Outcomes of meningococcal serogroup B disease in children after implementation of routine infant 4CMenB vaccination in England: an active, prospective, national surveillance study

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Summary

Background In 2015, the UK included 4CMenB, a multi-component, recombinant protein-based vaccine against meningococcal serogroup B (MenB) disease, in the national infant immunisation programme. We aimed to assess the effect of 4CMenB vaccination on the severity of MenB disease presentation and outcomes.

Methods In this active, prospective, national surveillance study, we used data from the UK Health Security Agency national surveillance of meningococcal disease. We included data from follow-up of children younger than 5 years with laboratory-confirmed MenB disease who were eligible for 4CMenB vaccination with general practice 3–6 months after disease onset. All invasive MenB isolates were tested using the Meningococcal Antigen Typing System to determine whether the isolate was potentially preventable by 4CMenB. Admission to intensive care, death, and, when possible, reported sequelae in survivors were reviewed alongside vaccine status. For the epidemiological analysis, we compared laboratory-confirmed MenB disease cases before 4CMenB implementation (Sept 1, 2010, to March 31, 2015) with those after implementation (Sept 1, 2015, to March 31, 2020). For clinical follow-up and outcomes, we included all children younger than 5 years with laboratory-confirmed MenB disease between Sept 1, 2015, and March 31, 2021.

Findings Between Sept 1, 2015, and March 31, 2021, there were 371 cases of MenB disease in children younger than 5 years, including 256 (69%) in those younger than 1 year and 128 (35%) in those younger than 3 months. After the introduction of 4CMenB, the peak age of patients with MenB disease shifted from 5–6 months to 1–3 months. Overall, 108 (29%) of 371 children were too young for vaccination, unvaccinated, or developed MenB disease within 14 days of the first dose. Of 110 meningococcal strains characterised, 11 (92%) of 12 were potentially preventable by 4CMenB in unvaccinated children compared with 53 (66%) of 80 in partly vaccinated and 11 (69%) of 16 in fully vaccinated children. 78 (21%) of 371 children required intensive care, and the case fatality ratio was 5% (17 of 371), with 11 of 17 deaths occurring before 1 year of age, including seven in infants who were too young (<8 weeks) for vaccination. Of 354 survivors, 57 (16%) had 74 sequelae reported; 45 (61%) of 74 were neurological, 17 (23%) were physical, two (3%) were behavioural or psychological, and ten (14%) were other complications. Prevalence of sequelae was similar in unvaccinated (15 [15%] of 98) and vaccinated (42 [16%] 256) children, as were composite outcomes of death or sequelae, and intensive care or death or sequelae.

Interpretation Cases of MenB disease in vaccine-eligible children declined after 4CMenB implementation, but morbidity in vaccinated and unvaccinated children remained unchanged, highlighting the importance of vaccination to prevent MenB disease. The lower peak age of infants with MenB disease after 4CMenB implementation, with a higher case fatality ratio in young infants, highlights the importance of timely vaccination.

Funding UK Health Security Agency.

Introduction

Invasive meningococcal disease is associated with substantial morbidity and mortality worldwide.[1] The disease typically begins suddenly with non-specific early symptoms but can progress rapidly, with most deaths occurring within 24 h of symptom onset, despite the best available medical care.[2,3] 12 different meningococcal serogroups are recognised based on their unique polysaccharide capsule, and serogroup B (MenB) is responsible for most cases of invasive meningococcal disease in Europe and elsewhere,[1] with the highest incidence in children younger than 5 years.[4,5]

In September, 2015, the UK became the first country to implement a broad-spectrum, recombinant protein-based meningococcal B vaccine (4CMenB, Bexsero, GSK Biologicals, Sovicille-Siena, Italy) programme into its national infant immunisation programme. Infants received a 2+1 schedule at 8 weeks, 16 weeks, and 1 year of age, alongside a limited catch-up programme for infants born during May–June, 2015, who received

Research in context

Evidence before this study

We searched PubMed on Feb 21, 2022, with the terms "meningococcal B vaccine" or "4CMenB" AND "meningococcal disease" or "meningococcal infection" AND "sequelae" or "complication" or "outcome" in children younger than 20 years, with no time restrictions and including all articles in English. Most studies on invasive meningococcal serogroup B (MenB) disease in children were published before 4CMenB introduction or focused on disease epidemiology before and after introduction of 4CMenB. One UK pre-vaccine study suggested that MenB strains that are targeted by 4CMenB might cause more severe disease in children than strains that are not. A study in Portugal reported fewer complications in a small number of 4CMenB-immunised children who developed meningococcal disease due to any serogroup than in unvaccinated children.

Added value of this study

Enhanced national surveillance linked with detailed strain characterisation during the first 5 years after 4CMenB implementation into the national infant immunisation programme allowed detailed assessment of disease severity and outcomes in a national cohort of children younger than 5 years with confirmed MenB disease in England. 4CMenB was associated with large and significant declines in the incidence of MenB disease in vaccine-eligible children, but we found no differences in the risk of intensive care admission, sequelae, or death associated with MenB disease in vaccinated compared with unvaccinated children. After 4CMenB implementation, the peak age at which MenB disease occurs fell from 5–6 months to 1–3 months, thus affecting unvaccinated infants, and case fatality rates were highest in younger infants.

