Original Article

Journal of INTERNAL MEDICINE

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doi: 10.1111/joim.12150

Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up

I. Persson[1], F. Granath[2], J. Askling[3], J. F. Ludvigsson[2,4], T. Olsson[5] & N. Feltelius[1,3]

From the [1]Medical Products Agency, Uppsala; [2]Unit of Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Stockholm; [3]Unit of Rheumatology, Department of Medicine, Karolinska Institutet, Stockholm; [4]Department of Paediatrics, Örebro University Hospital, Örebro; and [5]Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden

Abstract. Persson I, Granath F, Askling J, Ludvigsson JF, Olsson T, Feltelius N (Medical Products Agency, Uppsala; Unit of Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Stockholm; Unit of Rheumatology, Department of Medicine, Karolinska Institutet, Stockholm; Department of Paediatrics, Örebro University Hospital, Örebro and Department of Clinical Neurosciences, Karolinska Institutet, Stockholm; Sweden). Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. *J Intern Med* 2014; **275**: 172–190.

Objectives. To investigate the association between vaccination with Pandemrix and risk of selected neurological and immune-related diseases including narcolepsy.

Design. Population-based prospective cohort study using data from regional vaccination registries and national health registries.

Setting. Seven healthcare regions in Sweden comprising 61% of the Swedish population.

Subjects. Study population of 3 347 467 vaccinated and 2 497 572 nonvaccinated individuals (vaccination coverage ≈60%) followed between 2009 and 2011 for 6.9 million person-years after exposure and 6.0 million person-years without exposure.

Main outcome measure and analysis. First recorded diagnosis of neurological and immune-related diseases. Relative risks [hazard ratios (HRs) with 95% confidence intervals (CIs)] assessed using Cox regression, adjusted for covariates.

Results. For all selected neurological and immune-related outcomes under study, other than allergic vaccine reactions (for which we verified an expected increase in risk) and narcolepsy, HRs were close to 1.0 and always below 1.3. We observed a three-fold increased risk of a diagnosis of narcolepsy (HR: 2.92, 95% CI: 1.78–4.79; that is, four additional cases per 100 000 person-years) in individuals ≤20 years of age at vaccination and a two-fold increase (HR: 2.18, 95% CI: 1.00–4.75) amongst young adults between 21 and 30 years of age. The excess risk declined successively with increasing age at vaccination; no increase in risk was seen after 40 years of age.

Conclusions. For a large number of selected neurological and immune-related diseases, we could neither confirm any causal association with Pandemrix nor refute entirely a small excess risk. We confirmed an increased risk for a diagnosis of narcolepsy in individuals ≤20 years of age and observed a trend towards an increased risk also amongst young adults between 21 and 30 years.

Keywords: cohort study, narcolepsy, neurological/immune-related diseases, Pandemrix.

Introduction

In September 2009, the ASO3 adjuvanted (including squalene and alpha tocopherol) A(H1N1) vaccine Pandemrix (GlaxoSmithKline, Brentford, UK) was authorized for use in the EU; over 30 million individuals were subsequently vaccinated [1]. In Sweden, Pandemrix was exclusively used in

a mass vaccination programme launched in October 2009, resulting in an overall vaccination coverage of about 60% [2].

In mid-2010, an unexpected increase in the occurrence of narcolepsy in children and adolescents emerged from adverse drug reaction reports on Pandemrix in Sweden and Finland, and these reports have since been substantiated in epidemiological studies in these two countries [3–5]. We have previously reported a four-fold increase in the risk of a diagnosis of narcolepsy in Sweden [3]. Similar observations have been made regarding narcolepsy risk in children/adolescents in Ireland [6], the UK [7] and France [8]. With respect to adults, a three- to five-fold increased risk of narcolepsy was recently reported in Finnish individuals aged 20–64 years [9], and the findings of the French study [8] suggested a four-fold increased risk of narcolepsy in vaccinated individuals (mainly with Pandemrix) 20 years of age and above [8].

Because of an assumed immunological mechanism in the pathophysiology of narcolepsy, possible adverse effects of vaccination on other neuroimmunological and autoimmune diseases are considered relevant.

Previous experience of other influenza vaccines has led to concerns about the risks of immune-related reactions [10, 11] and neurological adverse events such as Guillain–Barré syndrome (GBS) [12–14] and Bell's palsy [15, 16]. Data on the safety of the adjuvanted vaccine Pandemrix (other than with regard to narcolepsy) have, however, so far been lacking. A small excess risk of GBS was suggested in a Canadian cohort study [17], but no change in the risk of GBS amongst vaccinated individuals was found in two European studies [18, 19]. The risk of convulsions in vaccinated children did not seem to be increased in two recent studies [20, 21]. In a previous registry study, no adverse effects were observed on GBS, multiple sclerosis (MS), type 1 diabetes (T1D) or rheumatoid arthritis, whereas small excess risks were found for Bell's palsy, paraesthesia and inflammatory bowel disease in individuals with medical risk factors (analyses of narcolepsy were not conclusive due to small numbers of cases) [22]. However, this study was limited to the Stockholm population and to a follow-up of about 1 year after vaccination.

Because of the findings regarding narcolepsy, concerns have been raised for the general safety of the Pandemrix vaccine leading to the initiation of the present broad safety study of targeted neurological and immune-related outcomes in a large study population and with a prolonged follow-up period.

The objectives of this study were (i) to investigate the association between vaccination with Pandemrix and selected neurological and immune-related diseases, (ii) to confirm the association with narcolepsy in vaccinated children/adolescents and (iii) to explore this association in adults.

The study was undertaken by the Medical Products Agency (MPA) in collaboration with Karolinska Institutet and the seven participating healthcare regions/counties.

Subjects and methods

Study design

We performed an observational register-based cohort study with prospectively collected population-based data.

Setting

Vaccinations with Pandemrix were carried out between 1 October 2009 and 31 March 2010. All Swedish residents were offered the ASO3 adjuvanted vaccine Pandemrix. Healthcare workers and groups considered to be at high risk of complications from influenza, such as pregnant women and patients with serious medical conditions (i.e. chronic heart or lung disease, diabetes mellitus, chronic liver or kidney failure, immune suppression, extreme obesity and severe neuromuscular disease), were prioritized to receive early vaccination. The overall vaccine coverage in our study population was 57%, but varied with geography and with age (highest at 0–9 years of age and lowest at 20–29 years) (Table 1).

Participants

The original study population of 5 933 762 individuals consisted of all inhabitants, as of 1 January 2009, of seven Swedish regions (the healthcare regions of Skåne and Västra Götaland and the counties of Kalmar, Östergötland, Stockholm, Värmland and Norrbotten). We excluded individuals who died (n = 40 656), emigrated from Sweden (n = 13 633), had inconsistent information on migration (n = 43) or moved out of the study area (n = 34 391) before the start of the study period on

Table 1 *Description of study population characteristics, by vaccination status (all ages)*

	All		Vaccination status			
			No		Yes	
	n	%	*n*	%	*n*	%
All	5845039	100	2497572	42.7	3347467	57.3
County of residence on 1 January 2009						
Stockholm	1952294	33.4	913107	46.8	1039187	53.2
Östergötland	416335	7.1	150196	36.1	266139	63.9
Kalmar	229359	3.9	119267	52.0	110092	48.0
Skåne	1198101	20.5	431536	36.0	766565	64.0
Västra Götaland	1535027	26.3	639361	41.7	895666	58.3
Värmland	268846	4.6	117012	43.5	151834	56.5
Norrbotten	245077	4.2	127093	51.9	117984	48.1
Age on 1 January 2009						
0–9 years	666795	11.4	156065	23.4	510730	76.6
10–19 years	724186	12.4	268835	37.1	455351	62.9
20–29 years	737590	12.6	427752	58.0	309838	42.0
30–39 years	806541	13.8	361494	44.8	445047	55.2
40–49 years	823718	14.1	395285	48.0	428433	52.0
50–59 years	730034	12.5	332115	45.5	397919	54.5
60–69 years	678906	11.6	275888	40.6	403018	59.4
70–79 years	399435	6.8	157574	39.4	241861	60.6
≥80 years	277834	4.8	122564	44.1	155270	55.9
Gender						
Male	2903015	49.7	1329915	45.8	1573100	54.2
Female	2942024	50.3	1167657	39.7	1774367	60.3
Education level[a]						
≤9 years	769439	13.2	404644	52.6	364795	47.4
≤12 years	2365964	40.5	1079506	45.6	1286458	54.4
≤14 years	356894	6.1	152572	42.7	204322	57.3
>14 years	1725413	29.5	578795	33.5	1146618	66.5
Research training	78589	1.4	23366	29.7	55223	70.3
Unknown	548740	9.4	258689	47.1	290051	52.9
Income quartiles[b]						
Q1	1437217	24.6	803843	55.9	633374	44.1
Q2	1463780	25.0	666155	45.5	797625	54.5
Q3	1472498	25.2	538814	36.6	933684	63.4
Q4	1471544	25.2	488760	33.2	982784	66.8
Place of birth[c]						
Nordic	4790793	82.0	1910032	39.9	2880761	60.1
EU (North)	86097	1.5	46941	54.5	39156	45.5
EU (Mediterranean)	142541	2.4	85080	59.7	57461	40.3
EU (East)	38357	0.7	24067	62.7	14290	37.3
Europe non-EU	225743	3.9	127671	56.6	98072	43.4

