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Current Drug Safety, 2018, *13*, 107-112

RESEARCH ARTICLE

Register-Based Ecologic Evaluation of Safety Signals Related to Pneumococcal Conjugate Vaccine in Children

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Abstract: ***Background*:** In clinical trials of Pneumococcal Conjugate Vaccines (PCV), some adverse events have been reported more frequently in the PCV vaccinated. Ten-valent PCV (PCV10) was introduced into the Finnish National Vaccination Programme (NVP) in September 2010.

***Objective*:** We conducted an ecologic register-based study to investigate further the reported adverse events after PCV.

***Methods*:** This study included data obtained from the Finnish nationwide, population-based registers. First diagnoses of febrile seizures, breath-holding, urticarial rash, asthma and Kawasaki's disease were included as outcomes obtained from the hospital discharge register. Data from Finnish Population Register during 2000-2014 for children age from 3 months to 10 years were used to estimate annual incidence rates. Incidence rate ratios of the outcomes were calculated between the target cohort of children eligible for PCV10 during 2010-2014 and a reference cohort before the NVP introduction (2004-2008).

***Results*:** No increases in the incidence of the adverse events after PCV10 introduction were found except for urticarial rash (incidence rate 2.48 *vs*. 1.60/1000 pyrs; incidence rate ratio, 1.54;95% CI 1.42-1.67). This increase was seen also in the unvaccinated older age groups in the post-vaccination era. The higher incidence of urticarial rash after the PCV10 introduction was due to the inclusion of diagnoses made in general medicine specialty in the discharge register because of a concomitant administrative change.

***Conclusion*:** The results do not support public health concerns related to the previously reported adverse events. Concomitant changes in health care administration and coding introduced bias, which was controlled after further evaluation of the data. We consider this register-based approach with real-world data feasible in the signal validation process after any signal detection.

ARTICLE HISTORY

Received: December 22, 2017
Revised: March 29, 2018
Accepted: April 03, 2018

DOI:
10.2174/1574886313666180406164151

Keywords: Pneumococcal conjugate vaccine, safety, epidemiology, signal validation, population-based study, register-based study.

1. INTRODUCTION

Pneumococcal Conjugate Vaccines (PCV) were developed to prevent disease due to the serotypes most commonly associated with severe Invasive Pneumococcal Disease (IPD) in children [1]. Public health benefits of PCVs in the vaccination programmes are considerable due to reductions of not only IPD, but also non-IPD syndromes [2, 3]. Furthermore, reduction in disease rates has been observed also in unvaccinated populations due to the indirect herd protection [4, 5]. Pneumococcal Conjugate Vaccine (PCV) was introduced in the Finnish National Vaccination Programme (NVP) after thorough cost effectiveness analysis required by the formal decision making process put in place in Finland [6].

PCVs are generally considered safe with hundreds of millions of doses administered worldwide. In the European Union, post-licensure medicinal product pharmacovigilance system relies on spontaneous reporting to the EudraVigilance database [7] in the detection of new safety signals. After signal detection, the signals need to be evaluated in the signal management process ("signal validation") to verify whether further analysis is needed to confirm the signal after the validation [8].

The reporting to the EudraVigilance database is based on spontaneous notifications from healthcare professionals or patients with suspicion of an adverse reaction to a medicinal product. Determination of causality based on individual case reports is especially challenging [9]. The validity of this kind

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2212-3911/18 $58.00+.00 © 2018 Bentham Science Publishers

Current Drug Safety

of passive register is highly dependent on the reporting activity (suspected to be low). Additionally, any events with non-immediate temporal relationships are rarely suspected as adverse reactions, and thus, not reported. However, the main deficiency in this kind of register is that it includes information only on vaccinated cases with an adverse reaction, and therefore this system does not enable any risk estimation between vaccinated and unvaccinated persons. In addition to spontaneous reporting, other sources of potential safety signals are previous scientific research, international safety databases, clinical queries, or media.

