The risk of Kawasaki disease after Pneumococcal conjugate & Meningococcal B vaccine in England: a self-controlled case-series analysis

Keywords: Kawasaki disease; Pneumococcal conjugate vaccine; Meningococcal B vaccine; self-controlled case-series

Abstract

Kawasaki disease (KD) is an uncommon condition occasionally reported after childhood vaccination. Admissions with a KD-compatible diagnosis identified from a national database in England were linked to immunisation records to investigate the risk after pneumococcal conjugate (PCV) or meningococcal B (MenB) vaccines. Both are given at 2/4/12 months of age but were introduced sequentially, allowing their effects to be separately assessed. A total of 553 linked admissions in 512 individuals were validated as KD. The relative incidence (RI) within 28 days of PCV doses 1 or 2 measured by the self-controlled case-series method was 0.62 (95% confidence interval (CI) 0.38-1.00) with a significantly decreased risk after dose 3 (RI 0.30 (95% CI 0.11-0.77)). For MenB vaccine, the RI after doses 1 or 2 was 1.03 (95% CI 0.51-2.05) and 0.64 (95% CI 0.08-5.26) after dose 3. This study shows no evidence of an increased risk of KD after either vaccine.

Introduction

Kawasaki disease (KD) is an uncommon condition of unknown aetiology that mainly affects children under the age of 5 years. Symptoms include a persistent fever (for at least 4 days), polymorphous rash, lymphadenopathy and mucocutaneous changes. In 20-25% of untreated patients, it can cause coronary artery aneurysms; KD is the most common cause of acquired heart disease in children in high income countries. KD is commonly treated with intravenous immunoglobulin (IVIg) and aspirin. The disease occurs globally but has the highest incidence in Japan, Korea and Taiwan (1). A study using primary care data from the United Kingdom (UK) reported an incidence of 9.1 per 100,000 person years in children <5 years of age, with no obvious increase in the period 2008-2012 (2).

Individual cases of KD have been reported following childhood vaccination (3-5), including with the pneumococcal conjugate vaccine (PCV) and meningococcal serogroup B vaccine (4CMenB™, also known as Bexsero™) (6).A post-licensure safety study of the 13-valent

PCV (PCV13) using the Vaccine Safety Datalink network in the United States (US) suggested a possible elevated risk of KD after PCV13 when compared with the 7-valent PCV (PCV7) (7). However, no elevated risk after PCV13 was found in a subsequent study using an alternative US linked dataset (8). In Singapore, a post-licensure study of PCV13 showed an increased risk of complete cases of KD, defined as prolonged fever with at least 4 typical clinical manifestations, but this was only evident after the first dose (9). The risk of KD after MenB vaccine has not, to date, been assessed in a post-licensure epidemiological study.

In the UK, PCV was first introduced into the routine immunisation schedule as a 7-valent vaccine (PCV7) in September 2006 and was replaced by the 13-valent PCV (PCV13) in April 2010. Prior to January 2020 (when the UK changed to a two-dose PCV13 schedule), infants received two PCV13 doses at 2 and 4 months of age with a booster dose at around age 12 months. Meningococcal B vaccine (MenB) was added to the UK schedule in September 2015, and is also given as a three-dose schedule at 2, 4 and 12 months.

Using the self-controlled case-series method (SCCS) and a large linked dataset, we investigated whether there is an increased risk of KD in the 4 weeks following PCV or MenB vaccination. The sequential changes to the UK vaccination schedule since 2006 allows for the effect of each vaccine, if any, to be assessed.

Material and methods

Finished Consultant Episodes of KD (ICD10 code M303) were identified in the first four diagnosis fields from the Hospital Episodes Statistics (HES) dataset, which holds information on all admissions to a National Health Service (NHS) hospital in England (10). An event within 30 days of an earlier event was considered part of the same episode. Using patient-unique NHS numbers, episodes for KD in children aged 0 to 731 days at admission in the period 01/09/2006 to 31/07/2018 were linked to vaccination histories held on the Child

Health Information System (CHIS) System C, which represents approximately 40% of the birth cohort in England and is geographically dispersed. Analysis was carried out on KD admissions whose vaccination history was in the CHIS. In addition to PCV and MenB vaccination records, information on some other concomitant vaccines recommended at 2, 4 and 12 months throughout the study period was also extracted and linked; for the first and second doses of PCV and MenB this was a diphtheria/tetanus/acellular pertussis (DTaP) containing vaccine and for the booster dose, it was the measles/mumps rubella (MMR) vaccine.

