Risk of hospitalisation with fever following 4CMenB vaccination: self controlled case series analysis

Heather Murdoch¹, Lynn Wallace², Jennifer Bishop², Chris Robertson³,⁴, J. Claire Cameron¹

¹Immunisation Team, Health Protection Scotland, National Services Scotland, 5 Cadogan Street, Glasgow, G2 6QE

²Consultancy Services, Information Services Division, National Services Scotland, 5 Cadogan Street, Glasgow, G2 6QE

³University of Strathclyde, Department of Mathematics and Statistics, 26 Richmond Street, Glasgow G1 1XH,

⁴International Prevention Research Institute, Lyon, France

✉ Corresponding author: heather.murdoch@nhs.net

Tel: 00 44 141 300 1159
ABSTRACT

Objective
To investigate a possible association between fever admissions and 4CMenB vaccine

Design
4CMenB is given at 8 and 16 weeks in the first year of life. Self controlled case series using linked routinely collected healthcare data, where the risk period was the 3 days immediately following receipt of a vaccine dose.

Patients
Children aged under one year in Scotland pre- and post-introduction of 4CMenB vaccine

Main outcome measures
Hospitalisations for fever attributable to 4CMenB vaccine

Results
The post-introduction model showed an increased risk in the three days after dose 1 (relative incidence (RI), 10.78; 95% CI, 8.31, 14.00) and dose 3 (RI, 9.80; 95% CI, 7.10, 13.62), with a smaller increased risk after dose 2 (RI, 2.20; 95% CI, 1.27, 3.82). The magnitude of these effects was greater than in the pre-introduction model. The attributable fractions were 90.7%, 54.8% and 89.7%, equating to 162, 14 and 84 vaccine attributable cases per 100,000 doses respectively (Table 2).

This is equivalent to 103 extra hospitalisations in Scotland annually, based on a birth cohort of 55,100 and extrapolated to 1440 across the UK based on a birth cohort of 777,165.

Conclusion
There is an increased risk of hospital admission with fever within three days of the routine childhood immunisations at 8 and 16 weeks following introduction of 4CMenB vaccine. The results indicate that further understanding of current use of prophylactic paracetamol is
needed and that communication to parents and health professionals may need re-examined
to reinforce guidance.
INTRODUCTION

Meningococcal disease is a systemic bacterial infection caused by *Neisseria meningitidis*, an organism commonly carried harmlessly in the nasopharynx.[1] In the UK, meningococcal disease serogroup B is responsible for the highest number of cases and remains the main cause of infant deaths from infectious disease.[2] The disease has a rapid onset and even with prompt treatment survivors can be left with serious long term sequelae such as deafness, epilepsy and limb amputations.[3] Vaccination is therefore the most effective control measure. Although recent years have seen a decline in meningococcal disease across the UK, new virulent strains can arise resulting in national outbreaks such as MenW, which prompted introduction of MenACWY vaccine into the adolescent and student programme.[2,4]

The 4CMenB vaccine, Bexsero® was introduced in Scotland in September 2015 and offered to all babies born on or after 01 July, 2015 at their routine appointments at 8 weeks, 16 weeks and 12-13 months.[5] There was also an initial catch up programme for babies born on or after 1 May 2015 and who were attending for vaccinations at 3 and 4 months. Fever is a known side-effect when administered alongside other routine vaccines, with highest rates within 6 hours. Other side-effects such as irritability, drowsiness and loss of appetite were also reported.[6,7,8] Results of a clinical trial indicated that administration of prophylactic paracetamol significantly reduced reports of fever by 40-50% to around the expected occurrence prior to the introduction of 4CMenB. Reports of other symptoms were also reduced.[9] As a result, the UK Joint Committee on Vaccination and Immunisation (JCVI) recommended 3 doses of infant paracetamol following vaccinations at 8 and 16 weeks, with the first dose given at the time of the vaccination followed by 2 further doses at 4-6 hour intervals, regardless of whether fever develops.[4]

