Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study

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Summary

Background Safety data for the multicomponent meningococcal group B vaccine (4CMenB) has so far been limited to experience from clinical trials and isolated local outbreaks. Since the UK is the first country to implement a nationwide routine immunisation programme with 4CMenB (at age 8 weeks, 16 weeks, and then 1 year), we aimed to assess the safety of 4CMenB in this setting.

Methods In this prospective surveillance study, we assessed suspected adverse reactions of 4CMenB in children up to age 18 months reported in the UK Yellow Card Scheme and primary care records extracted from the Clinical Practice Research Datalink (CPRD). We proactively assessed reports of fever, local reactions, Kawasaki disease, seizures, and sudden death, and compared the number of spontaneous reports with the expected number of events based on background incidence and the number of children vaccinated. We also identified any unexpected adverse reactions and estimated compliance with subsequent doses of routine vaccinations.

Findings From Sept 1, 2015, to May 31, 2017, approximately 1·29 million children aged 2–18 months received about a combined 3 million doses of 4CMenB. 902 reports of suspected adverse reactions were received through the UK Yellow Card Scheme, of which 366 (41%) were related to local reactions and 364 (40%) related to fever. The only unexpected finding was that 160 reports of local reactions described a persistent nodule at the site of injection, usually without other local symptoms. There were 55 (6%) reports of seizures, with an age-adjusted observed-to-expected ratio of 0·13 (95% CI 0·10–0·17). Ecological analyses found similar rates of seizures within 7 days of routine immunisation in the periods before and after 4CMenB introduction, with incidence rate ratios of 1·30 (95% CI 0·56–3·00) at age 2 months, 1·53 (0·49–4·74) at age 4 months, and 1·26 (0·69–2·32) at age 12 months. Of the 902 reports, three (<1%) were of Kawasaki disease (observed-to-expected ratio 1·40, 95% CI 0·29–4·08) and three (<1%) of sudden infant death syndrome within 3 days of vaccination in children aged 2–4 months (0·44, 0·12–1·14). Analysis of routine immunisations recorded in CPRD found that 11 602 (95·1%) of 12 199 children had received the second dose of 4CMenB by 26 weeks of age, 1793 (84·7%) of 2117 had received the third dose by 62 weeks of age, and 4CMenB introduction had not reduced compliance with doses of other routine vaccinations.

Interpretation We found no significant safety concerns after widespread use of 4CMenB in UK infants, and the vaccine appears to have been well accepted by parents. However, it is important to continue monitoring the safety and long-term effect of the immunisation programme in the UK to further characterise the reported suspected adverse reactions.

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Introduction

In September, 2015, the UK became the first country to implement a nationwide routine infant immunisation programme with a multi-component, broad-spectrum meningococcal group B vaccine (4CMenB; Bexsero, GlaxoSmithKline Biologicals, Belgium).[1] Before this programme, the use of 4CMenB was limited mainly to clinical trials and in localised disease outbreaks. As advised by the UK Joint Committee on Vaccination and Immunisation,[2] the vaccine is recommended for all infants alongside their routine immunisations at age 8 weeks (diphtheria, tetanus, and acellular pertussis, inactivated polio, and *Haemophilus influenzae* type b vaccine [DTaP/IPV/Hib]; 13-valent pneumococcal conjugate vaccine [PCV13]; and the oral rotavirus vaccine) and age 16 weeks (DTaP/IPV/Hib and PCV13), followed by a booster on their first birthday, given concomitantly with an *H influenzae* type b and meningococcal C combination vaccine; the measles, mumps, and rubella (MMR) vaccine; and PCV13. Children attending for their routine vaccinations at 12 weeks of age were also eligible for 4CMenB vaccination as a limited catch-up at the beginning of the immunisation programme. There was no catch-up campaign for older cohorts. Because of high

Research in context

Evidence before this study

We considered published reports of pre-licensure pivotal clinical trials and post-licensure use in Canada of the multicomponent meningococcal group B vaccine (4CMenB). In these reports, 4CMenB was associated with high rates of local reactions and fever when given at the same time as other routine infant vaccines. However, very rare adverse reactions and the potential effect of the increased reactogenicity can only be identified and characterised during use in large population cohorts.

Added value of this study

Following widespread use of 4CMenB in UK infants, the safety profile appears consistent with that seen in clinical trials, with local reactions and fever being the most commonly reported adverse reactions. Additionally, our study showed no significant new safety concerns arising and high compliance with the second and third 4CMenB doses, and the addition of 4CMenB to the routine infant immunisation schedule did not seem to have had an adverse effect on compliance with other vaccinations.

