Investigation of the association between narcolepsy and vaccination with Pandemrix

Darina O'Flanagan
Director HPSC HSE
AS Barret, S Cotter, C Bonner, C Crowe, B Lynch, B Sweeney, M Foley, H Johnson, B Mc Coy, E Purcell

Finnish Slides Hanna Nohynek THL

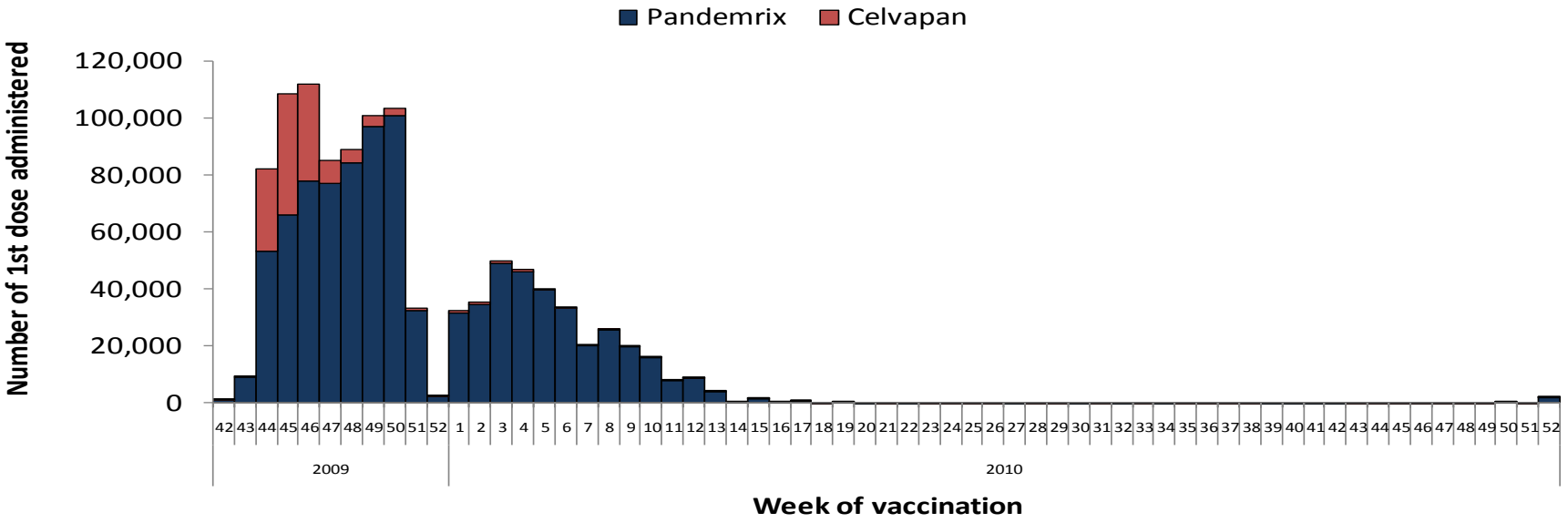
Narcolepsy

- Chronic sleep disorder characterised by:
  - Excessive daytime sleepiness (EDS)
  - Cataplexy
  - Sleep paralysis
  - Hypnagogic hallucinations
  - Other symptoms: weight gain, poor concentration, emotional lability
- Age at onset of symptoms is usually between 15-40 years

Brighton case definition

Level	In the presence of
Level 1	Excessive daytime sleepiness AND/OR Suspected cataplexy AND CSF hypocretin-1 deficiency
Level 2	Excessive daytime sleepiness AND Definite cataplexy AND Level 1 or 2 MSLT abnormalities (mean sleep latency <8 min for adults and <12 min for children AND/OR at least 2 sleep-onset REM periods)
Level 3	Excessive daytime sleepiness AND Level 1 MSLT abnormalities (mean sleep latency <8 min for adults and <12 min for children AND at least 2 sleep-onset REM periods)

