## Early evidence of effectiveness against group B meningococcal disease and population impact of a reduced infant schedule with 4CMenB vaccine in England: a national observational cohort study

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**Conflicts of interest**

SNL and RB perform contract research for vaccine manufacturers (including GSK, Pfizer, Sanofi Pasteur) on behalf of St. George’s University of London and Public Health England, respectively, but receive no personal remuneration. The Immunisation, Hepatitis and Blood Safety Department has provided GSK with post-marketing surveillance reports on meningococcal, haemophilus influenzae and pneumococcal infections which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. NJA declares no conflicts of interest.

**Role of the funding source:** The authors had sole responsibility for the study design,data collection, data analysis, data interpretation, and writing of the report. The authors are all employed by Public Health England, the study funder, which is a public body—an executive agency of the Department of Health. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

**Background**

In September 2015, the United Kingdom became the first country to introduce the multicomponent group B meningococcal (MenB) vaccine (4CMenB, Bexsero®) into a publicly-funded national immunisation programme. A reduced two-dose priming schedule was offered to infants at 2 and 4 months, alongside an opportunistic catch-up for 3- and 4-month-olds. 4CMenB was predicted to protect against 73-88% of MenB strains. This study aimed to assess the effectiveness and impact of 4CMenB in vaccine-eligible infants in England.

**Methods**

Public Health England conducts enhanced surveillance through a combination of clinical, public health and laboratory reporting. Laboratory-confirmed cases are followed-up with PHE local Health Protection Teams, general practitioners and hospital clinicians to collect demographic data, vaccination history, clinical presentation and outcome. For cases diagnosed between 01 September 2015 and 30 June 2016, vaccine effectiveness (VE) was assessed using the screening method. Impact was assessed by comparing MenB cases in vaccine-eligible children to equivalent cohorts in the previous four years and to cases in vaccine-ineligible children.

**Findings**

4CMenB coverage in infants eligible for routine vaccination was high, achieving 95.5% for one dose and 88.6% for two doses by six months of age. Two-dose VE was 82.9% (95% CI, 24.1%-95.2%) against all MenB cases, equivalent to a VE of 94.2% against the highest predicted MenB strain coverage of 88%. Compared to the pre-vaccine period there was an IRR 50% reduction in MenB cases in the vaccine-eligible cohort (37 vs. average 74 cases; IRR, 0.50; 95% CI, 0.36-0.71; P<0.001)irrespective of the infants’ vaccination status or predicted MenB strain coverage. Similar reductions (≈40%) were observed even after adjusting for disease trends in vaccine-eligible and vaccine-ineligible children.

**Interpretation**

The two-dose 4CMenB priming schedule was highly effective in preventing MenB disease in infants. Cases in vaccine-eligible infants halved in the first ten months of the programme.

**Funding:** PHE

**Introduction**

In September 2015, the United Kingdom (UK) became the first country to introduce the multi-component, protein-based meningococcal vaccine (4CMenB; Bexsero®, GSK) into a national, publicly-funded infant immunisation programme.1 The vaccine was offered to all infants born since 01 July 2015 at 2, 4 and 12 months alongside their routine immunisations. Catch-up vaccination was also opportunistically offered to 3- and 4- month -olds attending their routine immunisation visits, who were eligible for a 3-4-12 and 4-12 month schedule, respectively.

Prior to 4CMenB introduction, the UK immunisation schedule has included the group C meningococcal (MenC) conjugate vaccine since 1999.2 As an emergency response to a national outbreak of group W meningococcal (MenW) disease, 13-18 year-olds and new university entrants are being offered the quadrivalent MenACWY conjugate vaccine since August 2015.3 These conjugate vaccines target the polysaccharide capsule of meningococci and do not offer cross-protection against other meningococcal capsular groups, such as group B (MenB), which remains responsible for most invasive meningococcal disease (IMD) cases in the UK, especially in young children.1

It has not been possible to develop effective conjugate vaccines against MenB because its polysaccharide capsule is structurally homologous to glycoproteins in foetal neural cell adhesion molecules, making them poorly immunogenic self-antigens.4 4CMenB is a novel vaccine composed of three recombinant proteins – factor H-binding protein [fHbp], Neisserial heparin-binding antigen [NHBA], and Neisserial adhesin A [NadA] – and the outer membrane vesicles (OMV) from the New Zealand outbreak strain (NZ98/254), which incorporates the immunodominant Porin A (PorA) P1.4 protein.5 The vaccine was licensed in Europe in January 2013 on the basis of immunogenicity and safety studies alone. 4CMenB induces high titres of bactericidal antibodies against the target vaccine antigens but, as yet, protection against invasive disease has not been demonstrated.