Several adverse events following immunization have been reported with higher frequencies after PCVs in at least one of the previously published large clinical trials. These include febrile seizures [1, 10-12], breath-holding [13], urticarial rash (hives) [12, 14], hyperactive airway disease and/or asthma [11] and Kawasaki's disease [15].

We used Finnish health register data to investigate whether the incidence of these diseases previously associated with PCV increased after large-scale PCV introduction in Finland to evaluate the feasibility of the real-world register data in the signal validation with a comparison of both vaccine-eligible and vaccine-ineligible cohorts.

2. MATERIALS AND METHODS

This nationwide, population-based, ecologic before-after study is based on diagnoses obtained from the Finnish hospital discharge register (Care Register for Health Care) and population data from the Finnish Population Information System [16].

2.1. Study Population

Ten-valent PCV was introduced into the Finnish NVP in September 2010 to be administered in a 2+1 schedule (doses at 3, 5, and 12 months of age) without a catch-up programme. The target cohort consisted of PCV10-eligible children after NVP introduction (born June 2010-September 2014) and the age- and calendar-time matched reference cohort of PCV10-ineligible children before NVP introduction (born June 2004-September 2008) (Fig. **1**). Over 30 000 children received PCV10 in the nationwide PCV10 trial (FinIP) which enrolled children between February 2009 and August 2010, and therefore this period was excluded from the study [2-4]. Information on individual vaccination data was not available in this study. However, the estimated PCV10 vaccination coverage in the vaccine-eligible target cohort was 94% in 2012 and 95% in 2014 [8]. In contrast, the uptake of any PCV in the reference cohort, estimated based on national sales figures) was below 2%. The target cohort was followed from 3 months of age until the end of 2014 and the reference cohort from 3 months of age until the end of 2008 (age during the follow up varied between 3 and 54 months). Population data between years 2000 and 2014 of children from 3 months to 10 years of age was used to estimate incidence rates of the outcome diseases.

2.2. Outcomes

Outcome data from the hospital discharge register including information on inpatient admissions and ambulatory outpatient visits in the hospital (both emergency department visits and scheduled visits) maintained by the National Institute for Health and Welfare (THL) were used. The diagnoses (main, secondary) of the following diseases leading to hospital contact were collected (Classification of Diseases, tenth version, ICD-10): febrile seizures (R560), breath-holding (R068), urticarial rash (L500, L501, L509), acute bronchitis (J209, J219, J2190, J2199), asthma (J450, J451, J458, J459, J46) and Kawasaki's disease (M303).

2.3. Statistical Analyses

Descriptive analyses on annual incidence of the outcome diseases were conducted for children aged from 0 to 10 years during 2000-2014 (age groups 0-1 years, 2-5 years and 6-10 years) to estimate trends in the outcome diseases. Incidence rates (IR) per 1000 person years (pyrs) of the first occurrence

