampling Period	Sept 2014 – March 2015	2018 Mar-May; Sept-Nov	
Vaccination Schedule	MCC boost (aged 13-14yo)	MCC boost (aged 13-14yo) MenACWY (from Sept 2015)	
MenACWY Vaccination Coverage (England; age-year specific cohort)	n/a	80.95%	
Age in years	15 16 17 18 19	15 16 17 18 19	
% of cohort	3.4 52.6 40.3 3.26 0.45	0.01 65.3 31.9 2.6 0.01	
mean	16.45 years	16.38 yrs	- 0.07 years (-0.06 to - 0.09 yrs) $p < 0.001$
Gender M:F:non-binary	41% : 59% : n/a	38% : 61% : 0.5 %	Binary gender M:F -2.5% (-1.4% to - 3.9%) $p < 0.001$
Self-identified Ethnicity			$p < 0.001$
White	80.3%	79.2%	
Asian / Asian British	10.0%	9.6%	
Black/African/Caribbean/Black British	4.7%	4.7%	
Mixed/multiple ethnic	3.2%	4.2%	
Other ethnic group	1.6%	1.9%	
Not reported	0.1%	0.4%	
Current sore throat	23.5%	19.5%	- 4.0% (-3.0% to -5.0%) $p < 0.001$
Antibiotics currently or in the last month	13.5 %	10.1 %	-3.4% (-2.6% to - 4.2%) $p < 0.001$
Cigarette smoking (any amount) in last week	9.2%	6.8%	-2.4% (- 1.7% to -3.1%) $p < 0.001$
Vape / E-cigarette use (any amount)	3.5%	6.2%	2.7% (2.2% to 3.2%) $p < 0.001$
Household smokers (inside or outside)	27.1%	20.0%	-7.1% (- 6.0% to - 8.2%) $p < 0.001$
Any attendance at club/pub/parties in the last week	33.2%	29.4%	-3.8% (-2.6% to - 5.0%) $p < 0.001$
Intimate kissing in last week	33.5%	28.5%	-5.0% (-3.8% to - 6.2%) $p < 0.001$
Regular Partner / Girlfriend / Boyfriend	26.6%	24.9%	-1.7% (- 0.6% to – 2.8%) $p < 0.001$

Survey completion rate: 2014-15 99.7%; 2018 99.6%

Table 2 Meningococcal carriage prevalence and odds ratio of carriage after the introduction of the MenACWY adolescent vaccination programme in August 2015

	Meningococcal Carriage					
	2014/15 (n=10624)		2018 (n= 13434)			
	n	%	n	%	Odds Ratio* [95% CIs]	*p*
any *N. meningitidis*	616	5.80%	603	4.49%	0.76 [0.68 - 0.86]	<0.001
genogroup C, W, Y**	216	2.03%	96	0.71%	0.35 [0.27 - 0.44]	<0.001
serogroup C, W, Y	*147*	*1.38%*	*37*	*0.28%*	*0.20* [*0.14* - *0.29*]	*<0.001*
genogroup C	7	0.07%	17	0.13%	1.96 [0.81 - 4.73]	0.135
serogroup C	*1*	*0.01%*	*0*	*0.00%*	. . - .	.
genogroup W	36	0.34%	12	0.09%	0.27 [0.14 - 0.51]	<0.001
serogroup W	*26*	*0.24%*	*5*	*0.04%*	*0.16* [*0.06* - *0.40]*	*<0.001*
genogroup Y	170	1.60%	68	0.50%	0.31 [0.23 - 0.41]	<0.001
serogroup Y	*118*	*1.11%*	*33*	*0.25%*	*0.22* [*0.15* - *0.32*]	*<0.001*
genogroup B	134	1.26%	165	1.23%	0.97 [0.77 - 1.22]	0.801
serogroup B	*73*	*0.69%*	*75*	*0.56%*	*0.81* [*0.59* - *1.12]*	*0.205*
other genogroups***	122	1.15%	168	1.25%	1.01 [0.87 - 1.39]	0.446
capsule null (cnl)	152	1.43%	174	1.29%	0.90 [0.72 - 1.12]	0.355

*adjusted odds ratio with study site as a co-variable

** genogroup C, W, Y, includes 3 genogroup ambiguous W/Y isolates of which two were serogroup W, other single genogroup classifications do not included these isolates

***other includes genogroups E, H, K, L, X or Z or incomplete capsular group after manual capsular assignment

Table 3 Carriage of clonal complexes listed by of genogroups C, Y, and W before and after implementation of the MenACWY immunisation programme