Pandemic Influenza Vaccination



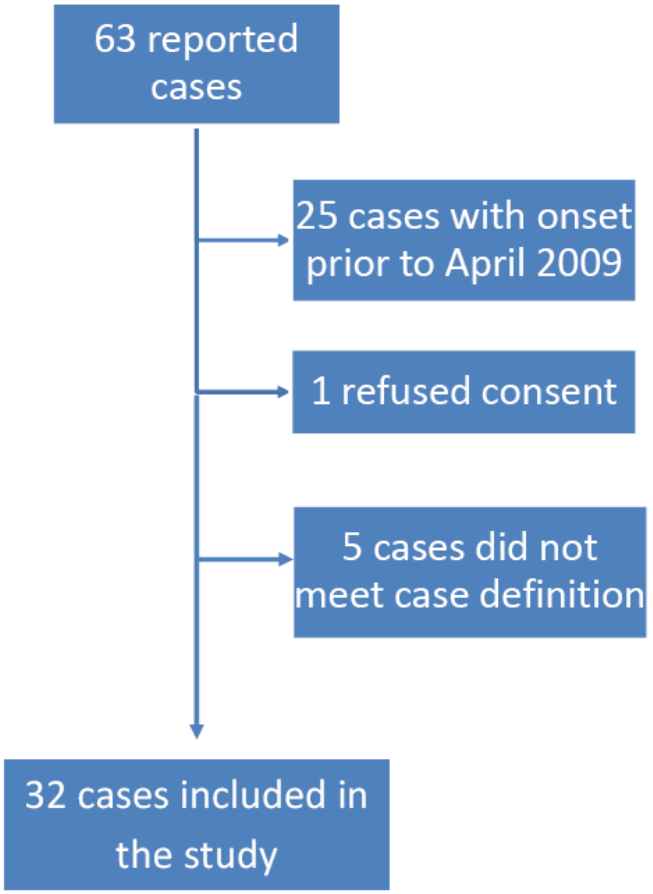
Age group	Population of Ireland (*Census 2006*)	Number of first shot vaccination with Pandemrix	Population vaccine uptake (Pandemrix)
0-4	271,714	129,942	47.8%
5-19	852,454	339,312	39.8%
20+	3,085,412	474,229	14.4%
Unknown	-	3,413	-
Total	4,209,310	946,896	22.5%

Study Methods

- A retrospective population- based cohort study was conducted
- Narcolepsy Active case finding by contacting all
  - Sleep clinics
  - Neurologists
  - Paediatricians
  - General practitioners (GP)
  - Psychiatrists
  - Psychologists
  - Public health nurses
- GP and hospital records accessed with patient consent to verify diagnosis and dates of onset.
- Vaccination denominator data accessed via 2 vaccination databases
- Primary study period:
  - 1st April 2009 → 31st December 2010
- Study cohorts:
  - Born between 2006-2010 (aged 0-4 years)
  - Born between 1991-2005 (aged 5-19 years)
  - Born before 1991 (aged 20 years or older)

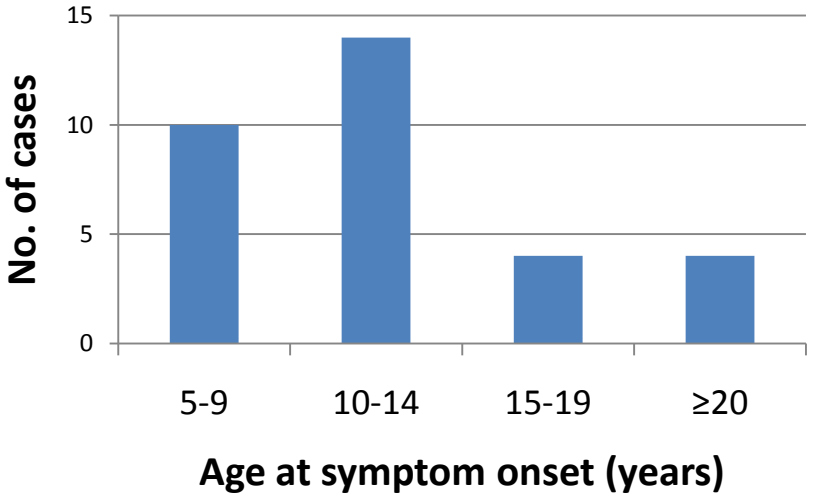
Study Case Definition

- A case of narcolepsy was defined as:
  - Having onset of narcolepsy symptoms during the primary study period (01/04/2009-31/12/2010)
  - Fulfilling the Brighton case definition for narcolepsy
  - Diagnosis confirmed by 2 neurologists blinded to vaccination status of cases