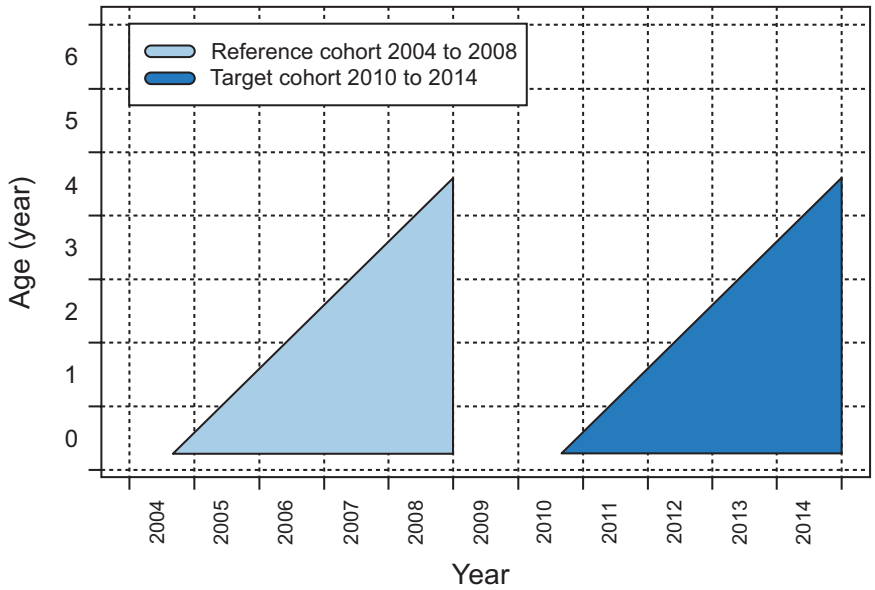

Fig. (1). Target and reference cohorts for evaluating safety signals related to pneumococcal conjugate vaccine in children.

of diagnosis of the outcome diseases after 3 months of age were compared between the PCV10-eligible and the reference cohort. Subjects with a diagnosis before 3 months of age were excluded from each analysis. Incidence rate ratios (IRR) with 95 percent confidence intervals (95% CI) for the outcome diseases were calculated using Poisson regression. Additional analyses were conducted according to the age at follow-up (age 3-7, or 12-15 months and age 8-11, or >=16 months) to evaluate, whether the IR in the target cohort compared to the reference cohort was higher soon after the scheduled vaccinations.

3. RESULTS

Among Finnish children aged less than 2 years, the annual incidence rates varied between the outcome diagnoses during 2000-2014. Acute bronchitis showed the highest incidence (Mean annual IR=27.6 / 1000 pyrs, annual range 23.3-33.5), followed by asthma (Mean=11.1, annual range 8.6-14.1), febrile seizures (Mean=5.2, annual range 4.6-6.2) urticarial rash (Mean=2.4, annual range 1.8-3.2) and Kawasaki´s disease (Mean=0.2, annual range 0.1-0.3) (Figs. **2** and **3**). The incidences rates were stable or decreasing, except for the incidence rate of urticarial rash which increased after the introduction of PCV10 in the NVP in the population aged less than 2 years, but also in older age-groups (2-5 years, 6-9 years) (Fig. **2**).

According to the cohort analyses, incidence rate of urticarial rash was higher among the target cohort when compared to the reference cohort (incidence rate, IR 2.48 *vs*. 1.60 / 1000 pyrs; incidence rate ratio IRR, 1.54; 95% CI 1.42-1.67) (Table **1**). Incidence rates of acute bronchitis, asthma and Kawasaki´s disease were lower among the target cohort in relation to the reference cohort.

In further exploration, the incidence of urticarial rash diagnoses recorded in general medicine emergency care, but

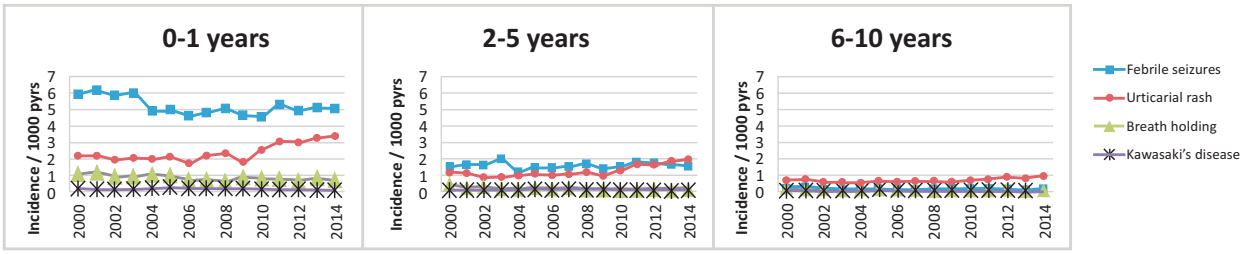

Fig. (2). Annual incidence of febrile seizures, urticarial rash, breath holding and Kawasaki's disease (per 1000 person years) in children aged 3 months to 10 years by age groups, Finland 2000-2014.