		2014/15		2018	
Genogroup	Clonal Complex	*n*	% of genogroup	*n*	% of genogroup
C					
	ST-269	3	50.0%	9	52.9%
	ST-41/44	0		4	23.5%
	ST-11	0		1	5.9%
	ST-1157	0		1	5.9%
	ST-162	1	16.7%	0	
	ST-231	1	16.7%	0	
	ST-35	0		1	5.9%
	not assigned	1	16.7%	1	5.9%
	Total	**6**		**17**	
W					
	ST-11	24	66.7%	7	58.3%
	ST-22	12	33.3%	3	25.0%
	ST-865	0		1	8.3%
	not assigned	0		1	8.3%
	Total	**36**		**12**	
Y					
	ST-23	143	84.1%	63	94.0%
	ST-167	14	8.2%	0	
	ST-174	4	2.4%	0	
	ST-1157	0		3	4.5%
	ST-103	1	0.6%	0	
	ST-41/44	0	0.0%	1	1.5%
	not defined	1	0.6%	0	
	not assigned	7	4.1%	1	1.5%
	Total	**170**		**68**	

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Gender M:F:non-binary	41% : 59% : n/a	38% : 61% : 0.5 %	Binary gender M:F -2.5% (-1.4% to - 3.9%) $p < 0.001$
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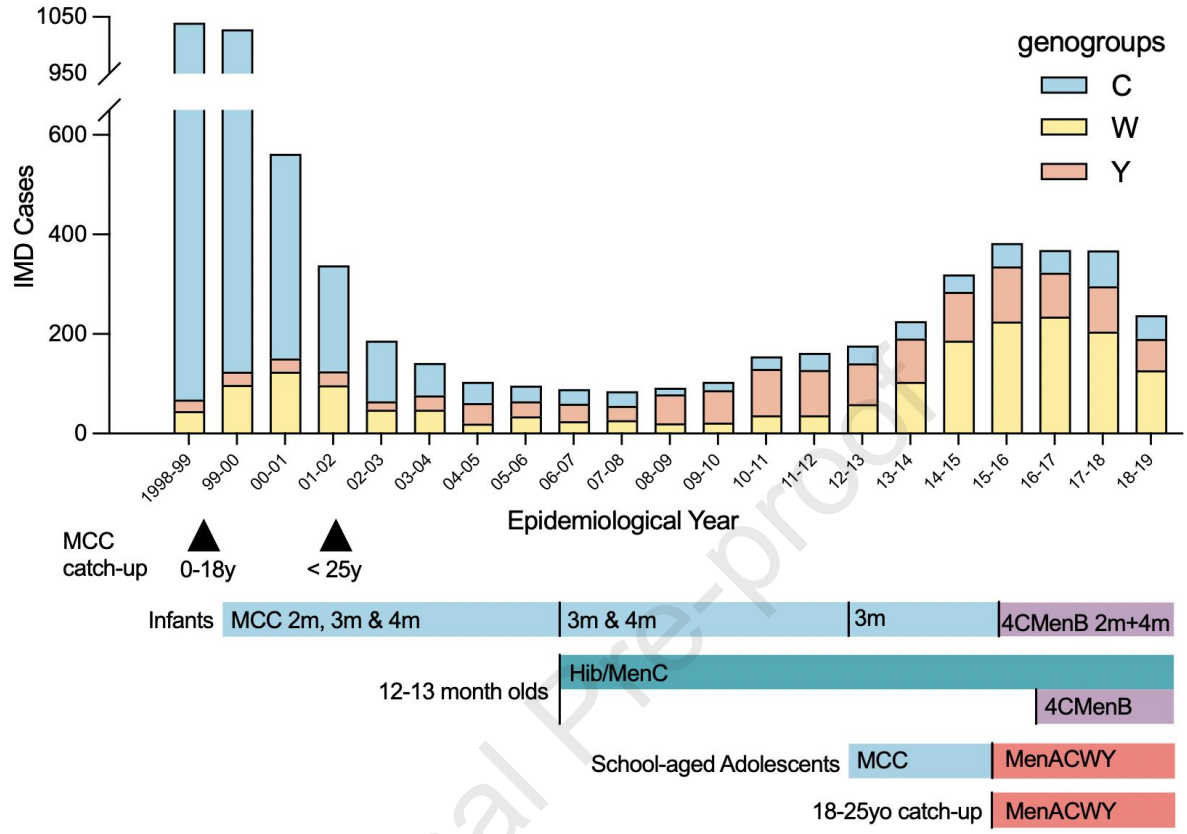
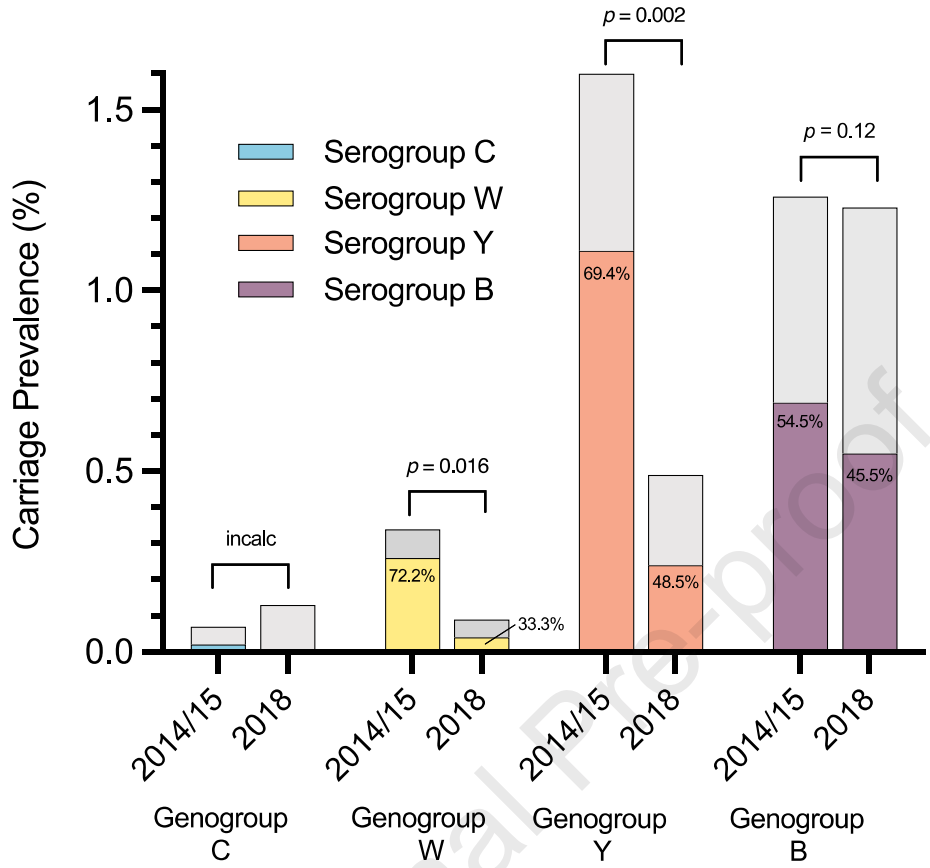
Figure 1 Meningococcal Vaccine Schedule & Invasive Meningococcal Disease due to genogroups C, W or Y in England & Wales 1998-2018 by epidemiological year