Implications of all the available evidence

The similar morbidity in vaccinated and unvaccinated children highlights the crucial role of vaccination for preventing meningococcal disease and, consequently, its complications. The shift towards a younger peak age at which MenB disease occurs after 4CMenB implementation and the higher case fatality rates in younger infants emphasise the importance of timely vaccination. Timely vaccination and an earlier first 4CMenB dose at, for example, 6 weeks of age, with a shorter interval between the first two 4CMenB doses could potentially prevent additional cases in young infants.

4CMenB at their 12-week, 16-week, or both 12-week and 16-week routine immunisation visits. 4CMenB contains four meningococcal antigens: factor H-binding protein (fHbp), *Neisseria* adhesin A (NadA), neisserial heparin-binding antigen (NHBA), and porin A (Por A) and was estimated to protect against 73–88% of invasive MenB infections before routine immunisation in England.[6,7] 4CMenB uptake in infants has remained high in England, with 92·1% of eligible infants receiving their first two doses by 12 months of age and 89·0% receiving their 1-year booster by 24 months of age during 2020–21.[5]

The UK Health Security Agency (UKHSA; formerly Public Health England) has conducted surveillance of invasive meningococcal disease for more than two decades after the introduction of MenC polysaccharide-conjugate vaccines in 1999. In 2015, surveillance was enhanced to monitor the impact of 4CMenB.[8] Within 12 months of the programme, vaccine effectiveness was estimated to be 82·9% (95% CI 24·1–95·2) against all MenB cases after two doses, equivalent to a vaccine effectiveness of 94·2% assuming the highest predicted MenB strain coverage by 4CMenB of 88%.[7] During the first 3 years of the programme, there were 169 MenB cases in vaccine-eligible children, and an estimated 277 (95% CI 236–323) cases were prevented.[9]

In England, invasive MenB disease case fatality remains low (<5%),[10–12] but survivors might be left with long-term complications, including hearing loss, blindness, seizures, and motor deficits, after meningitis as well as digit and limb amputations and extensive skin scarring after septicaemia.[13] Follow-up of children with confirmed MenB disease before 4CMenB implementation in England found that up to a third of survivors had at least one long-term complication and 10% had major deficits.[14]

The effect of 4CMenB on disease outcomes in children is not known. We aimed to describe the epidemiology of MenB disease since 4CMenB implementation and the risk of severe disease, sequelae, and death in children younger than 5 years with laboratory-confirmed MenB disease during the first 5·5 years of the programme in England.

Methods

Study design and data sources

In this active, prospective, national surveillance study, laboratory-confirmed invasive MenB disease cases were identified through national enhanced surveillance of invasive meningococcal disease undertaken by the UKHSA, as described previously, between September, 2015, and March, 2021.[8] Hospital laboratories routinely submit invasive meningococcal isolates to the UKHSA meningococcal reference unit for confirmation of disease, phenotyping and, since July, 2010, whole-genome sequencing. All invasive MenB isolates were tested using the Meningococcal Antigen Typing System (MATS) to determine whether the isolate was potentially preventable by 4CMenB. The meningococcal reference unit additionally provides a free national meningococcal PCR testing service for all patients with suspected invasive meningococcal disease in England. MATS testing can only be performed on meningococcal isolates, and therefore it is not possible to ascertain whether

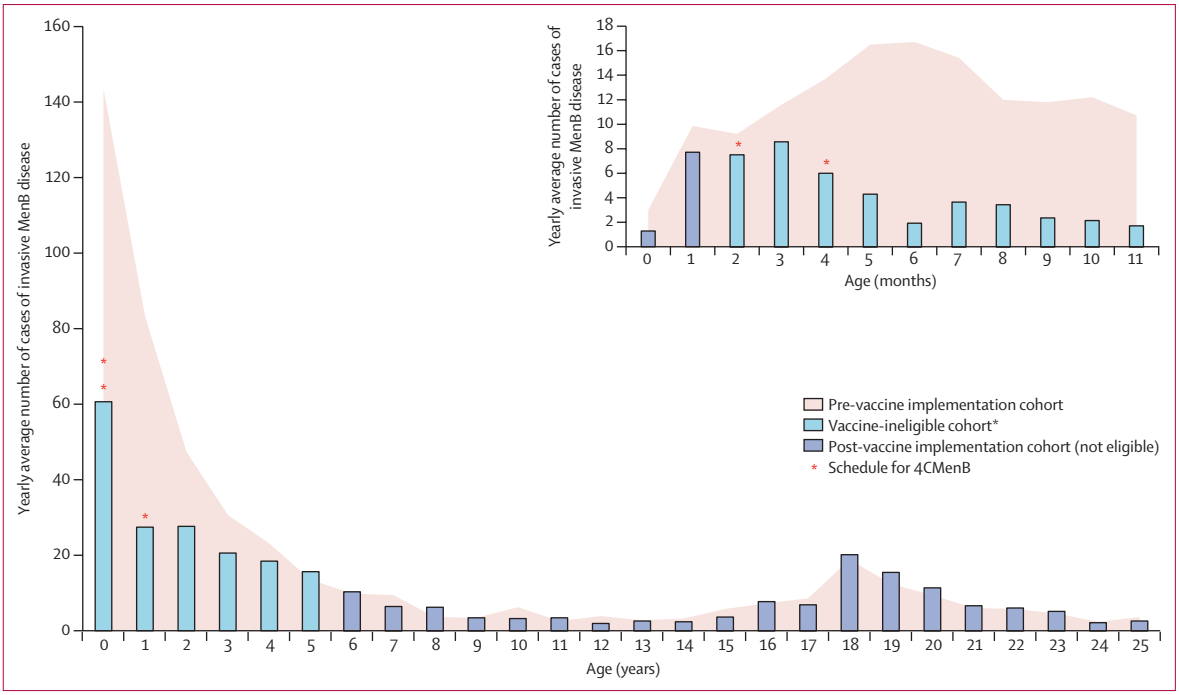

Figure: **Yearly average of invasive MenB disease cases in England, pre-vaccine implementation (Sept 1, 2010, to March 31, 2015) and post-vaccine implementation (Sept 1, 2015, to March 31, 2020)**
MenB=meningococcal serogroup B. *Ineligible because of age younger than 8 weeks or because they were born before May 1, 2015.

