



CLINICAL REVIEW

Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis



Tomi O. Sarkanen ^{a, b, *}, Anniina P.E. Alakuijala ^{b, c}, Yves A. Dauvilliers ^{d, e},
Markku M. Partinen ^{b, f}

^a Central Finland Central Hospital, Department of Neurology, Jyväskylä, Finland

^b University of Helsinki, Department of Neurological Sciences, Helsinki, Finland

^c HUS Medical Imaging Center, Helsinki University Central Hospital, Department of Clinical Neurophysiology, Finland

^d Gui-de-Chauliac Hospital, CHU Montpellier, Inserm, U1061, France

^e National Reference Centre for Orphan Diseases, Narcolepsy, Idiopathic hypersomnia and Kleine-Levin Syndrome, Sleep Disorders Center, France

^f Helsinki Sleep Clinic, Vitalmed Research Centre, Finland

ARTICLE INFO

Article history:

Received 1 January 2017

Received in revised form

22 May 2017

Accepted 14 June 2017

Available online 20 June 2017

Keywords:

Narcolepsy

Cataplexy

H1N1

Influenza

Pandemrix

Vaccination

Autoimmune diseases

SUMMARY

An increased incidence of narcolepsy was seen in many countries after the pandemic H1N1 influenza vaccination campaign in 2009–2010. The H1N1 vaccine – narcolepsy connection is based on observational studies that are prone to various biases, e.g., confounding by H1N1 infection, and ascertainment, recall and selection biases. A direct pathogenic link has, however, remained elusive. We conducted a systematic review and meta-analysis to analyze the magnitude of H1N1 vaccination related risk and to examine if there was any association with H1N1 infection itself. We searched all articles from PubMed, Web of Science and Scopus, and other relevant sources reporting the incidence and risk of post-vaccine narcolepsy. In our paper, we show that the risk appears to be limited to only one vaccine (Pandemrix®). During the first year after vaccination, the relative risk of narcolepsy was increased 5 to 14-fold in children and adolescents and 2 to 7-fold in adults. The vaccine attributable risk in children and adolescents was around 1 per 18,400 vaccine doses. Studies from Finland and Sweden also appear to demonstrate an extended risk of narcolepsy into the second year following vaccination, but such conclusions should be interpreted with a word of caution due to possible biases. Benefits of immunization outweigh the risk of vaccination-associated narcolepsy, which remains a rare disease.

© 2017 Elsevier Ltd. All rights reserved.

Introduction

Narcolepsy is a complex chronic hypersomnia syndrome affecting approximately 20–50 per 100,000 persons [1–4]. The previously reported estimated incidence is approximately 1 per 100,000 persons per year with the peak of onset at the 2nd decade [4–6]. Two distinct disease categories can be distinguished. Narcolepsy type 1 (NT1) is likely caused by an autoimmune-mediated destruction of hypocretin-producing neurons in the lateral hypothalamus [7,8]. NT1 is almost always associated with cataplexy. In narcolepsy type 2 (NT2), there is no hypocretin deficiency or cataplexy.

An increased incidence of narcolepsy was observed in six European countries after the pandemic influenza A virus, A(H1N1)

pdm09 (“swine flu”), vaccination campaign during the winter 2009–2010. The first signal was observed in Finland and Sweden, followed by France, England, Ireland, and Norway – all the countries where AS03-adjuvanted pandemic vaccine Pandemrix (GlaxoSmithKline Biologicals, Wavre, Belgium) was widely used [9–15]. In the European Union and European Economic Area (EU/EEA), three centrally and five nationally authorized vaccines were used with coverage of at least 46.2 million people [15]. Five vaccines had no adjuvant, two had MF59-adjuvant and one, Pandemrix, had AS03 adjuvant. Pandemrix was the most used vaccine (over 30.5 million people vaccinated) in Europe. In the United States, over 90 million doses of pandemic H1N1 vaccination were administered in 2009–2010, but no adjuvanted vaccines were used [16].

One particular problem with the observational studies is their proneness to various biases such as confounding by natural H1N1 infection, and ascertainment, recall and selection biases. For instance, a seasonal and temporary increase in the incidence of narcolepsy was also seen in China after the 2009–2010 pandemic

* Corresponding author. Central Finland Central Hospital, Department of Neurology, Keskussairaalantie 19, 40620, Jyväskylä, Finland. Fax: +358 9 440 260.
E-mail address: tomi.sarkanen@ksshp.fi (T.O. Sarkanen).

Abbreviations			
ANSM	Agence nationale de sécurité des médicaments et des produits de santé, France	MeSH	Medical Subject Heading (US National Library of Medicine, NIH)
CI	confidence interval	MPA	Medical products agency, Sweden
CSF	cerebrospinal fluid	MSLT	multiple sleep latency test
ECDC	European center for disease control	NP	nucleoprotein
EDS	excessive daytime sleepiness	NT1	narcolepsy type 1
EU/EEA	European Union and European economic area	NT2	narcolepsy type 2
HLA	human leukocyte antigen	OR	odds ratio
HPSC	Health protection surveillance centre	PRISMA	reporting items for systematic reviews and meta-analyses
ICSD-2	International classification of sleep disorders, 2nd edition	REM	rapid eye movement
ICSD-3	International classification of sleep disorders, 3rd edition	RR	relative risk
		THL	National institute for health and welfare, Finland
		VAESCO	Vaccine adverse event surveillance & communication

influenza A virus without clear relation to any vaccine [17–19]. This implicates the possibility that the H1N1 virus per se could be a triggering factor for the development of narcolepsy at least in Asian population. Furthermore, it was recently reported that influenza virus is capable of damaging hypocretinergic neurons in immune-depleted mice causing a narcolepsy-resembling phenotype [20].

Narcolepsy has also been a rare, underdiagnosed disease with long delay between onset of symptoms and diagnosis [21]. Therefore, the recognition of the syndrome may have been limited especially among primary health care practitioners before increased media attention after H1N1-related cases. Simply an increase in attention towards this disease could lead to increase in the number of diagnosed cases without an actual rise in incidence. The methods in the observational studies are also somewhat heterogeneous. For example, incorrect case confirmation and inaccurate gathering of information on the symptom onset and vaccination date could cause ascertainment bias [22].

Even if observational studies could prove strong connection between vaccination and narcolepsy, the true causative relationship requires a pathogenic-proven link. However, specific biological mechanisms behind the vaccine-associated narcolepsy are still incompletely understood [8]. Some evidence exists on increased immune response against viral nucleoprotein in Pandemrix in subjects who have genetic predisposition to narcolepsy by HLA DQB1*06:02 allele [23].

Taken into account biological and epidemiological controversies in connection between narcolepsy, H1N1 influenza virus infections and vaccinations, we conducted a systematic review and meta-analysis to clarify the risk of narcolepsy associated with H1N1 vaccines and infections.

Methods

Literature search and selection criteria

We searched PubMed, Web of Science, and Scopus for all articles reporting incidence and risk of Pandemrix H1N1-vaccination-associated narcolepsy in November 2016 without a language restriction. The full search string was (narcolepsy[MeSH] OR narcolepsy) AND (vaccines[MeSH] OR vaccination[MeSH] OR influenza [MeSH] OR Pandemrix OR vaccines OR vaccination).

We also checked the references of all relevant studies and review articles to identify additional sources. Webpages of National Institute for Health and Welfare (THL) in Finland, Medical Products Agency (MPA) in Sweden, Norwegian Medicines Agency, Health Protection Surveillance Centre (HPSC) in Ireland, Public Health

England, Agence Nationale de Sécurité des Médicaments et des Produits de Santé (ANSM) in France, and European Centre for Disease Control (ECDC) were checked for their reports on narcolepsy. We followed Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in conducting and reporting of the study.

Eligibility criteria

Two authors (TS, MP) assessed the articles for eligibility based on first the title, then the abstract, and finally the full text. We included all studies and reports that evaluated the risk of narcolepsy or the number of narcolepsy cases after Pandemrix vaccination. We also included studies assessing the risk of narcolepsy after other A(H1N1)pdm09 vaccines in the qualitative synthesis. In case of overlapping data, the most recent and comprehensive study was used. Only cases fulfilling Brighton criteria 1–3 or International classification of sleep disorders 2 criteria for narcolepsy (excessive daytime sleepiness (EDS) and low cerebrospinal fluid (CSF) hypocretin or positive multiple sleep latency test (MSLT) were used in analysis) in order to avoid wrong diagnoses [24].