Three different methods were applied to validate the ICD10 coding of KD HES episodes. Cases were considered validated if they had one or more of the following: an ICD10 code for coronary artery aneurysm (ICD10 I254) seven days before the KD HES episode or up to and including 90 days after; an Office of Population and Censuses Survey (OPCS) code in HES for immunoglobulin (IVIg) use (X961/ X353) seven days either side of the KD episode; or linkage with a record of IVIg administration in the National Immunoglobulin Database (which holds details of all NHS prescriptions of IVIg for rare disorders) and with date of receipt of IVIG 0-10 days after the admission date for the KD episode.

Analysis was carried out using the SCCS method, which only uses cases and automatically controls for fixed individual level confounding, such as sex and socio-economic status (11). Using this method, the relative incidence (RI) is calculated by assigning person time for each individual into post-vaccination risk and background periods, and comparing the rate at which KD events occur in each period. The risk period examined was 0-28 days after each dose with a pre-specified sensitivity analysis splitting the risk period into 0–7 days and 8–28 days. The analysis was split into dose 1 or 2 with dose 3 separately due to a low number of cases in children under 12 weeks of age (figure 1).

When applying the SCCS method the event itself should not influence the exposure (vaccination), however it is likely that a temporary deferral of vaccination may occur due to the KD hospitalisation. To allow for this when using the method, a 7 day window prior to the date of vaccination is excluded from the baseline (since this will have few events), and in a sensitivity analysis a 14 day window and no window were also assessed. Age was adjusted for as a time varying confounder in the SCCS analysis using 4-week age intervals.

As the valency of the PCV changed during the study period, an interaction between PCV vaccine type and risk was included for those who received PCV. Although MenB was usually given at the same time as PCV, the inclusion of the period prior to introduction of MenB allows estimation of the PCV effect in the absence of MenB, and thus allows for the estimation of the independent effect of MenB.

Results

A total of 2,018 HES episodes in 1,691 children had the ICD10 code for KD. Of these, 1,060 HES episodes (51.9%) linked to a child in CHIS who had received at least one of PCV or MenB vaccine. The KD diagnosis could be validated for 553/1060 (52.2%) linked episodes, of which 485 (87.7%) had the KD diagnosis recorded in the primary diagnosis field. Validation was by the National Immunoglobulin Database in 198/553 (35.8%) episodes, while 328 (59.3%) were validated by the additional ICD and OPCS coding within HES and 27 (4.9%) episodes using all three methods. Fewer episodes could be validated in earlier years of the study as the National Immunoglobulin Database only started in 2008 and was initially incomplete. The 553 validated KD cases occurred in 512 children, of whom 27 had two and 14 between 3-5 episodes in the study period; 331 (64.6%) children were male. A KD diagnosis was observed to be rare in the first few weeks of life with a relatively stable

distribution up to a year of age and some evidence of a decline in numbers in the second year of life (Figure 1).

As per the UK immunisation schedule, PCV was usually given at the same time as a DTaP-containing vaccine for the first and second doses, and with MMR vaccine for the third dose. Following MenB introduction, the majority of doses were given concomitantly with PCV (Table 1). Of 553 validated KD episodes with a linked CHIS record, 25 occurred within 28 days of PCV given on its own, 47 episodes were within 28 days of PCV and Men B given concomitantly and there were no cases within 28 days with a Men B received on its own. The frequency distribution of the cases pre and post each vaccine dose revealed that for the third dose there was a relative deficiency of cases in the 4 weeks following vaccination (Figure 2). No cases were observed in the 7 day period before the third dose.