PCR-confirmed cases are potentially preventable by vaccination, unless the strain is identified by PCR as PorA serosubtype 1.4.

Invasive meningococcal disease is a notifiable disease in the UK, and clinicians have a legal duty to notify each case to UKHSA local health protection teams for appropriate public health assessments, investigations, and actions to prevent secondary cases.[15] For all cases, health protection teams routinely collected data on clinical presentation, vaccination status, comorbidities, risk factors, and recent travel history. These data are recorded on HPZone, a national web-based case management system used by health protection teams to record public health events and actions. After 4CMenB implementation in September, 2015, children younger than 5 years were followed up with their general practitioner at 3–6 months after disease onset to request a copy of the hospital discharge summary and completion of a short questionnaire to collect gestational age, length of hospital stay, paediatric intensive care unit (PICU) admission, and post-invasive MenB disease sequelae. Additionally, we retrieved the patients' hospital records from the Hospital Enhanced Surveillance (HES)[16] database to ascertain PICU admission when the information was missing. Fatalities were identified using UK Office of National Statistics death certification, along with information in HPZone, HES, general practice questionnaires, and the Patient Demographic Service, an online database that includes real-time vital status with date of death for all patients registered with the UK National Health Service.[16]

These data were collected as part of routine surveillance of a childhood vaccination programme under Section 60 of the Health and Social Care Act 2001 (now subsumed into the National Information Governance Board for Health and Social Care, with Section 60 now Section 251 of the National Health Service Act 2006) to process confidential patient information with exemption for the requirement for consent.

Data management and analysis

We used SQL Server Management Studio (version 18.11), Microsoft Access 365, to record, manage, and clean the data. For the epidemiological analysis, we compared laboratory-confirmed MenB disease cases before 4CMenB implementation (Sept 1, 2010, to March 31, 2015) with those after implementation (Sept 1, 2015, to March 31, 2020). These time windows allowed comparison of similar calendar periods while excluding social restrictions during the pandemic period (after March, 2020). For clinical follow-up and outcomes, we included all children younger than 5 years with laboratory-confirmed MenB disease between Sept 1, 2015, and March 31, 2021.

We categorised children born since May 1, 2015, as eligible for 4CMenB vaccination either through catch-up or routine immunisation. Cases in children younger than 8 weeks were categorised as not yet 4CMenB-eligible,

	Unimmunised				Immunised				Total (n=371)
	Not eligible (n=46)	Unvaccinated (n=42)	One vaccine dose up to 14 days before disease onset (n=20)	Total unimmunised (n=108)	One vaccine dose 14 days after disease onset (n=105)	Two vaccine doses (n=82)	Three vaccine doses (n=76)	Total immunised (n=263)	
Sex									
Female	26 (57%)	17 (40%)	10 (50%)	53/165 (32%)	45 (43%)	39 (48%)	28 (37%)	112/165 (68%)	165 (44%)
Male	20 (43%)	25 (60%)	10 (50%)	55/206 (27%)	60 (57%)	43 (52%)	48 (63%)	151/206 (73%)	206 (56%)
Age at onset of invasive MenB disease, years									
Younger than 1	46 (100%)	32 (76%)	20 (100%)	98/256 (38%)	101 (96%)	57 (70%)	0	158/256 (62%)	256 (69%)
1	0	6 (14%)	0	6/56 (11%)	1 (1%)	19 (23%)	30 (39%)	50/56 (89%)	56 (21%)
2	0	3 (7%)	0	3/34 (9%)	1 (1%)	4 (5%)	26 (34%)	31/34 (91%)	34 (9%)
3	0	1 (2%)	0	1/21 (5%)	2 (2%)	1 (1%)	17 (22%)	20/21 (95%)	21 (6%)
4	0	0	0	0	0	1 (1%)	3 (4%)	4/4 (100%)	4 (1%)
Ethnicity									
Asian	0	1 (2%)	0	1/5 (20%)	3 (3%)	0	1 (1%)	4/5 (80%)	5 (1%)
Black	1 (2%)	0	1 (5%)	2/4 (50%)	0	2 (2%)	0	2/4 (50%)	4 (1%)
Mixed	1 (2%)	0	1 (5%)	2/9 (22%)	1 (1%)	3 (4%)	3 (4%)	7/9 (78%)	9 (2%)
Other	1 (2%)	1 (2%)	1 (5%)	3/6 (50%)	1 (1%)	1 (1%)	1 (1%)	3/6 (50%)	6 (2%)
White	27 (59%)	27 (64%)	10 (50%)	64/231 (28%)	66 (63%)	54 (66%)	47 (62%)	167/231 (72%)	231 (62%)
Not known	16 (35%)	13 (31%)	7 (35%)	36/116 (31%)	34 (32%)	22 (27%)	24 (32%)	80/116 (69%)	116 (31%)
Prematurity									
No	33 (72%)	32 (76%)	14 (70%)	79/266 (30%)	76 (72%)	62 (76%)	49 (64%)	187/266 (70%)	266 (72%)
Yes	2 (4%)	3 (7%)	2 (10%)	7/37 (19%)	11 (10%)	10 (12%)	9 (12%)	30/37 (81%)	37 (10%)
Not known	11 (24%)	7 (17%)	4 (20%)	22/68 (32%)	18 (17%)	10 (12%)	18 (24%)	46/68 (68%)	68 (18%)
Comorbidity									
No	44 (96%)	42 (100%)	20 (100%)	106/358 (30%)	99 (94%)	80 (98%)	73 (96%)	252 (70%)	358 (96%)
Yes	1 (2%)	0	0	1/7 (14%)	3 (3%)	2 (2%)	1 (1%)	6/7 (86%)	7 (2%)
Not known	1 (2%)	0	0	1/6 (17%)	3 (3%)	0	2 (3%)	5/6 (83%)	6 (2%)