Other countries have not yet introduced 4CMenB into their national programmes because of the high vaccine price and low MenB incidence, leading to unfavourable health economic assessments, as well as uncertainties around strain coverage, vaccine safety and effectiveness.6-9 In March 2014, the UK Joint Committee on Vaccination and Immunisation (JCVI) concluded that 4CMenB could be cost-effective,10 with a reduced two-dose infant priming schedule,11 and after a year of negotiation with the vaccine manufacturer, an infant immunisation programme with 4CMenB was announced in March 2015,12 and the first infants were vaccinated on 01 September 2015. Here, we report the first estimates of effectiveness and the early impact of the programme in England.

**Methods**

***Case ascertainment and follow-up***

Public Health England (PHE) conducts enhanced national surveillance of IMD in England through a combination of clinical, public health and laboratory reporting. The PHE Meningococcal Reference Unit (MRU) provides a national service for confirming, grouping and characterising invasive meningococcal isolates.13 The MRU also provides free PCR-testing of clinical samples from patients with suspected IMD across England. Consequently, case ascertainment has remained consistently high.14 Laboratory-confirmed cases are followed-up with PHE local Health Protection Teams (HPTs), general practitioners and hospital clinicians to collect demographic data, vaccination history, clinical presentation and outcome of infection.

***Vaccine effectiveness (VE)***

Vaccine effectiveness was estimated for vaccine-eligible infants (born on or after 01 May 2015) with laboratory-confirmed invasive MenB disease diagnosed between 01 September 2015 and 30 June 2016. If 4CMenB was protecting infants from MenB disease, then the proportion of vaccinated MenB cases would be expected to be lower than the proportion vaccinated in the comparator groups. The comparator group included all children in England who were eligible for the vaccine. This is known as the screening method.15The VE is calculated as 1-(PCV/(1-PCV))/(PPV/(1-PPV)), where PCV is the proportion of vaccinated MenB cases and PPV is the vaccine coverage in age-matched infants across England (the comparator cohort).

As part of the national immunisation programme, infants were invited to their GPs for routine vaccinations at 8, 12 and 16 weeks. Vaccine coverage increased exponentially during the week after infants became eligible (Figure 1). In order to avoid this period with rapidly increasing coverage and to allow two weeks for development of an adequate immune response after vaccination, VE for at least one dose was estimated using cases aged ≥77 days (11 weeks of age) and for two doses using cases aged ≥133 days (17 weeks of age). Doses were discounted if IMD was diagnosed within 14 days of vaccination; therefore, an infant who developed MenB disease five days after the second dose of 4CMenB would be considered to have received a single dose of vaccine in the analysis.

Population vaccine coverage in England was obtained from ImmForm, an online system used by PHE to collect vaccine coverage for some national immunisation programmes. Monthly data are automatically uploaded by general practice (GP) information technology (IT) suppliers for each cohort reaching 26 weeks of age in the survey month. The denominator is the number of infants who, in the survey month, reach 26 weeks of age, and numerators are the number of infants in the denominator who received the first and the second dose of 4CMenB between 8-26 weeks of age.16 To control for any confounding by age and time, for each MenB case vaccine coverage was estimated for all infants in England who were born in the same month and at an age in days exactly 14 days younger than the age of the case on the specimen date (the comparator group). Since Immform does not collect individual dates of births or dates of vaccination, vaccine coverage for comparators was estimated by adjusting the six-month ImmForm coverage using actual dates of birth and dates of vaccination for ≈36,000 infants receiving their first dose and ≈26,000 receiving their second dose, as supplied by five Child Health Information Systems (CHIS) in different geographical areas across England (**Supplement 1).**

To estimate two-dose VE, those who developed IMD after only one dose were excluded. Two dose vaccine coverage was also adjusted to exclude those partially vaccinated (adjusted coverage = 2 dose coverage/(1- coverage of exactly 1 dose)).

