TECHNICAL REPORT

Narcolepsy in association with pandemic influenza vaccination

A multi-country European epidemiological investigation

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Three country-specific comments and disclaimers from Finland, France and Norway are available in annex 1.

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Contents

Abbreviations

ABC tool	Automatic Brighton Classification tool
BC	Brighton Collaboration
CHMP	Committee for Medicinal Products for Human Use at EMA
CI	Confidence interval
CRF	Case report form
CSF	Cerebrospinal fluid
EBV	Epstein-Barr virus
ECDC	European Centre for Disease Prevention and Control
EDS	Excessive daytime sleepiness
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EU-NN	European Union Narcolepsy Network
GBS	Guillain-Barré Syndrome
GP	General Practitioner
GPRD	General Practice Research Database (UK)
GWA	Genome-wide association
HLA	Human Leukocyte Antigen
HPV	Human papilloma virus
ILI	Influenza-like illness
ICPC	International classification of primary care
IPCI	Integrated primary care information database, the Netherlands
IR	Incidence rate
MPA	Medical Products Agency (Sweden)
MSLT	Multiple sleep latency test
OR	Odds ratio
PhWP	Pharmacovigilance Working Party at EMA
PPV	Positive predictive values
PY	Person-years
REM	Rapid eye movement
RTS	Referral to specialist
SAGE	Strategic Advisory Group of Experts on Immunization
SAS	Statistical analysis system software
SPSS	Statistical product and service solutions software
THL	National Institute for Health and Welfare (Finland)
UMLS	Unified medical language system
URI	Upper respiratory infections
VAESCO	Vaccine Adverse Event Surveillance and Communication
VENICE	Vaccine European New Integrated Collaboration Effort
WHO	World Health Organization

Executive summary

Narcolepsy is an underdiagnosed disease of widely unknown etiology. This report summarises the results from two epidemiological studies conducted by the Vaccine Adverse Event Surveillance and Communication (VAESCO) Consortium undertaken in eight European Union (EU)/European Economic Area (EEA) countries in order to investigate a possible association between an unexpected increase in narcolepsy cases following the use of influenza A(H1N1)pdm09 vaccines. The VAESCO studies on narcolepsy include Sweden and Finland, which originally reported the safety signal (the signalling countries). Apart from Sweden and Finland, the studies include the following six EU/EEA Member States: Denmark, Italy, France, the Netherlands, Norway and the United Kingdom (UK). These six countries are hereafter referred to as non-signalling countries when they are being referred to collectively.

Background

Spontaneous case reports

Cases of narcolepsy occurring in children and adolescents following vaccination with Pandemrix were reported in August 2010 by Sweden and Finland. As requested by the Pharmacovigilance Working Party, spontaneous reports were solicited nationally in EU Member States and were reported to the EU EudraVigilance system maintained by the European Medicines Agency (EMA). In Finland, the appearance of the cases were also reported to European authorities and the World Health Organization (WHO) via the Early Warning and Response System. Later in 2010 several other EU countries reported narcolepsy cases following vaccination to the EudraVigilance database. The VAESCO Consortium was already proactively undertaking surveillance for a series of twelve conditions (anaphylaxis, encephalitis, Gullain-Barré Syndrome (GBS), Bell's palsy, neuritis, convulsions, vasculitis, demyelinization, transverse myelitis, autoimmune hepatitis, thrombocytopenia, and sudden death) that were identified as events of special interest related to influenza A(H1N1)pdm09 vaccines by regulatory and health authorities. The surveillance consisted of background incidence estimates and two specific epidemiological studies using case control and self-control case series analyses concerning possible associations between GBS and influenza A(H1N1)pdm09 vaccines. Following the reports by Sweden and Finland it was decided to also investigate the signal of narcolepsy. A majority of the cases reported to EudraVigilance were in children and adolescents aged 5–19 years old. Cases in vaccinated younger children and adults were reported to a lesser extent. New cases are still being reported to the EudraVigilance system in 2012, some with first symptoms of excessive daytime sleepiness (EDS) dated during 2010. The majority of the narcolepsy reports submitted to EudraVigilance came from VAESCO countries.

Pandemic vaccines used in Europe 2009–10

Eight influenza A(H1N1)pdm09 vaccines [Cantgrip (Cantacuzino), Celvapan (Baxter), Celltura (Novartis), Fluval P (Omnivest), Focetria (Novartis), Pandemrix (GSK), Panenza (Sanofi Pasteur) and PanvaxH1N1 (CSL)] were licensed within the EU/EEA area during the 2009 pandemic. International recommendations on which groups should be offered vaccination and in what order, came from the Strategic Advisory Group of Experts (SAGE) Committee of the WHO and the EU Health Security Committee, though there were then national decisions on priority groups taking this guidance into account. Pandemrix was the most used vaccine in Europe. Based on national reports the EMA estimated that as of 8 August 2010, at least 38.6 million people in EU/EEA countries had been vaccinated: >30.5 million with Pandemrix, >560,000 with Celvapan and >6.5 million with Focetria. When the information available for the nationally authorised vaccines was included, the total rose to at least 46.2 million people. The monovalent influenza A(H1N1)pdm09 vaccines were hardly used after the new seasonal trivalent influenza vaccines became available in the summer and autumn of 2010. However, when shortages of seasonal influenza vaccine occurred in at least three EU Member States (Ireland, Portugal and the UK), left-over Pandemrix was used on a small scale in the autumn and winter of 2010. Young people however, in the age groups where narcolepsy cases occurred were generally not offered the vaccine.

The following VAESCO Member States offered Pandemrix only: Finland, Sweden, Norway, and Denmark. Italy offered only Focetria. The UK offered mainly Pandemrix, but Celvapan was also available in limited quantities. In other countries a variety of combinations were offered: e.g. the Netherlands offered Focetria (to patients at risk for influenza complications) and Pandemrix (to children below six years of age and the family members of infants). France offered Pandemrix, Focetria, Celvapan and Panenza to selected groups. Three VAESCO EU Member States (Finland, Norway and Sweden) recommended vaccines to their entire populations while other Member States recommended vaccines only to selected risk groups, notably individuals with chronic disorders. The three countries, Finland, Sweden and Norway offered school children and adolescents influenza A(H1N1)pdm09 vaccine through their school health system, explaining why high coverage rates were obtained in these age groups. Vaccine supply was initially limited, requiring sequencing of roll-out of vaccines. In some countries children and adolescents were offered the vaccine early as they were identified as being particularly associated with disease transmission.

The condition of narcolepsy

Narcolepsy is a rare chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally. The primary symptom is excessive daytime sleepiness (EDS). There are various theories as to its cause including auto-immune phenomenon, and there is a strong genetic predisposition with a specific common HLA type known as DQB1*0602 associated with most cases. Iatrogenic cases have not been cited before as a cause to any extent although infections as risk factor have been proposed, including influenza. The incidence of new cases has been estimated at around 0.74–1.37 per 100 000 person-years (PY) depending on the way the condition is defined. However, since narcolepsy is a chronic condition, the prevalence of individuals in the population is considerably higher. Narcolepsy is thought to affect men and women equally. However, a male predominance has been found in some studies. Previously narcolepsy has only been rarely reported for children (under age 16 years). The first symptoms typically develop in adolescence or early adulthood and the majority of cases are diagnosed in early adulthood, some however are diagnosed very late. The disease may take years to develop or may be more acute (within weeks).

The usual presenting feature of narcolepsy is repetitive episodes of profound sleepiness that may occur daytime both at rest and during periods of activity (eg. talking or eating). Sleep attacks may be very brief (microsleeps) resulting in lapses in attention and in mood disturbances (patients may be initially misdiagnosed with for example attention deficit hyperactivity disorder or depression). In addition, symptoms such as cataplexy (sudden onset of short episodes of muscle tone loss), sleep paralysis (people experiencing temporary paralysis on falling asleep or awakening), and hypnagogic hallucinations (hallucinations that occur at the point of falling asleep) may occur. EDS is not specific for narcolepsy, since it may occur in other sleep disorders, but the presence of cataplexy is specific for narcolepsy. To facilitate epidemiological investigations, a case definition was developed by the Consortium in collaboration with European narcolepsy experts (Brighton level 1–3 with level 1 being most certain, see section 6.1.2).

Narcolepsy can be diagnosed by a combination of laboratory tests. A nocturnal sleep study test determines whether lowered sleep efficiency with frequent stage shifts and arousals is present. A multiple sleep latency test (MSLT) is used to identify short sleep latency during day time. Determining cerebrospinal fluid levels of hypocretin is a relatively new diagnostic tool and identification of reduced levels has great value for the diagnosis. Available treatments are only symptomatic. Options include non-pharmacologic therapy such as sleep hygiene (promoting regular sleep patterns) and psychosocial support. Pharmacologic therapy may help and includes central nervous system stimulant drugs such as modafinil, methylphenidate and amphetamines, or tricyclic antidepressants as a first line treatment for cataplexy. All these drugs may be associated with possible serious side effects.

Study objectives

The study objectives were to investigate a possible association between infections, vaccination and narcolepsy through assessing:

- background and subsequent incidence rates of narcolepsy diagnoses by age and time
- any change in narcolepsy incidence rates after April 2009 (i.e. the beginning of the 2009 influenza A(H1N1) pandemic in Europe) and after October 2009 (i.e. the beginning of immunisations in Europe), to assess the effect of the vaccine safety signal on a population level.
- the potential association between risk factors including influenza, other infections, vaccinations (notably the influenza A(H1N1)pdm09 vaccine) and narcolepsy.

Study methods

The VAESCO studies on narcolepsy applied a tested harmonised multinational approach based on a standardised infrastructure for applying common study protocols in a distributed fashion for both the incidence rate and case control studies.

Background and subsequent incidence rates

Eight different linked large healthcare databases from seven countries were used (Denmark, Finland, Italy, the Netherlands, Norway, Sweden, and the United Kingdom). Mapping of disease codes for identification of narcolepsy cases was performed based on the Unified Medical Language System (UMLS). All sites used common data input files (events and population) and employed Jerboa software, a study tailored Java-based script for standardised data elaboration and de-identification. Further analysis and pooling of shared anonomysed aggregate data was conducted centrally at the Erasmus University Medical Center. Unlike for the case control study cases in the background and incident rates study which were validated by narcolepsy experts based on medical charts in only one country (the Netherlands).

Case control study

In the case control study, eight countries participated (Denmark, Finland, Italy, the Netherlands, Norway, Sweden, and the United Kingdom). Similar to the approach that had been applied to study the association between influenza A(H1N1)pdm09 vaccine and Guillain Barré Syndrome [1], a common protocol, common case report forms (CRFs), a common Brighton Collaboration case definition (allowing case validation) and automated case classification (ABC) tool, and detailed instructions for data collection was applied. To accommodate for differences in data collection, and to allow for quality control at the stage of data entry, the CRFs were transformed into an online data entry system called Chameleon. The data entry tool allowed for standardised data capture from field studies and transferred the data in the common input files that are required for Jerboa. Jerboa was further used to prepare the case control analytical datasets, which were completely de-identified data that could be shared centrally (across country borders) for further analysis. Three different datasets were generated by Jerboa, based on the selected three different index dates that were utilised in the analysis. In the primary analysis it was the referral to MSLT and in the sensitivity analyses it was the date of onset of EDS and the date of narcolepsy diagnosis (diagnosis date). In principle, the EDS onset date would be the preferred index date as it would be closer to the start of the disease than the MSLT referral date, and causal factors should occur and be measured prior to start of the disease. In the design phase it was decided not to use EDS as the primary index date since onset of disease is mostly insidious and thus accurate measurement (recall) is challenging, especially across multiple countries and in the presence of awareness of a potential association. Exposure to vaccinations and other risk factors was always assessed prior to the respective index date, when the index dates changed (EDS, MSLT or diagnosis date). Controls were selected from the underlying source population and matched to the cases on at least age, sex and index date (in some countries also on region), in different ways depending on available infrastructures. Implementation of the common protocol and data collection differed per country based on ethical requirements and the healthcare system structure, and was monitored closely. Analyses were conducted at the Erasmus University Medical Center, in collaboration with all study sites. Quality control was undertaken and queries were sent out to all centres. Each of the study sites received the data and had the opportunity to comment on the data prior to release or to formulate country specific comments. Three countries, Finland, France and Norway have taken the opportunity to formulate country specific comments and disclaimers, see annex 1.

Statistical analysis

To address as carefully as possible firstly, the influence of regulatory activities on active case finding and following media attention on identification of narcolepsy cases and secondly, potential biases towards identification of vaccinated cases, a sequence of sensitivity analyses addressing different index dates and study periods were selected. The protocol for the case control study, which was approved in 2010 by all partners, defined as the primary analysis is an approach that considered all cases and controls with a referral for MSLT data in the primary study period (between 1 April 2009 and 30 June 2010), and subsequently a series of sensitivity analyses to assess the impact of the design choices on the estimate of association between influenza A(H1N1)pdm09 vaccine and narcolepsy. The latter included variations of:

- the index dates (from date of MSLT referral backwards in time to date for onset of EDS or forward to the date of diagnosis)
- the study period (primary (April 2009– 30 June 2010)/secondary (April 2009-end of recruitment)/tertiary (April 2009– 28 February 2010)
- confounding controls (matched versus unmatched)
- subanalyses

To overcome limitations in statistical power, cases diagnosed after June 2010 could still enter the primary analysis if their index date (MSLT referral) fell between April 2009 and July 2010, and therefore the primary analysis was not completely devoid of potential regulatory/media attention effects that would affect the chance or speed of being diagnosed. To exclude any potential attention effect, sensitivity analyses were done to restrict cases to those with both the diagnosis as well as the index date (EDS or MSLT referral) in the primary study period. Sensitivity analyses were restricted to cases with diagnosis prior to the start of attention.

Study results

Key findings of the background and subsequent incidence rate study are:

Findings before the 2009 pandemic

- The pooled background incidence rate of diagnosed narcolepsy was low and stable at around 1 per 100 000 person years (PY) between 2000 and 2010 (0.85/100 000 PY prior to the vaccination campaign). These estimates are in line with published data. It was therefore assumed that the VAESCO sites had the ability to identify cases as they were diagnosed in respective populations.
- Incidence rates were age dependent with a peak between 15–30 years of age in women especially, and a smaller peak around 60 years of age. The incident rates in children <5 years and 5–19 years were low (0.12/100 000 PY and 0.56/100 000 PY, respectively)
- Background rates were comparable between the signalling and non-signalling countries prior to the start of the vaccination campaigns: 0.87 /100 000 PY and 0.83 /100 000 PY, respectively.

Findings after April 2009 (i.e. beginning of 2009 pandemic and before vaccination campaigns start)

- No increased incidence rate of narcolepsy was observed due to the 2009 pandemic itself.

Findings after September 2009 (i.e. beginning of immunisations in Europe)

- The overall incidence rates of narcolepsy differed significantly between the signalling and non-signalling countries after the start of the vaccination campaigns: 1.67/100 000 PY vs. 0.95/100 000 PY, respectively.
- In the signalling countries the following incidence rates were identified:
  - In Finland, an increase in the incidence rate of narcolepsy diagnoses after September 2009 was observed in children and adolescents 5–19 years of age with relative risk of 6.4 (95%CI 4.2-9.7).
  - In Sweden, an increase in the 5–19 year age group with a relative risk of 7.5 (95%CI 5.2–10.7) was also observed after September 2009.

  This is consistent with the initial signals reported in these countries for Pandemrix using descriptive and different analytic techniques.

- The pattern was different in the other five non-signalling study countries during the period for which data could be analysed. While in Denmark a small increase in the incidence rate of narcolepsy was also observed, the upward trend started earlier, prior to the start of the vaccination campaign (focusing on risk groups only) and in a different age group. In the Netherlands, no increase in incidence was seen in the influenza A(H1N1)pdm09 vaccine targeted age groups (children <6 years and adults ≥60 years). This was also the case in Italy and the UK. In all of these countries the vaccination coverage was low in the 5–19 year age group. In Norway, where prevalent and incident narcolepsy cases could not be well differentiated, since the database only captured data from 2008 and onwards and could not well identify previously diagnosed (prevalent) cases, no change in narcolepsy diagnosis/visit rates were seen until the end of 2010 in spite of high vaccination coverage with Pandemrix in this country. However, Norwegian data received later in the study show that Pandemrix exposed cases started to be reported in 2011.
- Background rates in the UK and the Netherlands were determined with population-based medical records, including specialist and General Practitioner (GP) records. Here, GPs receive information on diagnosis made by specialists. However, this may be delayed and could explain an observed reduction in the rates at the end of the study period in the UK.
- Validation of the events in the Netherlands not only reduced the incidence rates but also reversed an increased rate that was initially seen in the incidence rates in 2009/2010 for adults. Validation of the cases for the background rates was not done in the other countries. Thus, the effects of an undetected change in positive predictive values (PPV) over time in these countries on time trends of incidence rates could not be determined.

Key elements and findings of the case control study are:

- Case-validation was undertaken based on the ad hoc case definition developed by narcolepsy specialists of the European Narcolepsy Network together with vaccine safety specialists according to the Brighton Collaboration process.

Descriptives

- A total of 249 cases with verified narcolepsy were submitted (135 from non-signalling countries). A total of 152/249 cases entered the primary analysis (MSLT referral date during April 2009–30 June 2010) (signalling/non-signalling: 63/89). Of those 152 cases, 88 were children/adolescents (signalling/non-signalling: 44/44) and 64 adults (signalling/non-signalling: 19/45). The overall exposure prevalence to influenza A(H1N1)pdm09 vaccine for primary analysis was 59% in children/adolescents (signalling/non-signalling: 93% /25%) and 17% in adults (signalling/non-signalling: 26%/13%). For nine cases (4%), an MSLT referral date was missing and they were excluded from the primary analysis. Several additional cases in UK, Sweden and France, who had their MSLT referral date in the primary period were pending consent, review, matching to controls and/or data collection at the time of the data closure (December 2011).
- The overall mean age of the cases was 17 years for cases with MSLT referrals in the primary study period (range 4–63 years of age) and 15 years for cases with MSLT referrals from April 2009 till the end of recruitment (range 3–64 years of age). Mean age in the primary study period was 13.5 for Finland and 18.5 years for Sweden. In the non-signalling countries mean age was lowest in Norway (15.4 years) and highest in Denmark (33 years).
- The Brighton Collaboration case definition was applied in all countries, in signalling countries 70% of adults were classified as level 1–3, for the non-signalling countries this was 77%. In children/adolescents percentages of level 1–3 were 95% and 92% respectively in signalling and non-signalling countries.
- The prevalence of cataplexy among narcolepsy cases was equally high in exposed and non-exposed children/adolescents. The prevalence of cataplexy in children was high both in signalling and non-signalling countries (91% in signalling countries and 81.6% in non-signalling). In adults the prevalence of cataplexy was 63% in signalling countries and 66% in non-signalling.
- Clusters of MSLT referral dates were seen for exposed children in the signalling countries in January to February 2010 (Finland) and after July 2010 (Finland and Sweden), coinciding with the time that one of the Finnish paediatric neurologists first discussed a potential association with colleagues at a scientific conference (first peak), and the media attention following regulatory activities (second peak).
- Peaks in MSLT referral dates were not observed in children/adolescents nor adults in non-signalling countries.
- By protocol, all countries were asked to include all cases diagnosed until November 2010. For most countries, cases diagnosed after 2010 continued to be included. However, the data show that this was not done systematically. For example, no adult cases diagnosed after May 2011 were included, while paediatric cases diagnosed up to November 2011 were included, and these were primarily exposed children.
- The median time between EDS and diagnosis is shorter in exposed as compared to non-exposed cases (see figure 2). This difference in time leads to the inclusion of more exposed than non-exposed cases towards the end of the recruitment period, which is after August 2010. Since cases diagnosed after attention can enter in the analysis of the index date in the primary study period, attention related bias cannot be excluded.
- Difference in lag times between influenza A(H1N1)pdm09 vaccine exposed/non-exposed subjects, children/adolescents and adults, and differences in recruitment periods may render analyses based on the total recruitment period (secondary study period) susceptible to biases related to time factors.

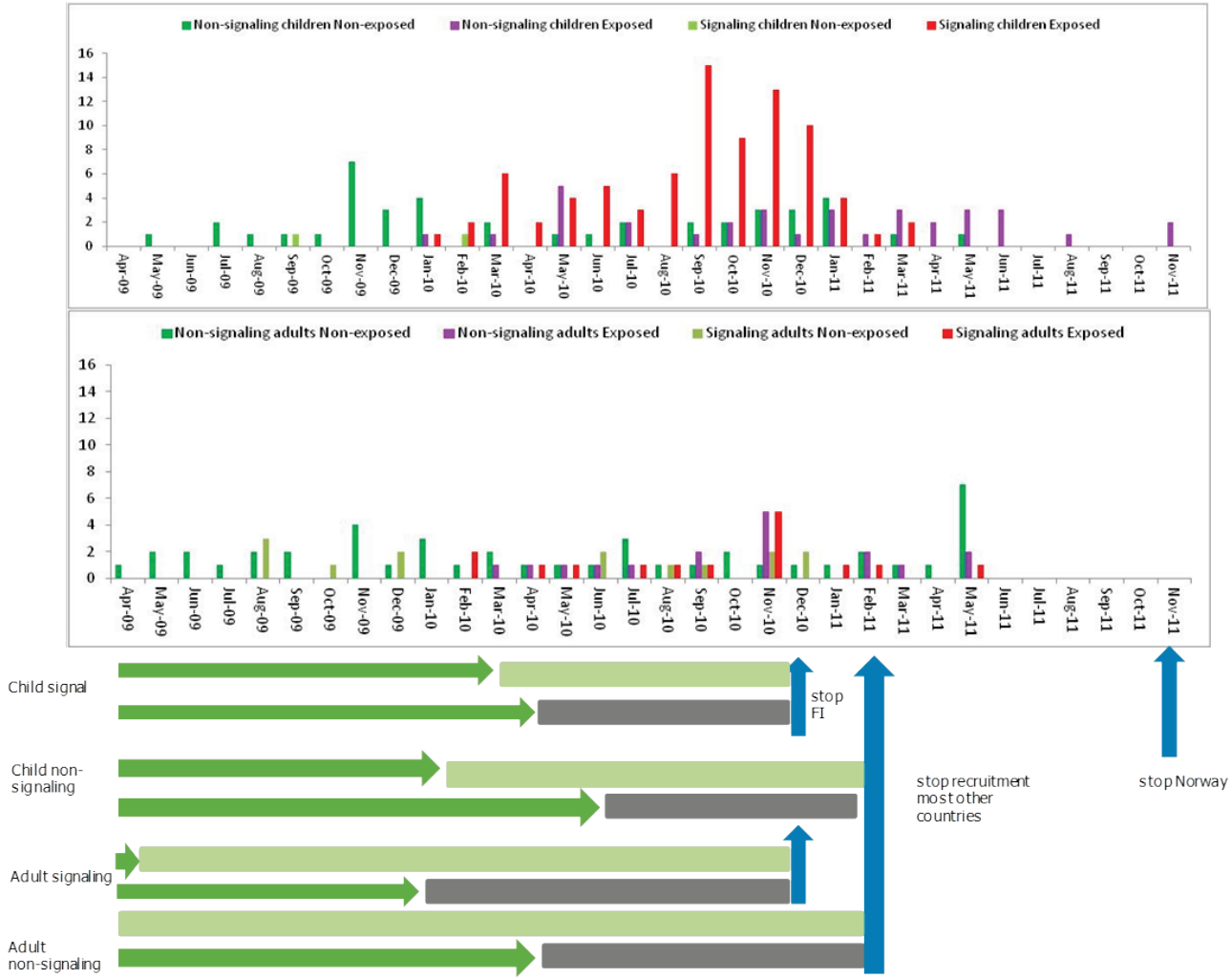
Exposure to influenza A(H1N1)pdm09 vaccination in narcolepsy cases

The number of exposed cases in the different study periods and using different index dates are shown directly below.

Table 1. Narcolepsy cases and odds of exposure status to influenza A(H1N1)pdm09 vaccination for the primary and sensitivity analyses

	Exposed	Non-exposed	Total
Signalling countries			
Primary period			
EDS as index date	73	12	85
MSLT referral as index date	46	17	63
Diagnosis as index date	24	10	34
Additional cases after primary period			
EDS as index date	4	0	4
MSLT referral as index date	48	3	51
Diagnosis as index date	74	6	80
Non-signalling countries			
Primary period			
EDS as index date	36	32	68
MSLT referral as index date	17	46	63
Diagnosis as index date	11	48	59
Additional cases after primary period			
EDS as index date	4	3	7
MSLT referral as index date	29	43	72
Diagnosis as index date	40	39	79

Figure 1.Recruitment over time based on month of diagnosis of children/adolescents (upper) and adults (lower histogram)



Arrow blocks: the light green and grey blocks shows the median lag time between EDS date and diagnosis in exposed (light green bars) and non-exposed (grey bars) subjects, showing the difference in time. The dark green arrows show until which point in time at least 50% of the cases that would have occurred start of the study period could have been included given the recruitment period and the lag time. The difference in length of the green arrows for exposed and non-exposed shows the potential for differential inclusion based on the fact that the lag times differed between exposed and non-exposed.

Primary analysis

Brand specific differences of influenza A(H1N1)pdm09 vaccines could not be assessed reliably due to very low exposure rates of other vaccines beyond Pandemrix in the main age groups where cases occurred.

Non-signalling countries

- One of the aims of the association study was to test the hypothesis generated in children and adolescents in the signalling countries. As hypotheses should generally not be tested in the same sample or population generating the signal, the non-signalling countries provide a useful source of information in Europe.
- In the pooled primary analysis of all ages in non-signalling countries (France, Italy, Netherlands, United Kingdom, Denmark, and Norway) influenza A(H1N1)pdm09 vaccination was not associated with a significant increase in the risk of narcolepsy following influenza A(H1N1)pdm09 vaccination (unadjusted OR=2.3 95%CI 0.9–6.3).
- There was no significant difference in the association measure between adults and children/adolescents in non-signalling countries (OR=3.7 for adults (95%CI 0.7–20.7) vs. 1.6 (95%CI 0.5–6.1) in children/adolescents). In France a significant increase in risk was observed in adults (RR=11.2 (95%CI 1.4-infinity), this is being further investigated, especially since adult cases were still being incorporated when the current data-set was established and a potential selection bias cannot be excluded with the current data. No other country reported a significant increased risk in adults although the estimates in the Netherlands, Denmark, and the UK were elevated but unstable however, and not statistically significant.
- None of the physician/patient reported infections (including 2009 pandemic infection, streptococcal infection, Epstein-Barr Virus (EBV) infection), no other vaccines [including seasonal influenza vaccines and human papilloma virus vaccines (HPV)] were significantly associated with narcolepsy and major confounders were not detected in the countries for which co-variates were provided (France, Italy, Netherlands, Norway, Sweden, the United Kingdom). Adjustment for co-variates showed an increase in risk for children/adolescents and a decrease of risk in adults. Asthma and influenza-like illness (ILI) as co-morbidity had the largest impact on the association estimate in the paediatric/adolescent cases. This was suggestive of children/adolescents not being given influenza A(H1N1)pdm09 vaccination due to co-variates such as respiratory tract infections.

Signalling countries

- No significant association with pandemic vaccination was observed in adults in the two signalling countries for the primary analysis (OR 1.2 (95%CI 0.2–9.1).
- In the signalling countries, a strong association (OR 14.2 (95%CI 2.5–infinity) was observed between Pandemrix vaccination and narcolepsy in children and adolescents. In Finland, the VAESCO case control study utilised the same cases, which were validated in an unblinded fashion for the previous national cohort study. In Sweden, the VAESCO study also followed the previous national studies, but case inclusion was done *de novo* for the VAESCO study for ethical committee requirement reasons. Blinded validation of cases was done. It was only possible to incorporate data from less than half of the potentially eligible cases in Sweden by the end of the VAESCO contractual period, and therefore a potential selection of cases cannot be excluded.
- The risk estimates in signalling countries seemed highest within 180 days following vaccination, however due to the short duration of the study period, the full hazard function cannot be observed.

Sensitivity analyses

Many sensitivity analyses were undertaken to investigate the robustness of the association between influenza A(H1N1)pdm09 vaccines and narcolepsy and the possible effects of design choices and time regarding the study period and index dates.

Secondary study period (all countries)

- The sensitivity analysis based on the secondary study period (April 2009–end of recruitment), which includes the period after the start of regulatory attention and subsequent media attention found that the odds ratio for the association between influenza A(H1N1)pdm09 vaccination and narcolepsy increased in all age groups and in both signalling/non-signalling countries compared to the primary study period.
- Although the increases in risk estimates followed the increase in regulatory/media attention and the direction was anticipated because of a potential regulator/media attention bias, this sensitivity analysis cannot prove nor reject a direct relation with the attention.
- One other contributing factor for the increase in the risk estimates is the selective inclusion of exposed subjects towards the end of the recruitment period because lag times between onset of disease/ MSLT referral and diagnosis were shorter in exposed children/adolescents after media attention. It could not be excluded that the period after the primary study period introduces bias because of these issues, which may synergize the potential effect of the regulatory/media attention on the diagnosis rate. Since the primary period is suffering less from these potential biases (although it still includes bias due to resetting of index dates that may enter in primary period whereas cases were diagnosed after regulatory/attention), it is recommended that data from the secondary period be interpreted with caution.

Tertiary study period (Finland)

- In Finland a tertiary study period was investigated, which lasted from April 2009 until February 2010 (point in time when discussion about potential association in children/adolescents started among neurologists). Restriction of cases to those with specialist referral dates in this period resulted in a substantial reduction of the association between influenza A(H1N1)pdm09 vaccination and narcolepsy in children (from 11 to 5.8), yielding a non-significant association (OR=5.8, 95%CI: 0.96–infinity).

Index date

- In the case-control study the EDS date was missing for 27 (10%) of the 249 cases that were included for the MSLT referral analysis. In 18 cases only the year of onset was provided (month and day were missing), and for 86 cases only the month and year were supplied. Only in Finland were all EDS dates supplied. In Sweden, Norway and France where interviews were performed, the EDS date was also missing or not precise for some of the cases. Retrospective assessment of the EDS date carries a potential risk for bias. This is particularly so when media attention has already spread the news about an association, evaluators were not blinded to exposure (Norway and Finland), or reimbursement is provided for exposed children with narcolepsy such as in Sweden and Finland.
- Sensitivity analyses on the EDS date, are not necessarily free of a potential regulatory/media bias, since many of the cases with EDS onset in the primary study period, were diagnosed after the start of attention.
- In the signalling countries, using the EDS date as index date resulted in some reduction of the odds ratio for the association between influenza A(H1N1)pdm09 vaccination and narcolepsy in children/adolescents from 14.2 (using the date for MSLT referral) to 11.4 though statistical significance was retained (95%CI 3.4–61).
- The increased risk for narcolepsy following influenza A(H1N1)pdm09 vaccination based on the EDS date was consistent for the non-signalling countries and when pooled became statistically significant (OR=4.6, 95%CI: 1.7–13.7). The only potential distorting effect that might contribute to a potential overestimation was the fact that cases with EDS onset in the primary period, could still be diagnosed after the start of regulatory/media attention and be affected by the changes in lag times between exposed and non-exposed.

Analyses restricted to cases diagnosed before professional/regulatory/media attention started

- The only analysis that would not suffer from the potential effects on shortening of diagnostic work up times due to professional/regulatory/media attention would be the analysis that includes only the cases diagnosed before the start of that attention. The problem is that because of the short period (Finland until March 2010, other countries until July 2010), the low incidence of disease and the lag time between EDS, MSLT referral and narcolepsy diagnosis, few cases remain for this analysis.
- Pooling the data from all countries (signalling and non-signalling) based on the cases diagnosed before the start of any attention left 70 cases (38 children/adolescents and 32 adults) and 437 controls for the MSLT analysis (MSLT referral in primary period) and 31 cases (23 children/adolescents and 8 adults) and 156 controls for the analysis on EDS date as index date during the primary study period.
- Based on these restrictions the data were pooled across signalling and non-signalling countries and showed a non-significant association between influenza A(H1N1)pdm09 vaccination and narcolepsy in children/adolescents (OR=3.3, 95%CI 0.6–24) using MSLT referral as index date, whereas the OR was 4.3 (95%CI 0.6–48) using EDS as index date. In adults an increased risk was observed but this was mainly driven by data from France where analyses to evaluate potential biases are still underway.
- For the future, the statistical power can be increased by a) pooling across all the studies performed in Europe (Swedish Medical Products Agency, Finnish National Institute for Health and Welfare, Irish Health Service Executive and Health Protection Surveillance Centre, UK Health Protection Agency), b) finalising case inclusion especially in France and Sweden where many cases could not be included until now but also elsewhere; c) extending the investigations beyond Europe where media attention was less pronounced.

Case validity

Restriction of the cases to those with cataplexy or Brighton Classification (BC) criteria levels 1–2 showed opposite effects on the strength of the association between signalling and non-signalling countries.

- Restriction to BC level 1–2 in the signalling countries resulted in little change of the OR from 14.2 in children/adolescents to 13.9 (95%CI 2.4–infinity), and from 1.2 to 4 (95%CI 0–26.2) in adults.
- In the non-signalling countries, the restriction to BC level 1–2 resulted in an increase of the OR from 1.6 to 1.9 (95%CI 0.5–8.0) in children/adolescents and decrease from 3.7 to 2.6 (95%CI 0.3–21.7) in adults.

Conclusions/considerations

This report summarises the results from the VAESCO contract study 'Narcolepsy in association with pandemic influenza vaccination' comprising an assessment of changes in incidence rates of narcolepsy after the start of the influenza A(H1N1)pdm09 vaccination campaigns and a formal hypothesis testing study to assess the narcolepsy safety signal.

Background and subsequent incidence rates of narcolepsy by age and time

- The pooled background incidence rate of diagnosed narcolepsy was low and stable at around 1 per 100 000 PY between 2000 and 2010 (0.85/100 000 PY prior to the vaccination campaigns).
- Lower background rates of diagnoses were observed among children: <5 years and 5–19 years (0.12/100 000 PY and 0.56/100 000 PY, respectively
- No increased incidence rate of narcolepsy was observed in temporal association with the 2009 pandemic itself.
- The overall incidence rates of narcolepsy differed substantially between the signalling and non-signalling countries after the start of the vaccination campaigns: 1.67/100 000 PY vs. 0.95/100 000 PY, respectively.
- In the signalling countries the following incidence rate patterns were identified:
  - In Finland, an increase in the incidence rate of narcolepsy diagnoses after September 2009 was observed in children and adolescents 5–19 years of age with a relative risk of 6.4 (95%CI 4.2-9.7).
  - In Sweden, a similar increase was also observed after September 2009 in the 5–19 year age group with a relative risk of 7.5 (95%CI 5.2–10.7).

The pattern was different in the other non-signalling five study countries during the period for which data could be analysed. While in Denmark a small increase in the incidence rate of narcolepsy was also observed, the upward trend started earlier, prior to the start of the vaccination campaign (focusing on risk groups only) and in a different age group. In the Netherlands, the UK and Italy no increase in incidence was seen, however vaccination coverage was low in all the non-signalling countries.

Associations of narcolepsy with risk factors including influenza, other infections, influenza A(H1N1)pdm09 vaccination and other vaccinations

- The primary analysis focusing on the primary study period before professional/regulatory and media attention in the signalling countries Finland and Sweden showed an association between pandemic influenza immunisation and narcolepsy in children and adolescents (5-19 years) but not in adults. This confirmed observations made with different methodologies in those countries in national studies.
- A similar association in the primary analysis was not found in the non-signalling countries.
- Sensitivity analyses highlight the importance of time-related factors for the strength of association. It should be noted that sensitivity analyses of different study periods and different index dates may contain a mixture of potential vaccine and/or regulatory and media attention effects.
- All epidemiologic studies investigating the association between the influenza A(H1N1)pdm09 vaccine and narcolepsy have the challenge to address a multitude of time-related biases, and results obtained beyond the primary study period should be interpreted cautiously.
- To increase statistical power for further association analyses on these observations, especially for cases diagnosed prior to regulatory/media attention the following possibilities should be considered:
  - pooling all data available across Europe (including data from studies when completed from the Swedish Medical Products Agency, Finnish National Institute for Health and Welfare, Irish Health Service Executive and Health Protection Surveillance Centre, and the UK Health Protection Agency)
  - finalising VAESCO study case inclusion especially in Finland, France, and Sweden where many cases could not be included at the time of completion of the contract and which is particularly important for this investigation
  - including further European countries with significant vaccine coverage such as Ireland
  - extending the investigations beyond Europe in countries where narcolepsy cases could be diagnosed and where media attention was less pronounced but where Pandemrix and other pandemic vaccines (including the adjuvanted Arepanrix) were offered for children.
- The observations are sufficiently strong and consistent for children in the signalling countries using different methodologies to warrant further investigations as to a possible mechanism. While it is the case that the vaccine concerned is one with a novel adjuvant there is a confounding factor in Europe in that this was the only vaccine offered for children in any volume in Europe. Hence it cannot be concluded that the adjuvant is the cause of the observation. Equally there is also the possibility that it is the combination of vaccination

and influenza transmission or another unrecognised infection or environmental factor in individuals with developing nervous systems. There will be a role also for animal models and mechanistic studies.

As of August 2012 more than 600 narcolepsy cases (including more than 100 in adults) have been reported spontaneously to the EMA EudraVigilance database following the influenza A(H1N1)pdm09 vaccination. Cases are still being reported in 2012 but in lower numbers compared to 2010–2011. Surprisingly, more than 500 of the cases originate from Member States being part of the current VAESCO project. Continued investigations are needed in the VAESCO countries as well as in other countries where influenza A(H1N1)pdm09 vaccines were used.

1 Background

The Vaccine Adverse Event Surveillance and Communication (VAESCO)[1] project has been carried out by a Consortium under the auspices of the European Centre for Disease Prevention and Control (ECDC). The long term aim of the work is to create an independent infrastructure and epidemiological resource in support of vaccine safety monitoring and investigation in Europe. Following the appreciation of the influenza A(H1N1) pandemic in the spring of 2009 the project was accelerated considerably by ECDC and Consortium members so as to be able to potentially detect and investigate what were considered to be the more likely adverse events following immunisation with the new pandemic vaccines as part of post-marketing surveillance[2]. In the summer of 2010 authorities in Sweden and Finland reported an unusual number of cases of narcolepsy in children in association with use of the pandemic vaccine Pandemrix. Hence ECDC and the VAESCO consortium added narcolepsy to the conditions under study.

This chapter will describe publicly available information on 1) definition and epidemiology of narcolepsy, 2) the type of influenza A(H1N1)pdm09 vaccines that were used in the EU, 3) the extent of use of those vaccines especially in the countries participating in this study.

1.1 Narcolepsy: definition, symptoms and diagnosis

Narcolepsy is a disabling sleep disorder which interferes severely with normal daily activities, interpersonal relations, education, and job opportunities. The International Classification of Sleep Disorders is the widely accepted classification of this clinical entity [2, 3]. Narcolepsy with cataplexy is recognised as a specific entity due to the strong association with Human Leukocyte Anitgen (HLA) haplotype DQB1*0602 and hypocretin deficiency in cerebrospinal fluid (CSF) [4], a relation that is hardly present in narcolepsy without cataplexy or other sleep disorders with paroxysmal hypersomnia.

The classic clinical syndrome consists of the combination of execessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnagogic hallucinations. EDS is the principal complaint. It is characterised by a continuous feeling of sleepiness with episodes of irresistible sleep during the day and sleep fragmentation during the night with an inability to stay asleep. However, the total daily duration of sleep remains virtually unaltered [3]. Cataplexy is the only symptom specific of narcolepsy. It is described as episodes of bilateral loss of muscle tone with a sudden onset and short duration (less than two minutes). Apart from extra ocular and respiratory, all striated muscles may be affected. Laughter and other expressions of emotional states may trigger a cataplectic attack. Besides the aforementioned symptoms, people with narcolepsy are often obese.[3, 5]

Narcolepsy can be diagnosed by a combination of tests. The sleep complaints of people with narcolepsy are reflected in the findings on overnight polysomnography. Nocturnal sleep studies show a reduced sleep efficiency with frequent stage shifts and arousals. Multiple sleep latency tests reveal a very short sleep latency during the day. Furthermore, people with narcolepsy typically have multiple sleep-onset REM periods (i.e. the occurrence of REM sleep within 15 min after sleep onset). These findings also have diagnostic value, although the specificity is not optimal. In the absence of cataplexy, sleep registrations are mandatory to make a diagnosis of narcolepsy. Determining cerebrospinal fluid levels of hypocretin is a relatively new diagnostic tool and has great value in making the diagnosis [6]. This has important consequences for research; pathophysiological studies gain more value when homogenous patient groups are included, and hypocretin measurements provide this opportunity.

Epidemiology of narcolepsy

Narcolepsy is a disabling chronic sleep disorder, severely interfering with normal daily activities, interpersonal relations, education, and job opportunities [2, 3]. The classic clinical syndrome consists of EDS, cataplexy, sleep paralysis, and hypnagogic hallucinations. EDS is characterised by a continuous feeling of sleepiness with episodes of irresistible sleep during the day and sleep fragmentation during the night. However, EDS is not specific for narcolepsy. It may occur in many other sleep disorders [7].

The estimated prevalence of narcolepsy is 20–50 per 100 000 in Western countries [3, 8, 9]. It is thought to affect men and women equally. However, a male predominance has been found in some studies. The first symptoms typically develop in adolescence or early adulthood and the majority of cases are diagnosed in early adulthood, some however are diagnosed very late [10]. The disease may take years to develop or may be more acute (within weeks), the acute onset is often seen in children [8, 11]. Dauvilliers described two peaks of onset around 15 and

[1] http://vaesco.net/vaesco.html

[2] for anaphylaxis, encephalitis, Gullain-Barré Syndrome (GBS), Bell's palsy, neuritis, convulsion, vasculitis, demyelinization, transverse myelitis, autoimmune hepatitis, thrombocytopenia, and sudden death

36 years of age [12]. Since narcolepsy is a rare disease and commences with unspecific symptoms, the diagnosis is frequently missed or made with a long diagnostic delay (ranging between 1–60 years), especially in adults [13].

Currently little is known about the etiology of narcolepsy without cataplexy. An autoimmune process is hypothesised to cause loss of hypocretin-producing neurons in narcolepsy. This is strongly associated with the HLA subtype DQB1*0602 [4]. As only very few carriers of this allele develop narcolepsy, other factors must contribute to the development of narcolepsy. Recently streptococcal infection markers and antibodies against the protein Tribbles homolog 2 have been reported as well as influenza infection [14, 15, 16]. Considering the age of onset of symptoms it is thought that an exposure which could trigger narcolepsy would occur during or before adolescence [9]. There have only been a few studies focusing specifically on environmental factors and disease inducing or promoting health events preceding clinical manifestation of narcolepsy. However, these types of studies are hampered by the considerable uncertainties around etiology and pathogenesis of narcolepsy as well as the associated methodological difficulties, such as underdiagnosis and recall-bias [9]. As far as the study groups is aware, no association had ever been made between vaccination and narcolepsy occurrence prior to 2010.

Narcolepsy and immunity

The tight association with specific HLA polymorphisms is suggestive for narcolepsy to be mediated by an autoimmune process. Several studies have aimed to characterise a potential mechanism. Longstreth *et al* hypothesised type I diabetes to be a comparable disease model. In this model, the hypocretin cells in the hypothalamus can be targeted by the immune system in individuals with a specific genetic predisposition, when triggered by environmental factors. This may lead to hypocretin producing cell destruction. The manifestation and severity of narcolepsy symptoms then depends on the degree of hypocretin producing cell depletion. However, in spite of these observations and increased efforts to delineate the role of neurophysiological sleep regulatory pathways, the etiology and pathophysiology of narcolepsy remains to be elucidated.

Using genome-wide association (GWA) studies in caucasians with replications in three further ethnic groups, an association between narcolepsy and polymorphisms in the TRAα (T-cell receptor alpha) locus was found, with highest significance at rs1154155 (average allelic odds ratio 1.69, genotypic odds ratios 1.94 and 2.55, P < 10–21, 1 830 cases, 2 164 controls) [17]. Recently a protective effect of the corresponding HLA gene was found in a GWA study demonstrating the effect of immunity in narcolepsy [18].

