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Estimating primary care attendance rates for fever in infants after meningococcal B vaccination in England using national syndromic surveillance data

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ABSTRACT

Background: In September 2015, the United Kingdom became the first country to introduce the multi-component group B meningococcal vaccine (4CMenB) into a national infant immunisation programme. In early clinical trials 51–61% of infants developed a fever when 4CMenB was administered with other routine vaccines. Whilst administration of prophylactic paracetamol is advised, up to 3% of parents may seek medical advice for fever following vaccination. We used research-level general practitioner consultations to identify any increase in attendances for all-cause fever in vaccine-eligible infants following 4CMenB introduction in England.

Methods: Consultations for infant all-cause fever in the year following the vaccine introduction were identified from The Phoenix Partnership (TPP) ResearchOne general practice database using Read (CTV3) codes. Average daily consultation rates and incidence rate ratios (IRRs) were calculated for vaccine-eligible age groups and compared to the two years preceding vaccine introduction. The difference between pre- and post-vaccine all-cause fever consultations was estimated.

Results: All-cause fever consultations in vaccine-eligible 7–10 week olds were 1.6-fold higher (IRR, 1.58; 95% CI, 1.22–2.05) compared to the two previous years and 1.5-fold higher (IRR 1.47; 95% CI, 1.17–1.86) in 15–18 week-olds. There were no significant differences in 0–6 or 11–14 week-olds. Applying the difference between pre- and post-vaccine consultation rates to the 4CMenB vaccine-eligible age groups across England estimated 1825 additional fever consultations in the year following 4CMenB introduction.

Conclusions: We found a small but significant difference in all-cause fever consultation rates in vaccine-eligible infants who would have received 4CMenB with other vaccines.

1. Introduction

In September 2015, the United Kingdom (UK) became the first country to introduce the multicomponent group B meningococcal (MenB) vaccine (4CMenB; GSK Biologicals, Rixensart, Belgium) into a national, publicly-funded infant immunisation programme [1–3]. 4CMenB is licensed to protect against MenB, which is the major capsular group causing invasive meningococcal disease (IMD) in infants, young children and adults in Europe and other industrialised countries [1,4,5]. Approximately 600 people a year in England are diagnosed with invasive MenB disease, with around half the cases occurring in children under five years of age, especially infants under one year of age [3].

The UK infant 4CMenB programme was implemented as a two-dose schedule at 2 and 4 months of age, with a booster at 12 months. An opportunistic catch-up programme was also implemented, whereby infants attending for their routine three-month and four-month primary immunisations were offered the vaccine at a 3–4–12 and 4–12 month schedule, respectively. Infants born before 01 May 2015 were not eligible to receive 4CMenB [6,7]. The 4CMenB vaccination has been reported to have been well-accepted with high uptake. Preliminary estimates of vaccine coverage evaluated at the end of July 2017 indicated high uptake with

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95.7% coverage for one dose and 87.7% for two doses by six months of age [8].

4CMenB has now been shown to be highly effective, with MenB cases halving in vaccine-eligible infants within 10 months of the programme [9]. However, early clinical trials revealed that 51–61% of infants developed a fever over 38 °C after 4CMenB was administered with other routine infant vaccines [10]. Consequently, parents are advised to administer three doses of prophylactic paracetamol after primary immunisation, with the first dose given at the time of vaccination, followed by two additional doses at 4–6 h intervals [11]. In clinical trials, prophylactic use of paracetamol has been shown to halve the rates of post-vaccination fever without affecting immune responses to any of the vaccine antigens [12].

UK-based studies from Belfast [13], Scotland [14] and Oxford [15] demonstrated an increased risk of attendance at emergency departments for adverse effects, including fever, following 4CMenB vaccination and despite the administration of prophylactic paracetamol [13]. The Scottish study estimated an additional 1430 annual hospitalisations in the UK as a result of 4CMenB vaccination [14]. In Quebec, Canada, where this vaccine was given with recommendations for prophylactic paracetamol to all children as part of a regional MenB outbreak control campaign, up to 3% of parents still sought medical opinion for fever after 4CMenB [16]. Given that 776,000 infants in the UK are vaccinated with two primary immunisation doses every year [17], this rate of healthcare seeking behaviour reported in Quebec could potentially result in up to 47,000 additional medical attendances for fever per year.

