Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment (SOMNIA): a Study to Assess the Risk of Narcolepsy Following Adjuvanted 2009 H1N1 Influenza Vaccines

Advisory Committee on Immunization Practices (ACIP) meeting

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On behalf of the SOMNIA team

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- 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 CDC.
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- These slides are adapted from previous presentations by Dr. Miriam Sturkenboom and Dr. Steve Black, with assistance from Dr. Daniel Wiebel and Dr. Frank DeStefano.

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Outline

- Background and rationale
- Incidence rate study
- Case-control study
- Conclusions

Background and rationale

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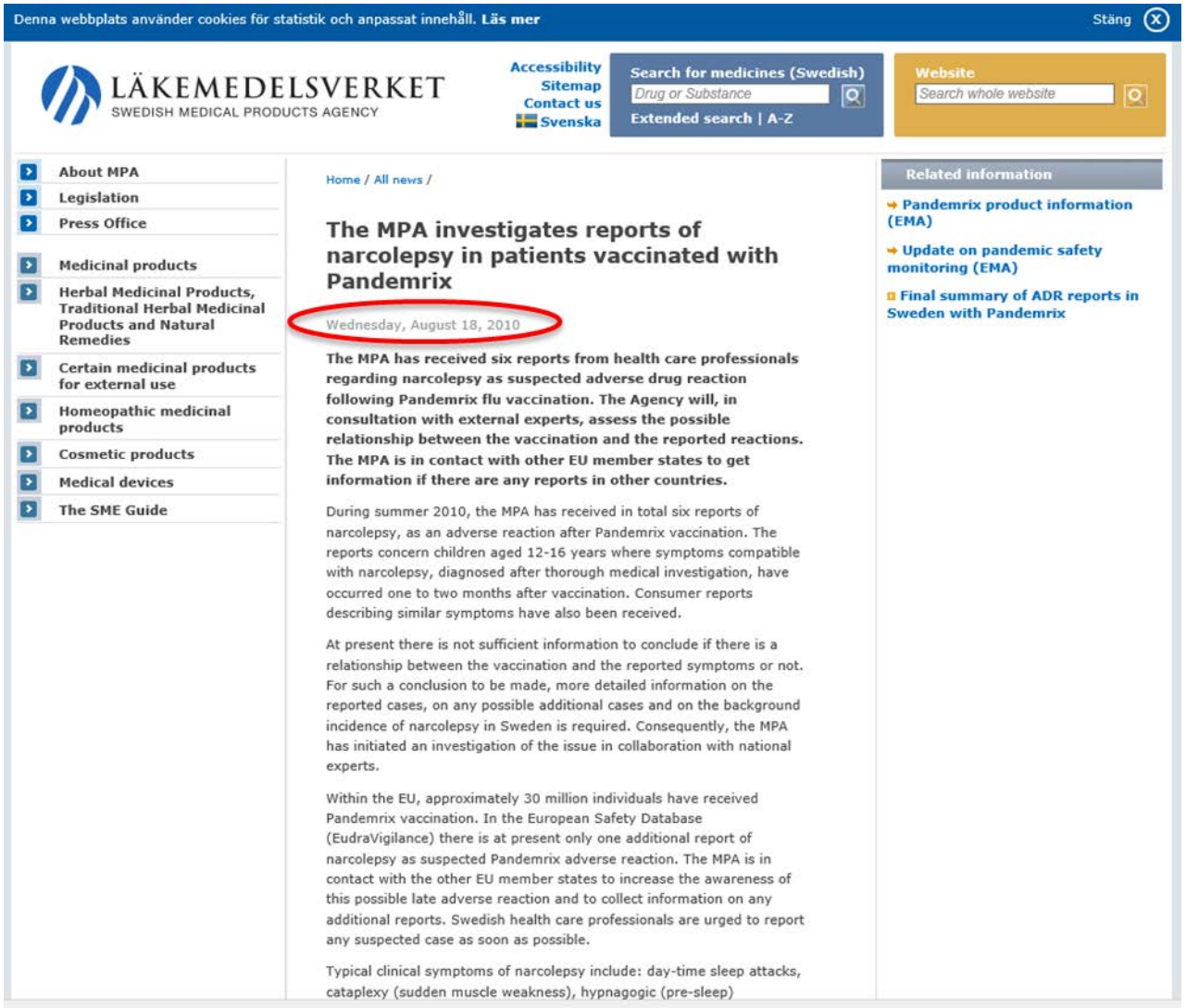

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The MPA investigates reports of narcolepsy in patients vaccinated with Pandemrix

Wednesday, August 18, 2010

The MPA has received six reports from health care professionals regarding narcolepsy as suspected adverse drug reaction following Pandemrix flu vaccination. The Agency will, in consultation with external experts, assess the possible relationship between the vaccination and the reported reactions. The MPA is in contact with other EU member states to get information if there are any reports in other countries.

During summer 2010, the MPA has received in total six reports of narcolepsy, as an adverse reaction after Pandemrix vaccination. The reports concern children aged 12-16 years where symptoms compatible with narcolepsy, diagnosed after thorough medical investigation, have occurred one to two months after vaccination. Consumer reports describing similar symptoms have also been received.

At present there is not sufficient information to conclude if there is a relationship between the vaccination and the reported symptoms or not. For such a conclusion to be made, more detailed information on the reported cases, on any possible additional cases and on the background incidence of narcolepsy in Sweden is required. Consequently, the MPA has initiated an investigation of the issue in collaboration with national experts.