Data are n (%) or n/N (%). MenB=meningococcal serogroup B.

Table 1: **Demographic information on invasive MenB disease cases in England in children younger than 5 years between Sept 1, 2015, and March 31, 2021**

and children who had received one vaccine dose up to 14 days before onset of invasive MenB disease were considered unimmunised because there was insufficient time for them to mount an immune response.

Severe invasive MenB disease was defined as PICU admission, death, or both due to invasive MenB disease. As nearly all children with invasive MenB disease were previously healthy, and invasive MenB disease is associated with rapid progression to multi-organ failure, the primary reason for PICU admission would be intensive care support for severe invasive MenB disease. As part of an additional sensitivity analysis, we created composite outcomes accounting for severe disease grouping death or sequelae and death or sequelae or PICU as outcomes.

Based on published research, we categorised reported post-invasive MenB disease sequelae into three major groups: physical, neurological, and behavioural or psychological.[13] The statistical results presented are mostly descriptive due to the small case numbers. The surveillance questionnaire collected limited clinical, laboratory, treatment, and risk factor data, and therefore we were unable to adjust on potential confounders for detailed analysis. Where appropriate, we calculated crude odds ratios (ORs) with 95% CIs and χ^2 p values. We used the Student's *t* test to ascertain significance of the differences seen pre-vaccine and post-vaccine implementation. ORs and χ^2 Mantel-Haenszel p values were obtained using STATA (version 15).

Role of the funding source

All authors are employees of the funder, and within those roles they were responsible for data collection, data analysis, data interpretation, writing of the manuscript, and the decision to submit the manuscript for publication.

Results

In England, children younger than 5 years accounted for 692 (38%) of 1804 laboratory-confirmed invasive MenB cases after 4CMenB implementation (September, 2015–March, 2020), which was 19% lower (1531 [57%] of 2691) than pre-vaccine years (September, 2010–March, 2015; p<0·0001). In both periods, infants (age <1 years) had the highest case numbers among children, which then declined with increasing age until adolescence (figure). In children younger than 5 years, average annual cases after 4CMenB implementation (148 cases per year) were

	Children with invasive MenB disease (n=371)	Negative MATS result (n=34)	Positive MATS result (n=76)
Unvaccinated	42 (11%)	1/12 (8%)	11/12 (92%)
One vaccine dose 14 days after disease onset	105 (28%)	16/48 (33%)	32/48 (67%)
Two vaccine doses	82 (22%)	11/32 (34%)	21/32 (66%)
Three vaccine doses	76 (20%)	5/16 (31%)	11/16 (69%)
One vaccine dose up to 14 days before disease onset	20 (5%)	1/2 (50%)	1/2 (50%)
Not eligible	46 (12%)	..	..

Data are n (%) or n/N (%). MATS= Meningococcal Antigen Typing System. MenB=meningococcal serogroup B.

Table 2: **Vaccination status and MATS results in the study population**

See Online for appendix

	Children with invasive MenB disease (n=371)
Symptoms	
Meningitis	105 (28%)
Septicaemia	199 (54%)
Meningitis and septicaemia	60 (16%)
Other*	7 (2%)
Signs of shock	
No	231 (62%)
Yes	113 (30%)
Not known	27 (7%)
PICU admission	
No	293 (79%)
Yes	78 (21%)
Survival	
Alive	354 (95%)
Death	17 (5%)
Time from symptom onset to death, h	
<24	5/17 (29%)
24	11/17 (65%)
48	1/17 (6%)

Data are n (%) or n/N (%). MenB=meningococcal serogroup B. PICU=paediatric intensive care unit. *Three children had septic arthritis cases and four had unspecified symptoms.

Table 3: **Clinical presentation, PICU admission, survival, and time from symptom onset to death in the study population**

55% lower than the pre-vaccine average (328 cases per year), but, despite a significant reduction in case numbers (p<0·0001), infants still accounted for the majority of MenB cases: 666 (44%) of 1531 before and 236 (34%) of 692 after vaccine implementation. Before vaccine introduction, the peak age in cases was 5–6 months, which shifted to 1–3 months after vaccine implementation with much lower case numbers (figure). During those periods, cases among children aged 5 years or older remained constant, with 1158 MenB cases pre-vaccine versus 1112 post-vaccine implementation (appendix p 5). Although MenB remained the most common pathogen responsible for invasive meningococcal disease in England, the implementation of the routine immunisation programme saw increasingly high uptake in the 18 months after implementation: more than 90% for the first and second doses and around 87% for the booster dose (appendix pp 3–4).