Public Health England (PHE) coordinates a suite of national syndromic surveillance systems including daily consultation data from general practitioners (GPs) [18]. This study aimed to use research-level GP data from this national syndromic surveillance system to identify whether there had been an increase in GP attendances for all-cause fever in infants following 4CMenB introduction in England.

2. Methods

Fever consultations were identified using Read (CTV3) codes, a concept-based clinical coding system used by UK GPs [19,20]. Seventy-two Read codes describing fever, pyrexia and febrile convulsions were compiled by the multi-disciplinary research team and used to search GP consultation records (Supplementary Table S1).

The number of daily consultations with any of the pre-defined fever Read codes, by week of age, for children aged under one year for the twelve month period following the introduction of the vaccine (September 01, 2015 to August 31, 2016) was obtained from The Phoenix Partnership (TPP) ResearchOne GP database [21]. The ResearchOne database consists of pseudonymised clinical and administrative data drawn from electronic patient records held on the TPP SystmOne clinical management system (a system used by approximately 2700 (34%) GP practices across England) [22]. Historical data on the number of daily all-cause fever consultations for the twelve month periods (September to August) of the previous two years (2013–14 and 2014–15) were also extracted for comparison. Approval to use these data for this study was obtained from the TPP ResearchOne Project Committee.

We defined specific age-groups of vaccine-eligible and non-eligible infants (Table 1). The catch-up cohort of infants born in May and June 2015 would have been eligible for their first dose at 16 weeks and 12 + 16 weeks of age, respectively, during September 2015 only (i.e. during one of the 12 months across the 2015–16 surveillance year).

Table 1
Vaccine eligible and non-eligible age groups included in the study.

Age group (weeks)	4CMenB vaccine eligibility
0–6	Pre-vaccination infants
7–10	Eligible for first routine dose
11–14	Eligible for second routine immunisations (should not include 4CMenB)
15–18	Eligible for third immunisations (should include second 4CMenB dose in the routine cohort)

Average daily all-cause and fever consultation rates per 100,000 registered practice population were calculated for these designated age groups for the twelve-month period (September 01, 2015 to August 31, 2016) and the corresponding historical comparison periods.

Incidence rate ratios (IRRs) were calculated using Stata (v13) [23] to compare the all-cause fever consultation rate (by age group) for the twelve month period of September 01, 2015 to August 31, 2016 with the same twelve month periods of the previous two years combined (2013–14 plus 2014–15).

To assess the representativeness of the study population, the age/sex profile of all children aged under five years in the ResearchOne dataset in 2015 was compared to the 2015 mid-year estimated England age/sex profile [17] (Supplementary Fig. S1). The proportion of infants/children in each single year of age was broadly similar between the dataset population and the England population. The ResearchOne dataset infant population was therefore considered generally representative of the England population. This was used to estimate changes in all-cause fever consultations extrapolated to England pre- and post-4CMenB by age group and total all-cause fever consultations in the year following 4CMenB introduction.

3. Results

3.1. Study population

The number of GP practices in the study dataset increased from 358 on September 01, 2013 to 388 on August 31, 2016 and the registered practice population of infants (<1 year-olds) increased from 32,181 to 33,831. Infant all-cause daily consultations during September 01, 2013 to August 31, 2016 were consistent, with clear seasonal peaks during each winter period (Fig. 1).

3.2. All-cause fever consultations

Over the 3-year study period, there were 2,149,987 all-cause infant consultations of which 5593 were recorded as fever (0.26%). Of these fever consultations, 1029 (18.4%) were for infants aged 0 to 18 weeks. In this age group, the most frequently recorded clinical diagnoses were "Pyrexia" and "Fever symptoms", accounting for 44.7% of the fever consultations.

During the year following 4CMenB introduction, there were 414 fever consultations in 0–18 week-olds (0.10% of total, all-cause consultations), with an average of 1.9 daily fever consultations. The average daily all-cause fever consultation rate in 2015–16 was 11.18 per 100,000, higher than in the same periods of 2013–14 and 2014–15 (9.55 per 100,000 and 7.58 per 100,000 respectively) (Fig. 2).

3.3. Incidence rate ratios

In the year following 4CMenB introduction, all-cause fever consultation rates in 7–10 week olds were 1.6-fold higher (IRR 1.58,

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