Within the EU, approximately 30 million individuals have received Pandemrix vaccination. In the European Safety Database (EudraVigilance) there is at present only one additional report of narcolepsy as suspected Pandemrix adverse reaction. The MPA is in contact with the other EU member states to increase the awareness of this possible late adverse reaction and to collect information on any additional reports. Swedish health care professionals are urged to report any suspected case as soon as possible.

Typical clinical symptoms of narcolepsy include: day-time sleep attacks, cataplexy (sudden muscle weakness), hypnagogic (pre-sleep)

Related information

- Pandemrix product information (EMA)
- Update on pandemic safety monitoring (EMA)
- Final summary of ADR reports in Sweden with Pandemrix

Pandemrix is a monovalent AS03-adjuvanted influenza A (H1N1) vaccine manufactured by GSK that was used widely in Europe during the 2009 H1N1 influenza pandemic

Narcolepsy

- Central nervous system disorder characterized by excessive daytime sleepiness (EDS) and abnormal manifestations of rapid eye movement (REM) sleep
  - Sleep attacks, disrupted nocturnal sleep, sleep paralysis, hypnagogic hallucinations, cataplexy
  - Chronic disease, treated with medication and behavior modification, no cure
- Two diagnostic entities
  - Narcolepsy with cataplexy, narcolepsy without cataplexy
- Brighton Collaboration case definition exists*
  - Primarily based on presence of symptoms and an abnormal multiple sleep latency test (MSLT) characteristic of narcolepsy

* Poli et al. Narcolepsy as an adverse event following immunization: case definition and guidelines for data collection, analysis and presentation. Vaccine. 2013;31(6):994-1007.

Narcolepsy pathogenesis

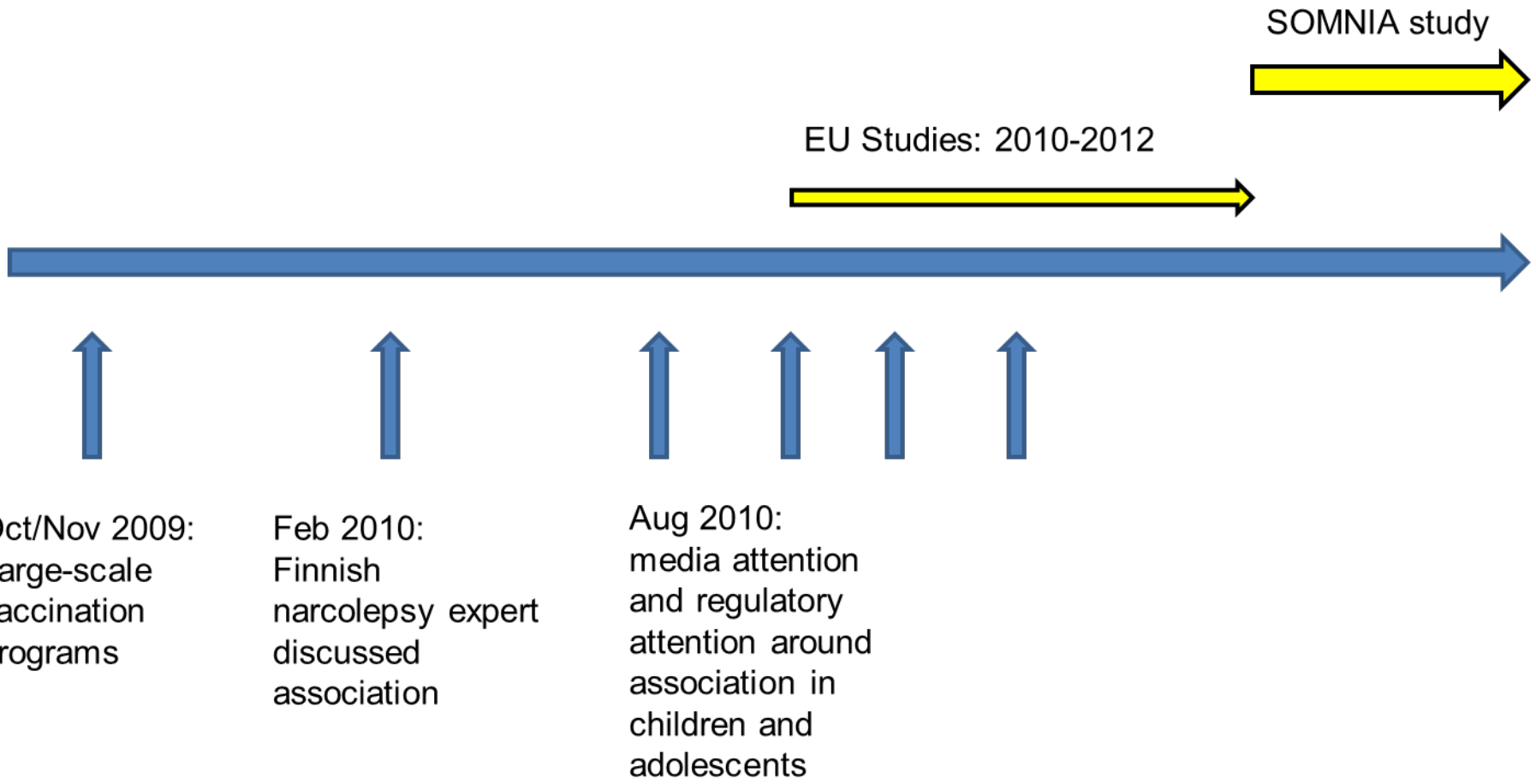
- Narcolepsy with cataplexy thought to be caused by damage to hypocretin secreting neurons in the hypothalamus
- Strongly associated with the HLA DQB1*0602 allele
  - Present in 5%-38% of people
- Thought to be autoimmune and a multi-event process
- Suspected infectious triggers include
  - Febrile illness
  - Influenza infections
  - β-hemolytic streptococcal infections