Data extraction

Data extraction was performed independently by two reviewers (TS, MP). Any disagreement was solved by discussion. Data extraction included: country or study area, author, publication year, study type, age of subjects, duration of follow-up or collection period, number of vaccinated and unvaccinated subjects, vaccination coverage, reported country-specific narcolepsy incidence rate before and after 2009 influenza A H1N1 vaccination campaign in vaccinated and unvaccinated subjects, relative risk (RR) in cohort studies or odds ratio (OR) in case–control studies, 95% confidence interval (CI), and vaccine attributable risk of narcolepsy. In the analyses, relative risks and odds ratios were used interchangeably because narcolepsy is a rare disease and in such cases these two ratios are very close to each other.

Dutch population data were retrieved from Statistics Netherlands and Swiss population data from Swiss Federal Statistics Office for calculations of RR in these countries. There is limited information on the incidence of narcolepsy in toddlers but for the Netherlands reports, background incidence was evaluated to be approximately 1 per 800,000 children aged less than five year based on vaccine adverse event surveillance & communication (VAESCO) data [15].

Risk of bias in individual studies

Observational studies are prone to various ascertainment, recall and selection biases (e.g., lack of blinding to vaccination status, lack of validation of cases, and increased media attention) but also to confounding such as H1N1 infection per se. We reviewed and detailed on those potential biases for all the post-Pandemrix narcolepsy studies.

Statistical analysis

Statistical analyses were performed using STATA version 14.1 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX, USA: StataCorp LP). Relative risks or odds ratios were used for pooled analysis of all included studies. The results are presented with 95% confidence intervals (CI) using a random-effects model. Statistical heterogeneity across the studies was evaluated using I^2 statistics.

Results

Included studies

Literature search resulted in 310 articles (Fig. 1) after removal of duplicate papers. Additional ten articles were included outside of the search as explained in the methods section [12,15,25–32].

Seventy-five reviews were excluded, but their reference lists were examined to include any appropriate articles not retrieved in the literature search. After screening for the titles and abstracts, full texts of 78 articles were read. Forty-nine studies either analyzed duplicate populations with the studies included in the final analysis or were not relevant. Eleven studies or reports were included in the final meta-analysis (Table 1) [9–12,14,29,31,33–35]. Three additional Pandemrix studies [13,36,37], and fifteen non-Pandemrix studies were included in the qualitative synthesis (Table 2) [17–19,32,38–48].

The majority of the studies analyzed comprised of register cohort studies (Table 1). Two case-coverage studies and one case–control study were also included. We also added a paper from Netherlands Pharmacovigilance Centre reporting cases of narcolepsy in children aged six months to five years after Pandemrix vaccination [31]. Only children with confirmed narcolepsy (Brighton classes 1–3) and onset after Pandemrix vaccination were included in meta-analysis from this study (7 out of 20 reported cases). We analyzed the studies divided into two subgroups: 1) children and adolescents, and 2) adults.

Index dates and study period

Five different index dates were used in the studies: onset of symptoms, first healthcare contact, referral to specialist, referral to MSLT, and final diagnosis. The onset of symptoms would be the

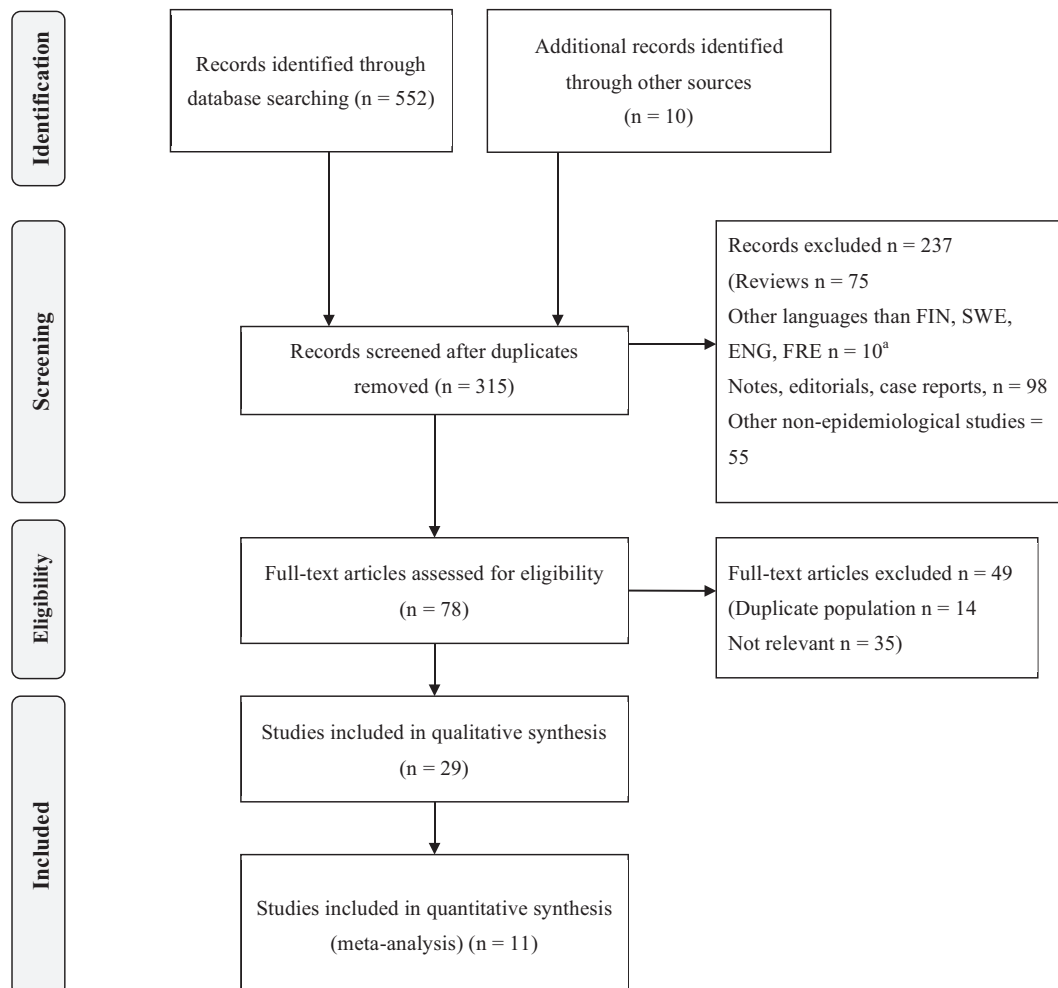


Fig. 1. PRISMA flow diagram of included studies. FIN, Finnish; SWE, Swedish; ENG, English; FRE, French. A 2 Norwegian, 4 Danish, 1 German, 1 Portuguese, 1 Russian, 1 Turkish. English titles and/or abstracts screened for relevant information.

Table 1
Summary of included Pandemrix studies in the meta-analysis.

