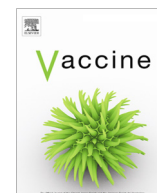


Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Narcolepsy and adjuvanted pandemic influenza A (H1N1) 2009 vaccines – Multi-country assessment

Daniel Weibel^{a,*}, Miriam Sturkenboom^b, Steven Black^c, Maria de Ridder^a, Caitlin Dodd^a, Jan Bonhoeffer^{d,e}, Ann Vanrolleghem^a, Nicoline van der Maas^f, Gert Jan Lammers^{g,h}, Sebastiaan Overeemⁱ, Angela Gentile^j, Norberto Giglio^j, Vanesa Castellano^j, Jeffrey C. Kwong^k, Brian J. Murray^l, Karen Cauch-Dudek^k, Diana Juhasz^k, Michael Campitelli^k, Alexandre N. Datta^m, Ulf Kallweit^{n,o}, Wan-Ting Huang^p, Yu-Shu Huang^q, Chung-Yao Hsu^r, Hsi-Chung Chen^s, Maria Giner-Soriano^t, Rosa Morros^t, Carles Gaig^u, Ester Tió^v, Silvia Perez-Vilar^{a,w}, Javier Diez-Domingo^w, Francisco Javier Puertas^x, Lawrence W. Svenson^y, Salaheddin M. Mahmud^z, Bruce Carleton^{aa}, Monika Naus^{aa}, Lisen Arnheim-Dahlström^{ab}, Lars Pedersen^{ac}, Frank DeStefano^{ad}, Tom T. Shimabukuro^{ad}

^a Medical Informatics Department, Erasmus Medical Center, Rotterdam, The Netherlands

^b Julius Global Health, University Utrecht Medical Center, Utrecht, The Netherlands

^c Cincinnati Children's Hospital, Cincinnati, OH, USA

^d Infectiology and Vaccinology University Children's Hospital, Basel, Switzerland

^e Brighton Collaboration Foundation, Basel, Switzerland

^f Dept. Epidemiology and Surveillance, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

^g Leiden University Medical Centre, Leiden, The Netherlands

^h Sleep-Wake Center SEIN, Heemstede, The Netherlands

ⁱ Sleep Medicine Centre Kempenhaeghe, Heeze, The Netherlands

^j Hospital de Niños Ricardo Gutiérrez, Ciudad Autónoma de Buenos Aires, Argentina

^k Institute for Clinical Evaluative Sciences (ICES), Ontario, Canada

^l Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Canada

^m University Hospital Basel, Basel, Switzerland

ⁿ Bern University Hospital and University of Bern, Bern, Switzerland

^o Witten/Herdecke University, Department of Rehabilitation, Witten/Herdecke, Germany

^p Taiwan Centers for Disease Control, Taipei, Taiwan

^q Department of Child Psychiatry and Sleep Center, Chang Gung Memorial Hospital and University, Taoyuan, Taiwan

^r Department of Neurology and Sleep Disorders Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

^s Department of Psychiatry and Center of Sleep Disorders, National Taiwan University Hospital, Taipei, Taiwan

^t Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Barcelona, Spain

^u Neurology Service and Multidisciplinary Sleep Disorders Unit, Hospital Clinic of Barcelona, Barcelona, Spain

^v Althaia Xarxa Assistencial Universitària de Manresa, Neurology Service, Manresa, Barcelona, Spain

^w Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat (FISABIO), Vaccine Research, Valencia, Spain

^x Servicio de Neurofisiología, Hospital Universitari de la Ribera, Valencia, Spain

^y Division of Preventive Medicine, University of Alberta, Alberta, Canada

^z Vaccine and Drug Evaluation Centre, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Manitoba, Canada

^{aa} Faculty of Medicine, University of British Columbia, British Columbia, Canada

^{ab} Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

^{ac} Clinical Medicine/Epidemiology, Aarhus University, Aarhus, Denmark

^{ad} Centers for Disease Control and Prevention (CDC), Immunization Safety Office, Atlanta, USA

ARTICLE INFO

Article history:

Received 19 December 2017

Received in revised form 25 July 2018

Accepted 2 August 2018

Available online xxx

ABSTRACT

Background: In 2010, a safety signal was detected for narcolepsy following vaccination with Pandemrix, an AS03-adjuvanted monovalent pandemic H1N1 influenza (pH1N1) vaccine. To further assess a possible association and inform policy on future use of adjuvants, we conducted a multi-country study of narcolepsy and adjuvanted pH1N1 vaccines.

Methods: We used electronic health databases to conduct a dynamic retrospective cohort study to assess narcolepsy incidence rates (IR) before and during pH1N1 virus circulation, and after pH1N1 vaccination

* Corresponding author at: Erasmus Medical Center, Postbox 2040 3000 CA, Rotterdam, The Netherlands.

E-mail address: weibeldaniel@gmail.com (D. Weibel).

<https://doi.org/10.1016/j.vaccine.2018.08.008>

0264-410X/© 2018 The Authors. Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please cite this article in press as: Weibel D et al. Narcolepsy and adjuvanted pandemic influenza A (H1N1) 2009 vaccines – Multi-country assessment. Vaccine (2018), <https://doi.org/10.1016/j.vaccine.2018.08.008>

Keywords:

Narcolepsy
 Pandemic H1N1 influenza
 Adjuvant
 AS03
 MF59

campaigns in Canada, Denmark, Spain, Sweden, Taiwan, the Netherlands, and the United Kingdom. Using a case-control study design, we evaluated the risk of narcolepsy following AS03- and MF59-adjuvanted pH1N1 vaccines in Argentina, Canada, Spain, Switzerland, Taiwan, and the Netherlands. In the Netherlands, we also conducted a case-coverage study in children born between 2004 and 2009.

Results: No changes in narcolepsy IRs were observed in any periods in single study sites except Sweden and Taiwan; in Taiwan incidence increased after wild-type pH1N1 virus circulation and in Sweden (a previously identified signaling country), incidence increased after the start of pH1N1 vaccination. No association was observed for Arepanrix-AS03 or Focetria-MF59 adjuvanted pH1N1 vaccines and narcolepsy in children or adults in the case-control study nor for children born between 2004 and 2009 in the Netherlands case-coverage study for Pandemrix-AS03.

Conclusions: Other than elevated narcolepsy IRs in the period after vaccination campaigns in Sweden, we did not find an association between AS03- or MF59-adjuvanted pH1N1 vaccines and narcolepsy in children or adults in the sites studied, although power to evaluate the AS03-adjuvanted Pandemrix brand vaccine was limited in our study.

© 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

In fall 2009, large-scale vaccination campaigns were implemented globally in response to the influenza A (H1N1) pandemic (pH1N1). Different inactivated monovalent vaccines were used; the United States used unadjuvanted vaccines, whereas in Europe, MF59-(Focetria, Novartis Vaccines and Diagnostics) and AS03-adjuvanted (Pandemrix, GSK biologicals) vaccines were mostly used. In Canada, AS03-adjuvanted Arepanrix (ID Biomedical Corp., a subsidiary of GSK Biologicals) was used. Arepanrix and Pandemrix had similar pH1N1 antigens and used the same AS03 adjuvant; however, there were slight differences in the manufacturing processes for the two vaccines. In August 2010, case reports from Sweden and Finland emerged describing narcolepsy in children following vaccination with Pandemrix [1–6].