Table 1 (*Continued*)

	All		Vaccination status			
			No		Yes	
	n	%	*n*	%	*n*	%
Asia	356913	6.1	184741	51.8	172172	48.2
Africa	97303	1.7	60233	61.9	37070	38.1
North America	27419	0.5	14445	52.7	12974	47.3
South America	66774	1.1	36284	54.3	30490	45.7
Oceania	3112	0.1	1962	63.0	1150	37.0
Soviet Union	8975	0.2	5324	59.3	3651	40.7
Unknown	1012	<0.1	792	78.3	220	21.7
No of ambulatory care visits[d]						
0	3623955	62.0	1623888	44.8	2000067	55.2
1	950855	16.3	384585	40.4	566270	59.6
2	475602	8.1	188057	39.5	287545	60.5
≥3	794627	13.6	301042	37.9	493585	62.1
No of hospitalizations[d]						
0	5321754	91.0	2294174	43.1	3027580	56.9
1	383876	6.6	148826	38.8	235050	61.2
2	80271	1.4	31220	38.9	49051	61.1
≥3	59138	1.0	23352	39.5	35786	60.5

[a]Highest attained level for adults, or for the mother or father in the case of children/adolescents.
[b]Household disposable income for the taxation year 2008, in quartiles.
[c]Place of birth for all individuals, except if born abroad to parents born in Sweden, then classified as Swedish. For those born in Sweden to parents born out of Sweden, categorization was based on country of birth of the parents, if in different countries it is based on that of the mother.
[d]Healthcare consumption during 1 year prior to study start, defined as both the number of hospital admission and the number of ambulatory care visits at specialist clinics.

1 October 2009; thus, 5 845 039 eligible individuals remained for follow-up, that is, 61% of the Swedish population (Table 1).

Data sources and exposure

Registration of vaccination status was considered to be complete in four of the seven regions, because in these regions reimbursement to the vaccination centres required registration of the vaccinated individual. In the three other regions (the counties of Kalmar, Värmland and Norrbotten; together comprising 13% of the study population), a web-based system for vaccination registration was used, which required informed consent. As a result of the absence of consent, 16–22% of the vaccinated individuals in these three counties could not be correctly ascertained as exposed because their personal identification number (PIN, the unique 10-digit number, that is given to every newborn in Sweden) could not be included and thus not be linked to the vaccination registers; therefore, they remained in the study population as unexposed. Registrations included the PIN, vaccine dose (half the adult dose is initially given to children below 12 years of age), order of vaccination (first, and in children also the second dose) and the date and site of vaccination.

Using the PIN, the individual's vaccination data were linked to the following nationwide and virtually complete registers: (i) the Population Registry (Statistics Sweden), to delineate the study population and to define the exposed (i.e. all those registered as vaccinated) and the unexposed (assumed to be all remaining individuals belonging to the study population) cohorts, and further to define socio-economic and demographic variables, (ii) the National Patient Register, the Prescribed Drug Register and the Cancer Registry (National

Board of Health and Welfare), to identify hospitalizations and non-primary care outpatient visits to identify the outcomes under study, and covariates, (iii) the Medical Birth Register (National Board of Health and Welfare), to identify pregnancy status at vaccination, which was used as a covariate, and (iv) the National Cause of Death Register (National Board of Health and Welfare), to define deaths during follow-up.

Outcomes

We selected a set of neurological and immune-related outcomes for the present study based on (i) previous influenza vaccine safety issues including narcolepsy [3–5, 10–16], (ii) results from our previous study of H1N1 vaccination in Stockholm county [22], and (iii) recommended follow-up of adverse events of special interest [23]. On the basis of data on physician-assigned International Classification of Diseases, 10th revision (ICD-10) codes from hospitalizations and outpatient specialized care visits (i.e. referrals) from the Patient Register, supplemented with data on prescriptions from the Prescribed Drug Register, 10 neurological outcomes including narcolepsy and 31 other immune-related conditions were defined (Table 2). As many of the outcomes reflect chronic conditions that may have an insidious onset, and because we had access to data for dates of visits and admissions rather than the date of the actual onset of first symptom of a disorder, we also identified possible 'prodromal' conditions, or outcome-specific medications (Table 2). In all analyses, those individuals fulfilling the outcome definition before study start, using a 5-year 'look-back' period, were considered to have prevalent disease and were excluded from risk assessment.

Statistical analysis

In an observational real-life study of *de facto* vaccination with outcomes derived from routine healthcare data, we sought to address the two main threats to the validity of the findings: (i) the possibility for selection bias due to targeted recruitment to vaccination of high-risk groups, and (ii) the possibility of reverse causality because of prodromal states (preceding the date of the end-point diagnosis) that may lead to vaccination rather than the other way round. Thus, a stepwise statistical approach was adopted.

First, we explored potential and measureable predictors of vaccination: age, gender, county, education, income, ethnicity, number of hospital admission, number of ambulatory care visits at specialist clinics and presence of diagnosed conditions (according to ICD-10 codes) during 1 year prior to the start of the study. Potential predictors were listed (Table 1) and assessed using Cox regression. Analyses of the association between vaccination and the occurrence of the outcomes under investigation were subsequently adjusted for these predictors in different models (see below).

Secondly, because medical risk groups were initially considered a priority, all assessments of vaccination risks were stratified according to the time-point of vaccination (first 45 days of the programme were categorized as 'early', and vaccinations occurring thereafter as 'late').

Thirdly, to avoid erroneous inclusion of prevalent outcomes, we used outcome definitions (Table 2), that is, prodromal diagnoses or treatments, to exclude individuals with existing disease (in addition to the basic outcome definition, based on first occurrence according to the diagnosis code).

Fourthly, for each study outcome, relative risks were presented overall and by time since vaccination, as well as with respect to age at vaccination for selected outcomes.

Fifthly, to verify that the study design was able to identify expected outcomes, vaccination reactions (ICD-10 code T88.1) were included as a 'positive control'.

Finally, to illustrate the impact of selection to/not to vaccinate individuals with particular characteristics and morbidities, all-cause mortality was included as an outcome.

Follow-up began on 1 October 2009 and ended on the first date of a registered outcome, migration from the study region, death or 31 December 2011 (the end of the study period; maximum follow-up was 27 months).

The associations between vaccine exposure and the predefined outcomes were assessed through Cox regression using calendar time as the time-scale with zero defined as 1 October 2009. Vaccination status was introduced as a time-dependent dummy variable taking the value 0 from study start until the date of vaccination and thereafter

Table 2 *Definition of outcomes in the follow-up of vaccinated and unvaccinated cohorts*

Outcome/diagnosis	ICD-10 codes for first identification of outcome	Additional ICD-10 codes for the exclusion of prevalent disease (to define *first* onset)	Prescribed drugs (i) to identify prevalent disease (first onset) and (ii) to help define specific outcome/diagnosis
Immune-related/autoimmune diseases			
Rheumatoid arthritis	M05, M06, M12.3	M25, M12, M13	Prednisolone, methotrexate, salazopyrin, chloroquine phosphate, leflunomide, TNF inhibitors, rituximab, abatacept, anakinra, tocilizumab
Juvenile idiopathic arthritis	M08	M05, M06, M12.3, M25, M13	NSAIDs, prednisolone, methotrexate, salazopyrin, chloroquine phosphate, leflunomide, TNF inhibitors, rituximab, abatacept, anakinra, tocilizumab
Crohn's disease	K50	K51	ASA[a], immunosuppressive medicines including azathioprine and methotrexate, mercaptopurine, TNF-alfa inhibitors
Ulcerative colitis	K51	K50, see Crohn's disease above	See Crohn's disease above
Type 1 diabetes mellitus	E10, first admission before 30 years of age	E11–14	