Authors, reference number	Country	Type	Age group (y)	Follow-up period		Number of subjects or follow-up years				
				Start	End	Vaccinated		Unvaccinated		
						NC	Healthy	NC	Healthy	
Children and adolescents										
Dauvilliers Y. et al., 2013 [33]	France	CC	<18	Apr 1, 2009	Apr 30, 2011		21	N/A ^a	14	N/A ^a
Heier M. et al., 2013 [10]	Norway	RC	4–19	Nov 1, 2009	Dec 31, 2011	1st y	48	470,000	3	470,000
Jokinen J. et al., 2014 [30]	Finland	RC	4–19	Jan 1, 2009	Dec 31, 2012	2nd y	5	470,000	2	470,000
						1st y	93	687,000	7 ^b	692,000 ^b
						1–2 y	33	687,000	“	“
						>2 y	13	751,000	“	“
Lareb 2015 [31]	The Netherlands	Report	0.5–5				7	589,000	NA	450,000 ^c
Miller E. et al., 2013 [11]	England	CCov	4–18	Jan 1, 2008	Jul 31, 2011		11	360,000	64	8,130,000
MPA 2011 [12]	Sweden	RC	<20	Jan 1, 2009	Dec 31, 2010		69	1,624,000	7	1,093,000
Nohynek H. et al., 2012 [9]	Finland	RC	4–19	Jan 1, 2009	Aug 15, 2010		46	511,000	7	986,000
O’Flanagan D. et al., 2014 [14]	Ireland	RC	5–19	Apr 1, 2009	Dec 31, 2010		19	160,000	5	620,000
Persson I. et al., 2013 [34]	Sweden	RC	0–20	Oct 1, 2009	Dec 31, 2011		126	966,000		425,000
Adults										
Dauvilliers Y. et al., 2013 [33]	France	CC	≥18	Apr 1, 2009	Apr 30, 2011		11	N/A	16	N/A
Jokinen J. et al., 2013 [29]	Finland	RC	20–65	Jan 1, 2009	Dec 31, 2011		24	3,151,477	14	6,705,173
Jokinen J. et al., 2014 [30]	Finland	RC	20–74	Jan 1, 2009	Dec 31, 2012	1st y	17	1,841,000	7 ^b	5,802,000 ^b
						1–2 y	15	1,841,000	“	“
						>2 y	2	1,825,000	“	“
							2	470,000	1	2,850,000
O’Flanagan D. et al., 2014 [14]	Ireland	RC	≥20	Apr 1, 2009	Dec 31, 2010		23	310,000	NA	428,000
Persson I. et al., 2013 [34]	Sweden	RC	21–30	Oct 1, 2009	Dec 31, 2011		18	445,000	NA	361,000
			31–40				40	1,627,000	NA	1,283,000
			>40				5	650,000	35	1,340,000
Stowe J. et al., 2016 [35]	England	CCov	≥18	Sep 1, 2009	Oct 30, 2011					

NC, narcolepsy; CC, case–control; RC, register cohort; CCov, case-coverage; N/A, not applicable; NA, not available.

^a Number of vaccinated and unvaccinated subjects cannot be given because of the case–control design.

^b Number of unvaccinated cases reported for the full follow-up period until the end of 2012.

^c Estimated from Statistic Netherlands.

Table 2
Summary of narcolepsy incidence studies from countries where Pandemrix vaccination was not used.

Authors, reference number	Area	Study type	Collection period	Pandemic vaccine	Vaccine coverage	Vaccination associated risk of narcolepsy
Choe Y. et al., 2012 [38]	South Korea	Ecological	Jul 2006 to Jun 2011	MF59-ADJ, non-ADJ	26.10% ^f	Not increased
Duffy J. et al., 2014 [40]	US	Register cohort	Oct 2009 to Dec 2011	Non-ADJ ^a	~10%	Not increased (OR ~1 in different age groups).
Han F. et al., 2011 [17]	Beijing, China	Case series	1996–2011	Non-ADJ	5.6%	3-fold increase, not associated with vaccination
Han F. et al., 2013 [18]	Beijing, China	Case series	1998 to Sep 2012	Non-ADJ	5.6%	Risk reduced to normal after 2 y
Harris T. et al., 2014 [43]	Ontario, Canada	Reported adverse effects ^d	Until Apr 2013	AS03-ADJ ^b	37% ^e	Not increased
Kim W.J. et al., 2015 [44]	South Korea ^g	Ecological	2007–2013	MF59-ADJ, non-ADJ	NR	Not increased
Montplaisir J. et al., 2014 [46]	Québec, Canada	CC, S-CCS, RC	Jan 2009 to Dec 2010	AS03-ADJ ^b	57%	Small increase possible ^e
Tsai T.F. et al., 2011 [48]	Worldwide	Reported adverse effects	Until Jul 2010	MF59-ADJ	N/A	Not increased
Wu H. et al., 2014 [19]	Shanghai, China	Case series	2003–2012	Non-ADJ	NR	3-fold increase, not associated with vaccination

ADJ, adjuvanted; OR, odds ratio; CC, case control, S-CCS, self-controlled case series; RC, register cohort; RR, relative risk; NR, not reported, N/A, not applicable.

^a Monovalent inactivated vaccine and monovalent live attenuated influenza vaccine during the pandemic period in 2009, and trivalent inactivated vaccine and live attenuated influenza vaccine during the seasonal influenza vaccination campaign in 2010–2011.

^b Arepanrix (GlaxoSmithKline Inc, Mississauga, Ontario, Canada; GlaxoSmithKline Biologicals, Wavre, Belgium).

^c RR 16 wk after vaccination CC 1.48 (0.37–7.03), S-CCS 2.96 (0.71–12.39), RC 4.32 (1.50–11.12). Attributable risk 1 per million vaccine doses.

^d From Pharmacovigilance databases and clinical trials.

^e Based on the number of distributed vaccines, not administered.

^f 87% in age group under 18 y.

^g Active duty soldiers and military officers in the Korean military.

most natural and ideal index date, but it is difficult to assess objectively in retrospect and it is possibly prone to a recall bias. The symptom onset was used as the primary index date in the Norwegian and British studies, while it was included in sensitivity analyses in the other studies [10,11]. The first health care contact confirmed from patient records is the earliest objective time point to be used as the index date. It was used in the primary analysis in the Finnish and Irish studies [9,14,29,30]. These studies were the

only studies reporting also the referral to specialist as the index date. The referral to MSLT was reported only in the French study where it was also the primary index date [33]. The date of diagnosis was used as the primary date in the Swedish studies [12,34].

Different study periods with the ending point from August 2010 to the end of year 2012 were used based on the time of publication of the study and media awareness of the link between vaccination and narcolepsy (to minimize ascertainment bias, see Discussion).

Risk of post-vaccination narcolepsy

The total number of narcolepsy cases in included studies was 376 vaccinated and 95 unvaccinated children and adolescents. Total follow-up number of vaccinated children and adolescents were 5.1 million, and unvaccinated 11.3 million person years. For adults, the corresponding figures were 133 vaccinated, 59 unvaccinated narcolepsy cases, and 9.0 million follow-up vaccinated healthy adults and 12.1 million follow-up unvaccinated healthy adults (Table 1).

In children and adolescents, RR of post-Pandemrix narcolepsy during the primary analysis period was 14.32 (95% CI 8.92 to 22.99) if the onset of symptoms was used as the index date. Corresponding figures were 9.68 (4.88, 19.23) if the first healthcare contact, and 5.02 (3.36, 7.51) if the diagnosis was used as the index date (Fig. 2).

In adults, RR was 7.01 (3.40, 14.46) using the onset, 8.08 (3.86, 16.89) using the healthcare contact, and 2.95 (1.88, 4.62) using the diagnosis as the index date (Fig. 3).

Heterogeneity measured by I^2 statistic was very low, 0% in all subgroups, except for the healthcare contact in children and adolescents where $I^2 = 44.1%$, nevertheless, it was statistically insignificant ($P = 0.167$).

The vaccine attributable risk approximately one year after the vaccination could be calculated from five studies in children and adolescents [9–12,14]. Only a crude estimate can be given because of varying follow-up periods and index dates; however, a

calculation made from number of exposed and unexposed cases and healthy subjects indicates an approximate 1 case per 18,400 vaccines (95% CI 1 per 16,700, 1 per 20,400) or 5.4 cases per 100,000 vaccines. In adults, the small number of cases, except for Jokinen et al. study, makes calculations less robust; vaccine attributable risk based in Jokinen et al., Stowe et al., and O’Flanagan et al. studies was 1 per 181,000 (95% CI 1 per 141,000, 1 per 254,000), using the healthcare contact as the index date in all three studies. These calculations were made from primary follow-up periods, which ended from August 2010 to April 2011.

Narcolepsy risk estimates after a year from the initial vaccination were available only from Finnish and Swedish register studies [12,29,30,34]. In Finland, RR based on healthcare contact in one to two years after the vaccination was 4.7 (2.2, 11.7) in children and adolescents, and 6.8 (2.8, 17.7) in adults, returning to baseline in two years after vaccinations. In Sweden, RR based on diagnosis after at least one year from the vaccination was 2.66 (1.50, 4.72) in subjects aged less than 20 y, and 2.24 (0.86, 5.85) in subjects aged 21–30 y. Still, onset of symptoms occurred most often during the first three to six months following vaccination.