***Vaccine Impact***

Vaccine impact was estimated for vaccine-eligible MenB cases (born on or after 01 May 2015, aged 10 weeks and diagnosed between 01 September 2015 and 30 June 2016) as follows (**Table 1**):

1. Incidence rate ratios (IRRs) were estimated for vaccine-eligible cases compared to cases diagnosed in the equivalent time period during the four years before vaccine introduction. Within the vaccine-eligible cohort, IRRs were also specifically calculated for: the catch-up cohort (infants born in May or June 2015) the routine cohort eligible for the first dose (born on or after 01 July 2015 with MenB disease at 10-17 weeks of age) and for both doses (born on or after 01 July 2015 with MenB disease at ≥18 weeks of age).
2. To take into account possible changes over time in the absence of MenB vaccination, these IRRs were then adjusted using changes in incidence in all children aged <5 years with MenB disease who were not in the vaccine-eligible or equivalent cohorts for the same time periods as (i) above. The ratios of the IRRs between the vaccine-eligible and ineligible cohorts were calculated using a Poisson regression model, which allowed calculation of 95% confidence intervals (CI) for the IRR ratio.
3. An interrupted time-series model was then fitted to four years of pre-vaccine data for each of the vaccine-eligible cohorts and to five years (four pre-vaccine years plus the current year) for the vaccine-ineligible cohorts. Poisson regression was used to estimate an overall trend, with a factor for each of the individual cohorts. Vaccine impact was then estimated by comparing the 2015/16 data in vaccine-eligible cohorts with that predicted by the overall trend analysis.

For the Poisson regression models, to assess model fit, the residual deviance and degrees of freedom were assessed by a chi-squared test. The main difference between the models in (ii) and (iii) above is that the latter assumes a common underlying trend whereas the former assumes that the year-to-year changes were similar within age cohorts but not necessarily as a trend.

**Ethical approval**

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases (http://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made). This includes PHE’s responsibility to monitor the safety and effectiveness of vaccines, and as such, individual patient consent is not required.

**Role of funder**

The authors had sole responsibility for the study design, data collection, data analysis, data interpretation, and writing of the report. The authors are all employed by Public Health England, the study funder, which is a public body and an executive agency of the Department of Health. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

**Results**

*Vaccine coverage*

In England, 4CMenB introduction rapidly achieved high vaccine coverage; in the routine cohort, vaccine coverage by birth month ranged between 94.8-95.5% for one dose and 84.8-88.6% for two doses by six months of age **(Figure 1; SUPPLEMENT TABLE S2)**. Coverage for the catch-up cohort born in June 2015 was 88.8% and 75.2% for one and two doses, respectively, and, for the May 2015 cohort, was 76.6% for the single dose that they were eligible for.

*Vaccine-eligible children*

Between 01 September 2015 and 30 June 2016 (10 months), there were 55 laboratory-confirmed IMD cases in vaccine-eligible infants (born on or after 01 May 2015 aged ≥10 weeks at diagnosis), including 37 (67%) MenB, 11 (20%) MenW, five (9%) MenY and two (4%) ungrouped due to low colony forming units in the submitted clinical samples. Most infants with MenB disease (27/37, 73%) were confirmed by PCR only, six by culture only (16%) and four (11%) by both methods. Fifteen (41%) had meningitis, 13 (35%) septicaemia and seven (19%) had both meningitis and septicaemia, while two (5%) had other clinical presentations. One child died aged 15 weeks and had received one 4CMenB dose seven weeks before disease onset.

Of the 37 MenB cases, four were among infants born in May 2015 (two unvaccinated, one after a single dose and one who inadvertently received two doses) and five in June (two unvaccinated and three after one dose). The remaining 28 MenB cases were eligible for routine vaccination; two were unvaccinated, 17 had received one dose and nine had received two 4CMenB doses. There was no evidence of temporal or geographical clustering of cases in vaccinated infants, who developed disease across the age range (25-44 weeks at diagnosis). None of the unvaccinated children had contraindications to receiving 4CMenB.

Three vaccinated infants, all in the routine cohort, developed disease within 14 days of their first (at 2 and 4 days) or second (at 10 days) dose of 4CMenB and were classified as being unvaccinated and having had a single dose, respectively. Of the eight infants classified as unvaccinated, four were not eligible for two doses of 4CMenB; two because they were born in May and two because they were diagnosed before they were due their second dose.

For the two-dose VE analysis, eight of the nine MenB cases in the routine cohort (the infant who developed disease within 10 days of the second dose was excluded), one infant born in late May who had inadvertently received two 4CMenB doses and four unvaccinated infants were included. The May-born infant was matched with vaccine coverage for infants born in June. The average matched vaccine coverage for the two-dose cohort across England was 92.9% and estimated VE was 82.9% (95% CI, 24.1% to 95.2%).