Outcome/diagnosis	ICD-10 codes for first identification of outcome	Additional ICD-10 codes for the exclusion of prevalent disease (to define *first* onset)
Neurological diseases		
Guillain–Barré syndrome	G61.0	
Multiple sclerosis	G35–37	
Optic neuritis	H46	
Acute disseminated encephalomyelitis (ADEM)	G04.0	
Bell's palsy	G51.0	
Narcolepsy	G47.4	G47.0-G47.3, G47.8, G47.9
Polyneuropathy	G62	
Paraesthesia	R20.2	
An-/hypoaesthesia	R20.0, R20.1	
Epilepsy grand mal	G40.3	

Table 2 (*Continued*)

Outcome/diagnosis	ICD-10 codes for first identification of outcome	Additional ICD-10 codes for the exclusion of prevalent disease (to define *first* onset)	Prescribed drugs (i) to identify prevalent disease (first onset) and (ii) to help define specific outcome/diagnosis
Other immune-related/autoimmune diseases for exploratory analyses			
Reactive/idiopathic inflammatory arthritis	M02, M03, M13		
Arthralgia UNS[b]	M25.5		
Systemic inflammatory disease	M32, M33, M34, M35.0, M35.1	M25, M13, M 05, M06, M07, M08, M09	NSAIDs, prednisolone, chloroquine phosphate, azathioprine
Sjögren's syndrome	M35.0	M32, M33, M34, M35.1	
SLE	M32	M33, M34, M35.0, M35.1	NSAIDs, prednisolone, chloroquine phosphate, azathioprine
Scleroderma	M34		
Dermatopolymyositis	M33		
Cutaneous vasculitis	L95.8, L95.9		
Myasthenia gravis	G70		
Thyroiditis	E06		
Addison's disease	E27.1, E27.2		
Purpura, thrombocytopenia including HSP	D69		
ITP	D69.3		
Agranulocytosis	D70		
Haemolytic anaemia, including HUS[c]	D59.0-D59.3		
Hypothyreosis	E03	E05 or E06	ATC=H03A[d]or H03B[e]
Hyperthyreosis	E05		
Urticaria	L50		
Erythema multiforme including Stevens–Johnson syndrome	L51		
Stevens–Johnson syndrome	L51.1		
Exfoliative dermatitis	L26		
Erythema nodosum	L52		
Allergic reaction	T78		
Anaphylactic reaction	T78.2		
Vaccination reactions	T88.1		
Asthma	J45-J46		ATC=R03[f]x

TNF, tumour necrosis factor; NSAID, nonsteroidal anti-inflammatory drug; SLE, systemic lupus erythematosus; HSP, Henoch–Schönlein purpura; ITP, idiopathic thrombocytopenic purpura; HUS, haemolytic uraemic syndrome.
[a]Acetylsalicylic acid.
[b]Joint pain, without specification.
[c]Haemolytic uraemic syndrome.
[d]Thyroid preparations.
[e]Antithyroid preparations.
[f]Drugs for obstructive airway diseases.

the value 1, that is, individuals contributed unexposed person-time until their date of vaccination (if vaccinated), and exposed person-time thereafter. Five models were applied, the first by adjusting for age (in 5-year bands), gender and county (model 1), then successively adding potential confounders: education and income (model 2), number of hospital admissions and ambulatory care visits (model 3), pregnancy status and presence of diagnoses defined by ICD-10 codes (model 4) and ethnicity (model 5). Variable categorizations are shown in Table 1. We used the SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) in all analyses.

Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Because this was a safety study with the aims of detecting possible outcomes and confirming narcolepsy, we chose not to adjust for multiple comparisons. In the main results, HRs are presented from model 4, except T1D and all-cause mortality for which the results from model 5 are shown (ethnicity was considered to be of potential importance for these outcomes). All analyses were further stratified for different aspects of time. First, analyses were stratified according to the time-point of vaccination – within 45 days from the start of follow-up (early cohort) and after more than 45 days (late cohort) – in order to determine the potential residual effect of bias due to channelling of high-risk groups (expected to be over-represented early on in the vaccination campaign). This stratification of vaccinated individuals was obtained by separate time-dependent variables for the early and late cohorts. The reference group for the two exposure groups was all individuals still not vaccinated at each calendar day of follow-up. Secondly, we assessed risk according to the time of vaccination (time during the vaccination period in quartiles) both in comparison with nonvaccinated and also as an internal comparison within vaccinated individuals. Thirdly, to reflect outcomes with a suspected rapid onset after vaccination (e.g. GBS and Bell's palsy), analyses were stratified by follow-up time (i) within 6 weeks versus more than 6 weeks since vaccination and (ii) within 1 year versus more than 1 year after vaccination, to determine whether associations were sustained in the longer term. This stratification of risk according to time for vaccinated individuals was also assessed by time-dependent covariates where separate dummy variables were created for the first 6 weeks/1 year after vaccination versus more than 6 weeks/1 year after vaccination. The reference group for these two strata of exposed person-time is all unexposed person-time at each calendar day of follow-up.

Ethical approval

The study was approved by the Ethics Review Board in Uppsala in January 2011. Approval was granted, conditional on information about the study being reported through newspapers in the seven regions/counties (Registration No. 2011/427).

Results

Characteristics of the cohorts and predictors of vaccination

Overall, we found that vaccinated individuals had a higher level of education, higher income, were more often born in a Nordic country and consumed more healthcare compared with nonvaccinated individuals (Table 1). Virtually, all groups of medical diagnoses were more prevalent amongst those who were vaccinated (data not shown). There were also differences in the above-mentioned characteristics between individuals vaccinated early (≤45 days) and later during the study period. Those vaccinated in the early phase had a greater disease burden in terms of prior healthcare consumption, whereas those vaccinated later seemed to have a lower or baseline prevalence in comparison with unvaccinated individuals. We noted similar patterns for vaccination prediction in individuals ≤20 years of age.

The overall observation times were approximately 6.9 million person-years in the vaccination cohort after exposure and 6.0 million person-years in the nonexposed cohort and in the exposed cohort before the time of vaccination.

Occurrence and relative risks of vaccine reactions and death from all causes

Overall, 147 vaccinated individuals were diagnosed with vaccine reactions (i.e. reactions that were sufficiently serious to require hospital contact, that is, through specialist care or admission) resulting in a 20-fold increased risk during the first 6 weeks following vaccination (HR: 19.6, 95% CI: 10.5–36.3), but little increase thereafter (Table 2) (vaccine reactions in the unexposed cohort were assumed to be associated with other vaccines).

The adjusted HR (model 5) for death from any cause following vaccination was just below unity

(HR: 0.95, 95% CI: 0.94–0.96; based on 65 490 and 57 877 deaths amongst the vaccinated and nonvaccinated individuals, respectively). When stratified by age, the mortality rate was more than 30% lower amongst young vaccinated individuals (10–29 years) and reduced by 10–15% in older age groups. When stratified by time since vaccination, the mortality rate following vaccination was increased by approximately 20% in those vaccinated during the first half of the vaccination period compared with unvaccinated individuals, whereas mortality was reduced by 20–30% in those vaccinated during the later period (Appendix Fig. A1).

Occurrence and relative risks of selected neurological outcomes

Table 3 and Fig. 1 show adjusted HRs (model 4, for outcome definitions excluding cases with prodromal states or medications at the start of vaccination) for neurological outcomes (including narcolepsy, for comparison). Of the 11 overall HRs, six had a lower 95% CI above 1.0; however, four of these HR estimates were below 1.1 (the exceptions being narcolepsy and acute disseminated myeloencephalitis; the latter was based on only three exposed cases in the ≤6-week window). In the early vaccination cohort, the point estimates for Bell's palsy, polyneuropathy, paraesthesia and epilepsy were slightly increased (all HRs below 1.2); all risk estimates were close to baseline for GBS and MS.

Occurrence and relative risks of selected immune-related outcomes

Table 3 and Fig. 1 show the HRs for non-neurological autoimmune or immune-related outcomes. Overall, for the 30 investigated outcomes, we found that HRs for 14 were above unity (with a lower 95% CI above 1.0), 11 of which were in the range 1.1–1.2, but only three were greater than 1.2. The increased estimates were generally at a higher level in the early versus the late vaccination cohort, with the highest estimates for Sjögren's syndrome and agranulocytosis (HR: 1.48, 95% CI: 1.31–1.66 vs. HR: 1.38, 95% CI: 1.27–1.50, respectively). For the composite outcome of inflammatory systemic diseases, the risk estimate was not different from baseline (HR: 1.00; 95% CI: 0.85–1.17).