Synthesis of Pandemrix studies not included in meta-analysis

A four-year status of narcolepsy after H1N1 vaccination in Norway was published as an abstract in an European Sleep

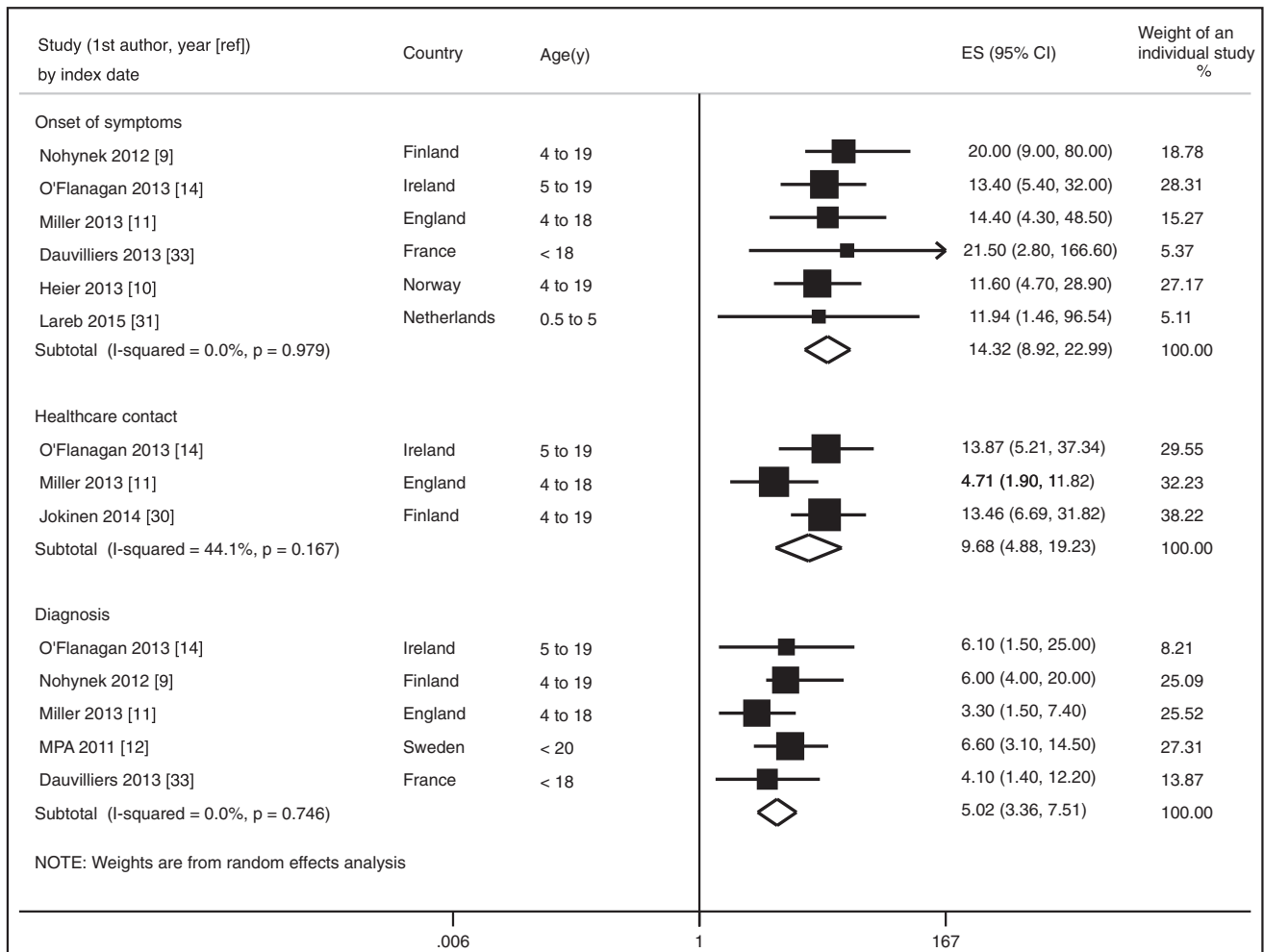


Fig. 2. Forest plot of studies assessing the risk of narcolepsy related to Pandemrix vaccine in children and adolescents using different index dates. ES, effect size; CI, confidence interval.

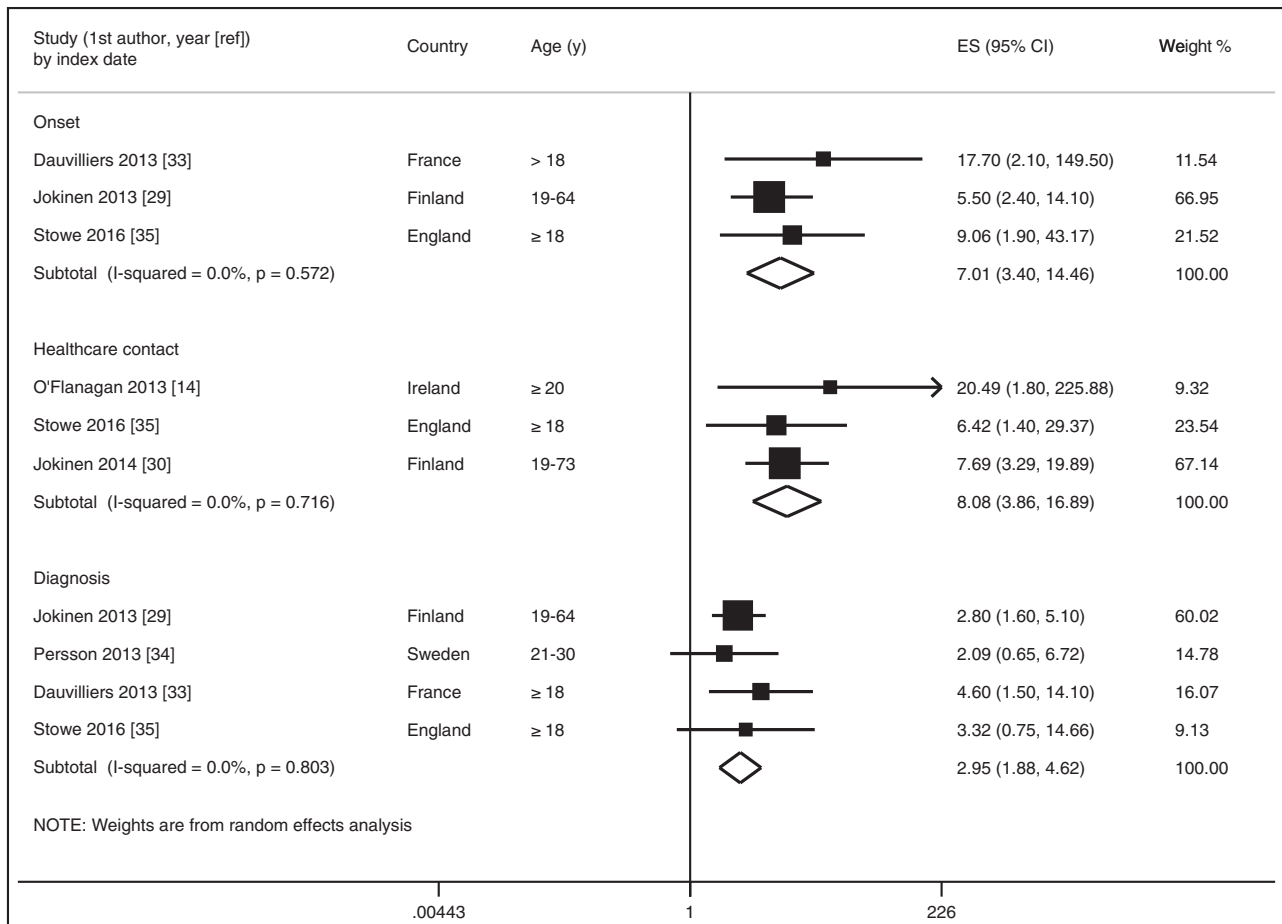


Fig. 3. Forest plot of studies assessing the risk of narcolepsy related to Pandemrix vaccine in adults using different index dates. ES, Effect size; CI, Confidence Interval.

Research Society meeting of 2014 [36]. The authors reported some vaccine-related adult cases and a decreased incidence in 2012–2013 compared to 2010–2011.