Implications of all the available evidence

Alongside the emerging data for vaccine effectiveness, the experience so far from the UK routine immunisation programme shows that 4CMenB has a favourable benefit–risk profile. It is important that safety remains under continual review to further characterise the reported suspected adverse reactions.

reported numbers of fever and other vaccine-associated reactions when 4CMenB is coadministered with the other routine immunisations in those aged 1 year,[3,4] three doses of prophylactic paracetamol are recommended to be given with the 8-week and 16-week immunisations; the first dose of paracetamol should be administered around the time of vaccination with two additional doses at 4–6 h intervals.[5,6]

For more on the **Medical Dictionary for Regulatory Activities** see https://www.meddra.org/

Early data suggested that laboratory-confirmed cases of invasive meningococcal group B infection halved in vaccine-eligible infants during the first 10 months of the immunisation programme, with an estimated effectiveness of 94% against vaccine-preventable strains.[7] The Medicines and Healthcare Products Regulatory Agency (MHRA) has statutory responsibility for the safety of vaccines and medicines in the UK, and the UK National Institute for Biological Standards and Control (NIBSC) is a batch release authority for 4CMenB. In this study, we aimed to present the outcome of an MHRA and NIBSC proactive pharmacovigilance strategy for 4CMenB since its introduction in the UK's routine infant immunisation programme.

For more on the **Council for International Organizations of Medical Sciences** see https://cioms.ch/pharmacovigilance/

Methods

Data sources

We assessed suspected adverse reactions of 4CMenB using data from the UK Yellow Card Scheme. Introduced in 1964, the Yellow Card Scheme is a passive safety surveillance system through which health-care professionals and members of the public can report a spontaneous suspected adverse reaction to any vaccine or medicinal product directly to the MHRA. Yellow Cards can be submitted by post, online, or via a smartphone application. Pharmaceutical companies are also legally obliged to report serious adverse reactions for their products to regulatory authorities, and these serious adverse reactions are included in and evaluated by the MHRA as Yellow Card reports. All Yellow Card reports are routinely reviewed on a weekly basis by the MHRA to detect potential new safety signals; a signal might be a new adverse reaction or a change in a known adverse reaction. The MHRA follows up reports via letter or email to obtain additional clinical details of a suspected individual's adverse reaction report, if necessary. Reported events are coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) terminology, a standardised, medically validated system used internationally for the regulation of medicines. Additionally, MedDRA groups categorise adverse drug reaction terms in a hierarchical structure whereby the preferred term, which is the most specific, is grouped under broader headings that are all subsequently contained within a System Organ Class, which is the most general group in the hierarchy. It is the preferred term level that is used for pharmacovigilance activities, such as safety signal detection.

For more on the **UK Yellow Card Scheme** see https://yellowcard.mhra.gov.uk/

The seriousness of a suspected adverse reaction is first decided by the reporter selecting one or more of six criteria, determined by a working group of the Council for International Organizations of Medical Sciences, by ticking the appropriate box on the Yellow Card: patient died because of the reaction; life-threatening reaction; resulted in an admission to hospital or prolonged inpatient treatment; congenital abnormality; involved persistent or significant disability or incapacity; or the reaction was deemed medically significant. Second, specific MedDRA preferred terms are defined as serious by default by the MHRA. In this study, we limited data extraction to reports in children aged up to 18 months. This criterion allowed for the capture of suspected adverse reactions following late administration of the recommended booster at 1 year of age. Suspected adverse reactions in older children and adults who were likely to have received the vaccine privately outside of the national immunisation programme were excluded, because vaccine use data in these cohorts were not available.

Additionally, we assessed incidence of adverse events and compliance of 4CMenB using data from the Clinical

Practice Research Datalink (CPRD), which holds electronic patient data from 22 million patient records throughout the UK, including demographic, clinical, prescribing, immunisation, and referral data. The CPRD has been shown to be representative of the general UK population with respect to age, sex, and ethnicity,[8] and the data have been extensively used in epidemiological research and to support previous vaccine safety assessments.[9–13]

Outcomes

Reports of fever, seizures, local reactions, Kawasaki disease, and sudden death were prespecified as outcomes of interest for proactive assessment. Seizures and Kawasaki disease were selected because isolated cases were reported in the pivotal prelicensing studies.[3,4] Sudden death was selected because of its peak incidence around the age of the primary immunisations.[14] Because of concerns that the high frequencies of vaccine-related systemic adverse events (ie, fever and irritability) identified during the clinical trials could affect acceptance of subsequent immunisation doses, compliance and timing of the second and third immunisations were also selected for proactive assessment.

Statistical analysis

We did observed versus expected analyses to compare the number of spontaneous reports received through passive surveillance with an expected number derived from the background incidence of the condition in the target population and the number of children vaccinated. Seizures, Kawasaki disease, and sudden death were prespecified for routine evaluation via the observed versus expected analysis; however, any other adverse events of interest could be incorporated into this analysis as required. For seizures, we estimated age-specific historical background incidence within 7 days of routine immunisations using CPRD data for the 5 years before 4CMenB implementation. For Kawasaki disease, we used published incidence data.[15] For sudden death, we estimated the background rates within the first year of life for 2014 using data from the UK Office for National Statistics.[16] Additionally, we estimated the number of infants vaccinated during the surveillance period using CPRD data projected to figures across the UK.