Suspected Adverse Events Following Immunisation (AEFI) are reported to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) via the yellow card scheme. We
developed a supplementary method to proactively identify potential AEFI resulting in hospital admission. [10] This has been used to monitor rotavirus, shingles, HPV and more recently 4CMenB vaccines. Ongoing monitoring showed a signal for fever admissions corresponding to the start of the 4CMenB programme. Due to inherent time lags in completion of hospital admission data, this pattern of repeating signal became more conclusive after a few months. We therefore decided to investigate, conducting a self-controlled case series analysis (SCCS), using linked routine healthcare data. This method has previously been used to investigate potential AEFI, having advantages including control of sex, location, and underlying health.[11,12,13]

METHODS

Self controlled case series (SCCS) analysis

SMR01 data is held by Information Services Division (ISD) and unit of analysis is an “episode”. An episode is generated when a patient is discharged; transferred between hospitals or specialties or to a different consultant. Episodes are grouped as continuous inpatient stays (CIS) and each CIS defined as a case.

Fever cases were extracted from September 2014 until July 2016 for infants using the ICD10 code “R50” and included if recorded in any diagnostic position during the hospital stay. Age was defined as on admission.

Vaccination records for all children born between January 2013 and August 2016 were extracted from the Scottish Immunisation & Recall System (SIRS). This study concentrated on vaccinations given at 8, 12 and 16 weeks. DTaP-IPV-Hib records were examined, to enable a consistent comparator pre- and post-introduction of 4CMenB. In Scotland, uptake rates by 12 months of age for complete primary courses of immunisation against DTaP-IPV-Hib are high, with rates around 97%. Uptake of 4CMenB vaccine for the first routine cohort (born July 2015) was 95.7% for one dose and 82.4% for two doses of vaccine at six months.
of age, rising to 94.5% for two doses at age 12 months [14,15]. Table 1 shows the current routine childhood schedule for infants.

Table 1 Routine childhood immunisation schedule in Scotland (2016)

<table>
<thead>
<tr>
<th>Age</th>
<th>Immunisations</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 weeks</td>
<td>• DTaP/IPV/Hib</td>
</tr>
<tr>
<td></td>
<td>• Pneumococcal (PCV)</td>
</tr>
<tr>
<td></td>
<td>• Rotavirus</td>
</tr>
<tr>
<td></td>
<td>• Meningococcal group B (4CMenB)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>• DTaP/IPV/Hib</td>
</tr>
<tr>
<td></td>
<td>• Rotavirus</td>
</tr>
<tr>
<td></td>
<td>• Meningococcal group C (MenC)*</td>
</tr>
<tr>
<td>16 weeks</td>
<td>• DTaP/IPV/Hib</td>
</tr>
<tr>
<td></td>
<td>• Pneumococcal (PCV)</td>
</tr>
<tr>
<td></td>
<td>• Meningococcal group B (4CMenB)</td>
</tr>
</tbody>
</table>

* MenC was removed from the routine childhood immunisation schedule in September 2016

Vaccination records were matched with fever cases using the Community Health Index (CHI) number. Fever cases without a CHI number were excluded, which resulted in one case being excluded. Patients were included whether they had received no, partial or full (three) doses of DTaP-IPV-Hib. Eight fever cases did not match to SIRS records and were included as non-vaccinated patients.

Patients were excluded if the time between birth and first dose of DTaP-IPV-Hib was less than 20 days as assumed to be due to inaccurate recording, resulting in exclusion of 5 fever cases.

Age in days at time of vaccination and fever admission were calculated and the risk period defined as 3 days post-DTaP-IPV-Hib vaccination. Figure 1 shows an example of a SCCS design of a single patient timeline with 2 fever admissions.

The analysis was based on each case of fever, rather than just the first case for each patient, consistent with the study methodology. The rationale was that the risk after each
vaccine dose at 8, 12 and 16 weeks would differ due to the differences in vaccination schedule; therefore each dose was assigned a different risk factor (1, 2 and 3). The observation period (the rest of the year) was assumed to have the same “risk” and therefore coded as 0 (Figure 1).

The data were split into pre- and post-4CMenB vaccine introduction, from September 2014 to August 2015 and September 2015 to June 2016 respectively, and the RIs for each time period calculated. In the pre-4CMenB vaccination period the RIs are for the DTaP-IPV-Hib doses while in the post-4CMenB vaccination period for DTaP-IPV-Hib /4CMenB doses.