The one-dose VE analysis included 20 infants who had received a single dose (including one who developed disease 10 days after the second dose) and eight unvaccinated infants (including the two infants who developed disease 2 and 4 days after the first dose). The average matched coverage for the one-dose cohort across England was 76.2% and estimated VE was 22.0% (95% CI, -105% to 67.1%). For at least one 4CMenB dose, the average matched coverage was 91.0% and estimated VE was 64.0% (95% CI, 8.9% to 84.0%).

**Vaccine impact**

MenB cases in the different vaccine-eligible and comparator cohorts are summarised in **Table 1**. Compared to their peers matched by age and time period for the four pre-vaccine years, there was a 50% reduction (IRR, 0.50; 95% CI, 0.36-0.71; P<0.001) in MenB cases in the vaccine-eligible cohort, compared to a non-significant 14% reduction in the unvaccinated cohort (**Table 1**). Adjusting for this 14% disease reduction in the comparator cohort gave an estimated 42% reduction (relative IRR, 0.58, 95% CI, 0.40-0.85; P=0.005) in the vaccine-eligible cohort. The greatest impact was observed in the catch-up cohort (58% relative reduction), with a 38% relative reduction in the routine cohort old enough to have received two 4CMenB doses and 24% in infants in the routine cohort who developed disease during a period when they could have been protected by their first dose (MenB disease at 10-17 weeks). Analysis using the pre-vaccine trends model estimated a slightly lower vaccine impact, with a 36% overall reduction in cases **(Table 1).** There was no evidence of lack of fit based on residual deviance and degrees of freedom; p=0.28 for non-trend model and p=0.18 for trend model, thus providing assurance that trends in MenB disease were consistent in the different age cohorts in recent years.

**Discussion**

A reduced two-dose infant priming schedule of the novel, multicomponent, protein-based 4CMenB vaccine was 82.9% effective in preventing MenB disease in infants aged <12 months. During the first ten months of the programme, MenB cases halved in vaccine-eligible infants, providing further evidence of vaccine efficacy. This measure of impact does not take into account the vaccination status of the infants or whether the infecting MenB strain was vaccine-preventable. The findings are robust, with similar results even after adjusting for disease trends in the four years prior to vaccine introduction and in non-vaccine eligible children.

4CMenB was licensed on immunogenicity and safety data only without an efficacy trial and with the knowledge that not all MenB strains would be covered by the vaccine. 4CMenB targets proteins which, unlike the polysaccharide capsule, may be present or absent on the surface of meningococci. Each protein also varies in the degree of surface expression and the extent to which vaccine-induced antibodies recognise and bind these proteins. To predict MenB strain coverage by 4CMenB-induced antibodies, the Meningococcal Antigen Typing System (MATS) – a qualitative and quantitative ELISA for fHbp, NHBA and NadA expression - was developed.17 A strain is considered vaccine-preventable if MATS-positive for any of the three antigens or if the strain harbours PorA P1.4.

The MATS assay provides a conservative estimate of strain coverage and, in 2007/08, predicted that 73% of MenB isolates from IMD patients in England and Wales would be killed by pooled post-vaccination sera.18 The serum bactericidal antibody assay with human complement (hSBA) using pooled post-immunisation infant sera, however, predicted 88% coverage against a diverse panel of MenB strains from patients in England and Wales.19 With differing strain coverage estimates, uncertainties surrounding the vaccine’s effectiveness grew when, in a recent United States (US) university outbreak, sera from a third of 499 participants who received two doses of 4CMenB were unable to kill the outbreak strain in hSBA20 despite this strain being predicted by MATS to express two vaccine antigens (fHbp and NHBA). In infants, the protection offered by 4CMenB is expected to be lower because, compared to adolescents, they are less likely to mount cross-protective antibodies against strains with unmatched vaccine antigens.21

The final economic analysis used to support 4CMenB introduction in the UK suggested that a reduced 2-dose infant priming schedule, 88% predicted strain coverage and 95% efficacy had the potential to prevent a quarter (26%) of all meningococcal cases in the first five years of the programme and could be cost-effective.11 Our results are remarkably aligned with the model. If, as predicted by hSBA, 88% of MenB strains were covered by 4CMenB,19 then the VE against vaccine-preventable strains would be 94.2%. Although the confidence intervals for the two-dose VE are wide because of small numbers of cases, the estimates are statistically significant and findings are supported by the impact analysis demonstrating a significant reduction in MenB cases in vaccine-eligible infants. The lower and non-significant VE after one dose was expected because a single dose of OMV vaccine is poorly immunogenic in infants.22,23 These results, however, will require confirmation through longer-term surveillance. An important observation, even with the small number of cases, was the large proportion of cases (50%, 10/20) in the routine cohort who developed MenB disease after 16 weeks, the age at which they would have become eligible for their second 4CMenB, and thus might potentially have been prevented through timely vaccination.