1.2 Licensed monovalent influenza A(H1N1)pdm09 vaccines for the 2009 pandemic

Several different vaccines were used to protect populations against the 2009 (H1N1) pandemic influenza. Non-adjuvanted monovalent vaccines, similar to the regular seasonal influenza vaccines containing split influenza virus or only hemagglutinin and neuraminidase surface proteins, were mainly used in the USA and Australia, and on a limited scale in Europe (France, Spain) and other countries.

Within the EU, adjuvanted pandemic vaccines were most widely used. Two different types of adjuvanted vaccines were licensed centrally by the EMA. Both contain a new generation of squalene based adjuvants: Focetria (Novartis) with the MF59 adjuvant and Pandemrix (GSK) containing AS03. Arepanrix used in Canada is similar to Pandemrix, however produced at a different site. Table 2 shows the composition of all centrally licensed products in the EU [19].

Pandemrix was the most used vaccine in Europe. Based on national reports the EMA estimated that as of 8 August 2010, at least 38.6 million people in EU/EEA countries had been vaccinated: >30.5 million with Pandemrix, >560,000 with Celvapan and >6.5 million with Focetria. When the information available for the nationally authorised vaccines was included, the total rose to at least 46.2 million people.

The WHO SAGE committee on immunisation recommended that all countries should immunise their healthcare workers as a first priority to protect the essential health infrastructure. The SAGE Committee also suggested prioritisation of groups for consideration for vaccination in the order listed here, but noted that countries needed to determine their order of priority based on country-specific conditions:

- pregnant women
- individuals aged > six months with one of several chronic medical conditions, including asthma and morbid obesity
- healthy young adults (aged > 15 years and < 49 years)
- healthy children
- healthy adults aged >= 49 years and < 65 years
- healthy adults aged 65 years and older.

Recommendations and implementation differed largely between EEA countries (see table 3).

As a result of the urgency of the situation, the shortage of vaccines and the limited availability of immunisation registries in EU/EEA countries there was incomplete information on how the different national pandemic influenza programs had been implemented, and which vaccination coverage had been achieved. In March 2010, ECDC requested the Vaccine European New Integrated Collaboration Effort (VENICE) consortium to undertake a survey of Member States to obtain this information [19]

Table 1.1.1. Overview of vaccines against influenza A(H1N1)pdm09 available in the European Union in December 2009*.

Name, producer	Product description	Culture medium	Haemagglutinin content	Adjuvant emulsion	Number of doses
Celvapan, Baxter	Whole virion, wild-type A/California/7/2009 (H1N1), inactivated	Vero cell-derived	7.5 µg	None	All > 6 months, 2 x 0.5 mL
Pandemrix, GSK	Split-virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated, adjuvanted	Egg-derived	3.75 µg (per full dose)	AS03	Adults, adolescents and children ≥ 10 years, 1 x 0.5 mL
			1.87 µg (per half dose)		Children 6 months–9 years, 2 x 0.25 mL
Focetria, Novartis	Surface-antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)-like strain, inactivated, adjuvanted	Egg-derived	7.5 µg	MF59C.1	Adults, adolescents and children ≥ 9 years, 1 x 0.5 mL
					Children 6 months–8 years, 2 x 0.5 mL
Fluval P, Omnivest	Whole virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated, adjuvanted	Egg-derived	6 µg (per full dose)	Aluminium phosphate	Adults and adolescents > 12 years, 1 x 0.5 mL
			3 µg (per half dose)		Children 12 months–12 years, 1 x 0.25 mL
Panenza, Sanofi Pasteur	Split-virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated	Egg-derived	15 µg (per full dose)	None	Adults, adolescents and children > 8 years, 1 x 0.5 mL. Elderly > 60 years and children 3–8 years, 2 x 0.5 mL
			7.5 µg (per half dose)		Children 6–35 months, 2 x 0.25 mL
Celtura, Novartis	Surface-antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)-like strain, inactivated, adjuvanted	MDCK cell-derived	3.75 µg	MF59C.1	Adults 18–40 years, children 3–17 years, 1 x 0.25 mL
					Adults > 40 years, 2 x 0.25 mL
PanvaxH1N1, CSL	Split-virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated	Egg-derived	15 ug	None	Adults, adolescents and children > 9 years, 1 x 0.5 mL
CANTGRIP, Cantacuzino	Split-virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated	Egg-derived	15 ug	None	Adults ≥ 18 years, 1 x 0.5 mL

Source: Eurosurveillance [19]

**In some countries the number of doses and dosage changed over time.*

Table 1.1.2. Population groups recommended for pandemic influenza vaccine in the European Union Member States and European Economic Area countries that had vaccination recommendations during the 2009 pandemic, influenza A(H1N1)pdm09 vaccination survey, August 2010 (n=27 countries).

Population groups	Number of countries (n)
Age (n=26)[a]	
Children	
All (≥6 months – <18 years)	13
Some age groups[b]	6
Only in risk groups/underlying conditions	7
Adults	
All (≥18 years)	13
Some age groups[c]	3
Only in risk groups/underlying conditions	10
All ages	
All age groups	12
Chronic diseases and underlying conditions (n=27)	
Respiratory	27
Cardiovascular	27
Renal	27
Neurological /neuromuscular	26
Metabolic (including diabetes)	26
Hepatic	25
Immunosuppression due to disease or treatment	25
Any condition compromising respiratory function	21
Hematologic	18
Haemoglobinophathies	16
Morbid obesity (Body Mass Index ≥40 kg/m^2)	16
Pregnant women	27
All	25
Only with additional risk condition	2
Any trimester[a]	12
Either second or third trimester	14
Postpartum if not vaccinated	12
Occupations (n=27)	
Healthcare	27
Police	12
Military	11
Firefighters	9
Border control	7
Educational	7
Public transport	6
Energy	7
Finance /banking	3
Immigration/custom	1
Other populations (n=27)	
Close contacts (cocooning strategy)[d] of:	
Infants ≤6 months of age	12
Individuals in risk groups	9
Residents of long term care facilities	14

Source: Eurosurveillance [19]

[a] One country did not answer this question. [b] Some children (n=6): >1 year–2 years (Estonia); 6 months–5 years (England); 6 months–4 years (Netherlands); 12 months–18 years (Hungary); 6 months–12 years (Portugal); >16–17 years (Romania).

[c] Some adults: >60 years (Netherlands); 18–27 years (Italy); ≥65 years (England).

[d] Definition and rationale for "cocooning": Infants ≤6 months of age having little if any immunity to influenza if their mothers were not vaccinated during pregnancy are at higher risk of influenza-related complications. To ensure infant protection, immediate household contacts (representing its cocoon) should be vaccinated against influenza A(H1N1)pdm09 so they will not transmit the virus to the baby. The same concept applies to individuals with some chronic diseases (e.g., patients with hematopoietic stem cell transplants) since the immune response to the vaccine may be inadequate, vaccination of contacts (household members, healthcare workers, and other individuals) is recommended.

Table 1.1.3. Pandemic vaccination coverage among specific groups of population by countries in European Union and European Economic Area during the 2009 pandemic influenza A(H1N1)pdm09 vaccination survey, August 2010 (n=22 countries).

	Vaccination coverage (%)				
Countries	Overall[a] (n=22)	≥ 6 months of age with chronic diseases and underlying conditions (n=9)	Pregnant women[b] (n=12)	Children[c] (n=12)	Healthcare workers[d] (n=13)
Austria	3	–	–	–	–
Cyprus	3	–	–	–	–
Czech Republic	0.6	–	0	–	7
Denmark	–	20	–	–	–
England	–	38	15	24	40
Estonia	3	21	5	–	21
Finland	50	–	–	74	–
France	8	–	23	10	–
Germany[e]	8	12	9	–	16
Greece	3	–	–	–	–
Hungary	27	–	9	–	68
Iceland	46	–	–	45	–
Ireland	23	48	32	46	31
Italy	4	13	12	0.3	15
Luxembourg	6	8	–	7	–
Malta	23	–	–	–	40
Netherlands	30	72	58	74	50
Norway	45	–	–	55	–
Portugal	6	–	18	15	35
Romania	9	–	–	–	51
Spain	27	24	9	–	12
Sweden[f]	59	–	–	–	–
Slovenia	5	–	1	1	–
Slovakia	0.4	–	–	0.2	3

Source: Eurosurveillance [19]

[a] Some countries recommended pandemic vaccine for some population groups but calculated overall vaccination coverage.

[b] Pregnant women: all countries that provided vaccination coverage recommended vaccination to all pregnant women (with or without risk indication).

[c] Groups for which vaccination coverage were measured: France, Iceland, Italy, Norway and Slovenia (n=5), ≥6months–<18years of age;
England, ≥6 months–<5 years of age; Finland, ≤15 years of age; Ireland, >6months–<15years or age; Luxembourg, at risk; Netherlands, ≥6 months–4years of age; Portugal, ≥6 months–12 years of age.

[d] Healthcare workers: Czech Republic, England, Malta, Netherlands, Portugal (n=5) recommended pandemic vaccine to only healthcare workers with close contact with patients; Estonia recommended for healthcare workers with close contact with patient and with no contact with patients, but contact with potentially contaminated material; Hungary, Malta, Romania, Spain, Sweden and Slovakia (n=6) recommended pandemic vaccine to all healthcare workers.

[e] Data for age groups ≥14 years.

[f] In Sweden - more recent data [10] reported higher vaccination coverage from four regions, suggesting that vaccination coverage may have been higher than reported at time of survey. The vaccination coverage was on average 67 % for children and adolescents under the age of 20 and 51% for adults in four regions (with immunisation registries) in Sweden. These four regions have around 5.3 million inhabitants (the whole of Sweden is 9.1 million), which corresponds roughly to 57 % of the Swedish population [13].

Vaccination coverage figures in this table were rounded.

Figure 1.1.2. Vaccination programmes for pandemic influenza vaccine in the European Union Member States and European Economic Area countries that organised national pandemic influenza vaccination during the 2009 pandemic influenza A(H1N1)pdm09 vaccination survey, August 2010 (n=26 countries.

Pandemic vaccination programme with a defined starting week but no defined end at the time of the survey

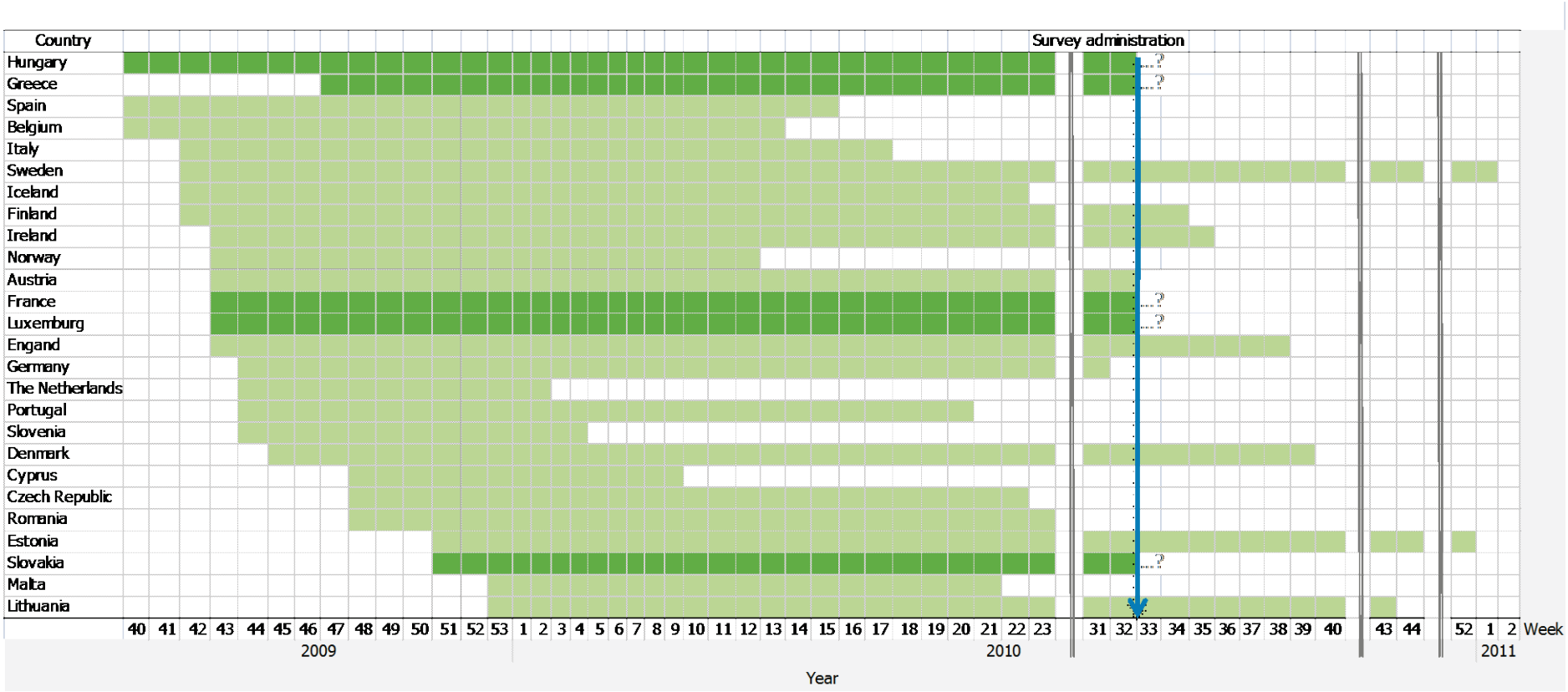
Pandemic vaccination with a defined starting and finishing week

→ Survey administration date

— Breaks between weeks in the year 2010

The figure covers the period from 28 Sep 2009 to 9 Jan 2011.

Due to lack of space in the figure there are breaks (grey lines) between weeks in the year 2010.



Source: Eurosurveillance [19]

2 VAESCO studies on narcolepsy

VAESCO is a project initiated and coordinated by ECDC and implemented by a VAESCO consortium which is a network of investigators from EU Member States who explore the feasibility and benefits of collaborative post-licensure epidemiological studies investigating the safety of human vaccines. ECDC, in collaboration with the European Medicines Agency, the European Commission and the VAESCO consortium recognised the need for concerted international action to enhance the capacity of national immunisation programs to independently, consistently, and credibly gather epidemiological data on vaccine uptake, effectiveness, and rates and risk factors for specific events of interest. They also recognised that a common strategy of EU Member States based on generally accepted standards allows for larger studies yielding results with increased precision and accuracy and thus adds value to national efforts and data.

Further, a shared methodology strengthens national decision-making by facilitating the interpretation of local data in the European context through scientific validation processes by including data from multiple European countries. Concerted action among EU member states will shore up local capacity through the support of internationally recognised experts in the field. It may also compensate for the lack of national capacity through the added benefit of international collaborative engagement. Further, it will allow for studying the effects of heterogeneity in vaccine exposure, in terms of uptake and type of vaccine.

On request of ECDC, the VAESCO consortium has previously addressed background rates of various pre-specified events and investigated the association between influenza A(H1N1)pdm09 vaccination and GBS. Upon initial discussions and brainstorming of various study design options between ECDC and the VAESCO leads, the consortium was asked by ECDC to generate a protocol in August 2010 to address the safety concerns regarding narcolepsy that were raised in Finland and Sweden. The study contract was signed in December 2010 by ECDC at which point the study could officially start.

2.1 Aim and objectives of studies

The aim of the VAESCO narcolepsy study is to assist in providing more information on the association between vaccinations, infections and narcolepsy and the potential public health impact. The specific objectives were to assess:

- the background rate of narcolepsy
- a potential change in narcolepsy rates after April 2009 (i.e. beginning of H1N1 pandemic in Europe) and October 2009 (i.e. beginning of immunisations in Europe), respectively
- the potential association between risk factors including influenza, infections, vaccinations and narcolepsy in an analytical study.

2.2 Methods

2.2.1 Setting

The VAESCO narcolepsy study is conducted in multiple European countries participating in the VAESCO consortium (Denmark, Finland, France, Italy, the Netherlands, Norway, Sweden, and the United Kingdom). Information collection is harmonised, a standardised case definition of narcolepsy is used, and local data management is standardised. The method for identifying potential patients with narcolepsy as well as the related exposure and co-variate information has been adapted to the diagnostic work-up of narcolepsy and the available data sources in each country. Electronic population-based health care databases were the preferred data source as they allow for non-selective sampling of controls. However in some countries, these databases do not exist, do not capture a large enough population or do not allow for outpatient case recruitment. Therefore dedicated case recruitment networks through referral sleep centres/hypocretin assessment labs have been used as well. Each data centre was responsible for obtaining the necessary approvals for participating in this study in their own country.

Given that the signal on a potential association between influenza A(H1N1)pdm09 vaccination and narcolepsy was raised in Sweden and Finland, and media/regulatory attention in these countries was considerable, the study assesses the impact of including data from these countries on the overall study result, as recommended by the EMA Committee for Medicinal Products for Human Use (CHMP).

2.2.2 Design

The background rates of narcolepsy have been determined through a dynamic retrospective cohort study.

Risk factors for narcolepsy are studied through a retrospective case-control study.

2.2.3 Study period

Background rates

Background rates were calculated over the period 2000–2010 and reported over the following calendar time periods:

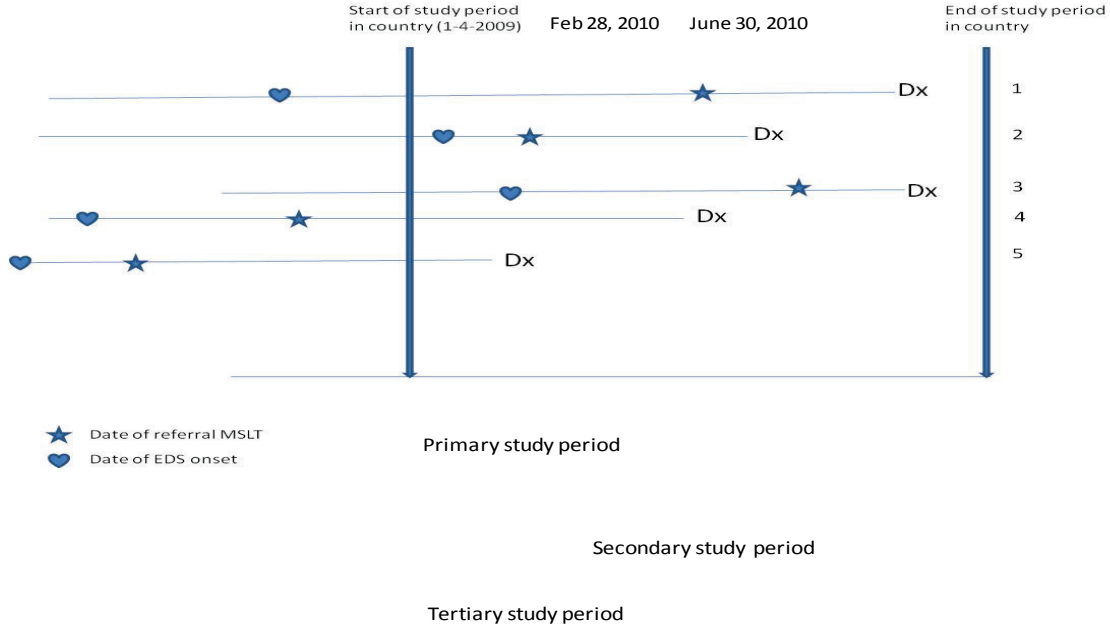
- pre-pandemic influenza 2000–March 2009
- pandemic influenza-pre vaccination(April 2009–September 2009)
- during/post pandemic influenza and vaccination (October 2009–June 2010). Based on the exact start of the vaccination campaign the post-vaccination period may be changed in onset.

Results have been shared with the EMA Pharmacovigilance Working Party and EMA CHMP in February, April and July 2011.

Case control

The primary study period is April 2009–30 June 2010. The index date of the case should fall within this period to be considered for the primary analysis. The secondary study period includes the primary period and all cases diagnosed after 1 July 2010 until the moment that sites could recruit the cases. Cases with index dates over the entire recruitment period were included in the secondary study period. The choice of the primary risk period was based on the fact that in most countries, regulatory awareness and media attention started in August 2010. In Finland neurologists have been investigating the association between the H1N1 vaccine and narcolepsy since February[3]. Censoring on July 2010 is an attempt to be able to separate the potential vaccine-only effect from a combined vaccine and awareness effect. For Finland, a third study period is specifically defined that ranges from April 2009– 28 February 2010 for sensitivity analyses (see figure 2.1.1).

Figure 2.1.1. Graphic display of study periods and index dates.



Case accrual time

The actual case identification period is longer and extended beyond the end of the study period to allow for more complete case accrual and adequate right censoring even when sensitivity analyses are done on other index dates. While the events making up the signal were described in the reports from Sweden and Finland to be characterised as having a short time interval between exposure and outcome and rapid progression of disease, the diagnosis of some cases presenting may be delayed for several months to years. This implies that cases that would be part of the primary study period could be identified even later, due to the delayed onset. Including cases identified after July 2010 carries a risk of increased awareness to narcolepsy (since the signal was out). This was addressed in the study design and statistical analysis plan. The effect of diagnostic suspicion bias is investigated in a sensitivity analysis, which includes cases which have their index date (date of first referral for MSLT) after 30 June 2010 and after February 2010 in Finland.

[3] Available at: http://www.hs.fi/kotimaa/artikkeli/Yle%2BSuomalaisneurologit%2Btutkineet%2BH1N1-rokotteen%2Bhaittoja%2Bjo%2Bkuukausia/1135259621663&usg=ALkJrhjLYaN_GuzQIZ3dSCumy4IGtpRdpQ

Index dates

Three index dates were investigated, the date of onset of EDS, the date of MSLT referral and the date of diagnosis of narcolepsy. The primary index date was defined as the date of referral for MSLT even though this may be later than the date of actual disease onset.

It is recognised that the time from onset of disease to diagnosis of narcolepsy may be long and there is great uncertainty about defining the exact date of onset in most settings. Therefore, the date of first referral for MSLT (showing abnormalities) rather than the time of onset or diagnosis, was defined as the primary index date. In pre-specified sensitivity analyses we apply both the date of diagnosis and the date of onset of EDS as alternative index dates. For efficiency reasons we did not include cases who had the onset of symptoms prior to 1 January2005. Although this introduces left censoring issues (potential exclusion of subjects who had their primary index date during the study period, but had symptoms already prior to 2005), it was not feasible to retrospectively collect information over such a long period.

To allow for analysis of the three different index dates, the analyses of the narcolepsy case control study was conducted on three different datasets, each of them was created by Jerboa Vaccine from the same Chameleon input files (tailored electronic data capture form for input of data from the case report forms (CRFs), that was created specifically for this study).

The selection criteria for the three different datasets were:

Primary analysis

1) **Date of MSLT referral as index date**. All cases diagnosed up until the most recent data collection with the date of referral for MSLT from April 2009 onwards and onset of symptoms after 1 January2005. All cases with MSLT dated between 1 April 2009 and 30 June 2010 were included in the primary analysis. In Finland date of referral to specialist was used instead of date of referral for MSLT.

Sensitivity analyses on index dates

2) **Date of onset of EDS as index date in primary study period**. All cases diagnosed up until the most recent data collection, with the date of onset of EDS between 1 April 2009 until 30 June 2010.

3) **Date of diagnosis as index date in primary study period.** All cases with the date of narcolepsy diagnosis from April 2009– 30 June 2010 and onset of symptoms after 1 January 2005.

2.2.4 Source population

The source population comprises all persons in each country, region, or database at risk of developing narcolepsy (excluding chronic cases). The setting differs from country to country and two types of source populations were identified:

Primary source population - this was drawn from settings that can enumerate the underlying population. Generally these are population-based health care databases (available in Denmark, United Kingdom, the Netherlands) with the option of linking outcome and exposure data to the well-defined population. Controls were selected using a population-based approach.

The source population was required to have one year of active registration to allow for adequate data collection and reduce the likelihood of exposure- or outcome misclassification.

Background rate estimations were done exclusively in primary source populations that at the very least, can link outcomes to the population.

Additional source population - this was derived from settings that collect narcolepsy cases through specialist referral centres, diagnostic sleep centres or hypocretin assessment labs (Finland, Norway, Sweden, France). The source population (catchment area of the centre) is generally less well definable. The possibility of selecting controls from the same source population was evaluated for each data source and was a pre-requisite for eligibility to contribute as a centre/country.

Note: although most case reports in Finland concern adolescents, age restriction has not been done since cases occurred in all age groups, and from a medical/etiological perspective there is no reason to believe that a potential association between influenza A(H1N1)pdm09 vaccine and narcolepsy would be restricted to children/adolescents only.

2.2.5 Study population

The primary outcome of interest was narcolepsy with and without cataplexy in all ages (Brighton Collaboration classes 1–4)

Case definition

There are three main diagnostic classes of narcolepsy according to the American Academy of Sleep Medicine and the International Classification of Sleep Disorders: narcolepsy with cataplexy, narcolepsy without cataplexy, and secondary narcolepsy. Based on this classification, an *ad hoc* case definition of narcolepsy has been developed according to the Brighton Collaboration format [20]. The working group developing the ad *hoc case* definition comprised of globally recognised narcolepsy experts including members of the European Union Narcolepsy Network (EU-NN) in addition to vaccinologists, paediatricians, immunologists, and epidemiologists, to ensure applicability to pre- and post-licensure clinical vaccine safety studies in diverse settings and geographic regions [21]. The case definition was then under consultation by a wider group of experts as part of the formal Brighton Collaboration process to develop standardised case definitions and was approved (see section 6.1.2).

Narcolepsy is rare in children and adolescents [8]. In children less than five years of age, the diagnosis of narcolepsy can rarely be made reliably. Preschool children take habitual daytime naps, have varying reasons for interrupted night time sleep, may report experiences similar to hypnagogic hallucinations, and may not be able to give a history of sleep paralysis. School-aged children may present with the reappearance of daytime naps after they had previously discontinued regular napping. Often the sleepiness presents as behavioural problems, decreased performance, inattentiveness, lack of energy, or bizarre hallucinations. It is not uncommon for physicians to misinterpret some of these symptoms as primarily psychological or psychiatric and this may lead to inappropriate management including initial referral to psychiatric or educational rather than neurologic or sleep disorder services. Since clinical manifestation may be different in children, the CRF and case definition differed slightly between children and adolescents.

Case ascertainment

As cases all patients diagnosed with narcolepsy were considered. Where possible, specialist letters, chart review and additional follow-up information was requested anonymously from the reporting physician in order to classify cases according to the BC narcolepsy case definition. Case ascertainment was done on the basis of the Automated Brighton Classification (ABC) tool. Case report forms were developed and were distributed to all centres (please see section 6.1.2). All events reaching BC levels 1–4 are included in the analyses. Sensitivity analyses were done restricting the cases to levels 1–2 or 1–3. Level one and two comprised of the best phenotyped patients.

Case finding

Background and incidence rate study

For the background rate calculation, cases were obtained from the automated registries based on diagnosis codes. No further validation was done for initial rates. Codes were created based on mapping by the UMLS according to a process developed in the EU-ADR project [22]. Codes were supplied to all centres. Validation of codes/text was done in the Netherlands on the basis of retrospective review of medical records /discharge/specialist's letters and questionnaires from GPs.

Case control study

Case finding methods differed by country depending on the health care structure and available resources for case finding. The preferred/recommended choice was to identify cases from population-based databases to avoid selection bias. In countries that could not identify cases from population-based registries, a dedicated comprehensive case identification (e.g. a network of sleep/hypocretin labs) was used. In each instance, the sites needed to ensure lists of all potentially eligible cases were kept and case attrition diagrams supplied. Table 2 shows the case finding methods in each of the participating countries.

Controls

For each case of narcolepsy (BC case definitions 1–4), four to ten population-based controls were identified from the national registries/database or from the GP practice where the case was registered. The most cost-efficient number is four controls per case, but as more controls will always increase power, especially with high concordance of exposure, ten controls was preferred. Controls were matched on year of birth, sex and index date (i.e. the date of onset of narcolepsy) and also by region/practice in Norway, Italy and UK. Based on the type of source population (see above) different approaches were used for control sampling:

- For primary source populations (electronic population-based health care databases), controls were sampled automatically from the underlying source population (matching factors). This was done in Finland, Sweden, Denmark, and the UK.
- For additional source populations: Norway, Italy, Netherlands and France (e.g. when cases are reported by neurologists/sleep labs) the following approaches were used:
  - The preferred option was to select community controls from the GP office of the case as medical history data for the case would mostly have had to be collected from the same GP. Controls were matched on age and gender and the index date of the case. This was done in the Netherlands. If controls could not be obtained from same GP they could be sampled from other GPs while keeping the matching.
  - In Norway, a list was created from the administrative files based on postal code, age and sex, and the controls were contacted by phone to obtain consent.
  - Hospital/specialist based controls were not recommended. However in Italy and France there were no other options. In Italy controls were obtained from the Cephalalgia centre.
  - In France, individuals with the following diseases were eligible to be included as controls except if the disease for admission was a recommendation or contraindication for vaccination:
    - motor developmental disorders, cognitive developmental disorders
    - asthma
    - chronic obstructive pulmonary disease, cystic fibrosis
    - congenital heart disease, congestive heart failure, coronary heart disease
    - stroke
    - immune deficiency
    - sickle-cell disease
    - diabetes mellitus (Type I or Type II)
    - chronic kidney failure
    - liver failure
    - secondary immune deficiency (related to AIDS, cancer, chronic use of corticosteroids, other)
    - history of allergic reaction to flu vaccine or one of its components
    - history of allergic reaction to egg, egg albumin, gentamycin sulphate, thiomersal, formaldehyde, sodium desoxycholate

Exposure and co-variate data collection for case control study

The primary exposures of interest in the case control study were:

Infections

Information on medical visits for preceding infections (streptococcal throat infection, sepsis due to any cause, EBV infections, and ILI) were preferably obtained from the GP for cases and controls over a period of five years (to allow for sensitivity analyses on index date). In Sweden, Norway, Italy and France data were obtained by interview with the patients; in the Netherlands and the UK, data were obtained from electronic medical records. In Denmark and Finland co-variate data was not collected.

Vaccinations

The date of administration, type (brand) and dose was recorded for each vaccine over a period of five years (to allow for sensitivity analyses on the index date). The main focus was on seasonal influenza vaccination and influenza A(H1N1)pdm09 vaccines. Other vaccines were recorded as well e.g. HPV vaccine. Information on exposure to vaccinations had to be obtained from vaccination registries or medical records to avoid information bias.

Other risk factors

Factors related to differences in immunity such as such as malignancy, primary and secondary immune compromising diseases (e.g. HIV infection, transplantation or use of immunosuppressants), pregnancy and auto-immune disorders were collected for cases and controls from the medical records/GPs or patients (interview).

Additional morbidities that could be risk factors for narcolepsy were also collected (asthma, migraine, and diabetes). Information on use of antibiotics, antidepressants, benzodiazepines, anti-epileptics and other psychotropic medication were recorded.

2.2.7 Overview of implemented methods by country

Table 2.1.1 Overview of implemented methods by country.

Country	Cases	Case verification	Controls identification	Vaccination exposure source	Co-variate source
Finland	Finnish cohort study (children) hospital registry (adults) No consent required	Medical charts, review by neurologists (not blinded)	Population registry No consent required	Vaccine registry	Not collected
Sweden	Letters to relevant sleep clinics/laboratories Consent required	Medical charts review by neurologist (blinded to exposure)	Population based registry Consent required	Patient interview by research nurse;	Patient interview by research nurse
Norway	Four health regions; sleep centres, hospital database-outpatient visits database; Oslo university hospital reference lab for hypocretin (consent)	Verification by specialist, CRF1 by specialist or sleep centre (not blinded to exposure)	Norwegian population registry – matched on area code informed consent required	Vaccine registry	Interview pt records of specialists or GPs
Italy	Emilia Romagna (sleep centres, ICD9 347) consent required	University of Bologna that will also validate the diagnosis	Headache centre in the same hospital. Consent required	Regional databases	Interview by investigator from sleep centre
Denmark	Danish Centre for Sleep Medicine Glostrup Hospital, University of Copenhagen No consent required	Neurologist from the sleep centre extract the list of cases. All patients in the sleep centre with a (Polysomnogram) test + MSLT	Danish Civil Registration System including all Danish residents (registry). No consent required	The national vaccination registry	Not collected
United Kingdom	GPRD (representative of UK) Primary care database. No consent required	Extraction of electronic medical records and specialist information from GPs (blinded to exposure)	Controls extracted from GPRD. No consent required	Codes from GPRD	Medical record (electronic)
Netherlands	Sleep centres: 16 sleep centres, academic and non-university hospitals No consent required	Chart review, case classification with Brighton definition, review done by two narcolepsy experts (blinded to exposure)	GP database. GP of case From IPCI database. No consent required	Electronic medical GP records	Electronic medical GP records
France	Sleep centres academic /specialists	Chart review, case classification with Brighton definition by specialists themselves, consent required	Hospital Consent required	Patient interview. Followed by Vaccination registry	Interview /charts

Table 2.1.1 provides an overview of the methods for case identification, verification, control identification and data collection per country. Each country used the approved VAESCO protocol (version 4.2), the CRFs, the instructions documents and data collection tools (see appendices), but differences occurred in implementation of the study due to the health care structure and privacy safeguards. Due to the large potential for diagnostic awareness and recall bias, centres were advised to use registries for data collection on exposures and to record the completeness and approaches for case identification.

2.2.8 Quality control on data collection

Instructions were used to train personnel involved in data collection. Since the study was retrospective, utmost attention was paid to the collection of unbiased information (cases and controls may recall differently if they are asked). Therefore data was collected from registries, medical records and physicians rather than patients. Discussions took place with each study centre to make sure that retrieval of co-variate information was done similarly for cases and controls to avoid information bias. Registries with objective information on exposures/morbidities were recommended as much as possible to avoid recall bias. Physicians/researchers conducting abstraction of charts were held to be blinded to exposure status and unaware of the main study question about the potential association. Copies of source data were kept at the local databases and preferably double data abstraction and entry was done.

The question of whether inclusion in the study was related to influenza A(H1N1)pdm09 vaccination exposure in centres that recruited cases from neurologists/physicians was scrutinised as far as possible.

Instructions for case identification with codes and definitions for co-variates were generated and made available to all collaborators.

Handling of missing information on specific variables

- Missing parts of dates were labelled in CHAMELEON.
- If (parts of) the index date were missing the case set was deleted for the case control set referring to that index date, except for the EDS date. EDS missing days and months were imputed if the year of EDS onset was provided.
- Antibiotics use dates had to be completed for the month and year: this means that only day can be missed (but month and year have to be filled in the CRF).
- All other dates needed only year to be accepted: this means that day and month could be missing and were imputed. This was true for infections, cataplexy, exposures (all vaccinations including influenza A(H1N1)pdm09 and seasonal vaccination flu).

Missing parts of dates were imputed in CHAMELEON/Jerboa before outputting the data sets

- If year and month are known, only day needs to be imputed. This is done as a random integer between 1 and 30 (or 31 or 29 or 28 depending on the specific month). The function used to do that is the rand(x,y) function (JAVA) that generates (pseudo) random integer numbers between x and y. The error is ≤ 15 days.
- If only year was known (and month and day are missing) a two-step procedure was used:
  - a (random) month was generated as month = rand(1,12)
  - taking into account the month generated before, a day was generated as rand(1,30) (or 31, 29,28 depending of the imputed month).
- The level of missingness was indicated to allow for sensitivity analyses.

2.2.9 Analysis

Background rates: Incidence rates of narcolepsy were calculated by age, sex, calendar year and month. The low incidence of narcolepsy does not allow for interrupted time series analyses at the country level. However, incidence rates with 95% confidence intervals were calculated for the pre-pandemic, pandemic, and post pandemic vaccination period.

Case control study: Odds ratios and exact 95% confidence intervals were calculated using a multivariate conditional logistic regression. Co-variates were included into the multivariate model if significantly ($p<0.05$) associated with narcolepsy, and changing the point estimate between either influenza A(H1N1)pdm09 vaccination or influenza and narcolepsy by at least 10%.

The primary reference category for estimation of the effects of vaccinations and other risk factors was no exposure/exposure prior to index date. To study effects of timing of exposure to vaccinations, different risk windows for exposure were defined: 0–7 days, 8–42 days, 43–180 days, and >180 days before index date for influenza A(H1N1)pdm09 vaccination, an analysis on any time prior was conducted as well. Exposure to all other co-variates (except chronic disease) was initially classified as exposed in the year prior (yes/no). In case of strong association, further sub-categorisation was done for the risk window. In subsequent analyses, the exposure was further divided into first and second administrations (i.e. dose-effect). The influence of different adjuvants/excipients was studied by categorising the exposures by the type of vaccine as surrogate. Stratified analyses were conducted to estimate the effect in specific subgroups e.g. children/adolescents (0–18 years), calendar time (primary period: April 2009-June 30 2010; secondary period: April 2009-latest, and tertiary period: April 2009–February 28 2010), country (signalling countries: Finland/Sweden vs. non-signalling) and outcome (BC levels 1–2, BC levels 1–3 and BC levels 1–4). Sensitivity analyses to assess the effects of bias are described below (limitations section). For all analyses statistical significance at a p-value<0.05 was accepted.

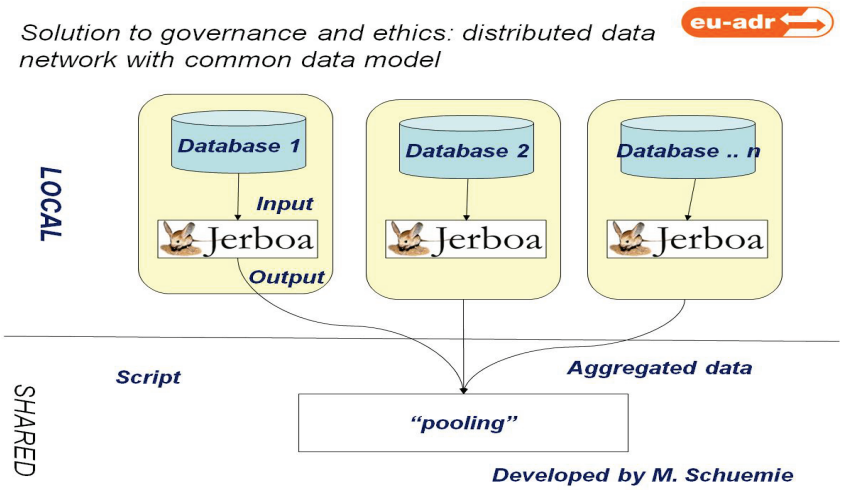
All analyses were done according to a pre-specified consented statistical analysis plan that was created by a team of epidemiologists and statisticians and endorsed by the VAESCO consortium. For quality control and review, all analyses incorporated in this report were conducted independently by two epidemiologists/statisticians in parallel using the Statistical Analysis System (SAS) and Statistical Product and Service Solutions (SPSS) at the Erasmus University Medical Center (except for exact estimations). All analyses were discussed and shared with the participating countries prior to submission of the report. To overcome problems in the estimation of confidence intervals in instances of low numbers, exact confidence intervals were calculated. Sensitivity analyses were done which released the matching, in these analyses, the matching variables were adjusted for: age (categorised and entered as categorical); calendar year; month (as categorical); country and sex.

3 Data elaboration and pooling infrastructure

3.1 Background rates

A distributed data approach was used for the calculation of background rates, a concept that was developed in EU-ADR [23]. In short, centres create harmonised input of the population and event file according to strict instructions. Jerboa Vaccine was based on the Jerboa software used in EU-ADR [23] and was used for standardised calculation of crude, stratified and standardised incidence rates. Jerboa Vaccine is an open license JAVA based script that runs locally, it outputs excel sheets with rates that were shared with the study-coordinating centre for further pooling and elaboration. All incidence rate scripts have been verified against standardised SAS scripts. The conceptual framework for data elaboration and sharing is depicted below.

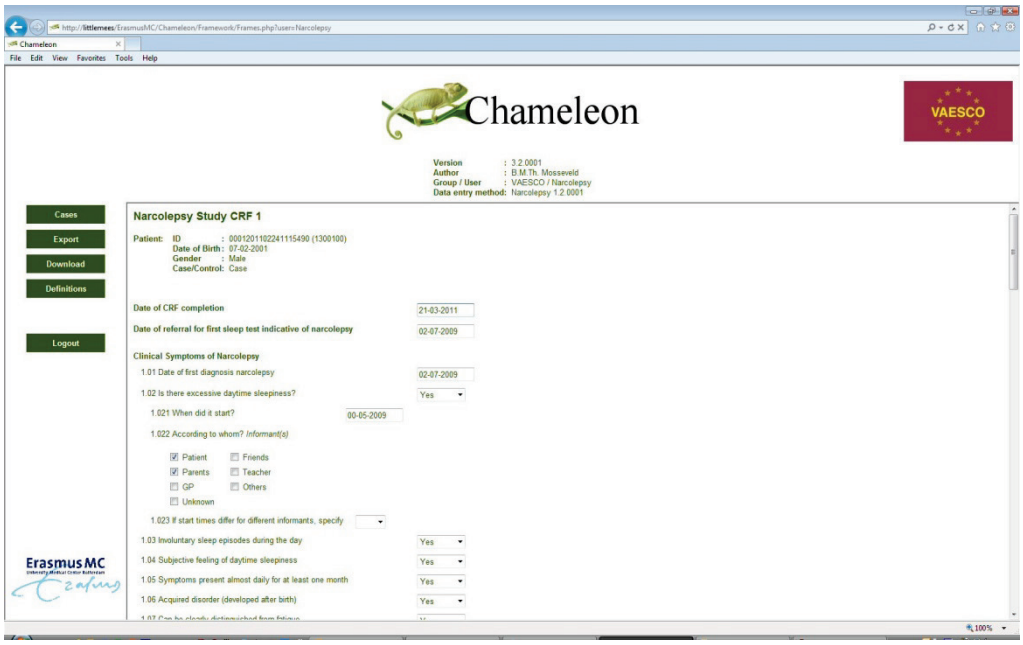
Figure 3.1.1 Conceptual framework for distributed calculation of background rates according to a harmonised process [23]



3.2 Data collection by case report forms for the case control study in selected countries

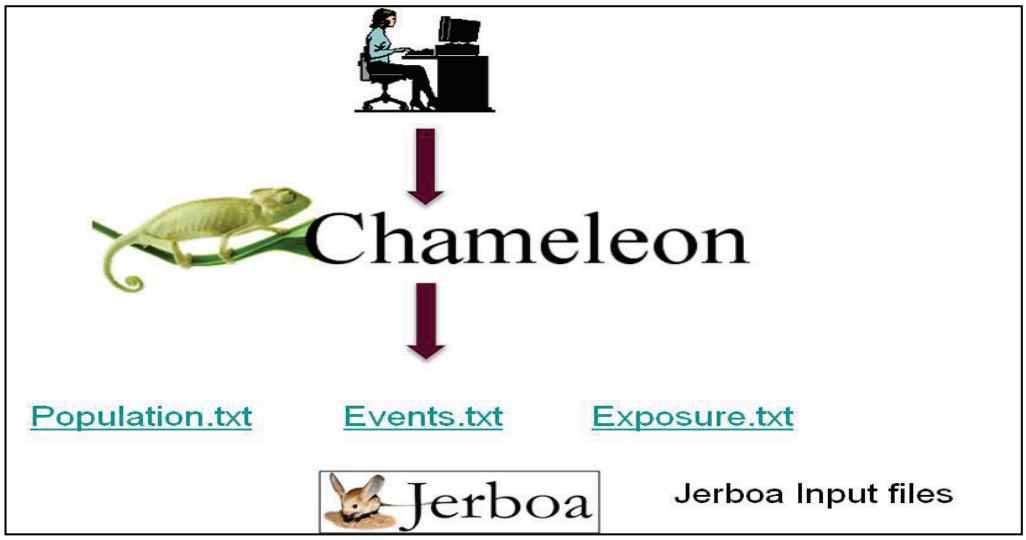
The narcolepsy case control study was also conducted in countries (Finland, Norway, Sweden, France, Italy) that did not have fully automated data on the outcome, exposure, or co-variates. Therefore the distributed data network concept was adapted to allow for flexibility in the creation of the common input files. This was done via standardised CRFs for data collection. To accommodate for differences in data collection prior to data entry to the Jerboa input files, and to allow for quality control at the stage of data entry, the CRFs were transformed into an online data entry system called CHAMELEON (see figure 3.2.1–3).