Narcolepsy epidemiology*

- Onset can occur at any age, but peaks during teenage years
  - Very rare under age 5 years old
  - Rare after age 40 years old
- Prevalence estimates vary widely
  - Israel: 0.23 per 100,000
  - United States: 30-56 per 100,000
  - Japan: 160 per 100,000
- There is often a long delay from symptom onset to diagnosis (can be many years)

* Silber et al. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep 2002;25:197-202; Longstreth et al. Prevalence of narcolepsy in King County, Washington, USA. Sleep Med 2009;10:422-426; Partinen et al. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. Lancet neurology 2014;13:600-613

Pandemrix*-narcolepsy timeline



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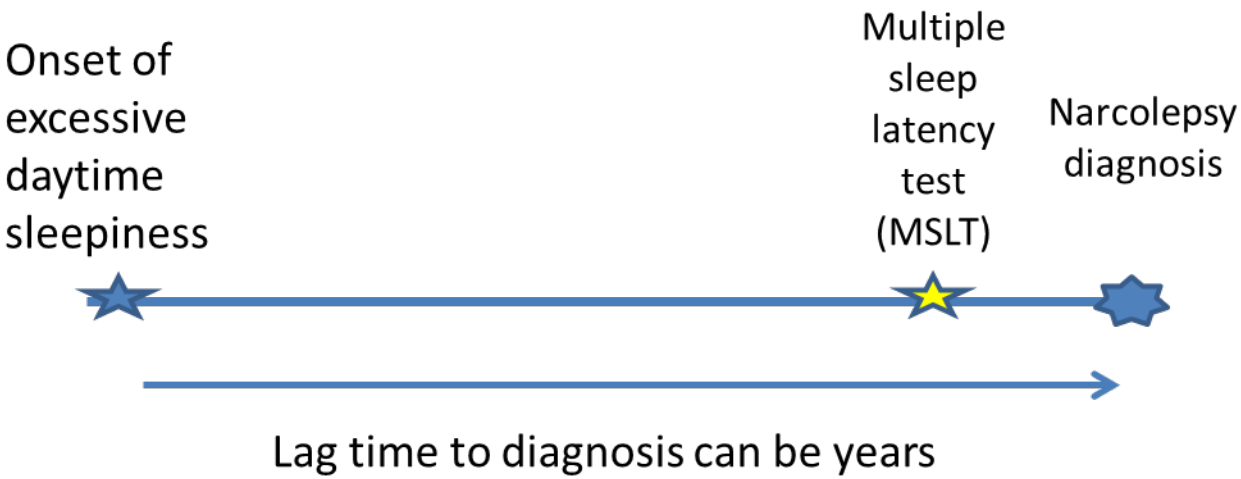
Potential impact of awareness



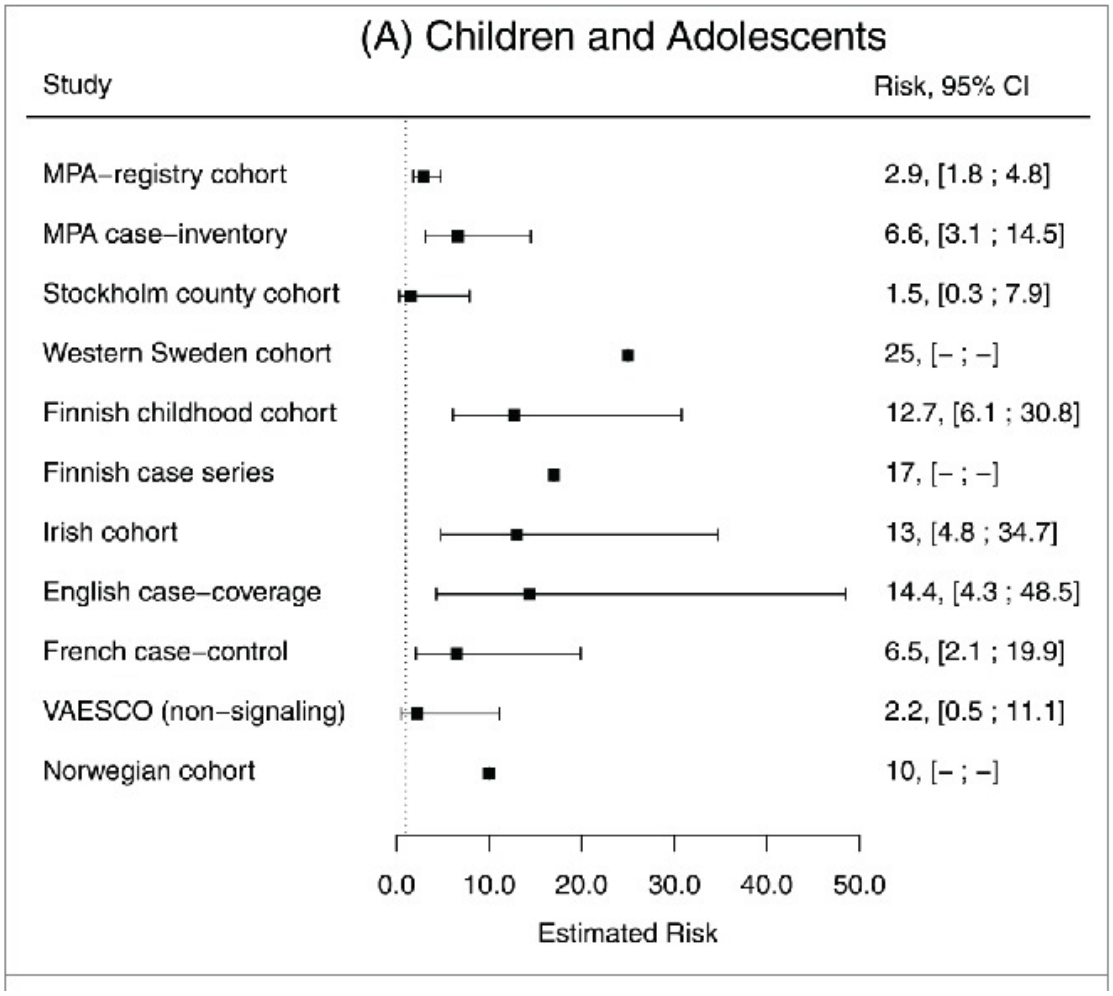
What will happen upon awareness (media, public, provider)?