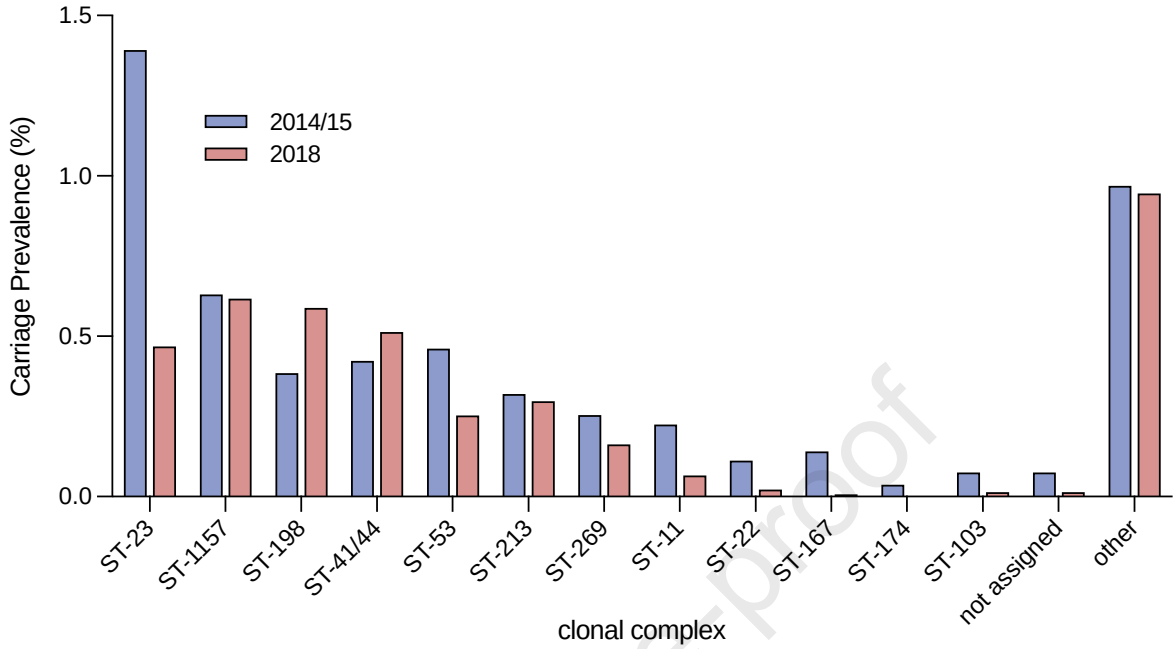
IMD - Invasive Meningococcal Disease (culture and/or PCR-confirmed, data collected by Public Health England Meningococcal Reference Unit); m - months; MCC - Meningococcal C conjugate vaccine.; MenACWY - quadrivalent meningococcal serogroup ACWY polysaccharide conjugate vaccine; Hib-MenC - Haemophilus influenzae type B & meningococcal C conjugate vaccine; 4CMenB - sub-capsular protein surrogate meningococcal B vaccine (Bexsero, GSK) introduced Sep 2015. MCC single-dose catch-up given in 1999 aged 0-18 years old and an expanded in 2002 to < 25 years old who were unvaccinated. Infant MCC ceased in July 2016. Adolescent vaccines given in schools at 13-14 years old. MenACWY commenced in schools in 2015, with a staggered catch-up over 1 year (Scotland) and 3 years (England, Wales) to vaccinate all those aged 14-18. A community / General Practitioner catch-up programme was implemented for school leavers up to 25 years old, but uptake was low.