In a survey of 29/30 sleep centers in Switzerland, where only adults (18–60 y) were vaccinated with Pandemrix, seven post-Pandemrix narcolepsy cases and one case after a vaccination with Focetria were found [37]. Overall vaccination coverage was approximately 17% and Pandemrix was used in 60% of vaccinations yielding approximately 400,000 to 500,000 vaccinated subjects. Mean diagnostic delay in the survey was 13.4 mo and six out of eight patients were diagnosed in 2010.

Synthesis of non-Pandemrix studies

No other vaccines outside of Pandemrix demonstrated clear narcolepsy association. In Québec, Canada, where AS03-adjuvanted Arepanrix vaccine was used, reported RR in 16 wk after the vaccination was 1.48 (0.37–7.03) using a case–control method, 2.96 (0.71–12.39) using a self-controlled case-series method, and 4.32 (1.50–11.12) using a cohort method, yet vaccine attributable risk was only 1 per 1,000,000, which is significantly lower than in European studies (Tables 2 and 3) [46]. Post-marketing safety data from Ontario, Canada, does not support an increased risk of narcolepsy associated with Arepanrix, either [43]. An increased risk was not seen in South Korea or in the US, where Pandemrix vaccine was not used [38,40,41,44]. Pharmacovigilance database explorations or spontaneous reports have not shown increased risk of

narcolepsy associated with MF59-adjuvanted vaccines with estimated over 23 million administered doses [32,48].

There also appears to be some evidence of rising incidence of narcolepsy in relation to H1N1, but disjointed from vaccination. In Beijing and Shanghai area, there was a 3-fold increase during the post-pandemic period unrelated to any vaccine that suggests a temporal association between a peak in H1N1 infection and a peak in narcolepsy incidence 3–6 mo later [17–19]. This incidence decreased back to baseline two years after the H1N1 pandemic suggesting that infection with the 2009 H1N1 strain was associated with narcolepsy onset. Also in Germany, an age-standardized adjusted incidence rate increased more than three-fold between pre- and post-pandemic periods [47]. The increase started already in the spring 2009, and the incidence density ratio was 3.57 (95% CI 1.94, 7.00). The study was, however, based only on non-validated register diagnoses and no vaccine history was available. The overall vaccine coverage in Germany was 4–8%, mostly with Pandemrix.

Table 3
Number of narcolepsy cases in non-Pandemrix-studies.

Authors, reference number	Vaccinated		Non-vaccinated	
	NC	Healthy	NC	Healthy
Duffy J. et al., 2014 [40]	2	650,000	NA	NA
Han F. et al., 2011 [17]	8	NA	134	NA
Harris T. et al., 2014 [43]	0	4,800,000	N/A	N/A
Montplaisir J. et al., 2014 [46]	8	4,500,000	16	3,400,000
Tsai T.F. et al., 2011 [48]	0	79,000	N/A	N/A

NC, narcolepsy; NA, not available; N/A, not applicable.

Differences between vaccinated and unvaccinated narcolepsy subjects

Clinical characteristics of the patients were reported in four risk-association studies and four separate papers (Table 4) [10,14,33,49–51]. Studies differed in evaluation of differences between vaccinated and unvaccinated narcolepsy subjects. For instance, there was a shorter diagnostic delay and shorter time from EDS to cataplexy in Finland and France, more prevalent cataplexy near the disease onset in the UK, and a presence of multiple symptoms at the disease onset in Sweden in the vaccinated subjects. All these slight differences in clinical and polysomnographic features greatly relate to disease duration and make it difficult to determine the direct effect of Pandemrix.

Discussion

In this meta-analysis we found a 5- to 14-fold increase in incidence of narcolepsy in children and adolescents and a 3- to 7-fold increase in adults in the countries where Pandemrix vaccine was widely used in 2009–2010 (Finland, France, Ireland, the Netherlands, Norway, Sweden and the UK). The risk in the observational studies is dependent on the used index date. Use of onset of symptoms as index date produced the highest risk followed by date of healthcare contact, referral to sleep studies, and date of diagnosis. The vaccine attributable risk of narcolepsy was significant especially in children and adolescents (1 per 18,400). In HLA DQB1*06:02 positive individuals, this would transfer to the risk of approximately 1 per 4500 doses (0.022% per dose) considering that the frequency of HLA DQB1*06:02 allele in general population is around 25%. It seems that the risk window for the vaccine-induced narcolepsy was as long as two years, but this finding needs to be interpreted with caution because of possible biases and lack of studies confirming this finding.

Heterogeneity in our meta-analysis was very low, except for children and adolescent subgroup with the first healthcare contact as the index date, although insignificant P-value ($I^2 = 44%$, $P = 0.167$) discredits a true heterogeneity. Miller et al's. study may possibly have caused heterogeneity by the different design (case-coverage vs. cohort and case–control) and the different case collection method (contact with sleep centers vs. national or regional registries) [11].

Observational studies are prone to various other biases such as ascertainment, recall and selection biases, and confounding. Post-Pandemrix narcolepsy studies are no exception [52–54]. Ascertainment bias could be caused by the lack of blinding to vaccination

Table 4

Comparison of demographic, clinical characteristics, and HLA typing between the total number of vaccinated and unvaccinated children and adolescent narcolepsy cases [10,12,14,33,49–51].

	Vaccinated	Unvaccinated	P
Females	129/244 (53%)	53/113 (47%)	0.294
Cataplexy	194/206 (94%)	63/80 (79%)	<0.001
Hypnagogic hallucinations	65/178 (37%)	59/102 (58%)	0.001
Sleep paralysis	31/158 (20%)	28/102 (27%)	0.141
Disturbed sleep	87/121 (72%)	63/102 (62%)	0.108
Behavioral problems	52/147 (35%)	23/72 (32%)	0.615
Rapid weight gain near onset	89/170 (52%)	39/102 (38%)	0.024
HLA DQB1*06:02 positive	144/147 (98%)	58/65 (89%)	0.006
CSF hypocretin <110 pg/mL	108/110 (98%) ^a	19/22 (86%)	0.008

CSF, cerebrospinal fluid.

All the reported figures represent only cases for which the characteristic was reported, not the whole study population.

Statistically significant differences ($P < 0.05$) in bold.

^a In vaccinated group one subject with hypocretin level of 121 pg/mL and one "borderline".

status, the lack of validation of cases, or by the increased media attention. Increased awareness of narcolepsy and confounding are particularly interesting with respect to this matter. Bias caused by media attention could be affected by collection or follow-up periods in the studies. Exactly identical follow-up periods could not be obtained from the papers. Most studies reported at least the risk during the first year following vaccination and this period was also used in the primary quantitative meta-analysis. In Nohynek et al's. study, the follow-up period ended already in August 2010 to avoid possible bias caused by media attention [9]. If the follow-up period was extended to December 2010, the decrease in risk ratio was rather modest, from 12.7 (6.1, 30.8) to 11.4 (5.6, 27.5). It is unlikely that the original risk ratio would have been explained by the increased awareness only, as the risk was still clearly elevated. On the other hand, a similar increased awareness was raised also in Sweden, Norway, and France, while in these studies the follow-up period lasted until the end of 2010 or 2011. Therefore, a small bias due to the increased awareness cannot be excluded in these studies [9,10,12,33,34]. In the studies from the UK and Ireland, even if the follow-up period was longer, the media impact was probably weak, as there was no increased media attention in these countries demonstrated by Google searches, for instance [11,14]. The risk of post-Pandemrix narcolepsy in these countries was comparable with other studies also implying that increased media awareness cannot fully explain the connection.

Most studies were conducted using ICSD-2 classification in which narcolepsy is divided into narcolepsy-cataplexy and narcolepsy without cataplexy. The updated ICSD-3 was published in 2014, after most of the studies used in meta-analysis. In ICSD-3 narcolepsy categories are narcolepsy type 1 (NT1) characterized by hypocretin deficiency (typically including cataplexy), and narcolepsy type 2 (NT2) with normal hypocretin levels, and no cataplexy. Brighton criteria are a classification based on level of diagnostic certainty of narcolepsy [24]. Brighton classification level 1 denotes narcolepsy with proven hypocretin deficiency proven by lumbar puncture. Level 2 includes cases with unambiguous cataplexy and positive sleep study findings (mean sleep latency in MSLT ≤ 8 min and two or more sleep onset REM sleep periods). Level 3 equals level 2 but without cataplexy in the absence of other mimicking disorders. It is common that cataplexy develops several months after onset of EDS. Therefore, Brighton classification levels 1 and 2 and also 3 can be considered accurate. Using Brighton and ICSD-2 criteria for the diagnosis ascertainment reduces possible bias caused by lack of blinding, since diagnosis is based on objective sleep studies and/or cerebrospinal fluid analysis which are not dependent on reviewers' subjective opinion. The only exception in case verification was National Patient Register based study by Persson et al., but most diagnoses retrieved had been validated against case data in the previous study by the MPA [12,34]. Also in the Dutch data, we chose only confirmed cases with Brighton classification levels 1 to 3. We also ignored the cases that had their onset before vaccination. This resulted in 7 out of 20 reported cases. Therefore, probability of false positives seems rather low. Nonetheless, blinding to vaccination status in conduction of the chart review may be difficult. Bias is possible if reviewers classify vaccinated cases more often as having narcolepsy than unvaccinated cases.