We did an ecological analysis using CPRD data to compare post-vaccination seizure incidence in the 5 years before 4CMenB implementation (from Sept 1, 2010, to Aug 31, 2015) and 20 months after 4CMenB implementation (from Sept 1, 2015, to June 30, 2017). We calculated the number of infants with any seizure (febrile or non-febrile) recorded in CPRD and the quarterly incidence of seizure within 7 days of routine immunisation at 8 weeks and 16 weeks of age as well as after the booster separately for both time periods (pre-4CMenB and post-4CMenB introduction). We defined an incident seizure as an event with no previous seizure within the previous 14 days. We estimated incidence rate ratios (IRRs) using Poisson regression. Additionally, we did sensitivity analysis using post-vaccination data at age 3 years 4 months when children routinely receive booster doses of MMR and DTaP/IPV vaccines but not 4CMenB to identify any change in the incidence of recorded seizures over time due to factors unrelated to 4CMenB.

To estimate compliance with subsequent vaccinations, we extracted immunisation records of children younger than 5 years for the 4CMenB, PCV13, or rotavirus vaccines from the CPRD. We identified two study cohorts: the pre-4CMenB cohort (ie, infants born between July 1, 2013, and June 30, 2015, who received their first dose of either PCV13 or rotavirus vaccine at 6–10 weeks of age) and the post-4CMenB cohort (ie, infants born on or after July 1, 2015, who received their first dose of either PCV13 or rotavirus vaccine at 6–10 weeks of age between Sept 1, 2015, and Oct 31, 2016). Using Kaplan-Meier curves, we compared the age at vaccination for subsequent PCV13 and rotavirus vaccine doses across the two cohorts. Furthermore, Kaplan-Meier curves for 4CMenB vaccination at 16 weeks and 1 year in the post-4CMenB cohort were compared with the post-4CMenB curve for PCV13 at 16 weeks and 1 year cohorts. We used the log-rank test to assess equality between the survival curves of the pre-4CMenB and post-4CMenB cohorts for each vaccine and dose. In all cohorts, date of birth was assumed to be the 15th of the month. All CPRD code lists are available on request from the authors. We did all the statistical analyses using Stata (version 11.2).

Role of the funding source

There was no funding source for the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Sept 1, 2015, to May 31, 2017, an estimated 1·29 million first doses, 1·17 million second doses, and 585 000 third doses were administered to approximately 1·29 million infants in the UK as part of the national immunisation schedule. During this 20-month surveillance period, the MHRA received 902 Yellow Card reports, of which 467 (52%) were coded as serious, for 4CMenB in children younger than 18 months across the UK (including all reports with unspecified age), equivalent to a passive reporting rate of suspected adverse reactions of 0·3 per 1000 doses administered (figure). The 902 reports included 2429 adverse event terms (MedDRA preferred terms; table 1), most of which were considered recovered or resolved at the time of reporting or last update (table 2). Of the 902 reports, 476 (53%) were for boys and 411 (46%) for girls, and 15 (2%) did not specify sex. Health-care professionals submitted 711 (79%) of the 902 reports, with 191 (21%) from parents or carers. The type of MedDRA