In the case of Pandemrix and narcolepsy, the impact of the change in lag time among vaccinated cases appears most prominent early after the signal, and may subside later

Wijnans et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. Vaccine. 2013 Feb 6;31(8):1246-54.

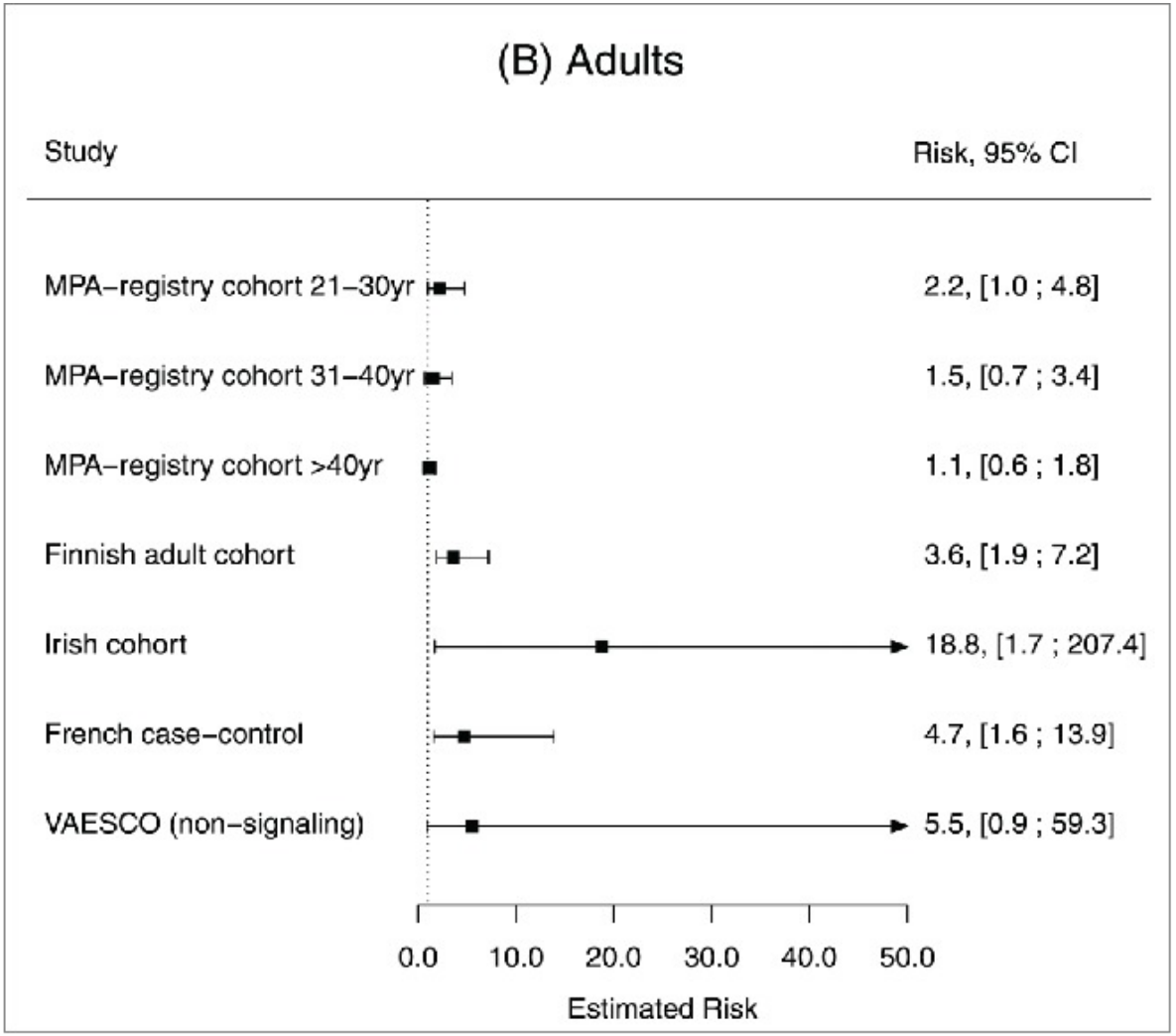
Summary of data on Pandemrix and narcolepsy in children*

Figure 1.