Figure 3.2.1. CHAMELEON data entry system screenshot



Following data entry Jerboa Vaccine created output files deprived of identifiable data elements. These datasets were sent to the data centre and pooled across countries. Data were transferred as encrypted dataset to the coordinating study centre. Study numbers will start by country code followed by study number. Guidelines for completing the CRFs were supplied.

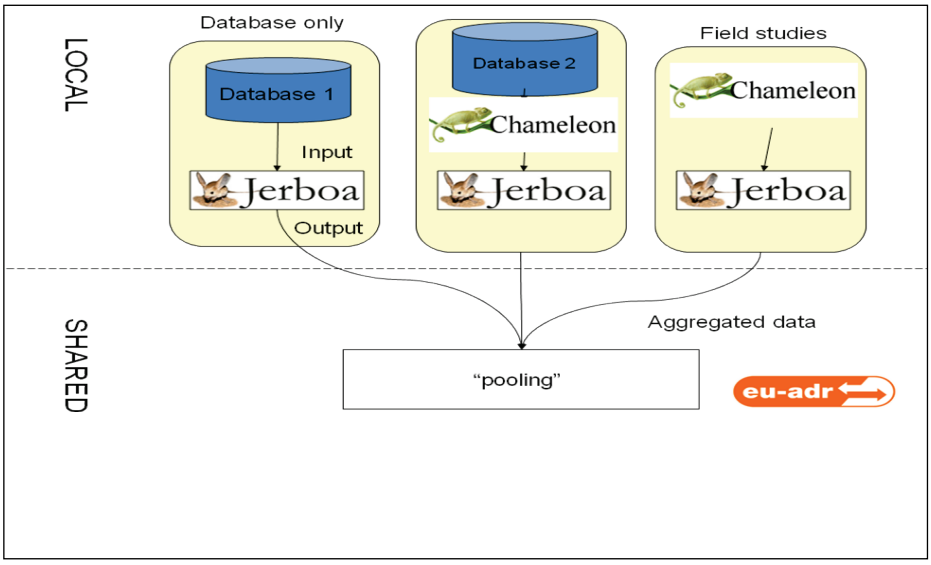
Figure 3.2.2. Chameleon-Jerboa Workflow



Pooling

Encrypted Jerboa output files were submitted to Erasmus University Medical Center where they were pooled for quality control and analysis. Each centre was asked for quality control through queries and was presented with the data prior to sharing this outside of the consortium.

Figure 3.2.3. Adapted and flexible distributed data network approach



4 Ethical considerations

Each country took the appropriate measures to legally obtain the required data for this study and to verify the governance and ethical requirements. The Jerboa Vaccine data infrastructure was implemented to address governance issues regarding sharing of data, only de-identified data are shared, without any reference to dates. Whereas processing of de-identified electronic health care data is often possible without consent, the current case control study required consent and ethical approval in many countries, because data on co-variates needed to be collected. The situation is described in table 4.1.

This study is conducted under the principles of the Helsinki declaration (59th World Medical Association General Assembly, Seoul, October 2008) and carefully considers local and European legislation on medical research in humans and the Directive 95/46 EC for secondary use of health care data[4].

Table 4.1 Required ethical approvals and process in each participating country

	Ethics approval needed/obtained	Governance approval for use of registries	Patient consent required
Norway	Yes/Yes	Yes	Yes (interview /chart review)
Sweden	Yes/Yes	No	Yes (interview /chart review)
Finland	Yes/Yes	Yes (ombudsman)	No
Denmark	No/No	General approval for use of registries not study specific	No
Netherlands	Yes (full application waived)	Yes (IPCI)	No
UK	No/No	Yes (ISAC)	No
France	Yes/Yes	Yes	Yes
Italy	Yes/Yes	No	Yes

[4] Available at: http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf

5 Results - background and incidence rates

This report provides non-validated rates of narcolepsy diagnoses for most of the countries, except for the Netherlands.

5.1 Diagnosis incidence rates of narcolepsy

5.1.1 Contributing databases/countries

Incidence rates of narcolepsy were calculated for eight centres in seven countries (see table and figure 5.).

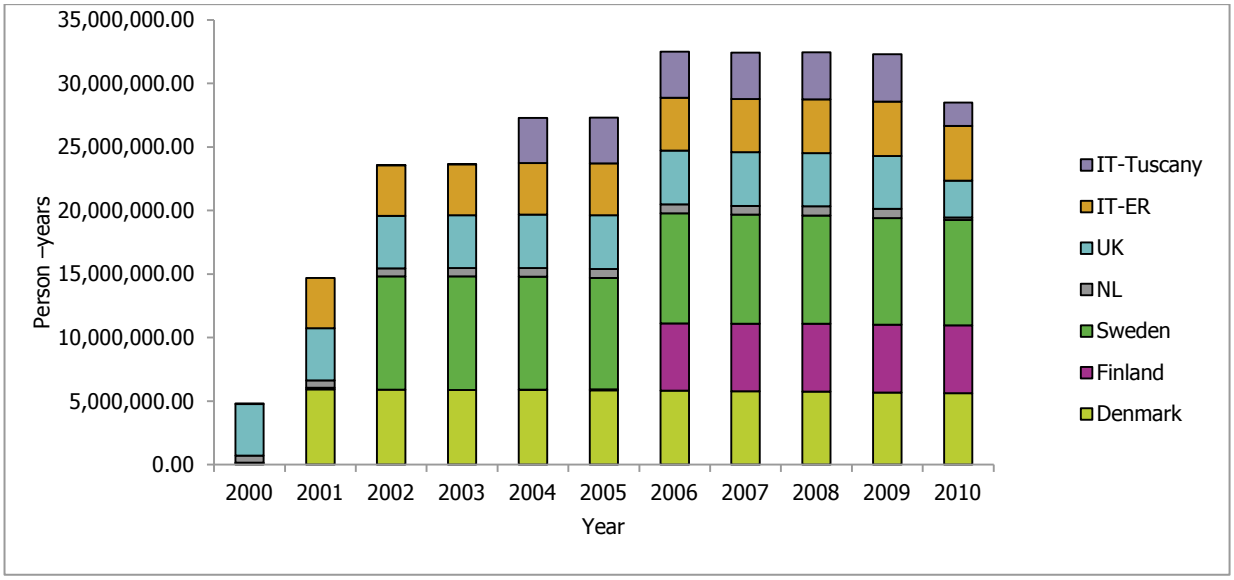
Table 5. Databases that were used for the calculation of narcolepsy diagnosis incidence rates in the VAESCO study

Datasource		Population covered	Type of data	Disease coding schemes	Codes used
Medical record databases					
United Kingdom GPRD		3.5 million	Population based medical records (GP and specialist diagnoses)	READ	F27.00, F270.00, F271.00, F27z.00
Netherlands IPCI		1 million	Population based medical records (GP and specialist diagnoses)	Narratives	GP/spec./hosp. diagnoses (text & validation)
Administrative databases national					
Denmark		5.5 million	Inpatient and outpatient diagnoses	ICD10	G47.4 (primary)
Sweden		9 million	Inpatient and outpatient diagnoses	ICD10	G47.4 (primary)
Finland		5 million	Inpatient and outpatient diagnoses	ICD10	G47.4 (primary/secondary)
Administrative databases regional					
Italy Emilia Romagna		3million	Inpatient diagnoses	ICD9-CM	347.00, 347.01, 347.10, 347.11
Italy Tuscany		3million	Inpatient diagnoses	ICD9-CM	347.00, 347.01, 347.10, 347.11

Codes that were used in the different dictionaries included: READ: F27.00, F270.00, F271.00, F27z.00; ICD-9: 347.00, 347.01, 347.10, 347.11; ICD-10: for G47.4 and ICPC there was no code and text searches were performed.

The total amount of follow-up amounted to 280 million person-years in the countries that could supply data through the Jerboa Vaccine system (see below). The size of the databases and the number of years with available data varied considerably between countries (see figure 5.). Denmark, Emilia Romagna region in Italy and Sweden provided data up to December 2010. Finland provided data up to December 2009. For 2010 age specific counts were provided. For the Tuscany region in Italy, the Netherlands-IPCI database and the UK general practice research database (GPRD) database, data were provided up to June, July, and October 2010 respectively.

Figure 5. Cumulative amount of person-time contributions by country and calendar year for the databases participating in the narcolepsy background rate study.



5.1.2 Cases and rates (all countries)

Specific country issues

In Finland individual level population data could not be used for record linkage with the events. The population input file for Jerboa was generated on the basis of the age and sex distribution provided by Finnish national statistics. Cases were added and submitted through Jerboa except for 2010, for which only age-specific case counts were supplied. For 2010 the age distribution of 2009 was utilised but monthly rates could not be calculated.

In Norway the registries were used to generate the population and case aggregate counts. Data were submitted as counts and not through Jerboa. Data were transformed into similar output tables by the data management centre. Since diagnostic data were only available from 2008, prevalent cases cannot be excluded especially at the beginning. This may lead to higher rates than expected. For children/adolescents this is assumed to be a smaller issue than for adults. Thus, Norway was not included in the pooled background rate analyses but presented separately.

For Italy, cases were retrieved from a discharge diagnosis registry. Table 5.1.1 demonstrates the number of cases in the various data sources.

The total number of events over the datasets that could be pooled was 2 608.

Table 5.1.1 Number of narcolepsy cases and person-time by country, age and period (run in period 1 year)

Age group	<5		5–19		20–59		60+		Total	
	Events	Person years	Events	Person years	Events	Person years	Events	Person years	Events	Person years
All periods and all countries	16	12799232	389	47078002	1607	151639211	596	67998483	2608	279514928
All countries per period*										
before Apr 2009	13	10768869	214	38529298	1273	123190932	492	54209585	1992	226698685
Apr–Sep 2009	0	636874	21	2645520	96	8715246	28	4203936	145	16201577
after Sep 2009–Dec 2010	3	1393488	154	5903184	238	19733032	76	9584962	471	36614666
Per country and period										
Denmark										
before Apr 2009	4	2956217	70	9276075	430	26507878	127	9600136	631	48340307
Apr-Sep 2009	0	168434	10	530670	35	1513983	11	638972	56	2852059
Oct 2009–Dec. 2010	2	415340	20	1307898	95	3722075	23	1613836	140	7059148
Finland										
before Apr 2009	0	1067325	25	3058982	125	9328552	28	3925942	178	17380801
Apr–Sep 2009	0	148859	7	465041	14	1418339	2	645264	23	2677503
Oct 2009–Dec 2010	0	370342	67	1155659	46	3524606	20	1608053	133	6658660
Netherlands-IPCI (validated)										
before Apr 2009	0	382389	2	1152660	5	3409295	0	1110673	7	6055018
Apr–Sep 2009	0	19412	1	67789	3	201074	0	78709	4	366983
Oct 2009–July 2010	0	19751	1	71454	1	212248	0	84745	2	388198
Sweden										
before Apr 2009	4	1812490	60	11896404	368	34356779	195	15444590	627	63510263
Apr–Sep 2009	0	0	1	720442	20	2337035	6	1153437	27	4210915
Oct 2009–Dec 2010	0	0	60	1658312	69	5823022	23	2915889	152	10397224
United Kingdom-GPRD										
before Apr 2009	2	2204139	46	6898825	268	20948055	92	8513115	408	38564135
Apr–Sep 2009	0	123161	1	367346	16	1109949	5	481019	22	2081474
Oct 2009–October 2010	1	231731	4	692403	11	2107655	7	918839	23	3950627
Italy-Emilia Romagna										
before Apr 2009	2	1516057	7	3966515	51	18465073	34	9814277	94	33761923
Apr-Sep 2009	0	101021	1	265421	5	1151005	1	623522	7	2140970
Oct 2009–Dec 2010	0	254446	1	673296	12	2873998	2	1567652	15	5369391
Italy-Tuscany										
before Apr 2009	1	830251	4	2279836	26	10175301	16	5800851	47	19086239
Apr–Sep 2009	0	75987	0	228811	3	983861	3	583014	6	1871673
Oct 2009–July 2010	0	101880	1	344163	4	1469428	1	875949	6	2791420

**excluding Norway and not all GPs updated until the end.*

Figure 5.1.1 shows the age and sex related incidence of narcolepsy. The incidence of narcolepsy diagnosis is age dependent. A peak is observed between 15 and 30 years of age. Around the age of 50–75 a second peak is visible.

The incidence rate is very similar between males and females after age 40, but females have much higher rates in the category 15–40 years of life, although this was dominated by data from Denmark.

Figure 5.1.1 Pooled incidence of narcolepsy diagnosis by age and sex for all non-signalling countries and including signalling countries (2000 to 2010).

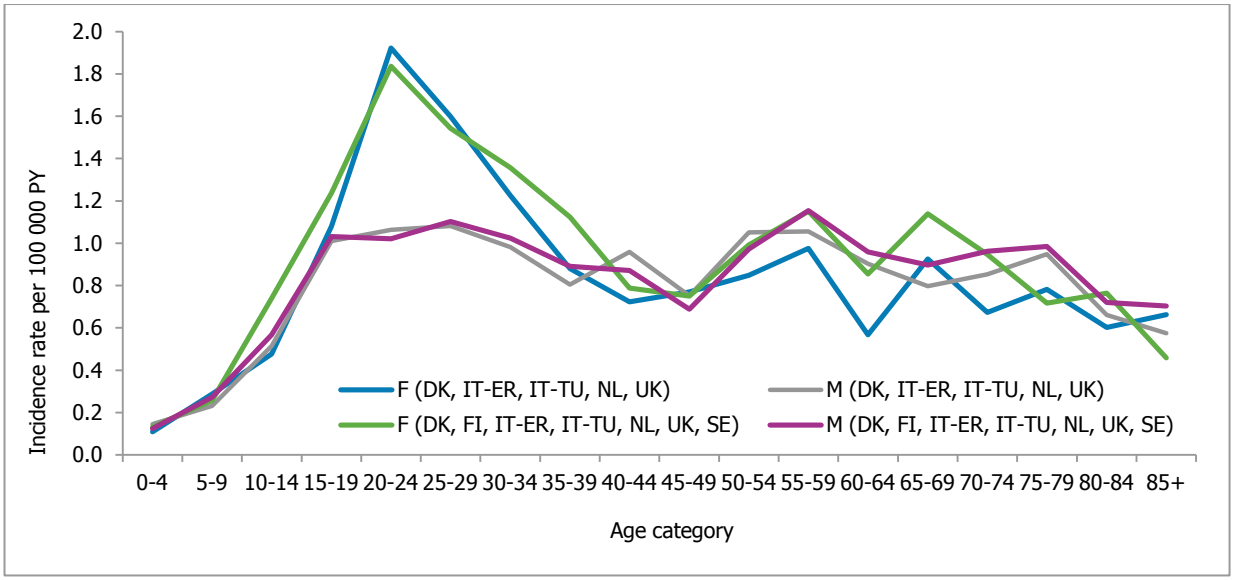


Table 5.1.2. Incidence rate of narcolepsy by country (2000–2010, excluding Norway)

	< 5 years		5–19 years		20–59 years		60+ years		Group Total	
	IR	95%CI	IR	95%CI	IR	95%CI	IR	95%CI	IR	95%CI
Pooled*	0.13	(0.07–0.20)	0.83	(0.75–0.91)	1.06	(1.01–1.11)	0.88	(0.81–0.95)	0.93	(0.90–0.97)
Denmark	0.17	(0.07–0.35)	0.90	(0.74–1.09)	1.91	(1.76–2.07)	1.36	(1.16–1.58)	1.42	(1.33–1.52)
Finland	0.00	-	2.12	(1.73–2.56)	1.30	(1.12–1.49)	0.81	(0.61–1.06)	1.25	(1.12–1.39)
Italy (Tuscany & Emilia Romagna)	0.10	(0.03–0.28)	0.18	(0.10–0.29)	0.29	(0.23–0.35)	0.30	(0.23–0.28)	0.27	(0.23–0.31)
Sweden	0.22	(0.07–0.52)	0.85	(0.71–1.01)	1.07	(0.98–1.18)	1.15	(1.00–1.31)	1.03	(0.96–1.10)
United Kingdom (GPRD)	0.12	(0.03–0.31)	1.22	(1.09–1.37)	1.02	(0.93–1.11)	1.05	(0.86–1.27)	1.02	(0.93–1.11)
Netherlands (IPCI) (non-validated)	0.00	-	0.93	(0.51–1.57)	1.65	(1.28–2.09)	0.86	(0.46–1.49)	1.26	(1.02–1.55)
Netherlands (IPCI) (validated)	0.00	-	0.31	(0.10–0.74)	0.24	(0.12–0.43)	0.00	-	0.19	(0.11–0.32)

**Excluding Norway, including Finland 2010 and validated NL-IPCI rates. IR= Incidence rate*

In general the crude incidence rates are quite similar between the countries and the pooled estimate is 0.93 per 100 000 PY (95% 0.90–0.97) considering all countries and the entire period.

5.1.3 Effect of age and calendar time on the incidence of narcolepsy diagnosis (all countries)

If the data are presented by influenza A(H1N1)pdm09 vaccination period (pre-pandemic influenza, pandemic influenza-pre vaccination and (post) pandemic influenza and vaccination), Finnish data for 2010 can be included. In table 5.1.3 pooled and country specific rates are given by age and influenza/vaccination period with rate ratios estimating the relative change in pre-vaccination and post-vaccination diagnosis rates. The country specific rate ratios show significant increases in the 5–19 age group and in Finland (RR: 6.4; 95% CI: 4.2–9.7), Sweden (RR: 7.5 95% CI: 5.2–10.7) and Denmark (RR: 1.9 95% CI: 1.1–3.1). In Finland an increase was also observed in the over 60 year age group (RR: 1.9 95% CI: 1.1-3.3), and in Denmark in the 20–59 year age group (RR: 1.5 95% CI: 1.2-1.9). In the UK a significant decrease in narcolepsy diagnoses between the pre and post vaccination periods was observed in the 20–59 year age group (RR: 0.41 95% CI: 0.22–0.74).

Table 5.1.3. Incidence of narcolepsy diagnoses by period, age and country

Age group	<5 years		5-19 years		20-59 years		60+ years	
	n[2)]	IR	n	IR	n	IR	n	IR
Signalling								
Sweden								
before Apr 2009	4	0.22	60	0.50	368	1.07	195	1.26
Apr–Sep 2009	0		1	0.14	20	0.86	6	0.52
Till Sep 2009	4	0.22	61	0.48	388	1.06	201	1.21
Oct. 2009–dec 2010	0		60	3.62	69	1.18	23	0.79
RR (95% CI) [1)]		0.00		7.5 (5.2–10.7)		1.1 (0.9–1.5)		0.6 (0.4–1.0)
Finland								
before Apr 2009	0	0.00	25	0.82	125	1.34	28	0.71
Apr–Sep 2009	0	0.00	7	1.51	14	0.99	2	0.31
Till Sep 2009	0	0.00	32	0.91	139	1.29	30	0.66
Oct. 2009–Dec 2010	0	0.00	67	5.80	46	1.31	20	1.24
RR (95% CI) [1)]		NA		6.4 (4.2–9.7)		1.01 (0.7–1.4)		1.90 (1.1–3.3)
Non-signalling								
Denmark								
before Apr 2009	4	0.14	70	0.75	430	1.62	127	1.32
Apr–Sep 2009	0	0.00	10	1.88	35	2.31	11	1.72
Till Sep 2009	4	0.13	80	0.82	465	1.66	138	1.35
Oct 2009–Dec 2010	2	0.48	20	1.53	95	2.55	23	1.43
RR (95% CI) [1)]		3.8 (0.7–20.5)		1.9 (1.1–3.1)		1.5 (1.2–1.9)		1.05 (0.7–1.6)
Netherlands-IPCI (validated)								
before Apr 2009	0	0.00	2	0.17	5	0.15	0	0.00
Apr–Sep 2009	0	0.00	1	1.48	3	1.49	0	0.00
Till Sep 2009	0	0.00	3	0.25	8	0.22	0	0.00
Oct 2009–July 2010	0	0.00	1	1.40	1	0.47	0	0.00
RR (95% CI) [1)]		NA		5.7 (0.6–54)		2.13 (0.27–17)		NA
United Kingdom-GPRD								
before Apr 2009	2	0.09	46	0.67	268	1.28	92	1.08
Apr–Sep 2009	0	0.00	1	0.27	16	1.44	5	1.04
Till Sep 2009	2	0.09	47	0.65	284	1.29	97	1.08
Oct 2009–Oct 2010	1	0.43	4	0.58	11	0.52	7	0.76
RR (95% CI) [1)]		5.0 (0.5–55.4)		0.9 (0.3–2.5)		0.4 (0.2–0.7)		0.7 (0.3–1.5)
Italy (ER/Tuscany)								
before Apr 2009	3	0.13	11	0.18	77	0.27	50	0.32
Apr–Sep 2009	0	0.00	1	0.20	8	0.37	4	0.33
Till Sep 2009	3	0.12	12	0.18	85	0.28	54	0.32
Oct 2009–Dec 2010	0	0.00	2	0.20	16	0.37	3	0.12
RR (95% CI) [1)]		0.00		1.1 (0.2–4.9)		1.33 (0.78–2.28)		0.38 (0.12–1.22)

[1)] RR=IR after/IR before; [2)] n=Events

5.1.4 Changes in diagnosis incidence rates of narcolepsy by calendar time (all countries)

Figure 5.1.2 shows that the pooled incidence rate of narcolepsy diagnosis is quite stable over time until July 2010 when it rises steeply. Few countries were able to deliver data for the entire year of 2010 (only Sweden and Denmark). At the tail of the graph an increase is observed but this is mostly driven by data from Denmark and Sweden. Finnish data for 2010 were not included since data for the year 2010 were not submitted through Jerboa and could not be separated by month.

Figure 5.1.2. Incidence of narcolepsy diagnosis by time (pooled, excluding Norway and data from Finland for 2010, including validated rates for the Netherlands-IPCI) (IR per 100 000 PY)

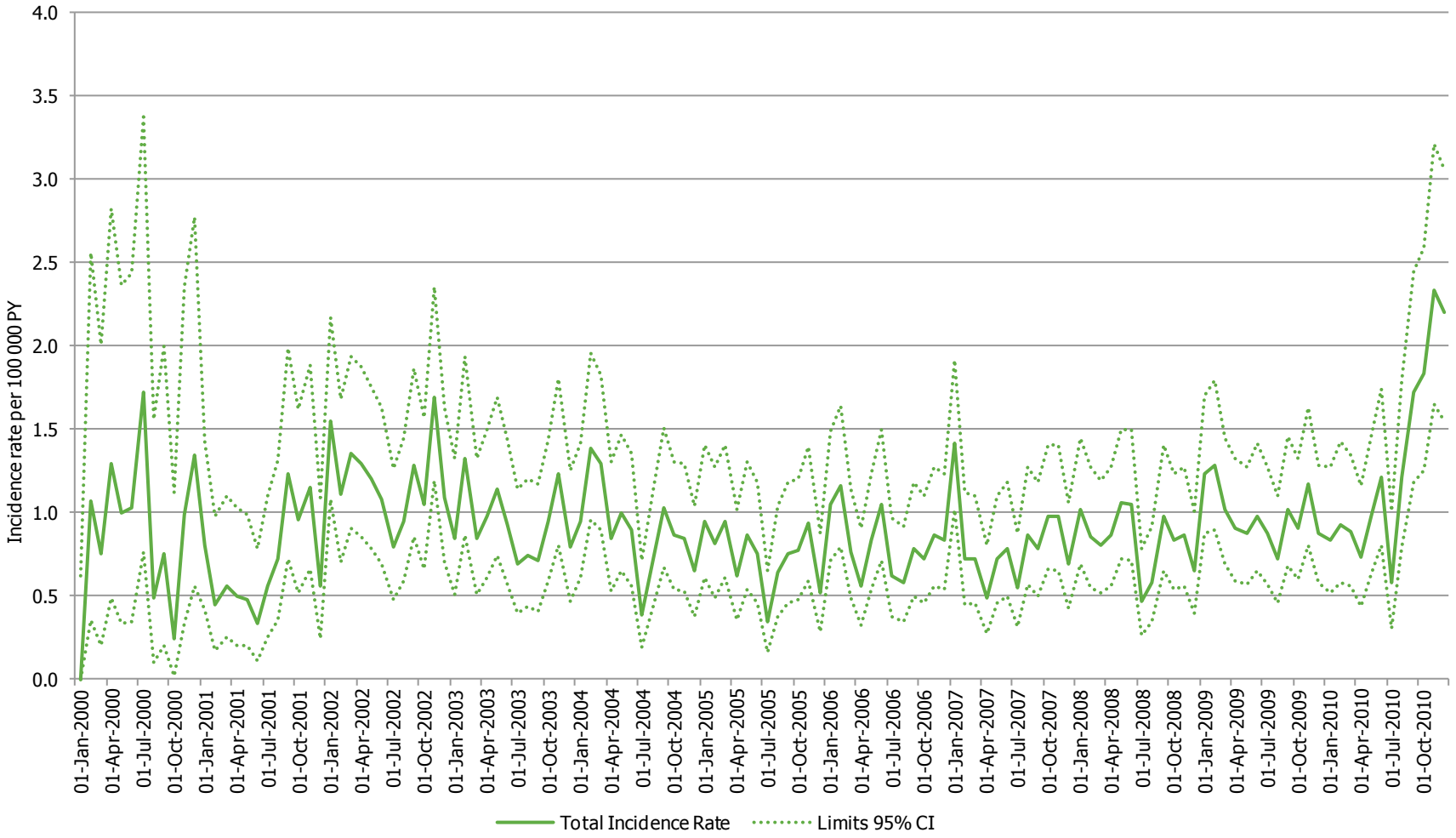
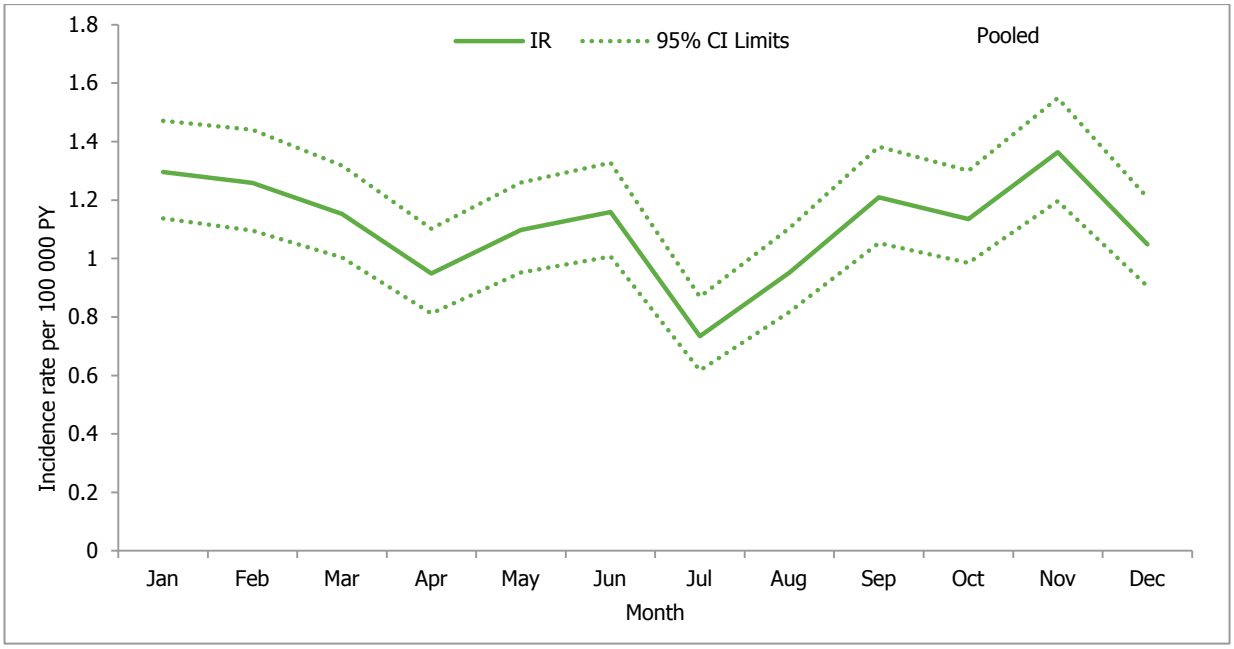


Figure 5.1.4. Incidence of narcolepsy diagnosis by calendar month (2000–2010), all countries except Norway)



The diagnosis rates exhibit a seasonal pattern and appear highest around January with a marked dip in July.

5.1.5 Cases and rates per country

Incidence of narcolepsy diagnosis in Denmark

Table 5.1.4. Cases and person-time distribution by age and calendar time

Age	<5		5–19		20–59		60+		Total	
Year	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years
2000	0	108069	0	3230	0	9078	0	2962	0	123339
2001	0	357440	2	1172312	33	3309451	14	1085289	49	5924492
2002	0	352273	5	1160252	42	3297472	22	1096852	69	5906848
2003	0	348371	11	1147606	49	3277963	11	1114032	71	5887972
2004	0	346376	11	1137920	38	3261269	17	1140551	66	5886116
2005	1	342622	9	1121002	51	3220425	15	1165956	76	5850005
2006	1	339952	9	1105927	76	3180691	14	1197577	100	5824146
2007	0	338878	9	1089235	58	3125875	15	1227879	82	5781866
2008	2	339117	9	1076124	64	3077010	12	1256899	87	5749150
2009	0	335821	19	1058619	66	3019744	19	1274244	104	5688427
2010	2	331073	16	1042416	83	2964958	22	1290704	123	5629151
Total	**6**	**3539991**	**100**	**11114643**	**560**	**31743936**	**161**	**11852944**	**827**	**58251514**

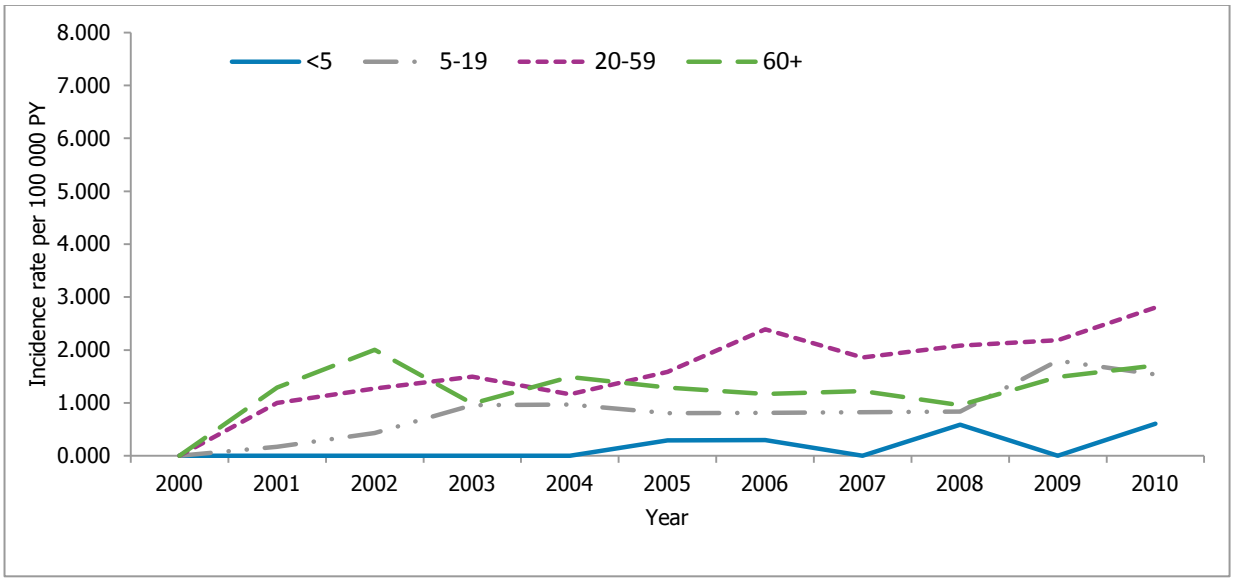
The overall incidence rate of narcolepsy diagnosis in Denmark was 1.42 (95%CI: 1.33–1.52). The rate in females was slightly higher than in males 1.57 vs. 1.27 per 100 000 PY.

Table 5.1.5. Incidence rate of narcolepsy diagnosis by year and sex per 100 000 PY

	Women	95%CI	Men	95%CI	Total	95%CI
2000	0.00	-	0.00	-	0.00	-
2001	0.88	(0.59–1.27)	0.78	(0.51–1.14)	0.83	(0.62–1.08)
2002	1.08	(0.76–1.51)	1.25	(0.90–1.71)	1.17	(0.92–1.47)
2003	1.36	(0.99–1.83)	1.05	(0.73–1.47)	1.21	(0.95–1.51)
2004	1.19	(0.84–1.63)	1.05	(0.73–1.47)	1.12	(0.87–1.42)
2005	1.54	(1.14–2.04)	1.06	(0.73–1.48)	1.30	(1.03–1.62)
2006	2.06	(1.59–2.63)	1.37	(1.00–1.85)	1.72	(1.40–2.08)
2007	1.52	(1.12–2.02)	1.32	(0.95–1.79)	1.42	(1.14–1.75)
2008	1.73	(1.30–2.26)	1.29	(0.93–1.76)	1.51	(1.22–1.86)
2009	1.92	(1.46–2.48)	1.73	(1.30–2.27)	1.83	(1.50–2.21)
2010	2.54	(2.00–3.18)	1.83	(1.37–2.38)	2.19	(1.82–2.60)
Total	**1.57**	**(1.43–1.72)**	**1.27**	**(1.14–1.40)**	**1.42**	**(1.33–1.52)**

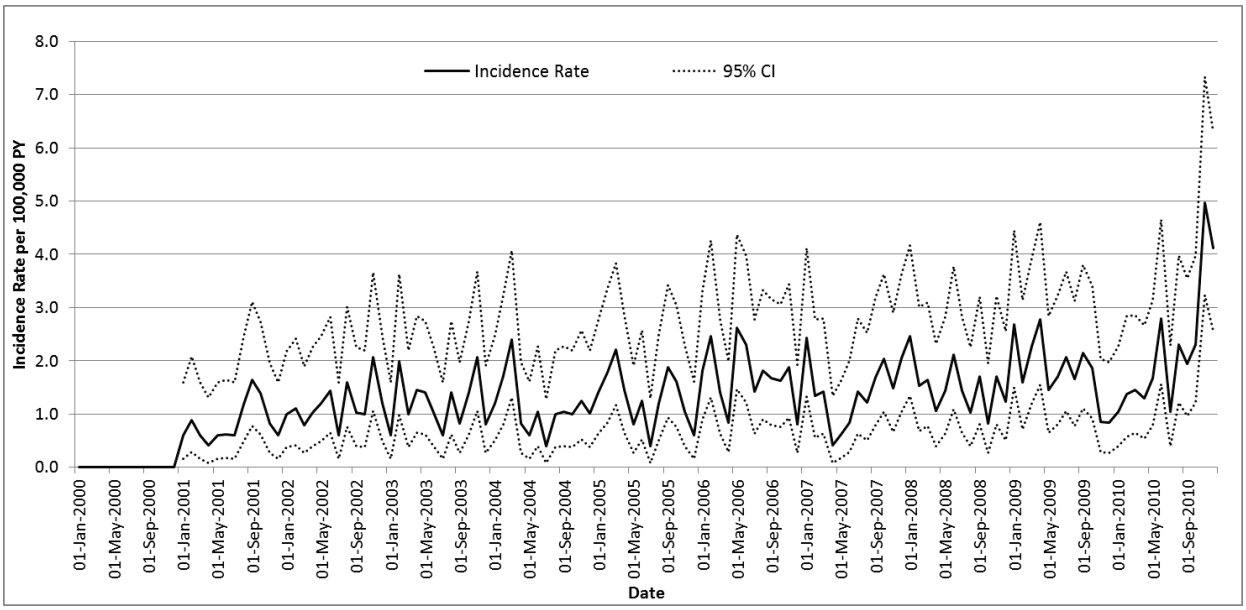
Figure 5.1.5 shows the change in incidence rates over time. In persons 5–19 and 60+ years of age the incidence of narcolepsy diagnosis increased in 2009. These groups were not targeted specifically for influenza A(H1N1)pdm09 vaccination. Only the patients at risk of influenza related complications were offered influenza A(H1N1)pdm09 vaccination. In the 20–59 year olds there is a gradual increase over time that continues after 2009.

Figure 5.1.5. Incidence of narcolepsy diagnosis by age and year per 100 000 PY



In Denmark the overall incidence of narcolepsy diagnosis was stable over time with a significant increase after September 2010.

Figure 5.1.6. Incidence of narcolepsy diagnosis by month per 100 000 PY



5.1.6 Incidence of narcolepsy diagnosis in Finland

Table 5.1.6. Cases and person-time distribution by age and calendar time

Age	<5		5–19		20–59		60+			
Year	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years
2000	0	0	0	0	0	0	0	0	0	0
2001	0	0	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0	0	0
2004	0	29131	0	0	0	0	0	0	0	29131
2005	0	87640	0	0	0	0	0	0	0	87640
2006	0	289576	5	948984	38	2897906	9	1160054	52	5296519
2007	0	292316	5	942609	44	2873647	6	1202831	55	5311404
2008	0	295646	13	937971	29	2857611	11	1249379	53	5340607
2009	0	296109	9	925059	46	2821166	10	1283498	65	5325831
2010**	0	296109	67	925059	28	2821166	14	1283498	109	5325831
Total	**0**	**1586526**	**99**	**4679682**	**185**	**14271497**	**50**	**6179259**	**334**	**26716964**

***2010 cases added manually: not supplied through Jerboa, and rates based on 2009 population composition*

The overall incidence rate of narcolepsy diagnosis in Finland was 1.05 (95%CI: 0.92–1.20). The rate in females was slightly higher than in males 1.13 vs. 0.97 per 100 000 PY. These data differ slightly from the recently published data from Partinen et al [24].

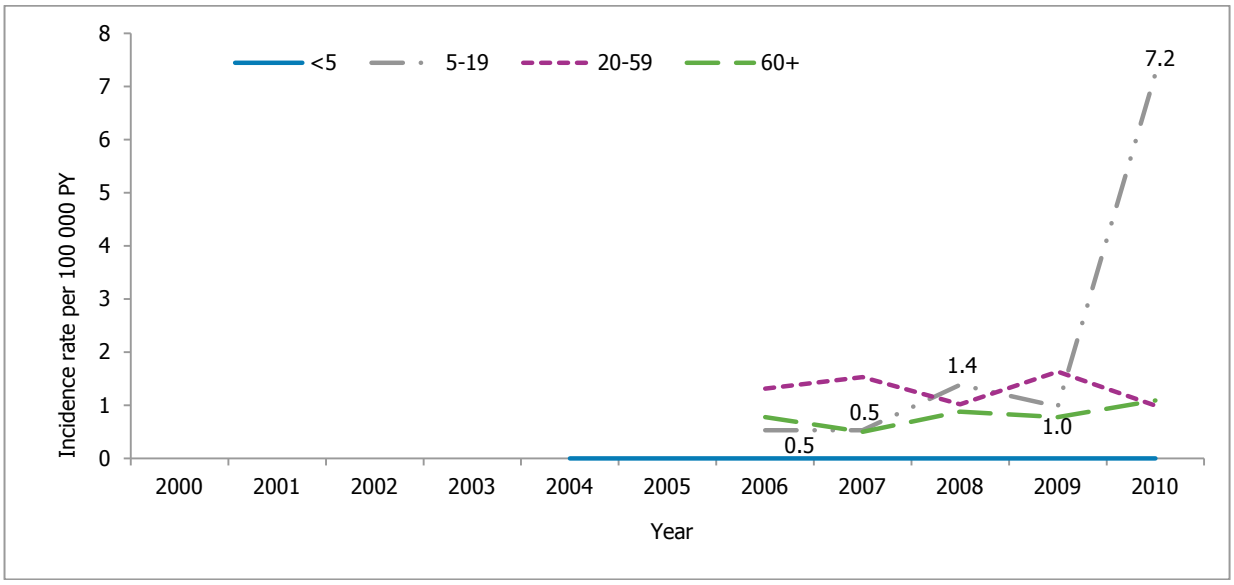
Table 5.1.7. Incidence rate of narcolepsy diagnosis by year and sex per 100 000 PY

	Women	95%CI	Men	95%CI	Total	95%CI
2000		-		-		-
2001		-		-		-
2002		-		-		-
2003		-		-		-
2004	0.00	-	0.00	-	0.00	-
2005	0.00	-	0.00	-	0.00	-
2006	1.11	(0.76–1.56)	0.85	(0.55–1.26)	0.98	(0.74–1.28)
2007	1.03	(0.70–1.47)	1.04	(0.70–1.49)	1.04	(0.79–1.34)
2008	0.99	(0.67–1.42)	0.99	(0.66–1.43)	0.99	(0.75–1.29)
2009	1.40	(1.01–1.90)	1.03	(0.70–1.48)	1.22	(0.95–1.55)
2010		-		-	2.05	(1.69–2.46)
Total	**1.13**	**(0.94–1.34)**	**0.97**	**(0.80–1.18)**	**1.05**	**(0.92–1.20)**

**2010 cases added manually*

Figure 5.1.7 shows the change in incidence rates over time, with a steep increase in the 5–19 years of age category.

Figure 5.1.7. Incidence of narcolepsy diagnosis by age and year per 100 000 PY



2010 data were submitted as counts, not through Jerboa

5.1.7 Incidence of validated narcolepsy diagnosis in the Netherlands

The Dutch data were obtained from IPCI, a general practice medical record database. Since there is no specific international classification of primary care (ICPC) code for narcolepsy, potential cases were identified by looking for text strings. In the Netherlands-IPCI database 86 cases were identified through a text search followed by a review of the electronic medical record to discard obvious false positives (e.g. sleep test for different indications). After validation of these 86 cases by narcolepsy experts according to the BC criteria, a predictive value (PPV) for 'text searches' of less than 50% (even lower when with insufficient data were kept in denominator) was found. Of the 86 cases, 43 had another diagnosis, 24 had insufficient data or no test and two cases were prevalent cases but correct diagnoses. As can be seen in figure 5.1.8, the time-pattern of the incidence rate changed substantially after validation.

Table 5.1.8. Cases and person-time distribution by age and calendar time

Age	<5		5-19		20-59		60+		Total	
Year	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years
2000	0	36 355	0	103 065	0	311 940	0	85 464	0	536 824
2001	0	38 559	0	111 055	1	332 683	0	94 516	1	576 813
2002	0	40 918	0	119 443	0	355 442	0	105 060	0	620 863
2003	0	42 758	0	126 875	1	375 112	0	114 946	1	659 691
2004	0	43 916	0	132 553	0	388 891	0	124 457	0	689 817
2005	0	43 295	1	131 927	0	386 312	0	128 121	1	689 655
2006	0	42 708	1	130 115	0	382 851	0	131 928	1	687 602
2007	0	42 164	0	129 578	1	379 418	0	138 056	1	689 215
2008	0	41 831	0	134 674	1	397 720	0	149 961	1	724 186
2009	0	38 752	2	135 290	5	401 404	0	157 003	7	732 449
2010	0	10 296	0	37 327	0	110 845	0	44 615	0	203 083
Total	**0**	**421 552**	**4**	**1 291 902**	**9**	**3 822 617**	**0**	**1 274 126**	**13**	**6 810 198**

Upon inclusion of ascertained cases only, the overall incidence rate of narcolepsy diagnosis in the Netherlands reduced from 1.2 per 100 000 to 0.20 per 100 000 PY (95%CI: 0.11–0.43), the pattern also changed shape (see figure 5.1.8), part of which may be due to lack of data for most recent cases. The validated rates rather than the unvalidated rates were used in the pooled estimates. The rate in females was slightly higher than in males 0.23 vs. 0.15 per 100 000 PY.