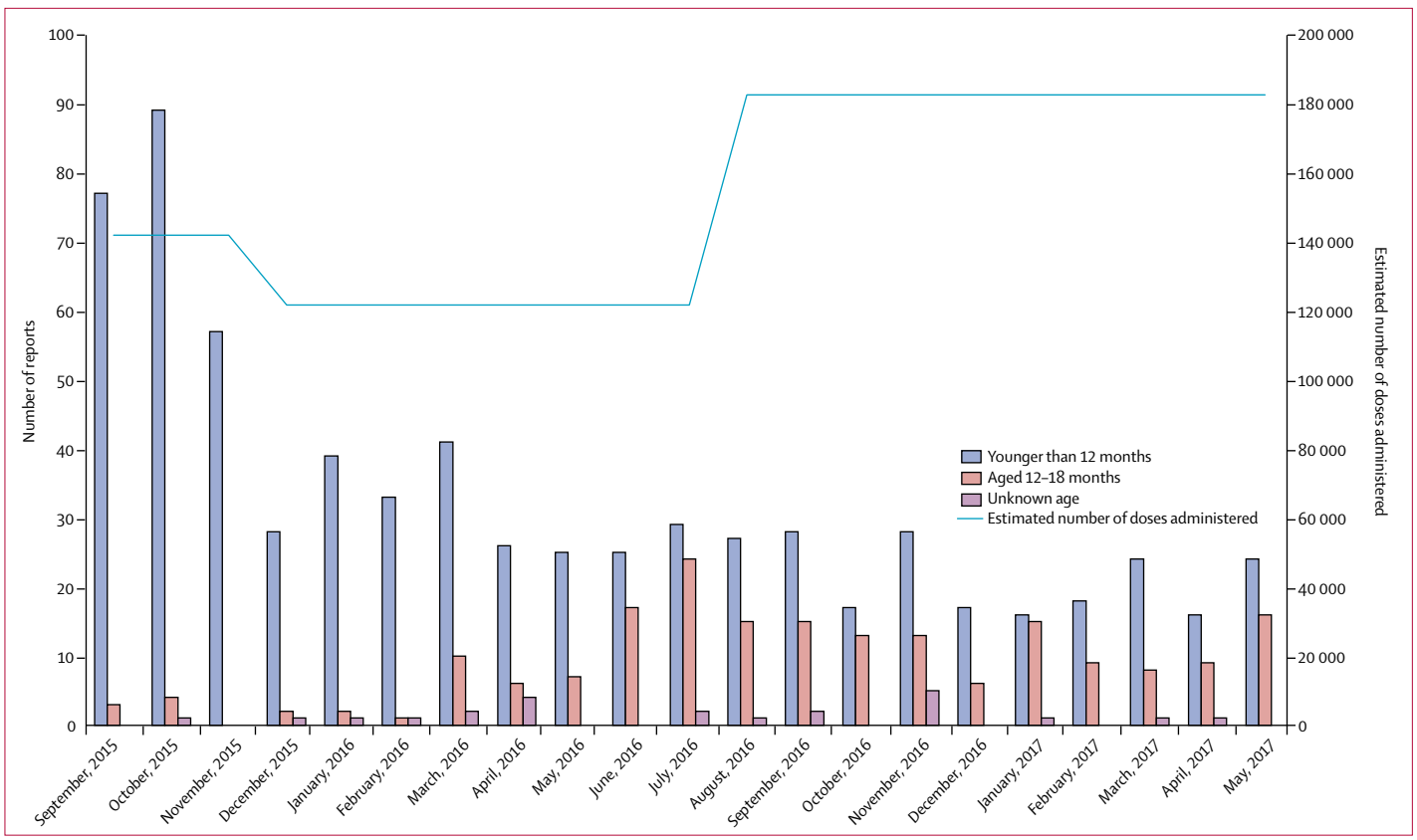

Figure: **Number of Yellow Card reports and estimated number of administered doses per month, by age group**
The number of administered doses was estimated with the assumption that monthly vaccination rate was constant.

preferred terms reported by health-care professionals and parents or carers were broadly the same.

Of the 902 reports, 364 (40%) were of fever, including the MedDRA terms "pyrexia", "body temperature increased", and "feeling hot". Of these reports, 134 (37%) were in children aged 8 weeks, 46 (13%) in those aged 12 weeks, and 64 (17%) in those aged 16 weeks. An additional 40 (11%) reports of fever were in children aged 5–11 months and 72 (20%) in those aged 12–18 months. Age was not reported in eight (2%) cases. 139 (38%) of the reports referenced seeking emergency medical attention or admission to hospital, including 26 undergoing a lumbar puncture or full septic screen; there were no reports of a confirmed bacterial infection. At the time of last reporting, the child had recovered or was recovering in 290 (80%) of the 364 reports, 27 (7%) were stated as not recovered, and 47 (13%) were reported as having an unknown outcome. 212 (58%) were reported as serious. Although there was incomplete reporting of the actual magnitude or severity of fever in the Yellow Card reports, those that were reported as serious tended to refer to a high fever, with some reporting a temperature of more than 40°C. There was insufficient information about paracetamol use in these reports.

There were 55 reports of seizures associated with 4CMenB (table 3), comprising 6% of the 902 Yellow Card reports. In the pre-4CMenB period, background incidence of seizures within 7 days of routine vaccination was 10·6 per 100 000 doses at age 2 months, 6·7 per 100 000 at age 4 months, and 34·1 per 100 000 at age 12 months. Therefore, 137 seizure episodes would be expected within 7 days after the first dose, 78 after the second dose, and 199 after the booster dose. On the basis of spontaneous reports, the age-adjusted observed-to-expected ratio was 0·13 (95% CI 0·10–0·17). At 2 months of age, 32 seizures following vaccination were identified among 286 432 infants in the CPRD across the whole study period (overall incidence of 11·2 per 100 000 vaccinees). Similar rates were observed before and after 4CMenB introduction (10·6 per 100 000 *vs* 13·8 per 100 000 vaccinees; IRR 1·30, 95% CI 0·56–3·00). Similar findings were observed after the second dose at age 4 months (16 seizures among 219 515 infants, overall incidence 7·3 per 100 000 vaccinees; 6·7 per 100 000 *vs* 10·2 per 100 000 vaccinees; IRR 1·53, 95% CI 0·49–4·74) and 12-month dose (92 seizures among 262 641 infants, overall incidence 35·0 per 100 000; 34·1 per 100 000 *vs* 43·1 per 100 000 vaccinees; 1·26, 0·69–2·32). Sensitivity analysis for childhood vaccination at age 3 years 4 months when 4CMenB is not

routinely administered identified 26 seizures among 270 271 vaccinees (overall incidence 9·6 per 100 000 vaccinees), with a significant increase in seizure incidence in the period after 4CMenB introduction (IRR 2·91, 95% CI 1·13–7·48).