Narcolepsy is a chronic debilitating sleep disorder with a suspected autoimmune etiology. Genetic predisposition also appears to play a role; narcolepsy with cataplexy (with hypocretin deficiency) is highly associated with HLA-DQB1*06:02, while narcolepsy without cataplexy (and normal hypocretin levels) is less associated with HLA-DQB1*06:02, but still more so than in the general population. Narcolepsy/cataplexy is characterized by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, hypnagogic hallucinations and fragmented nighttime sleep. Symptoms often emerge gradually and may initially be non-specific [7–10]. The insidious onset can result in diagnostic delays of months to years, making it challenging to study exposures that might cause or contribute to disease occurrence [11].

Several European studies were initiated to rapidly evaluate the possible association between Pandemrix-AS03 and narcolepsy [1,2,4,5,12–18]. These studies are summarized in reviews by Verstraeten et al. [19], Sturkenboom [20] and Sarkanen et al. [21]. Several studies showed an increased risk, but results were variable within and across studies and subject to methodological challenges due to narcolepsy epidemiology and increased awareness about the association. Most studies focused on Pandemrix-AS03 and data were limited on other adjuvanted pH1N1 vaccines, including Arepanrix-AS03 and Focetria-MF59 [22,23].

To better understand the relationship between narcolepsy and different adjuvanted pH1N1 vaccines, we organized an international research network, including study sites within and outside of Europe, where adjuvanted vaccines were used and little or no substantial concerns were raised about an association with narcolepsy in local media. Drawing on the expertise of clinicians, research scientists and public health officials within the network, we implemented the Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment (SOMNIA) study.

2. Methods

2.1. Study site selection

We used a stepwise process to identify, recruit, and select participating study sites for incidence rates and case-control analyses. First, we identified countries that used adjuvanted 2009 pH1N1 vaccines using information obtained from the World Health Organization and from the two vaccine manufacturers. We excluded countries where compensation programs for narcolepsy associated with pH1N1 vaccination existed because we believed this could potentially bias case ascertainment with vaccinated cases potentially being evaluated sooner or differently than non-vaccinated cases. Finland, Norway and Sweden were excluded from the case-control study on this basis. In addition, Finland and Sweden had been signaling countries. Of note Sweden, as a signaling country was included in the incidence rate study to provide a reference comparison, but data from Sweden were not pooled in the incidence rate analysis. Working with national, regional and local health officials, academics, and sleep centers, we assessed whether potential study sites had acceptable availability and accessibility of vaccination and outcome data. Israel, South Korea and Cuba, were excluded because of lack of exposure information. Brazil was eliminated because obtaining timely administrative approvals was not feasible. Finally, we engaged in discussions with prospective investigators to gauge willingness and ability to participate in the incidence rate or case-control studies and confirm existence of acceptable data and data systems to participate using the common study protocol. After completing these steps and obtaining the necessary clearances we included the final set of countries in our analysis.

All sites used the same protocol, the same data collection materials and common analytics, but sites could implement the protocol based upon their local processes and health care structure. For quality control, the study coordination team verified implementation of the protocol with all sites during monthly calls. The data management team further verified all the data and discussed potential biases with the sites. Sites were responsible for verification of their results and decisions on inclusion of the data and could access remotely the secure data sharing environment. These distributed data management procedures have been previously described [24].

2.2. Narcolepsy incidence rates analysis

We estimated narcolepsy incidence rates (IR) at ten study sites (in seven countries) using population-based electronic health record databases from general practitioners (GP) (Spain [Valencia

Table 1
Overview of study sites for the IR, case-control and case-coverage analyses.

	Study site (vaccines)	IR		Case-control or case-coverage		
		Data source	Codes and algorithms	Case identification	Controls source	pH1N1 vaccine exposure
Europe	Switzerland (Pandemrix-AS03, Focetria-MF59)			14 hospitals & sleep centers, no consent required	Matched in same hospital of case, no consent required	General practitioner (GP) medical record
	Spain, Catalonia (Pandemrix-AS03, Focetria-MF59)	SIDIAP general practitioners' database	ICD-10 code G47.4	Sleep units at 13 public hospitals until end of 2013 & also in SIDIAP. No consent required	SIDIAP database, no consent required	SIDIAP database
	Spain, Valencia (Pandemrix-AS03, Focetria-MF59)	SIA regional general practitioners' databases	ICD-9CM codes 347. ^a with Manual validation	Identified from 24 sleep centers and electronic registries (inpatient and outpatient databases)	SIA general practitioners' database, no consent required	Obtained from electronic registry
	The Netherlands (Pandemrix-AS03, Focetria-MF59)	IPCI general practitioners' databases	Free text narcolepsy & MSLT, cases manually validated	Four sleep centers (academic and non-university hospitals). Consent required	IPCI general practitioners' database, no consent required	<ol style="list-style-type: none"> 1. Electronic medical GP records for all patients 2. For cases also from vaccination card and public health agency to estimate completeness in GP records
	The United Kingdom (Pandemrix-AS03)	THIN general practitioners' databases	Read codes F27.00; F270.00; F271.00; F27z.00			
	Denmark (Pandemrix-AS03)	Danish Civil Registration System covering the Northern and Central Region of Jutland in Denmark linked to Danish National Patient Register	ICD-10 code G47.4, inpatient, ambulatory care and emergency room diagnosis			
	Sweden	Patient register at the National board of health, Population from population register at Statistics Sweden	ICD-10 code G47.4, diagnosis in and outpatient			
South America	Argentina (Focetria-MF59)			13 MSLT sites, pediatric, adult neurology and respiratory centers in Buenos Aires, verbal consent	General practitioners, verbal informed consent conducted	Vaccination cards from cases and controls
North America (Canada)	Ontario (Arepanrix-AS03)			Patient charts at sleep units after using physician billing claims to generate initial list of MSLTs performed, limited to maximum age ≤ 24	Matched from ICES provincial database of all residents with health insurance, no consent required	<ol style="list-style-type: none"> 1. Primary care physician (PCP), family physicians' and pediatricians' charts; 2. Public health unit records (electronic databases, and physician billing claims data)
North America (Canada)	Alberta (Arepanrix-AS03)	Cases identified and population denominator established with claims/hospital record linkage databases	ICD9-CM codes 347. ^a with MSLT procedure			
	Manitoba (Arepanrix-AS03)	Population-based Hospital and Physician Claims databases linked to Manitoba Health Population Registry	ICD9-CM codes 347. ^a with MSLT procedure			

(continued on next page)

Table 1 (continued)