Narcolepsy Cases

- 22 (69%) female and 10 (31%) male
- Age distribution of cases:



- 30 cases vaccinated against pandemic influenza
  - 25 vaccinated before symptom onset
    - 24 received Pandemrix
    - 1 received Celvapan
  - 5 vaccinated after symptom onset
    - Considered as unvaccinated in study analysis
- 2 cases did not receive any pandemic influenza vaccinations

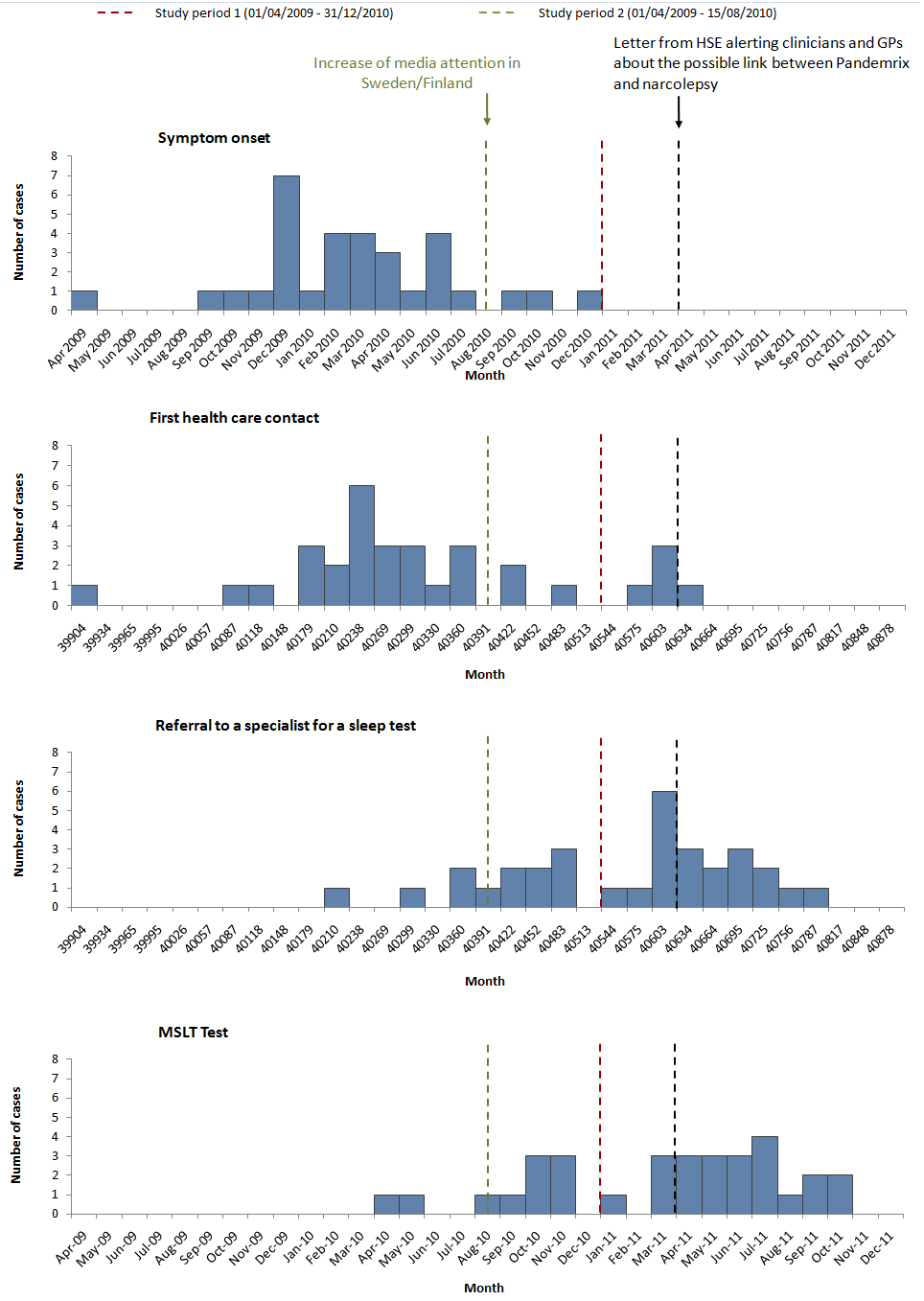


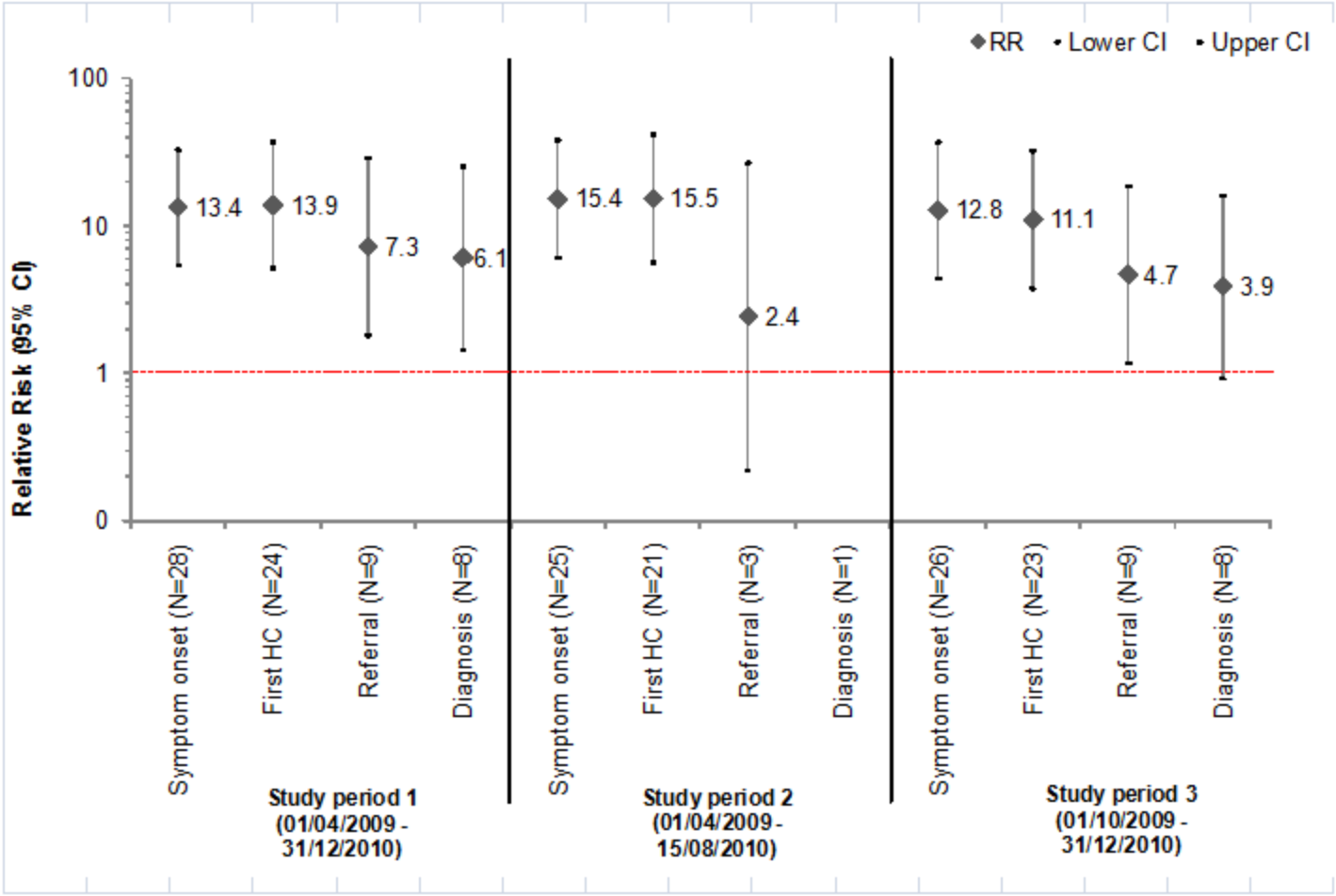
Figure 2: Distribution of narcolepsy cases according to different estimated onset dates (n=32), April 2009-December 2012, Ireland