*Verstraeten T et al. Pandemrix™ and narcolepsy: A critical appraisal of the observational studies. Hum Vaccin Immunother. 2016;12(1):187-93.

Summary of data on Pandemrix and narcolepsy in adults*



*Verstraeten T et al. Pandemrix™ and narcolepsy: A critical appraisal of the observational studies. Hum Vaccin Immunother. 2016;12(1):187-93.

Where we were prior to the SOMNIA study with our understanding of Pandemrix and narcolepsy

- Many studies in Europe, some with variable results within the study
  - Limited power to produce definitive results
- Media and regulatory awareness might have impacted diagnosis patterns in European countries
  - Challenging to control or account for because of the short time period between vaccination and awareness
- No clear biologic mechanism to explain findings

CDC-sponsored SOMNIA study

Rationale:

- Inform pandemic preparedness for influenza vaccines
- Further evaluate AS03-adjuvanted pH1N1 vaccines
- Address the lack of data on MF59-adjuvanted pH1N1 vaccines

Scope:

- Assess the risk of narcolepsy following both AS03- and MF59-adjuvanted monovalent 2009 pH1N1 vaccines

Objectives:

- To evaluate any trends in incidence rates over time of narcolepsy diagnoses
- To evaluate a possible association between vaccination, infections and narcolepsy

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Incidence rate study

Incidence rate study sites

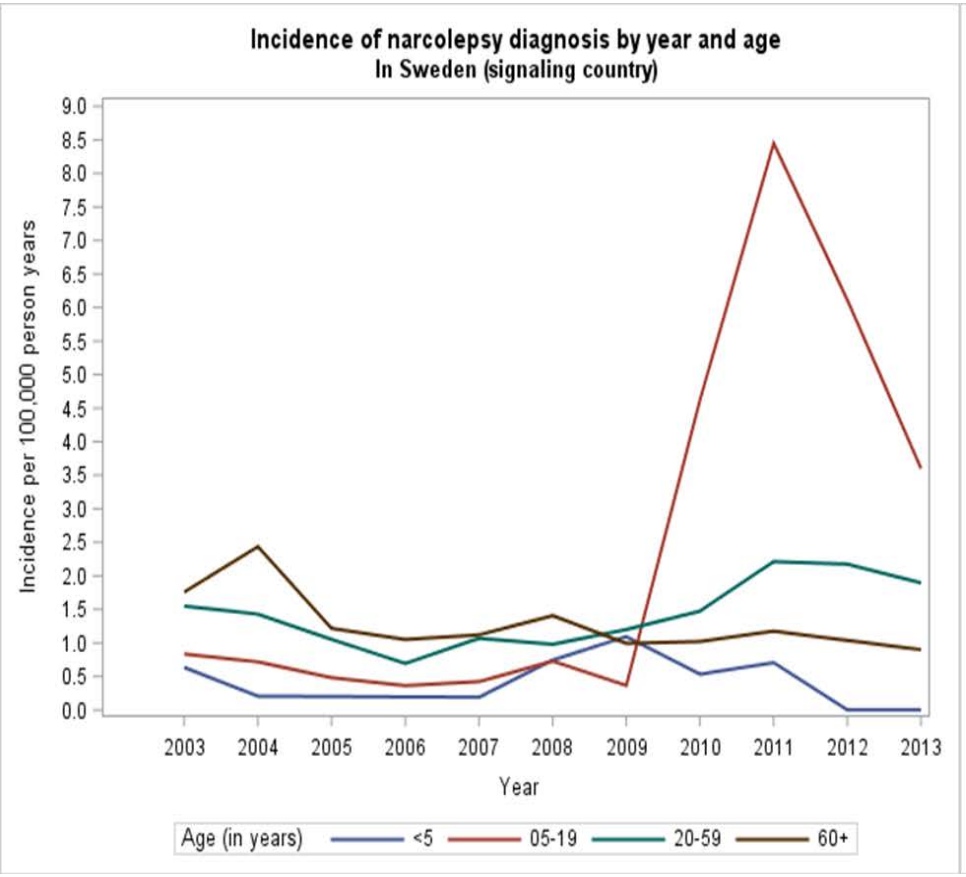
Country/Province	Adjuvanted pH1N1 vaccine used
Canada	
Manitoba	Arepanrix (AS03)*
Alberta	Arepanrix (AS03)
British Columbia	Arepanrix (AS03)
Denmark	Pandemrix (AS03)
The Netherlands	Pandemrix (AS03), Focetria (MF59)
Spain	
Valencia	Focetria (MF59), Pandemrix (AS03)
Catalonia	Focetria (MF59), Pandemrix (AS03)
Sweden	Pandemrix (AS03)
Taiwan	Focetria (MF59)
United Kingdom	Pandemrix (AS03)

*Arepanrix is a monovalent AS03-adjuvanted influenza A (H1N1) vaccine manufactured by GSK/ID Biomedical Corp. in Canada and was used in Canada during the 2009 H1N1 influenza pandemic