Occurrence and relative risks of a diagnosis of narcolepsy

A total of 126 cases of diagnosed narcolepsy (after the exclusion of one prodromal case diagnosed with another sleep disturbance) were observed amongst vaccinated individuals ≤20 years of age, resulting in an overall three-fold risk increase in this age group (HR: 2.92, 95% CI: 1.78–4.79; Table 3). The magnitude of the risk increase did not vary markedly between the early and late vaccination cohorts, nor was there any difference in HRs between the first and second year following vaccination ($P > 0.05$). We calculated that this overall risk increase would correspond to an attributable incidence of 4.0 additional cases per 100 000 vaccinated children/adolescents per year.

The risk estimate for narcolepsy was (i) increased two-fold (HR: 2.18, 95% CI: 1.00–4.75) in young adults (21–30 years; 23 exposed cases), (ii) slightly increased (HR: 1.53, 95% CI: 0.68–3.44; 18 cases) in individuals aged 31–40 years, and (iii) close to the baseline level (HR: 1.06, 95% CI: 0.64–1.76; 40 cases) in those aged >40 years. Hence, the relative risk of narcolepsy during the study period declined successively with increasing age at vaccination (P for trend = 0.012) (Fig. 2). However, the decreasing trend amongst adults as a group was not statistically significant (P for trend = 0.14).

Figure 3 shows an increase in the crude incidence rates of narcolepsy, for individuals ≤20 years of age, in 2011 as compared with 2009–2010; this increase was greatest in the vaccinated cohort, but present also in the unvaccinated group. In those aged 21–30 years, a smaller increase in the incidence was observed, but restricted to vaccinated individuals. There was no change in the incidence amongst vaccinated or unvaccinated individuals above 31 years of age.

Discussion

The main findings of this study were that for a broad range of selected neurological and immune-related diagnoses, risk estimates varied around 1.0 and were, when increased, generally at a low level (10–30% increase), providing no convincing evidence for an association with the vaccination. Furthermore, we confirmed a positive association between a diagnosis of narcolepsy and Pandemrix vaccination both in individuals ≤20 years of age and in young adults aged 21–30 years. These associations seemed robust across models.

The main threats to the validity in this study were the possibility that pre-existing morbidity may have introduced bias and led to both over- and underestimations of risks, and uncertainty regard-

Table 3 *Risk estimates (HRs and 95% CI) overall, for early (vaccinated ≤45 days) and late (>45 days) cohorts; for observation periods up to and including 6 weeks and longer than 6 weeks, and up to and including 1 year and longer than 1 year after vaccination. From top to bottom: vaccination/allergic reactions, neurological diseases and immune-related diseases*

	No. of	Overall		Early cohort		Late cohort		≤6 weeks		>6 weeks		≤1 year		>1 year	
Disease/ICD-10 code	events	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Vaccination reaction/T88.1	147	6.14	(3.96–9.52)	6.14	(3.90–9.67)	6.14	(3.68–10.2)	19.6	(10.5–36.3)	1.33	(0.78–2.27)	9.37	(5.71–15.4)	1.24	(0.59–2.61)
Urticaria/L50	12 231	1.12	(1.09–1.16)	1.17	(1.13–1.21)	1.09	(1.05–1.13)	1.05	(0.95–1.16)	1.13	(1.09–1.17)	1.08	(1.03–1.12)	1.17	(1.12–1.22)
Allergic reaction/T78	9021	1.05	(1.01–1.08)	1.13	(1.08–1.18)	0.99	(0.95–1.03)	1.28	(1.14–1.44)	1.03	(0.99–1.07)	1.03	(0.98–1.08)	1.06	(1.01–1.12)
Anaphylactic reaction/T78.2	1099	1.05	(0.95–1.16)	1.12	(0.99–1.27)	1.00	(0.89–1.12)	1.36	(0.91–2.03)	1.03	(0.93–1.14)	1.00	(0.86–1.15)	1.10	(0.96–1.26)
Narcolepsy ≤20 years/G47.4	126	2.92	(1.78–4.79)	3.35	(1.95–5.76)	2.61	(1.53–4.44)	–	–	3.13	(1.89–5.19)	3.68	(1.45–9.34)	2.66	(1.50–4.72)
Narcolepsy, >20 years/G47.4	81	1.35	(0.93–1.95)	1.54	(0.99–2.38)	1.20	(0.78–1.86)	1.41	(0.45–4.41)	1.35	(0.92–1.98)	1.12	(0.66–1.88)	1.59	(0.97–2.61)
Narcolepsy, 21–30 years/G47.4	23	2.18	(1.00–4.75)	1.98	(0.78–5.06)	2.36	(0.98–5.71)	–	–	2.29	(1.03–5.09)	2.09	(0.65–6.72)	2.24	(0.86–5.85)
Narcolepsy, 31–40 years/G47.4	18	1.53	(0.68–3.44)	2.36	(0.95–5.89)	1.04	(0.39–2.74)	2.88	(0.34–24.7)	1.39	(0.59–3.27)	1.30	(0.46–3.72)	1.91	(0.56–6.59)
Narcolepsy, ≥40 years/G47.4	40	1.06	(0.64–1.76)	1.22	(0.67–2.23)	0.94	(0.51–1.72)	1.24	(0.29–5.23)	1.04	(0.62–1.77)	0.84	(0.41–1.74)	1.28	(0.66–2.48)
GBS/G61	170	1.03	(0.81–1.32)	0.97	(0.70–1.33)	1.08	(0.82–1.42)	1.32	(0.68–2.54)	1.00	(0.78–1.30)	0.89	(0.62–1.26)	1.17	(0.85–1.62)
MS/G35-37	1003	1.04	(0.95–1.15)	1.09	(0.96–1.23)	1.01	(0.90–1.13)	0.66	(0.46–0.95)	1.08	(0.97–1.19)	0.98	(0.85–1.12)	1.11	(0.97–1.27)
Optic neuritis/H46	298	0.95	(0.79–1.13)	1.14	(0.92–1.42)	0.82	(0.66–1.01)	0.56	(0.27–1.17)	0.98	(0.81–1.17)	0.98	(0.77–1.24)	0.91	(0.71–1.17)
ADEM/G04.0	11	1.41	(0.35–5.73)	2.46	(0.53–11.5)	0.77	(0.13–4.43)	15.2	(1.77–130)	0.69	(0.16–2.90)	1.04	(0.21–5.23)	2.67	(0.27–26.4)
Bell's palsy/G51	3151	1.07	(1.01–1.13)	1.18	(1.10–1.27)	1.00	(0.93–1.06)	1.08	(0.90–1.30)	1.07	(1.01–1.14)	1.05	(0.97–1.14)	1.09	(1.01–1.18)
Polyneuropathy/G62	2722	1.08	(1.01–1.15)	1.19	(1.11–1.29)	0.98	(0.91–1.06)	1.03	(0.85–1.26)	1.08	(1.02–1.16)	1.01	(0.93–1.10)	1.15	(1.05–1.25)
Paraesthesia/R20.2	5425	1.07	(1.02–1.11)	1.13	(1.08–1.20)	1.02	(0.97–1.07)	1.29	(1.12–1.48)	1.05	(1.01–1.10)	1.06	(0.99–1.12)	1.08	(1.02–1.14)
An-/hypoaesthesia/ R20.0/R20.1	875	1.00	(0.90–1.12)	1.11	(0.97–1.26)	0.93	(0.83–1.06)	0.89	(0.63–1.26)	1.01	(0.91–1.13)	0.98	(0.84–1.13)	1.03	(0.89–1.19)
Epilepsy grand mal/G51.0	2805	1.06	(1.00–1.13)	1.16	(1.08–1.25)	0.99	(0.93–1.07)	1.13	(0.93–1.37)	1.06	(0.99–1.12)	1.03	(0.95–1.12)	1.10	(1.01–1.19)
RA/M05-06, M12.3	2608	1.07	(1.01–1.14)	1.16	(1.08–1.26)	1.02	(0.95–1.09)	1.12	(0.91–1.39)	1.07	(1.01–1.14)	1.02	(0.94–1.11)	1.13	(1.04–1.23)
Juvenile idiopathic arthritis/M08	422	1.13	(0.92–1.38)	1.06	(0.83–1.34)	1.18	(0.95–1.47)	0.93	(0.49–1.77)	1.15	(0.93–1.41)	1.14	(0.85–1.51)	1.12	(0.86–1.46)