We chose three index dates to be included in our analysis: onset of symptoms, healthcare contact, and diagnosis. The exact date of onset of symptoms is often difficult to remember and it is prone to a recall bias. Moreover, narcolepsy manifests as a heterogeneous clinical syndrome with either severe and abrupt symptom onset or a more progressive development often described in adults, with several months or years between daytime sleepiness and cataplexy onset [55]. The patient's first healthcare contact regarding

narcolepsy symptoms could be a more objective measure, but it was not reported in all the studies. The date of diagnosis is probably the most easily obtained index date (from registries or patient records) but since the delay between onset and diagnosis can be very variable and rather long (i.e., 8–12 y in recent EU countries [53]), using only the diagnosis as the index date could also cause a bias.

Recall bias could affect the onset date and vaccination status if obtained only from the patient. In most of the studies, vaccination registries were used and using the healthcare contact as the index date should decrease a recall bias as well. Using dates of referral to specialist, referral to MSLT, or diagnosis as index dates could result in the exposure misclassification, if the subject was vaccinated after the symptom onset but before these dates and would therefore be classified as “exposed”. Variation in the diagnostic delay makes the temporal association between vaccination and narcolepsy difficult to investigate.

There were also some variations in defining the age groups. In most of the studies, the youngest patients or controls were four to five years old, and the age group division to young and adults was made using 17–20 y of age. Lareb report was an exception with the youngest patients being only two to four years of age [31]. In the Netherlands, Pandemrix was used only in children aged 0.5–5 y with a very low incidence of idiopathic narcolepsy (i.e., without vaccination) in this specific age group. Relative risk calculated from this report was similar to other included studies suggesting an increased risk of Pandemrix-associated narcolepsy also in this age group. However, those results should be interpreted with caution because of the lack of previous epidemiological and confirmed data. We used VAESCO and Statistic Netherlands data for background incidence rate approximation in the Netherlands.

To ensure comprehensives, we searched thoroughly all available English and non-English sources reporting incidence of narcolepsy after H1N1 infection or vaccination. Reports from all countries where Pandemrix was used in large amounts have been included. We have also included significant number of studies from countries where other vaccines were used in the qualitative analysis. We considered using funnel plots and e.g., Egger and Beggs test to detect publication bias but, unfortunately, number of our studies is limited (less than 10 per age group) which makes these test inaccurate [56].

Data and differences on clinical presentation of Pandemrix-associated and idiopathic narcolepsy need to be interpreted with caution. It is possible that subjects with a more severe phenotype are diagnosed earlier after the vaccination than those with milder symptoms (Table 4). The disease course between idiopathic and Pandemrix-associated narcolepsy seemed similar in a recent study [57]. Vaccine associated cases are characterized by high frequency of HLA DQB1*06:02, cataplexy and hypocretin deficiency. Currently, no data supports increased risk of NT2 after Pandemrix or any other vaccine.

The question of role and impact of potential confounding by concomitant or previous A(H1N1)pdm09 infection is interesting and also rather controversial. If an H1N1 infection had been the major causative factor, one would expect to see an increased incidence also in other countries than in those where Pandemrix was used. So far, an increase without vaccination has been reported only in China [17–19]. In Germany, a modest increase in the incidence of narcolepsy was seen already from the spring 2009 onwards, but there are no epidemiological data on the effect of H1N1 infection or vaccination [47].

An ongoing case–control study called systematic observational method for narcolepsy and influenza immunization (SOMNIA) was designed to assess incidence of narcolepsy in the context of confounding influenza infection, increased awareness and vaccinations [58]. Preliminary results supported a small increase in the

incidence of narcolepsy during pre-pandemic period, possibly because of increased awareness, better diagnostic practices or true association with H1N1 influenza infection [12,58]. It is to be noted that in the countries, where the SOMNIA study was finally conducted (Denmark, UK, Canada, Taiwan, the Netherlands, and Spain), Pandemrix was not used at all or it was used rarely. Therefore, the power for making inferences about the use of Pandemrix as a risk factor for developing narcolepsy is very low.

Vaarala et al. have previously identified changes in viral nucleoprotein (NP) in Pandemrix and an increased response against NP in narcoleptic children [23]. Similar changes were not observed with Arepanrix that included also AS03 adjuvant (17). Subsequently, these two vaccines should not be compared to each other because of their proteomic differences [23]. The viral component of Pandemrix (D-PAN) was produced in Dresden, Germany. The viral component of Arepanrix (Q-PAN) was produced in Quebec, Canada [8]. The purification methods differed from each other, which may explain the differences in the structure, and also differences related to increased incidence of narcolepsy in countries where mainly Pandemrix was used against no or only slightly increased incidence in countries where Pandemrix was not used. Nevertheless, a recent animal study implicated the possible role of H1N1 infection itself affecting the sleep-wake system [20]. A mathematical model suggested that in Norway over half of the people vaccinated against A(H1N1)pdm09 could have been already infected with the pandemic virus before the vaccination [59]. Conversely, in a recent study serological evidence of more frequent H1N1 infections among vaccinated subjects with narcolepsy was not found [60].

The exact disease mechanism of vaccination-triggered narcolepsy remains unknown. Other non-adjuvanted or adjuvanted pandemic vaccines even with the same AS03 adjuvant are not associated with increased risk of narcolepsy. The finding of antibodies to hypocretin receptor 2 in a significant proportion of Finnish Pandemrix-associated narcoleptic patients implicates molecular mimicry as a possible causative mechanism [61]. These antibodies may cross-react with influenza NP but their involvement in the pathophysiology of NT1 remains controversial [62].

Data on benefits of the pandemic H1N1 vaccination clearly outweigh the unexpected and unfortunate risk of narcolepsy. There was a justifiable reason to believe that A(H1N1)pdm09 would have been a very aggressive virus with high morbidity and mortality, especially in younger age groups [63]. Fortunately, the virus proved to be more similar to seasonal influenza viruses in these terms. It is still estimated that in the United States alone, A(H1N1)pdm09 caused 270,000 hospitalizations and over 12,000 deaths, most of the latter occurring in persons under 65 y of age [64]. Hospitalization rate was increased especially in younger age groups. Globally the pandemic may have caused more than 200,000 respiratory and 83,000 cardiovascular deaths [65].

The result of increased risk of narcolepsy after Pandemrix vaccination has been produced in many studies from different countries. Moreover, the increased risk has been observed in all the countries where Pandemrix was used in large amounts. Albeit the fact that the observational studies are affected by various biases, the association with Pandemrix and narcolepsy remains strong as seen in our meta-analysis. After recognizing the risk of narcolepsy associated with Pandemrix vaccine, it is important to continue to follow the incidence rates in the countries where Pandemrix was used to monitor the length of the time window during which the risk was increased. Reports comparing the incidence during pre- and post-pandemic time periods are valuable even if Pandemrix was not used, although the increased awareness makes comparisons to pre-pandemic period difficult. Further neuroimmunological studies are required to better understand the link between narcolepsy type 1 and Pandemrix vaccine.

Practice points

Epidemiological data from observational studies assessing risk of narcolepsy after H1N1 pandemic vaccines show that:

1. The risk of narcolepsy appears to have increased in children, adolescents and to a lesser extent also in adults after vaccination with Pandemrix.
2. The elevated risk is only associated with Pandemrix-vaccine and not any other AS03 adjuvanted or any other pandemic or seasonal vaccine.
3. The risk is associated only with narcolepsy type 1
4. The risk seems to remain at an increased level for two years after vaccination. However, these data need to be interpreted with caution because of the possible biases in the studies.
5. Narcolepsy is still a rare disease and benefits of vaccines undoubtedly outweigh the associated risk of narcolepsy and other autoimmune diseases
6. Observational studies are prone to various biases, e.g., confounding by natural H1N1 infection, and ascertainment, recall and selection biases.