Figure 5.1.8. Change of incidence rates in the Netherlands upon validation (IR per 100 000 PY)

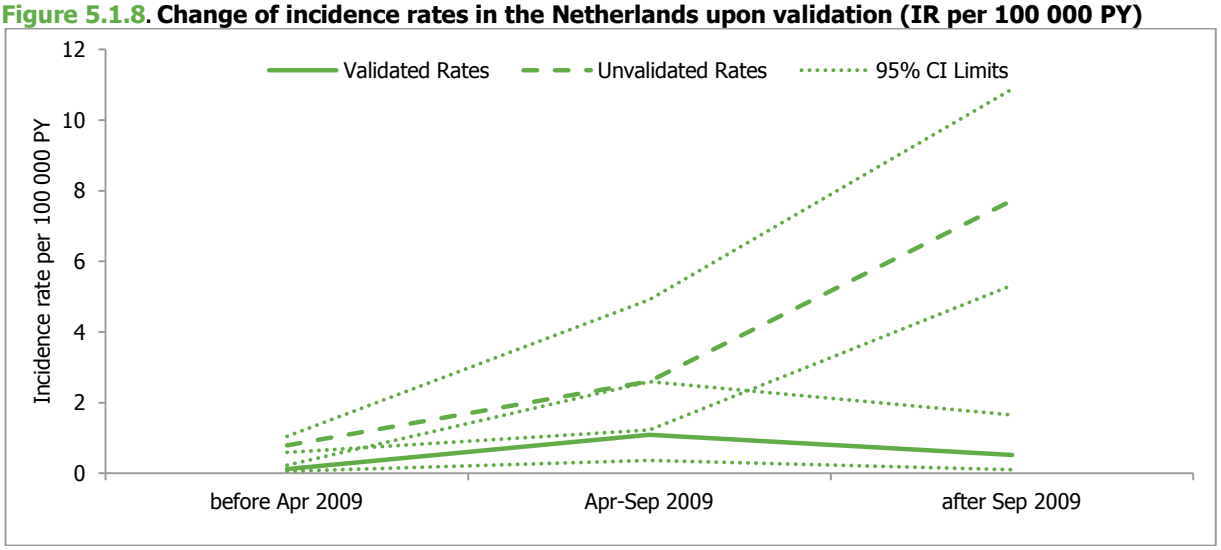
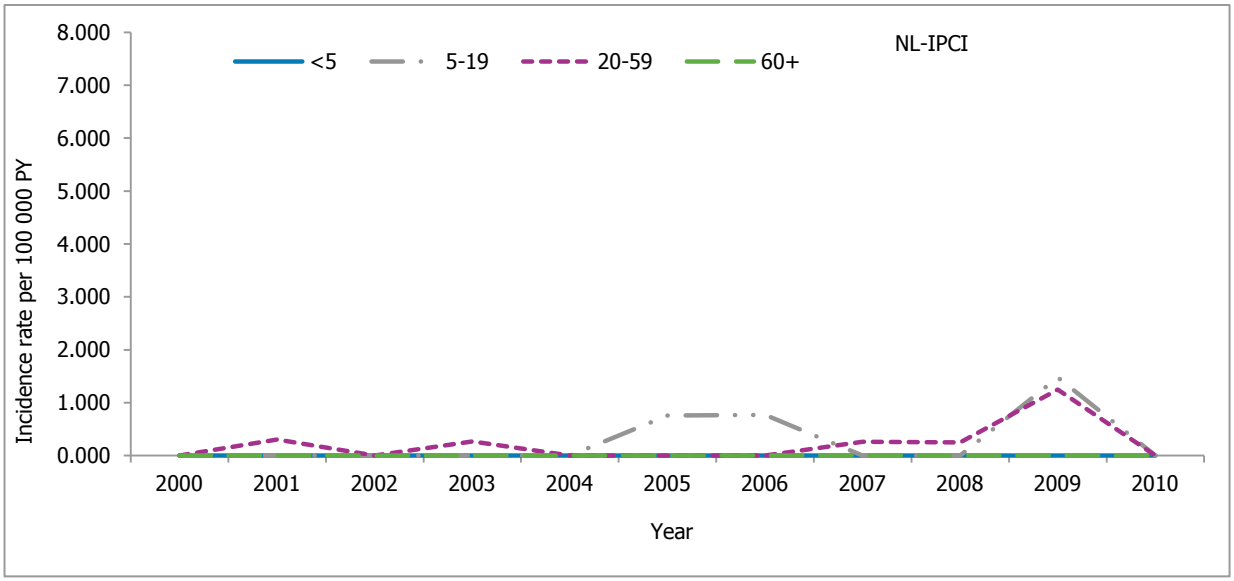


Table 5.1.9. Incidence rate of narcolepsy diagnosis by year and sex per 100 000 PY

	Women	95%CI	Men	95%CI	Total	95%CI
2000	0.00	-	0.00	-	0.00	-
2001	0.34	-	0.00	-	0.17	-
2002	0.00	-	0.00	-	0.00	-
2003	0.30	-	0.00	-	0.15	-
2004	0.00	-	0.00	-	0.00	-
2005	0.28	-	0.00	-	0.15	-
2006	0.28	-	0.00	-	0.15	-
2007	0.28	-	0.00	-	0.15	-
2008	0.00	-	0.28	-	0.14	-
2009	0.80	(0.22–2.13)	1.12	(0.38–2.67)	0.96	(0.43–1.88)
2010	0.00	-	0.00	-	0.00	-
Total	**0.23**	**(0.11–0.43)**	**0.15**	**(0.06–0.33)**	**0.20**	**(0.11–0.32)**

A change in incidence rates over time in the 5–19 and 20–59 years of age the incidence of narcolepsy diagnosis increased in later years are shown in Figure 5.1.9, although all rates were very unstable. These groups were not targeted specifically for influenza A(H1N1)pdm09 vaccination. In general the patients at risk for complication of influenza infections and all those aged < 5 years were offered influenza A(H1N1)pdm09 vaccination.

Figure 5.1.9. Incidence of narcolepsy diagnosis by age and year per 100 000 PY



5.1.8 Incidence of narcolepsy diagnosis in Italy-Tuscany

Table 5.1.10. Cases and person-time distribution by age and calendar year

Age	<5		5–19		20–59		60+		Total	
Year	Events	Person-years	Events	Perso-years	Events	Person-years	Events	Person-years	Events	Person-years
2000	0	0	0	0	0	0	0	0	0	0
2001	0	0	0	0	0	0	0	0	0	0
2002	0	13 980	0	0	0	0	0	0	0	13 980
2003	0	42 390	0	0	0	0	0	0	0	42 390
2004	1	142 035	2	420 026	6	1 918 985	1	1 069 836	10	3 550 883
2005	0	145 265	0	424 971	4	1 934 836	5	1 078 324	9	3 583 396
2006	0	147 765	0	432 404	2	1 942 126	2	1 099 048	4	3 621 342
2007	0	149 849	1	440 718	3	1 942 219	7	1 122 771	11	3 655 557
2008	0	151 516	1	449 774	9	1 954 318	1	1 146 079	11	3 701 686
2009	0	149 731	1	456 634	8	1 962 614	3	1 162 703	12	3 731 682
2010	0	655 86	0	228 284	1	973 492	1	581 054	2	1 848 416
Total	**1**	**1 008 118**	**5**	**2 852 810**	**33**	**12 628 589**	**20**	**7 259 814**	**59**	**23 749 331**

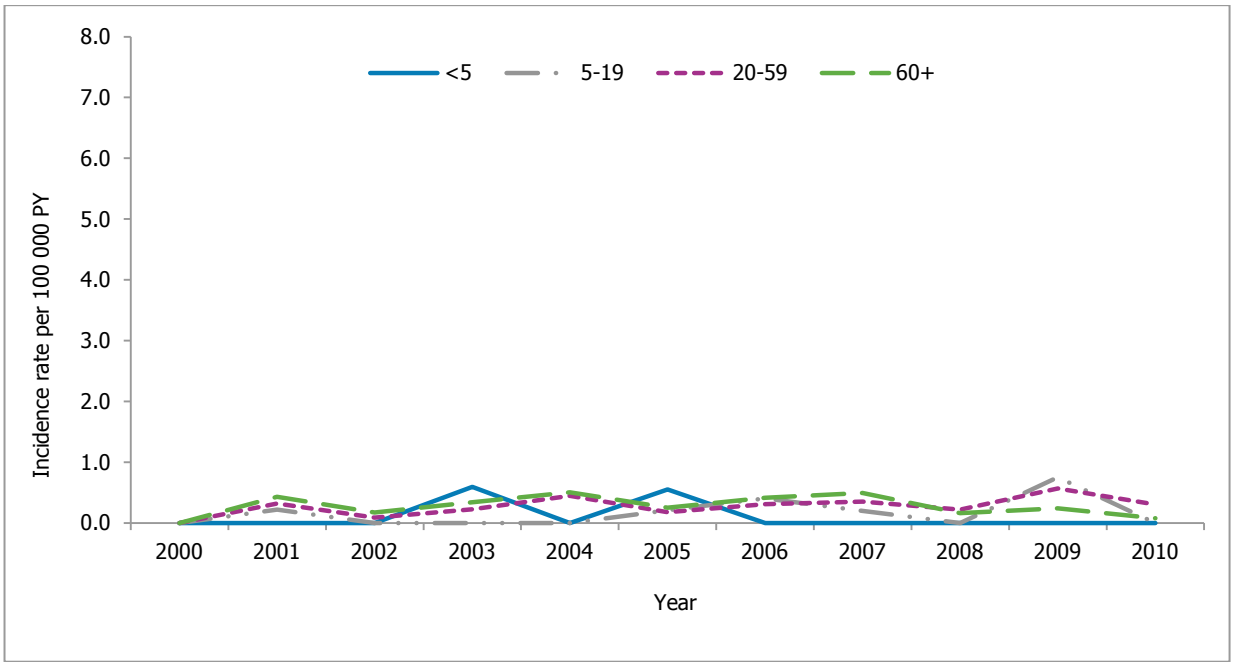
The overall incidence rate of narcolepsy diagnosis in Tuscany was 0.24 (95%CI: 0.19–0.32). The rate in females was slightly lower than in males 0.23 vs. 0.26 per 100 000 PY. This rate is much lower than in other countries since cases in Italy are based on hospital discharge diagnoses.

Table 5.1.11. Incidence rate of narcolepsy diagnosis by year and sex (IT-Tuscany) per 100 000 PY

	Women	95%CI	Men	95%CI	Total	95%CI
2000		-		-		-
2001		-		-		-
2002	0.00	-	0.00	-	0.00	-
2003	0.00	-	0.00	-	0.00	-
2004	0.38	(0.17–0.74)	0.18	(0.05–0.47)	0.28	(0.14–0.50)
2005	0.21	(0.07–0.51)	0.29	(0.11–0.64)	0.25	(0.12–0.46)
2006	0.16	(0.04–0.42)	0.06	-	0.11	(0.04–0.26)
2007	0.31	(0.13–0.65)	0.29	(0.11–0.63)	0.30	(0.16–0.52)
2008	0.21	(0.07–0.49)	0.40	(0.18–0.78)	0.30	(0.16–0.51)
2009	0.21	(0.07–0.49)	0.45	(0.21–0.85)	0.32	(0.18–0.54)
2010	0.10	-	0.11	-	0.11	-
Total	**0.23**	**(0.16–0.33)**	**0.26**	**(0.18–0.37)**	**0.24**	**(0.19–0.32)**

Figure 5.1.10 shows the change in incidence rates over time, in none of the age categories was an increase observed on a population level. In Italy vaccination uptake was very low.

Figure 5.1.10. Incidence of narcolepsy diagnosis by age and year per 100 000 PY



5.1.9 Incidence of narcolepsy diagnosis in Italy-Emilia-Romagna

Table 5.1.12. Cases and person-time distribution by age and calendar year

Age	<5		5–19		20–59		60+		Total	
Year	Events	Person years	Events	Person years	Events	Person years	Events	Person years	Events	Person years
2000	0	48 694	0	1 245	0	6056	0	3 161	0	59 155
2001	0	158 920	1	45 2071	7	2 193 680	5	1 158 598	13	3 963 269
2002	0	163 268	0	455 205	2	2 194 152	2	1 165 205	4	3 977 830
2003	1	168 497	0	460 690	5	2 202 784	4	1 172 494	10	4 004 465
2004	0	174 275	0	469 591	10	2 227 332	6	1 183 910	16	4 055 109
2005	1	180 276	1	478 896	4	2 248 524	3	1 185 971	9	4 093 667
2006	0	185 582	2	493 743	7	2 272 881	5	1 196 548	14	4 148 754
2007	0	190 894	1	506 112	8	2 270 202	6	1 212 226	15	4 179 435
2008	0	196 471	0	519 345	5	2 284 833	2	1 231 011	7	4 231 660
2009	0	201 318	4	529 829	13	2 295 680	3	1 243 440	20	4 270 268
2010	0	203 329	0	538 506	7	2 293 953	1	1 252 885	8	4 288 672
Total	**2**	**1 871 524**	**9**	**4 905 233**	**68**	**22 490 076**	**37**	**12 005 451**	**116**	**41 272 284**

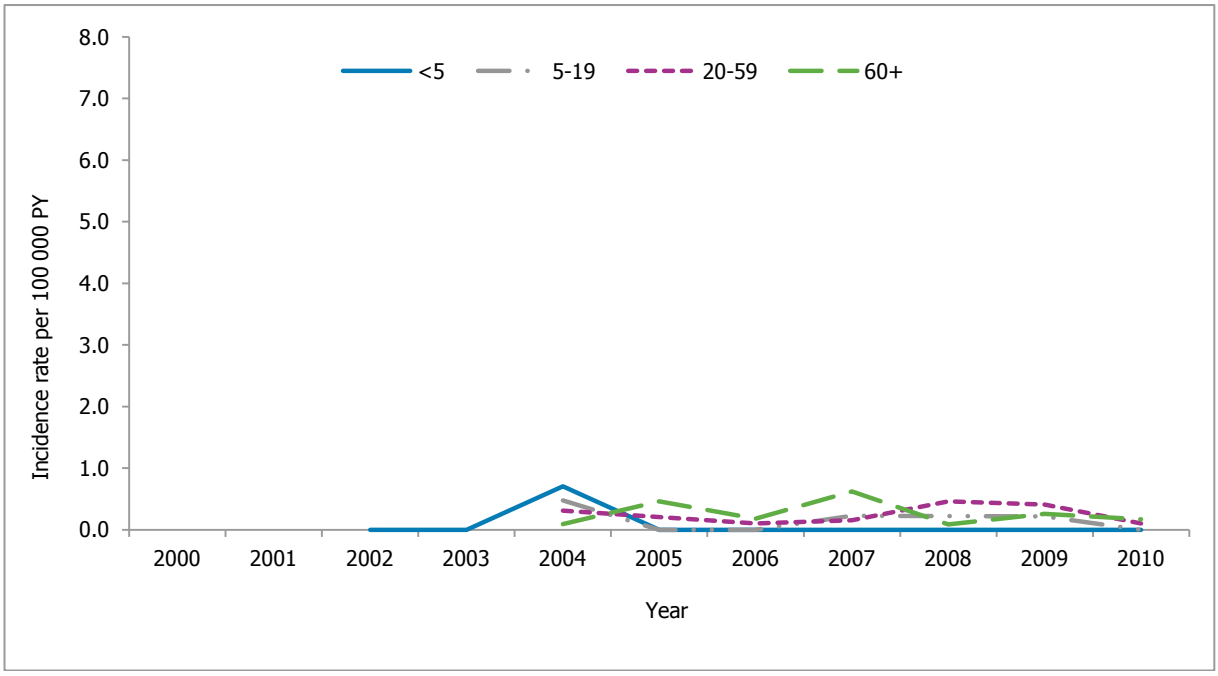
The overall incidence rate of narcolepsy diagnosis in Emilia Romagna was 0.28 (95%CI: 0.23–0.34) per 100 000 PY. The rate in females was slightly lower than in males 0.23 vs. 0.34 per 100 000 PY. This rate is much lower than in other countries since cases in Italy are based on hospital discharge diagnoses, it is consistent with the rate in Tuscany.

Table 5.1.13. Incidence rate of narcolepsy diagnosis by year and sex per 100 000 PY

	Women	95%CI	men	95%CI	Total	95%CI
2000	0.00	-	0.00	-	0.00	-
2001	0.20	(0.07–0.47)	0.47	(0.23–0.86)	0.33	(0.18–0.54)
2002	0.00	-	0.21	(0.07–0.49)	0.10	(0.03–0.24)
2003	0.24	(0.09–0.53)	0.26	(0.10–0.56)	0.25	(0.13–0.44)
2004	0.24	(0.09–0.53)	0.56	(0.30–0.97)	0.39	(0.23–0.63)
2005	0.19	(0.06–0.45)	0.25	(0.10–0.55)	0.22	(0.11–0.40)
2006	0.47	(0.24–0.83)	0.20	(0.07–0.47)	0.34	(0.19–0.55)
2007	0.23	(0.09–0.51)	0.49	(0.25–0.87)	0.36	(0.21–0.58)
2008	0.14	(0.04–0.37)	0.19	(0.07–0.46)	0.17	(0.07–0.32)
2009	0.41	(0.20–0.75)	0.53	(0.28–0.92)	0.47	(0.30–0.71)
2010	0.14	(0.04–0.36)	0.24	(0.09–0.53)	0.19	(0.09–0.35)
Total	**0.23**	**(0.17–0.30)**	**0.34**	**(0.27–0.43)**	**0.28**	**(0.23–0.34)**

Change in incidence rates over time are shown in Figure 5.1.11, in none of the age categories was an increase observed on a population level in 2010. In Italy vaccination uptake was very low.

Figure 5.1.11. Incidence of narcolepsy diagnosis by age and year (Emilia Romagna) per 100 000 PY



5.1.10 Incidence of narcolepsy diagnosis in Sweden

Table 5.1.14. Cases and person-time distribution by age and calendar time

Age	<5		5–19		20–59		60+		Total	
Year	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years
2000	0	47 327	0	0	0	0	0	0	0	47 327 45
2001	0	140 009	0	0	0	0	0	0	0	140 009
2002	1	459 010	9	1 678 923	88	4 780 938	55	2 000 779	153	8 919 651
2003	2	416 636	12	1 679 011	58	4 791 634	27	2 032 229	99	8 919 511
2004	1	327 348	8	1 678 093	58	4 791 952	33	2 080 479	100	8 877 873
2005	0	234 619	5	1 659 766	44	4, 747 472	21	2 119 635	70	8 761 493
2006	0	141 037	6	1 644 317	27	4 717 769	19	2 168 506	52	8 671 631
2007	0	46 499	6	1 627 662	39	4 691 230	17	2 215 072	62	8 580 465
2008	0	0	11	1 562 392	40	4 685 593	17	2 265 171	68	8 513 156
2009	0	0	5	1 437 466	46	4 661 711	16	2 299 923	67	8 399 101
2010	0	0	59	1 307 525	57	4 648 534	19	2 332 118	135	8 288 178
Total	**4**	**1 812 489**	**121**	**14 275 158**	**457**	**42,516,836**	**224**	**19 513 916**	**806**	**78 118 401**

The overall incidence rate of narcolepsy diagnosis in Sweden was 1.00 (95%CI: 0.96–1.10) per 100 000 PY. The rate in females was slightly higher than in males 1.18 vs. 0.88 per 100 000 PY.

Table 5.1.15. Incidence rate of narcolepsy diagnosis by year and sex per 100,000 PY

Year	Women	95%CI	Men	95%CI	Total	95%CI
2000	0.00	-	0.00	-	0.00	-
2001	0.00	-	0.00	-	0.00	-
2002	1.78	(1.42–2.20)	1.65	(1.31–2.07)	1.72	(1.46–2.00)
2003	1.31	(1.01–1.68)	0.91	(0.66–1.22)	1.11	(0.91–1.35)
2004	1.38	(1.07–1.76)	0.86	(0.62–1.17)	1.13	(0.92–1.36)
2005	0.75	(0.52–1.04)	0.85	(0.61–1.16)	0.80	(0.63–1.00)
2006	0.80	(0.57–1.10)	0.40	(0.24–0.62)	0.60	(0.45–0.78)
2007	0.88	(0.63–1.19)	0.56	(0.37–0.83)	0.72	(0.56–0.92)
2008	0.91	(0.66–1.23)	0.69	(0.47–0.97)	0.80	(0.63–1.01)
2009	1.06	(0.79–1.41)	0.53	(0.34–0.78)	0.80	(0.62–1.01)
2010	1.75	(1.38–2.19)	1.51	(1.17–1.92)	1.63	(1.37–1.92)
Total	**1.18**	**(1.07–1.29)**	**0.88**	**(0.79–0.98)**	**1.0**	**(0.96–1.10)**

A change in incidence rates over time is shown in Figure 5.1.12 with a steep increase in the 5–19 years age category consistent with that seen in Finland.

Figure 5.1.12. Incidence of narcolepsy diagnosis by age and year per 100 000 PY

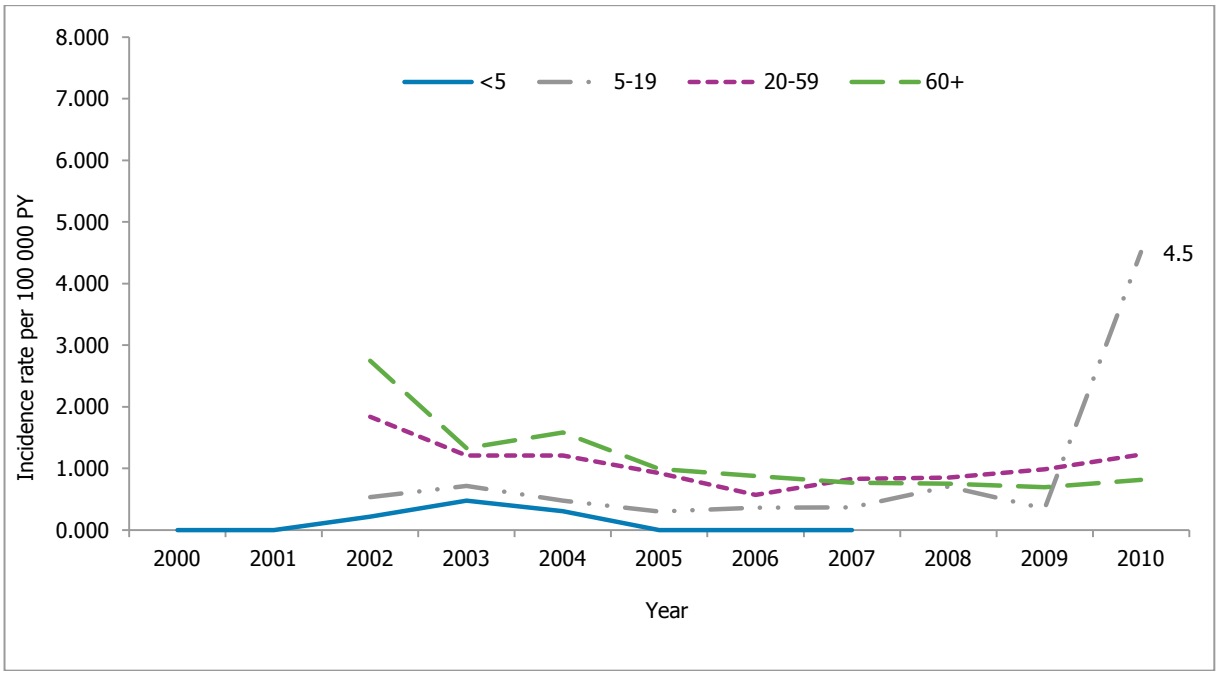
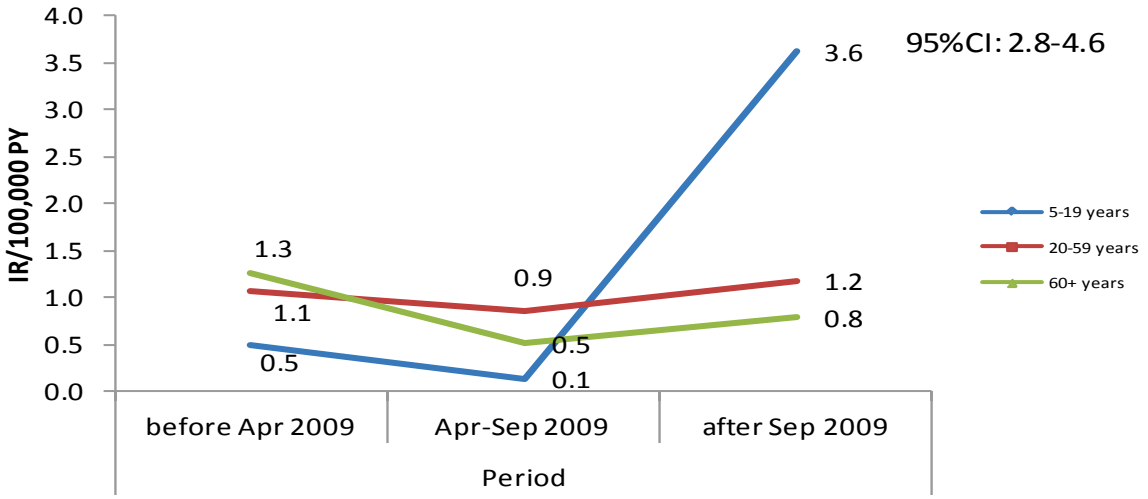


Figure 5.1.13. Incidence of narcolepsy diagnosis by age and period per 100 000 PY



5.1.11 Incidence of narcolepsy diagnosis in the United Kingdom

In the GPRD, cases were identified through READ codes. Case verification, carried out as part of the case control arm of the study, suggests the codes used to estimate the narcolepsy background rates have a very low positive predictive value. This low PPV suggests that if verification had been completed for the UK the rates might be similar to those reported for the Netherlands and Italy, however this is not represented yet in the background rates.

Table 5.1.16. Cases and person-time distribution by age and calendar time

Age	<5		5–19		20–59		60+		Total	
Year	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years	Events	Person-years
2000	0	241 136	5	712 046	31	2 228 471	7	879 610	43	4 061 261
2001	1	239 029	1	724 628	26	2 246 631	11	887 601	39	4 097 889
2002	1	235 368	8	736 434	33	2 261 823	16	895 486	58	4 129 112
2003	0	233 077	6	746 882	26	2 272 141	7	904 916	39	4 157 017
2004	0	233 956	2	760 516	39	2 290 632	14	919 819	55	4 204 923
2005	0	236 748	8	767 840	23	2 299 791	7	932 855	38	4 237 234
2006	0	238 415	8	765 075	24	2 291 737	10	942 135	42	4 237 362
2007	0	241 148	2	757 348	27	2 266 601	8	953 348	37	4 218 445
2008	0	244 745	6	746 375	28	2 241 016	10	961 148	44	4 193 283
2009	1	245 810	2	731 138	31	2 212 343	10	960 231	44	4 149 522
2010	0	169 600	3	510 291	7	1 554 474	4	675 825	14	2 910 189
Total	**3**	**2 559 031**	**51**	**7 95573**	**295**	**24 165 659**	**104**	**9 912 973**	**453**	**44 596 236**

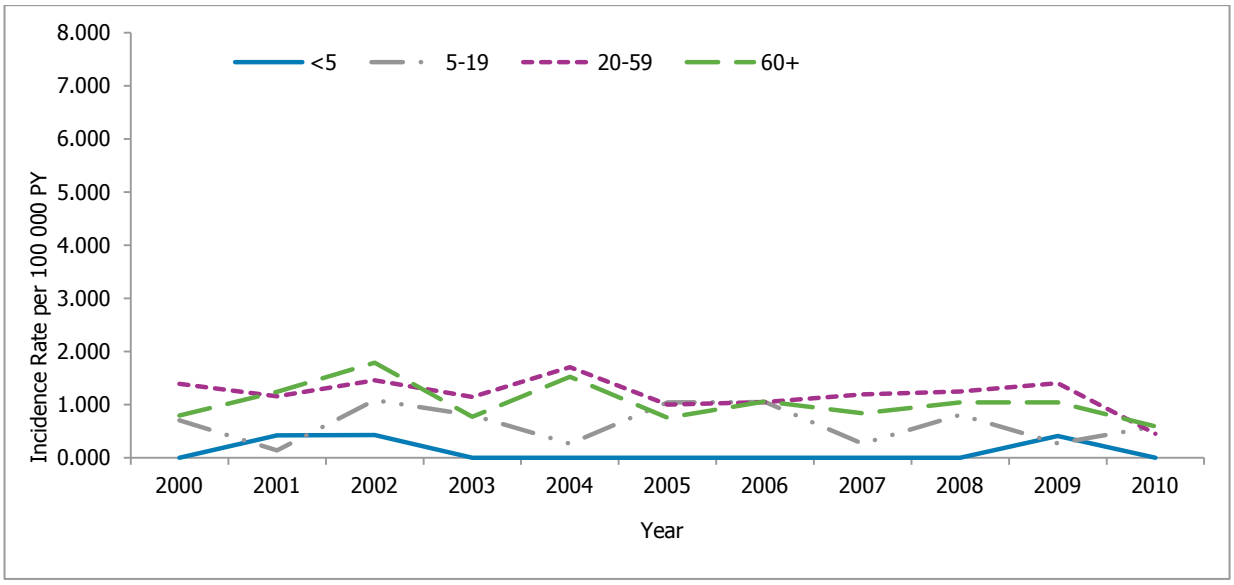
The overall incidence rate of narcolepsy diagnosis in the UK was 1.02 (95%CI: 0.93–1.11) per 100 000 PY. The rate in females was slightly lower than in males 0.96 vs 1.07 per 100 000 PY.

Table 5.1.17. Incidence rate of narcolepsy diagnosis by year and sex per 100 000 PY

	Women	95%CI	Men	95%CI	Total	95%CI
2000	0.93	(0.58–1.42)	1.19	(0.78–1.74)	1.06	(0.78–1.41)
2001	0.78	(0.46–1.23)	1.13	(0.73–1.66)	0.95	(0.69–1.29)
2002	1.25	(0.84–1.81)	1.56	(1.08–2.17)	1.40	(1.08–1.80)
2003	0.96	(0.60–1.45)	0.92	(0.57–1.40)	0.94	(0.68–1.27)
2004	1.14	(0.75–1.67)	1.48	(1.02–2.07)	1.31	(1.00–1.69)
2005	1.13	(0.74–1.65)	0.66	(0.38–1.08)	0.90	(0.64–1.22)
2006	1.08	(0.70–1.59)	0.90	(0.56–1.38)	0.99	(0.72–1.33)
2007	0.94	(0.60–1.43)	0.81	(0.49–1.27)	0.88	(0.63–1.20)
2008	1.04	(0.67–1.55)	1.05	(0.68–1.57)	1.05	(0.77–1.39)
2009	0.86	(0.53–1.33)	1.26	(0.84–1.82)	1.06	(0.78–1.41)
2010	0.27	(0.09–0.65)	0.69	(0.35–1.23)	0.48	(0.28–0.79)
Total	**0.96**	**(0.84–1.10)**	**1.07**	**(0.94–1.21)**	**1.02**	**(0.93–1.11)**

The change in incidence rates over time is shown in Figure 5.1.13, in none of the age categories was an increase observed on a population level in 2010.

Figure 5.1.14. Incidence of narcolepsy diagnosis by age and year



5.1.12 Narcolepsy diagnosis rates in Norway

Norway could not run the Jerboa software, and they could not entirely exclude prevalent cases (very little history available). Therefore Norwegian data have not been pooled with other countries.

Table 5.1.18. Cases and person-time distribution by age and calendar year

Age	<5		5–19		20–59		60+		Total	
Year	*Events*	*Person-years*	*Events*	*Person-years*	*Events*	*Person-years*	*Events*	*Person-years*	*Events*	*Person-years*
2000	0	0	0	0	0	0	0	0	0	0
2001	0	0	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0	0	0
2008	1	293 803	17	929 143	138	2 543 563	57	970 662	213	4 737 171
2009	1	298 460	10	932 970	88	2 575 349	31	992 473	130	4 799 252
2010	0	303 928	9	935 829	50	2 604 587	17	1 013 855	76	4 858 199
Total	**2**	**896 191**	**36**	**2 797 942**	**276**	**7 723 499**	**105**	**2 976 990**	**419**	**14 394 622**

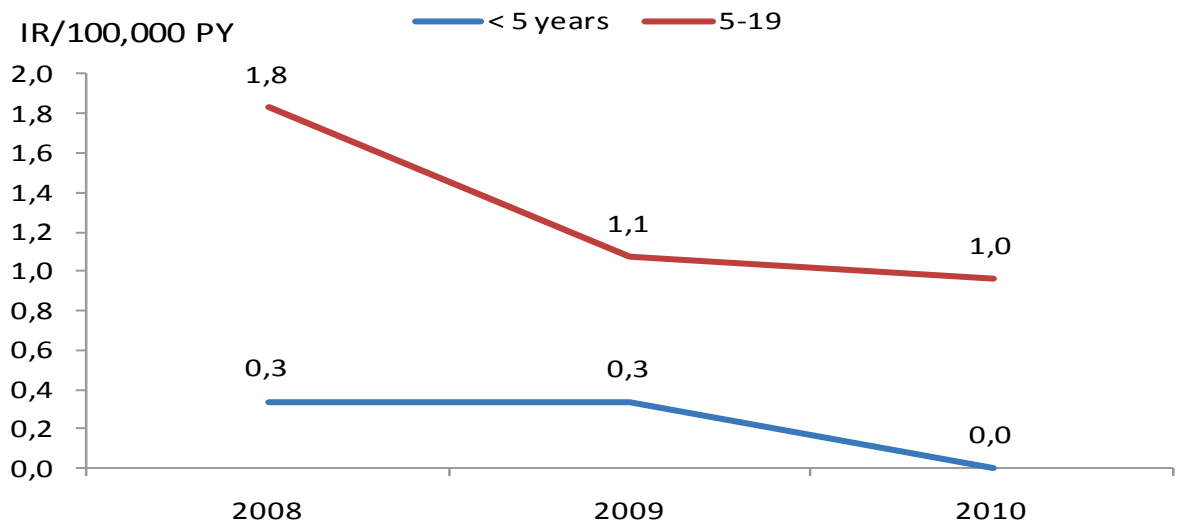
The overall rate of narcolepsy diagnosis/visits in Norway was 2.94 per 100 000 PY. The rate in females was higher than in males. This rate is much higher than in other countries since cases in Norway can be prevalent cases.

Table 5.1.19. Rate of narcolepsy diagnosis/visits by year and sex per 100 000 PY

	Women	95%CI	Men	95%CI	Total	95%CI
2000		-		-		-
2001		-		-		-
2002		-		-		-
2003		-		-		-
2004		-		-		-
2005		-		-		-
2006		-		-		-
2007		-		-		-
2008	5.43	(4.55–6.42)	3.56	(2.86–4.38)	4.50	(3.92–5.13)
2009	3.49	(2.81–4.30)	1.92	(1.42–2.54)	2.71	(2.27–3.21)
2010	1.73	(1.26–2.31)	1.40	(0.99–1.93)	1.56	(1.24–1.95)
Total	**3.54**	**(3.12–3.99)**	**2.33**	**(2.00–2.71)**	**2.94**	**(2.67–3.23)**

It is less likely to have prevalent cases in young people, therefore the rate is likely to be reflective of the incidence rate.

Figure 5.1.15. Incidence of narcolepsy diagnosis by age and year



Although it is not known whether the rates are actual incidence rates (and therefore the rate may be slightly higher than expected in 2008 at the beginning of follow-up), an increase in paediatric/adolescent cases was not seen until 2011.

6 Results: case control study

The statistical analysis plan of the case control study defines a primary analysis and a series of sensitivity analyses. The latter include variation of the index dates (from MSLT referral to EDS and diagnosis date); variation of the study period (primary/secondary/tertiary); variation in confounding control (matched versus unmatched); and sub-analyses. Results are described first for all countries together (section 6.1) and subsequently by country (sections 6.2–6.10)

6.1 All countries

6.1.1 Case attrition and time

This analysis is based on the data that centres could provide until the end of December 2011. In some countries case/control recruitment is still ongoing (France, Sweden, United Kingdom).

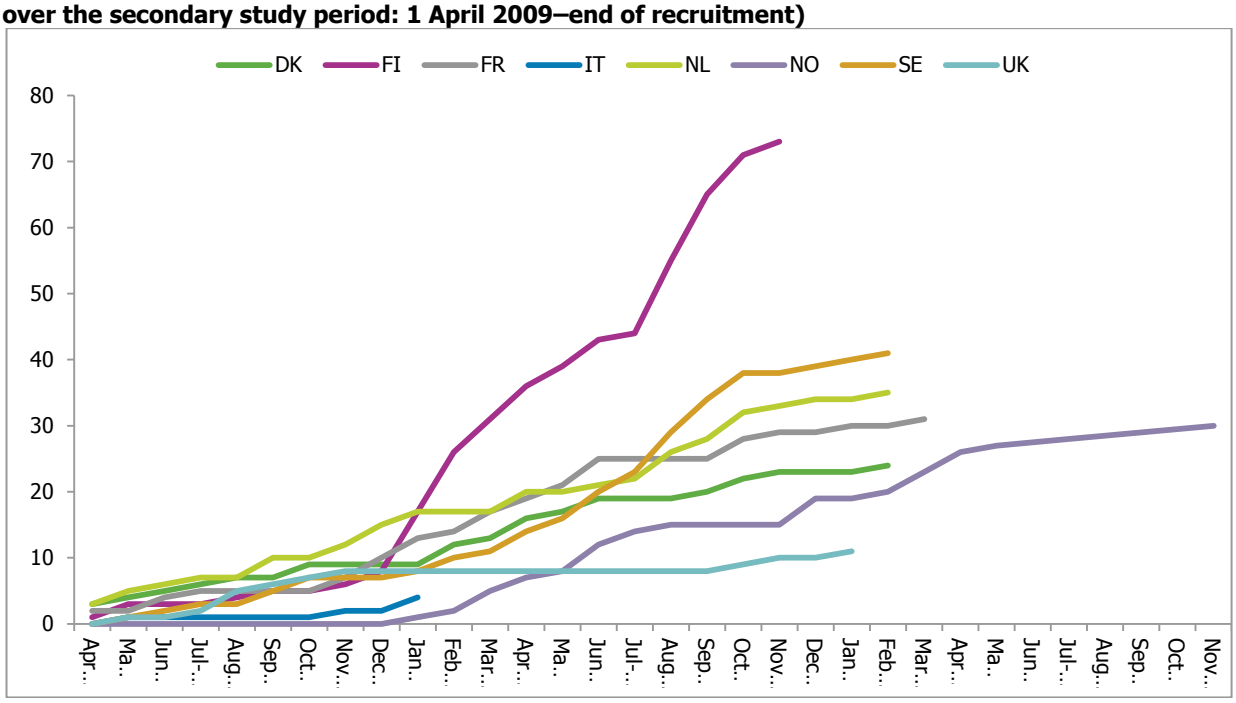
Table 6.1.1. Data by country

	Signalling		Non-signalling						Total
	Finland	Sweden	Netherlands	Denmark	United	Italy	Norway	France	
Size of source pop. (million)	5.5	9.4	10	4	4	4.3 (ER)	5	Unknown	>42
Influenza A(H1N1)pdm09 vaccine uptake rate in general population[22]	~50%	59%	30%	~6%	~8%	~9.5% (ER)	45%	~8%	
Primary study period (1 April 2009– 30 June 2010)									
Number of cases with MSLT referral in primary study period	43	20	21	19	8	4	12	25	152
Controls for cases in primary study period	430	50	210	95	171	16	44	47*	1063
Secondary study period (1 April 2009–end of data recruitment)									
Number of cases with MSLT referral data during April 2009–end	73	41	35	24	11	4	30	31	249
Total number of controls	730	91	347	120	246	16	110	60	1720

**one control missing in submitted data file ER: Emilia Romagna*

A total of 249 cases with valid dates of MSLT referral were submitted (signalling /non-signalling 114/135). A total of 152 cases entered into the primary analysis (MSLT referral date during April 2009–30 June 2010) (signalling/non-signalling: 63/89). Of those 152 cases, 88 were children/adolescents (signalling/non-signalling: 44/44) and 64 adults (signalling/non-signalling: 19/45). In the period after June 2010, 75 children/adolescents were included (signalling/non-signalling: 43/32) and 22 adults (signalling/non-signalling: 8/14).

Figure 6.1.1 Cases recruited over time (on the basis of MSLT referral date) by country (cumulatively over the secondary study period: 1 April 2009–end of recruitment)



DK – Denmark, FI – Finland, FR-France, IT – Italy, NL – the Netherlands, NO – Norway, SE – Sweden, UK – United Kingdom

Different countries have different periods of case recruitment as shown in Figure 6.1. The primary study period stopped on 30 June 2010 and the index date should fall between the start (1 April 2009) and end of the study period. However for the secondary study period, cases could be recruited as late as possible with most countries continuing recruitment into 2011. In Italy the last recruited eligible case had a referral date in January 2010, no other cases with diagnoses until November 2010 were eligible. Finland continued recruitment until December 2010 and had a substantial increase in cases after February 2010.

Differences in the recruitment period between countries may have an impact on the estimations (especially if diagnostic work up has changed) and this will mostly affect the secondary study period. It can impact on the primary study period, if the recruitment period is not long enough to actually capture all the cases that would have been eligible for the primary study period. This could happen because of the long lag time between EDS onset, MSLT referral and diagnosis, which one needs to be diagnosed with in order to be included in the study (see section 7 for further discussion).

Figure 6.1.2 Number of paediatric/adolescent cases (y-axis) recruited over time (time on the basis of MSLT referral date) by exposure to influenza A(H1N1)pdm09 vaccine (secondary period: April 2009–end of recruitment)

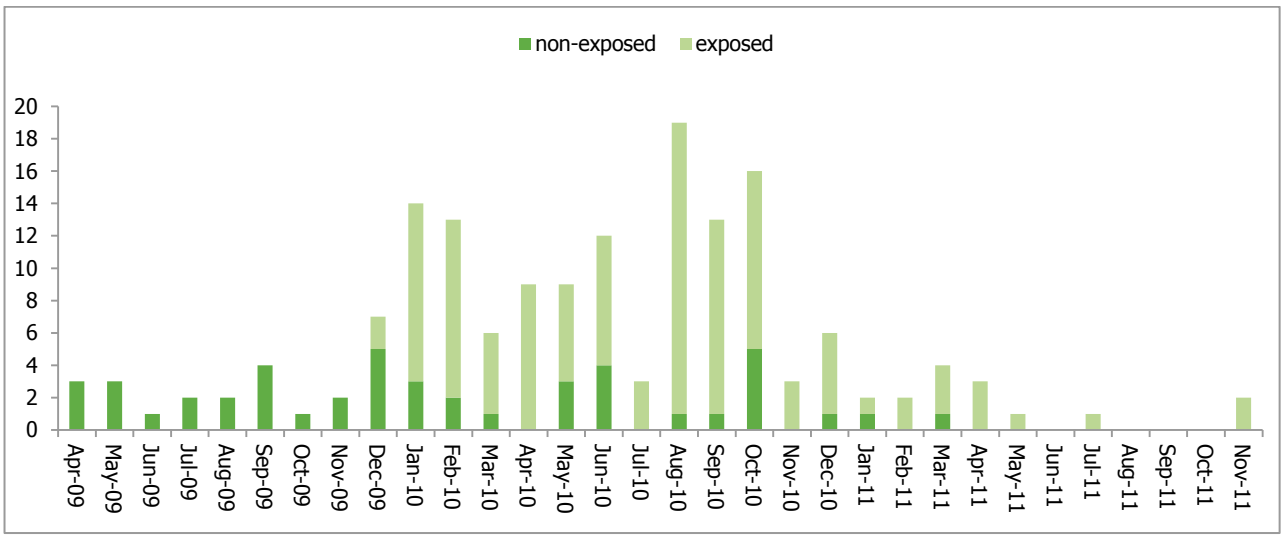
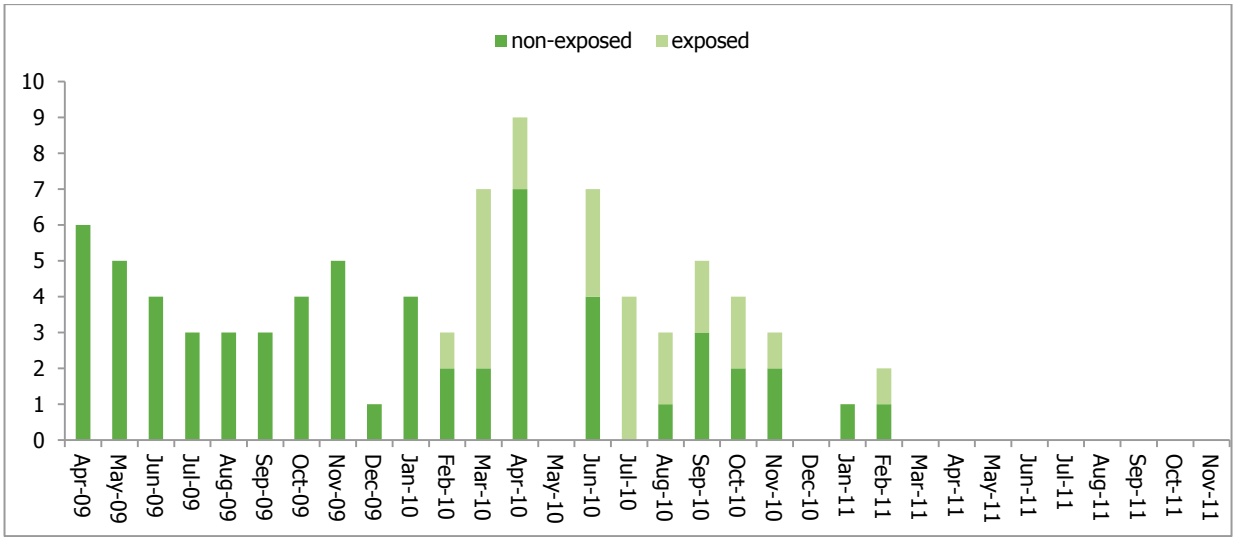


Figure 6.1.3 Number of adult cases (y-axis) recruited over time (time on the basis of MSLT referral date) by exposure to influenza A(H1N1)pdm09 vaccine (secondary period: April 2009-end of recruitment)



In the paediatric/adolescent population cases especially, as shown in figure 6.1.2, the number of exposed cases with MSLT referral dates suddenly increased in January 2010, with a peak in August 2010. The non-exposed paediatric/adolescent cases had a more regular pattern over time. Recruited cases with MSLT referral dates from May 2011 onwards were exposed cases only, which could point to a potential selective recruitment. The pattern in adults (figure 6.1.3) was less pronounced. While there was a peak of MSLT referral dates in March and April 2010, no cases with MSLT referral dates after February 2011 were recruited.