366 (41%) of 902 reports were of injection site or localised skin reactions, or both (which included all relevant MedDRA preferred terms), of which 120 (33%) were reported as serious. Serious criteria were often based on the presence of multiple reactions (eg, pain, swelling, and redness). Most reports of seriousness related to the local reaction was a result of the severity or duration of the reaction, including the ability to move their vaccinated limb or bear weight. Overall, 663 individual preferred terms were included in these reports, of which 377 (57%) were reported to be recovered or recovering (200 [30%] of 663 recovered, 12 [2%] recovered with sequelae, 165 [25%] recovering, 146 [22%] not recovered, and 140 [21%] not known). Similar proportions were observed for serious reports, with a total adverse reaction of 229 MedDRA preferred terms (68 [30%] recovered, five [2%] recovered with sequelae, 47 [20%] recovering, 45 [20%] not recovered, and 64 [28%] not known). Among 146 reports of the outcome as not recovered at the time of reporting, 57 (39%) were associated with a local mass, nodule, or induration. There were at least 160 reports referring to a mass or nodule at the site of injection, often described as being hard and pea-sized, and many persisted for weeks to months following vaccination, without other local symptoms. There were 16 (4%) of 366 reports of suspected cellulitis; however, the available information suggested they generally represented extensive local reaction following vaccination rather than secondary infection.

There were three (<1%) reports of Kawasaki disease after 4CMenB. One occurred in a 3-month-old child who became unwell the day following vaccination; this child developed coronary artery aneurysms and was diagnosed with Kawasaki disease a few days later. The second case was of a 2-month-old child who became acutely unwell with pyrexia 5 days after receiving 4CMenB, and was diagnosed with left and right coronary aneurysms, which recovered on treatment. The third case was diagnosed in a 4-month-old child but no additional information was provided. Using a conservative estimate of eight per 100 000 annual cases,[15] two to three cases of Kawasaki disease would be expected to have occurred within 7 days of vaccination among the 1·4 million vaccinated infants, and the observed-to-expected ratio was 1·40 (95% CI 0·29–4·08).

Five (<1%) of 902 reports had a fatal outcome, including one report of sudden infant death syndrome (SIDS), one report of sudden unexplained death, and three reports of death, all within 3 days of receiving 4CMenB alongside routine infant vaccinations. Two of the three reports of death were excluded from our observed versus expected analysis of SIDS or sudden unexplained death in infancy, as one was was subsequently confirmed as being due to an underlying medical condition, and one occurred in a child older than 12 months. In 2014, the UK background incidence of SIDS in the first year of life was 0·3 per 1000 livebirths,[16] with 83% of cases estimated to occur within the first 4 months of life and 40% between 2 and 4 months of age.[14] Consequently, 420 cases of SIDS would be expected to occur among 1·4 million vaccinated infants, including 168 cases between age 2 and 4 months and nine cases within 3 days of vaccination. With three reported cases of SIDS or sudden unexplained death in children aged 2–4 months in this age group, the observed-to-expected ratio was 0·44 (95% CI 0·12–1·14).

	Number of adverse events in serious reports	Number of adverse events in non-serious reports	Total
Cardiac disorders	34	1	35
Ear and labyrinth disorders	0	1	1
Eye disorders	17	0	17
Gastrointestinal disorders	101	65	166
General disorders and administration site conditions	434	593	1027
Immune system disorders	11	4	15
Infections and infestations	59	14	73
Injury, poisoning, and procedural complications	14	1	15
Investigations	65	15	80
Metabolism and nutrition disorders	44	26	70
Musculoskeletal and connective tissue disorders	44	12	56
Nervous system disorders	183	20	203
Pregnancy, puerperium, and perinatal conditions	1	0	1
Psychiatric disorders	110	86	196
Renal and urinary disorders	2	0	2
Respiratory, thoracic, and mediastinal disorders	88	11	99
Skin and subcutaneous tissue disorders	124	173	297
Social circumstances	1	0	1
Vascular disorders	46	29	75

MedDRA=Medical Dictionary for Regulatory Activities.

Table 1: **Distribution of suspected adverse reactions received by MedDRA System Organ Class**

	Total number of reactions (n=2429)	Total number of reactions reported as serious (n=1489)
Fatal	5 (<1%)	5 (<1%)
Not recovered or not resolved	373 (15%)	225 (15%)
Recovered or resolved	1147 (47%)	704 (47%)
Recovered or resolved with sequelae	25 (1%)	17 (1%)
Recovering or resolving	414 (17%)	221 (15%)
Unknown	465 (19%)	317 (21%)

Data are n (%). The reaction outcomes detailed in all the tables are stated at the time of reporting or last update, so might not always reflect whether there was subsequent recovery.

Table 2: **Reported outcomes of adverse events**

See Online for appendix

Our review of other selected adverse events (table 4) and all reported events (appendix) did not identify any new or unexpected vaccine-related adverse reactions.