Research agenda

Further studies are needed

1. To find the biological explanation for the association between H1N1 vaccination and narcolepsy type 1
2. To follow the incidence of narcolepsy after the pandemic time period to determine post-vaccination risk window
3. To better understand the natural history of post Pandemrix NT1
4. To recognize in all countries the Pandemrix-vaccine association with narcolepsy to compensate victims accordingly

Conflicts of interest

Dr. Dauvilliers reports personal fees from UCB, Bioprojet, Jazz, Theranexus, and Actelion, outside of the submitted work. Dr. Partinen reports grants from Academy of Finland and personal fees from UCB, GSK, Leiras-Pharma, MSD, and Orion, outside of the submitted work. Dr. Alakuijala reports no disclosures.

Acknowledgements

We thank Eric Burns for language editing. Dr. Sarkanen reports grants from the Finnish Medical Foundation during conduct of the study.

References

- [1] Partinen M. Epidemiology of sleep disorders. In: Montagna P, Chokroverty S, editors. *Handb clin neurol*. Elsevier, B.V.; 2011. p. 275–314.

- [2] Hublin C, Kaprio J, Partinen M, Koskenvuo M, Heikkilä K, Koskimies S, et al. The prevalence of narcolepsy: an epidemiological study of the Finnish twin cohort. *Ann Neurol* 1994;35:709–16.
- [3] Longstreth Jr WT, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. *Sleep* 2007;30:13–26.
- [4] Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted county, Minnesota: a population-based study. *Sleep* 2002;25:197–202.
- [5] Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. *Vaccine* 2013;31:1246–54.
- [6] Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. *Lancet* 2007;369:499–511.
- [7] Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med* 2000;6:991–7.
- [8] Partinen M, Kornum BR, Plazzi G, Jennum P, Julkunen I, Vaarala O. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. *Lancet Neurol* 2014;13:600–13.
- *[9] Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, et al. AS03 adjuvanted H1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. *PLoS One* 2012;7:e33536.
- *[10] Heier MS, Gautvik KM, Wannag E, Bronder KH, Midtlyng E, Kamaleri Y, et al. Incidence of narcolepsy in Norwegian children and adolescents after vaccination against H1N1 influenza A. *Sleep Med* 2013;14:867–71.
- *[11] Miller E, Andrews N, Stellitano L, Stowe J, Winstone AM, Shneerson J, et al. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. *BMJ* 2013;346:f794.
- *[12] Medical Products Agency. Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations – results of a case inventory study by the MPA in Sweden during 2009–2010, Narcolepsy – Case inventory study in Sweden 2009–2010, 2011, pp. 1–20. Available at: https://lakemedelsverket.se/upload/nyheter/2011/Fallinventeringsrapport_pandemrix_110630.pdf [Accessed 15 December 2016].
- *[13] Dauvilliers Y, Montplaisir J, Cochen V, Desautels A, Einen M, Lin L, et al. Post-H1N1 narcolepsy-cataplexy. *Sleep* 2010;33:1428–30.
- *[14] O’Flanagan D, Barret AS, Foley M, Cotter S, Bonner C, Crowe C, et al. Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009–December 2010. *Euro Surveill* 2014;19:15–25.
- [15] European Centre for Disease Prevention and Control. Narcolepsy in association with pandemic influenza vaccination (a multi-country European epidemiological investigation). Stockholm, 2012 [online]. Available at: <http://ecdc.europa.eu/en/publications/Publications/Vaesco%20report%20FINAL%20with%20cover.pdf>. [Accessed 4 December 2016].
- [16] Centers for Disease Control and Prevention. Final estimates for 2009–10 seasonal influenza and influenza A (H1N1) 2009 monovalent vaccination coverage – United States, August 2009 through May, 2010. Secondary final estimates for 2009–10 seasonal influenza and influenza A (H1N1) 2009 monovalent vaccination coverage – United States, August 2009 through May, 2010, 2011 [online]. Available at: http://www.cdc.gov/flu/fluview/coverage_0910estimates.htm-ref4. [Accessed 4 December 2016].
- [17] Han F, Lin L, Warby SC, Faraco J, Li J, Dong SX, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann Neurol* 2011;70:410–7.
- [18] Han F, Lin L, Li J, Dong XS, Mignot E. Decreased incidence of childhood narcolepsy 2 years after the 2009 H1N1 winter flu pandemic. *Ann Neurol* 2013;73:560.
- [19] Wu H, Zhuang J, Stone WS, Zhang L, Zhao Z, Wng Z, et al. Symptoms and occurrences of narcolepsy: a retrospective study of 162 patients during a 10-year period in Eastern China. *Sleep Med* 2014;15:607–13.
- [20] Tesoriero C, Codita A, Zhang MD, Cherninsky A, Karlsson H, Grassi-Zucconi G, et al. H1N1 influenza virus induces narcolepsy-like sleep disruption and targets sleep-wake regulatory neurons in mice. *Proc Natl Acad Sci U S A* 2016;113:E368–77.
- [21] Luca G, Haba-Rubio J, Dauvilliers Y, Lammers GJ, Overeem S, Donjacour CE, et al. Clinical, polysomnographic and genome-wide association analyses of narcolepsy with cataplexy: a European Narcolepsy Network study. *J Sleep Res* 2013;22:482–95.
- [22] Sturkenboom MCJM. The narcolepsy-pandemic influenza story: can the truth ever be unraveled? *Vaccine* 2015;33(2):B6–13.
- *[23] Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, et al. Antigenic differences between AS03 adjuvanted influenza A(H1N1) pandemic vaccines: implications for Pandemrix-associated narcolepsy risk. *PLoS One* 2014;9:e114361.
- [24] Poli F, Overeem S, Lammers GJ, Plazzi G, Lecendreux M, Bassetti CL, et al. Narcolepsy as an adverse event following immunization: case definition and guidelines for data collection, analysis and presentation. *Vaccine* 2013;31:994–1007.
- [25] Investigation of an increase in the incidence of narcolepsy in children and adolescents in 2009 and 2010-final report of National Narcolepsy Study Steering Committee, (2014) Available at: <http://health.gov.ie/wp-content/>

* The most important references are denoted by an asterisk.