Figure 6.1.4 Number of influenza A(H1N1)pdm09 vaccine exposed paediatric/adolescent cases (y-axis) in signalling and non-signalling countries (time on the basis of MSLT referral date, secondary period: April 2009–end of recruitment).

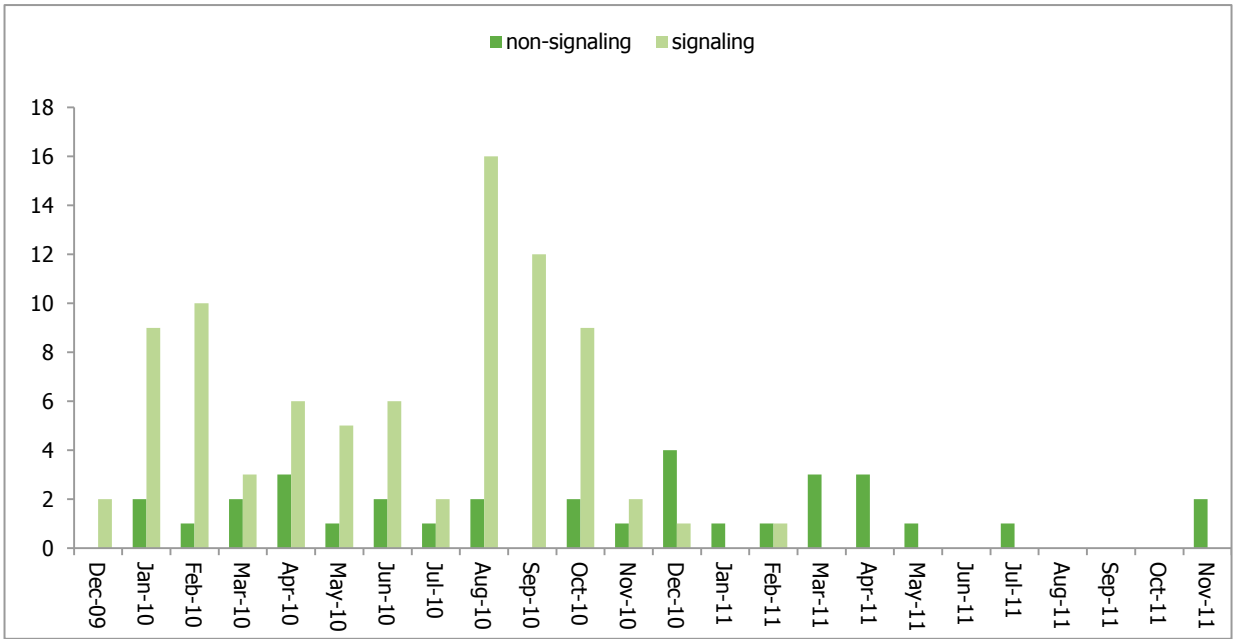
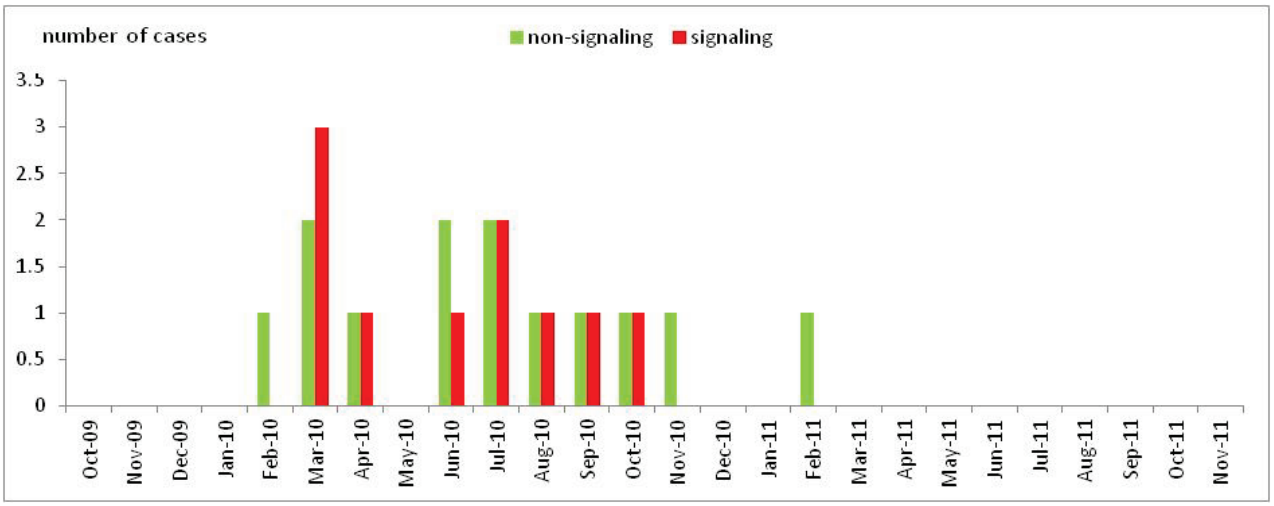


Figure 6.1.4 shows paediatric/adolescent influenza A(H1N1)pdm09 vaccine exposed cases only, stratified by signalling and non-signalling countries. The number of exposed cases in the non-signalling countries is quite stable over time and no important peaks are observed. The distribution of exposed cases in the signalling countries shows a bimodal pattern with a first peak in February 2010 and a more pronounced peak in August 2010.

In the adult influenza A(H1N1)pdm09 vaccine exposed cases, (figure 6.1.5) there is no difference in pattern of recruitment over time between signalling and non-signalling countries. However, it is striking that neither prior to February 2010 nor after February 2011 were any exposed cases with MSLT referral dates in that period recruited.

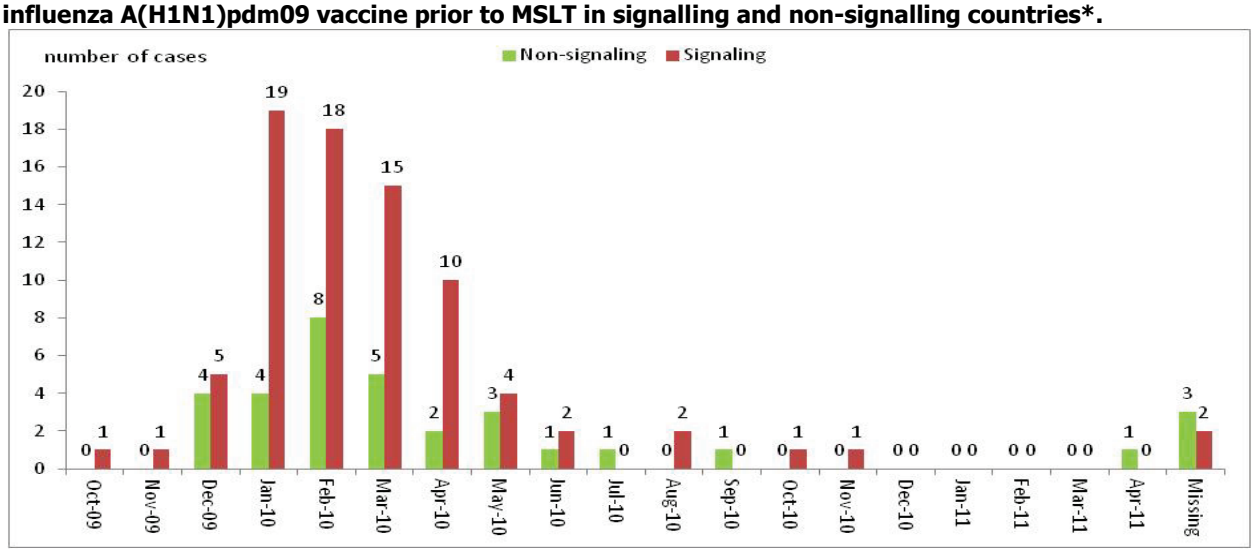
Figure 6.1.5 Number of influenza A(H1N1)pdm09 vaccine exposed adult cases recruited over time in signalling and non-signalling countries (entire (secondary) period) timing based on MSLT referral date



The time pattern that was observed in exposed paediatric/adolescent cases can be determined by right censoring: to be included people needed to have enough time to be diagnosed and the case accrual time in a specific country needed to be long enough (see section 7).

To further explore the time patterns in exposed paediatric/adolescent cases the EDS onset month was plotted for cases who were exposed to the influenza A(H1N1)pdm09 vaccine prior to the MSLT referral date (note this is an important left censoring condition).

Figure 6.1.6 Month of EDS onset in paediatric/adolescent cases of narcolepsy who were exposed to influenza A(H1N1)pdm09 vaccine prior to MSLT in signalling and non-signalling countries*.



** pattern of EDS dates may differ slightly from EDS dataset since the EDS month is approximated in the MSLT dataset (only index month is available for privacy reasons in data sharing)*

Figure 6.1.6 shows the pattern of EDS onset in paediatric/adolescent cases who were exposed to the influenza A(H1N1)pdm09 vaccine prior to MSLT referral. The absolute numbers differed between signalling and non-signalling countries, however a similar trend was observed between January and April 2010.

6.1.2 Case characteristics

Age

Age distribution of cases differs between the signalling and non-signalling countries as shown in Figure 6.1.7. The signalling countries have included more children/adolescents, the non-signalling countries, Denmark in particular, have relatively more adults.

Figure 6.1.7 Age distribution (x-axis) of all cases by non-signalling and signalling countries for the total (secondary) study period (April 2009–end of recruitment) (y-axis: number of cases)

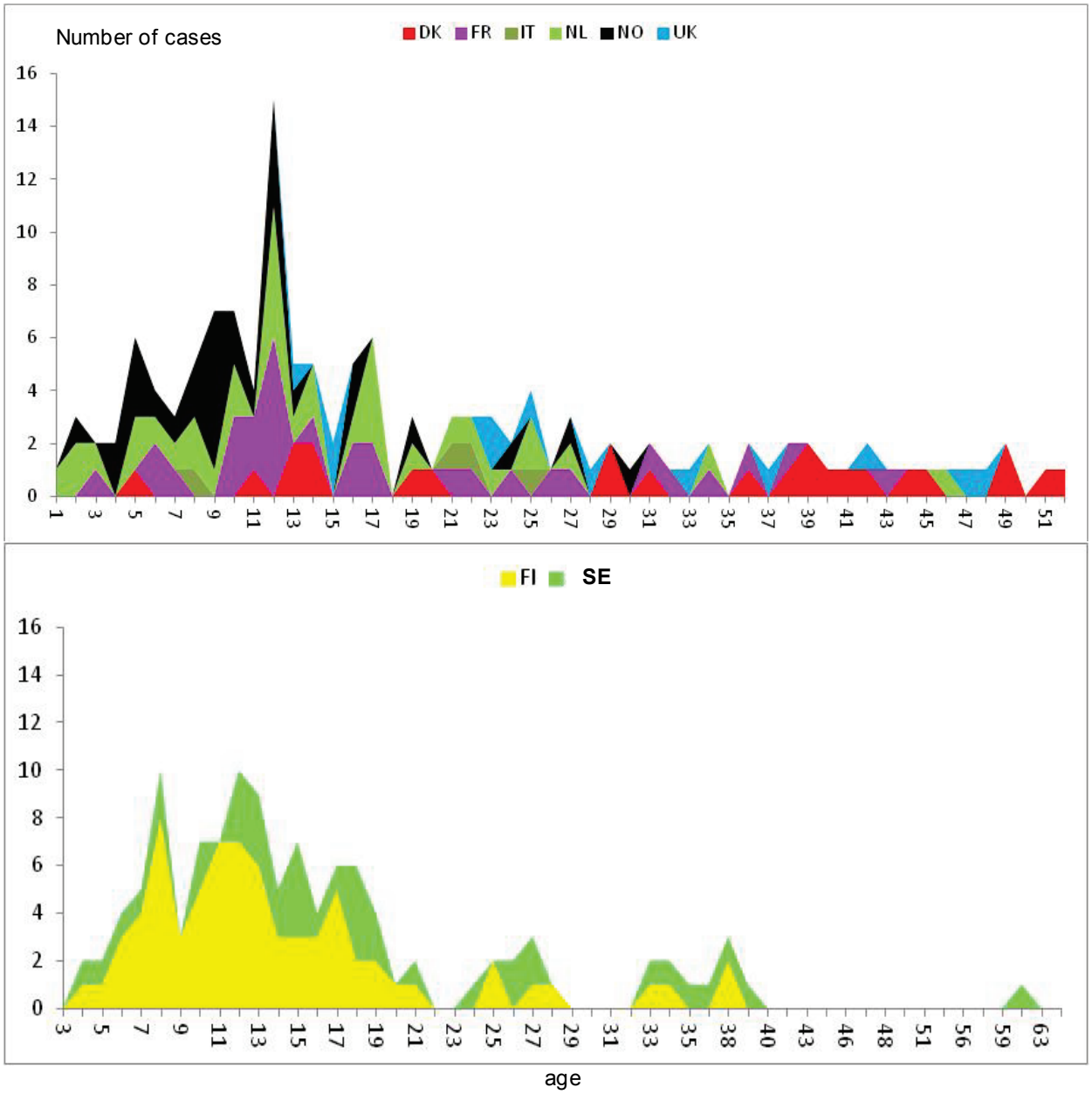
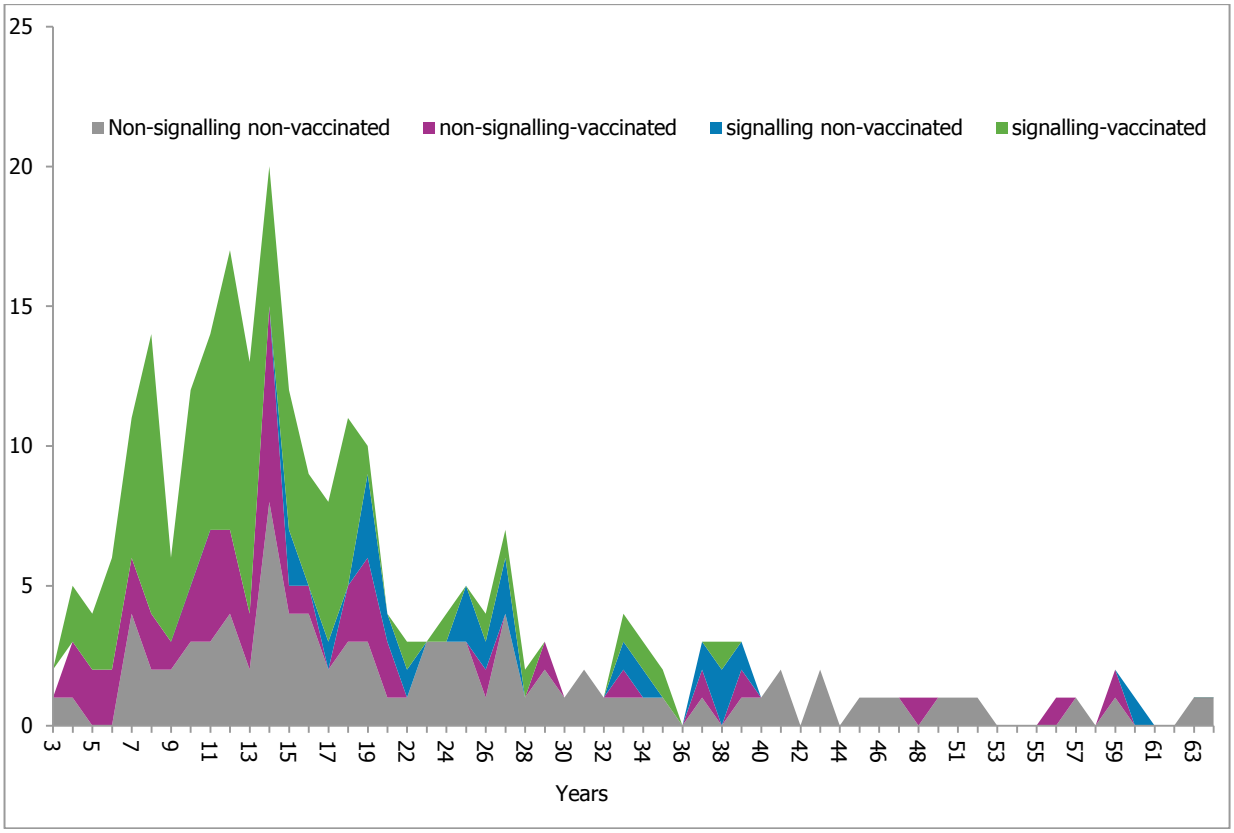


Figure 6.1.8 Age distribution of all cases (n=249) by exposure to influenza A(H1N1)pdm09 vaccine for the total (secondary) study period (April 2009–end of recruitment) (y-axis: number of cases)



Age distribution of all cases by age, signalling country and influenza A(H1N1)pdm09 vaccination exposure is shown in Figure 6.1.8. Very few cases, both in signalling and non-signalling countries occur at advanced ages. Figure 6.1.9 shows the age distributions by year of diagnosis for signalling (green) and non-signalling (blue) countries. In the signalling countries the age decreases significantly over time (p=0.005), the median age was 20 in 2009 and dropped to 13 in 2010 and 13.5 in 2011. In the non-signalling countries the age at diagnosis did not change over time (p=0.39), it was 18 in 2009 and 2010 and 14 in 2011.

Figure 6.1.9 Box plot of age in the year of diagnosis for signalling and non-signalling countries

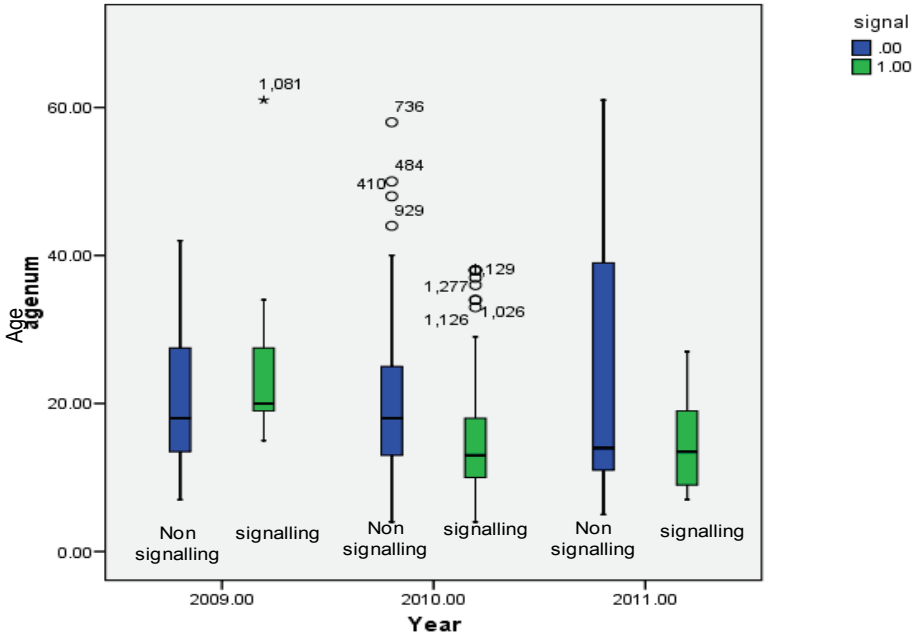


Table 6.1.2. Overview of age distribution in cases with MSLT referral dates prior and after 30 June 2010 (total n=249)

	N	Mean age	Std. Deviation	Minimum	Maximum
MSLT referral in primary study period (1 April 2009-30 June 2010)					
Finland	43	13.8	7.3	4	34
Sweden	20	23.0	12.7	8	61
France	25	21.5	11.2	5	48
Italy	4	21.0	7.5	10	27
Netherlands	21	17.4	7.7	4	37
Norway	12	15.4	8.7	4	32
Denmark	19	33.4	16.7	7	63
UK	8	31.0	13.2	17	57
Total	152	20.4	12.4	4	63
MSLT referral after primary period (1 July 2010–end)					
Finland	30	14.2	7.5	6	38
Sweden	3	32.0	21.4	15	56
France	6	15.2	9.3	8	33
Italy	14	15.1	12.9	3	52
Netherlands	18	11.5	4.5	6	26
Norway	21	15.8	9.3	4	39
Denmark	5	46.8	17.2	21	64
UK	3	32	21	15	56
Total	**97**	**16.5**	**12.2**	**3**	**64**

The mean age was lowest in Norway and Finland followed by the Netherlands and Italy during the primary study period. The cases with MSLT referrals after June 2010 had lower mean ages than the cases with MSLT referral dates in the primary study period.

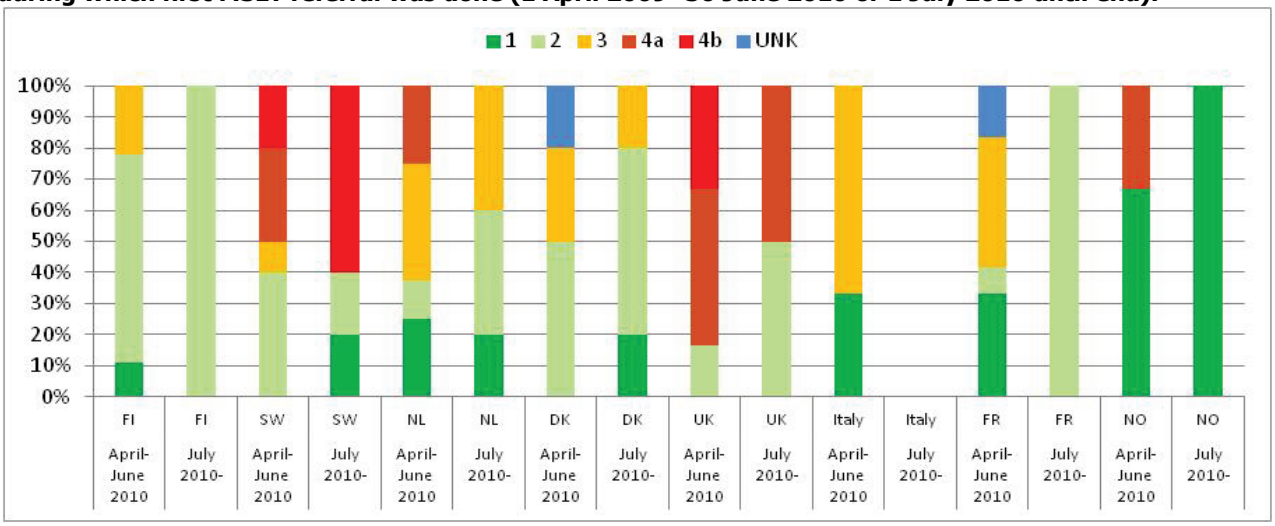
Brighton criteria case classification

A Brighton Collaboration working group created a case classification to support the study. Although the final document has not been published the following draft criteria were utilised.

Brighton Collaboration case classification for narcolepsy [21]

Level 1:	EDS and/or suspected cataplexy and CSF hypocretin deficiency
Level 2:	EDS + cataplexy (definite) + Level 1 or 2 MSLT abnormalities
Level 3:	EDS + level 1 MSLT abnormalities
Level 4a:	Reported narcolepsy by a specialist without information
Level 4b:	Narcolepsy mentioned but lack of information

Figure 6.1.10 Brighton Collaboration diagnostic certainty levels for adult cases by country and period during which first MSLT referral was done (1 April 2009- 30 June 2010 or 1 July 2010 until end).*



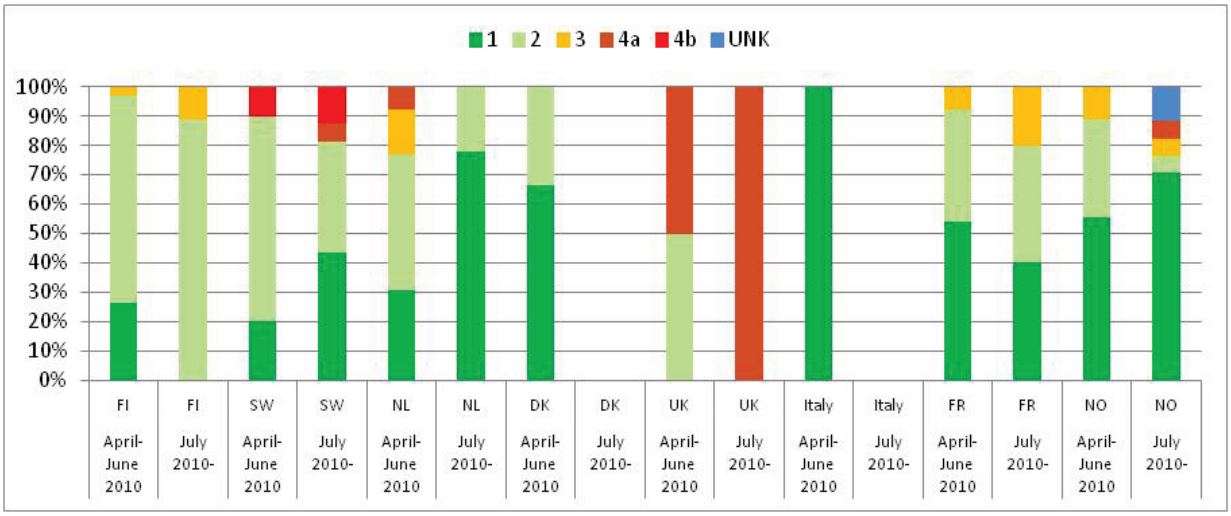
FI – Finland, SW – Sweden, NL – Netherlands, DK – Denmark, UK – United Kingdom, FR – France, NO – Norway.

** See number of cases per time period and country in table 6.1.7*

Figure 6.1.10 shows that in adults the percentage of cases with BC level 1–2 varies considerably across the countries, with the lowest percentage in the UK and Sweden, where for some cases information retrieval could not be completed. In general there is a tendency that the percentage of BC level 1–2 in adults increases after June 2010.

In signalling countries 70% of adults were classified as level 1–3, for the non-signalling countries this was 77%. In children/adolescents percentages of level 1–3 were 95% and 92% in signalling and non-signalling countries respectively. In children/adolescents the percentage of cases with level 1–2 is consistently very high (figure 6.1.11), in both the signalling and the non-signalling countries (except the UK).

Figure 6.1.11 Brighton Collaboration diagnostic certainty levels for paediatric/adolescent cases by country and period during which first MSLT referral was done (1 April 2009- 30 June 2010 or 1 July 2010 until end).*

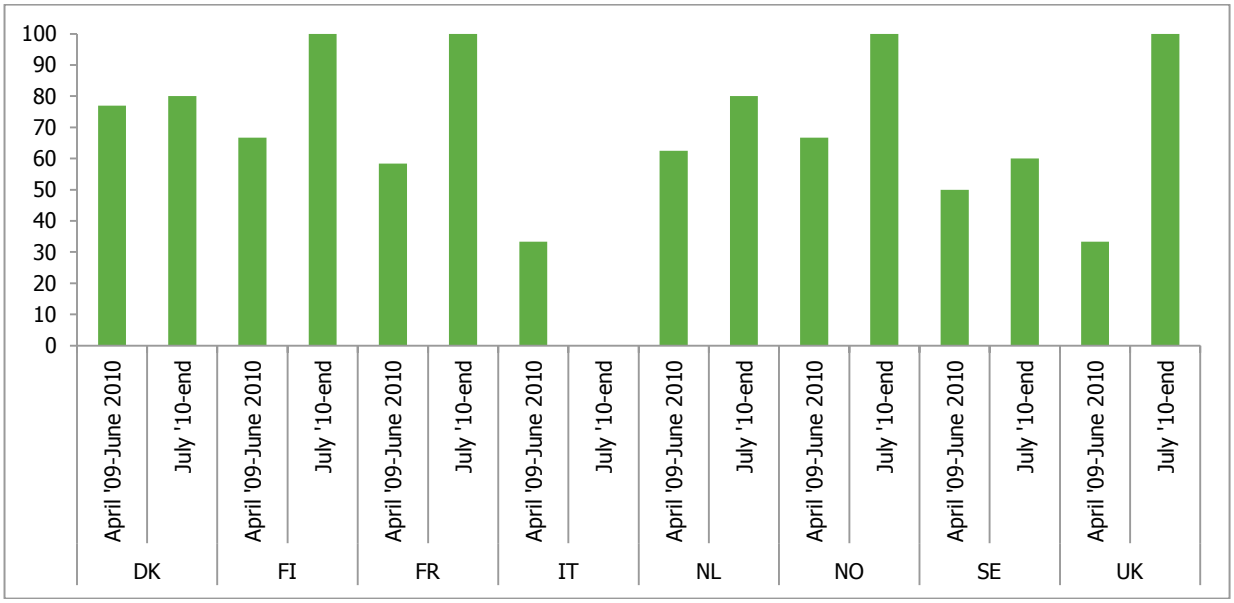


FI – Finland, SW – Sweden, NL – Netherlands, DK – Denmark, UK – United Kingdom, FR – France, NO – Norway.

** See number of cases per time period and country in table 6.1.7*

Cataplexy prevalence in cases with MSLT referrals during the study period

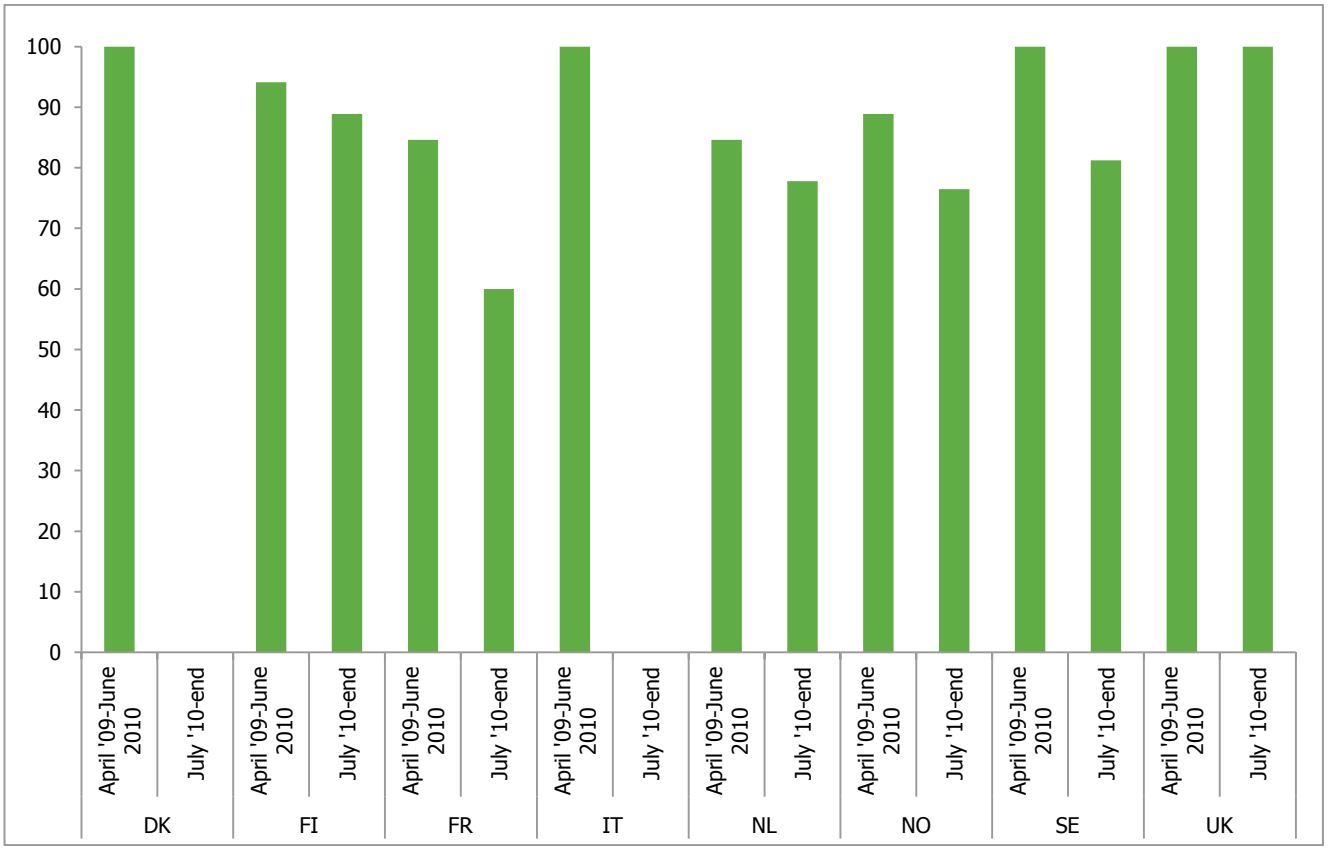
Figure 6.1.12. Percentage of cataplexy prevalence in adult cases by country and period during which first MSLT referral was done (1 April 2009- 30 June 2010 or 1 July 2010 until end of recruitment).*



DK – Denmark, FI – Finland, FR – France, IT – Italy, NL – Netherlands, NO – Norway, SE – Sweden, UK – United Kingdom

** See number of cases per time period and country in table 6.1.7*

Figure 6.1.13. Percentage of cataplexy prevalence in paediatric/adolescent cases by country and period during which first MSLT referral was done (1 April 2009- 30 June 2010 or 1 July 2010 until end of recruitment).*

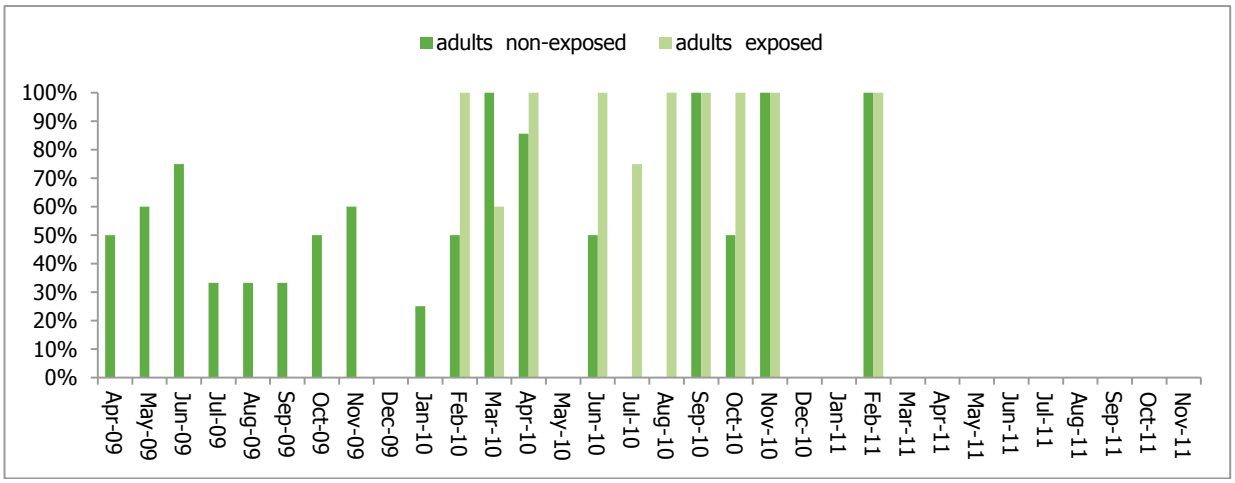


DK – Denmark, FI – Finland, FR – France, IT – Italy, NL – Netherlands, NO – Norway, SE – Sweden, UK – United Kingdom

See number of cases per time period and country in table 6

Figures 6.1.12 and 6.1.13 show that the prevalence of cataplexy is much higher in paediatric/adolescent cases than in adult cases. It is interesting that the prevalence of cataplexy in adult cases is higher in cases with MSLT referral dates after 30 June. In children/adolescents the prevalence was slightly lower in cases with MSLT referral dates after 30 June 2010. The prevalence in Sweden is relatively low, which is due to the fact that several cases had unknown cataplexy status (awaiting information).

Figure 6.1.14. Percentage of cataplexy prevalence in influenza A(H1N1)pdm09 vaccine exposed adult cases by month during which first MSLT referral was done*



** percentages based on non-exposed and exposed totals*

The prevalence of cataplexy was very high in most countries, in particular in children/adolescents both in signalling and non-signalling countries (91% in signalling countries and 81.6% in non-signalling). In adults, the prevalence of cataplexy was 63% in signalling countries and 66% in non-signalling. This is important as there has been a suggestion that the exposed cases would be more severe. To further explore the relationship between influenza A(H1N1)pdm09 vaccine exposure and cataplexy the prevalence of cataplexy was explored in the cases by month of first MSLT referral.

Figure 6.1.15. Percentage of cataplexy prevalence in influenza A(H1N1)pdm09 vaccine exposed paediatric/adolescent cases by month during which first MSLT referral was done (percentages based on non-exposed and exposed totals).

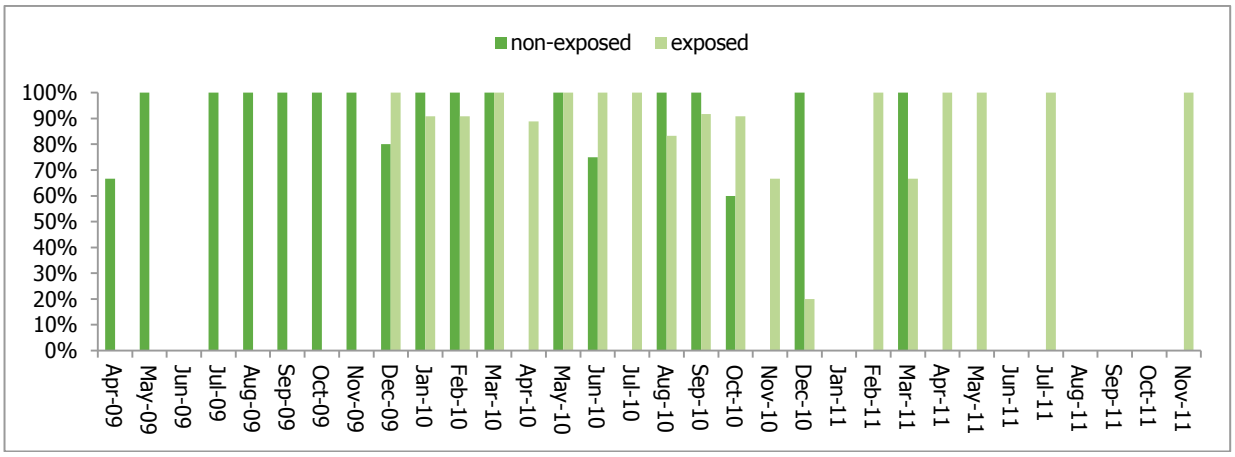
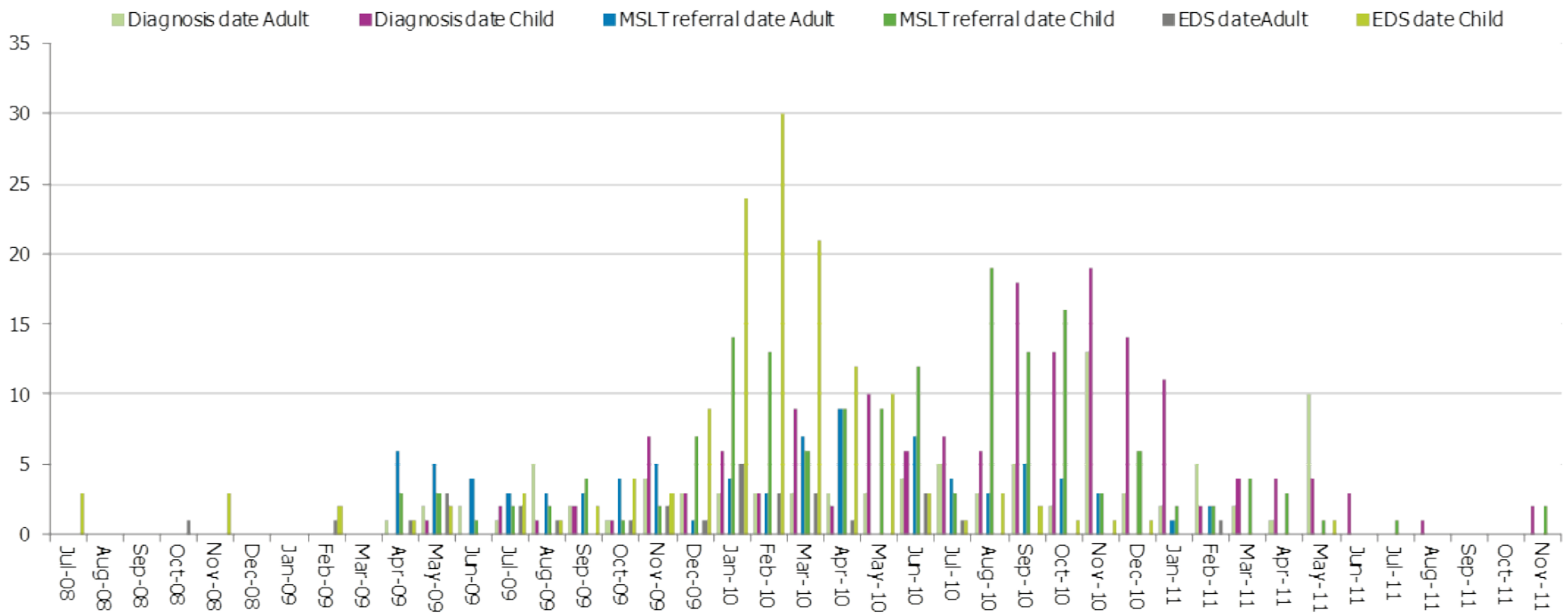


Figure 6.1.14 shows that in adults, the prevalence of cataplexy in cases with first MSLT prior to the start of the vaccination campaign is lower. The prevalence increases after February 2010 and is then similar in exposed and non-exposed. One should not over-interpret the graphs as the number of cases in each month can be quite low. Figure 6.1.15 shows that the pattern is different in children/adolescents, the prevalence of cataplexy is very stable and comparable between children/adolescents who are exposed and non-exposed to influenza A(H1N1)pdm09 vaccine.