NB: When the exact date of symptom onset was unknown, it was approximated to the 15th of the reported month

Risk of Narcolepsy in 5-19 year olds

- Incidence of narcolepsy in vaccinated
  - 5.7 per 100,000 person-years [95% CI: 3.4-8.9]
- Incidence of narcolepsy in unvaccinated
  - 0.4 per 100,000 person-years [95% CI: 0.1-1.0]
- Significant 13.9-fold higher risk of narcolepsy in vaccinated compared to unvaccinated individuals
- Absolute increase of 5 narcolepsy cases per 100,000 vaccinated 5-19 year olds
- The vaccine attributable risk of developing narcolepsy was 1:16,000 vaccinated 4-19 year olds (95% CI: 1 in 13,000 - 1 in 21,000).

Sensitivity Analysis



Potential Bias

- Although case finding was performed irrespective of the cases' vaccine status, some unvaccinated cases may have not yet been diagnosed or reported at the time of the report.

- In the 5-19 year old age group:
  - Additional 36 unvaccinated cases would need to be diagnosed for RR of narcolepsy to become non-significant [RR=1.7; 95% CI: 0.98-2.92]
  - Additional 60 unvaccinated cases would need to be diagnosed for the risk of narcolepsy to disappear [RR=1.07; 95% CI: 0.6-1.8]

Reports from Other Countries

- Sweden:
  - 81 cases of narcolepsy in children/adolescents under 19 years.
  - An almost seven-fold higher risk in those vaccinated compared to those unvaccinated
  - A more recent study reports a risk of 3 in the under 20s and also increased risk of 2 in those aged 21-30

- Finland:
  - 79 cases of narcolepsy reported in 4-19 years olds.
  - 12.7 times the risk of narcolepsy in vaccinated compared to unvaccinated 4-19 year old.
  - No increase in narcolepsy was noted in children ages under 4 years or in adults over 19 years
- **Vaccine attributable risk for developing narcolepsy**
- **= 6 / 100 000 among those vaccinated 4-19 years of age**
- **= 1 / 16 000**

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28 March 2012

PLoS one

AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland

Hanna Nohynek[1*], Jukka Jokinen[1], Markku Partinen[2], Outi Vaarala[1], Turkka Kirjavainen[3], Jonas Sundman[1], Sari-Leena Himanen[4], Christer Hublin[5], Ilkka Julkunen[6], Päivi Olsén[7], Outi Saarenpää-Heikkilä[8], Terhi Kilpi[1]

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PLoS one

Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland

Markku Partinen[1,2,15*], Outi Saarenpää-Heikkilä[3], Ismo Ilveskoski[4], Christer Hublin[5], Miika Linna[6], Päivi Olsén[7], Pekka Nokelainen[8], Reija Alén[9], Tiina Wallden[10], Merimaaria Espo[10], Harri Rusanen[11], Jan Olme[12], Heli Sätilä[13], Harri Arikka[14], Pekka Kaipainen[15], Ilkka Julkunen[16], Turkka Kirjavainen[17]

How many individuals in the susceptible age group were exposed ?

Country	Pandemrix^{R} Doses given to 4-19 yr old	Comment
Sweden	~1 000 000	
Finland	668 000	
Ireland	339 312	
Norway	470 000	5-18 year olds
France	?	
Germany	~700 000	
Great Britain	~295 000	5-16 year olds
Canada, entire country	~ 1 200 000	Pandemrix-like Arepanrix^{R}
Canada, Quebec	793 448	5-18 year olds

VAESCO CASE CONTROL STUDY (HYPOTHESIS TESTING)

- **Design:** Case control study
- **Study Period:** April 2009-July 2010 (after July: sensitivity analysis)
- **Setting:** 8 countries: **FI**, **SW**, NO, DK, NL, UK, FR, IT
- **Cases:** Validated by Brighton case classification
- **Index date:** Date of first referral to sleep center (primary)
  date of diagnosis and date of first symptoms
  (sensitivity)
- **Controls:** Matched on country/age/sex/index date
- **Exposure:** H1N1 vaccine, other vaccines, infections
- **Data collection:** harmonized methods and pooling