Dynamic retrospective cohort study

Element	Feature
Periods	• Before the H1N1 pandemic • During the H1N1 pandemic but pre-vaccination • During/post-H1N1 pandemic and pH1N1 vaccination
Population	• 10 databases in 7 countries (540 million person years)
Data source	• Electronic healthcare databases (General Practitioner [GP], claims)
Validation	1. Positive predictive value for the period of case control study 2. All cases in the database (Netherlands, FISABIO)
Analysis	• By country, by age group, by period • Join point analysis, IRR between periods
Level of detail	• Differences in the level of granularity that could be submitted for privacy reasons

Incidence rates: Sweden vs. other countries



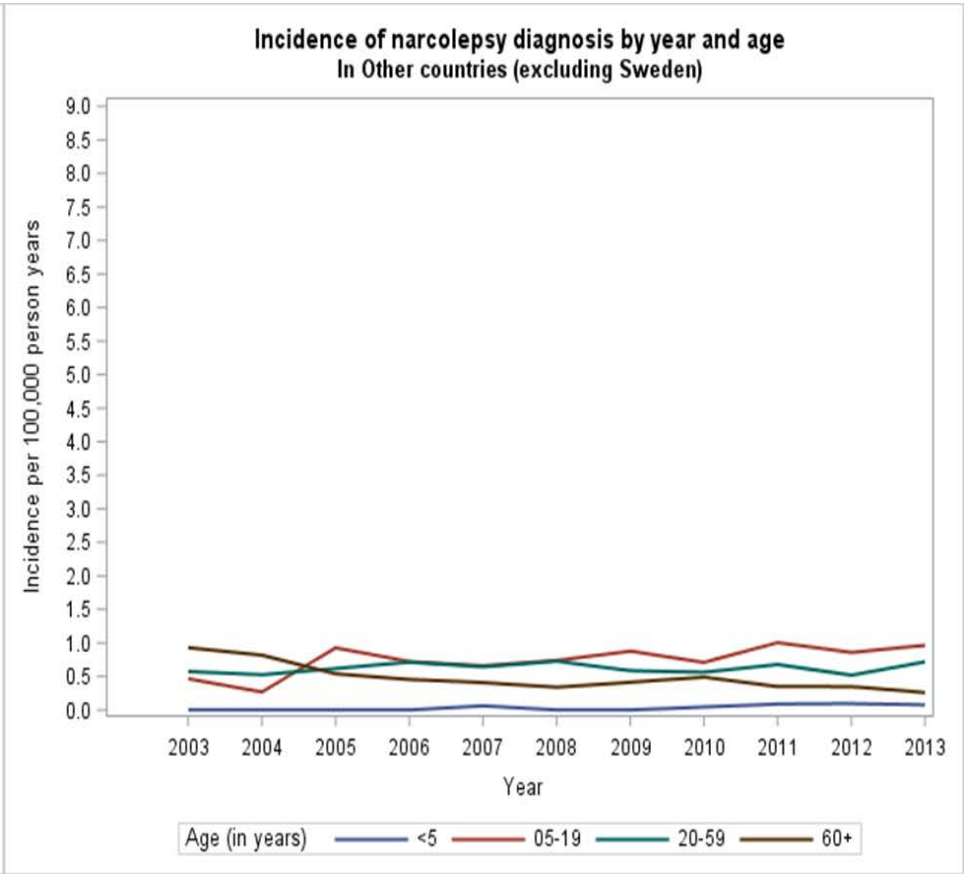
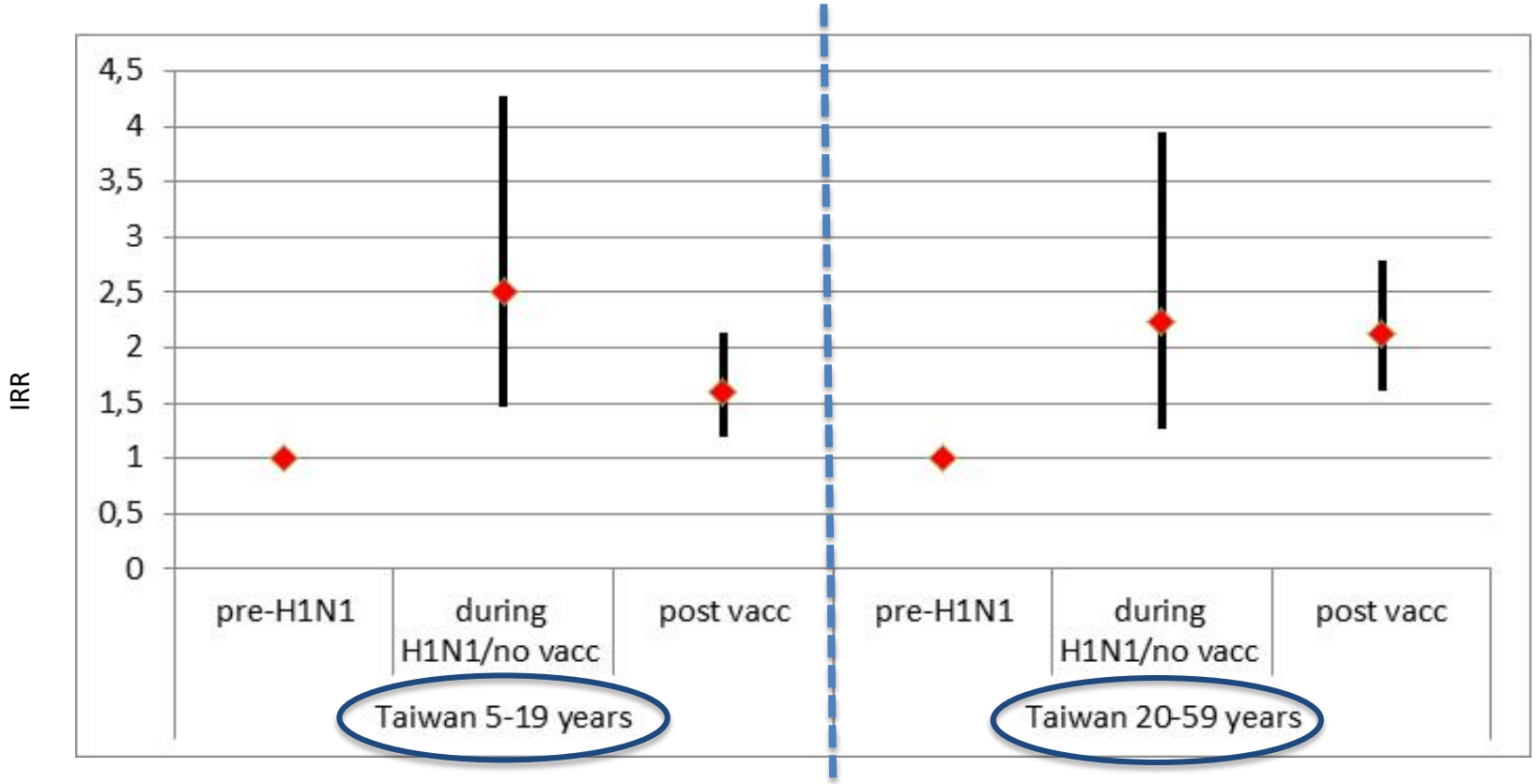