Clinical follow-up of children younger than 5 years with laboratory-confirmed MenB disease after 4CMenB implementation included all eligible cases until March, 2021, covering periods of COVID-19 pandemic lockdowns, with restrictions starting from March, 2020. Between Sept 1, 2015, and March 31, 2021, there were 715 cases of MenB disease in children younger than 5 years; of those, 371 children born from May 1, 2015, were included in our study. 256 (69%) of 371 cases were in infants, including 128 (35%) in infants younger than 3 months, and 206 (56%) were male (table 1).

Surveillance questionnaires were completed for all children. Eight (2%) of 371 children had underlying comorbidities, including seven (2%) with non-immuno-compromising conditions and one (<1%) diagnosed with inherited complement deficiency after MenB disease. Six (2%) children had chickenpox within 4 weeks before onset of invasive MenB disease. Additionally, 37 (10%) children were known to have been born prematurely, including two (1%) who were extremely preterm (<28 weeks gestation), six (2%) who were very preterm (28 to <32 weeks gestation), and 29 (8%) who were moderate-to-late preterm (32 to <37 weeks gestation).

4CMenB vaccination status was available for all cases: 108 (29%) of 371 children were unimmunised and 263 (71%) were immunised through vaccination. 46 (43%) of 108 unimmunised cases were infants younger than 8 weeks who were too young for their first dose, 42 (39%) were unvaccinated, and 20 (19%) developed MenB disease within 14 days of their first dose (table 2). The remaining 263 children received at least one 4CMenB dose at least 14 days before onset of invasive MenB disease: 105 (28%) one dose, 82 (22%) two doses, and 76 (21%) three doses (table 2).

MATS testing results with PorA PCR typing of the responsible MenB strains was available for 110 (34%) of 325 children who were eligible for 4CMenB vaccination (table 2). Among unvaccinated children, nearly all strains (11 [92%] of 12) were predicted to be susceptible to 4CMenB-induced antibodies, compared with 53 (66%) of 80 in those with one or two doses and 11 (69%) of 16 in fully vaccinated children (table 2).

259 (70%) of 371 children presented with septicaemia, either alone (199 [54%]) or accompanied with meningitis (60 [16%]), 105 (28%) presented with meningitis alone, and seven (2%) had another focus of infection, mainly septic arthritis (three children; table 3). The median length of hospital stay was 6 days (IQR 4–9; reported for 321 cases) and 4 days (2–6; reported for 45 cases) in a PICU among survivors. 57 (29%) of 199 children presenting with septicaemia alone, 12 (20%) of 60 with both septicaemia and meningitis, seven (7%) of 105 with meningitis alone, and two (29%) of seven with other

presentations were admitted to a PICU. Septic shock was reported in 113 (33%) of 344 children, including 56 (72%) of 78 admitted to a PICU. Four (57%) of seven children with underlying health conditions were admitted to a PICU. Children with underlying health conditions were more likely to require PICU admission compared with children without pre-existing conditions (74 [20%] of 364; crude OR 5·21, 95% CI 1·12–24·1, p=0·018). PICU admission rates were not significantly different across immunisation status categories (p>0·3; appendix p 2): eight (19%) of 42 unvaccinated children, ten (22%) of 46 children too young for vaccination, two (10%) of 20 with one vaccine dose within 14 days of invasive MenB disease onset, 17 (16%) of 105 with one dose, 22 (27%) of 82 with two doses, and 19 (25%) of 76 with three doses were admitted to a PICU.

The case fatality ratio was 5% (17 of 371 cases; table 3), with 16 of 17 deaths occurring within 1 day of developing symptoms and 11 were in infants (ie, aged <1 year). The case fatality ratio was 6% (12 of 199 cases) in children presenting with septicaemia alone, 5% (three of 60) in children with septicaemia and meningitis, and 2% (two of 105) with meningitis alone.

Ten of 17 deaths occurred in children who were too young to receive the vaccine (seven [15%] of 46 infants aged <8 weeks), who were eligible for three doses but were unimmunised (two [3%] of 62), or who contracted invasive MenB disease within 14 days of their first vaccine dose (one [5%] of 20). This compared with three deaths (3%) among 105 children who had received one dose of 4CMenB, none among 82 children receiving two doses, and four (5%) among 76 children with three doses.

MATS results were available for three children who died: one had received three vaccine doses and was MATS negative, one unvaccinated child was MATS positive for NHBA only, and one child who had received one vaccine dose was MATS positive for both NHBA and fHbp.

Of 354 survivors, 57 (16%) were identified with sequelae in the follow-up. A single complication was identified in 43 (12%) children, two sequelae in 11 (3%), and three in three (1%). Of the 74 sequelae reported, 45 (61%) were neurological complications, 17 (23%) were physical, two (3%) were behavioural or psychological, and ten (14%) included other complications (table 4).

Neurological sequelae included mainly hearing loss (24 [7%] of 354 children) and epilepsy (ten [3%]; table 4). Physical sequelae included amputation of single or multiple limbs, or digit loss (six [2%]), hydrocephalus (four [1%]), and skin scarring (two [1%]). Children admitted to a PICU were more likely to develop sequelae than those who did not require intensive care (25 [32%] of 78 *vs* 33 [11%] of 293; crude OR 3·7, 95% CI 2·0–6·9, p<0·0001). No difference was seen in the prevalence of sequelae in children born prematurely compared with those born at term (ten [27%] of 37 *vs* 44 [17%] of 266; crude OR 1·9, 95% CI 0·8–4·2, p=0·12).