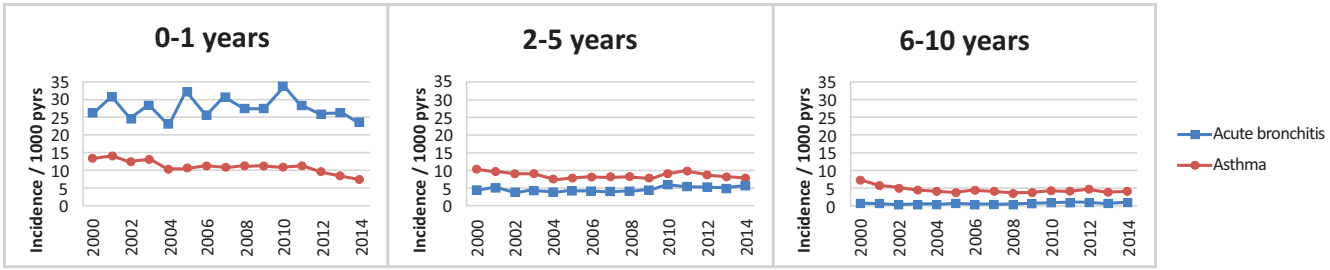

Fig. (3). Annual incidence of acute bronchitis and asthma diagnoses among chidren aged <2, 2-5 and 6-10 years, Finland 2000-2014.

Table 1. Incidence rates of selected previously reported safety signals associated with Pneumococcal conjugate vaccine (PCV) in the target cohort of PCV10-eligible and the reference cohort of PCV10-ineligible children and incidence rate ratio (IRR) with 95% confidence intervals in the target cohort in relation to the reference cohort.

Diagnosis (ICD-10 Codes)	All first-only Diagnoses			First-only Diagnoses, General Medicine Excluded		
	Incidence/1000 Person Years		IRR (95% CI)	Incidence/1000 Person Years		IRR (95% CI)
	Target Cohort 2010-2014	Reference Cohort 2004-2008		Target Cohort 2010-2014	Reference Cohort 2004-2008	
Febrile seizures (R560)	3.42	3.46	0.99 (0.93-1.05)	3.22	3.45	0.94 (0.88-1.00)
Breath-holding (R068)	0.52	0.53	0.98 (0.84-1.15)	0.50	0.53	0.94 (0.80-1.10)
Urticarial rash (L500, L501, L509)	2.48	1.60	1.54 (1.42-1.68)	1.43	1.57	0.91 (0.83-1.00)
Acute bronchitis (J20, J20.9, J21.9)	17.61	19.96	0.88 (0.86-0.91)	15.60	19.85	0.79 (0.76-0.81)
Asthma (J45 or J46)	7.29	9.14	0.80 (0.77- 0.83)	7.19	9.14	0.79 (0.76-0.82)
Kawasaki's disease (M303)	0.10	0.15	0.68 (0.48-0.94)	0.10	0.15	0.68 (0.48-0.94)

not in other specialties, increased after the introduction of PCV10 (Fig. **4**). When the diagnoses made in general medicine were excluded, there was no difference in the incidences of urticarial rash between the target cohort and the reference cohort (IR 1.43 / 1000 pyrs *vs*. IR 1.57 / pyrs, IRR 0.91, 95% CI 0.83-1.00) (Table **1**). Regarding other outcomes, results were similar regardless of inclusion or exclusion of diagnoses made in general medicine. Results were similar between the target cohort and the reference cohort in the stratified analyses by age (3-7 or 12-15 months and 8-11 or >=16 months), suggesting no modification effect of age on the association between PCV10 and the outcomes (Table **2**).