Table 3 (*Continued*)

Disease/ICD-10 code	No. of events	Overall		Early cohort		Late cohort		≤6 weeks		>6 weeks		≤1 year		>1 year	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CD/K50	1538	1.15	(1.06–1.25)	1.23	(1.11–1.36)	1.10	(1.01–1.21)	1.36	(1.05–1.76)	1.14	(1.05–1.24)	1.18	(1.05–1.32)	1.13	(1.01–1.26)
CD, 0–20 years/K50	401	1.47	(1.21–1.77)	1.39	(1.11–1.75)	1.52	(1.23–1.88)	3.67	(1.94–6.94)	1.37	(1.13–1.67)	1.76	(1.32–2.34)	1.28	(1.01–1.63)
CD, ≥21 years/K50	1137	1.09	(0.99–1.19)	1.20	(1.07–1.35)	1.02	(0.91–1.13)	1.11	(0.83–1.48)	1.09	(0.99–1.19)	1.09	(0.96–1.23)	1.09	(0.96–1.24)
Ulcerative colitis/K51	2177	1.09	(1.02–1.17)	1.17	(1.08–1.28)	1.04	(0.96–1.12)	0.91	(0.72–1.16)	1.11	(1.03–1.19)	1.04	(0.95–1.14)	1.14	(1.04–1.26)
T1D, <30 years of age/E10	971	1.13	(1.00–1.29)	1.16	(1.00–1.35)	1.11	(0.96–1.28)	1.24	(0.83–1.85)	1.12	(0.98–1.28)	1.13	(0.95–1.34)	1.14	(0.95–1.36)
T1D, 0–9 years/E10	497	1.07	(0.87–1.32)	1.08	(0.86–1.36)	1.05	(0.84–1.32)	1.37	(0.76–2.48)	1.04	(0.84–1.29)	1.08	(0.81–1.43)	1.06	(0.80–1.41)
T1D, 10–19 years/E10	370	1.23	(1.00–1.51)	1.20	(0.93–1.54)	1.25	(1.00–1.57)	1.01	(0.53–1.93)	1.25	(1.01–1.55)	1.20	(0.91–1.58)	1.27	(0.95–1.69)
T1D, 20–29 years/E10	104	1.09	(0.83–1.42)	1.39	(0.98–1.96)	0.90	(0.64–1.25)	1.48	(0.56–3.86)	1.07	(0.81–1.40)	1.10	(0.76–1.59)	1.07	(0.73–1.58)
IDIOPAT INFL ART/ M02-03, M13	6599	1.12	(1.07–1.17)	1.21	(1.15–1.27)	1.06	(1.01–1.11)	1.05	(0.92–1.20)	1.13	(1.08–1.18)	1.11	(1.04–1.18)	1.13	(1.07–1.20)
Arthralgia, unspecified/M25.5	21 781	1.09	(1.07–1.12)	1.16	(1.12–1.19)	1.05	(1.03–1.08)	1.10	(1.02–1.19)	1.09	(1.07–1.12)	1.09	(1.06–1.13)	1.10	(1.06–1.13)
INFL SYST DIS/ M32-35.0, M35.1	383	1.00	(0.85–1.17)	1.08	(0.88–1.32)	0.94	(0.78–1.13)	0.73	(0.39–1.36)	1.02	(0.86–1.20)	0.91	(0.72–1.13)	1.10	(0.88–1.38)
Sjögren's syndrome /M35.0	1070	1.21	(1.09–1.34)	1.48	(1.31–1.66)	0.98	(0.87–1.12)	0.96	(0.69–1.35)	1.23	(1.11–1.37)	1.15	(0.99–1.32)	1.28	(1.11–1.48)
SLE/M32	413	0.95	(0.81–1.11)	1.16	(0.96–1.39)	0.77	(0.64–0.94)	1.15	(0.71–1.89)	0.93	(0.79–1.09)	0.95	(0.77–1.18)	0.94	(0.75–1.17)
Scleroderma/M34	146	0.84	(0.65–1.08)	0.76	(0.55–1.06)	0.90	(0.67–1.19)	0.58	(0.22–1.57)	0.86	(0.66–1.11)	0.78	(0.56–1.10)	0.90	(0.63–1.28)
Polydermatomyositis /M33	142	1.21	(0.91–1.61)	1.17	(0.83–1.65)	1.25	(0.90–1.72)	1.10	(0.41–2.93)	1.22	(0.91–1.63)	1.18	(0.80–1.76)	1.24	(0.85–1.81)
Cutaneous vasculitis UNS/L95.8 L95.9	376	1.01	(0.86–1.20)	1.21	(0.99–1.47)	0.86	(0.71–1.05)	0.59	(0.31–1.14)	1.05	(0.88–1.24)	0.99	(0.78–1.25)	1.03	(0.83–1.30)
Purpura, TT/D69	3515	1.07	(1.01–1.14)	1.27	(1.19–1.36)	0.91	(0.85–0.97)	1.05	(0.87–1.26)	1.08	(1.01–1.14)	1.03	(0.95–1.11)	1.12	(1.04–1.21)
ITP/D69.3	491	1.15	(0.99–1.34)	1.30	(1.09–1.56)	1.02	(0.85–1.23)	1.17	(0.75–1.83)	1.15	(0.98–1.35)	1.06	(0.87–1.30)	1.26	(1.01–1.57)
Agranulocytosis/D70	2387	1.15	(1.08–1.24)	1.38	(1.27–1.50)	0.98	(0.90–1.07)	1.05	(0.83–1.33)	1.16	(1.08–1.25)	1.12	(1.01–1.24)	1.19	(1.08–1.30)
Haemolytic anaemia/ D59.0-D59.3	240	1.06	(0.85–1.31)	1.18	(0.92–1.52)	0.94	(0.72–1.21)	0.74	(0.39–1.39)	1.09	(0.88–1.36)	0.91	(0.68–1.22)	1.21	(0.91–1.62)
Hypothyroidism/E03	4224	1.09	(1.03–1.14)	1.17	(1.10–1.24)	1.02	(0.97–1.09)	1.06	(0.84–1.33)	1.09	(1.03–1.14)	1.10	(1.02–1.19)	1.08	(1.01–1.15)
Hyperthyroidism/E05	4006	1.02	(0.97–1.07)	1.13	(1.06–1.20)	0.94	(0.88–0.99)	1.21	(1.04–1.41)	1.00	(0.95–1.05)	0.99	(0.93–1.06)	1.04	(0.97–1.12)
Thyroiditis/E06	1716	1.07	(0.99–1.17)	1.17	(1.07–1.29)	0.99	(0.90–1.09)	0.93	(0.72–1.20)	1.09	(1.00–1.18)	1.00	(0.89–1.12)	1.15	(1.03–1.29)

Table 3 (*Continued*)

Disease/ICD-10 code	No. of events	Overall		Early cohort		Late cohort		≤6 weeks		>6 weeks		≤1 year		>1 year	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Addison's disease/ E27.1, E27.2	141	1.01	(0.77–1.32)	1.34	(0.98–1.82)	0.74	(0.52–1.04)	0.51	(0.20–1.32)	1.07	(0.81–1.41)	1.10	(0.75–1.60)	0.94	(0.65–1.35)
Myasthenia gravis/G70	225	1.20	(0.96–1.49)	1.20	(0.91–1.57)	1.20	(0.93–1.54)	0.46	(0.20–1.06)	1.29	(1.03–1.62)	1.06	(0.78–1.44)	1.36	(1.00–1.85)
Erythema multiforme/L51	485	1.20	(1.03–1.41)	1.27	(1.05–1.55)	1.15	(0.96–1.38)	1.04	(0.58–1.87)	1.21	(1.03–1.43)	1.07	(0.85–1.33)	1.36	(1.09–1.69)
SJS/L51.1	52	1.59	(0.95–2.65)	1.66	(0.89–3.09)	1.54	(0.87–2.72)	–	–	1.91	(1.11–3.28)	1.49	(0.73–3.03)	1.69	(0.84–3.39)
Exfoliative dermatitis/L26	26	0.88	(0.48–1.60)	1.05	(0.51–2.13)	0.73	(0.34–1.56)	0.46	(0.05–4.17)	0.93	(0.49–1.75)	1.05	(0.45–2.43)	0.74	(0.33–1.69)
Erythema nodosum/L52	286	0.93	(0.77–1.12)	1.00	(0.79–1.26)	0.87	(0.70–1.09)	0.61	(0.31–1.18)	0.96	(0.79–1.17)	0.81	(0.62–1.06)	1.05	(0.81–1.36)
Asthma/J45-J46	9129	1.08	(1.04–1.12)	1.02	(0.97–1.07)	1.12	(1.08–1.17)	1.10	(0.97–1.26)	1.08	(1.04–1.12)	1.06	(1.01–1.12)	1.10	(1.04–1.15)

HR, hazard ratio; CI, confidence interval; GBS, Guillain–Barré syndrome; MS, multiple sclerosis; ADEM, acute disseminating encephalomyelitis; RA, rheumatoid arthritis; CD, Crohn's disease, IDIOPAT INFL ART, idiopathic inflammatory arthritis; INFL SYST DIS, inflammatory systemic disease; SLE, systemic lupus erythematosus; TP, thrombocytopenic purpura, ITP, idiopathic thrombocytopenic purpura; SJS' Stevens–Johnson syndrome.