	Identifiable sequelae (n=64)
Physical sequelae	17
Amputation	6
Hydrocephalus	4
Skin scarring	2
Recurrent pseudomeningocele	1
Renal pole scarring	1
Distal radial growth arrest	1
Necrotic eschars	1
Peripheral nerve damage	1
Neurological sequelae	45
Hearing loss	24
Epilepsy	10
Developmental delay	3
Significant speech delay	2
Muscle weakness	2
Mobility issues	1
Sleep myoclonus	1
Severe brain injury	1
Peripheral vestibular dysfunction (gait imbalance)	1
Behavioural or psychological sequelae	2
Communication problems	2

MenB=meningococcal sergroup B.

Table 4: **List of sequalae reported after invasive MenB disease recovery in the study population**

The proportion of children with sequelae was not significantly different between the unvaccinated cohort (including those not eligible and vaccinated within 14 days of contracting invasive MenB disease) and the vaccinated cohort (one, two, or three doses): 15 (15%) of 98 versus 42 (16%) of 256 (crude OR 1·1, 95% CI 0·6–2·1; p=0·80), and when comparing ORs between the unvaccinated and each immunisation status category (p>0·3; appendix p 1).

We conducted an additional sensitivity analysis, creating a composite of death or sequelae and death or sequelae or PICU admission as an outcomes and found no significant differences between the vaccinated and unvaccinated groups (appendix p 2).

Discussion

The national MenB infant immunisation programme in England was associated with a sharp decline in cases of MenB disease in the target population, with a 55% reduction in infants younger than 1 year during Sept 1, 2015–March 31, 2020, compared with the same pre-vaccine period in 2010–15. Previous studies have shown that 4CMenB is very effective in preventing MenB disease in children,[17] with real-world evidence to show vaccine cross-protection against other meningococcal serogroups.[18,19] As a result of the successful 4CMenB immunisation programme, laboratory-confirmed MenB disease case numbers in infants have decreased. The age distribution of cases has shifted, with an earlier peak

at 1–3 months of age, affecting unvaccinated and under-vaccinated infants, as opposed to the pre-vaccine peak at 5–6 months, when most infants will have received two vaccine doses in the post-vaccine implementation period.[9]

Invasive meningococcal disease continues to affect previously healthy children with no underlying conditions, with the youngest having the most severe outcomes, highlighting the importance of vaccination to prevent invasive meningococcal disease. Known risk factors associated with invasive meningococcal disease include complement deficiency, asplenia, and HIV.[20] Although children with laboratory-confirmed invasive MenB disease were not systematically assessed for underlying risk factors, our national surveillance follow-up of 371 cases of MenB disease identified only one child diagnosed with inherited complement deficiency after having invasive MenB disease, suggesting that such rare risk factors were unlikely to be responsible for invasive meningococcal disease in vaccinated or unvaccinated children.

The lower peak age in infants with invasive meningococcal disease after 4CMenB implementation has important implications: we need to increase awareness among clinicians, parents, and policy makers of this shift, predominantly affecting unvaccinated and under-vaccinated infants, and the higher case fatality ratio in younger infants (aged <1 year) than in older children (aged 1–5 years).[21] Furthermore, we need more detailed clinical studies to understand risk factors for severe and fatal invasive meningococcal disease outcomes in younger infants.

Second, our findings highlight the importance of timely infant immunisation. Currently, 4CMenB is offered at 8 weeks and 16 weeks of age, with a booster at the age of 1 year in the UK. We recently reported that timely 4CMenB vaccination in infants has the potential to prevent a significant proportion of MenB cases in infants.[22] Additionally, clinical trials are currently underway to compare the immunogenicity of a shorter interval (4 weeks) with the current longer interval (8 weeks) between the two 4CMenB priming doses in infancy,[23] which could provide earlier protection with two doses in the age group currently most at risk of MenB disease. Another potential strategy for reducing MenB disease in early infancy could be to give the first 4CMenB dose earlier at, for example, 6 weeks of age. Furthermore, we found that 92% of cases in unvaccinated children were caused by a MenB strain predicted to be covered by 4CMenB compared with 69% in vaccinated children, highlighting that many cases could have been prevented through timely vaccination and high uptake.

Finally, we found a similar risk of PICU admission, death, and sequelae among survivors in children elgible for vaccincation with laboratory-confirmed MenB disease, irrespective of vaccination status. Thus, although 4CMenB prevents MenB disease in young children, we found no evidence of less severe disease, using multiple outcome measures, in those who went on to develop MenB disease. Reassuringly, the case fatality ratio remained low in both vaccinated and unvaccinated cohorts at less than 5%, similar to the pre-vaccine era.[10] Before 4CMenB implementation in England, national follow-up found deficits in 87 (36%) of 244 children (mean age 6·5 years) who survived MenB disease compared with 49 (15%) of 328 controls without MenB disease (2·7, 95% CI 1·8–4·1, p<0·0001), with major disabling deficits in 21 (9%) survivors and six (2%) controls (matched OR 5·0, 2·0–12·6, p=0·001).[14] The prevalence of sequelae in the previous study was higher than the 16% among survivors in our cohort, but our follow-up at 3–6 months after invasive MenB disease was shorter than the 3-year follow-up in the previous study. In our cohort, intelligence quotient, mental health, and neurocognitive functions were seldom reported or tested due to the very young age and shorter follow-up interval. For the main physical complications, however, the sequelae in our cohort were similar to the previous follow-up for any sensorineural hearing loss (7% *vs* 7%) and major or minor amputations (2% *vs* 2%).[14] Our prevalence of at least one sequela in 16% of survivors was similar to the 13% reported for children younger than 5 years with invasive meningococcal disease due to any serogroup during 2012–17 in France, although the prevalence of epilepsy in that study was similar (3·7%) but that of hearing loss was lower (2·8%).[24] Reassuringly, the French study, which included invasive meningococcal disease cases across all age groups, found children younger than 5 years to have the lowest risk of sequelae. Compared with infants and young children, in particular, several studies have reported adolescents to have more prevalent and more severe negative physical, emotional, educational, and mental health outcomes after invasive meningococcal disease, especially non-MenB compared with MenB disease.[25] The MenACWY vaccine is routinely offered to teenagers under the UK vaccination programme.