The SCCS analysis demonstrated no evidence of an increased risk in the 28 days after either PCV or MenB, or within the 0-7 or 8-28 day risk windows (Table 2). A significant reduction in risk was seen for PCV after dose 3 within the 0-28 day risk period (RI 0.30 (95% CI 0.11-0.77)) largely attributable to the reduction in the 8-28 day period (RI 0.19 (95% CI 0.05-0.78) (Table 2). After adjusting for the PCV effect, MenB vaccine showed no reduction in risk after the third dose (RI 0.64 (95% CI 0.08-5.26)). The results for PCV dose 3 were similar in the sensitivity analysis which removed the pre-vaccination low risk period, with a RI of 0.31 (95% CI 0.12-0.81) within the 0-28 day risk period and a RI of 0.29 (95% CI 0.11-0.75) when a 14 day rather than 7 day period prior to vaccination was excluded from the baseline. There was no evidence of a difference in the effect of the PCV7 and PCV13 when the interaction was tested (p=0.34 for doses 1 or 2 and p=0.62 for dose 3).

Discussion

Using the SCCS method, we found no evidence of an increased risk of KD after PCV (7- or 13-valent) or MenB vaccine. This is reassuring, given the potential signals for PCV from earlier studies (7) and anecdotal reports of cases occurring following MenB vaccination (6). In our study, the relative incidence estimates in the 28 days after PCV were generally less than one with a large and significantly reduced risk in the 8-28 days after the third dose (Table 2). The previous US studies (7,8) had insufficient power to stratify by dose or interval within the 28 day post-vaccination period, while the more recent study by Yung et al (9) did stratify by dose and showed a non-significantly reduced risk within 28 days of the 3rd dose (0.34 (95% CI 0.08-1.4)).

A protective effect against hospital admission for an infection is sometimes seen shortly after vaccination and has been attributed to a temporary healthy vaccinee effect resulting from children being more likely to be taken for vaccination when they are well than when incubating an illness (12). KD usually presents with fever and rash; these symptoms often precede admission by a few days, which could result in a similar temporary healthy vaccinee effect as our analyses were based on date of admission, and not onset of symptoms. However, the apparent protective effect of PCV against KD was maximal in the 8-28 day post-vaccination period which seems too long an interval to be explained by such a temporary effect. This raises the possibility that vaccination may have a protective effect during the 28 day post-vaccination period – a time when the immune response is maximal. The effect was significant only after the third dose which was given concomitantly with MMR vaccine for 376/430 (87%) PCV booster doses (Table 1). Such a putative protective effect could therefore be due to the MMR rather than PCV, especially as MMR is a live vaccine that requires an initial phase of vaccine virus replication during the week following vaccination before the immune response can be generated. The aetiology of KD is still unknown, as is the mechanism whereby IVIg has such a pronounced therapeutic benefit, although IVIg-induced

immunomodulatory effects are thought to underpin the response (13). A protective effect of PCV or MMR vaccine, mediated via an as-yet unknown immune regulatory effect, cannot therefore be discounted.

As in the earlier studies by Baker et al (7) and Yung et al (9) our study benefitted from the strengths of the SCCS design which automatically controls for time invariant individual level confounders that could give rise to bias if not adequately adjusted for in a cohort or case-control study. While we did not review individual case notes, the presence of coronary artery aneurysm or IVIg treatment in association with the KD admission provided compelling evidence of the accuracy of the diagnosis. Anyway, inclusion of some non-KD cases in the analysis would be unlikely to generate a significant protective effect.

In conclusion, while our study shows no evidence of an increased risk of KD after either PCV or MenB vaccine, the results are consistent with a protective effect of either PCV or MMR when given in the second year of life that merits further investigation.