Study site (vaccines)	IR		Case-control or case-coverage	
	Data source	Codes and algorithms	Case identification	pH1N1 vaccine exposure
British Columbia (Arepanrix-AS03)	Cases originating from British Columbia Medical Services Plan database, denominator information established through national statistics	ICD9-CM codes 347 ^a following MSLT procedure code		
Taiwan (Focetria-MF59, AdimFlu-S unadjuvanted)	National population NHI ENROLL data linked to NHI claims data	Referral ICD-9-CM codes (347 ^a) in outpatient, ED, or inpatient after an MSLT referral	Recruited from three largest sleep centers in Taiwan, identified initially by MSLT referral from electronic data	National registry and National Health Insurance Database, data on H1N1 vaccination missing for 39% in schoolchildren 7–17 years and 44% for persons ≥ 18 years (all non-adjuvanted)

CP = general practitioner, BC = Brighton Collaboration, PCP = primary care physician.
^a Linked Medical Records = Population based medical records (GP and specialist diagnoses), directly linked; Population-based registry = Population based registries (emergency room, in and out patient diagnoses); Medical Record diagnoses + Census Population = In and outpatient diagnoses, case counts and population counts (census).

and Catalonia], the Netherlands, and the United Kingdom) or claims/record linkage databases (Canada [Manitoba, Alberta and British Columbia], Denmark, Sweden, and Taiwan). Study populations included individuals registered in the database for at least one year prior to start of follow-up. Follow-up started at the beginning of the study period (January 1, 2003) or the date of registration and ended at the earliest of the following: death, the patient moving, the end of the study period (December 31, 2013) or outcome occurrence. Cases were captured in these databases by identifying individuals with newly diagnosed narcolepsy with or without cataplexy. (Database codes and algorithms are shown in Table 1). In GP databases in the Netherlands and from records of sleep medicine specialists in Valencia, case finding algorithms were validated using the Brighton Collaboration case definition criteria for narcolepsy [25]. In other sites, we required both diagnostic codes for narcolepsy along with reimbursement claims for a multiple sleep latency test (MSLT) to reduce the risk of false positives. We calculated IRs by year and month and categorized them into three periods: (1) pre-pH1N1, (2) during wild-type pH1N1 virus circulation until the start of pH1N1 vaccination (country specific), and (3) from the start of pH1N1 vaccination through the end of the study in December 2013. Periods of wild-type pH1N1 virus circulation and vaccination varied by sites. We stratified IRs by age and sex and pooled aggregated person-time and case counts for further analysis. IR data from Sweden were analyzed separately since Sweden had been a priori identified as a signaling country, and hence, served as a comparator for other sites in our IR analysis [26,29]. We estimated incidence rate ratios (IRR), comparing the two latter periods to the pre-pH1N1 period, using Poisson regression.

2.3. Case-control analysis

Seven sites in six countries met our criteria for inclusion in the case-control study: Argentina, Canada (Ontario), Spain (Valencia and Catalonia), Switzerland, Taiwan, and the Netherlands (Table 1). All sites collected information in the same electronic case report forms (Chameleon, Erasmus Medical Center, Rotterdam, the Netherlands). Depending on data sharing restrictions, local investigators either transferred aggregated data to a secure remote research environment for further analysis and one stage pooling or ran the same analyses locally and transferred coefficients and counts for inclusion in a two-stage meta-analysis (Fig. 1).

2.3.1. Cases and controls

Local investigators identified narcolepsy cases at sleep centers using diagnosis lists or diagnostic test outcomes. Investigators

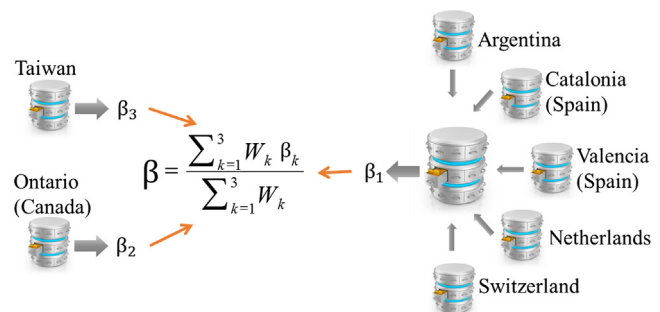


Fig. 1. Two-stage hybrid approach for pooling case-control data from study sites. The two-stage hybrid approach pooled case-control data to estimate an odds ratio from European Union country sites and Argentina (β_1). Odds ratios from Taiwan and Ontario (β_2 and β_3) were analyzed in a subsequent meta-analytic approach including the pooled odds ratio from European Union sites and Argentina (W_k = weight related to estimate β_k , being the reciprocal of its variance, Σ = summation operator, β = meta-analysis result for the odds ratio).

abstracted medical records, blinded for pH1N1 vaccination status, and classified cases into certainty levels using the Brighton Collaboration narcolepsy case definition [25]. Cases were included if they were classified as Brighton Collaboration level 1–4 for persons ≥ 16 years or level 1–2 for persons < 16 years, and had an MSLT referral and a diagnosis both made after March 31, 2009 (start of the H1N1 pandemic). Brighton Collaboration classification designates level 1 as the highest level of diagnostic certainty; levels have different cut-off values for MSLT results starting at age 16 years, which were maintained in the study. Primary index date was date of referral for diagnostic MSLT. Sites identified all cases diagnosed from April 1, 2009 until the end of 2015, but this varied by site based on feasibility (Table 1). The Netherlands required consent from cases because of the need to collect data from both GPs as well as the National Public Health Agency.

Up to 20 controls were matched to each case by site on age (year of birth), sex and index date. As per protocol, controls were selected from the population giving rise to the cases, identification could be implemented in different ways based on feasibility and health care structure. Ontario, Valencia, Catalonia, the Netherlands,

and Taiwan sampled controls from population-based health record databases. Argentina identified controls from primary care facilities in the same geographic area as the cases. Switzerland recruited controls from the same hospitals as cases, using auxiliary diseases not related to vaccination.

2.3.2. Exposure

The main exposure of interest was adjuvanted pH1N1 vaccination (i.e., Pandemrix-AS03, Arepanrix-AS03 or Focetria-MF59). We obtained information on vaccines similarly for cases and controls from medical records, vaccination registries, insurance databases, or vaccination cards. Only written or electronic records of immunization were accepted. Risk windows for pH1N1 vaccine exposure were any time prior to index date and further split in: 1–180 days, 181 days–2 years, and > 2 years before index date. The Ontario site provided the only data for Arepanrix-AS03; hence, there was no pooling of the Arepanrix-AS03 data as Ontario was unique. Taiwan, Argentina, the Netherlands, Switzerland, Valencia, and Catalonia contributed data for Focetria-MF59. The Netherlands, Switzerland, and Valencia contributed data for Pandemrix-AS03.

Table 2
Narcolepsy case characteristics for the case-control and case-coverage analysis by study site.