The analysis that adjusted for historic trends suggested a lower impact in vaccine-eligible cohorts because this was less affected by the increase in MenB cases in the non-eligible cohorts during 2015/16. In both analyses, a higher impact was observed in the catch-up cohort, despite the opportunistic schedule of one or two doses and lower vaccine coverage than the routine cohort. This cohort completed their recommended vaccinations prior to the meningococcal season when they would have reached the peak age for disease. In contrast, vaccine impact in the routine cohort would have been diluted by accumulation of younger infants who were being immunised throughout the surveillance period. Follow-up of cases through the next meningococcal season should provide more robust VE and impact estimates for the routinely vaccinated cohorts.

**Strengths and Limitations**

In England, enhanced national surveillance has been in place for more than two decades;2 the provision of a national reference laboratory, use of multiple data sources and the excellent support provided by public health and NHS staff ensures consistently high case ascertainment, allowing reliable assessment of trends over time. We also achieved very high vaccine coverage in the routine and the catch-up cohorts as soon as the programme was implemented,24,25 despite initial concerns about high rates of post-vaccination fever and the national recommendations to routinely offer prophylactic paracetamol with 4CMenB.1 Consequently, we have been able to measure vaccine effectiveness and impact one year after the programme was introduced. Given the uncertainties associated with this novel vaccine and the recent publication reporting sero-protection in only two-thirds of immunised adolescents,20 we hope our early results will reassure clinicians, immunisers and policy makers that the vaccine is effective in infants, even with a reduced two-dose priming schedule. A significant limitation that is unlikely to be overcome is that 70% of MenB cases in vaccine-eligible infants were confirmed by PCR only and the MATS assay requires culture isolates to assess strain coverage. MATS is also only currently validated for MenB and, therefore, assessment of 4CMenB impact on the other meningococcal capsular groups will be challenging.

Our initial results show a significant reduction in MenB cases among vaccine-eligible infants within ten months of introduction of 4CMenB into the UK. Although the vaccine is licensed using a three-dose priming schedule in infancy, short-term vaccine effectiveness against MenB disease was high after two doses. On-going national surveillance will continue to monitor the longer-term impact of the programme on disease burden alongside vaccine safety and disease severity in young children.

***Panel:* Research in context**

Systematic review

We searched PubMed with the terms “4CMenB”, “Bexsero”, “meningococcal serogroup B vaccine” and any combination of “vaccine effectiveness” or “impact”. Publication dates and languages were not limited. Our search results identified no data on the vaccine effectiveness or 4CMenB impact against invasive MenB disease.

4CMenB was licensed on immunogenicity and safety studies only. The vaccine induces bactericidal antibodies that target the respective antigens, which may be absent or variably expressed on the surface of different meningococci. Since 4CMenB contains multiple recombinant proteins in addition to the outer membrane vesicle (OMV), antibody concentrations or bactericidal activity against individual vaccine antigens do not reliably predict *in vitro* killing of meningococci. For this reason, the Meningococcal Antigen Typing System (MATS) was developed to screen large numbers of meningococcal strains and predict whether they would be killed by 4CMenB-induced antibodies. MATS is a qualitative and quantitative ELISA that quantifies expression of the vaccine-associated antigens (fHbp, NHBA and NadA) in combination with the ability of 4CMenB-induced antibodies to recognise these proteins on the surface of individual meningococcal isolates. For an isolate to be MATS-positive, antibodies against at least one vaccine antigen must exceed the positive bactericidal threshold, which is assigned on the basis of killing using post-vaccination sera from infants after their 12-month booster, or the isolate must possess homologous PorA (P1.4). In England and Wales, MATS predicted that 73% (95% CI, 57-87%) of invasive MenB disease isolates in 2007/08 would be killed by vaccine-induced antibodies in infants. In a SBA assay with human complement (hSBA), however, pooled sera from infants and adolescents immunised with 4CMenB killed 88% of a representative sample of MenB disease isolates from England and Wales during 2007/08. In the cost-effectiveness analysis, therefore, 4CMenB was predicted to protect against 73-88% of circulating MenB strains in the UK.