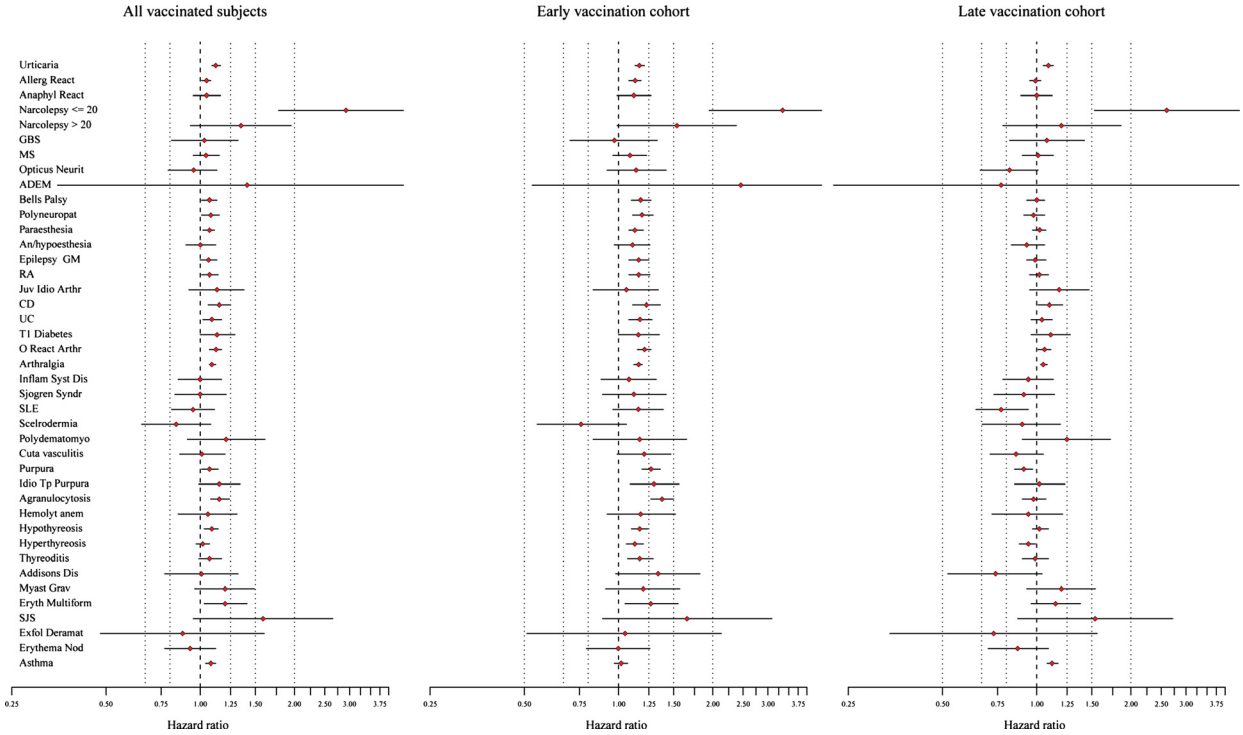

Fig. 1 *Summary plots (hazard ratios and 95% confidence intervals) for the entire study population and the early and late vaccination cohorts; for all three groups, the plots show (from top to bottom) allergic reactions, neurological diseases and immune-related diseases. GBS, Guillain–Barré syndrome; MS, multiple sclerosis; Epilepsy GM, epilepsy grand mal; ADEM, acute disseminated encephalomyelitis; RA, rheumatoid arthritis; Juv Idio Arthr, juvenile idiopathic arthritis; CD, Crohn's disease; UC, ulcerative colitis; O React Arthr, other reactive arthritis; Inflam Syst Dis, inflammatory systemic disease; SLE, systemic lupus erythematosus; Idio Tp Purpura, idiopathic thrombocytopenic purpura; SJS, Stevens–Johnson syndrome.*

ing the true onset time for some of the studied outcomes, which could lead to the inclusion of prevalent cases and thereby an error of reverse causality (vaccination could actually have occurred after the true onset of disease).

Interpretation of the data was influenced by four main observations. First, most HRs were reduced in magnitude after adjustment for healthcare consumption in the preceding year. Secondly, the risk estimate based on the first registered ICD code was often reduced after the exclusion of individuals with previous health care due to possible early states of the disease under study (Appendix Table A1). Thirdly, increased HRs were higher in the early than in the late vaccination cohort (Fig. 1). Further, a systematic analysis showed that 24 of all 42 overall HRs analysed were reduced when comparing time of vaccination in the last half with that of the first half of the vaccination period (data not shown). Finally, it is noteworthy that the risk of death (after adjustment) was lower in individuals vaccinated late in the programme, compared with unvaccinated individuals, but was higher in those vaccinated early (Appendix Fig. A1). Thus, these observations support the influence of selection of individuals for vaccination.

For the vast majority of outcomes, except vaccine reactions and narcolepsy, the adjusted HRs (Table 3 and Fig. 1) were close to or only marginally greater than 1. Thus, we believe that a cautious interpretation is warranted; a residual or unmeasured confounding, or reverse causality, might entirely or partly explain the low-level increases for some of the associations. However, at the same time and for this reason, a small increase in risk as a result of vaccination cannot be completely ruled out.

With the exception of narcolepsy, we could not establish convincing associations between Pandem-

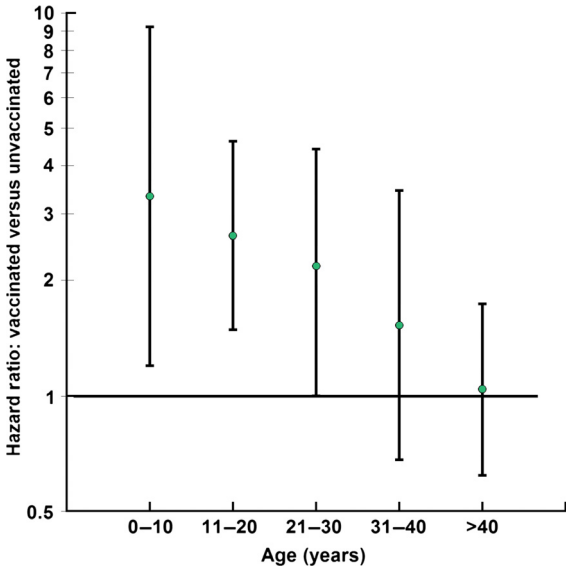

Fig. 2 *Hazard ratios and 95% confidence intervals (logarithmic scale) for diagnosed narcolepsy during the study period, by age at vaccination (P for trend = 0.012).*

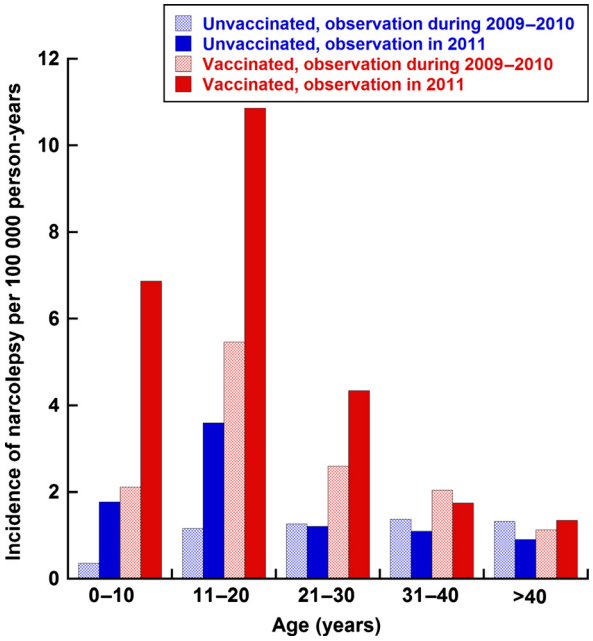

Fig. 3 *Crude incidence rates of diagnosed narcolepsy in the vaccinated and unvaccinated cohorts, according to age group and observation period (2009–2010 vs. 2011).*

rix vaccination and any of the neurological outcomes. This seemingly contradicts the results from the previous smaller study in Stockholm with a shorter follow-up period, in which small risk increases were observed for polyneuropathy, paraesthesia and Bell's palsy (which were considered to be caused partially or entirely by selection bias) [22].