Comparison of the two sets of RIs demonstrates the impact of the 4CMenB vaccine.

The relative incidence compares the period 3 days after vaccination for an individual to all days not included in that period for the same individual. Age was included as a covariate, taking different values every 30 days. The analysis was carried out as a conditional logistic regression, stratified by individual, with covariates of age group and whether or not the individual was in or out of the exposure period. The age group effect was used to control adjust for the different hospitalisation rates in for example, months 0-6 compared to months 6-12, and so the effect of the exposure period takes into account the known differences in hospitalisation rates associated with age. Age was restricted to those who were under 1 year at admission.

The case series analysis was carried out in R using the clogit function in the survival package to account for the repeated observations on the subjects and an offset of the logarithm of the interval length to account for the exposure period. The attributable fractions were calculated using the relative incidence (RI-1)/RI x 100 for each risk period of 3 days after each dose of DTaP-IPV-Hib. This was applied to calculate the attributable number of cases and a rate calculated using the relevant mid-year population estimates. Confidence intervals were obtained using a parametric bootstrap approach where the log relative risks were sampled from a normal distribution and the numbers of cases from Poisson
distributions, centred at the observed values. Medians and upper and lower 2.5%
percentiles are reported from the 10,000 bootstrap simulations.

3 Analysis of admissions for seizures including febrile seizures
SMR01 data was extracted for admissions for all cause seizures including febrile seizures
(R56, G40, G41) within 3 days of the routine child vaccinations at 8, 12 and 16 weeks and
compared pre- and post-vaccine introduction.

7 Analysis of lumbar puncture procedures
SMR01 data was extracted for admissions which included lumbar puncture procedures (LP)
using OPCS Classification of Interventions and Procedures version (OPCS4) codes
'A553','A558','A559' from 2011 to 2016 within 3 days of the routine child immunisations at 8,
12 and 16 weeks and compared pre- and post-vaccine introduction.

12 Analysis of Length of Stay
Length of stay was calculated from the extracted SMR01 data within 3 days of the routine
childhood vaccinations at 8, 12 and 16 weeks and compared pre- and post-vaccine
introduction.

16 Ethics
The investigation received approval from the NHS National Services Scotland Privacy
Advisory Committee.

19 RESULTS

Self controlled case series analysis
A total of 1435 fever cases were identified; 670 before 4CMenB introduction and 765
following introduction of the programme (Table 2).

Table 2 Number of fever cases pre- and post-4CMenB vaccine introduction

<table>
<thead>
<tr>
<th></th>
<th>Pre-4CMenB</th>
<th>Post-4CMenB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8
In the pre-introduction model, there was a significantly increased risk in the three days after both dose 1 and dose 3 (RI, 3.01; 95% CI: 1.99, 4.53, and RI, 2.51; 95% CI: 1.47, 4.27), (Table 3). The attributable fractions were 66.8% and 60.1% respectively. Calculation of vaccine attributable cases, based on an approximate vaccine uptake of 95%, was equivalent to 33 (95% CI: 20, 49) and 16 (95% CI: 7, 28) cases per 100,000 doses respectively. Dose 2 was not associated with an increased risk of fever admission (RI, 0.43; 95% CI: 0.14, 1.36).

The post-introduction model showed a greater increased risk in the three days after both dose 1 (RI, 10.78; 95% CI: 8.31, 14.00) and dose 3 (RI, 9.80; 95% CI: 7.10, 13.62) with a smaller increase risk after dose 2 (RI, 2.20; 95% CI: 1.27, 3.82), compared to the pre-introduction model. The attributable fractions were 90.7%, 54.8% and 89.7%, equivalent to 162 (95% CI: 129, 195), 14 (95% CI: 5, 25) and 84 (95% CI: 62, 109) vaccine attributable cases per 100,000 doses respectively (Table 3).
Table 2 Relative incidence of fever admission and attributable cases (per 100,000 vaccinations) in the 3 days following vaccination with DTaP-IPV-Hib dose pre- and post-introduction of 4CMenB