Compared to adolescents and adults, infants have lower cross-protection against MenB strains that are predicted by MATS to be non-vaccine preventable. Data from a recent MenB outbreak in the US showed that sera from a third of 499 participants who received two doses of 4CMenB ten weeks apart were unable to kill the outbreak strain using the hSBA assay, even though the outbreak strain was predicted by MATS to express two vaccine antigens.

Added value of this study

The UK is the first country to introduce 4CMenB into a publicly-funded, national immunisation programme. In England, vaccine coverage was high in all eligible cohorts, reaching 95.5% for one dose and 87.9% for two doses by six months of age in the first monthly cohort that was offered the recommended two-dose infant priming schedule two months apart (i.e. those born in July 2015). During the first 10 months of the programme, we estimated 2-dose vaccine effectiveness to be 82.9% against all MenB disease in infants under 12 months of age, which was equivalent to a VE of 94.2% against vaccine-preventable MenB strains, assuming the highest predicted strain coverage of 88%. By the end of June 2016, MenB cases in vaccine-eligible infants had nearly halved, irrespective of the infants’ vaccination status or expected vaccine strain coverage.

Implication of the evidence

We have provided the first evidence of protection against group B meningococcal disease conferred by the novel, multi-component 4CMenB vaccine in infants.

**Contributions**:

SRP, KB, HC and SR were responsible for the epidemiological surveillance data; KB, CW and JMW collected and contributed vaccine coverage data. SRP and NJA performed the data analysis and prepared the figures. SRP and SNL performed the literature search and wrote the first draft. SRP, NJA, MER, RB and SNL contributed to the data interpretation. All authors commented on the drafts of the paper and agreed with the final draft of the manuscript.

**Table 1: Numbers of laboratory confirmed MenB cases for five comparable annual time periods in England in cohorts eligible and non-eligible for 4CMenB vaccination and estimates of vaccine impact from different comparison models**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Comparison to the September to June period of  the four pre-vaccine years (2011/12-2014/15) | | | Trend Model | |
| Cohorts | Cases  (Sept 2015-June 2016) | Cases in equivalent pre-vaccine cohorts.  Mean count per year | IRR (95% CI), p-value | Impact estimate as relative IRR (95% CI), p-value | Cases in equivalent cohorts as predicted by the trend model | Impact estimate as trend model IRR (95% CI), p-value \* |
| Catch-up  (Born 1st May -30th June 2015) | 9 | 24.75 | 0.36 (0.18-0.72), 0.004 | 0.42 (0.21-0.85), 0.016 | 19.4 | 0.46 (0.23-0.93), 0.029 |
| Routine  ( Born on or after 1st July 2015 aged ≥18 weeks) | 18 | 33.75 | 0.53 (0.33-0.87), 0.012 | 0.62 (0.37-1.04), 0.07 | 26.4 | 0.68 (0.41-1.13), 0.134 |
| Routine  (Born on or after 1st July 2015 aged 10-17 weeks) | 10 | 15.25 | 0.66 (0.34-1.28), 0.216 | 0.76 (0.38-1.52), 0.439 | 11.9 | 0.84 (0.43-1.65), 0.606 |
| All combined | 37 | 73.75 | 0.50 (0.36-0.71), <0.001 | 0.58 (0.40-0.85), 0.005 | 57.8 | 0.64 (0.45-0.92), 0.015 |
| Comparator  (aged < 5 years with MenB disease and excluding vaccine-eligible and equivalent pre-vaccine cohorts) | 173 | 201 | 0.86 (0.73-1.01), 0.073 |  |  |  |

\*Based on a common trend fitted to all data including comparator cohorts

**Figure 1: Population coverage estimates for 4CMenB in England by age in days and month of birth for (a) dose 1 and (b) dose 2. Infants born in May 2015 were only eligible for a single dose of vaccine at 4 months of age.**

**a**

**b**

**Figure 2: Cases numbers for vaccine-eligible and comparator cohorts with MenB disease in England, with Poisson 95% confidence intervals and fitted trend. The vaccine-eligible cohort included infants born on or after 01 May 2015, aged ≥10 weeks and diagnosed between 01 September 2015 and 30 June 2016. The equivalent cohorts fulfilled the same criteria as the vaccine-eligible cohorts for each of the previous four pre-vaccine years. The comparator cohorts included all children aged <5 years with MenB disease excluding the vaccine-eligible and equivalent cohorts**