43 001 children had their first PCV13 dose aged 6–10 weeks in the pre-4CMenB cohort (over 24 months) and 17 788 in the post-4CMenB cohort (over 14 months; table 5). There was no difference in the age at first vaccination for PCV13 between the two cohorts (p=0·863). Of the infants who received a second dose, 39 407 (96·9%) of 40 654 in the pre-4CMenB cohort and 13 777 (97·9%) of 14 079 in the post-4CMenB cohort had received the dose by 26 weeks. Of the infants who received a third dose, 29 080 (91·8%) of 31 681 in the pre-4CMenB cohort and 3106 (97·9%) of 3173 in the post-4CMenB cohort had received their third dose by 62 weeks. The log-rank test showed no significant difference in the Kaplan-Meier curves between the cohorts for the second (p=0·20) and third doses (p=0·18; appendix). For rotavirus vaccine, 41 577 had received their first dose in the pre-4CMenB cohort and 17 530 in the post-4CMenB cohort. There was no difference in the age at first vaccination for rotavirus between the pre-4CMenB and post-4CMenB cohorts (p=0·71). 33 596 (85·1%) of 39 494 infants who received a second rotavirus dose had the vaccine at age 10–14 weeks, with no difference in the Kaplan-Meier curves (log-rank p=0·63). A total of 17 432 infants received their first dose of 4CMenB at 6–10 weeks of age. Of these infants, 12 199 had follow-up at age 26 weeks and 11 602 (95·1%) had received a second dose by then. For the 13 760 infants who received a second dose of 4CMenB, 9558 (69·5%) received it at 14–18 weeks and 13 465 (97·9%) received it by 26 weeks of age. Of the 2117 infants who received a first dose and had follow-up at age 62 weeks, 1793 (84·7%) had received the second and booster doses by that time. Of 2982 infants who received a third dose, 1342 (45·0%) received it at age 50–54 weeks, and 2921 (98·0%) by 62 weeks of age (appendix). There were no differences in the Kaplan-Meier curves between the cohorts and between vaccines (appendix).

	Number of events*
Seizure	17
Febrile convulsion	26
Generalised tonic-clonic seizure	9
Petit mal epilepsy	2
Partial seizures	3
Epilepsy	1
Seizure anoxic	1
Seizure-like phenomena	1
Status epilepticus	1
Tonic-clonic movements	1
Total reports	55

MedDRA=Medical Dictionary for Regulatory Activities. *More than one of these event terms might be included in a single report (ie, 55 reports included 62 relevant terms).

Table 3: **Reports of seizures as defined by the MedDRA preferred terms**

Discussion

After more than 3 million doses given to about 1·29 million infants over 20 months across the UK, our analysis is the most comprehensive assessment of 4CMenB safety to date. The safety profile of 4CMenB has been broadly as expected, with no serious safety concerns identified so far, and the anticipated reactogenicity has not adversely affected compliance with subsequent vaccine doses. Alongside the data for vaccine effectiveness, the experience so far from the UK routine immunisation programme shows that 4CMenB has a favourable benefit–risk profile.

	Total number of events reported in the System Organ Class	MedDRA preferred terms (n)*	Comments
Infections	73	Meningitis (n=2), bacterial meningitis (n=1), meningism (n=2), aseptic meningitis (n=3), encephalitis (n=1), or sepsis (n=10)	Reports generally related to infants seeking medical attention for an acute febrile illness following vaccination and were observed, investigated, or empirically treated for bacterial infection; no cases of confirmed bacterial infection were reported
Respiratory disorders	99	Breathing difficulty, including apnoea (n=20), hypopnoea (n=7), dyspnoea (n=15), and respiratory arrest (n=8)	These suspected adverse reactions generally occurred within hours of vaccination in the context of a febrile, inconsolable crying, or transient hyporesponsive episode; of these reports, 13 were in premature infants in neonatal units who were reported to have apnoea or oxygen desaturation episodes following immunisation; the reports of cardiac disorders, circulatory collapse, and shock were in the context of other events, such as seizures and syncope, or as part of an acute febrile reaction; where outcome was reported, all were recovered or recovering at the time of reporting
Nervous system disorders	203	Floppy infant (n=15), hypotonia (n=21), hypotonic-hyporesponsive episodes (n=2), and unresponsiveness to stimuli (n=24)	All reports were acute, transient, and mostly in the context of a febrile illness; where outcome was reported, all were recovered or recovering at the time of reporting

MedDRA=Medical Dictionary for Regulatory Activities. *n is the number of reports including each MedDRA preferred term.