	Netherlands	Switzerland	Spain, Catalonia	Spain, Valencia	Argentina	Canada, Ontario	Taiwan	Total
Children								
Total cases/controls [N]	22/205	22/132	5/100	11/220	11/86	28/55	51/510	150/1308
<i>Brighton level [%]</i>								
1	31.8	36.4	0	0	9.1	0	7.8	13.3
2	68.2	54.5	100	63.6	81.8	57.1	66.7	65.3
3	0	9.1	0	36.4	9.1	42.9	17.7	18.7
4a	0	0	0	0	0	0	7.8	2.7
Cataplexy present [%]**	95.5	86.4	100	63.6	90.9	57.1	72.5	76.7
<i>Age at diagnosis [%]</i>								
<6 yrs	4.5	0	0	9.1	0	0	0	1.3
6–12 yrs	50.0	40.9	60.0	90.9	63.6	21.4	37.3	43.3
13–18 yrs	45.5	59.1	40.0	0	36.4	78.6	62.7	55.3
<i>pH1N1 vaccination coverage cases [%]</i>								
Focetria-MF59	0	0	0	0	27.3	0	≤ 45.1	≤ 18.4
Pandemrix- and Arepanrix-AS03	31.8	0	0	0	0	≤ 17.9	0	≤ 33.1
Unadjuvanted	0	0	0	0	0	0	≤ 45.1	≤ 16.3
<i>pH1N1 vaccination coverage controls [%]</i>								
Focetria-MF59	3.4	3.8	0	2.3	10.5	0	0.6	2.1
Pandemrix- and Arepanrix-AS03	0	0	0	0	0	17.3	0	0.8
Unadjuvanted	0	0	0	0	0	0	37.3	15.9
Adults								
Total cases/controls [N]	32/280		13/260	36/720	4/12	39/75	86/860	210/2207
<i>Brighton level [%]</i>								
1	53.1		7.7	0	0	0	1.2	9.1
2	31.3		84.6	38.9	50.0	≤ 25.6	39.5	≤ 38.6
3	12.5		7.7	55.6	50.0	69.2	31.4	38.6
4a	3.1		0	5.6	0	≤ 12.8	27.9	≤ 15.2
Cataplexy present [%]**	78.1		84.6	41.7	50.0	25.6	41.9	47.2
<i>Age at diagnosis [%]</i>								
19–59 yrs	96.9		100	97.2	100	100	100	99.0
60+	3.1		0	2.8	0	0	0	1.0
<i>pH1N1 vaccination coverage cases [%]</i>								
Focetria-MF59	3.1		0	0	0	0	≤ 14.0	≤ 6.2
Pandemrix- and Arepanrix-AS03	0		0	0	0	≤ 12.8	0	1.4
Unadjuvanted	0		0	2.8	0	0	≤ 14.0	≤ 6.2
<i>pH1N1 vaccination coverage controls [%]</i>								
Focetria-MF59	2.5		0	0.1	33.3	0	1.1	1.0
Pandemrix- and Arepanrix-AS03	0		0.4	1.4	0	8.0	0	0.8
Unadjuvanted	0		0.4	0	0	0	8.8	3.5

*Nine child cases were included in a separate case-coverage study for reasons described in the methods. The child case total for the Netherlands includes nine from the case-coverage study and 13 from the case-control study.

**By definition, Brighton Collaboration (BC) narcolepsy case levels 1 and 2 have unambiguous cataplexy; BC narcolepsy case levels 3 and 4 may not have cataplexy. For inclusion in this study, children ages < 16 years are BC levels 1 and 2, children 17–18 years are BC levels 1–4, and adults ≥ 19 years are BC levels 1–4.

***Cell counts that represent case counts of five or fewer (for Ontario, Canada) or two or fewer (for Taiwan) cannot be displayed due to national patient privacy regulations. Therefore these are represented as range (i.e. $\leq n$).

2.3.3. Case-control analysis

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression or exact logistic regression if zero cells occurred. The reference category for estimation of the pH1N1 vaccination effect was no pH1N1 vaccination. Due to low exposure levels, we only present the analysis for the risk window of any time prior to the index date because this provided the maximum power.

To address potential awareness bias in the European Union (EU) sites, we analyzed data from two time periods, a “restricted” period and a “total” period. The restricted period analysis included cases from participating EU sites in the Netherlands, Valencia, Catalonia, and Switzerland only when they were diagnosed prior to onset of awareness about the narcolepsy signal in Europe (August 2010), and also cases from sites outside the EU diagnosed anytime during the entire study period. The total period analysis included cases from all sites for the entire study period, including cases from EU sites diagnosed after media attention.

We pooled data from sites using a hybrid approach (one stage pooling of matched case and control pairs for EU sites and Argentina, which could share data, and two-stage pooling with Taiwan and Ontario, which shared case counts and coefficients which were subsequently meta-analyzed with the one stage pooled data from EU sites and Argentina) (Fig. 1). Children were defined as ≤ 18 years of age and adults as ≥ 19 years. Due to incomplete pH1N1 vaccination information from GPs in children born between 2004 and 2009 in the Netherlands (because these children were vaccinated at local health agencies instead of GPs where we obtained exposure information for all study subjects), these cases and controls were excluded from the case-control analysis. However, cases born between 2004 and 2009 in the Netherlands were included in a post hoc case-coverage analysis (see below). In Switzerland, only child cases were included because of potential selection and information biases that was detected in adult cases. (Tables 1 and 2). In addition to using diagnostic MSLT referral as index date, we conducted sensitivity analyses using EDS onset date (requiring EDS starting after March 31, 2009). We used SAS v9.2 and statistical significance was set at p-value < 0.05 .

2.4. Case coverage analysis

In the Netherlands, cases born from 2004 through 2009 were analyzed using a case-coverage design. During the 2009 H1N1

pandemic these children were vaccinated with Pandemrix-AS03 at Municipal Health Services, and not through their GPs. Vaccinations for these children were registered in a nationwide database, Influxys, managed by the National Public Health Institute. Exposure in cases was therefore obtained from Influxys and exposure prevalence in the population for children born in the same year was obtained by calendar week and year of birth and used in the analysis, similar to the method used in the United Kingdom by Stowe et al. [27]. This post-hoc analytic approach allowed us to include information from the Netherlands, where individual exposure data was not available, to complement other data on Pandemrix-AS03.

2.5. Ethics committee approval

This study was conducted under the principles of the Helsinki declaration [28]. Each site was responsible for obtaining appropriate ethical approvals, the overall study was approved by the Institutional Review Board at Cincinnati Children’s Hospital Medical Center.

2.6. Role of the funding source

Two investigators (TS and FD) from the sponsoring organization, the U.S. Centers for Disease Control and Prevention, participated in development of the study design, analysis and interpretation of data, writing the report, and in the decision to submit the paper for publication.