SUPPLEMENT 1

**4CMenB VACCINE COVERAGE ESTIMATES BY AGE IN DAYS FOR INFANTS IN ENGLAND USING MULTIPLE ELECTRONIC DATABASES**

Methods for MenB vaccine coverage estimates

In order to rapidly assess vaccine coverage of this newly implemented immunisation programme, PHE has put in place a temporary sentinel surveillance system. [1] This uses general practice (GP) level MenB vaccine coverage data automatically uploaded via participating GP IT suppliers to the ImmForm website on a monthly basis. ImmForm is the system used by PHE to record vaccine coverage data for some immunisation programmes and to provide vaccine ordering facilities for the NHS. These data are then validated and analysed by PHE to check data completeness, identify and query any anomalous results and describe epidemiological trends. Monthly MenB vaccine coverage data are collected for each cohort reaching six months of age in the survey month where the denominator is the number of infants in a GP practice who, in the survey month, reach 26 weeks of age, and numerators are the number of infants in the denominator who received (a) 1st dose and (b) 2nd dose of Bexsero® (4CMenB) from eight weeks of age up to 26 weeks of age, including vaccinations given by other healthcare providers. GP data are aggregated by NHS England organisations (Clinical Commissioning Groups (CCGs), Area Teams (ATs) and NHS England Local Teams (LTs). Vaccine coverage at six months was available for cohorts born from May 2015 to December 2015. For cases born after December 2015, coverage was assumed to be the same as December 2015.

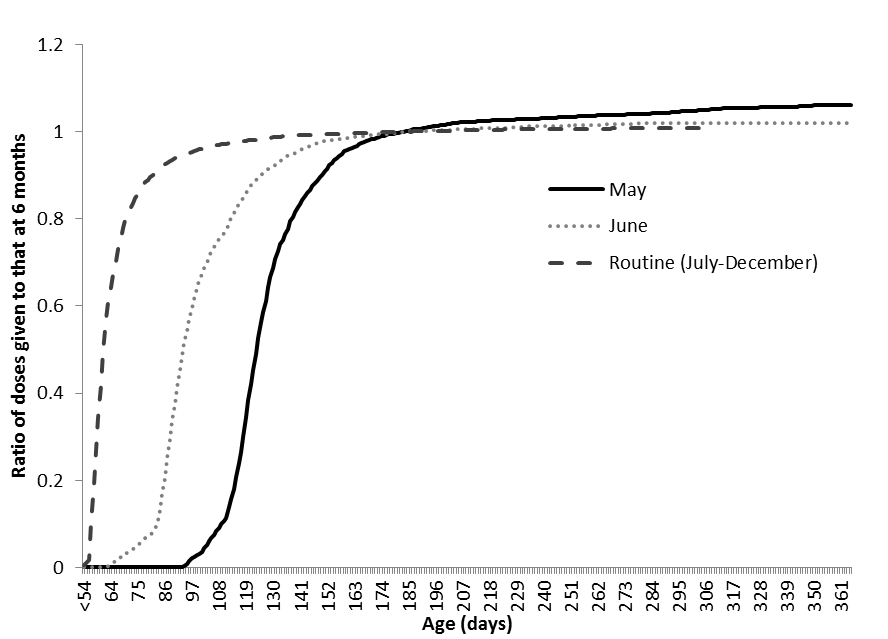
The local Child Health Information System (CHIS) is a patient administration system that provides a clinical record for individual children, including the precise dates of their vaccinations. Data from five CHIS from around England were used just to estimate the population age (in days) at first and second dose of 4CMenB. For four CHISs (Durham, Cornwall, Kent and Manchester) data were available on vaccinations given until the end of June 2016 and for Leicester up to 16 May 2016. The Leicester data were, therefore, only used for timing of the first dose because of limited follow-up period. The median ages as well as the 10th, 25th, 75th and 90th centiles were compared between the systems before combining them (Table S1). Overall, age at vaccination was available for ≈36,000 first doses and ≈26,000 second doses. Once combined, the proportion of all doses given by age 6 months that had been given by ages below 6 months was calculated (by monthly birth cohort) as well as the ratio of cumulative doses given at ages over 6 months compared to the number given by 6 months. For cohorts from born since 01 July 2015 (the routine cohorts), the age distributions were very similar; thus, an average based on the July-December birth cohorts was used for the ratios (Figure S1); these cohorts will have had ≥6 months follow-up e.g. a child born in June 2015 and diagnosed with IMD at 150 days would match to the population coverage at age 136 days. These ratios were then used to adjust the national ImmForm coverage data (Table S2, Figure 1).