Regarding GBS, previous reports on the association with adjuvanted H1N1 vaccines have shown inconsistent results [17–19, 22]. No association has been reported between Pandemrix vaccination and grand mal epilepsy convulsions [20, 21].

We also found that no positive associations could be established between Pandemrix and any of the immune-related disorders (except vaccination reactions). The outcomes studied represent a large group of autoimmune and chronic inflammatory diseases with variable clinical course and different pathogenetic mechanisms. For diseases such as rheumatoid arthritis, Crohn's disease and asthma – with typically chronic and relapsing courses and with the possible appearance of first symptoms long before the established diagnosis – we believe that it is difficult to determine the actual time of onset. Taking this uncertainty into account, and the increased risk estimates for Crohn's disease observed in individuals ≤20 years of age (Table 3), we propose that further investigations could be warranted. To date, the findings from one large study of H1N1 vaccination and risk of flare in Crohn's disease did not provide support for an adverse effect [24].

We did note slightly increased risk estimates for T1D in subjects aged 10–19 years (Table 3). However, a positive association between H1N1 vaccination and T1D seems less plausible when considering T1D incidence data from the nationwide SweDiabKids registry [25] in which the annual number of new cases in the relevant age group was relatively stable between 2007 and 2011 (440, 397, 411, 424 and 388 cases, respectively), thus with no increase following vaccination in 2009.

The absence of an increase in risk of events related to typical autoimmune diseases, for example systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis and autoimmune thyroiditis, would suggest a very specific immunological mechanism underlying the development of narcolepsy after Pandemrix exposure. It is of interest that most organ-specific inflammatory diseases, often regarded as autoimmune (with MS as an example), have combined causes involving lifestyle/environmental factors and predisposing genes, particu-

larly *HLA* class II genotypes. Almost 100% of patients with narcolepsy with cataplexy carry the HLA class II allele *DQB1*06:02* [26]. It is also interesting that *DRB1* and *DQB1* genes are closely located, and variants are in linkage disequilibrium; that is, they are co-inherited. *DRB1**15:01 and *DQB1**06:02 that predispose towards MS and narcolepsy, respectively, are thus always present together in the Swedish population. It is therefore noteworthy that in the present study, we found no risk increase for MS or monosymptomatic manifestations associated with MS, such as optic neuritis and sensory disturbances.

With regard to narcolepsy, our finding of a three-fold increased risk corroborates previous reports of an increased risk in children/adolescents [3–7, 27]. Of note, the higher-magnitude risk increases in other studies, where determination relied on clinical case ascertainment and medical record data [4–9], are not directly comparable with the present registry-based data. The overall risk estimate in the present study is somewhat lower than in our previous registry study [3], using the same registry-based ascertainment of diagnosed narcolepsy cases. This is likely to be due to the fact that the incidence of diagnosed narcolepsy also increased in the unvaccinated cohort in the current study (Fig. 3), highlighting the possibility of stimulated detection, diagnosis and reporting from a prevalent pool of cases. An increase amongst unvaccinated individuals could also be an effect of an external factor. This factor may be infection with the H1N1 influenza virus itself, as indicated in a study from China [28]; however, a recent study from Finland based on serological data could not demonstrate an association with the natural H1N1 infection [29].

Importantly, we also observed a two-fold increased risk of narcolepsy in young adults (21–30 years of age), which is considered to be valid in spite of the methodological limitations discussed above. The increased risk in adults is consistent with the findings from a recent Finnish study in 20- to 64-year-old participants [9] and a French study in individuals aged 20 years and older [8]; however, neither of these two studies presented results in narrower age groups. Although we showed an association in young adults and a declining risk with age (Fig. 2), it is neither possible (due to random variation) nor biologically relevant to define more precisely an upper age limit for the elevated risk.

Our findings raise questions regarding the mechanisms by which Pandemrix could exert differential effects according to age. Even if the peak incidence for naturally occurring narcolepsy is much in line with the findings in the present study, that is, <30 years of age [27], this does not rule out the possibility of a causal relationship in older individuals.

There are several strengths of this study: (i) the large study population (yielding about 6.9 and 6.0 million person-years of observation in the vaccinated and unvaccinated cohorts, respectively) allowing for subgroup analyses, (ii) the population-based approach, (iii) the high completeness of vaccination registration, (iv) the complete record linkage follow-up of selected health outcomes in national registries (independent of vaccination exposure) for more than 2 years, (v) and the availability of data on comorbidity and drug prescription registry data for definitions of incident outcomes and covariates.

However, a number of limitations should also be considered. Data from primary care were not available. The opportunity for identifying an outcome might be greater for individuals with medical risk factors, that is, those who were considered to warrant early vaccination and who were mainly cared for in a hospital setting, than for those vaccinated in the late phase and who received mainly primary care. Because of multiple analyses for over 50 outcomes, a number of false-positive risk estimates would be expected by chance.

There are also important limitations specifically regarding narcolepsy. First, ascertainment of narcolepsy cases was based on registered diagnoses; there was no opportunity in this study to validate these diagnoses. However, in the previous registry study [3], cases of narcolepsy from the National Patient Register were validated against case data from medical records examined by experts in a case inventory study [4]. Thus, amongst 44 cases subject to detailed scrutiny, the diagnosis was fully verified in 89%. Further, in the case inventory study [4], it was shown that the same diagnostic procedure, the multiple sleep latency test (MSLT), had been used for all included cases ($n = 81$). Thus, neurologists consistently apply an objective method such as MSLT for the diagnosis of narcolepsy in patients in Sweden. These observations indirectly support the validity of our registry diagnoses in the National Patient Register.

Secondly, we had no information on the date of onset of first symptoms of narcolepsy. Therefore, there is a possibility of inclusion of prevalent cases as well as of bias as a result of accelerated diagnosis in vaccine-exposed individuals, especially amongst adults. Our findings of an association also in young adults are, however, supported by the following observations: (i) a clear relationship with successively decreasing risk with increasing age at vaccination was present (Fig. 2), (ii) there was no indication of stimulated reporting in adults aged 20 years and older (in the unvaccinated subjects) (Fig. 3), thus challenging the possibility of bias due to stimulated reporting, and (iii) when comparing the results (crude incidence rates) for the early (2009–2010) and late (2011) observation periods, the risk relationship was observed also in the latter period for the age groups up to 21–30 years (Fig. 3). The problem of prevalent disease bias would be expected to decrease as observation time is extended; our finding would thus support a real risk increase in this age group. Furthermore, it is not plausible that a biological effect would cease abruptly at the age of 20 years. In the Swedish data, there was no clustering at the lower boundary of the young adult age group, that is, 12 cases were 21–25 years old and 11 cases were 26–30 years of age.

Finally, we had no information on influenza infections and other potential immunological triggers for individual study participants. Thus, there was no opportunity to determine whether other factors had acted in concert with the vaccination to affect the risk of narcolepsy.

Conclusions

In this large cohort study, we found no convincing evidence of a risk increase for selected neurological or immune-related diseases, except narcolepsy, in Pandemrix-vaccinated compared with unvaccinated individuals. We confirmed an increased risk of diagnosed narcolepsy in individuals ≤20 years of age vaccinated with Pandemrix and found a successively decreasing risk with age at vaccination, as well as an indication of an increase in risk also in young adults (aged 21–30 years).

We recognize that no epidemiological study, not even a study of this size, may entirely rule out small excess risks at the population level. Nor may such a study establish a cause–effect relationship in an individual patient. Nevertheless, the results of this study should have implications not only for future narcolepsy research but also for the development of new influenza vaccines.

Conflict of interest statement

IP and NF are employed by the MPA. None of the other authors has any conflict of interests to declare, including no relationships in the previous 3 years with companies that might have an interest in the submitted work.