3. Results

3.1. Narcolepsy incidence rates analysis

540 million person-years from ten sites in seven countries contributed to the narcolepsy IR analysis. In Sweden, a previously identified signaling country, IRs increased significantly after the start of its pH1N1 vaccination campaign for children 5–19 years (IRR = 9.01; 95% CI 6.89–11.80) and adults 20–59 years (IRR = 1.69; 95% CI 1.46–1.95). From 2011 onwards, narcolepsy IRs decreased in Sweden (Fig. 2). In other EU sites, narcolepsy IRs in the post-vaccination period did not change significantly compared to the pre-pH1N1 vaccination period. In Canada, where Arepanrix-AS03 was used, no changes in IRs were observed in any province sites in any age category. In Taiwan, pre-pH1N1 period narcolepsy

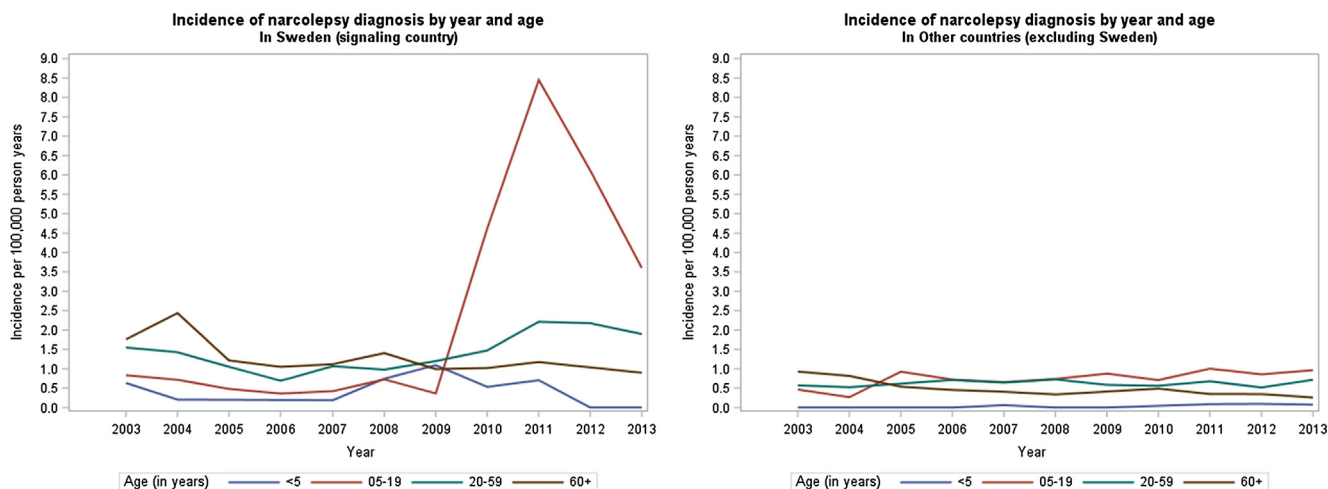


Fig. 2. Incidence rates of narcolepsy by age group and year from Sweden (left, a signaling country) and other study sites excluding Sweden (right, pooled data). Alberta, Canada (2003–2013); British Columbia, Canada (2003–2013); Manitoba, Canada (2003–2010); Catalonia, Spain (2007–2013); Valencia, Spain (2009–2013); Denmark (2003–2013), the Netherlands (2003–2013); Sweden (2003–2013), Taiwan (2003–2012), United Kingdom (2003–2013).

IR was lower (0.29 per 100,000 person-years, 95% CI 0.27–0.32) than in EU and Canadian sites (varying between 0.5 and 1.5 per 100,000 person-years) and we observed significant IR increases in children 5–19 years (IRR = 2.50; 95% CI 1.46–4.28) and adults 20–59 years (IRR = 2.23; 95% CI 1.26–3.94) during wild-type pH1N1 virus circulation prior to the vaccination campaign (also previously presented in Dodd et al. [29]).

3.2. Case-control and case-coverage analysis

According to information supplied to us by WHO and the manufacturers of the three adjuvanted 2009 pH1N1 vaccines, these vaccines were distributed in 47 countries. Many of these countries reportedly only used small amounts of vaccine in their private markets. Of these 47 countries, we selected 16 countries for potential participation in the study based upon our estimation of the likelihood that they would meet our eligibility criteria. Ten of the 16 potential participating countries were deemed ineligible after reviewing them against our eligibility criteria. (Of the sites we then approached, only the province of Quebec in Canada declined participation.) The six remaining countries participated in the case-control study.

We included 360 narcolepsy cases with MSLT referral during the study period: 150 were children ≤ 18 years and 210 were adults ≥ 19 years, which were matched to a total of 3515 controls (online supplement Table 1). For the restricted period analysis (excluding cases diagnosed after awareness in the EU), 96 child and 121 adult cases were included. For the total period analysis, 141 child and 210 adult cases were included. Nine child cases born between 2004 and 2009 from the Netherlands (all diagnosed after awareness) were only included in the case-coverage analysis.

Brighton Collaboration narcolepsy case definition diagnosis levels varied by site, with EU sites having more level 1 cases (23.40% in EU vs. 2.74% outside EU) and more cataplexy (73.06% in EU vs. 50.68% outside EU) (Table 2). Median delay between EDS onset and narcolepsy diagnosis was longer in adults compared to children and varied between sites, with a very short delay for Taiwan (online supplement Table 1). Shortening of delay was seen in children in some sites in the EU but not outside the EU following media and public awareness. In all sites, exposure to pH1N1 vaccine was low in cases and controls, except in Dutch children born between 2004 and 2009, with seven out of nine cases exposed to Pandemrix-AS03.

In the meta-analysis for the restricted period, exposure to any type of adjuvanted pH1N1 vaccine was not associated with narcolepsy in children or adults. The OR of the restricted period analysis in children ≤ 18 years of age was 0.80 (95% CI 0.21–3.01) for

Arepanrix-AS03 and 4.12 (95% CI 0.99–17.16) for Focetria-MF59. The OR of the restricted period analysis in adults was 1.00 (95% CI 0.21–4.81) for Arepanrix-AS03 and 0.71 (95% CI 0.16–3.14) for Focetria-MF59. The risk with Pandemrix-AS03 could not be estimated in the restricted period analysis due to the paucity of cases.

The total period analyses including all cases, as well as the separate case-coverage analysis in the Netherlands did not reveal an increased risk of narcolepsy in children or adults. The OR of the total period analysis in children ≤ 18 years was 0.80 (95% CI 0.21–3.01) for Arepanrix-AS03 and 1.40 (95% CI 0.43–4.64) for Focetria-MF59. In the case-coverage analysis, of the nine child cases born from 2004 through 2009, seven were exposed to Pandemrix-AS03, yielding an OR of 1.44 (95% CI 0.30–6.98). The OR of the total period analysis in adults was 1.00 (95% CI 0.21–4.81) for Arepanrix-AS03, 0.65 (95% CI 0.14–2.95) for Focetria-MF59, and 0.66 (95% CI 0–3.3) for Pandemrix-AS03 (Fig. 3).

Sensitivity analyses using EDS onset as index date for the total period reduced the number of cases considerably, either due to an EDS date before April 1, 2009 or missing EDS onset date. However, this analysis did not substantially alter the main findings of the total period analysis, which used MSLT referral as index date. For Arepanrix-AS03, OR estimates lowered to 0.29 (95% CI 0.03–2.65) in children and remained 1.00 (95% CI 0.05–18.9) in adults. For Focetria-MF59, the pooled estimate ORs were 2.06 (95% CI: 0.63–6.72) in children and 0.65 (95% CI: 0.14–2.95) in adults. For Pandemrix-AS03, ORs were 0.48 (95% CI 0.15–1.58) in children and 1.12 (95% CI 0–6.1) in adults.