Final report out; data incomplete, results confirmed FI and SW findings,
For other countries inconclusive

Hanna Nohynek

BMJ

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RESEARC

Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis


OPEN ACCESS

Elizabeth Miller *consultant epidemiologist*[1], Nick Andrews *senior statistician*[2], Lesley Stellitano *public health researcher*[1 3], Julia Stowe *research fellow*[1 4], Anne Marie Winstone *public health researcher*[1 3], John Shneerson *consultant physician*[5], Christopher Verity *consultant paediatric neurologist*[1 3]

those with a diagnosis by July 2011 the odds ratio was 14.4 (95% confidence interval 4.3 to 48.5) for vaccination at any time before onset and 16.2 (3.1 to 84.5) for vaccination within six months before onset. The relative incidence from the self controlled cases series analysis in those with a diagnosis by July 2011 with onset from October 2008 to December 2010 was 9.9 (2.1 to 47.9). The attributable risk was estimated as between 1 in 57 500 and 1 in 52 000 doses.

Conclusion The increased risk of narcolepsy after vaccination with ASO3 adjuvanted pandemic A/H1N1 2009 vaccine indicates a causal association, consistent with findings from Finland. Because of variable delay in diagnosis, however, the risk might be overestimated by more rapid referral of vaccinated children.

THL National AEFI register
Raported narcolepsy- cataplexy cases

	2010	2011	2012	Total
Narcolepsy+ Cataplexy	47	50	21	118
Narcolepsy	8	11	8	27
	55	**61**	**29**	**145**

Of the reports

< 19 year olds		125
19 year and older	20	

Report from South Korea

Vaccine 30 (2012) 7439–7442

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Vaccine

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Short communication

No association between influenza A(H1N1)pdm09 vaccination and narcolepsy in South Korea: An ecological study

Young June Choe [a,b,*], Geun-Ryang Bae [a,b], Duk-hyoung Lee [b]

[a] Division of Vaccine Preventable Disease Control and National Immunization Program, Republic of Korea
[b] Center for Disease Prevention, Korea Centers for Disease Control and Prevention, Osong, Republic of Korea

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ABSTRACT

Background: There is concern about a possible association between influenza A(H1N1)pdm09 vaccination and narcolepsy. In this study, we assessed the incidence and incidence rate of narcolepsy in the South Korean population before and after the implementation of an A(H1N1)pdm09 vaccination campaign to see if vaccination led to a change in the occurrence of narcolepsy.

Methods: We conducted an ecological study, comparing incident cases and incidence rates for newly diagnosed narcolepsy case-patients in South Korea, between July 2006 and June 2011. We used data from the Health Insurance Review Agency and Korea Centers for Disease Control and Prevention, which have limited information on case ascertainment. During vaccination campaign period, South Korea used non-adjuvanted and MF59-adjuvanted A(H1N1)pdm09 vaccines.

Results: Generally, incidence rate was highest in prepandemic period. No trend toward increase in the incidence of narcolepsy after pandemic period was found. Observation of incidence by season did not suggest any time pattern for occurrence of narcolepsy.

Conclusion: No increase in cases or incidence rate for narcolepsy during the A(H1N1)pdm09 vaccination campaign was found in South Korea. Our data do not support the use of MF59-adjuvanted or non-adjuvanted A(H1N1)pdm09 vaccine as a trigger for narcolepsy on a population level.

ORIGINAL ARTICLE

Narcolepsy Onset Is Seasonal and Increased following the 2009 H1N1 Pandemic in China

Fang Han, MD,[1] Ling Lin, MD, PhD,[2] Simon C. Warby, PhD,[2] Juliette Faraco, PhD,[2] Jing Li, BS,[1] Song X. Dong, MD,[1] Pei An, BS,[1] Long Zhao, BS,[1] Ling H. Wang, MD,[1] Qian Y. Li, MD,[1] Han Yan, MD,[1] Zhan C. Gao, MD,[1] Yuan Yuan, MD,[1] Kingman P. Strohl, MD,[3] and Emmanuel Mignot, MD, PhD[2]

Objective: Narcolepsy is caused by the loss of hypocretin/orexin neurons in the hypothalamus, which is likely the result of an autoimmune process. Recently, concern has been raised over reports of narcolepsy in northern Europe following H1N1 vaccination.