Acknowledgements

The study was funded solely by the MPA. The MPA supervised the work and approved the views and conclusions presented in the manuscript. We thank the study coordinator at the MPA, Maria Szirmai, MSc Pharm, and the medical officers at the Departments for Prevention of Communicable Diseases in the seven participating healthcare regions/county councils: regions of Skåne and Västra Götaland, Simon Werner and Per Follin, respectively, and counties of Kalmar, Östergötland, Stockholm Värmland and Norrbotten, Claes Söderström, Britt Åkerlind, Åke Örtqvist, Olle Wiik and Anders Österlund, respectively.

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Correspondence: Ingemar Persson, Medical Products Agency, PO Box 26, SE-751 03 Uppsala, Sweden.
(fax: 46 18 54 85 66; e-mail: ingemar.persson@mpa.se).

Figure A1. *Mortality (adjusted hazard ratios and 95% confidence intervals) in age groups and by quartiles of the vaccination time-point (Q1–Q4) during the study period.*

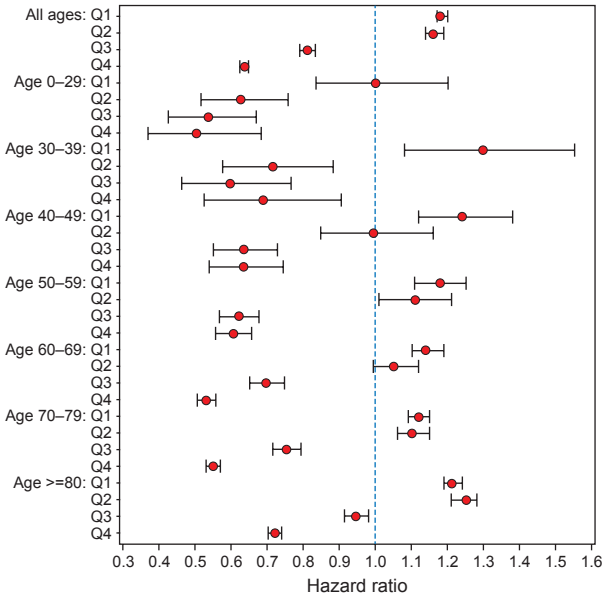

Table A1 *Overall hazard ratios (HRs) and 95% confidence intervals (95% CIs) for all outcomes, showing changes in the magnitude of HRs after adjustment for covariates in the basic model (HR2; adjusted for age, gender, county, income and education) and in the fully adjusted model (HR4; additionally adjusted for specialist healthcare consumption, ICD-10 diagnoses and pregnancy), and further after exclusion of subjects with prodromal states before the study period (for outcomes where relevant, see Table 2)*

		Basic model		Fully adjusted model		Prodromal exclusion		
Disease/ICD-10 code	No. of events	HR2	95% CI	HR4	95% CI	No. of events	HR	95% CI
Vaccination reaction/T88.1	147	7.41	(4.72–11.6)	6.14	(3.96–9.52)			
Urticaria/L50	12 231	1.18	(1.15–1.22)	1.12	(1.09–1.16)			
Allergic reaction/T78	9021	1.11	(1.08–1.15)	1.05	(1.01–1.08)			
Anaphylactic reaction/T78.2	1099	1.13	(1.03–1.25)	1.05	(0.95–1.16)			
Narcolepsy, ≤20 years/G47.4	127	2.87	(1.75–4.69)	2.93	(1.79–4.80)	126	2.92	(1.78–4.79)
Narcolepsy, >20 years/G47.4	88	1.60	(1.12–2.28)	1.42	(0.99–2.03)	81	1.35	(0.93–1.95)
GBS/G61	170	1.11	(0.88–1.42)	1.03	(0.81–1.32)			
MS/G35-37	1003	1.08	(0.98–1.19)	1.04	(0.95–1.15)			
Optic neuritis/H46	298	1.01	(0.85–1.21)	0.95	(0.79–1.13)			
ADEM/G04.0	11	2.17	(0.64–7.35)	1.41	(0.35–5.73)			
Bell's palsy/G51	3151	1.13	(1.07–1.19)	1.07	(1.01–1.13)			
Polyneuropathy/G62	2722	1.23	(1.16–1.31)	1.08	(1.01–1.15)			
Paraesthesia/R20.2	5425	1.15	(1.10–1.20)	1.07	(1.02–1.11)			
An-/hypoaesthesia/R20.0/R20.1	875	1.10	(0.99–1.22)	1.00	(0.90–1.12)			

Table A1 (*Continued*)

Disease/ICD-10 code	No. of events	Basic model		Fully adjusted model		Prodromal exclusion		
		HR2	95% CI	HR4	95% CI	No. of events	HR	95% CI
Epilepsy grand mal/G51.0	2805	1.11	(1.05–1.18)	1.06	(1.00–1.13)			
RA/M05-06, M12.3	4418	1.21	(1.15–1.27)	1.12	(1.07–1.18)	2608	1.07	(1.01–1.14)
Juvenile idiopathic arthritis/M08	720	1.31	(1.13–1.51)	1.18	(1.02–1.37)	422	1.13	(0.92–1.38)
CD/K50	2045	1.30	(1.22–1.40)	1.20	(1.11–1.29)	1538	1.15	(1.06–1.25)
Ulcerative colitis/K51	2920	1.25	(1.18–1.33)	1.16	(1.09–1.23)	2177	1.09	(1.02–1.17)
T1D, <30 years/E10	980	1.21	(1.07–1.38)	1.14	(1.01–1.30)	971	1.13	(1.00–1.29)
REACTIVE IDIOPAT INFLAM ART/M02-03, M13	6599	1.20	(1.15–1.25)	1.12	(1.07–1.17)			
Arthralgia, unspecified/M25.5	21 781	1.17	(1.15–1.20)	1.09	(1.07–1.12)			
INFL SYST DIS/M32-35, M35.1	1342	1.27	(1.16–1.38)	1.13	(1.04–1.24)	383	1.00	(0.85–1.17)
Sjögren's syndrome/M35.0	1070	1.37	(1.24–1.52)	1.21	(1.09–1.34)	269	1.00	(0.83–1.21)
SLE/M32	413	1.09	(0.94–1.27)	0.95	(0.81–1.11)			
Scleroderma/M34	146	0.91	(0.71–1.17)	0.84	(0.65–1.08)			
Polydermatomyositis/M33	142	1.34	(1.01–1.77)	1.21	(0.91–1.61)			
Cutaneous vasculitis UNS/L95.8 L95.9	376	1.14	(0.96–1.34)	1.01	(0.86–1.20)			
Purpura, thrombocytopenia/D69	3515	1.22	(1.16–1.30)	1.07	(1.01–1.14)			
ITP/D69.3	491	1.27	(1.09–1.47)	1.15	(0.99–1.34)			
Agranulocytosis/D70	2387	1.32	(1.24–1.42)	1.15	(1.08–1.24)			
Haemolytic anaemia/D590-D593	240	1.21	(0.98–1.50)	1.06	(0.85–1.31)			
Hypothyroidism/E03	17 470	1.18	(1.15–1.21)	1.08	(1.06–1.11)	4224	1.09	(1.03–1.14)
Hyperthyroidism/E05	4006	1.08	(1.03–1.14)	1.02	(0.97–1.07)			
Thyroiditis/E06	1716	1.20	(1.11–1.30)	1.07	(0.99–1.17)			
Addison's disease/E27.1, E27.2	141	1.10	(0.84–1.43)	1.01	(0.77–1.32)			
Myasthenia gravis/G70	225	1.30	(1.04–1.61)	1.20	(0.96–1.49)			
Erythema multiforme/L51	485	1.26	(1.07–1.48)	1.20	(1.03–1.41)			
Exfoliative dermatitis/L26	26	1.03	(0.57–1.85)	0.88	(0.48–1.60)			
Erythema nodosum/L52	286	0.98	(0.81–1.18)	0.93	(0.77–1.12)			
Asthma/J45-J46	30 356	1.51	(1.48–1.54)	1.44	(1.41–1.47)	9129	1.08	(1.04–1.12)

Note

GBS, Guillain–Barré syndrome; MS, multiple sclerosis; ADEM, acute disseminating encephalomyelitis; RA, rheumatoid arthritis; CD, Crohn's disease; T1D, type 1 diabetes mellitus; IDIOPAT INFL ART, idiopathic inflammatory arthritis; INFL SYST DIS, inflammatory systemic disease; SLE, systemic lupus erythematosus; ITP, idiopathic thrombocytopenic purpura.