In Denmark, where 4CMenB is not routinely offered,[26] invasive meningococcal disease due to any serogroup during 2005–20 was associated with at least one sequela in 22% of survivors younger than 5 years, with hearing loss being most prevalent (6·8%),[27] similar to our cohort, where neurological sequelae were most prevalent and comprised mainly hearing loss (7%) and epilepsy (3%), emphasising the importance of adhering to recommended follow-up and assessment, including hearing tests, after hospital discharge.[28] Hearing loss in children is negatively associated with speech, language, education, social functioning, cognitive abilities, and quality of life, but early identification and management, with hearing aids and cochlear implants, for example, will improve prognosis.[29]

So far, only one study, designed as a matched control, has attempted to assess disease severity in children vaccinated with 4CMenB and including all meningococcal serogroups in children aged up to 18 years.[17] In Portugal, there were no deaths or sequelae among 11 children with

invasive meningococcal disease due to any serogroup (median age 22 months) who had received at least one 4CMenB dose compared with 23 deaths or reported sequelae in 87 unimmunised children (median age 14 months), with a difference of 26% (95% CI 2–37).[17]

Severe sequelae, such as those observed in our cohort, can negatively affect the health-related quality of life of survivors of invasive meningococcal disease and, consequently, of their caregivers years after infection.[13] In the UK, it is estimated that long-term sequelae after a single case of severe invasive meningococcal disease could cost the National Health Service between £590 000 and £1 090 000 (£1 250 000–3 320 000 undiscounted), with discounted costs from a government perspective ranging between £1 360 000 and £1 720 000 (£3 030 000–4 470 000 undiscounted).[30]

The major strength of our study was the inclusion of all cases of MenB disease across England over a decade, covering the implementation of a national immunisation programme, alongside enhanced national surveillance with follow-up of all confirmed cases. The rarity of the condition, and incomplete MATS results, means that most of our analysis is descriptive without subgroup analysis or adjustment for confounding factors. The priority of national surveillance was to ensure high questionnaire completion rates to monitor vaccine impact and effectiveness; thus, detailed clinical data, laboratory, and radiological investigations or treatment was not collected, which might have identified factors associated with severe outcomes.

Moreover, we followed-up children at 3–6 months after diagnosis and, therefore, focused on early sequelae. Physical growth impairment, mental health, and psychological complications might become apparent several years after invasive meningococcal disease, especially after infection in infancy or early childhood.[31] Importantly, physical and neurological complications after invasive meningococcal disease are easier to diagnose than behavioural and psychological changes, especially in young children. Finally, it is possible that some complications we attribute to invasive meningococcal disease might have occurred independently in those children.

4CMenB has significantly reduced the risk of invasive meningococcal disease in young children, but MenB disease is not less severe in vaccinated than in unvaccinated children. Case fatality remains below 5%, but with significant sequelae in 16% of survivors at 3–6 months after their illness. Prevention of invasive meningococcal disease, therefore, remains the most effective way for preventing deaths and severe disability after infection. It is important that infants are vaccinated in a timely manner because 4CMenB is offered at an age associated with highest risk of invasive meningococcal disease. Further studies are needed to assess the medium-term to longer-term effects of invasive meningococcal disease on the physical and mental health of children and of potential benefits of an earlier infant schedule with a shorter interval between doses.

Contributors

AAM, HC, and SNL contributed to methodology, formal analysis, investigation, data curation, writing of the original draft of the report, review and editing of the report, and creation of the graphs. SR, SAC, JL, and XB were involved in data curation and review and editing of the report. SNL, HC, and RB were involved in conceptualisation and review and editing of the report. HC, AAM, and SR verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SNL, RB, JL, SAC, and XB carry out contract research for vaccine manufacturers (including GlaxoSmithKline, Pfizer, and Sanofi Pasteur) on behalf of St George's University of London (SNL) and UKHSA but receive no personal remuneration. The Immunisation and Vaccine Preventable Diseases Division at UKHSA has provided vaccine manufacturers 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. All other authors declare no competing interests.

Data sharing

Data collected under UKHSA national surveillance are regularly published online. Anonymised data are available to be shared with researchers who provide a methodologically sound proposal. Proposals should be directed to immunisation@ukhsa.gov.uk; to gain access, data requestors will need to sign a data sharing agreement. Data will be available indefinitely.

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References

1 Parikh SR, Campbell H, Bettinger JA, et al. The everchanging epidemiology of meningococcal disease worldwide and the potential for prevention through vaccination. *J Infect* 2020; **81:** 483–98.

2 WHO. Meningitis. 2021. https://www.who.int/health-topics/meningitis#tab=tab_1 (accessed Sept 8, 2022).

3 WHO. Meningococcal meningitis. https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/meningococcal-meningitis (accessed Sept 8, 2022).