4. Discussion

The SOMNIA study, a multi-country effort that included data from sites on four continents, did not find an increase in narcolepsy IRs associated with pH1N1 vaccination campaigns (except in Sweden, a previously identified signaling country) nor did it detect significant associations between narcolepsy following any adjuvanted pH1N1 vaccines studied. To our knowledge, this is the largest and most geographically diverse study with the longest study period examining the association between adjuvanted pH1N1 vaccines and narcolepsy. Oil-in-water adjuvants like AS03 and MF59 increase immunogenicity of influenza vaccines making them attractive (or possibly necessary) for use in future pandemic influenza vaccines, and they may have the potential to improve the performance of seasonal influenza vaccines [30]. Assessing the safety of these adjuvants has substantial public health and clinical importance.

In our study, the IR of narcolepsy increased in Sweden beginning in summer 2010 and declined in 2011, especially in children

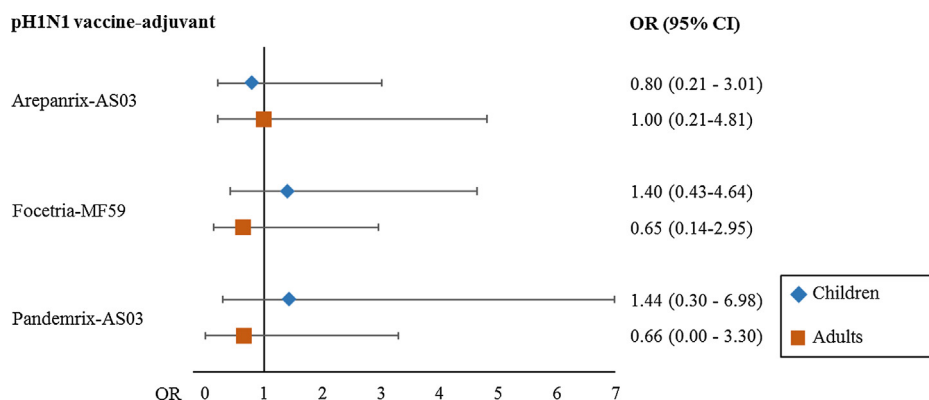


Fig. 3. Odds ratios (OR) for narcolepsy and 95% confidence intervals (CI) by vaccine brands in the total period analysis for children (≤ 18 years) and adults (≥ 19 years). Arepanrix-AS03: case-control study in Ontario, Canada. Focetria-MF59: two-stage random effects meta-analysis of data from Taiwan, Argentina, the Netherlands, and Valencia and Catalonia, Spain. Pandemrix-AS03: case-coverage study in the Netherlands for children and case-control study in Valencia, Spain, for adults.

5–19 years. No similar increase in IR of narcolepsy was observed at any of the other participating sites. However, in Taiwan, a site with a very short lag time between symptom onset and diagnosis of narcolepsy, a significant increase in IR of narcolepsy was observed during circulation of wild-type pH1N1 virus but prior to pH1N1 vaccination, a phenomenon also reported in China, which had low (unadjuvanted) vaccination coverage [31].

Ontario, where vaccination coverage was 32.2% [32], provided case-control data on Arepanrix-AS03; no association with narcolepsy was found in children or adults, which contrasts with a prior finding from a study in Quebec, where a small increase in risk was found, although with large confidence intervals [23]. Since Arepanrix-AS03 has the same adjuvant and a similar pH1N1 antigen as the Pandemrix-AS03 vaccine used in Finland and Sweden, it appears that the association for Pandemrix-AS03 and narcolepsy observed in some European countries is not likely due to the AS03 adjuvant or the pH1N1 antigen in the vaccine alone. Focetria-MF59 was not associated with narcolepsy in children or adults in this study, although the upper limit of the confidence interval cannot exclude a small increase in risk in children. This is consistent with prior observations of a lack of association (or just a few case reports) in countries using this vaccine [33]. Because of low vaccination coverage in sites for Pandemrix-AS03, we were constrained in our ability to evaluate the possibility of an association in our case-control study; our data from the Netherlands are based on a small number of children who were between six months and five years of age at vaccination.

The SOMNIA study contributes to our understanding of the epidemiology of narcolepsy before, during, and after the 2009 H1N1 influenza pandemic and pH1N1 vaccination campaigns. Importantly, it contributes to the body of evidence regarding the possible association between adjuvanted pH1N1 vaccines and narcolepsy as an adverse event following immunization. Prior data, mostly from Europe, predominantly involved Pandemrix-AS03 exposure and included many cases diagnosed shortly after increased media attention and public awareness. Inclusion of the cases diagnosed in the time period immediately after heightened media attention, may overestimate an association, which is supported by the simulations of Wijnans et al. [34]. Awareness about a possible association with Pandemrix-AS03 may have resulted in vaccinated cases being diagnosed sooner than they normally would have been, resulting in apparent clusters of narcolepsy [35]. We attempted to address this potential bias by including countries outside the EU and countries in the EU that experienced less media and public awareness; we also conducted an analysis restricting cases in Europe to those diagnosed before attention arose. Additionally, we minimized potential bias from accelerated diagnosis of vaccinated cases by recruiting cases up to five years after knowledge of a possible association became widespread. The findings of our SOMNIA study indicate that the impact of media and public awareness, and the resulting detection bias, may have diminished over time. Our risk estimates of narcolepsy following adjuvanted pH1N1 vaccination for the restricted period analysis compared to the total period analysis did not differ substantially. This is in contrast to the prior Vaccine Adverse Event Surveillance & Communication (VAESCO) study of EU countries, which had a much shorter case accrual period [35]. Overall, our study did not find an increased risk of narcolepsy following vaccination with AS03- or MF59-adjuvanted pH1N1 vaccines based on the total period analysis.

Although we did not detect any significant associations between adjuvanted pH1N1 vaccination and narcolepsy beyond Sweden, we acknowledge the overall trend of evidence of an increased risk associated with Pandemrix-AS03 [5,14,15,23]. A biologic mechanism to explain this observation has not been established, but it has been postulated that an interaction involving the immune responses to administration of Pandemrix-AS03 and

infection with wild-type pH1N1 virus could be a contributing factor [20]. This would explain the apparent presence of an association in Finland, Sweden and Norway where wild-type virus circulated coincident with the vaccination program, whereas no association was seen in Ontario where wild-type virus was no longer circulating at the time of the vaccination program. We were not able to address this hypothesis in the SOMNIA study, but it remains a focus area that will likely require a global cooperative research effort.

This retrospective and observational study has several limitations. Despite multiple study sites, statistical power in the restricted period analysis was limited due to fewer cases and low pH1N1 vaccination coverage (online supplement Table 2). For Focetria-MF59, the only country with high coverage in the at-risk age group was Argentina, but the number of cases was low. Although we used standardized case definitions, case misclassification could have occurred as diagnostic procedures and information capture differed across sites. Nonetheless, our application of the Brighton Collaboration case definition criteria for all cases decreased the likelihood of misclassification. Misclassification of exposure could have happened from incomplete recording of pH1N1 vaccinations due to lack of access to school vaccination records in Taiwan. Non-exhaustive inclusion of cases in Ontario (due to distance) and the Netherlands (timeliness of consent) led to incomplete inclusion of cases at the data lock point. For the Netherlands, where consent for study participation was needed, vaccinated cases might be more likely to give consent (given public awareness), which could overestimate the risk; however no significant association was observed. For Ontario, data collection had not been totally completed by the end of the study, but this was not related to vaccination status and therefore impacted power alone. Selection bias was detected in Switzerland for the adult cases (not for children), when we compared our cases to a published series of exposed cases [36], demonstrating lack of inclusion of exposed cases in adults – this led to exclusion of adult cases and controls in Switzerland. Finally, although we used a common protocol across all sites, it was necessary to provide flexibility for implementation at the local study site level for identifying cases and controls. This might have introduced variability; however, the main criterion in selecting controls was that they be representative of individuals receiving pH1N1 vaccination in the general population and that exposure information was obtained similarly for cases and controls.