<table>
<thead>
<tr>
<th>Model and dose</th>
<th>Pre-4CMenB vaccine introduction</th>
<th>Post-4CMenB vaccine introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of events</td>
<td>RI (95% CI)</td>
</tr>
<tr>
<td>Dose 1</td>
<td>27</td>
<td>3.00 (1.99, 4.53)</td>
</tr>
<tr>
<td>Dose 2</td>
<td>3</td>
<td>0.43 (0.14, 1.36)</td>
</tr>
<tr>
<td>Dose 3</td>
<td>15</td>
<td>2.51 (1.47, 4.27)</td>
</tr>
</tbody>
</table>
The total number of additional hospitalisations was estimated by comparing attributable cases before and after the introduction of 4CMenB vaccine. Therefore following dose 1 the attributable cases would be 128/100,000 (95% CI: 93, 165), which in a birth cohort of 55,100 (Scotland 2015) equivalent to 68 (95% CI: 49, 90) hospitalisations, extrapolated to 940 (95% CI: 680, 1210) in the UK (UK, 2015). Similarly, for dose 3 the attributable cases would be 67 (95% CI: 43, 94) per 100,000 equating to 35 extra hospitalisations in Scotland (95% CI: 22, 50) and 490 (95% CI: 680, 1210) in the UK. Therefore combining doses 1 and 3 together this would amount to 103 (95% CI: 80,126) extra hospitalisations in Scotland per year or 1440 (95% CI: 1120, 1770) across the UK.

Seizures including febrile seizures

The proportions of seizure cases within 3 days of the routine childhood immunisations at 8, 12 and 16 weeks were compared pre- and post-vaccine introduction. There were 12/765 (1.57%) cases pre-introduction period (Sep 2013 to August 2015) compared to 8/374 (2.13%) in the post- period (Sep 2015 to August 2016) (P=0.49).

Lumbar punctures

The proportions of LPs within three days of routine childhood immunisations at 8, 12 and 16 weeks were compared pre- and post-vaccine introduction. There were 17/520 (3.27%) in the pre-introduction period compared to 22/408 in the post-introduction period (5.39%) (p=0.11), which is not statistically significant. However as the absolute numbers are very low this may need monitored further.

Length of Stay

Most cases had a short length of stay of either '0' or '1' day. Following 4CMenB introduction, the increase was observed in short length of stays particularly with the '0' day stays outnumbering the '1' day stays approx 2:1. Following Dose 1 there were 13/27 (48.1%) of cases of <1 day length of stay pre-4CMenB introduction compared to 48/95 (50.5%)
(p=0.83). Following dose 3, there were 8/15 (53.3%) cases of <1 day length of stay pre-
4CMenB compared to 26/51 (50.9%) post-4CMenB (p=0.87).
DISCUSSION

This study has demonstrated the usefulness of proactively monitoring hospital admission data for potential AEFI and the ability to further investigate by linking to vaccination records using CHI.

The results have shown a significant increased risk of hospital admission with fever within three days of the routine childhood immunisation schedule at 8 and 16 weeks (dose 1 and 3) following introduction of 4CMenB. There was also a small but significant risk following vaccinations at 12 weeks post-introduction of 4CMenB. This is likely related to the catch-up campaign at the start of the programme as admissions mainly occurred in the first couple of months of the programme.[5] The results indicated that markers of severity such as all convulsions, including febrile, and length of stay were not significantly increased consistent with clinical trial findings.[8]

To provide context, we estimated the number of additional hospitalisations by comparing attributable risk pre- and post-introduction of 4CMenB vaccine as equivalent to 103 extra hospitalisations annually in Scotland and 1,440 across the UK.