Table 4: **Summary of other selected adverse events categorised according to the MedDRA System Organ Class**

Before 4CMenB was first licensed in Europe in 2013, safety was assessed in approximately 5000 infants and toddlers in clinical trials.[17] These trials found that the vaccine was associated with higher frequencies of local reactions and fever than other routine infant vaccines, particularly when given concomitantly, which were mostly transient and of mild-to-moderate severity.[3,4] Isolated cases of Kawasaki disease and febrile seizures were reported in these trials, although a causal association was not established and no increased risk of any specific serious adverse event was identified. A further trial found that paracetamol prophylaxis decreased both local reactions and fever without affecting the immune responses to 4CMenB or concomitant vaccines.[6] Before 4CMenB was implemented in the UK's routine vaccination programme, large-scale use of the vaccine was limited mainly to a local outbreak in Quebec, Canada, in 2014, when 43 740 individuals aged 2 months to 20 years received an initial dose. During this campaign, active and passive surveillance found the safety profile to be as expected, based on the clinical trials' experience, and no serious safety concerns were identified.[18,19]

Following immunisation of most UK infants in the first 20 months of the routine programme, the Yellow Card reporting rate for 4CMenB was less than half of that observed for the meningococcal group C conjugate vaccine when it was first introduced in the UK in 1999 (MHRA, unpublished data), when Yellow Card reports were accepted only from health-care professionals. We had anticipated a higher reporting rate for 4CMenB given the expected higher numbers of fever and local reactions associated with the vaccine, because parents can now report through the Yellow Card system, and as 4CMenB has the statutory black triangle symbol for a new product to encourage adverse reaction reporting.[20] Communications from public health authorities to raise awareness of the possible reactogenicity and to encourage use of paracetamol prophylaxis might have led to the lower than expected numbers of adverse events reported. Alternatively, the expectation of higher reactogenicity associated with 4CMenB might have led to lower numbers of reporting, because people are less likely to report something they expect to happen.

Overall, the preponderance of reports of acute febrile reactions and local reactions, as well as most other suspected adverse reactions and the relative proportion of these reactions across different MedDRA System Organ Classes, was largely as expected and broadly typical of Yellow Card reporting for vaccines routinely given at this age. A large proportion of the Yellow Card reports for 4CMenB also included the other concomitant routine vaccinations as co-suspect. The only unexpected observation from our study has been that almost half of the reported local reactions involved a subcutaneous nodule at the injection site, which was not associated with other symptoms, but often persisted for up to several months. Since a national recommendation was made for 4CMenB to be administered alone into the left lower limb, a causal association is possible. Such reports were not associated with any particular batch, and the available information does not allow us to identify any risk factors or speculate on the inflammatory mechanism for such nodules. We also could not derive a frequency of such events from passive surveillance but, based on these reports, the prescribing information about 4CMenB has been updated to include persistent nodules at the injection site as an expected local reaction.[21]

We received a number of serious Yellow Card reports of fever, but in many of these cases it was possibly the investigations—such as blood tests, lumbar punctures, and antibiotic treatment—as well as the subsequent hospital attendance or admission that prompted reporting of these cases as adverse events. These reports were not associated with serious outcomes or sequelae. Our analysis was not able to quantify the risk of invasive procedures such as lumbar puncture following 4CMenB, and there might be a greater propensity to report severe febrile events, including those resulting in hospital admission, via the Yellow Card Scheme. Additionally, our analysis was not able to evaluate the effect of paracetamol prophylaxis on reducing febrile reactions. However, separate studies in the UK have reported an increased rate for attendance at general practices or admission to hospitals for fever after 4CMenB at age 2 months and 4 months, with an associated increase in the number of investigations for bacterial infection.[22–26] These findings are perhaps not surprising given the current National Institute for Health and Care Excellence guidelines, which have a low threshold for investigation of fever in infants younger than 3 months.

	Pre-4CMenB cohort		Post-4CMenB cohort	
	Total number of doses given	Number (%) of doses given by recommended age	Total number of doses given	Number (%) of doses given by recommended age
Pneumococcal conjugate vaccine*				
Dose 1	43 001	43 001 (100%)	17 788	17 788 (100%)
Dose 2	40 654	27 133 (66·7%)	14 079	9800 (69·6%)
Dose 3	31 681	11 589 (36·6%)	3173	1440 (45·4%)
Rotavirus vaccine†				
Dose 1	41 577	41 577 (100%)	17 530	17 530 (100%)
Dose 2	39 494	33 000 (83·6%)	16 151	13 660 (84·6%)
4CMenB‡				
Dose 1	NA	NA	17 432	17 432 (100%)
Dose 2	NA	NA	13 760	9558 (69·5%)
Dose 3	NA	NA	2982	1342 (45·0%)

4CMenB=four component meningococcal group B vaccine. NA=not applicable. *Routine age for second dose of pneumococcal conjugate vaccine defined as 14–18 weeks, and for third dose as 50–54 weeks. †Routine age for second dose of rotavirus vaccine defined as 10–14 weeks. ‡Routine age for second dose of meningococcal group B vaccine defined as 14–18 weeks, and for third dose as 50–54 weeks.

Table 5: **Compliance with vaccinations according to childhood immunisation schedule before and after 4CMenB introduction**

For the **NICE guidelines on assessment and initial management for fever** see https://www.nice.org.uk/guidance/cg160/resources/fever-in-under-5s-assessment-and-initial-management-pdf-35109685049029

In absolute terms, this increase would not impose a large additional burden on the health-care system, since it equates to about 1400 admissions across the entire UK in 1 year.[23] Although this number would represent only 2–3% of the total hospital attendances in children aged 1–6 months, it highlights a need to reconsider the best way to manage acute febrile illness in infants within 48 h of their routine vaccinations.[27] Further analysis of the effect of paracetamol prophylaxis on medical attendance for fever might also be required.