4. DISCUSSION

We did not find increased incidences of the diseases that had been raised as potential safety signals in clinical trials after the PCV10 introduction except for urticarial rash. However, the increased incidence was also seen in unvaccinated older age groups than those eligible for PCV after the NVP introduction, suggesting other causes for the observed increase.

In the analyses by medical specialty and hospitalization type, we found that urticarial rash diagnoses made in general medicine emergency care, but not in other specialties, clearly increased since 2009, coinciding with the PCV10 introduction. When the diagnoses made in general medicine were excluded, the incidences in the target and reference cohorts were similar. In late 2000, a national development plan for social and health care started, where one goal was to combine previously separately organized municipal primary and secondary acute care services to enhance the quality and effectiveness of the acute care services [17, 18]. Outpatient on-call activity was combined with hospital emergency care, and consequently, patients previously diagnosed in primary care, were now included in the hospital discharge register, as the on-call activity was administrated in hospitals instead of outpatient health centers. It seems that this administrative change affected the evaluation of urticarial rash in our data. The IRR of acute bronchitis was similarly lower when general medicine notifications were excluded. Regarding other diagnoses, our study showed similar results regardless of inclusion or exclusion of diagnoses made in general medicine. Urticarial rash and acute bronchitis are typically diagnosed in primary care in general medicine specialty, while the other diagnoses are more severe and require follow-up or confirmation of the diagnosis resulting in the diagnoses made in other specialties than in general medicine emergency care. We found that the incidence of asthma was lower in the target cohort compared to the reference cohort before the introduction of PCV10. The decreased incidence was also seen in other age-groups than those eligible for PCV after the NVP introduction. During year 2006, there was an

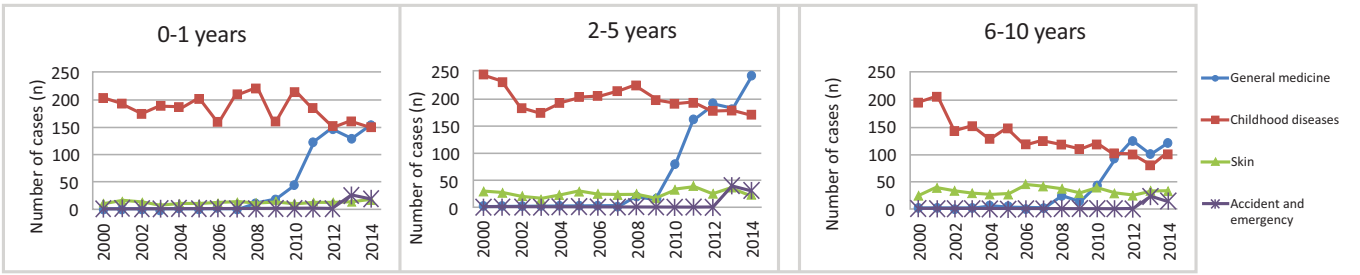

Fig. (4). Annual number of urticarial rash diagnoses in children aged from 3 month to 10 years, by age groups and medical specialty, Finland 2000-2014.

Table 2. Incidence rates of selected previously reported safety signals associated with Pneumococcal conjugate vaccine (PCV) in the target cohort of PCV10-eligible and the reference cohort of PCV10-ineligible children and incidence rate ratio (IRR) with 95% confidence intervals in the target cohort in relation to the reference cohort according to age, excluding general medicine specialty.