Analysis of lumbar puncture procedures was also carried out pre- and post-4CMenB vaccine. There is currently insufficient evidence that an observed increase is associated with 4CMenB however as the numbers are low this may need monitored further. This is particularly relevant as current guidance from NICE on management of fever in under 5s recommends lumbar puncture is carried out on all infants aged 1-3 months with fever who appear unwell.[16]

An increased risk of fever admissions prior to the introduction of the 4CMenB following vaccinations at 8 and 16 weeks (dose 1 and 3) was observed. This timing coincides with pneumococcal conjugate vaccine (PCV) administration. Fever is mentioned as a potential
adverse reaction for PCV with an increased level observed in clinical trials.[17] However the rates of admission were significantly higher following the introduction of 4CMenB vaccine. The increased risk of fever associated with 4CMenB vaccine when given along with other routine vaccinations is a known adverse event.[8] However results of a phase 2 randomised controlled trial indicated that giving prophylactic paracetamol reduced post-vaccination reactions including fever down to pre-4CMenB rates, without impacting on immunogenicity.[9] Therefore the JCVI recommended prophylactic paracetamol at the time of the vaccinations followed by a further 2 doses.[4,5] Adherence to this recommendation is not known. It is possible, particularly given the very young age of infants at the time of the first vaccination, that there may be some reluctance to give paracetamol before a fever is actually evident, which would reduce its impact. It is therefore unclear if any of these hospitalisations were avoidable. This is further strengthened by an initial analysis of community prescribing data from September 2015 until the October 2016 which showed approximately 1400 prescriptions were written by pharmacists for paracetamol 120mg/5ml liquid per month in Scotland, as part of a public health service for prophylaxis of post 4CMenB fever.[4,18] This is lower than expected given the high uptake of 4CMenB and size of the birth cohort (approximately 5000 births per month). It is not known however if this represents a real under use of paracetamol or whether parents are not getting prescriptions as they already hold stocks or purchase elsewhere. Recent studies have shown a rise in infants presenting to Accident and Emergency departments and consulting with general practitioners for fever despite recommendation for prophylactic use of paracetamol.[19,20] There may also be other factors which led to the increased risk of fever admissions post-introduction, including parental awareness of fever as a known side effect of 4CMenB vaccine, which we are unable to quantify.
The results indicate that further understanding of current use of prophylactic paracetamol is needed and that communication to parents and health professionals may need re-examined to reinforce guidance.

LIMITATIONS

There are a number of limitations to this study. To include as much data as possible in the post-introduction cohort, we did not limit admissions by date of birth. Therefore we may not capture every patient's first full year i.e. patient could be born in Feb 2016, admitted April 2016 and may or may not have had their vaccines. The post-4CMenB model was limited including a full year's data due to inherent delay in SMR01 completion at the time of analysis. In addition, we only looked at fever hospitalisations and were not able to assess impact on other areas including primary care consultations and attendances at A&E. Furthermore, we were only able to look at a relatively short period of time following vaccine introduction. However, none of these should alter the overall result of the study, but rather increase its power as further data accumulates.

CONCLUSION

There is an increased risk of admission to hospital with fever within three days of the routine childhood immunisation schedule at 8 and 16 weeks following the introduction of 4CMenB vaccine. Other markers for potential severity such as seizures including febrile have not significantly increased. There is a need for more information on paracetamol use among parents and care givers. Current communication to parents and health professionals on the importance of the use of prophylactic paracetamol may also need re-examined.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Child Health Team, Information Services Division (ISD) for provision of the SIRS data and William Malcolm, Pharmaceutical Advisor, HPS and Helen
Watson, Information Analyst ISD for the preliminary prescribing data. We are also grateful to all across NHS Scotland who contribute to high quality data recording and provision.

COMPETING INTERESTS

None declared

FUNDING

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

What is already known on this topic

Fever occurs at increased levels following 4CMenB vaccination, leading to prophylactic paracetamol being recommended for doses at 8 and 16 weeks.

Adherence to this recommendation is not known.

What this study has added

There are an estimated extra 1,440 hospitalisations for fever associated with 4CMenB vaccine each year across the UK.

Parents and vaccine providers should be reminded about the importance of following paracetamol recommendations, not waiting until fever develops.
1

Reference List


Nainani V BJSM. Presentation to Accident and Emergency following immunization with capsular group B meningococcal vaccine. 20th International Pathogenic Neisseria Conference, 4th-9th September 2016. Manchester, United Kingdom. 4-9-2016. 14-6-2017.

Ref Type: Abstract

Harcourt SMRBCCHLSEAJSGE. Infant fever trends following the launch of the meningococcal B vaccine in the UK. International Society for Disease Surveillance 2016 Conference Abstracts. 6-12-2016. 14-6-2017.

Ref Type: Abstract