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Table 1: Vaccines given concomitantly with PCV and MenB vaccine by dose in 512 children under 2 years of age with a validated ICD10 code for Kawasaki Disease and a linked immunisation record in CHIS

Vaccine	With	Dose1	Dose2	Dose3
PCV	No other	28	26	40
	DTaP	336	320	3
	MenB	5	1	11
	MMR	1	7	284
	DTaP/MenB	135	135	0
	DTaP/MMR	0	0	0
	MMR/MenB	0	0	92
	DTaP/MenB/MMR	0	1	0
MenB	No other	7	10	8
	DTaP	4	1	1
	PCV	5	2	10
	MMR	0	0	2
	DTaP/PCV	138	132	0
	DTaP/MMR	0	1	0
	MMR/PCV	2	2	88
	DTaP/PCV/MMR	0	1	0

Note: While the row totals have the same totals for the same vaccines in the PCV and MenB sections of the table the dose numbers can differ as the dose refers to PCV dose in the PCV part of the table and MenB dose in the MenB part of the table.

Table 2: Relative incidence (RI) and 95% confidence interval (CI) for admission to hospital in different post-vaccination risk periods in children under 2 years of age with a validated ICD 10 diagnosis for Kawasaki Disease and a linked PCV or MenB immunisation record in CHIS- 7 day pre-vaccination period excluded from the analysis.

Vaccine	Risk window (days)	Count	RI (95%CI)
PCV doses 1 or 2	0-28	36	0.62 (0.38-1.00)
	0-7	6	0.42 (0.16-1.11)
	8-28	30	0.68 (0.41-1.14)
PCV dose 3	0-28	5	0.30 (0.11-0.77)
	0-7	3	0.56 (0.15-2.06)
	8-28	2	0.19 (0.05-0.78)
MenB doses 1 or 2	0-28	14	1.03 (0.51-2.05)
	0-7	2	0.76 (0.15-3.87)
	8-28	12	1.10 (0.52-2.32)
MenB dose 3	0-28	1	0.64 (0.08-5.26)
	0-7	1	1.46 (0.15-13.89)
	8-28	0	0 (-)
PCV doses 1 ,2 or 3	0-28	41	0.51 (0.34-0.78)
MenB doses 1,2,or 3	0-28	15	1.03 (0.54-1.98)

Figure 1: Count of 553 hospital admission episodes for children with a validated ICD 10 diagnosis of Kawasaki Disease and with a linked PCV or MenB vaccination record by age in 4 week intervals between 01/09/2006 and 31/07/2018 in children under 2 years of age.