Figure adapted from: Dodd CN et al. PlosOne (submitted)

- No change in incidence rates over time in any of the countries or age groups beyond Sweden post-vaccination and in Taiwan during circulation of wild-type pH1N1 virus

Taiwan incidence rates over time



- Incidence rate increased during pH1N1 wild-type virus circulation before vaccination and went down after vaccination (mostly non-adjuvanted vaccine)
- Taiwan had a short diagnosis lag time (2 months between onset of excessive daytime sleepiness and narcolepsy diagnosis)

Case-control study

Case-control study sites

Country/Province	Adjuvanted pH1N1 vaccine used
Argentina	Focetria (MF59)
Canada Ontario	 Arepanrix (AS03)
The Netherlands*	Pandemrix (AS03), Focetria (MF59)
Spain Valencia Catalonia	 Focetria (MF59), Pandemrix (AS03) Focetria (MF59), Pandemrix (AS03)
Switzerland	Pandemrix (AS03), Focetria (MF59)
Taiwan	Focetria (MF59)

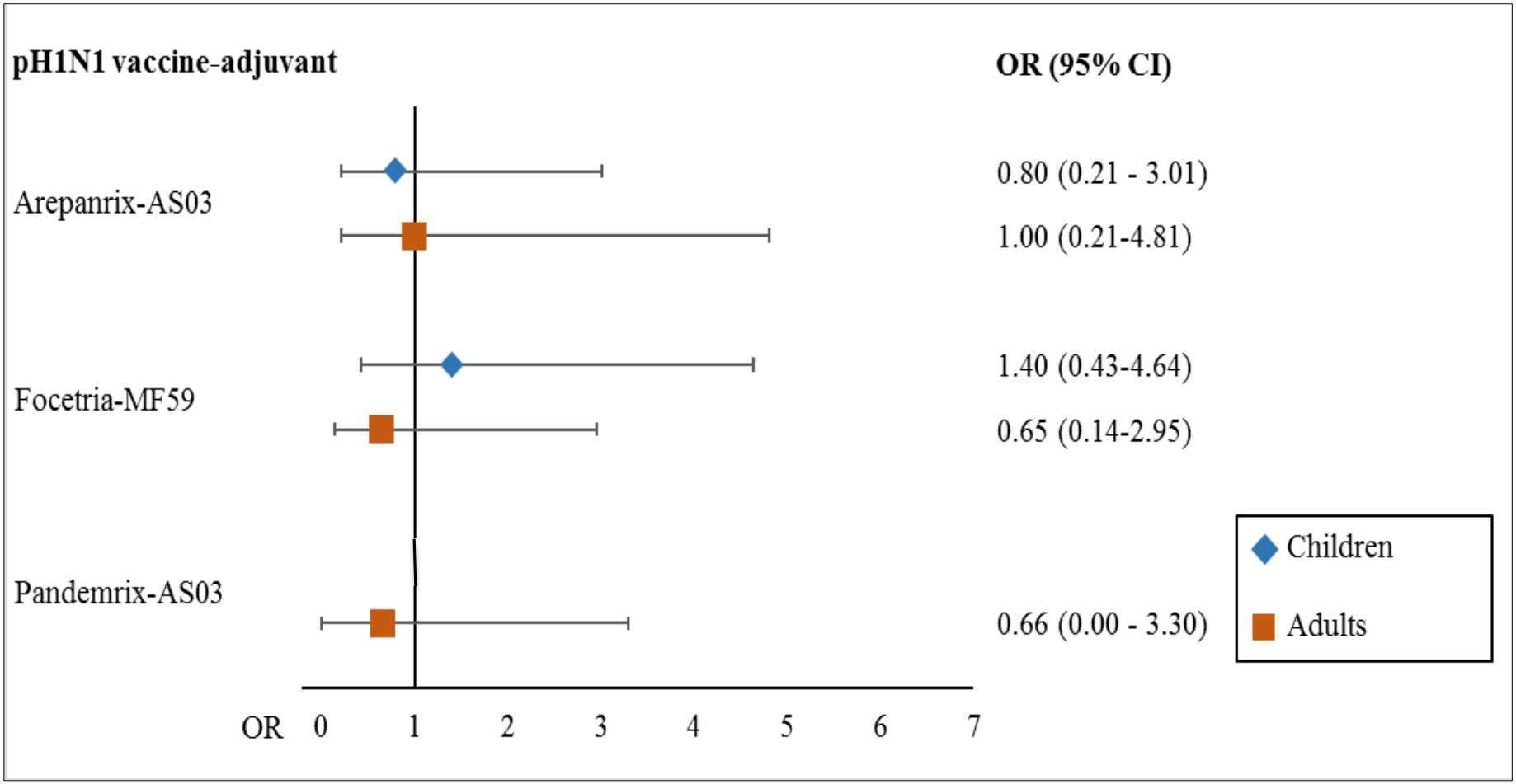
*In the Netherlands, cases born from 2004 through 2009 were analyzed using a case-coverage design in a post-hoc off protocol analysis.