Distribution of MSLT referral, diagnosis and EDS dates

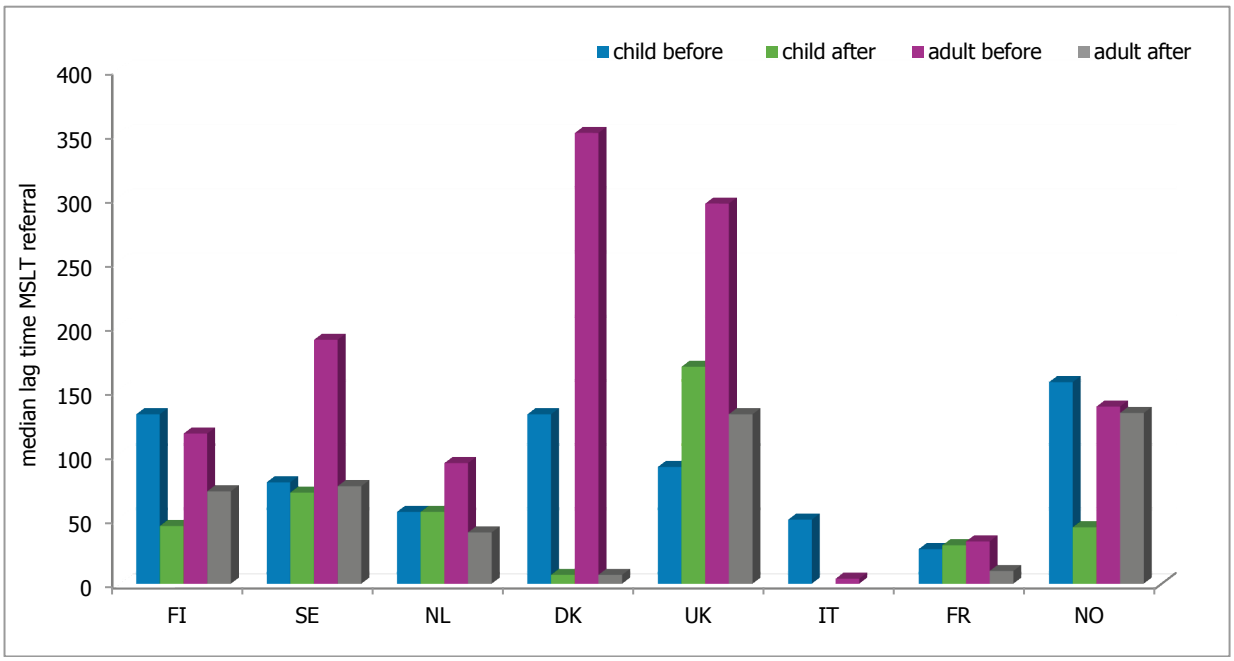
Figure 6.1.16 shows the distribution of EDS, MSLT referral and diagnosis dates over time.

Figure 6.1.16. Distribution of EDS, MSLT referral dates and diagnosis dates in children/adolescents and adults



The figure shows that there is a cluster of paediatric/adolescent cases with diagnosis dates and referral for MSLT dates after August 2010, whereas EDS dates cluster in Jan–Feb 2010 for children/adolescents

Figure 6.1.17. Median lag times (days) between referral for MSLT (Specialist referral for Finland) and diagnosis, prior to July 2010 and after 30 June 2010 in children/adolescents and adults



FI – Finland, SE – Sweden, NL – Netherlands, DK – Denmark, UK – United Kingdom, IT – Italy, FR – France, NO – Norway.

Figure 6.1.17 shows that the median lag times were quite substantial before July 2010, especially in Denmark and for adults in Sweden and the UK. In most countries there was a decrease in median lag time after June 2010, in particular in Finland, Sweden (adults only), the Netherlands (adults only), Denmark (children/adolescents and adults), France (adults only) and Norway (children/adolescents only).

6.1.3 Exposure to influenza A(H1N1)pdm09 vaccination

Table 6.1.3. Exposure to influenza A(H1N1)pdm09 vaccination by age (pooled) for cases with MSLT referral in primary study period (1 April 2009–30 June 2010) and in period after primary study period (1 July 2010–end).

Exposure		Child and adolescent cases		Child and adolescent controls		Adult cases		Adult controls	
		N	%	N	%	N	%	N	%
Primary study period (1 April , 2009–30 June 2010)									
Influenza A(H1N1)pdm09 vaccine	No	36	40.9	326	52.1	53	82.8	395	90.4
	Yes	52	59.1	300	47.9	11	17.2	42	9.6
Pandemrix		50		293		11		37	
Focetria				1		0		2	
Panenza		2							
Unknown				6				3	
Total subjects		**88**	**100**	**626**	**100**	**64**	**100**	**437**	**100**
1 July 2010–end									
Influenza A(H1N1)pdm09 vaccine	No	10	13.3	204	41.2	10	45.5	136	84.0
	Yes	65	86.7	291	58.8	12	54.5	26	16.0
Pandemrix		64		276		12		22	
Focetria		0		7		0		3	
Panenza		0		1		0		1	
Unknown		1		7		0		1	
Total subjects		**75**	**100**	**495**	**100**	**22**	**100**	**162**	**100**

The overall exposure prevalence to influenza A(H1N1)pdm09 vaccine for the primary analysis was 59% in paediatric and adolescent cases (signalling/non-signalling: 93%/25%) and 17% in adult cases (signalling/non-signalling: 26%/13%).

In the period after June 2010, the prevalence of exposure to influenza A(H1N1)pdm09 vaccines was higher both in the children/adolescents as well as adults, which is to be expected since all index dates occur after the start of the vaccination campaign. In the primary analysis there are at least six months where cases may occur prior to the start of the vaccination campaign.

Table 6.1.4 Exposure to influenza A(H1N1)pdm09 vaccination for cases and controls for cases with MSLT referral in primary study period (April 2009– 30 June 2010)

	Influenza A(H1N1)pdm09 vaccine	Child and adolescent cases	Child and adolescent controls	Adult case	Adult controls
Signalling					
Sweden	No	1	7	7	18
	Yes	9	13	3	12
Finland	No	2	78	7	71
	Yes	32	262	2	19
Total (% exposed)		**44 (93%)**	**360 (76%)**	**19 (26%)**	**120 (26%)**
Non-signalling					
France	No	9	15	8	26
	Yes	4	5	4	1
Italy	No	1	4	3	12
	Yes	0	0	0	0
the Netherlands	No	13	128	8	78
	Yes	0	2	0	2
Norway	No	2	14	1	5
	Yes	7	18	2	7
Denmark	No	6	30	13	64
	Yes	0	0	0	1
United Kingdom	No	2	50	6	121
	Yes	0	0	0	0
Total (% exposed)		**44 (25%)**	**266 (9.4%)**	**45 (13.3%)**	**317 (3.5%)**

Table 6.12 shows that Denmark does not contribute exposed cases in children/adolescents for the primary analysis, neither do the Netherlands, the UK and Italy. Denmark and the Netherlands have exposed controls and therefore contribute to the pooled analysis. Finland and Sweden have very few non-exposed cases in children/adolescents.

Table 6.1.5 Distribution of exposure to influenza A(H1N1)pdm09 vaccination for MSLT referral in the primary study period (1 April 2009–30 June 2010) and in the period after 30 June 2010.

	Influenza A(H1N1)pdm09 vaccine	Primary period		After June 30th - 2010		Secondary period	
		Cases	Controls	Cases	Controls	Cases	Controls
Signalling countries							
Sweden	No	8	25	1	17	9	42
	Yes	12	25	20	24	32	49
Finland	No	9	149	2	78	11	227
	Yes	34	281	28	222	62	503
Total (% exposed)		63 (73%)	480 (64%)	51 (94%)	341 (72%)	114 (82%)	821 (67%)
Non-signalling countries							
France	No	17	41	1	9	18	50
	Yes	8	6	5	4	13	10
Italy	No	4	16			4	16
	Yes	0	0	0	0	0	0
Netherlands	No	21	206	10	125	31	331
	Yes	0	4	4	12	4	16
Norway	No	3	19	1	17	4	36
	Yes	9	25	17	49	26	74
Denmark	No	19	94	3	23	22	117
	Yes	0	1	2	2	2	3
United Kingdom	No	8	171	2	71	10	242
	Yes	0	0	1	4	1	4
Total (% exposed)		89 (19%)	583 (6%)	46 (63%)	341 (22%)	135 (34%)	924 (12%)

In the period after 30 June 2010, the signalling countries included relatively more exposed cases.

Table 6.14 shows the discordant pairs for the primary analysis and the period after the primary period in signalling and non-signalling countries. In a standard matched analysis, exposure is compared between the matched case and control pairs. Due to the matched mode of estimation, concordant pairs fall out of the estimation and only discordant pairs remain. For the primary period these are 35 pairs in the signalling countries (majority from Finland which has 10 controls per case instead of Sweden that has 2.5 controls per case on average) and 26 pairs in the non-signalling countries. For the secondary period (total period after April 2009), in the signalling countries a total of 80 discordant pairs enter in the analysis and 60 pairs in the non-signalling countries. The majority of the discordant pairs in the non-signalling countries are from Norway and France followed by the Netherlands.

Table 6.1.6 Number of discordant influenza A(H1N1)pdm09 vaccination case controls pairs

	Primary period			Period after June 2010		
	Cases	Controls	Discordant pairs	Cases	Controls after	Discordant pairs
Signalling countries						
Finland	43	430	29	30	300	27
Sweden	20	50	6	21	41	18
Total	**63**	**480**	**35**	**51**	**341**	**45**
Non-signalling countries						
France	25	47	10	6	13	5
Italy	4	16	0	0	0	0
Netherlands	21	210	4	14	137	9
Norway	12	44	11	18	66	13
Denmark	19	95	1	5	25	4
United Kingdom	8	171	0	3	75	3
Total	**89**	**583**	**26**	**46**	**316**	**34**

6.1.4 Co-variates

Co-variates could not be collected in all countries, adjustment could only be done for Sweden, the Netherlands, Norway, the United Kingdom, Italy and France. Finland and Denmark did not provide co-variate information. In the non-signalling countries a low prevalence of co-variates was observed for many conditions.

The most frequent were infections (ILI or URI), use of antibiotics, asthma and auto-immune disease in children/adolescents. For adults the same factors were highly prevalent and in addition to depression, pregnancy and migraine.

Table 6.1.7. Distribution of co-variates for cases and controls for cases and controls with MSLT referral dates in primary study period (April 2009-30 June 2010) (excluding Denmark and Finland)

Chronic morbidity		Child and adolescent cases		Child and adolescent controls		Adult cases		Adult controls	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Epilepsy	no	47	97.9	254	99.2	40	95.2	273	96.8
	yes	1	2.1	2	0.8	2	4.8	9	3.2
Depression	no	47	97.9	252	98.4	38	90.5	235	83.3
	yes	1	2.1	4	1.6	4	9.5	47	16.7
Pregnancy	no	48	100.0	255	99.6	31	73.8	216	76.6
	yes	0	0.0	1	0.4	11	26.2	66	23.4
Diabetes	no	48	100.0	254	99.2	42	100	277	98.2
	yes	0	0.0	2	0.8	0	0.0	5	1.8
Asthma	no	45	93.8	222	86.7	40	95.2	250	88.7
	yes	3	6.3	34	13.3	2	4.8	32	11.3
Migraine	no	43	89.6	245	95.7	38	90.5	257	91.1
	yes	5	10.4	11	4.3	4	9.5	25	8.9
Immuno-compromised	no	48	100	256	100.0	42	100	282	100
	yes	0	0.0	0	0.0	0	0.0	0	0.0
Autoimmune disease	no	44	91.7	244	95.3	34	81.0	250	88.7
	yes	4	8.3	12	4.7	8	19.0	32	11.3

Table 6.1.8. Distribution of co-variates for cases and controls for cases and controls with MSLT referral dates in primary study period (April 2009–30 June 2010) (excluding Denmark and Finland)

Infections		Children and adolescents				Adults			
		cases		controls		cases		controls	
		N	%	N	%	N	%	N	%
Epstein Barr Virus	no	45	42	100	270	95.7	93.8	252	98.4
	yes	3	0	0.0	12	4.3	6.3	4	1.6
Bacteremia/Sepsis	no	48	42	100	281	99.6	100.0	256	100.0
	yes	0	0	0.0	1	0.4		0	
Streptococcal infection	no	48	42	100	278	98.6	100.0	252	98.4
	yes		0	0.0	4	1.4		4	1.6
Antibiotics	no	45	38	90.5	224	79.4	93.8	224	87.5
	yes	3	4	9.5	58	20.6	6.3	32	12.5
ILI 1 year prior	no	41	38	90.5	261	92.6	85.4	239	93.4
	yes	7	4	9.5	21	7.4	14.6	17	6.6
URI 1 year prior	no	36	32	76.2	201	71.3	75.0	217	84.8
	yes	12	10	23.8	81	28.7	25.0	39	15.2
HPV vaccination (last year)	no	46	42	100.0	281	99.6	95.8	250	97.7
	yes	2	0	0.0	1	0.4	4.2	6	2.3
Seasonal vaccination (last year)	no	48	42	100.0	270	95.7	100.0	253	98.8
	yes	0	0	0.0	12	4.3	0.0	3	1.2

**Unknown dates considered as exposed, unknown answer considered as not exposed*

Table 6.1.8 shows that exposure to other vaccinations was very low, in particular seasonal vaccination, which in most countries is targeted at the elderly (60 or 65 plus) and the persons at risk for influenza related complications. The exposure to respiratory infections (ILI/URI) in the year prior to exposure was slightly higher in paediatric/adolescent controls than in adults, antibiotics use was higher in adults. In general, exposure was higher in cases than controls. Pregnancy was relatively frequent in adults as well as auto-immune disorders.

Table 6.1.9 shows the association between reported co-variate data and narcolepsy. None of the co-variates was strongly associated with narcolepsy in the adults or children/adolescents. Upper respiratory tract infections seemed protective in adults.

Table 6.1.9 Association between co-variates and narcolepsy (excluding Denmark and Finland) for the primary study period (1 April 2009–30 June 2010, index date MSLT referral)

Co-variate		Children and adolescents			Adults		
		OR	LL	UL	OR	LL	UL
Co-morbidity/conditions							
Epilepsy	No						
	Yes	1.1	0.0	29.8	0.9	0.1	7.3
Depression	No						
	Yes	1.1	0.0	13.7	0.7	0.2	2.3
Pregnancy	No						
	Yes	2	0	78	1.0	0.2	3.7
Diabetes	No						
	Yes	2	0	28.3	1.9	0	20.3
Asthma	No						
	Yes	0.3	0.1	1.2	0.3	0.0	1.4
Migraine	No						
	Yes	2.3	0.5	11.0	0.6	0.1	2.4
Immuno-compromised	No						
	Yes	NA			NA		
Autoimmune disease	No						
	Yes	0.5	0.1	2.0	1.1	0.3	3.2
Infections							
ILI in last year	No						
	Yes	1.7	0.5	5.5	1.0	0.2	3.5
URI in last year	No						
	Yes	1.0	0.4	2.7	0.4	0.1	0.98
ILI or URI in last year	No						
	Yes	1.2	0.5	3.1	0.3	0.1	0.9
Epstein Barr Virus	No						
	Yes	1.6	0.2	10.9	NA	-	-
Bacteremia/Sepsis	No						
	Yes	NA			2.1	.	-Infinity
Streptococcal infection	No						
	Yes	0.3	0.0	2.8	1.5	0.0	22.6
Antibiotics	No						
	Yes	0.8	0.1	3.3	0.5	0.1	1.7
Other vaccinations							
Seasonal vaccination (last year)	No						
	Yes	0.4	0.0	3.6	0.3	0.0	1.8
HPV vaccination (last year)	No						
	Yes	0.9	0.1	7.3	2	0	78

NA: not assessable, confidence intervals and odds ratios based on exact estimations. UL: upper limit 95% confidence interval, LL: lower limit 95% confidence interval. OR=odds ratio

6.1.5 Crude associations between influenza A(H1N1)pdm09vaccinations and narcolepsy (pooled) in the primary analysis

Table 6.1.10 shows the association between influenza A(H1N1)pdm09 vaccination and narcolepsy in signalling and non-signalling countries. The data show heterogeneity between signalling and non-signalling countries both for children/adolescents as well as adults. Because of this heterogeneity pooled estimates would not be informative. The consortium has therefore decided to separate signalling and non-signalling countries for all subsequent analyses.

In signalling countries influenza A(H1N1)pdm09 vaccination is associated with a significant increase in risk of narcolepsy (exact OR=14.2, 95%CI 2.5–infinity, in unmatched analysis).

In non-signalling countries influenza A(H1N1)pdm09 vaccination is associated with a non-significant increase in risk of narcolepsy (OR=2.3, 95%CI: 0.9–6.3). Stratification by age shows that the association is higher in adults in non-signalling countries (3.7 for adults (95%CI 0.7–20.7) vs. 1.6 (95%CI 0.5–6.1) in children/adolescents). The higher estimate for adults is driven by France (see figure 6.1.19) and should be interpreted with significant caution as there was a potential selection towards inclusion of exposed cases in France (see section 6.8). Pending cases in the primary study period seem to have a lower exposure prevalence than the ones that have been included so far, however this may also happen for controls. Since the paediatric/adolescent data do not suffer from this problem, it is better to look at the stratum specific estimates and age pooled estimates should not be utilised.

Table 6.1.10. Pooled associations between influenza A(H1N1)pdm09 vaccine vaccination and narcolepsy (primary analysis: MSLT referral in primary study period).

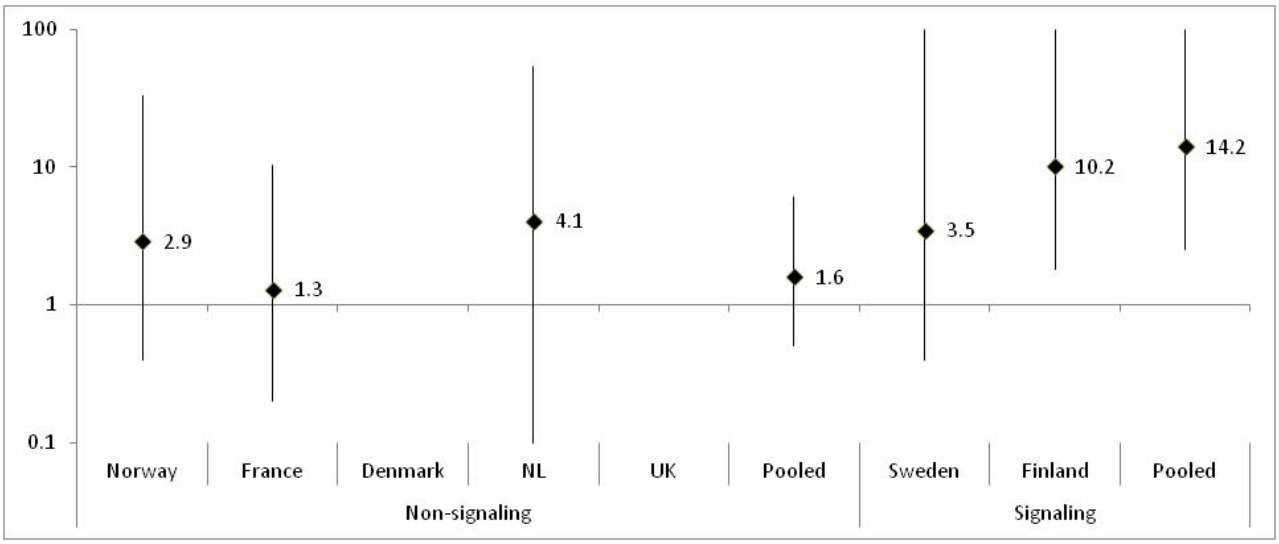
	Children and adolescents [a)]			Adults		
	OR	LL [b)]	UL [c)]	OR	LL [b)]	UL [c)]
Sweden and Finland (signalling)						
Influenza A(H1N1)pdm09 vaccination (exact & matched)	14.2	2.5	Infinity	1.2	0.2	9.1
Influenza A(H1N1)pdm09 vaccination (asymptotic & unmatched) [d)]	15.7	1.9	129	1.2	0.2	6.9
France, the Netherlands, the United Kingdom, Italy, Norway, Denmark (non-signalling)						
Influenza A(H1N1)pdm09 vaccination (exact & matched)	1.6	0.5	6.1	3.7	0.7	20.7
Influenza A(H1N1)pdm09 vaccination (asymptotic & unmatched) [d)]	1.8	0.6	5.7	4.1	0.94	18.2

[a)] ≤ 18; [b)] lower 95% confidence level; [c)] upper 95% confidence level; [d)] Sensitivity analysis

The country specific unadjusted estimates for the association between influenza A(H1N1)pdm09 vaccination and narcolepsy all showed wide confidence intervals (based on exact limits) (see figures 6.1.18 and 6.1.19). Pooling increased the power substantially, especially in the non-signalling countries. Due to the exact estimation for the matched analysis, the pooled analyses in signalling countries was higher than the estimate in Finland and Sweden separately, mostly because the Swedish estimate was based on a median value. The asymptotically derived OR (traditional) based on matched sets for Sweden was high and instable (>60,000) due to the low number of discordant pairs (n=6). Releasing the matching and adjusting for the matching factors yielded an odds ratio of 11.6 (95%CI 0.6–242) in Sweden for influenza A(H1N1)pdm09 vaccination and narcolepsy in children/adolescents.

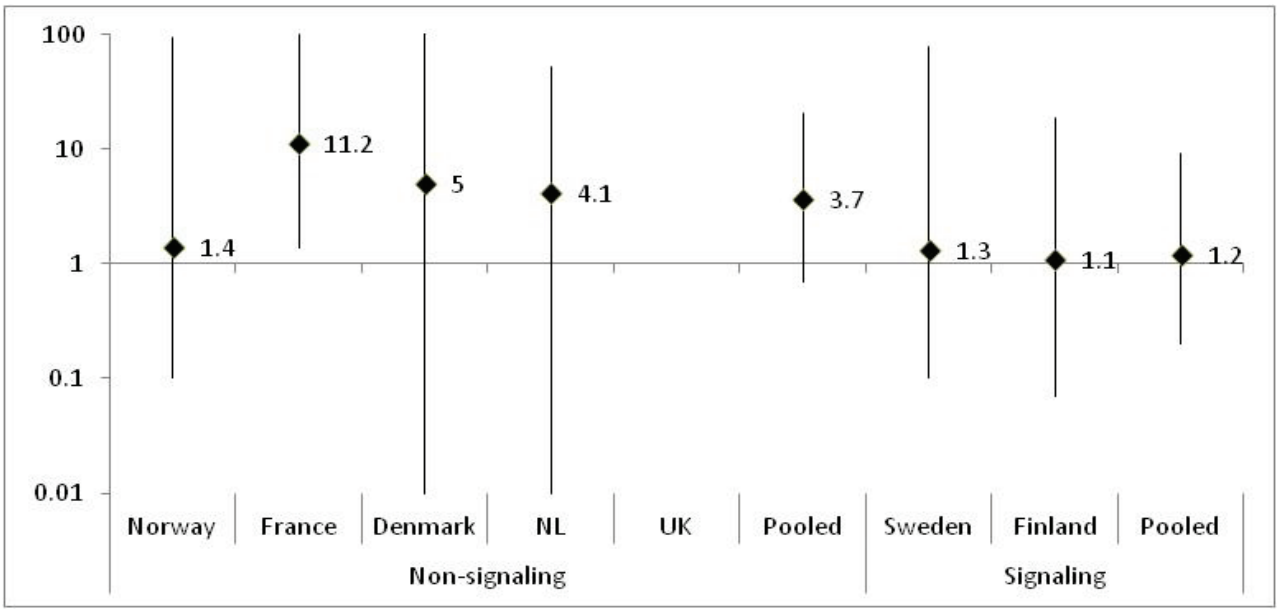
Since the matched analysis is based on the discordant pairs, a sensitivity analysis was also conducted using an unmatched analysis in which we adjusted for calendar month/year, sex, age (categorised) and country. The overall estimates from this unmatched analysis are very similar to the exact matched estimations (table 6.1.10), which indicates there is very little residual confounding from the matching factors when releasing the matching.

Figure 6.1.18. Association between influenza A(H1N1)pdm09 vaccination and narcolepsy in children and adolescents for the primary analysis (April 2009–June 30 2010) in signalling and non-signalling countries*



**Odds ratio y-axis logarithmic scale, exact estimation on matched pairs*

Figure 6.1.19. Association between influenza A(H1N1)pdm09 vaccination and narcolepsy in adults for the primary analysis in signalling and non-signalling countries*



**Odds ratio y-axis logarithmic scale*

In the signalling countries the association in children is higher than in adults (OR=14.2 95%CI 2.5–infinity in children vs. OR=1.2, 95%CI 0.2–9.1 in adults) and the data should not be pooled because of the interaction by age.

Table 6.1.11. Pooled associations between most recent influenza A(H1N1)pdm09vaccination and narcolepsy (primary analysis: MSLT referral in primary study period (April 2009–June 2010): focus on risk windows

Time since last vaccination	Children and adolescents [a]				Adults			
	Cases/ controls	OR	LL [b]	UL [c]	Cases/ controls	OR	LL [b]	UL [c]
Finland and Sweden (signalling)								
1–7 days [d]	0/0	NA			0/0	NA		
8–42 days [d]	4/23	15.8	1.6	Infinity	1/3	3.5	0.1	75.5
43–180 days [d]	29/214	11.4	1.9	Infinity	3/20	0.9	0.1	9.0
>180 days [d]	7/35	10.2	1.2	Infinity	1/7	0.8	0.0	20.4
France, the Netherlands, United Kingdom, Italy, Norway, Denmark(non-signalling)								
1–7 days [d]	0/0	NA			0/0	NA		
8–42 days [d]	1/3	0.6	0.0	19.7	0/0	NA		
43–180 days [d]	8/11	9.5	1.1	461	4/7	3.3	0.5	19.6
>180 days [d]	2/11	0.2	0.0	3.3	2/4	4.7	0.1	437.9

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact) [d] Time since last vaccination

In the signalling countries there is very little change in risk of narcolepsy by increasing time since the last influenza A(H1N1)pdm09 vaccination for children/adolescents, although the highest estimate is obtained during the first six weeks. In adults the confidence intervals are wide. In the non-signalling countries, the effect is highest for children/adolescents during the period 43–180 days after the influenza A(H1N1)pdm09 vaccination. These data should be interpreted very cautiously as the delay between vaccination and case occurrence was short in the primary analysis, and the hazard function could not be fully explored.

Table 6.1.12. Pooled unadjusted matched (exact) associations for influenza A(H1N1)pdm09 vaccination and narcolepsy (primary analysis: MSLT referral in primary study period): focus on brands

	Children and adolescents [a]			Adults		
	Cases/controls	OR	95%CI	Cases/controls	OR	95%CI
Signalling countries						
Pandemrix	41/273	14.0	2.4-infinity	5/29	1.2	0.2-9.1
Focetria	0/0	NA		0/0	NA	
Panenza	0/0	NA		0/0	NA	
Non-signalling countries						
Pandemrix	9/20	2.2	0.5-11.1	6/8	5.5	0.9-59.3
Focetria	0/1	NA		0/2	NA	
Panenza	2/0	NA		0/0	NA	

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact); NA: not assessable

Table 6.1.12 shows that Pandemrix is the vaccine that was associated with narcolepsy in the signalling countries, and it was the sole product utilised. In the non-signalling countries Pandemrix was mostly used, the association estimate for Focetria could not be reliably estimated.

6.1.6 Adjusted associations between influenza A(H1N1)pdm09 vaccination and narcolepsy

None of the co-variates was strongly associated with narcolepsy, however based on a 5% change in estimate when adding co-variates to the model one by one, several factors were identified that changed the primary association between influenza A(H1N1)pdm09 vaccination and narcolepsy. Adjustment for these confounding factors in the non-signalling countries resulted in an increase of the odds ratio (OR) in children/adolescents and a decrease in adults. In the Netherlands, the United Kingdom, France, Norway and Italy, the OR increased after adjustment for recorded/reported ILI, asthma, migraine, HPV vaccination and seasonal vaccination from 1.9 to 2.6.

In adults the opposite effect was observed, adjustment for recorded/reported upper respiratory tract infection, epilepsy, EBV and antibiotic use reduced the association measure from 3.9 to 3.7. In the signalling countries the effect of confounding adjustment on the matched association could not be estimated since Finland did not collect data on co-variates and Sweden had very few discordant pairs. Adjustment for upper respiratory tract infections in children in Sweden (unmatched) increased the estimate (from 11.6 to 17).

Table 6.1.13. Pooled adjusted odds ratios for the association between influenza A(H1N1)pdm09 vaccination and narcolepsy (primary analysis: MSLT referral in primary study period) in France, the Netherlands, the UK, Norway and Italy

	Children and adolescents [a)]			Adults		
	OR	LL [b)]	UL [c)]	OR	LL [b)]	UL [c)]
Sweden (signalling)						
Influenza A(H1N1)pdm09 vaccination	NA			NA		
France, Netherlands, United Kingdom, Italy and Norway (non-signalling)						
Unadjusted influenza A(H1N1)pdm09	1.7	0.50	6.3	4.7	0.8	35
Adjusted influenza A(H1N1)pdm09	2.6 [d)]	0.6	13.0	3.7 [e)]	0.6	45.5

[a)] ≤ 18; [b)] lower 95% confidence level (exact); [c)] upper 95% confidence level (exact); [d)] Adjusted for ILI, asthma, migraine, HPV vaccination and seasonal vaccination; [e)] adjusted for upper respiratory tract infections, epilepsy, EBV and antibiotic use

6.1.7 Sensitivity analysis on study time periods for all countries

As stated in the statistical analysis plan and in the methods section, the primary study period was chosen to be April 2009–30 June 2010. The index date of the case was supposed to fall within this period to be considered for the primary analysis. The secondary study period was the entire period and included the cases in the primary period as well as those with MSLT referral dates after 30 June 2010.

The choice of the primary risk period was based on the fact that media attention and regulatory awareness started in August 2010 in most countries. In Finland neurologists had been investigating the association between influenza A(H1N1)pdm09 vaccine and narcolepsy since February [25]. Censoring on July 2010 is an attempt to be able to separate the potential vaccine from the combined vaccine and awareness effect. For Finland specifically a third study period is defined that starts in April 2009 and ends 28 February 2010.

Table 6.1.14. Sensitivity analyses: date of MSLT during primary, secondary or tertiary study period (pooled, unadjusted, matched)

Type of analysis	Children and adolescents [a]			Adults		
	OR [b]	LL [c]	UL [d]	OR [b]	LL [c]	UL [d]
Sweden and Finland (signalling)						
Influenza A(H1N1)pdm09 vaccination (tertiary period) (April 2009–Feb 2010)	5.8	0.96	Infinity	0.6	0.0	22.3
Influenza A(H1N1)pdm09 vaccination (primary period) (April 2009–June 2010)	14.2	2.5	Infinity	1.2	0.2	9.1
Influenza A(H1N1)pdm09 vaccination (secondary period) (April 2009–end of recruitment)	36.3	6.6	Infinity	1.7	0.5	6.4
France, Netherlands, United Kingdom, Italy and Norway (non-signalling)						
Influenza A(H1N1)pdm09 vaccination (primary period) (April 2009–June 2010)	1.6	0.5	6.1	3.7	0.7	20.7
Influenza A(H1N1)pdm09 vaccination (secondary period) (April 2009–end of recruitment)	2.9	1.3	6.8	5.3	1.8	16.7

[a] ≤ 18; [b] exact OR; [c] lower 95% confidence level (exact); [d] upper 95% confidence level (exact);

The sensitivity analysis based on the secondary (total) recruitment period (1 April 2009–end of recruitment) shows that the odds ratios for the association between influenza A(H1N1)pdm09 vaccine and narcolepsy increase in all groups compared to the primary study period (1 April 2009–June 30, 2010).

In the signalling countries where regulatory/ media attention was high in the summer of 2010, the relative risk increases almost threefold from 14 to 36 if cases with MSLT tests after 30 June 2010 were included in the analysis, in adults the excess relative risk is doubling.

In the non-signalling countries similar increases were seen, but this mostly relied on Norway, France and the Netherlands (see table 6.4) where professional, regulatory, and media attention was substantial and recruitment continued into 2011. Since many more cases are included in the secondary period this analysis has more power, but unfortunately is not able to distinguish between a potential vaccine effect and a vaccine and (regulatory/professional /media) attention effect.

The potential vaccine effect alone can be studied in the primary period in the non-signalling countries and in the tertiary period for Finland. In Finland, the association measure is lower and non-significant in the tertiary period based on specialist referral dates (OR=5.8, 9%CI: 0.96–infinity).

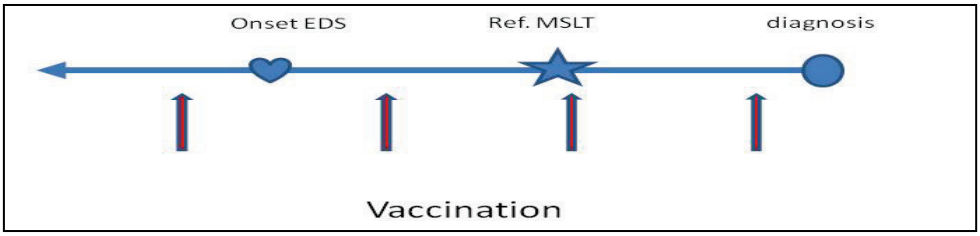
6.1.8 Sensitivity analysis on index dates for all countries

Theoretical background

Although the methods section already describes the differences between the index dates it is repeated here to aid the reader. Table 6.1.14 shows the results of various sensitivity analyses on the index dates. The primary analysis was done on MSLT referral as the index date as this was considered to be objectively assessable. As stated in the statistical analysis plan, the date of EDS which is closest to the onset of narcolepsy and therefore preferable as the index date is difficult to assess objectively in retrospect (stated by EU-NN experts). Due to the subjective nature it is particularly susceptible to bias if the vaccination status is known and the date is assessed in unblinded fashion (Finland/Norway), the research question/concern is known (all countries), and/or reimbursement is offered and information needs to be obtained from patients retrospectively (Sweden, Norway). It was anticipated by the narcolepsy experts that the EDS date may often be missing from prospectively collected information (medical charts). That is why analyses based on date of EDS onset were done as a sensitivity analysis. As described in the statistical analysis plan, as the date of MSLT referral is later than onset of narcolepsy, this index date may lead to misclassification of exposure (i.e. classifying as exposed subjects that were diagnosed after disease onset) (see figure 6.1.20 obtained from statistical analysis plan), but as long as exposure is assessed in the same way between cases and controls, and the exposure probability does not alter upon narcolepsy symptoms, this bias was anticipated to lead to only a slight underestimation of the risk.

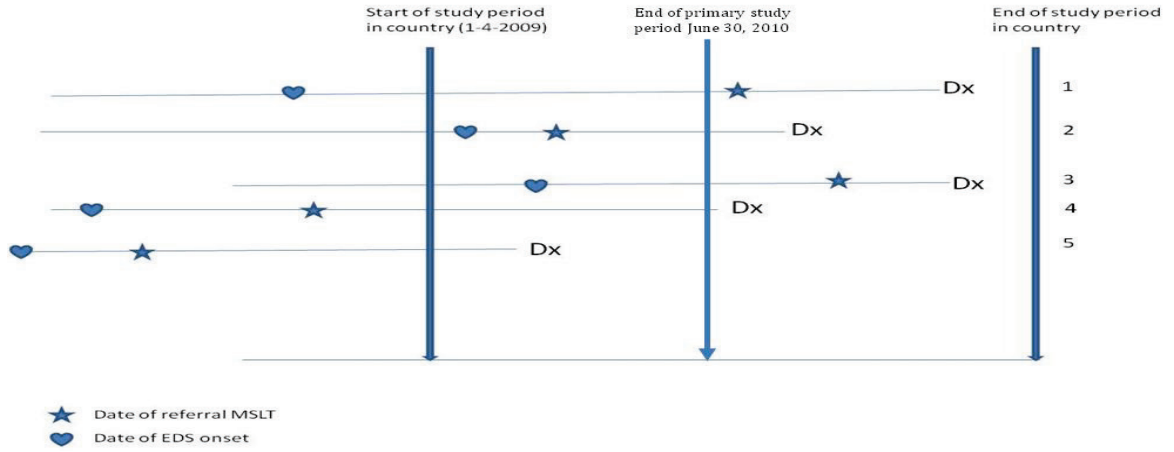
The date of narcolepsy diagnosis is much later in time than the date of disease onset. Using this date as index date might lead to even more misclassification of exposure. In line with the reasoning around the date for MSLT referral, the measure of association from the analysis using the date of diagnosis as index date should be lower than the estimate from the date of EDS onset or MSLT referral in case of a causal association.

Figure 6.1.20. Sequence of dates that are considered as potential index dates in the VAESCO narcolepsy study.



However, the case control sets based on EDS date or diagnosis dates do not only differ in terms of the exposure, as we have a primary and secondary study period that were used to look at the effect of awareness, the number of cases and controls also differ between the EDS, MSLT and diagnosis index date datasets based on the fact that the index date should fall in the primary period (April 2009–June 2010). Cases may be excluded from the primary analysis if the index date would be before 1 April 2009 which is more likely to happen for the EDS dataset. Additionally, if the index date would be after 30 June 2010, the cases/controls would not be included in the primary analysis. For the secondary period (April 2009–end) cases would fall out if the index date would be prior to April 2009. Figure 6.21 was modified from the SAP and shows how the inclusion may differ based on the relevant index date. All cases are included on the basis of diagnosis, dates of EDS and MSLT referrals are usually prior to that. Shifting the index dates could mean that cases would not be included in the primary risk period for EDS or MSLT datasets, if the index date would be prior to study start (1 April2009) or if the index date would not fall in primary period (1 April 2009–30 June 2010)

Figure 6.1.21. How a change in the index date may impact on the inclusion for the primary analysis.



The sensitivity analyses based on EDS as index date and diagnosis date as index date have three main differences compared to the MSLT analysis:

- a person may be unexposed in the EDS analysis and exposed in MSLT if vaccination with pandemic vaccine was done between EDS date and MSLT date
- a case (and its controls) may not appear anymore in the EDS analysis if the index date was prior to April 2009 or if the date of EDS was unknown
- in the primary study period of the EDS analysis many cases can be included that were referred for MSLT or diagnosed after the regulatory/media attention started.

For the dataset based on the date of diagnosis, the following differences may be expected with reference to the MSLT dataset:

- exposure may change: more persons are exposed prior to date of diagnosis than prior to date of MSLT since vaccination could have occurred between date of MSLT referral and diagnosis
- exclusion because the date of diagnosis is before April 2009 when referral for MSLT was later is unlikely, actually the dataset on date of diagnosis is expected to have more cases if the date of diagnosis was after April 2009 and the MSLT prior
- the primary study period for the diagnosis analysis excludes any effect of regulatory/media attention as all cases were diagnosed prior to start of that attention.

Table 6.1.15 shows the number of cases in the EDS, MSLT and diagnosis date datasets

Table 6.1.15. Number of cases in the datasets for the different index dates for the entire period (1 April 2009–end of recruitment)

	EDS		MSLT		Diagnosis	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Sweden	26	15.9	41	16.5	41	16.3
Finland	63	38.4	73	29.3	73	29.0
Subtotal signalling	89	54.3	114	45.8	114	45.2
France	28	17.1	31	12.4	40	15.9
Italy	0	0.0	4	1.6	4	1.6
Netherlands	13	7.9	35	14.1	36	14.3
Norway	26	15.9	30	12.0	30	11.9
Denmark	3	1.8	24	9.6	19	7.5
United Kingdom	5	3.0	11	4.4	9	3.6
Subtotal non-signalling	75	45.7	135	54.2	138	54.8
Total	**164**	**100.0**	**249**	**100**	**252**	**100**

Table 6.1.15 shows that there are a substantial number of cases that do not appear in the EDS dataset, and that the number of cases is slightly higher in the diagnosis dataset.

Results: sensitivity analysis on different index dates

Signalling countries

Table 6.1.16 shows that in signalling countries in the primary study period, the estimate for the EDS date (OR=11.4) in children/adolescents is actually lower than the estimate for the MSLT referral date (OR=14.2). The analysis based on diagnosis date shows that the association goes down. In adults the pattern of estimates is according to expectations: highest in EDS date analysis, and lowering from EDS to diagnosis date estimates in the signalling countries. In the secondary study period the same pattern is observed as in the primary analysis, although all estimates are higher.

Table 6.1.16. Sensitivity analyses on index dates (EDS, diagnosis) during primary study period (April 2009–June 2010) (pooled, unadjusted)

Type of analysis	Children and adolescents [a]			Adults		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Sweden & Finland (signalling)						
Influenza A(H1N1)pdm09 vaccination (EDS) primary period	11.4	3.4	61	2.3	0.1	40
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	14.2	2.5	Infinity	1.2	0.2	9.1
Influenza A(H1N1)pdm09 vaccination (Diagnosis) primary period	7.2	1.05	3.15	0.5	0.04	4.6
France, Netherlands, United Kingdom, Italy and Norway (non-signalling)						
Influenza A(H1N1)pdm09 vaccination (EDS) primary period	4.6	1.7	13.7	11.9	1.9	134
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	1.6	0.5	6.1	3.7	0.7	20.7
Influenza A(H1N1)pdm09 vaccination (Diagnosis) primary period	3.6	0.63	22.2	4.6	0.82	32.3

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact);

For the secondary period the estimates increases strongly as compared to the primary period for the MSLT referral and diagnosis index dates, but not for the EDS date in children/adolescents and adults in the signalling countries. In the non-signalling countries the effect is less pronounced, in particular regarding the EDS date.

Table 6.1.17. Sensitivity analyses on index dates (EDS, diagnosis) during secondary study period (April 2009–end of recruitment) (pooled, matched)

Type of analysis	Children and adolescents [a]			Adults		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Sweden & Finland (signalling)						
Influenza A(H1N1)pdm09 vaccination (EDS) secondary period	11.8	3.5	63	2.3	0.1	46.5
Influenza A(H1N1)pdm09 vaccination (MSLT) secondary period	36.3	6.6	Infinity	1.7	0.5	6.4
Influenza A(H1N1)pdm09 vaccination (Diagnosis) secondary period	24.1	4.1	977.0	1.0	0.3	3.2
France, Netherlands, United Kingdom, Italy and Norway (non-signalling)						
Influenza A(H1N1)pdm09 vaccination (EDS) secondary period	3.9	1.55	10.5	16.3	2.95	169
Influenza A(H1N1)pdm09 vaccination (MSLT) secondary period	2.9	1.3	6.8	5.3	1.8	16.7
Influenza A(H1N1)pdm09 vaccination (Diagnosis) secondary period	2.8	1.3	6.4	5.0	2.0	12.7

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact);

Table 6.1.18. Sensitivity analyses on index dates (EDS, diagnosis) during tertiary study period (April 2009–February 2010) (Finland, matched)

Type of analysis, Finland (signalling)	Children and adolescents [a]			Adults		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Influenza A(H1N1)pdm09 vaccination (EDS) tertiary period	9.0	2.0	89.5	2.7	0.1	Infinity
Influenza A(H1N1)pdm09 vaccination (MSLT) tertiary period	5.8	0.96	Infinity	0.6	0.0	22.3
Influenza A(H1N1)pdm09 vaccination (Diagnosis) tertiary period	1.8	0.0	68.3	0.4	0.0	Infinity

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact);

In Finland changing of the index date had an important effect of the risk estimates in the tertiary period, which includes the period of no attention in Finland, and at the end of February one neurologist discussed this potential association with his colleagues in Finland.

Non-signalling countries

In the non-signalling countries the estimate for the diagnosis date in the primary period is actually higher in children/adolescents and adults than for the MSLT referral date analysis (although with wide confidence intervals), whereas the strongest association is found for the EDS date analysis. In the secondary period the confidence intervals are narrower and a decrease in the strength of association is observed when changing the index dates from EDS to MSLT to diagnosis dates. For all index dates the association is stronger for adults than children.

Exploring possible reasons for differences between MSLT and EDS analyses

Table 6.1.19 shows the lag-times between EDS onset and the date of MSLT referral, plus the lag time between EDS onset and the date of diagnosis for cases that had imputed or full dates of EDS. In non-signalling countries the median lag time between EDS onset and MSLT referral was much shorter for exposed than non-exposed children/adolescents and adults. In the non-exposed it was around 11 months for children/adolescents and 15 months for adults. In the exposed it was seven months both for children/adolescents and adults. The median lag time between EDS onset and diagnosis of narcolepsy was also much shorter in exposed children/adolescents and adults than in non-exposed persons. In the non-signalling countries it was 13 months for non-exposed children/adolescents and 20 months for adults. In the exposed it was 10 months for children/adolescents and 11 months for adults.

In signalling countries, the median lag time between EDS onset and MSLT referral did not differ between exposed and non-exposed in children/adolescents (CAVE: there are only two non-exposed), yet it did in adults. Median lag time in non-exposed children/adolescents was around five months between EDS onset and MSLT referral and ten months to diagnosis. In adults this was 15 and 20 months respectively.