Figure 2 Carriage of meningococcal genogroups and serogroups before and after the introduction of the MenACWY adolescent vaccination programme in August 2015



Coloured shading – serogroup positive isolates. Grey shading serogroup negative isolates. Percentages in each column denote the proportion of genogroups that were serogroup positive with p-values shown for the difference in proportions of serogroup positive isolates at each time point. incalc - incalculable

Figure 3 Carriage prevalence by clonal complex in adolescents aged 15 – 19yrs before and after the introduction of the adolescent MenACWY vaccination programme in August 2015



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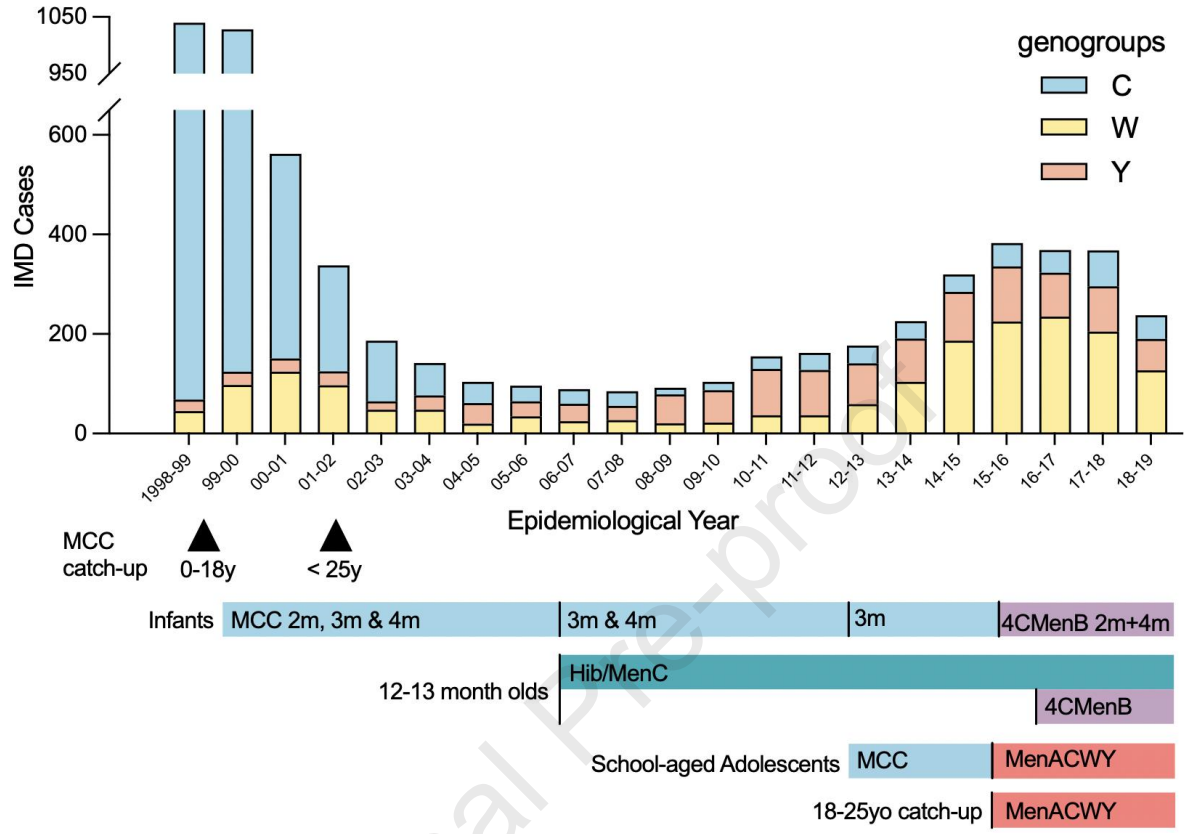