Retrospective case-control study*

Element	Feature
Index date	• Primary: Multiple sleep latency test (MSLT) referral • Secondary: Excessive daytime sleepiness (EDS) or cataplexy onset
Case definition	• Children ≤18 years: Brighton Classification levels 1-2 • Adults ≥19 years: Brighton Classification levels 1-4
Case finding	• Primarily through sleep centers
Case ascertainment	• Blinded review locally
Exposure	• AS03-adjuvanted, MF59-adjuvanted, other H1N109pdm and seasonal influenza vaccines, HPV vaccine
Covariates	• Infections, comorbidities
Analyses	• By country, by vaccine, pooled, restricted period (April 1, 2009 through July 31, 2010) and total period (April 1, 2009 through end of 2015) analyses
Other data	• Virus circulation

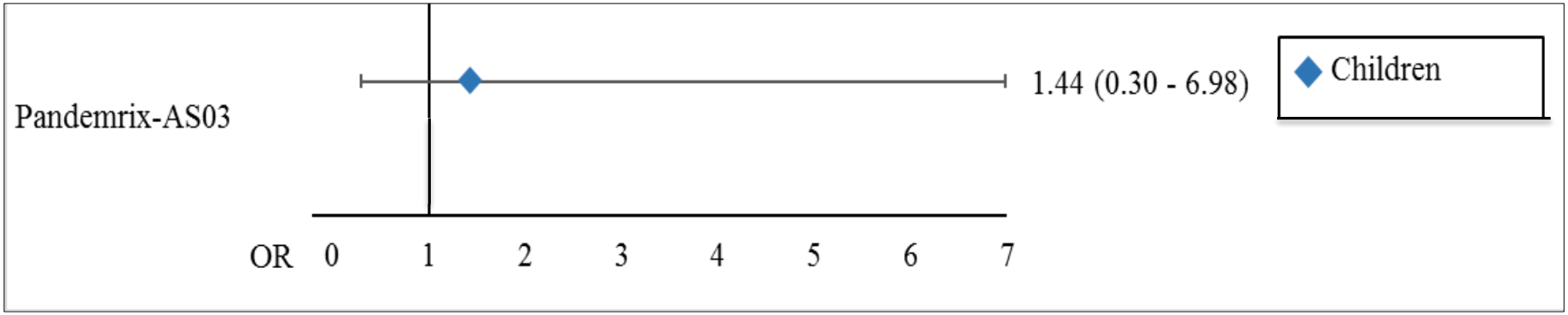
*In the Netherlands, cases born from 2004 through 2009 were analyzed using a case-coverage design in a post-hoc off protocol analysis.

Case-control total period analysis



- 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-control study in Valencia, Spain

Case-coverage total period analysis



- In the Netherlands, cases born from 2004 through 2009 were analyzed using a case-coverage design
  - Pandemrix exposure in cases was obtained through a national database
  - Exposure prevalence was then obtained in the population for children born in the same year by calendar week and year of birth
- The case-coverage analysis was a post-hoc, off protocol analysis in children in the Netherlands
- The design allowed investigators to include information from the Netherlands, where individual exposure data was not available

Conclusions

- Incidence rate study data did not show a rise in the rate of narcolepsy following vaccination except in the one signaling country included (Sweden, which used Pandemrix)
- Case-control analyses for AS03-adjuvanted pH1N1 vaccines (Arepanrix and Pandemrix) did not show evidence of an increased risk of narcolepsy, though data were limited for Pandemrix
- Case-coverage analysis for Pandemrix in children in the Netherlands did not show evidence of an increased risk of narcolepsy, but the number of exposed cases was small (N=7)
- Cases-control analysis for MF59-adjuvanted vaccine (Focetria) did not show evidence of an increased risk of narcolepsy

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- Taiwan: Wan-Ting Huang, Wei-Ju Su, Yu-Shu Huang
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