Table 6.1.19 Lag times (in days) by exposure and signalling country*

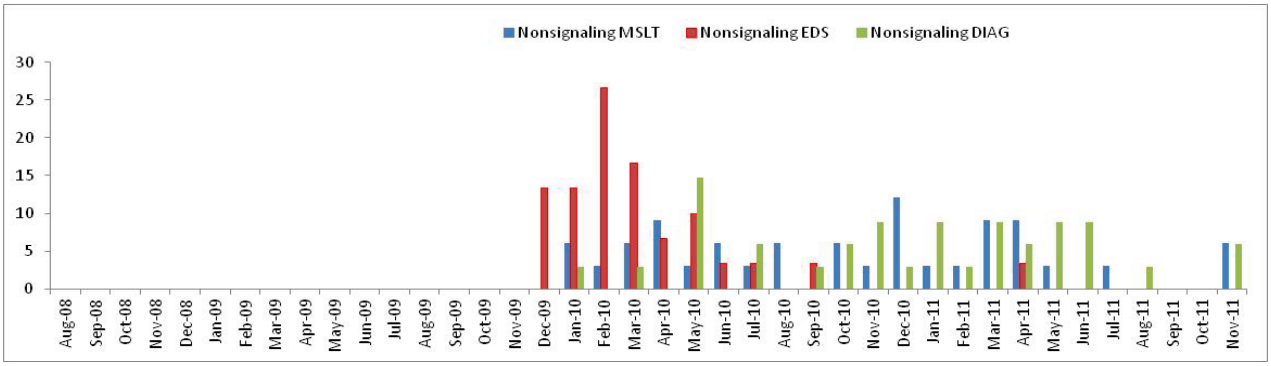
Influenza A(H1N1)pdm09 vaccine	Children and ≤18 adolescents				Adults			
	non-signalling		signalling		non-signalling		signalling	
	EDS- MSLT ref.	EDS- Diagnosis	EDS- MSLT ref.	EDS- Diagnosis	EDS- MSLT ref.	EDS- Diagnosis	EDS- MSLT ref.	EDS- Diagnosis
Non-exposed								
Mean	571	659	142	287	895	1030	649	769
STD	551	576	115	297	660	751	586	651
Median	**325**	**409**	**142**	**287**	**792**	**899**	**476**	**598**
N	42	42	2	2	37	37	10	10
Exposed								
Mean	278	350	194	280	463	558	119	267
STD	271	265	264	258	630	742	84	161
Median	**210**	**319**	**156**	**245**	**217**	**308**	**125**	**338**
N	32	31	83	83	16	16	7	7

**only possible if dates of EDS were provided*

Since the largest differences in results were observed in the children/adolescents, the distribution of index dates were more explored in children/adolescents.

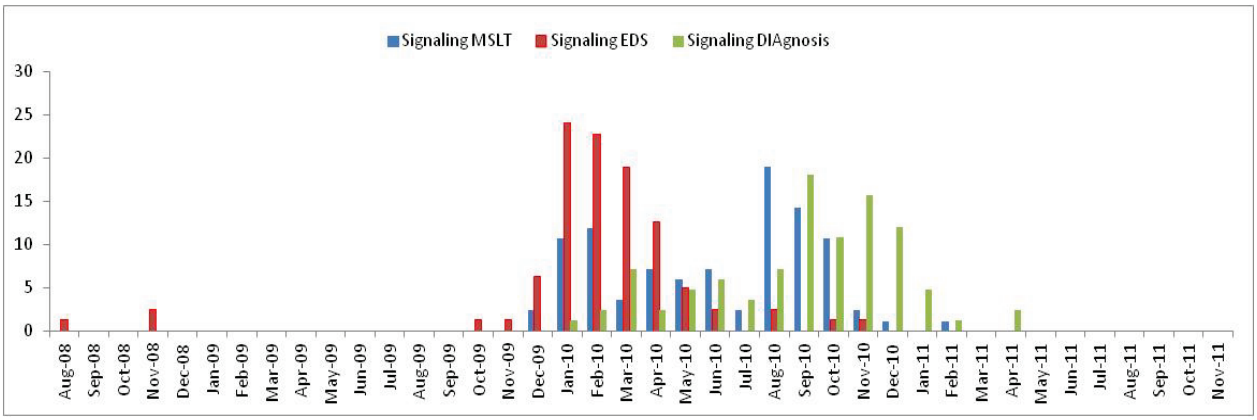
Figure 6.1.22 shows the distribution of EDS, MSLT referral and diagnosis dates in paediatric/adolescent influenza A(H1N1)pdm09 vaccine exposed cases over time. The figure showed that there is a cluster of paediatric/adolescent cases with diagnosis dates and referral for MSLT dates after August 2010, whereas EDS dates cluster in Jan–Feb 2010 for children/adolescents.

Figure 6.1.22 Number of MSLT, diagnosis and EDS dates in influenza A(H1N1)pdm09 vaccine exposed children and adolescents for non-signalling countries (% of cases on Y axis)*.



**graph based on 34 children and adolescents.*

Figure 6.1.23. Percentage of MSLT, diagnosis and EDS dates in influenza A(H1N1)pdm09 vaccine exposed children and adolescents in signalling countries*



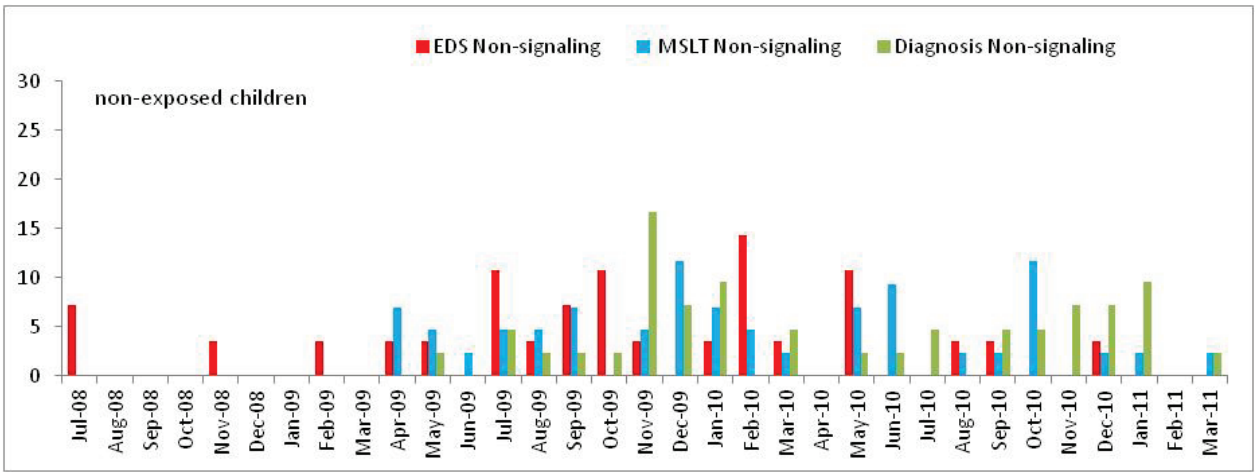
** based on 84 children and adolescents.*

Figure 6.1.223 and 6.1.23 show the distribution of dates in influenza A(H1N1)pdm09 vaccine exposed children/adolescents (vaccination assessed on the basis of the MSLT date). The pattern of MSLT and diagnosis differ considerably. Peaks were seen around February 2010 and August 2010 in the signalling countries, whereas there were more equal distributions in the non-signalling countries. Also in the non-signalling countries, the MSLT/diagnosis dates continued much further to the right since the recruitment time was longer in the non-signalling countries. In the non-signalling countries the EDS date pattern in exposed children/adolescents is very similar to the one in the signalling countries with a peak occurring in January–March 2010.

In Finland EDS onset date was assessed by experts who were not blinded for exposure, and an awareness effect cannot be ruled out. Most of the cases with EDS dates in the beginning of 2010 were actually diagnosed/referred after start of media attention. In the non-signalling countries most of the cases with EDS onset dates in January-March were also diagnosed/referred after the start of media attention.

Figure 6.1.24 shows the same distribution of dates in the non-exposed children/adolescents in the non-signalling countries and this pattern is different. Since exposure is conditional for graphs 6.1.23 and 6.1.24 the dates in those graphs do not provide dates before start of vaccination campaign, however if figure 6.1.24 is compared with figure 6.1.22, a peak is not seen during January–March 2010.

Figure 6.1.24. Number of MSLT, diagnosis and EDS dates in non-exposed (influenza A(H1N1)pdm09 vaccine) children and adolescents in signalling countries (% of cases on Y axis)



To further explore why the effect estimate from the EDS analysis was so different from the analysis MSLT referral date analysis estimate, several additional analysis were conducted. Shifting index dates has an effect on

- the inclusion of cases, since the new index date should be in the study period;
- classification of exposure;
- inclusion of cases in the analysis that were diagnosed/referred after the start of media attention.

The change in effect from MSLT to EDS is therefore a resultant of these three different factors.

Loss of cases due to EDS onset prior to study period

From table 6.1.20 it was observed that in the EDS analysis set many cases were lost (there are 164 in the EDS analysis and 249 for the entire period in the MSLT referral analysis). From the EDS analytical dataset it cannot be learnt why the excluded cases were excluded (as they were not there outputted) and this was therefore approximated with the MSLT referral dataset (in which the month of EDS onset can be calculated). By using the dataset that was utilised for the MSLT analysis, why cases would be excluded from the EDS analysis was explored, and how well the EDS onset date could be characterised.

Table 6.1.20. Cases in MSLT dataset (primary and secondary period) showing the estimation whether these would be present in the EDS dataset, and the exactness of EDS date.

	Sweden	Finland	France	Italy	Netherlands	Norway	Denmark	United Kingdom	Total (n)	Total (%)
Excluded cases										
Full EDS date available but before April 2009	0	9	3	1	4	0	11	3	31	12.4
EDS date before April 2009 imputed month	0	0	1	2	6	0	4	0	13	5.2
EDS date before April 2009 imputed day	2	0	3	1	10	0	0	0	16	6.4
No EDS date	12	0	1	0	1	4	5	4	27	10.8
Included cases in primary period	**25**	**62**	**22**	**0**	**13**	**24**	**3**	**3**	**152**	**61.0**
EDS date within period	1	62	7	0	0	7	2	3	82	32.9
Eligible with EDS imputed month	0	0	2	0	2	0	1	0	5	2.0
Eligible with EDS imputed day	24	0	13	0	11	17	0	0	65	26.1
Included cases with dates after June 2010	**2**	**2**	**1**	**0**	**1**	**2**	**1**	**1**	**10**	**4.0**
Eligible EDS date after June 2010	0	2	0	0	0	1	1	1	5	2.0
Eligible EDS date after June 2010 imputed day	2	0	1	0	1	1	0	0	5	2.0
Total	**41**	**73**	**31**	**4**	**35**	**30**	**24**	**11**	**249**	**100.0**

Table 6.1.20 and all of the analyses below are based on inexact estimation of the exact EDS index date as this is derived from the de-identified MSLT dataset where there is only one month of MSLT (for privacy issues: thus error may be plus or minus a month, therefore table 6.1.20 has two discrepant cases with respect to table 6.1.15). Case distribution in final EDS dataset is therefore slightly different, but since the EDS dataset only includes the cases that enter in the analysis for EDS, only this approximation approach could be used to explore the effects of bias.

Table 6.1.20 shows that a total of 10% of cases did not have an EDS date and the majority came from Sweden, Denmark and the UK, and are therefore excluded from the analysis. Around 23% of the cases have EDS onset prior to April 2009 and are excluded for this reason. A large percentage of included cases had imputed dates (mostly day). The cases that remain in the EDS analysis have a much higher prevalence of exposure to influenza A(H1N1)pdm09 ($p<0.001$) (see table 6.1.21).

Table 6.1.21. Exposure to influenza A(H1N1)pdm09 vaccination in cases who were in-and excluded from EDS analysis

	Influenza A(H1N1)pdm09 vaccine exposure (percentage based on column total)	
Cases	No	Yes
Not in EDS analysis	71 (81.6%)	16 (18.4%)
Included in EDS analysis	38 (23.5%)	124 (76.5%)

Table 6.1.21 creates the suggestion that the difference in exposure pattern between in-and excluded cases for the EDS analysis may result in a selection. There are however, good explanations for the reason that the percentage of exposure differs between cases that enter the EDS analysis or not which are: 1) missing EDS date; 2) EDS date before the start of the study period (April 2009). Since the influenza A(H1N1)pdm09 vaccination campaign only started in October 2009, all cases with index dates prior to April 2009 would be non-exposed per definition. If these cases are excluded the distribution is different (table 6.1.22). Cases with missing EDS dates did not have a higher level of exposure than cases with EDS onset dates in the study period.

Table 6.1.22. Exposure to influenza A(H1N1)pdm09 vaccination in cases who had missing EDS dates compared to cases who had EDS dates in primary study period (1 April 2009–June 2010)

	Influenza A(H1N1)pdm09 vaccine		
Cases	No	Yes	Total
EDS date within from 1 April 2009 onwards	35 (23.0%)	117 (77.0%)	152 (100%)
Missing EDS date	19 (70.4%)	8 (29.6%)	27 (100%)

Table 6.1.23. Sensitivity analyses exploring how the odds ratio for the primary analysis in children would change upon exclusion of cases that for one or more reasons would not enter in the EDS analysis*

Analysis step	Exposed [a)]	Controls	Cases	OR	LL[b)]	UL[c)]	Remark/ conclusion
Primary analysis (MSLT referral date)	No	241	33				
	Yes	25	11	1.7	0.6	5.2	Primary analysis
Sensitivity analysis in the MSLT dataset							
Excluding persons with EDS prior to 1 April 2009 (influenza A(H1N1)pdm09 vaccine assessed at MSLT date), (matched/asymptotical)	No	96	18				No change in estimate (no exposed cases/controls exit)
	Yes	25	11	1.7	0.6	5.2	
Taking out persons with missing EDS dates (influenza A(H1N1)pdm09 vaccine assessed at MSLT date) (matched/asymptotical)	No	239	33				Reduction of OR
	Yes	24	10	1.5	0.5	4.8	
Taking out cases with EDS prior to April 2009 OR missing EDS dates (influenza A(H1N1)pdm09 vaccine assessed at MSLT date) (matched/asymptotical)	No	94	18				Only effect of missing date
	Yes	24	10	1.5	0.5	4.8	

a) Influenza A(H1N1)pdm09 vaccine; [b)] lower 95% confidence level (exact); [c)] upper 95% confidence level (exact)

***primary analysis based on paediatric/adolescent cases with index dates between 1 April 2009 and June 30, 2010*

Table 6.1.23 shows that the exclusion of cases with missing EDS dates did not impact on the association measure in a substantial way, thus this cannot explain why the EDS analysis in the primary study period is so much higher than the analysis using MSLT referral dates.

Exposure change and impact of country

Table 6.1.24. Sensitivity analyses exploring how the odds ratio for the primary analysis in children would change upon re-classifying exposure*

Analysis step	Exposed [a)]	Controls	Cases	OR	LL[b)]	UL[c)]	Remark/ conclusion
Primary analysis (MSLT referral date)	No	241	33				Primary analysis
	Yes	25	11	1.7	0.6	5.2	
Sensitivity analysis in the MSLT dataset							
Taking out cases with EDS prior to April 2009 OR missing EDS dates but reclassifying exposure based on date of EDS (assuming no exposure if EDS< Oct 2009) (matched/asymptotical)	No	100	18				Large increase in risk. Only 6 controls reclassified to non-exposed
	Yes	18	10	4.4	0.9	22.3	

[a)] Influenza A(H1N1)pdm09 vaccine; [b)] lower 95% confidence level (exact); [c)] upper 95% confidence level (exact)

** primary analysis based on pediatric/adolescent cases with index dates between April 1, 2009 and June 30, 2010*

Table 6.1.24 shows the effect of reclassifying exposure to influenza A(H1N1)pdm09 vaccine based on EDS date, and exclusion of all cases with missing EDS dates and EDS prior to 2009. This analysis showed a substantial change in the odds ratio from 1.5 to 4.4. It was further assessed how this was possible based on the distribution of exposure in cases and controls and the changes upon re-classification. There was no change in exposure of cases, but only of controls (see table 6.1.22), six controls were reclassified as non-exposed. Review of these six controls and their matched pairs shows that the reclassification reduced the number of discordant pairs substantially and the entire analysis in the non-signalling countries relies on some discordant pairs, most of whom come from Norway. It was therefore hypothesised that unmatched analyses on the EDS data would allow for better use of all available data, but this did not affect the estimations, neither in the primary nor secondary period. Subsequently whether specific countries were particularly influential was looked at, but this was not the case.

Table 6.1.25. Analysis exploring the effect of matching on the effect estimate for the association between influenza A(H1N1)pdm09 vaccination and narcolepsy in children and adolescents using EDS as index date (EDS dataset primary study period: April 2009–June 2010)

Analysis step	Cases Exposed[a)]/ non-exposed	Controls Exposed [a)]/ non-exposed	OR	LL[b)]	UL[c)]	Remark/ conclusion
Primary period, EDS dataset analysis						
Primary study period (EDS onset as index date) (matched) EDS dataset (asymptotical)	27/23	56/162	4.6	1.8	11.5	
Primary study period (EDS onset as index date) (unmatched) EDS dataset (asymptotical)	27/23	56/162	4.5	1.8	10.9	No major efficiency gain by letting go of matching

[a)] Influenza A(H1N1)pdm09 vaccine; [b)] lower 95% confidence level (exact); [c)] upper 95% confidence level (exact)

Effect of media attention in MSLT/diagnosis on the EDS analysis

In order to explore whether media attention affecting referral and date of diagnosis could explain the change in influenza A(H1N1)pdm09 vaccine-narcolepsy estimates between the MSLT and EDS analysis, the EDS analysis was restricted to all cases who were diagnosed prior to the start of the media attention which was the sensitivity analysis that was planned and is described in section 6.1.11.

6.1.9 Sub-analysis in cases with cataplexy

One of the pre-specified sensitivity analyses regarded restriction of the analysis to cases with cataplexy. Table 6.1.26 shows the results for signalling and non-signalling countries.

Table 6.1.26. Association between influenza A(H1N1)pdm09 vaccination and narcolepsy in cases with cataplexy (lowest part: results for all cases as reference) for the primary study period (1 April 2009-June 30 2010)

Type of analysis	Children and adolescents [a)]			Adults		
	OR	LL [b)]	UL [c)]	OR	LL [b)]	UL [c)]
Sweden and Finland (signalling) restricted to cataplexy						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	8.0	1.3	Infinity	0.8	0.0	Infinity
France, Netherlands, United Kingdom, Italy and Norway (non-signalling) restricted to cataplexy						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	2.6	0.4	21.0	12.9	1.1	728
Sweden and Finland (signalling) (cataplexy & non-cataplexy)						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	14.2	2.5	Infinity	1.2	0.2	9.1
France, Netherlands, United Kingdom, Italy and Norway (non-signalling) (cataplexy & non-cataplexy)						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	1.6	0.5	6.1	3.7	0.7	20.7

[a)] ≤ 18; [b)] lower 95% confidence level (exact); [c)] upper 95% confidence level (exact);

Table 6.1.26 shows that in signalling countries the odds ratio for the association between influenza A(H1N1)pdm09 vaccination and narcolepsy decreases in children/adolescents (e.g. for MSLT as index dates: 14.2 in all cases and eight when restricting to cataplexy) when cases are restricted to those with cataplexy. In the non-signalling countries an opposite direction is observed, the odds ratio increases when restricting to cases with cataplexy. This direction was anticipated as restriction to cataplexy reduces misclassification of the narcolepsy cases and thereby potential non-differential misclassification.

6.1.10 Sub-analysis in cases with Brighton Collaboration narcolepsy criteria levels 1–2

One of the pre-specified sensitivity analyses regarded restriction of the analysis to cases with levels 1–2 of the BC narcolepsy criteria [21]. Table 6.1.27 shows the results for signalling and non-signalling countries.

Table 6.1.27. Association between influenza A(H1N1)pdm09 vaccination and narcolepsy in cases with BC levels 1–2 (lowest part: results for all cases as reference) for the primary study period (1 April 2009– 30 June 2010)

Type of analysis	Children and adolescents [a]			Adults		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Sweden and Finland (signalling) restricted to BC level 1–2						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	13.9	2.4	Infinity	4	0	262
France, Netherlands, United Kingdom, Italy and Norway (non-signalling) restricted to BC level 1–2						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	1.9	0.5	8.0	2.6	0.3	21.7
Sweden and Finland (signalling) (BC level 1-4)						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	14.2	2.5	Infinity	1.2	0.2	9.1
France, Netherlands, United Kingdom, Italy and Norway (non-signalling) (BC level 1-4)						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	1.6	0.5	6.1	3.7	0.7	20.7

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact);

Table 6.1.27 shows that in the signalling countries, the odds ratio for the association between influenza A(H1N1)pdm09 vaccination and narcolepsy in the paediatric/adolescent age decreases when restricting the cases to BC levels 1–2. This is consistent with the cataplexy sub-analysis presented in section 6.1.9. For adults in signalling countries, the opposite pattern has seen restriction to more homogeneous phenotypes as per BC classification results in an increase of the odds ratio, this was also seen in the cataplexy sub-analysis.

In the non-signalling countries, restriction to BC level 1–2 results in a slightly higher association estimate for influenza A(H1N1)pdm09 vaccination and narcolepsy in children/adolescents but lower in adults.

6.1.11 Sensitivity analysis focused on censoring upon diagnosis date (prior to start of media attention)

Table 6.1.28. Association between influenza A(H1N1)pdm09 vaccination and narcolepsy in cases with a narcolepsy diagnosis prior to start of regulatory/media attention

Type of analysis	Children and adolescents [a]			Adults		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Sweden and Finland (signalling) diagnosis prior to start of regulatory/media attention						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	8.0	1.32	Infinity	0.83	0.02	Infinity
France, Netherlands, United Kingdom, Italy and Norway (non-signalling) diagnosis prior to start of regulatory/media attention						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	2.6	0.4	21.0	13	1.1	727
Swedenand& Finland (signalling) diagnosis prior or after media attention (as per primary analysis)						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	14.2	2.5	Infinity	1.2	0.2	9.1
France, Netherlands, United Kingdom, Italy and Norway (non-signalling) (BC level 1-4) diagnosis prior or after media attention as per primary analysis)						
Influenza A(H1N1)pdm09 vaccination (MSLT) primary period	1.6	0.5	6.1	3.7	0.7	20.7

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact);

Table 6.1.28 is an attempt to remove potential bias due to regulatory/media attention by limiting it to the cases that were diagnosed prior to the start of media attention. In the signalling countries this results in a clear reduction of the association estimates and wide confidence intervals. In the non-signalling countries the estimate goes up, but the confidence intervals widen substantially. In Finland, the professional attention started in February. Restricting the analysis to the cases diagnosed prior to the start of any regulatory/media/professional attention (Finland end of February 2010), yielded the following numbers for the analysis, all countries were pooled to be able to estimate the association with most of the possible power given the restrictions. No significant association was observed between influenza A(H1N1)pdm09 vaccination and narcolepsy in children/adolescents whereas a significant increased risk was observed for adults, which was driven by the non-signalling countries (See table 6.1.29)

Table 6.1.29 Association between influenza A(H1N1)pdm09 vaccination and narcolepsy in cases with a narcolepsy diagnosis prior to start of regulatory/media attention

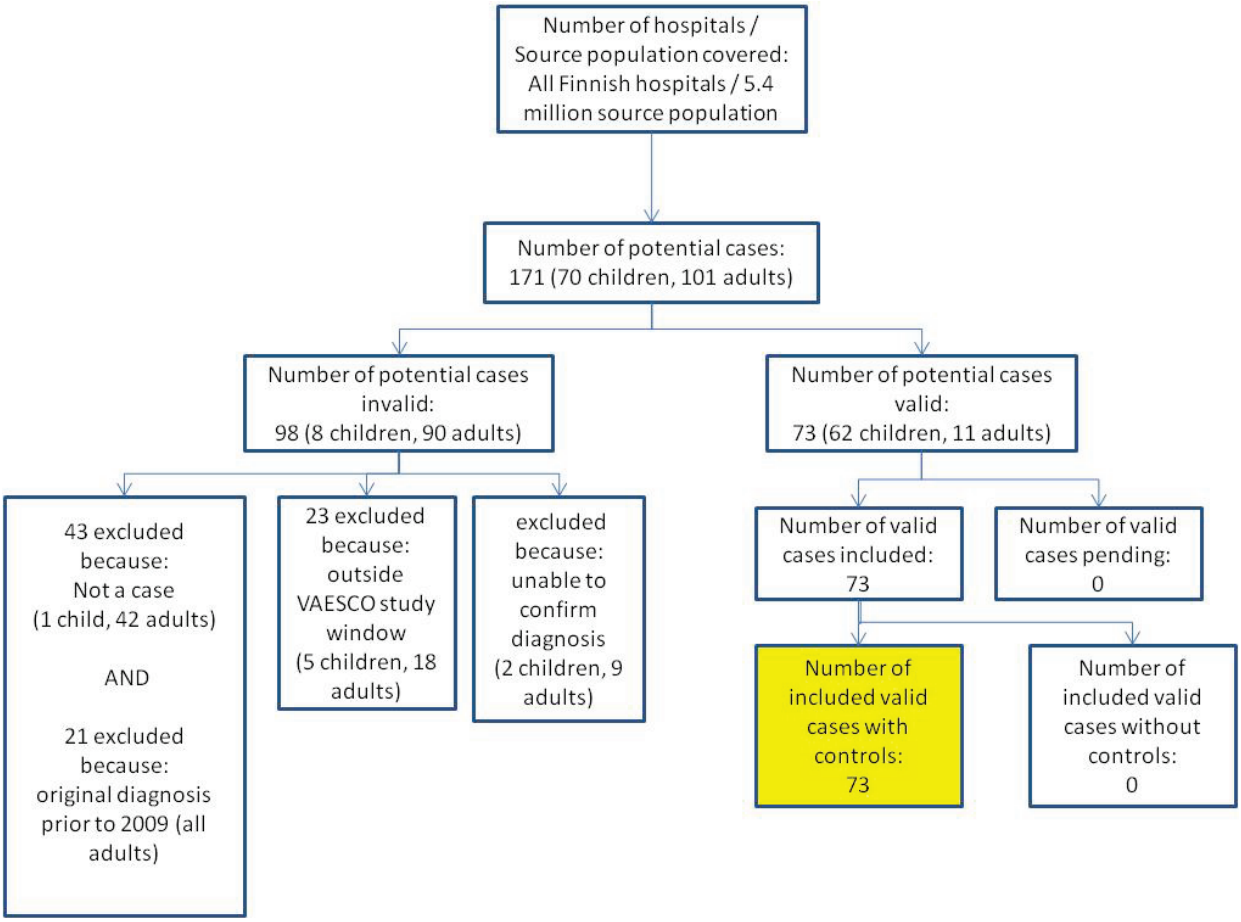
All countries together	Cases diagnosed before July 2010 (United Kingdom, Italy, Netherlands, Norway, Sweden, Denmark, France) and until February 28 2010 in Finland with MSLT in primary risk period	Cases diagnosed before July 2010 (United Kingdom, Italy, Netherlands, Norway, Sweden, Denmark, France) and until February 28 2010 in Finland with EDS date in primary risk period
# cases /controls	70/437	31/156
Children and adolescent cases	38	23
Adult cases	32	8
Exposed cases	15	13
Exposed controls	33	28
Association with influenza A(H1N1)pdm09 vaccination prior to index date	**OR (95%CI)***	**OR (95%CI)***
Children/adolescents	3.3 (0.6-24)	4.3 (0.6-48)
Adults	12.9 (1.1-728)	11.0 (0.8-668)

** based on exact estimations, matched*

6.2 Finland

6.2.1 Attrition diagram Finland

Figure 6.2. Case attrition diagram for Finland

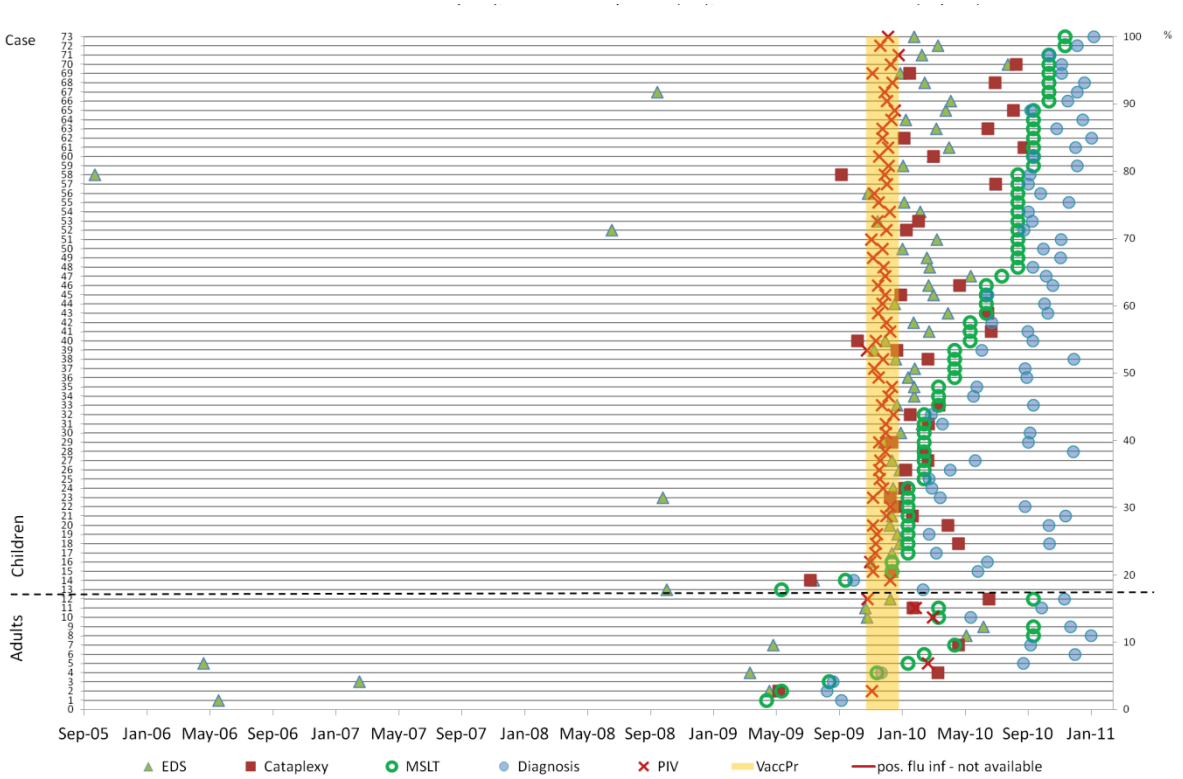


In Finland, paediatric children were obtained from the cohort study in line with the cohort study inclusion and exclusion criteria (exact criteria unknown). Based on the cohort protocol the primary index date was not the date of MSLT referral but the date of first referral to specialist. The adults were included on the basis of the VAESCO protocol and obtained from the HILMO registry. The false positive rate of a narcolepsy was very high for adults and very low for children. Exact reasons for exclusion on a case level were not supplied. Finally, only 11 adults were included.

6.2.2 Distribution of index dates Finland

Figure 6.2.1 shows the distribution of the dates of vaccination, date of first referral to specialist, date of diagnosis, date of onset of EDS and the date of cataplexy, ordered for adults and children and by being vaccinated with the influenza A(H1N1)pdm09 vaccine.

Figure 6.2.1. Distribution of index dates, vaccination date and cataplexy date for the 73 cases from Finland (MSLT should be read as first referral to specialist)



The graph shows that all but one vaccinated child has their date of first referral to a specialist after the vaccination, the pattern was different in adults. Although it may suggest that cases with referral date prior to vaccination were excluded this was not the case. All eligible cases occurring in 2009–2010 were included, as per protocol.

6.2.3 Cases and controls for primary and sensitivity analyses Finland

Table 6.2. Cases and controls in the primary and secondary analyses for Finland

Period	Analysis	Cases	Controls
Sensitivity index date primary period	EDS April 09–June 2010	61	610
Sensitivity index date secondary period	EDS April 09–latest	63	630
Sensitivity index date tertiary period	EDS April 09–February 2010	47	470
Primary index date primary period	Referral to specialist April 09–June 2010	43	430
Primary index date secondary period	Referral to specialist April 09–latest	73	730
Primary index date tertiary period	Referral to specialist April 09–February 2010	26	260
Sensitivity index date primary period	Diagnosis April 09–June 2010	23	230
Sensitivity index date secondary period	Diagnosis April 09–latest	73	730
Sensitivity index date tertiary period	Diagnosis April 09–February 2010	8	80

6.2.4 Lag times and recruitment

To assess whether the delays between referral to specialist (RTS) and diagnosis have changed upon 'knowledge' about a potential signal the delay times were calculated prior to February 2010, between February 2010 and 30 June 2010, and after 30 June 2010.

Table 6.2.1 shows the lag times between date of diagnosis and RTS for cases with RTS between April 2009 and February 2010. The lag time is not statistically different for adults and children.

Table 6.2.1 Lag time between referral to specialist and diagnosis for cases with RTS between April 2009 and February 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	6	127.6	115.2	117.0	8	292
Children/Adolescents	20	141.3	108.0	132.5	10	305
Total	26	138.1	107.5	122.5	8	305

The 95th percentile was 304 for children, it could not be calculated for adults.

Table 6.2.3 Lag time between referral to specialist and diagnosis for cases with RTS between March 2010 and June 2010.

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	3	136.3	69.6	147	62	200
Children/Adolescents	14	109.1	58.6	116.5	3	231
Total	17	113.9	59.2	120	3	231

Table 6.2.4 Lag time between referral to specialist and diagnosis for cases with RTS after June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	3	81.0	26.6	72	60.00	111
Children/Adolescents	27	47.5	33.5	45	-6.00	112
Total	30	50.9	34.1	47.5	-6.00	112

Table 6.2.4 shows that the lag time between RTS and diagnosis is shorter after June 2010, part of this may be caused by the right censoring.

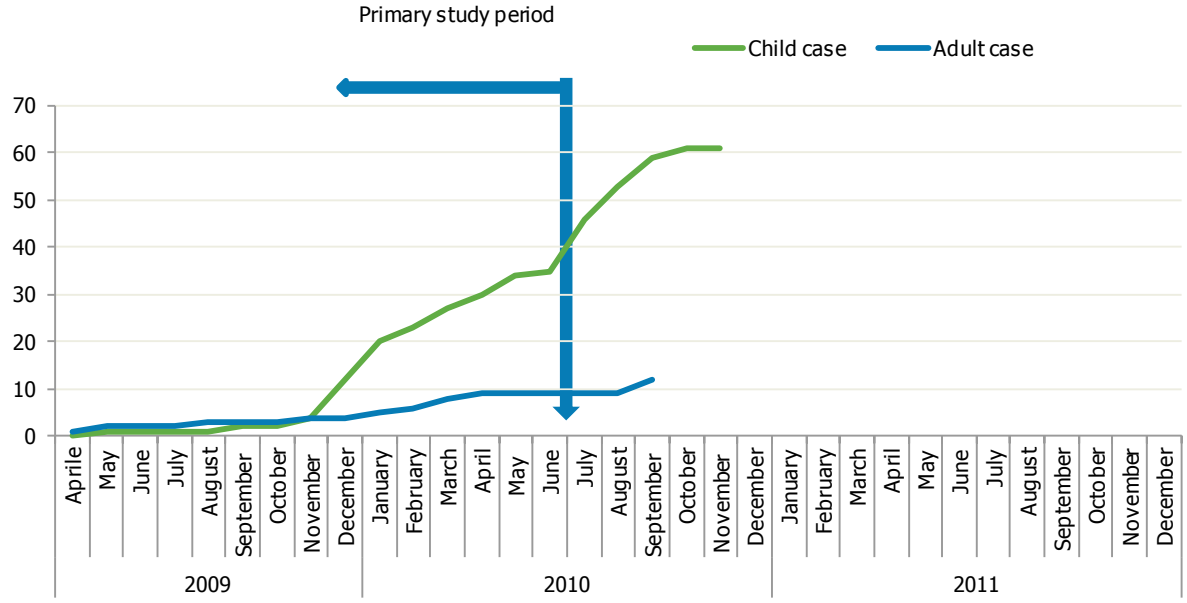
Table 6.2.5 Lag time between referral to specialist and diagnosis for cases with referral to specialist after June 2010 by influenza A(H1N1)pdm09 vaccination

	Exposed [a)]	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	No	2	91.5	27.5	91.5	72.00	111.00
	Yes	1	60.0	.	60.0	60.00	60.00
	Total	3	81.0	26.6	72.0	60.00	111.00
Children/Adolescents	Yes	27	47.5	33.5	45.0	-6.00	112.00
	Total	27	47.5	33.5	45.0	-6.00	112.00
Total	No	2	91.5	27.5	91.5	72.00	111.00
	Yes	28	48.0	33.0	45.0	-6.00	112.00
	Total	30	50.9	34.1	47.5	-6.00	112.00

[a)] *Influenza A(H1N1)pdm09 vaccine*

Whether influenza A(H1N1)pdm09 vaccination would shorten the delay between referral to specialist and diagnosis in children after the start of the media attention could not be tested as there was no non-exposed child.

Figure 6.2.2 Cumulative graph of case recruitment over time (based on referral to specialist date)



This graph shows that primarily only children and adolescents were added after 30 June 2010. Since the 90th percentile of the lag time between referral to specialist and diagnosis is around six to ten months, the question remains whether the recruitment period allowed for the lag time between referral to specialist and diagnosis to be passed and all cases, that occurred in the primary period, should be included. Only cases diagnosed until end of 2010 were included in the study (see dates graph). Although it would be valuable to verify whether cases diagnosed in 2011 would be eligible for the study, this was not possible due to long lag times in provision of data from the national authorities.

6.2.5 Descriptives (primary analysis) Finland (first referral in April 2009–June 2010)

Table 6.2.6. Case characteristics

		Children or adolescents		Adults	
		N	*%*	*N*	*%*
Age	0–5 yrs	2	5.9		
	6–12 yrs	22	64.7		
	13–18 yrs	10	29.4		
	19–59 yrs			9	100.0
Sex	F	18	52.9	4	44.4
	M	16	47.1	5	55.6
Brighton classification of diagnostic certainty (1–4)	1.00	9	26.5	1	11.1
	2.00	24	70.6	6	66.7
	3.00	1	2.9	2	22.2
Cataplexy reported	Empty			1	11.1
	No	1	2.9	2	22.2
	Unknown	1	2.9		
	Yes	32	94.1	6	66.7
Epworth sleep scale reported	Empty	34	100.0	9	100.0
Paediatric sleep scale reported	Empty	34	100.0	9	100.0
Behaviourally insufficient sleep reported	Empty	2	5.9	1	11.1
	No	31	91.2	7	77.8
	Unknown	1	2.9	1	11.1
Circadian rhythm disorder reported	Empty	2	5.9		
	No	32	94.1	7	77.8
	Unknown			1	11.1
	Yes			1	11.1
CSF Hypocretin levels reported	Empty	1	2.9	1	11.1
	No	22	64.7	6	66.7
	Yes	11	32.4	2	22.2
CSF Leukocyte results reported	No	27	79.4	9	100.0
	Yes	7	20.6		
CSF Protein results reported	No	32	94.1	8	88.9
	Yes	2	5.9	1	11.1
MSLT results reported	Empty			1	11.1
	Yes	34	100.0	8	88.9
Sleep latency REM results reported	Empty	3	8.8	2	22.2
	No	5	14.7	1	11.1
	Yes	26	76.5	6	66.7
HLA type reported	No	19	55.9	8	88.9
	Yes	15	44.1	1	11.1

Table 6.2.6. Case and control characteristics: morbidity Finland (unavailable)

Information on the co-variates was not supplied by Finland.

Table 6.2.7. Case and control characteristics: vaccinations Finland

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
Influenza A(H1N1)pdm09 vaccine	No	2	5.9	78	22.9	7	77.8	71	78.9
	Yes	32	94.1	262	77.1	2	22.2	19	21.1
Time since last influenza A(H1N1)pdm09 vaccination	not vaccinated	2	5.9	78	22.9	7	77.8	71	78.9
	8-42 days	4	11.8	23	6.8	1	11.1	3	3.3
	43-180 days	23	67.6	210	61.8	1	11.1	16	17.8
	>180 days	5	14.7	29	8.5				
Brand	not vaccinated	2	5.9	78	22.9	7	77.8	71	78.9
	Pandemrix	32	94.1	262	77.1	2	22.2	19	21.1
Dose	not vaccinated	2	5.9	78	22.9	7	77.8	71	78.9
	1 dose	32	94.1	262	77.1	2	22.2	19	21.1
Seasonal vaccination 2009/2010	EMPTY	34	100.0	340	100.0	9	100.0	90	100.0
HPV vaccination	EMPTY	34	100.0	340	100.0	9	100.0	90	100.0

Information on vaccinations other than influenza A(H1N1)pdm09 were not supplied

6.2.6 Association primary analysis Finland

Table 6.2.8. Associations between influenza A(H1N1)pdm09 influenza vaccination and narcolepsy in Finland

	Children and adolescents [a]			Adults			All		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Influenza A(H1N1)pdm09 vaccination (matched)	10.2	1.8	Inf [d]	1.11	0.07	18.7	5.6	1.3	53.1

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact); [d] Infinity

6.2.7 Sensitivity analyses Finland

Table 6.2.9. Sensitivity analysis: associations between influenza A(H1N1)pdm09 vaccination and narcolepsy

	Children and adolescents [a]			Adults		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Date of MSLT as index date						
Primary period	10.2	1.8	Infinity	1.11	0.07	18.7
Secondary period	21.1	3.8	Infinity	0.9	0.1	6.9
Tertiary period	5.8	0.96	Infinity	0.6	0.0	22.3
Date of EDS as index date						
Primary period	10.8	2.4	103	1.4	0.0	34.5
Secondary period	11.2	2.6	107	1.4	0.0	34.5
Tertiary period	9.0	2.0	89.5	2.7	0.1	Infinity
Date of diagnosis as index						
Primary period	7.2	1.0	315.3	0.5	0.0	4.7
Secondary period	15.9	2.7	647.9	0.84	0.11	5.30
Tertiary period	1.8	0.0	68.3	0.4	0.0	Infinity

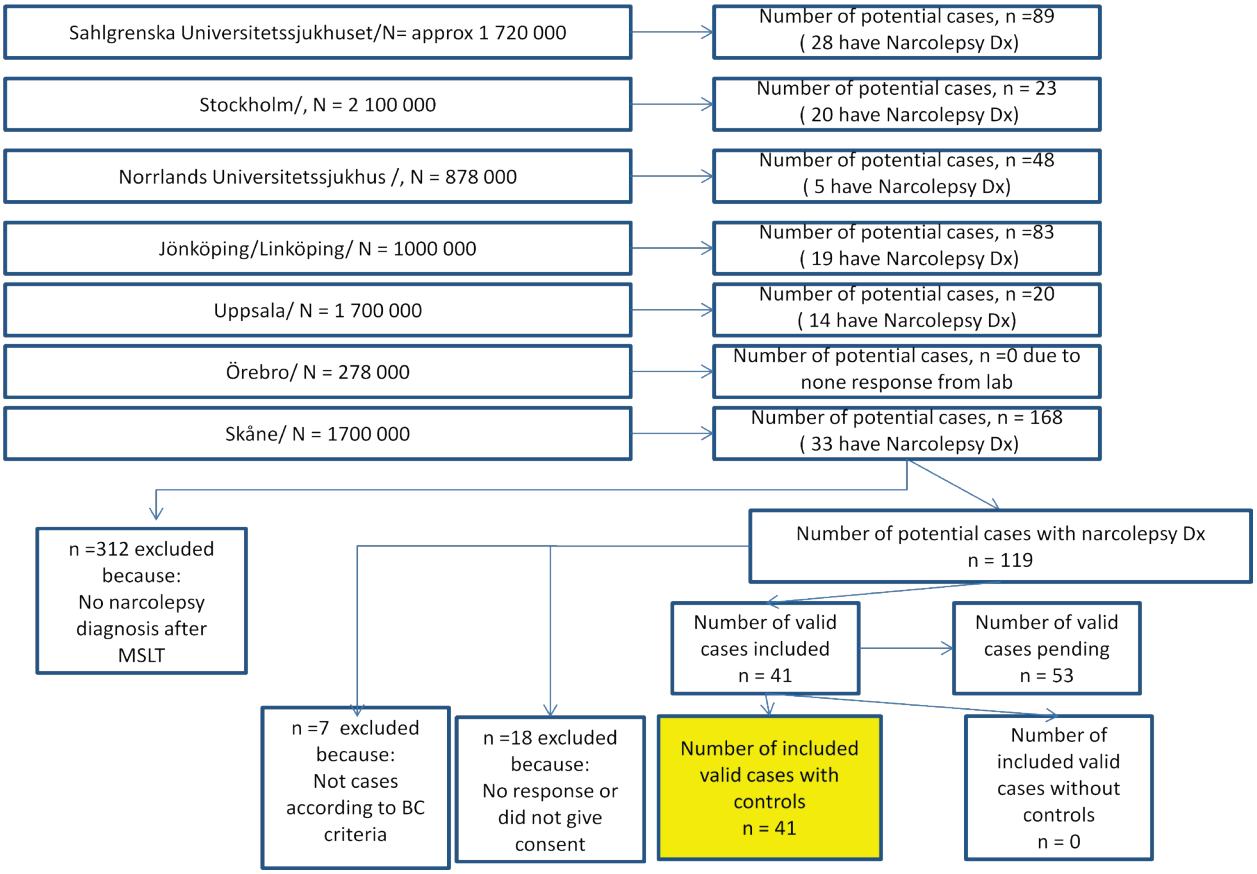
[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact)

6.3 Sweden

6.3.1 Attrition diagram Sweden

In Sweden, cases were obtained through MSLT labs and sleep centres. Most of cases in the current analysis were included in the MPA case inventory study. However the charts needed to be requested *de novo.* Cases were recruited through laboratories that conduct MSLT tests and charts were reviewed by a neurologist who was blinded to the vaccination status. Case recruitment is still ongoing and at least 53 cases are pending evaluation, consent and interview. Selection towards exposure cannot be verified as cases need to consent and be interviewed before.