5. Conclusion

We did not observe increases in population-based narcolepsy IRs associated with pH1N1 vaccination campaigns at participating sites, except for Sweden. In the case-control analysis, we did not detect evidence of a significant increased risk of narcolepsy following any of the adjuvanted pH1N1 vaccines in children or adults in our study population, although upper limits of estimates do not exclude small to moderate risks. The SOMNIA study highlights the usefulness of international collaboration in the evaluation of vaccine safety signals for rare adverse events. Using a common protocol and methods reduces heterogeneity, permits contribution of data from countries across the world, and allows for combining data for increased statistical power necessary to address questions about rare events.

6. Declaration of interests

Maria de Ridder, Caitlin Dodd, Jan Bonhoeffer, Ann Vanrolleghem, Gert Jan Lammers, Sebastiaan Overeem, Jeffrey C. Kwong, Karen Cauch-Dudek, Diana Juhasz, Michael Campitelli, Wan-Ting

Huang, Maria Giner-Soriano, Rosa Morros, Carles Gaig, Ester Tió, Silvia Perez-Vilar, Javier Diez-Domingo, Lawrence W. Svenson, Bruce Carleton, Lisen Arnheim-Dahlström, Lars Pedersen, Frank DeStefano, Tom T. Shimabukuro, Nicoline van der Maas, Brian J. Murray, Alexandre N. Datta, Ulf Kallweit, Yu-Shu Huang, Chung-Yao Hsu, Hsi-Chung Chen, Francisco Javier Puertas, Monika Naus have no conflicts of interest.

Daniel Weibel, receives consultancy honoraria from GSK for a consultancy related to malaria vaccine implementation in Africa, independent from any flu vaccines, or any work related to this publication.

Angela Gentile, Norberto Giglio, Vanesa Castellano received research contracts from the U.S. Centers for Disease Control and Prevention independent from this study.

Miriam Sturkenboom received honorarium from GSK and post-authorisation safety studies (PASS) research contracts independent from this study.

Salaheddin M. Mahmud received research funding from GSK, Merck, Pfizer, Roche and Sanofi Pasteur and speaking and consulting fees from GSK and Sanofi not related to this study.

Steven Black reports contracts from U.S. Centers for Disease Control, during the conduct of the study; other from GSK Vaccines, outside the submitted work.

We acknowledge funding from the U.S. Centers for Disease Control and Prevention (CDC), Atlanta, USA, under CDC contract number 200-2012-53425_addendum 0001.

7. Authors' contributions

All authors contributed to reviewing and commenting on the study design, results, and the final report and manuscript.

Miriam Sturkenboom, Steven Black and Jan Bonhoeffer wrote the study protocol and acquired funding. Miriam Sturkenboom and Steve Black wrote the study report.

Miriam Sturkenboom, Jan Bonhoeffer, Ann Vanrolleghem, Nicoline van der Maas, Gert Jan Lammers, Sebastiaan Overeem, Angela Gentile, Norberto Giglio, Vanesa Castellano, Jeffrey C. Kwong, Brian J. Murray, Karen Cauch-Dudek, Diana Juhasz, Michael Campitelli, Alexandre N. Datta, Ulf Kallweit, Wan-Ting Huang, Yu-Shu Huang, Chung-Yao Hsu, Hsi-Chung Chen, Maria Giner-Soriano, Rosa Morros, Carles Gaig, Ester Tió, Silvia Perez-Vilar, Javier Diez-Domingo, Francisco Javier Puertas, Lawrence W. Svenson, Salaheddin M. Mahmud, Bruce Carleton, Monika Naus, Lisen Arnheim-Dahlström, Lars Pedersen contributed to local implementation of the protocol in data collection, case review and reporting at the study site level.

Miriam Sturkenboom, Daniel Weibel, Maria de Ridder and Caitlin Dodd managed data collection across datasites and wrote the analysis plan. Maria de Ridder, Caitlin Dodd, Miriam Sturkenboom, Michael Campitelli, and Wan-Ting Huang conducted final pooled analyses and guided statistical and data quality assurance.

Two investigators (Tom T. Shimabukuro and Frank DeStefano) from the sponsoring organization, the U.S. Centers for Disease Control and Prevention, participated in development of the study design, analysis and interpretation of data, writing the report, and in the decision to submit the paper for publication.

8. Funding source

This study was funded by the Centers for Disease Control and Prevention (CDC), Atlanta, USA, under CDC contract number 200-2012-53425_addendum 0001.

9. Statement

This paper contains original unpublished work and is not being submitted for publication elsewhere.

10. Disclaimers

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Mention of a product or company name does not constitute endorsement by the CDC.

All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not necessarily reflect the opinions or policies of the British Columbia Ministry of Health.

At the time of study MCJM Sturkenboom was an employee of Erasmus University Medical Center, Rotterdam, Netherlands.

Acknowledgements

We thank the following individuals for their contributions to the SOMNIA study.

Valencia: Mónica Escobar Daroca, Macrina Sastre-Cantón, Lorena Platero-Sanchis, Marian Martín-Navarro for data collection. Local Ethics Committees, Sleep Units and hospital archives services from all public hospitals in the Valencia Region for facilitating study implementation.

Taiwan: Kai-Jen Wu, Hsin-Yi Dai, Shawn-Shuan Wu, Cheng-Fang Hsieh, Meng-Ni Wu, Pei-Yun Tsai, Chia-Chih Chuang, Hsin-Chun Lee, Hui-Chen Lin, and Chin-Hui Yang for assistance with case ascertainment and validation. The Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, for support in data coordination.

Ontario: Anne Marie Mior, Gregory Handrigan, Thuy Linh Do, Catherine Nevin, Kailey Dudek, Erik Juhasz, Roxine Kee, Rianne Kee, Lloyd Lim, Priscilla Leung, Rachel Savage, Alexander Kopp, Charlotte Ma, Nelson Chong, and all the participating public health units, sleep physicians, and primary care physicians in Ontario.

Switzerland: Jens-Georg Acker, Tom Allport, Valentin Arabin, Claudio Bassetti, Christian Baumann, Aristomenis Exadaktylos, Daniel Garcia, Jose Haba Rubio, Annette Hackenberg, Oskar Hasselmann, Raphael Heinzer, Christian Hillion, Oskar Jenni, Ramin Khatami, Ruth Löllgen, Marco Manconi, Sigrid von Manitius, Arto Nirkko, Stephen Perrig, Meret Ricklin, Thierry Rochat, Werner Strobel, Susi Strozzi, Johannes Mathis, Matthias Strub, Barbara Tettborn, Esther Werth, Franco Zellini for excellent collaboration on case and control identification, data collection and case ascertainment.