**Table S1: CHIS distribution of median ages at the time first and second dose of 4CMenB**

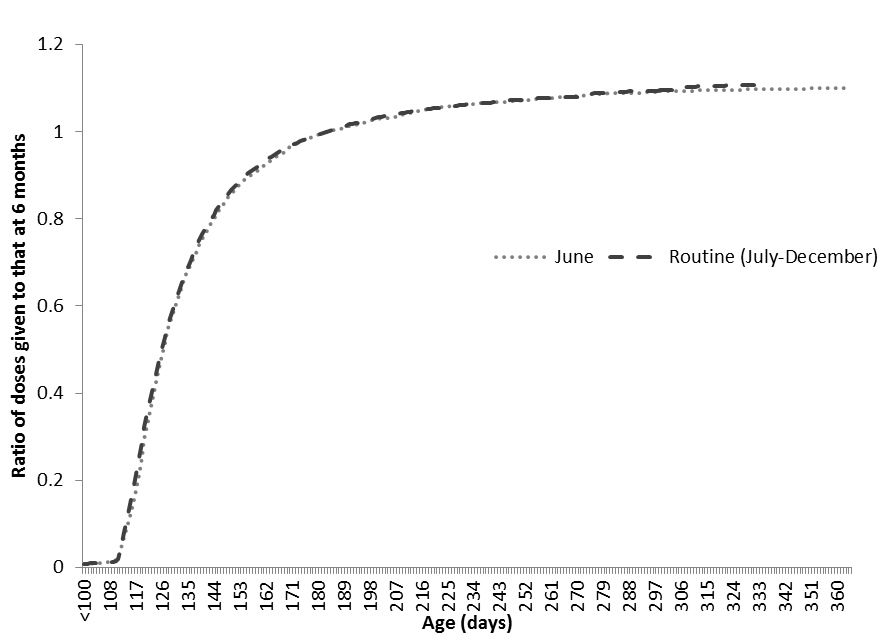
|  |  |  |
| --- | --- | --- |
| Area | Dose 1: 10-25-50-75-90 centiles | Dose 2: 10-25-50-75-90 centiles |
| Durham | 57-59-62-74-112 | 114-117-123-135-154 |
| Cornwall | 57-59-63-76-113 | 114-118-126-139-160 |
| Kent | 57-59-63-76-113 | 114-117-125-137-161 |
| Manchester | 57-59-64-80-118 | 115-122-135-155-183 |
| Leicester | 57-59-64-88-123 | 120-123-132-147-171 |

**Figure S1: Ratio of doses given by age relative to 6 months for A) dose 1 and B) dose 2.**

1. **First dose**

****

**B) Second dose**

****

**Table S2: Monthly ImmForm MenB coverage data for infants evaluated at 6 months**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort** | **Born May 2015** | **Born June 2015** | **Born July 2015** | **Born Aug 2015** | **Born Sep 2015** | **Born Oct 2015** | **Born Nov 2015\*** | **Born Dec 2015\*** |
| **Denominator1** | **45,132** | **48,361** | **54,882** | **50,361** | **56,096** | **52,985** | **53,563** | **49,322** |
| **Number vaccinated with dose 1** | **34,581** | **42,956** | **51,576** | **47,731** | **53,410** | **50,606** | **51,017** | **47,111** |
| **Dose 1 coverage** | **76.6%** | **88.8%** | **94.0%** | **94.8%** | **95.2%** | **95.5%** | **95.2%** | **95.5%** |
| **Number vaccinated with dose 2** | **n/a** | **36,373** | **46,519** | **43,370** | **48,733** | **46,594** | **47,323** | **43,704** |
| **Dose 2 coverage** | **n/a\*\*** | **75.2%** | **84.8%** | **86.1%** | **86.9%** | **87.9%** | **88.4%** | **88.6%** |

\*coverage estimates provided for analysis prior to finalised data being published on 23/09/2016

\*\* n/a: not applicable

1monthly denominators represents between 90-95% of all GP-registered infants in England

Further information:

[1] Provisional vaccine coverage estimates for the new meningococcal B (MenB) immunisation programme for England. Public Health England, 2016. (Accessed 15/08/2016, 2016, at <https://www.gov.uk/government/publications/meningococcal-b-immunisation-programme-vaccine-coverage-estimates.>)

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