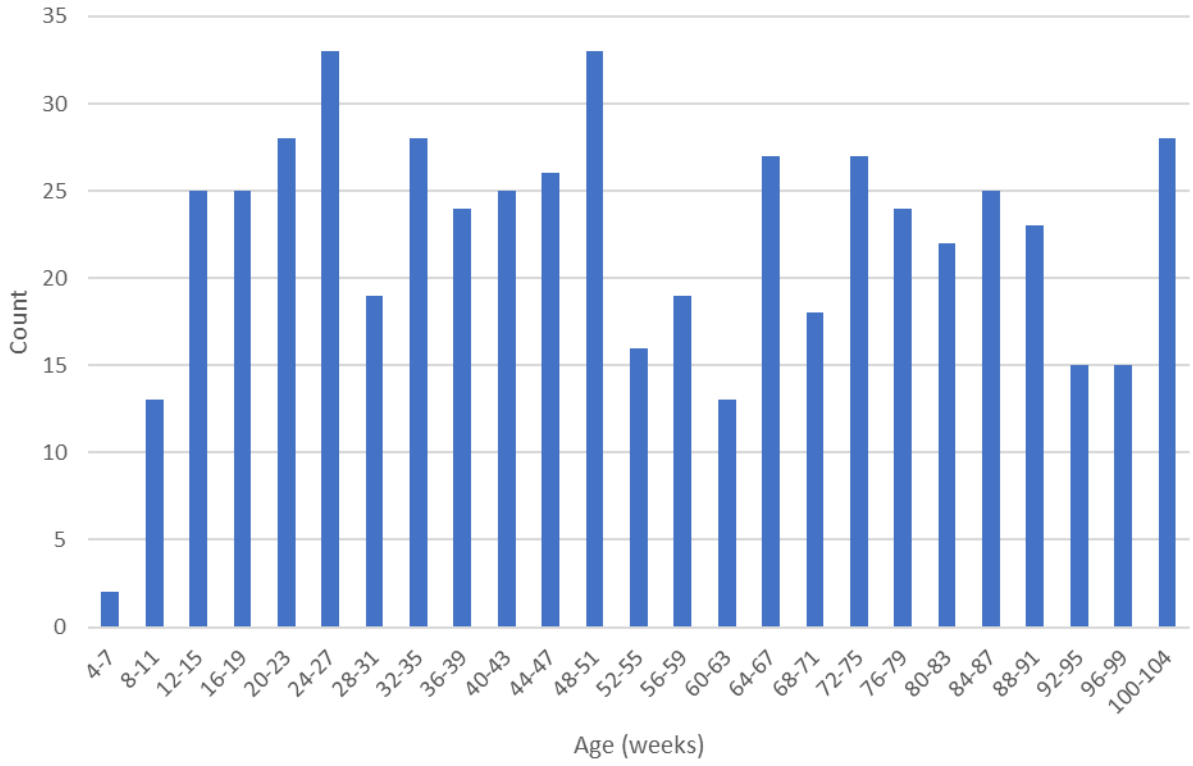
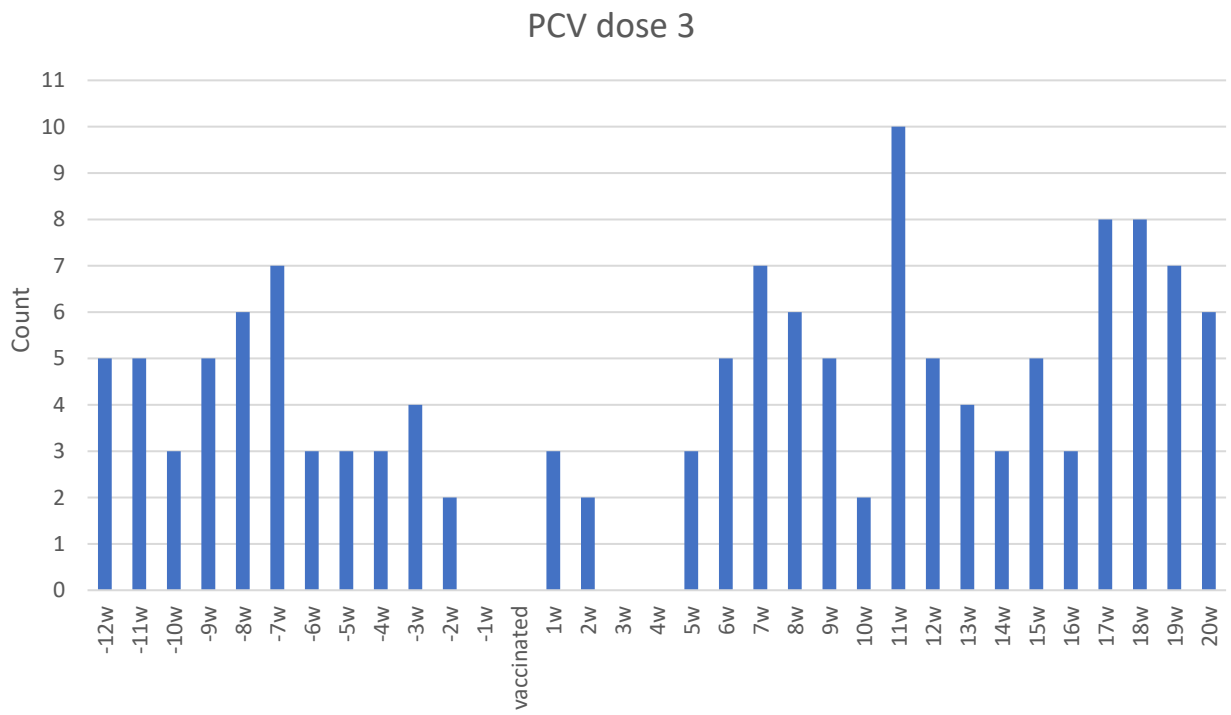


Figure 2: Frequency distrbution of validated hospital admissions for children with Kawasaki Disease around i) PCV dose 3 and ii) MenB dose 3

i)



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