Catalonia: Dr Gonzalo Calvo-Rojas, from Pharmacology Service, Hospital Clinic of Barcelona, for facilitating study coordination and contact with sleep disorders specialists. Albert Roso-Llorach, from IDIAP Jordi Gol, for his support in SIDIAP data management. All physicians from the Narcolepsy Catalan Network from sleep units from hospitals in Catalunya who collaborated in data collection for SOMNIA study: Joan Santamaria, Alex Iranzo, Carme Monasterio, Juan Luis Becerra, Marta Jiménez, Antonio Bové, Jaume Viñas, Albert Molins, Ion Álvarez, Núria Caballol, Gemma Sansa, Montserrat Pujol, Óscar Sans, Antonio Escartín, Odile Romero, M^{re} José Jurado, Roser Cambrodi.

The Netherlands: Petra van Mierlo, Judith Hoppenbrouwers (Sleep Medicine Centre Kempenhaeghe); Petra Oomen (Department of vaccine supply and prevention programmes, National Institute for Public Health and the Environment - RIVM); Peter Rijnbeek, Mees Mosseveld (Medical Informatics, Erasmus Medical Center).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.vaccine.2018.08.008>.

References

- [1] Medical Products Agency. 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. <https://lakemedelsverket.se/upload/nyheter/2011/PandemrixRegReport110328.pdf>.
- [2] Partinen M, Saarenpaa-Heikkilä O, Ilveskoski I, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. *PLoS ONE* 2012;7:e33723.
- [3] European Medicines Agency. Pandemrix: EPAR - Product Information; 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500038121&mid=WC0b01ac058009a3dc.
- [4] Bardage C, Persson I, Ortvist A, Bergman U, Ludvigsson JF, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. *BMJ* 2011;343:d5956.
- [5] Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. *PLoS ONE* 2012;7:e33536.
- [6] Gadroen K, Straus SM, Pacurariu A, Weibel D, Kurz X, Sturkenboom MC. Patterns of spontaneous reports on narcolepsy following administration of pandemic influenza vaccine; a case series of individual case safety reports in Eudravigilance. *Vaccine* 2016.
- [7] Kornum BR, Faraco J, Mignot E. Narcolepsy with hypocretin/orexin deficiency, infections and autoimmunity of the brain. *Curr Opin Neurobiol* 2011;21:897–903.
- [8] Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 2000;355:39–40.
- [9] Scammell TE. Narcolepsy. *N Engl J Med* 2015;373:2654–62.
- [10] Overeem S, Black 3rd JL, Lammers GJ. Narcolepsy: immunological aspects. *Sleep Med Rev* 2008;12:95–107.
- [11] Luca G, Haba-Rubio J, Dauvilliers Y, 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.
- [12] Dauvilliers Y, Arnulf I, Lecendreux M, et al. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. *Brain: J Neurol* 2013;136:2486–96.
- [13] Heier MS, Gautvik KM, Wannag E, et al. Incidence of narcolepsy in Norwegian children and adolescents after vaccination against H1N1 influenza A. *Sleep Med* 2013;14:867–71.
- [14] Miller E, Andrews N, Stellitano L, 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.
- [15] O'Flanagan D, Barret AS, Foley M, et al. Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009–December 2010. *Euro Surveill: Bulletin Européen sur les maladies transmissibles = Eur Commun Dis Bull* 2014;19:15–25.
- [16] Persson I, Granath F, Askling 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* 2014;275:172–90.
- [17] Szakacs A, Darin N, Hallbook T. Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination. *Neurology* 2013;80:1315–21.
- [18] Oberle D, Pavel J, Mayer G, Geisler P, Keller-Stanislawski B. German Narcolepsy Study G. Retrospective multicenter matched case-control study on the risk factors for narcolepsy with special focus on vaccinations (including pandemic influenza vaccination) and infections in Germany. *Sleep Med* 2017;34:71–83.
- [19] Verstraeten T, Cohet C, Dos Santos G, et al. Pandemrix and narcolepsy: a critical appraisal of the observational studies. *Hum Vaccin Immunother* 2015;1–7.
- [20] Sturkenboom MC. The narcolepsy-pandemic influenza story: can the truth ever be unraveled? *Vaccine* 2015;33(Suppl 2):B6–B13.
- [21] Sarkanen TO, Alakuijala APE, Dauvilliers YA, Partinen MM. Incidence of narcolepsy after H1N1 influenza and vaccinations: systematic review and meta-analysis. *Sleep Med Rev* 2018;38:177–86.
- [22] 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.
- [23] Montplaisir J, Petit D, Quinn MJ, et al. Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec. *PLoS ONE* 2014;9:e108489.
- [24] Trifiro G, Coloma PM, Rijnbeek PR, et al. Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how? *J Intern Med* 2014;275:551–61.
- [25] Poli F, Overeem S, Lammers GJ, et al. Narcolepsy as an adverse event following immunization: case definition and guidelines for data collection, analysis and presentation. *Vaccine* 2013;31:994–1007.
- [26] Wijnans L, Lecomte C, de Vries C, 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.
- [27] Stowe J, Andrews N, Kosky C, 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.
- [28] Association WM. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects; 2013. [http://www.wma.net/en/30publications/10policies/b3/index.html.pdf?print-media-type&footer-right=\[page\]/\[toPage\]](http://www.wma.net/en/30publications/10policies/b3/index.html.pdf?print-media-type&footer-right=[page]/[toPage]).
- [29] Dodd CN, de Ridder M, Huang W, et al. Incidence rates of narcolepsy diagnoses in Taiwan, Canada, and Europe: methods for rapid assessment of potential safety issues on a population level in the SOMNIA study. *PLoS One* 2018 [in press].
- [30] Even-Or O, Samira S, Ellis R, Kedar E, Barenholz Y. Adjuvanted influenza vaccines. *Expert Rev Vaccines* 2013;12:1095–108.
- [31] Han F, Lin L, Warby SC, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann Neurol* 2011;70:410–7.
- [32] Gilmour H, Hofmann N. H1N1 vaccination. *Health Rep* 2010;21:63–9.
- [33] Ahmed SS, Schur PH, MacDonald NE, Steinman L. Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: what is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants. *J Autoimmun* 2014;50:1–11.
- [34] Wijnans L, Dodd C, de Ridder M, et al. Pandemic influenza vaccine & narcolepsy: simulations on the potential impact of bias. *Expert Rev Vaccines* 2016;15:573–84.
- [35] ECDC. European Centre for Disease Prevention and Control. Narcolepsy in association with pandemic influenza vaccination (a multi-country European epidemiological investigation). Stockholm: ECDC; 2012. <http://ecdc.europa.eu/en/publications/Publications/Vaesco%20report%20FINAL%20with%20cover.pdf>.
- [36] Kallweit U, Mathis J, Jenni OG, 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.