- uploads/2014/03/Final_Report_of_National_Narcolepsy_Study_Steering_Committee.pdf. [Accessed 4th December 2016].
- [26] Medical Products Agency, Sweden. A registry based comparative cohort study in four Swedish counties of the risk for narcolepsy after vaccination with Pandemrix - A first and preliminary report, by the Medical Products Agency, 2011 [online]. Available at: https://lakemedelsverket.se/upload/nyheter/2011/Fallinventeringsrapport_pandemrix_110630.pdf. [Accessed 4 December 2016].
- [27] Medical Products Agency, Sweden. Registerstudie med fokus på neurologiska och immunrelaterade sjukdomar efter vaccination med Pandemrix, 2013 [online]. Available at: <https://lakemedelsverket.se/upload/nyheter/2013/PDX%20Rapport%20SV%20-%20registerstudie%207%20landsting%20regioner%202013-03-26.pdf>. [Accessed 4 September 2016].
- [28] European Centre for Disease Prevention and Control. The 2009 A(H1N1) pandemic in Europe. Stockholm: European Centre for Disease Prevention and Control, 2010 [online]. Available at: http://ecdc.europa.eu/en/publications/Publications/101108_SPR_pandemic_experience.pdf. [Accessed 4th December 2016].
- [29] Jokinen J, Nohynek H, Honkanen J, Vaarala O, Partinen M, Hublin C, et al. Pandemiarokotteen ja narkolepsian yhteys aikuisilla - Varmennettuihin rekisteritietoihin perustuva tutkimus: THL, 2013 [online]. Available at: https://www.julkari.fi/bitstream/handle/10024/104482/URN_ISBN_978-952-245-921-3.pdf?sequence=1. [Accessed 4 December 2016].
- [30] Jokinen J, Nohynek H, Vaarala O, Kilpi T. Pandemiarokotteen ja narkolepsian yhteys - vuoden 2012 loppuun mennessä kertyneisiin rekisteritietoihin perustuva seurantaraportti: THL, 2014 [online]. Available at: https://www.julkari.fi/bitstream/handle/10024/116234/URN_ISBN_978-952-302-255-3.pdf?sequence=1. [Accessed 4 December 2016].
- *[31] Netherlands Pharmacovigilance Centre Lareb. Update of Overview of Dutch cases of narcolepsy associated with Pandemrix, 2015 [online]. Available at: http://www.lareb.nl/getmedia/0834beb5-dd13-4d0a-9a5e-c545445d7a6a/Narcolepsy_Update_13nov2014.pdf. [Accessed 4 December 2016].
- [32] Netherlands Pharmacovigilance Centre Lareb. Update of Overview of Dutch cases of narcolepsy associated with Focetria [online]. Available at: http://www.lareb.nl/getdoc/680cdba8-809b-497a-a11e-05d9b8e2ead5/KWB_2014_1_pande. [Accessed 4 December 2016].
- *[33] Dauvilliers Y, Arnulf I, Lecendreux M, Monaca Charley C, Franco P, Drouot X, et al. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. *Brain* 2013;136:2486–96.
- [34] Persson I, Granath F, Asklung J, Ludvigsson JF, Olsson T, Feltelius N. 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* 2013;275:172–90.
- *[35] Stowe J, Miller E, Andrews N, Kosky C, Leschziner G, Shneerson JM, et al. Risk of narcolepsy after AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in adults: a case-coverage study in England. *Sleep* 2016;39:1051–7.
- [36] Heier MS, Gautvik KM, Waanag E, Bronder KH, Midtlyng E, Kamaleri Y, et al. Narcolepsy in Norway after 2009 +/- H1N1-vaccination - the 4 year status. *J Sleep Res* 2014;23.
- [37] Kallweit U, Mathis J, Jenni OG, Heinzer R, Haba-Rubio J, Baumann CR, et al. Post-H1N1 flu vaccination narcolepsy in Switzerland: a retrospective survey in the 30 sleep-certified Swiss centers. *Eur Neurol* 2016;75:105–8.
- [38] Choe YJ, Bae GR, Lee DH. No association between influenza A(H1N1)pdm09 vaccination and narcolepsy in South Korea: an ecological study. *Vaccine* 2012;30:7439–42.
- [39] Cohet C, Montplaisir J, Petit D, Quinn M-J, Ouakki M, Deceuninck G, et al. Applying the test-negative design to vaccine safety studies: risk of narcolepsy associated with A/H1N1 (2009) pandemic influenza vaccination in Quebec. *Pharmacoepidemiol Drug Saf* 2015;24:406–7.
- [40] Duffy J, Weintraub E, Vellozzi C, DeStefano F. Narcolepsy and influenza A(H1N1) pandemic 2009 vaccination in the United States. *Neurology* 2014;83:1823–30.
- [41] Haber P, Moro PL, Cano M, Lewis P, Stewart B, Shimabukuro TT. Post-licensure surveillance of quadrivalent live attenuated influenza vaccine United States, vaccine adverse event reporting system (VAERS), July 2013–June 2014. *Vaccine* 2015;33:1987–92.
- [42] Halsey NA, Talaat KR, Greenbaum A, Mensah E, Dudley MZ, Proveaux T, et al. The safety of influenza vaccines in children: an Institute for Vaccine Safety white paper. *Vaccine* 2015;33(5):F1–67.
- [43] Harris T, Wong K, Stanford L, Fediurek J, Crowcroft N, Deeks S. Did narcolepsy occur following administration of AS03-adjuvanted A(H1N1) pandemic vaccine in Ontario, Canada? A review of post-marketing safety surveillance data. *Euro Surveill* 2014;19.
- [44] Kim WJ, Lee SD, Lee E, Namkoong K, Choe KW, Song JY, et al. Incidence of narcolepsy before and after MF59-adjuvanted influenza A(H1N1)pdm09 vaccination in South Korean soldiers. *Vaccine* 2015;33:4868–72.
- [45] McCarthy NL, Gee J, Lin ND, Thyagarajan V, Pan Y, Su S, et al. Evaluating the safety of influenza vaccine using a claims-based health system. *Vaccine* 2013;31:5975–82.
- [46] Montplaisir J, Petit D, Quinn M-J, Ouakki M, Deceuninck G, Desautels A, et al. Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec. *PLoS One* 2014;9:e108489.
- [47] Oberle D, Drechsel-Bauerle U, Schmidtmann I, Mayer G, Keller-Stanislawski B. Incidence of narcolepsy in Germany. *Sleep* 2015;38:1619–28.
- [48] Tsai TF, Crucitti A, Nacci P, Nicolay U, Cioppa GD, Ferguson J, et al. Explorations of clinical trials and pharmacovigilance databases of MF59®-adjuvanted influenza vaccines for associated cases of narcolepsy. *Scand J Inf Dis* 2011;43:702–6.
- [49] Partinen M, Saarenpää-Heikkilä O, Ilveskoski I, Hublin C, Linna M, Olsen P, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. *PLoS One* 2012;7:e33723.
- [50] Winstone AM, Stellitano L, Verity C, Andrews N, Miller E, Stowe J, et al. Clinical features of narcolepsy in children vaccinated with AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in England. *Dev Med Child Neurol* 2014;56:1117–23.
- [51] Szakacs A, Darin N, Hallbook T. Increased childhood incidence of narcolepsy in Western Sweden after H1N1 influenza vaccination. *Neurology* 2013;80:1315–21.
- [52] Verstraeten T, Cohet C, Santos GD, Ferreira GL, Bollaerts K, Bauchau V, et al. Pandemrix and narcolepsy: a critical appraisal of the observational studies. *Hum Vaccin Immunother* 2016;12:187–93.
- [53] Bollaerts K, Shinde V, Dos Santos G, Ferreira G, Bauchau V, Cohet C, et al. Application of probabilistic multiple-bias analyses to a cohort- and a case-control study on the association between Pandemrix™ and narcolepsy. *PLoS One* 2016;11:e0149289.
- [54] Wijnans L, Dodd C, de Ridder M, Romio S, Weibel D, Overeem S, et al. Pandemic influenza vaccine & narcolepsy: simulations on the potential impact of bias. *Expert Rev Vaccines* 2016;15:573–84.
- [55] Lopez R, Barateau L, Evangelista E, Chenini S, Robert P, Jausset I, et al. Temporal changes in the cerebrospinal fluid level of hypocretin-1 and histamine in narcolepsy. *Sleep* 2017;40.
- [56] Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
- [57] Sarkanen T, Alakujala A, Partinen M. Clinical course of H1N1-vaccine-related narcolepsy. *Sleep Med* 2016;19:17–22.
- [58] Dodd C, Ridder M, Weibel D, DeStefano F, Shimabukuro T, Carleton B, et al. Narcolepsy incidence rates in the SOMNIA (Systematic observational method for narcolepsy and influenza immunization) study. *Pharmacoepidemiol Drug Saf* 2016;25.
- [59] Van Effeltherre T, Dos Santos G, Shinde V. Twin peaks: a/H1N1 pandemic influenza virus infection and vaccination in Norway, 2009?2010. *PLoS One* 2016;11:e0151575.
- [60] Melen K, Partinen M, Tynell J, Sillanpää M, Himanen SL, Saarenpää-Heikkilä O, et al. No serological evidence of influenza A H1N1pdm09 virus infection as a contributing factor in childhood narcolepsy after pandemrix vaccination campaign in Finland. *PLoS One* 2013;8:e68402.
- [61] Ahmed SS, Volkmuth W, Duca J, Corti L, Pallaoro M, Pezzicoli A, et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. 2015.
- [62] Vassalli A, Li S, Tafti M. Comment on “antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2”. *Sci Transl Med* 2015;7:314e2.
- [63] N.S.-O.I.A.H.N.V.I. Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans, *NEJM*, 360 (2009). pp. 2605–2615.
- [64] Shrestha SS, Swerdlow DL, Borse RH, Prabhu VS, Finelli L, Atkins CY, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009–April 2010). *Clin Infect Dis* 2011;52(1):S75–82.
- [65] Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng P-Y, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Inf Dis* 2012;12:687–95.