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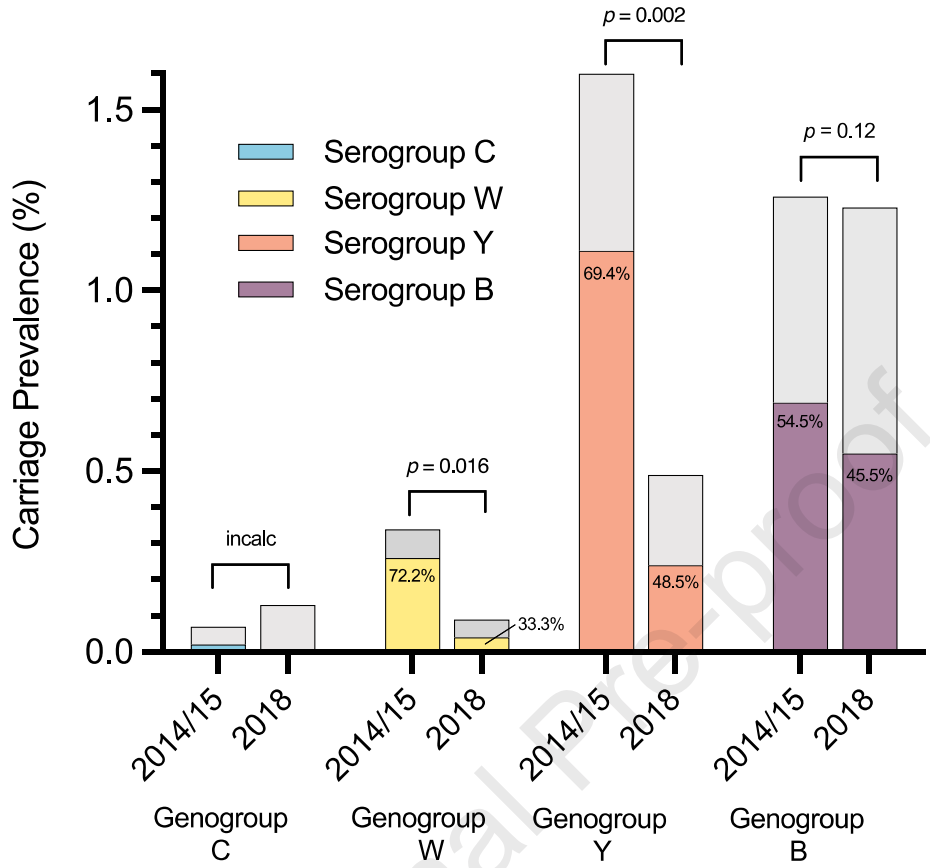
Figure 2 Carriage of meningococcal genogroups and serogroups before and after the introduction of the MenACWY adolescent vaccination programme in August 2015



Coloured shading – serogroup positive isolates. Grey shading serogroup negative isolates. Percentages in each column denote the proportion of genogroups that were serogroup positive with p-values shown for the difference in proportions of serogroup positive isolates at each time point. incalc - incalculable

Figure 3 Carriage prevalence by clonal complex in adolescents aged 15 – 19yrs before and after the introduction of the adolescent MenACWY vaccination programme in August 2015