Methods: The study is a retrospective analysis of narcolepsy onset in subjects diagnosed in Beijing, China (1998–2010). Self-reported month and year of onset were collected from 629 patients (86% children). Graphical presentation, autocorrelations, chi-square, and Fourier analysis were used to assess monthly variation in onset. Finally, 182 patients having developed narcolepsy after October 2009 were asked for vaccination history.

Results: The occurrence of narcolepsy onset was seasonal, significantly influenced by month and calendar year. Onset was least frequent in November and most frequent in April, with a 6.7-fold increase from trough to peak. Studying year-to-year variation, we found a 3-fold increase in narcolepsy onset following the 2009 H1N1 winter influenza pandemic. The increase is unlikely to be explained by increased vaccination, as only 8 of 142 (5.6%) patients recalled receiving an H1N1 vaccination. Cross-correlation indicated a significant 5- to 7-month delay between the seasonal peak in influenza/cold or H1N1 infections and peak in narcolepsy onset occurrences.

Interpretation: In China, narcolepsy onset is highly correlated with seasonal and annual patterns of upper airway infections, including H1N1 influenza. In 2010, the peak seasonal onset of narcolepsy was phase delayed by 6 months relative to winter H1N1 infections, and the correlation was independent of H1N1 vaccination in the majority of the sample.

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Country	Age group yrs	Study design	Definition of onset	Follow up period	Risk (RR/ OR)	95 % CI
Finland	4-19	RC	1. contact with HC	1.1.2009-15.8.2010	12.7	6.1 - 30.8
Sweden	≤19	RC	Date of dg G47.4	1.10.2009-31.12.2010	4.06	2.87 - 5.58
Ireland	5-19	RC	1. contact with HC	1.4.2009-31.12.2010	13.0	4.6 - 34.7
France	<19 ≥19	C-C	Date of referral MSLT	1.4.2009-30.4.2011	5.1 3.9	2.11 - 12.3 1.4 - 11.0
Norway	4-19	RC	Date of EDS by patient	1.10.2009 - 30.6.2010	14.5	
UK	4-19	SCCS CaseC	Date of EDS recorded by GP/centre	6 months post vaccination	16.2	3.1 – 84.5

- Pandemrix vaccination is associated with an abrupt increase in narcolepsy-cataplexy among children and teens, and possibly also in adults
- The relative risk varies between 3 to 14 / 100 000 in the susceptible age group
- The vaccine associated risk is small (<7 /100 000) but consistently seen in different populations where Pandemrix was used in large numbers in susceptible age group
- Such a rare event would not have been picked up in prelicensure trials
- In most countries, the postlicensure safety surveillance did not pick up the signal either

Members of the National Narcolepsy Study Steering Committee

- D O'Flanagan , AS Barret, S Cotter, C Bonner, C Crowe, B Lynch, B Sweeney, J Gilvarry, H Johnson,
- Expert neurologist reviewers: B Sweeney, B McCoy
- The Steering committee wishes to acknowledge the contribution of all clinicians both in hospital and primary care who have reported cases, HIPE data from ESRI and National Casemix Office and Health Intelligence Ireland, Departments of Public Health Medicine who organised retrieval of primary care notes, colleagues in public health and pharmacovigilance institutes in Finland, Sweden and Norway and the immunisation division in the European Centre for Disease Control for their assistance. The Steering committee wishes to acknowledge the support of Tara Kelly, Margaret Foley, Paula Flanagan, Kirsty Mackenzie, Lisa Domegan, Piaras O'Lorcain and Fiona Cloak in HPSC, Dr Martha McCann in Temple St Children's hospital, Dr Elaine Purcell In Mater Private Sleep Clinic and Dr David Webb in OLHC. Finally, the Steering committee wishes to thank all patients and their families who consented to participate in the study.,