Another area of potential concern highlighted before the immunisation programme was whether the expected reactogenicity of 4CMenB might adversely affect completion of the infant immunisation schedule. Our analysis using CPRD data did not identify any evidence of reduced compliance with subsequent doses, with almost 95% of those who received the first dose also receiving the second dose of 4CMenB, PCV13, or rotavirus vaccines by 6 months. This finding is reassuring and consistent with national vaccine coverage estimates for each of the vaccine doses.[28–31] The derivation of vaccination exposure from CPRD also showed good concordance with these national vaccine coverage data.

As with any form of passive surveillance, the Yellow Card Scheme has strengths and limitations. The main strengths are that the system covers the entire UK population, is permanent, easily accessible, and allows any member of the UK public to report a suspected adverse reaction in near real-time. It is, therefore, capable of rapidly identifying very rare adverse reactions. The main limitations are that the level of under-reporting is variable, because the scheme relies on an individual to suspect that an adverse reaction might have occurred and then to report it. Furthermore, a Yellow Card report is not proof that the vaccine has caused the reported event, and a coincidental association is possible.

Our use of CPRD as part of the surveillance strategy has enabled the rapid identification of a very large number of vaccinated individuals. Despite the size of the database, more data are required to accurately identify sufficient numbers of some rare events that are potentially associated with vaccination for use in near real-time surveillance.[32] Therefore, CPRD has been used primarily here to complement, and enhance, passive surveillance methods. Other strengths and weaknesses of electronic health-care record databases are well understood.[33] In particular, the analyses presented in our study were limited because the day of birth was not available (only month and year of birth were available), meaning these data had to be imputed. Furthermore, because this study relied on the primary care data from CPRD, there is possibly under-recording and delays in recording in the general practitioners' medical record as this relies on the transfer of data from hospital letters. However, underestimating background events would in fact lead to more sensitive observed versus expected analyses. Furthermore, any bias is unlikely to differ substantially before and after the introduction of 4CMenB.

The observed versus expected analyses were not adjusted for possible under-reporting to the Yellow Card Scheme. Passive reporting of seizures (including febrile seizures) was within the expected range before 4CMenB introduction, and the observed versus expected ratio was consistent with the ecological analysis of the CPRD records. However, the absolute numbers of seizures identified in the CPRD analysis were low at younger ages (n=48 at ages 2 and 4 months), which is not surprising given that febrile convulsions are usually diagnosed after 6 months of age, meaning that up to a 4·7-times increased risk could not be excluded on the basis of the upper 95% CI in children aged 4 months. In children aged 12 months, a greater than 2·3-times increased risk can be excluded in this way. The sensitivity analysis of the number of seizures following vaccinations at age 3 years 4 months was done to explore temporal trends in the recording of seizure unrelated to the introduction of 4CMenB. The significant increase observed after 4CMenB introduction is potentially a chance finding but provides reassurance that the non-significant increases in risk seen in the younger age groups in the ecological analyses do not reflect a true association between 4CMenB and seizures. The three reports of Kawasaki disease received to date are also consistent with the expected background incidence given the number of children vaccinated and that there is no clear biological plausibility for vaccination as a cause of Kawasaki disease. Furthermore, our observed versus expected analysis of Kawasaki disease was based on a UK background annual incidence in children younger than 5 years of eight per 100 000, with some evidence of increased rates during winter and spring.[15] Because another study based on enhanced surveillance before 4CMenB introduction estimated the UK incidence of Kawasaki disease within 28 days of immunisation at 2 months of age to be 27·4 (95% CI 8·8–84·8) per 100 000 person-years and at 4 months of age to be 9·5 (1·3–67·7) per 100 000 person-years, our observed versus expected analysis was, therefore, conservative.[34] In relation to SIDS or sudden unexplained death in infancy, we might expect a high level of reporting for cases that occur within a few days of vaccination; and because the few reports received are within the expected background incidence, this finding raises no safety concerns

In conclusion, no significant safety concerns have arisen after widespread use of 4CMenB in young children in the UK, and the vaccine appears to have been well accepted by parents. As with all vaccines, it is important that the safety and long-term effect of the immunisation programme continue to be monitored in the UK.

Contributors

All authors were involved in the study design. SS, JW, and KD analysed data from the Clinical Practice Research Datalink and did the statistical analysis. PB, EW, and CG extracted and analysed the Yellow Card data.

PB wrote the first complete manuscript draft. All authors contributed to further drafts and approved the final manuscript.

Declaration of interests

We declare no competing interests. At the time of the study, all authors were employed by the Medicines and Healthcare Products Regulatory Agency, which is an Executive Agency of the UK Department of Health.

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