Diagnosis (ICD-10 Codes)	Age 3-7 or 12-15 Months*		IRR (95% CI)	Age 8-11 or >=16 Months*		IRR (95% CI)
	Incidence/1000 Person Years			Incidence/1000 Person Years		
	Target Cohort 2010-2014	Reference Cohort 2004-2008		Target Cohort 2010-2014	Reference Cohort 2004-2008	
Febrile seizures (R560)	3.10	3.30	0.94 (0.84-1.05)	3.28	3.51	0.93 (0.87-1.01)
Breath-holding (R068)	0.82	0.86	0.94 (0.75-1.19)	0.36	0.38	0.94 (0.75-1.18)
Urticarial rash (L500, L501, L509)	1.61	1.74	0.93 (0.79-1.09)	1.35	1.49	0.90 (0.81-1.02)
Acute bronchitis (J20, J20.9, J21.9)	25.15	33.13	0.76 (0.73-0.79)	11.46	14.01	0.82 (0.79-0.85)
Asthma (J45 or J46)	4.49	7.29	0.62 (0.56-0.67)	8.36	9.95	0.84 (0.80-0.88)
Kawasaki's disease (M303)	0.07	0.20	0.36 (0.18-0.66)	0.11	0.13	0.90 (0.60-1.34)

*General medicine specialty excluded.

ongoing national programme on asthma, where one goal was to decentralize clinical treatment of adulthood, but also childhood asthma to primary care [19]. This goal of decentralization was also included in the national Care Guidelines 2006 [20]. These may have resulted in the reduction of incidence of asthma diagnoses after the introduction of PCV in our data based on hospital discharge register.

The outcome data were obtained on an individual level with information on first-event diagnosis, but we did not have information on individual vaccination data in this study. The ecologic before-after design is sensitive to time-related changes, such as changes in administration or in clinical diagnostic criteria, which may bias the results. However, the register-based approach allows also the use of more elaborate study designs, like the cohort design and the self-controlled case series, in the case also individual vaccination data were available.

The register data may be of low specificity, as no data validation has been performed for the outcome diagnoses. However, this lack of specificity should be similar between the follow-up periods, and thus, this kind of symmetric misclassification may result in false negative research findings. Additionally, data on the outcome diagnoses was obtained only from hospitals, which do not include diagnoses from primary care visits. It is possible that the incidence of urticarial rash diagnoses made in the primary care is increased among the target cohort. However, our focus in this study was to evaluate severe conditions leading to hospital contact. Nevertheless, our findings should be interpreted with caution.

This nationwide, register-based study has several strengths. We collected nationwide information on the diagnoses from all hospitals, including inpatient admissions and outpatient visits, which provided a comprehensive evaluation of the outcome diagnoses made in hospitals in the study population. Long follow-up time allowed estimation of precise estimates with narrow confidence intervals also for the infrequent outcomes. Information obtained from the Population Register enabled calculation of the background annual incidence rates of outcome diagnoses in specific age-groups in the entire Finnish population.

CONCLUSION

Our register-based approach to investigate previously reported adverse events related to PCV proved feasible. The results of this study seem credible and do not support public health concerns related to PCV10 safety signals.

Concomitant changes in health care administration and coding introduced bias, which was controlled after careful evaluation of the data. However, further evaluation including diagnoses from the primary care and other possible causes than PCV would be recommended. In the regulatory perspective, the safety signals could not be validated in this study, and there is no need for further, more elaborated, hypothesis testing studies.

We consider this register-based approach with real-world data feasible for the signal validation process in the post-marketing phase with considerable advantages like large data sets including unexposed cohorts also.

LIST OF ABBREVIATIONS

95% CI	=	95 percent Confidence Intervals
IR	=	Incidence Rate
IRR	=	Incidence Rate Ratio
NVP	=	National Vaccination Programme
NVR	=	National Vaccination Register
PCV	=	Pneumococcal Conjugate Vaccine
PCV10	=	Ten-valent Pneumococcal Conjugate Vaccine
PYRS	=	Person Years

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is approved by the Ethical Committee of the National Institute for Health and Welfare.

HUMAN AND ANIMAL RIGHTS

No animal were used in this study, Reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors are employees of the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline (GSK) Vaccines for the conduct of a nationwide effectiveness study of the 10-valent pneumococcal conjugate vaccine. This study did not receive any contribution from GSK.

ACKNOWLEDGEMENTS

Declared none.

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