4 UK Health Security Agency. Invasive meningococcal disease in England: annual laboratory confirmed reports for epidemiological year 2020 to 2021. Jan 25, 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1049331/hpr0122-IMD-ann__1_.pdf (accessed Sept 8, 2022).

5 UK Health Security Agency. Childhood vaccination coverage statistics 2020–21. Sept 30, 2021. https://digital.nhs.uk/data-and-information/publications/statistical/nhs-immunisation-statistics/england---2020-21 (accessed Sept 8, 2022).

6 Parikh SR, Newbold L, Slater S, et al. 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. *Lancet Infect Dis* 2017; **17:** 754–62.

7 Parikh SR, Andrews NJ, Beebeejaun K, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. *Lancet* 2016; **388:** 2775–82.

8 UK Health Security Agency. National enhanced surveillance of vaccination programmes targeting invasive meningococcal disease in England. December, 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1124997/UKHSA-meningococcal-surveillance-december-2022.pdf (accessed Sept 8, 2022).

9 Ladhani SN, Andrews N, Parikh SR, et al. Vaccination of infants with meningococcal group B vaccine (4CMenB) in England. *N Engl J Med* 2020; **382:** 309–17.

10 Ladhani SN, Flood JS, Ramsay ME, et al. Invasive meningococcal disease in England and Wales: implications for the introduction of new vaccines. *Vaccine* 2012; **30:** 3710–16.

11 Beebeejaun K, Parikh SR, Campbell H, et al. Invasive meningococcal disease: timing and cause of death in England, 2008–2015. *J Infect* 2020; **80:** 286–90.

12 Parikh SR, Campbell H, Gray SJ, et al. Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010–2015. *Vaccine* 2018; **36:** 3876–81.

13 Olbrich KJ, Müller D, Schumacher S, Beck E, Meszaros K, Koerber F. Systematic review of invasive meningococcal disease: sequelae and quality of life impact on patients and their caregivers. *Infect Dis Ther* 2018; **7:** 421–38.

14 Viner RM, Booy R, Johnson H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. *Lancet Neurol* 2012; **11:** 774–83.

15 Public Health England. Guidance for public health management of meningococcal disease in the UK. August, 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829326/PHE_meningo_disease_guideline.pdf (accessed Sept 25, 2022).

16 NHS Digital. Data services. 2022 https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services#p (accessed Sept 25, 2022).

17 Rodrigues FMP, Marlow R, Simões MJ, Danon L, Ladhani S, Finn A. Association of use of a meningococcus group B vaccine with group B invasive meningococcal disease among children in Portugal. *JAMA* 2020; **324:** 2187–94.

18 Ladhani SN, Campbell H, Andrews N, et al. First Real-world evidence of meningococcal group B vaccine, 4CMenB, protection against meningococcal group W disease: prospective enhanced national surveillance, England. *Clin Infect Dis* 2021; **73:** e1661–68.

19 Biolchi A, Tomei S, Brunelli B, et al. 4CMenB immunization induces serum bactericidal antibodies against non-serogroup B meningococcal strains in adolescents. *Infect Dis Ther* 2021; **10:** 307–16.

20 HM Treasury. The Green Book. 2013. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1076053/Meningococcal-greenbook-chapter-22_17May2022.pdf (accessed Sept 8, 2022).

21 UK National Institute for Health and Care Excellence. Fever in under 5s: assessment and initial management. https://www.nice.org.uk/guidance/ng1432019 (accessed Sept 25, 2022).

22 Ladhani SN, Campbell H, Amin-Chowdhury Z, Lucidarme J, Borrow R, Ramsay ME. Timing of meningococcal vaccination with 4CMenB (Bexsero®) in children with invasive meningococcal group B (MenB) disease in England. *Vaccine* 2022; **40:** 1493–98.

23 St George's Vaccine Institute. LionMenB—early protection against meningococcal B disease in infants. https://vaccine.ac.uk/research/lion-menb/ (accessed Sept 25, 2022).

24 Weil-Olivier C, Taha MK, Bouée S, et al. Care pathways in invasive meningococcal disease: a retrospective analysis of the French national public health insurance database. *Hum Vaccin Immunother* 2022; **18:** 2021764.

25 Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec, Canada, 1990–1994. *Clin Infect Dis* 1998; **26:** 1159–64.

26 European Centre for Disease Prevention and Control. Meningococcal disease: recommended vaccinations. https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=48&SelectedCountryIdByDisease=-1 (accessed Sept 25, 2022).

27 Voss SS, Nielsen J, Valentiner-Branth P. Risk of sequelae after invasive meningococcal disease. *BMC Infect Dis* 2022; **22:** 148.

28 UK National Institute for Health and Care Excellence. 2018 surveillance of meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (NICE guideline CG102). Oct 4, 2018. https://www.nice.org.uk/guidance/cg102/resources/2018-surveillance-of-meningitis-bacterial-and-meningococcal-septicaemia-in-under-16s-recognition-diagnosis-and-management-nice-guideline-cg102-pdf-8480868227269 (accessed Sept 25, 2022).

29 Lieu JEC, Kenna M, Anne S, Davidson L. Hearing loss in children: a review. *JAMA* 2020; **324:** 2195–205.

30 Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease: scenarios of severe meningitis and septicemia. *Paediatr Drugs* 2013; **15:** 49–58.

31 Belthur MV, Bradish CF, Gibbons PJ. Late orthopaedic sequelae following meningococcal septicaemia. A multicentre study. *J Bone Joint Surg Br* 2005; **87:** 236–40.