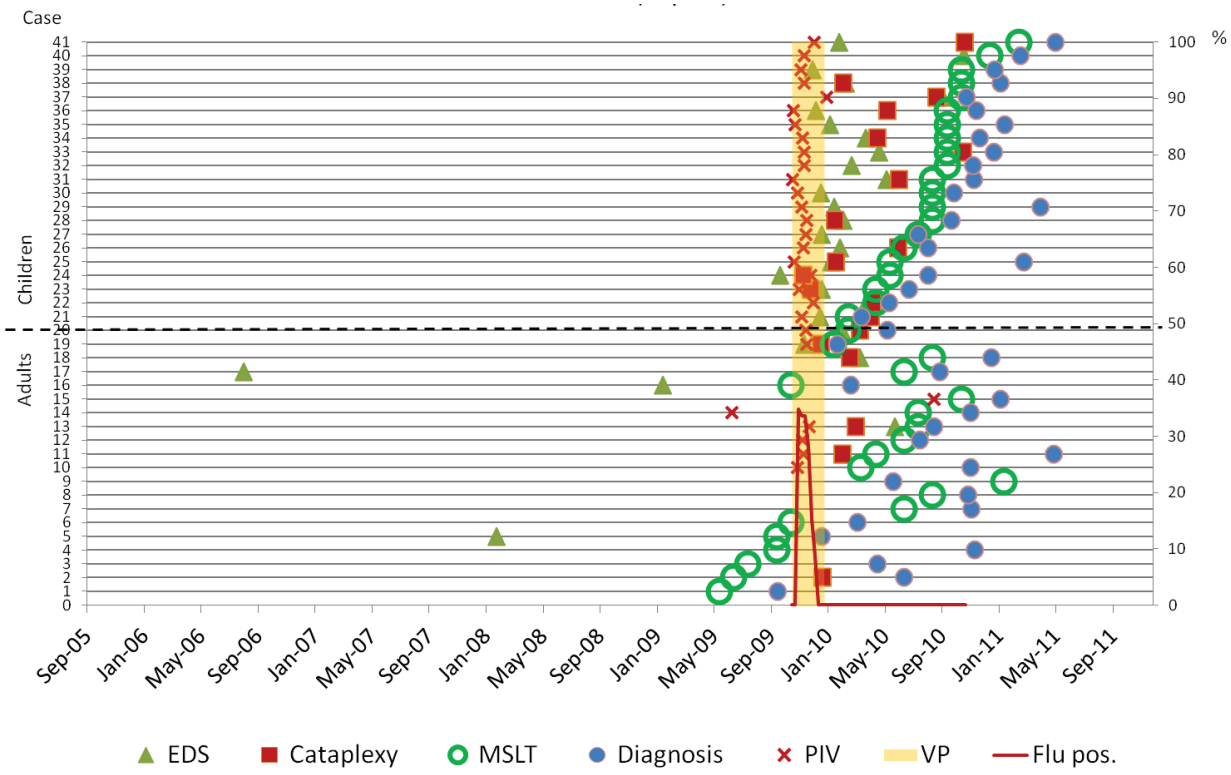
Figure 6.3. Case attrition diagram for Sweden



6.3.2 Distribution of index dates Sweden

Figure 6.3.2 shows the distribution of the dates of vaccination, date of first referral for MSLT, date of diagnosis, date of onset of EDS and the date of cataplexy, ordered for adults and children and by being vaccinated with the influenza A(H1N1)pdm09 vaccine.

Figure 6.3.2. Distribution of index dates, vaccination date and cataplexy date for the 41 included cases from Sweden



The graph shows that no vaccinated child had their date of MSLT referral before the vaccination, whereas in adults the picture is different. Many cases are still pending, and a selection towards vaccination could not be verified since consent was not obtained or the interview was not performed.

6.3.3 Cases and controls for primary and sensitivity analyses Sweden

Table 6.3. Cases and controls in the primary and sensitivity analyses for Sweden

Period	Analysis	Cases	Controls
Sensitivity index date primary period	EDS April 09–June 2010	24	51
Sensitivity index date secondary period	EDS April 09–latest	26	55
Primary index date primary period	MSLT referral April 09–June 2010	20	50
Primary index date secondary period	MSLT referral April 09–latest	41	91
Sensitivity index date primary period	Diagnosis April 09–June 2010	11	22
Sensitivity index date secondary period	Diagnosis April 09–latest	41	91

MSLT: Referral to sleep test, EDS: onset excessive daytime sleepiness.

6.3.4 Lag times and recruitment Sweden

To assess whether the delays between MSLT referral and diagnosis have changed upon 'knowledge' about a potential signal, the delay times were calculated prior to July 2010 and after 30 June 2010.

The tables show the lag times between date of diagnosis MSLT referral for cases with MSLT referral between April 2009 and February 2010. The lag time was statistically different for adults and children/adolescents prior to regulatory /media attention (p=0.012) but not after regulatory/media attention.

Table 6.3.1. Lag time between MSLT referral and diagnosis for cases with MSLT referral between April 2009 and June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adult	10	222.9	134.6	189.5	34	425
Child/adolescent	10	85.0	78.9	73.5	9	287
Total	20	153.95	128.6	111.5	9	425

The 95th percentile was 271 days for children/adolescents and 420 for adults.

Table 6.3.2. Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	5	13.8	143.5	76	-238	113
Children/Adolescents	16	78.3	53.1	70.5	.00	231
Total	21	63.	83.9	71	-238	231

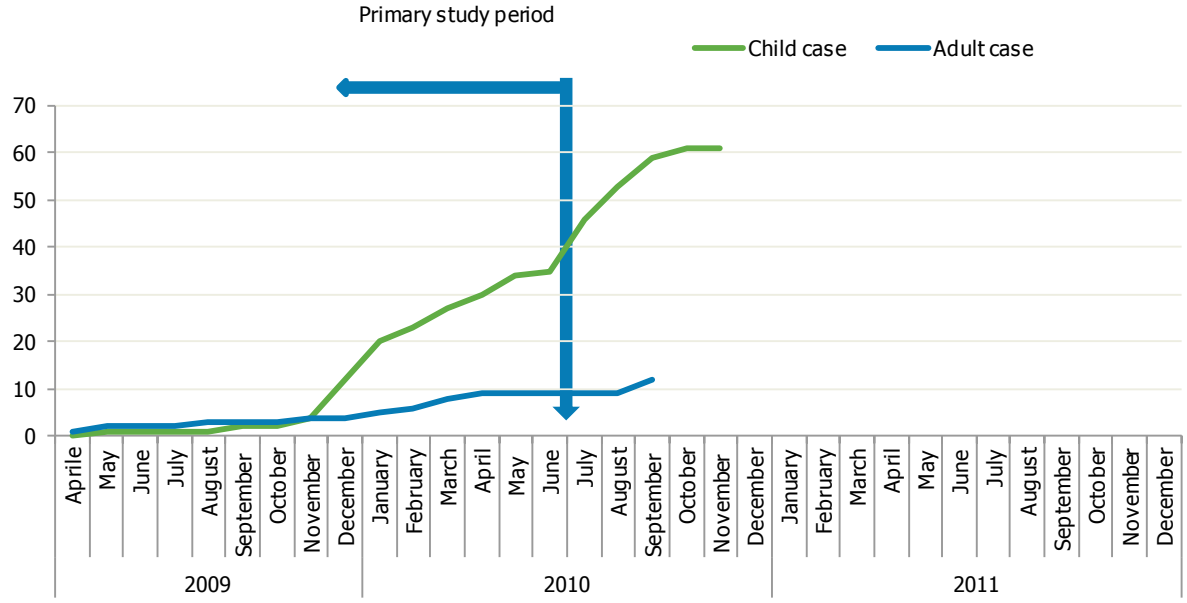
Table 6.3.3. Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010 by influenza A(H1N1)pdm09 vaccination

	Exposed [a)]	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	No	1	-238	.	-238	-238	-238
	Yes	4	76.8	32.6	80	34	113
	Total	5	13.8	143.6	76	-238	113
Children/Adolescents	Yes	16	78.4	53.2	70.5	.00	231
	Total	16	78.4	53.2	70.5	.00	231
Total	No	1	-238.0	.	-238	-238	-238
	Yes	20	78.1	48.9	73.5	.00	231
	Total	21	63.0	83.8	71	-238	231

[a)] *Influenza A(H1N1)pdm09 vaccine*

It was not possible to test whether influenza A(H1N1)pdm09 vaccination would shorten the delay between MSLT referral and diagnosis in children after the start of the regulatory/media attention as there was no non-exposed child.

Figure 6.3.3. Cumulative number of cases recruited over time based on MSLT referral date



The lag time between referral to MSLT and diagnosis was between 9–13 months, recruitment was extended until May 2011 which leaves a small chance that not all cases occurring during the primary study period would have had time to be diagnosed and be considered for inclusion. In Sweden however, the problem of not included (pending) cases is higher. Clearly more children/adolescents were added for the period after June 2010. It cannot be excluded that selection bias occurred due to the large incompleteness and inability to look at the exposure distribution in the non-included cases.

6.3.5 Descriptives (primary analysis: MSLT date in primary study period) Sweden

Table 6.3.4. Case characteristics Sweden

		Children and adolescents		Adults	
		N	%	N	%
Age	6–12 yrs	3	30.0		
	13–18 yrs	7	70.0		
	19–59 yrs			9	90.0
	60+			1	10.0
Sex	F	3	30.0	9	90.0
	M	7	70.0	1	10.0
Brighton classification of diagnostic certainty (1–4)	1	2	20.0		
	2	7	70.0	4	40.0
	3			1	10.0
	4A			3	30.0
	4B	1	10.0	2	20.0
Cataplexy reported	No			5	50.0
	Yes	10	100.0	5	50.0
Epworth sleep scale reported	12	1	10.0	1	10.0
	18			1	10.0
	19	1	10.0		
	Empty	5	50.0	2	20.0
	Unknown	3	30.0	6	60.0
Paediatric sleep scale reported	Empty	8	80.0	10	100.0
	Unknown	2	20.0		
Behaviourally insufficient sleep reported	No	9	90.0	9	90.0
	Unknown	1	10.0	1	10.0
Circadian rhythm disorder reported	No	9	90.0	9	90.0
	Unknown	1	10.0	1	10.0
CSF Hypocretin levels reported	No	2	20.0	6	60.0
	Unknown	4	40.0	4	40.0
	Yes	4	40.0		
CSF Leukocytes results reported	No	2	20.0	1	10.0
	Unknown	7	70.0	9	90.0
	Yes	1	10.0		
CSF Protein results reported	No	2	20.0	1	10.0
	Unknown	7	70.0	9	90.0
	Yes	1	10.0		
Sleep latency reported	Yes	10	100.0	10	100.0
HLA type reported	No			3	30.0
	Unknown	7	70.0	4	40.0
	Yes	3	30.0	3	30.0

Table 6.3.5. Case and control characteristics: morbidity Sweden

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
ILI in last year	No	8	100.0	13	86.7	6	85.7	24	96.0
	Yes			2	13.3	1	14.3	1	4.0
URI in last year	No	3	60.0	2	28.6	3	75.0	3	25.0
	Yes	2	40.0	5	71.4	1	25.0	9	75.0
ILI or URI in last year	No	8	80.0	14	70.0	9	90.0	20	66.7
	Yes	2	20.0	6	30.0	1	10.0	10	33.3
Epilepsy	No	10	100.0	20	100.0	10	100.0	28	93.3
	Yes							2	6.7
Depression	No	9	90.0	20	100.0	8	80.0	26	86.7
	Yes	1	10.0			2	20.0	4	13.3
Pregnancy	No	10	100.0	20	100.0	2	20.0	9	30.0
	Unknown date					2	20.0		
	Yes					6	60.0	21	70.0
Diabetes	No	10	100.0	20	100.0	10	100.0	30	100.0
Asthma	No	9	90.0	17	85.0	8	80.0	23	76.7
	Unknown					1	10.0		
	Unknown date	1	10.0					1	3.3
	Yes			3	15.0	1	10.0	6	20.0
Migraine	No	9	90.0	20	100.0	9	90.0	23	76.7
	Unknown							2	6.7
	Unknown date							1	3.3
	Yes	1	10.0			1	10.0	4	13.3
Immuno-compromised	No	10	100.0	20	100.0	10	100.0	30	100.0
Autoimmune disease	No	10	100.0	20	100.0	9	90.0	26	86.7
	Unknown date							1	3.3
	Yes					1	10.0	3	10.0
Epstein Barr Virus	No	10	100.0	17	85.0	9	90.0	29	96.7
	Unknown			1	5.0	1	10.0		
	Yes			2	10.0			1	3.3
Bacteremia/Sepsis	No	9	90.0	18	90.0	9	90.0	27	90.0
	Unknown	1	10.0	2	10.0	1	10.0	2	6.7
	Yes							1	3.3
Streptococcal infection	No	10	100.0	16	80.0	9	90.0	27	90.0
	Unknown			2	10.0	1	10.0		
	Unknown date			1	5.0				
	Yes			1	5.0			3	10.0
Antibiotics	No	10	100.0	16	80.0	10	100.0	25	83.3
	Unknown			3	15.0			1	3.3
	Unknown date							3	10.0
	Yes			1	5.0			1	3.3

Table 6.3.6. Case and control characteristics: vaccinations

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
Influenza A(H1N1)pdm09 vaccine	No	1	10.0	7	35.0	7	70.0	18	60.0
	Yes	9	90.0	13	65.0	3	30.0	12	40.0
Time since last pandemic vaccination	not vaccinated	1	10.0	6	30.0	7	70.0	15	50.0
	43–180 days	6	60.0	7	35.0	2	20.0	5	16.7
	>180 days	2	20.0	6	30.0	1	10.0	7	23.3
	vaccinated, date unknown	1	10.0						
	Unknown			1	5.0			3	10.0
Brand	Not vaccinated	2	20.0	8	40.0	7	70.0	18	60.0
	Pandemrix	8	80.0	10	50.0	3	30.0	10	33.3
	Unknown			2	10.0			2	6.7
Dose	not vaccinated	1	10.0	6	30.0	7	70.0	15	50.0
	1 dose	7	70.0	10	50.0	3	30.0	11	36.7
	2 doses	1	10.0	3	15.0			1	3.3
	unknown date	1	10.0	1	5.0			3	10.0
Seasonal vaccination 2009/2010	No	10	100.0	20	100.0	10	100.0	25	83.3
	Yes							5	16.7
HPV vaccination	No	10	100.0	20	100.0	10	100.0	29	96.7
	Yes							1	3.3

6.3.6 Associations (crude) primary analysis Sweden

Table 6.3.7. Association between vaccines, infections and narcolepsy

	Children and adolescent [a]			Adults			All		
	OR	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]
Influenza A(H1N1)pdm09 vaccination	3.5**	0.4	Infinity	1.3	0.1	78.6	3.9	0.4	183.9

*[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact); ** unbiased median estimate of exact odds ratio*

The unmatched estimate for the association between influenza A(H1N1)pdm09 vaccine and narcolepsy in children was 11.6 (95%CI 0.56–242), for adults it was 1.36 (95%CI 0.091–20.2).

6.3.7 Sensitivity analyses: Sweden

Table 6.3.8 Sensitivity analyses: associations between influenza A(H1N1)pdm09 vaccination and narcolepsy

	Children and adolescent [a]			Adults		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Date of MSLT as index date						
Primary period	3.5**	0.4	Infinity	1.3	0.1	79
Secondary period	2.69**	0.86	Infinity	2.9	0.5	30
Date of EDS as index date						
Primary period	12.6**	1.7	562	NA		
Secondary period	12.9	1.8	575	1**	0.03	Infinity
Date of diagnosis as index						
Primary period	1.78**	0.13	Infinity	0.23	0.00	3.2
Secondary period	11.5**	1.8	Infinity	1.19	0.27	5.9
Tertiary period						

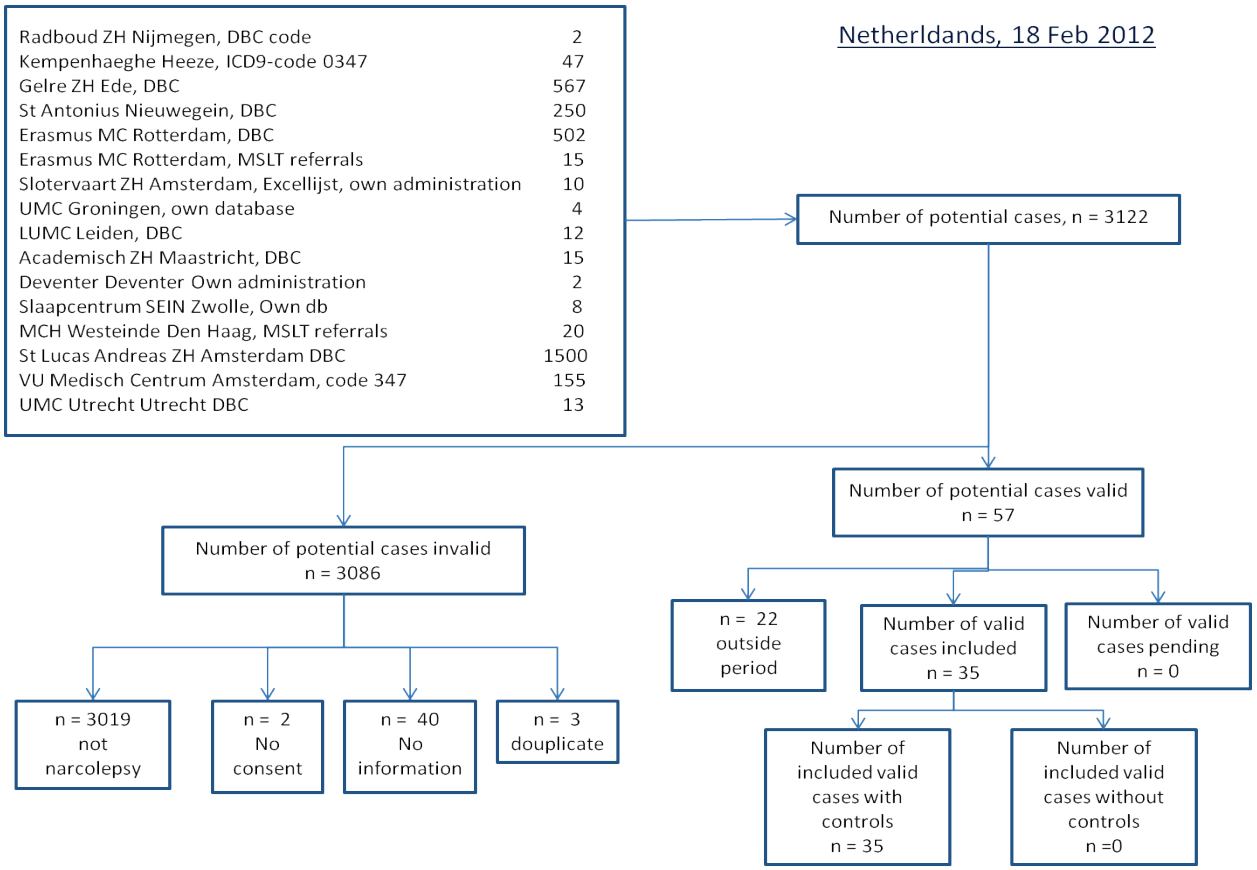
*[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact) **median unbiased estimates*

6.4 Netherlands

6.4.1 Case attrition diagram: the Netherlands

In the Netherlands, all sleep centres and specialised academic centres that are able to diagnose narcolepsy were identified by appointed Dutch narcolepsy experts. A request was made per hospital to extract the procedures or diagnosis codes for narcolepsy. All potential codes were reviewed. For all potential cases the charts were reviewed and the CRF was completed in the hospital. Completed CRFs together with specialist letters were reviewed by narcolepsy experts while being blinded for exposure. Currently 16 hospitals have been completed. From the 16 completed hospitals, 3 122 potential cases were identified. Of these, 3 064 were considered not to be a case (mostly because MSLT was done for other indication) and 57 were considered valid. Twenty two cases were excluded as the referral for MSLT fell outside the VAESCO period, or because symptoms existed prior to 1 January 2005, 36 cases could be included, each case had at least one control.

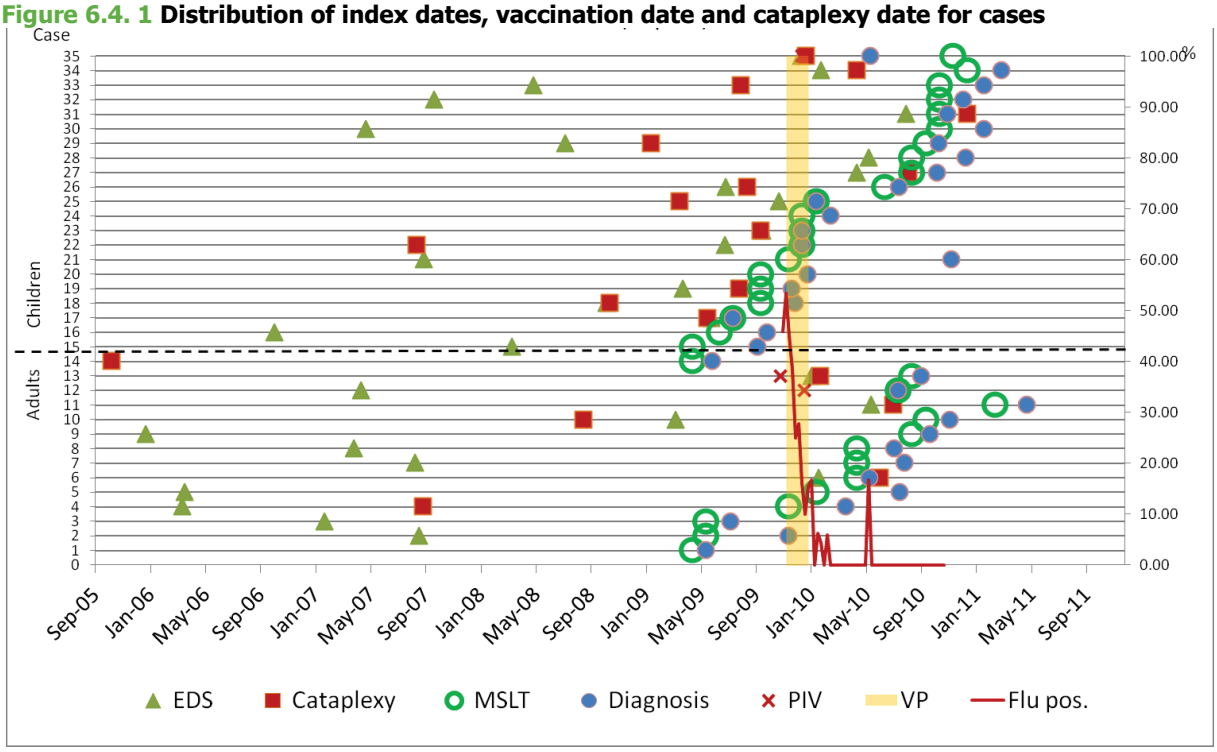
Figure 6.4. Case attrition diagram for the Netherlands



6.4.2 Distribution of index dates: Netherlands

Figure 6.4.1 shows the distribution of the dates of vaccination, date of referral for MSLT, date of diagnosis, date of onset of EDS and the date of cataplexy, ordered for adults and children and those being vaccinated with the influenza A(H1N1)pdm09 vaccine.

Figure 6.4. 1 Distribution of index dates, vaccination date and cataplexy date for cases



The graph shows that all the dates for MSLT referral spread evenly over the study period, both for adults and children/adolescents. Cases were included until January 2011, but not in all hospitals.

6.4.3 Cases and controls for primary and sensitivity analyses: the Netherlands

Table 6.4. Cases and controls in the primary and sensitivity analyses

Period	Analysis	Cases	Controls
Sensitivity index date primary period	EDS April 09–June 2010	12	120
Sensitivity index date secondary period	EDS April 09–latest	13	130
Primary index date primary period	MSLT referral April 09–June 2010	20	200
Primary index date secondary period	MSLT referral April 09–latest	35	347
Sensitivity index date primary period	Diagnosis April 09–June 2010	18	180
Sensitivity index date secondary period	Diagnosis April 09–latest	35	357

MSLT: Sleeping test referral, EDS: onset excessive daytime sleepiness.

6.4.4 Lag times and recruitment the Netherlands

To assess whether the delays between MSLT referral and diagnosis have changed upon 'knowledge' about a potential signal the delay times were calculated prior to July 2010 and after 30 June 2010.

The tables show the lag times between date of diagnosis and MSLT referral for cases with MSLT referral between April 2009 and June 2010. The lag time is not different for adults and children/adolescents. (p=0.595) prior to media/regulatory attention or after media/regulatory attention (p=0.93)

Table 6.4.1. Lag time between MSLT referral and diagnosis for cases with MSLT referral between April 2009 and June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	8	99.625	62.6	94.0	28.	185
Children/Adolescents	12	77.75	101.6	56.0	.00	361
Total	20	86.5	86.8	71.0	.00	361

The 75th percentile was 104 days for children/adolescents and 169 for adults, 95th was 296 for children, and for adults this could not be estimated.

Table 6.4.2. Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	5	36.8	27.3	40	.00	70
Children/Adolescents	9	40.7	90.6	56	-184	119
Total	14	39.3	72.7	53	-184	119

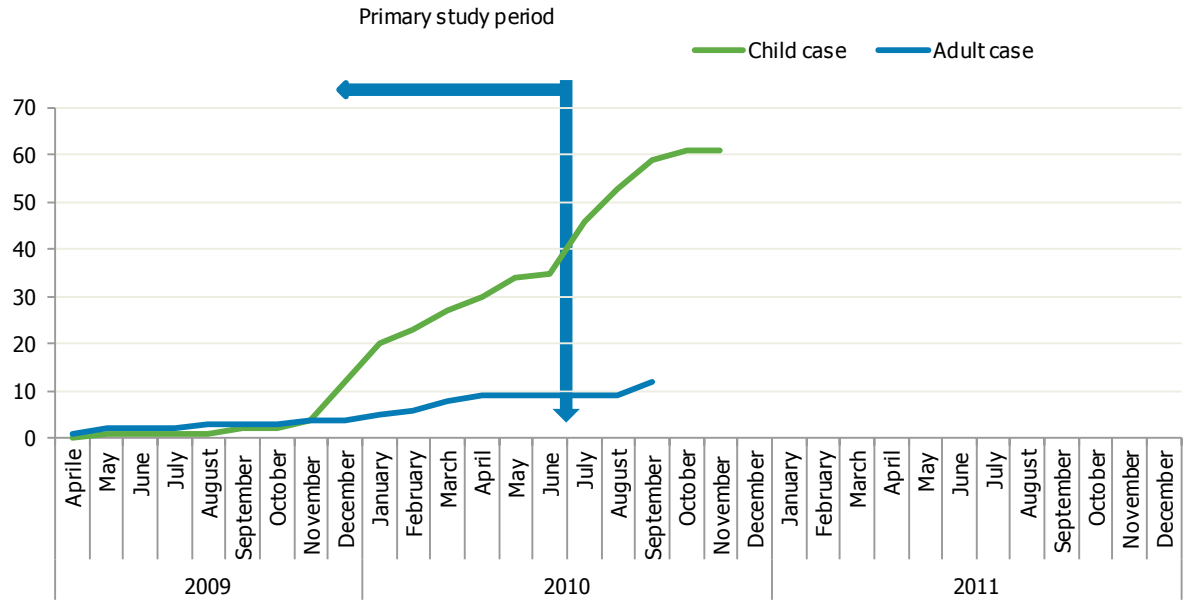
Table 6.4.5. Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010 by influenza A(H1N1)pdm09 vaccination

	Exposed [a)]	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	No	3	54.3333	15.0	53.0	40.00	70.0
	Yes	2	10.5000	14.8	10.5	.00	21.0
	Total	5	36.8000	27.3	40.0	.00	70.0
Children/Adolescents	No	7	61.5714	31.9	56.0	18.0	99.0
	Yes	2	-32.5000	214.3	-32.50	-184.0	119.0
	Total	9	40.6667	90.7	56.0	-184.0	119.0
Total	No	10	59.4000	27.3	54.5	18.0	99.0
	Yes	4	-11.0000	126.5	10.5	-184.0	119.0
	Total	14	39.2857	72.7	53.0	-184.0	119.0

[a)] *Influenza A(H1N1)pdm09 vaccine*

There was no statistical association between exposure to influenza A(H1N1)pdm09 vaccine and the lag time in children/adolescents or adults or overall, but this is based on very few cases.

Figure 6.4.2. Cumulative graph of recruited cases based on date of MSLT referral



The lag time between referral for MSLT and diagnosis is up to ten months. Case recruitment stopped in January 2011, which means that there is only a small opportunity that some cases that would be eligible for the primary analysis would not have been identified.

6.4.5 Descriptives (primary analysis: date of MSLT in primary study period): the Netherlands

Table 6.4.6. Case characteristics

		Child or adolescent		Adult	
		N	%	N	%
Age	0-5 yrs	4	19.0		
	6-12 yrs	9	42.9		
	13-18 yrs	8	38.1		
	19-59 yrs			13	100.0
Sex	F	6	28.6	7	53.8
	M	15	71.4	6	46.2
Brighton classification of diagnostic certainty (1–4)	1	10	47.6	3	23.1
	2	8	38.1	3	23.1
	3	2	9.5	5	38.5
	4A	1	4.8	2	15.4
Cataplexy reported	No	3	14.3	4	30.8
	Unknown	1	4.8		
	Yes	17	81.0	9	69.2
Epworth sleep scale reported	10			1	7.7
	11			1	7.7
	13			2	15.4
	14			1	7.7
	15	2	9.5	1	7.7
	16			1	7.7
	17			2	15.4
	18			1	7.7
	21			1	7.7
	4			1	7.7
	Unknown	19	90.5	1	7.7
Paediatric sleep scale reported	26	1	4.8		
	Empty	2	9.5	12	92.3
	Unknown	18	85.7	1	7.7
Behaviourally insufficient sleep reported	Empty			1	7.7
	No	18	85.7	12	92.3
	Unknown	2	9.5		
	Yes	1	4.8		
Circadian rhythm disorder reported	Empty			1	7.7
	No	21	100.0	12	92.3
CSF Hypocretin levels reported	Empty			1	7.7
	No	11	52.4	6	46.2
	Unknown	1	4.8	1	7.7
	Yes	9	42.9	5	38.5
CSF Leukocytes reported	Empty	1	4.8	3	23.1
	Unknown	13	61.9	8	61.5
	Yes	7	33.3	2	15.4
CSF Protein reported	Empty	1	4.8	3	23.1
	Unknown	13	61.9	8	61.5
	Yes	7	33.3	2	15.4
Sleep latency reported	No	3	14.3		
	Yes	18	85.7	13	100.0
HLA type reported	Empty			1	7.7
	No	6	28.6	7	53.8
	Yes	15	71.4	5	38.5

Table 6.4.7. Case and control characteristics: morbidity

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
ILI in last year	No	10	90.9	104	94.5	5	100.0	66	94.3
	Yes	1	9.1	6	5.5			4	5.7
URI in last year	No	5	83.3	47	79.7	3	100.0	24	55.8
	Yes	1	16.7	12	20.3			19	44.2
ILI or URI in last year	No	11	91.7	102	85.0	8	100.0	59	73.8
	Yes	1	8.3	18	15.0			21	26.3
Epilepsy	No	11	91.7	109	90.8	7	87.5	80	100.0
	Unknown	1	8.3	10	8.3				
	Yes			1	.8	1	12.5		
Depression	No	11	91.7	109	90.8	6	75.0	70	87.5
	Unknown	1	8.3	10	8.3	1	12.5	1	1.3
	Yes			1	.8	1	12.5	9	11.3
Pregnancy	No	12	100.0	110	91.7	7	87.5	77	96.3
	Unknown			10	8.3				
	Unknown dateY					1	12.5	1	1.3
	Yes							2	2.5
Diabetes	No	12	100.0	109	90.8	8	100.0	80	100.0
	Unknown			10	8.3				
	Yes			1	.8				
Asthma	No	12	100.0	97	80.8	8	100.0	71	88.8
	Unknown			10	8.3				
	Yes			13	10.8			9	11.3
Migraine	No	12	100.0	110	91.7	8	100.0	74	92.5
	Unknown			10	8.3			2	2.5
	Yes							4	5.0
Immuno-compromised	No	12	100.0	110	91.7	8	100.0	79	98.8
	Unknown			10	8.3			1	1.3
Autoimmune disease	No	11	91.7	110	91.7	8	100.0	77	96.3
	Unknown	1	8.3	10	8.3			1	1.3
	Yes							2	2.5
Epstein Barr Virus	No	11	91.7	100	83.3	8	100.0	62	77.5
	Unknown	1	8.3	19	15.8			10	12.5
	Yes			1	.8			8	10.0
Bacteremia/Sepsis	No	11	91.7	110	91.7	8	100.0	78	97.5
	Unknown	1	8.3	10	8.3			2	2.5
Streptococcal infection	No	11	91.7	110	91.7	8	100.0	77	96.3
	Unknown	1	8.3	10	8.3			2	2.5
	Unknown date							1	1.3
Antibiotics	No	11	91.7	104	86.7	8	100.0	64	80.0
	Unknown			2	1.7			2	2.5
	Yes	1	8.3	14	11.7			14	17.5

Table 6.4.8. Case and control characteristics: vaccinations

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
Influenza A(H1N1)pdm09 vaccine	No	12	100.0	118	98.3	8	100.0	78	97.5
	Yes			2	1.7			2	2.5
Time since last influenza A(H1N1)pdm09 vaccination	Not vaccinated	12	100.0	118	98.3	8	100.0	78	97.5
	8–42 days			1	.8				
	43–180 days							2	2.5
	>180 days			1	.8				
Brand	Not vaccinated	12	100.0	118	98.3	8	100.0	78	97.5
	Focetria			1	.8			2	2.5
	Unknown			1	.8				
Dose	Not vaccinated	12	100.0	118	98.3	8	100.0	78	97.5
	1 dose			2	1.7			1	1.3
	2 doses							1	1.3
Seasonal vaccination 2009/2010	No	12	100.0	120	100.0	8	100.0	78	97.5
	Yes							2	2.5
HPV vaccination	No	12	100.0	120	100.0	8	100.0	80	100.0

6.4.6 Associations (crude) primary study period the Netherlands

	Children and adolescent [a]			Adults			All		
	OR	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]
Influenza A(H1N1)pdm09 vaccination	NA			NA			NA	0	15.1

[a] ≤ 18; [b] lower 95% confidence level; [c] upper 95% confidence level;

Sensitivity analyses: the Netherlands

Table 6.4.9. Sensitivity analyses: associations between influenza A(H1N1)pdm09 vaccines and narcolepsy

	Children and adolescents [a]			Adults		
	OR	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]
Date of MSLT as index date						
Primary study period	NA			NA		
Secondary study period	2.3	0.2	13.8	3.9	0.3	37.8
Date of EDS as index date						
Primary study period	NA			NA		
Secondary study period	7.8**	0.3	565.6	4.1**	0.0	53.2
Date of diagnosis as index						
Primary period	NA			NA		
Secondary period	2.0	0.2	11.3	3.9	0.6	25.4

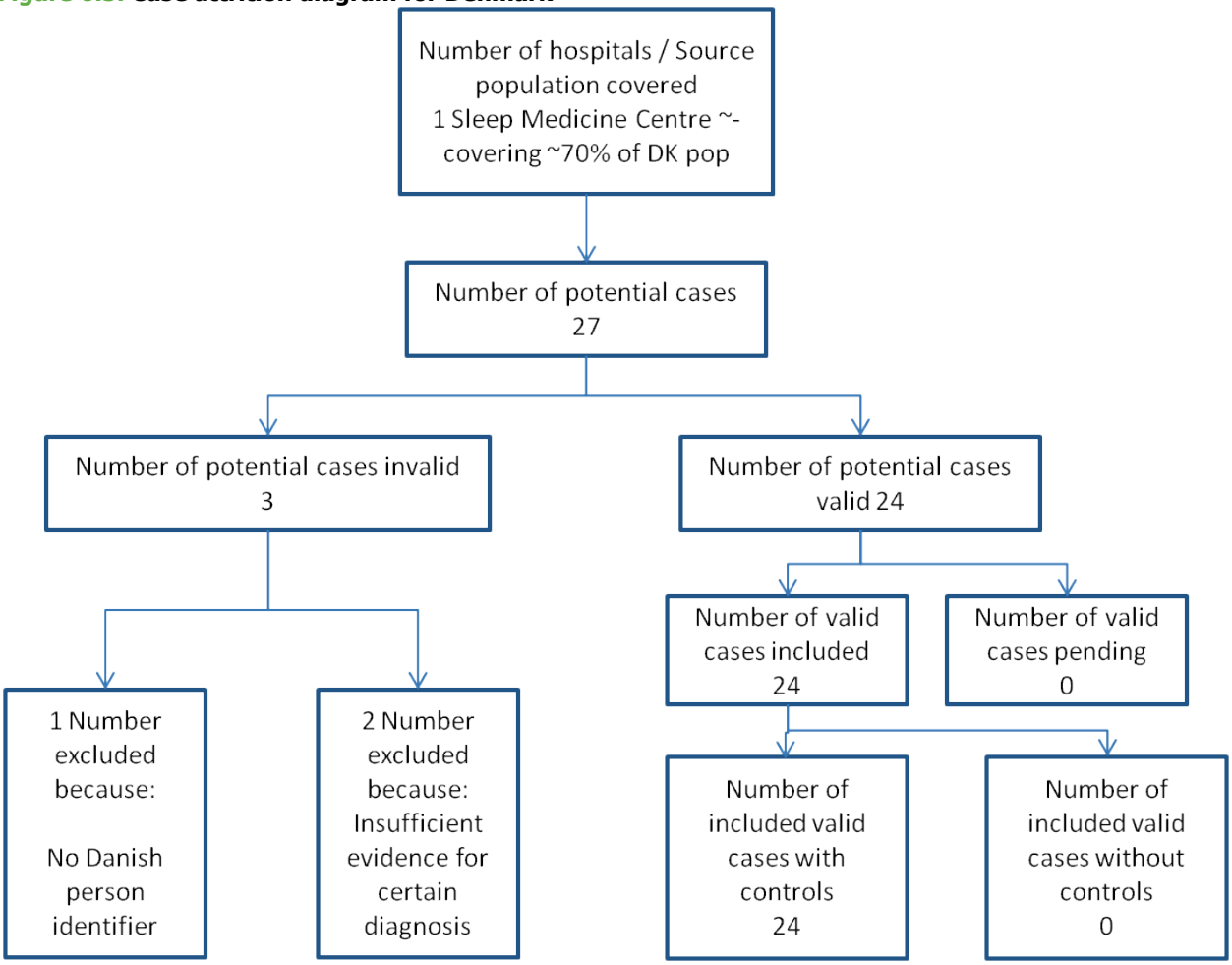
*[a] ≤ 18, [b] lower 95% confidence level, [c] upper 95% confidence level ** median unbiased estimate; NA=not assessable*

6.5 Denmark

6.5.1 Attrition of cases Denmark

In Denmark one sleep centre was used for case recruitment, this centre is supposed to serve around 70% of the Danish population. Case identification and validation has been completed and for each, case controls were identified. Twenty seven cases were reviewed by narcolepsy experts from the sleep centre, and 24 were considered valid. Consent was not required.

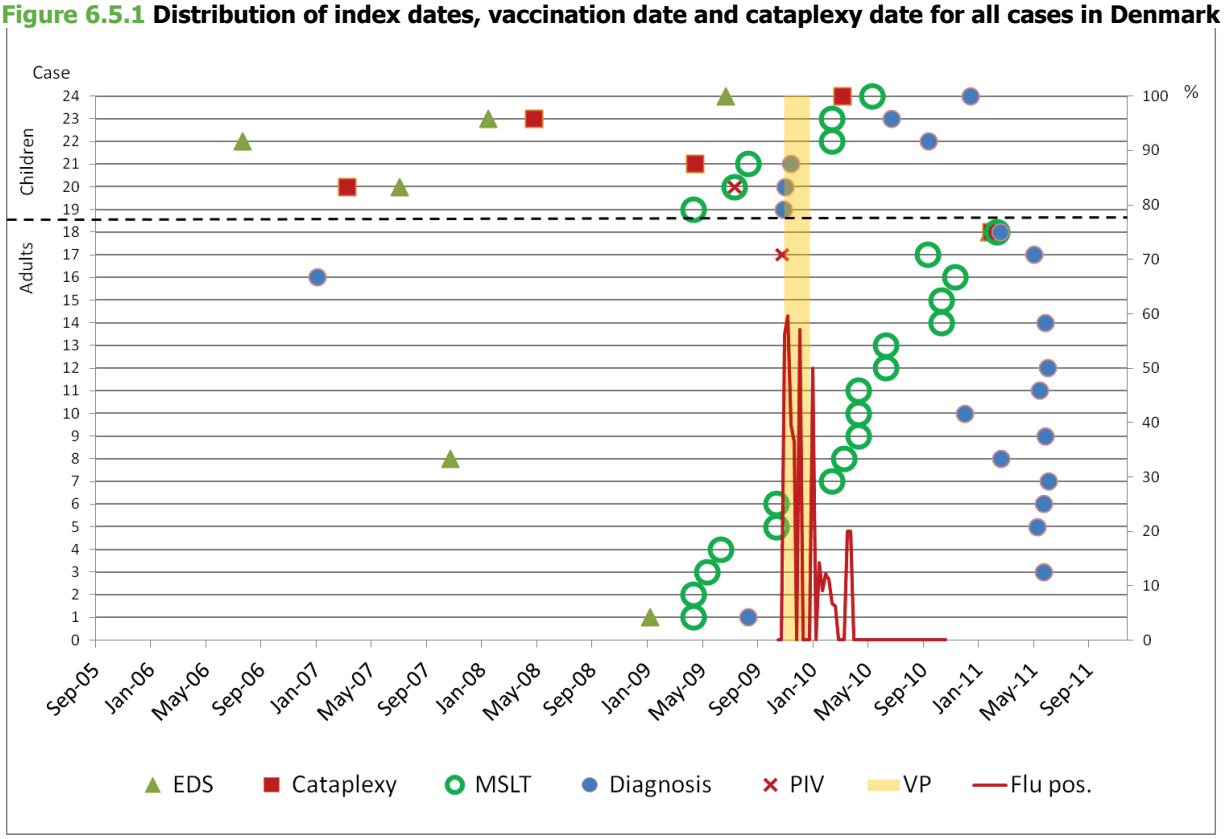
Figure 6.5. Case attrition diagram for Denmark



6.5.2 Distribution of index dates Denmark

Figure 6.5.1 shows the distribution of the dates of vaccination, date of referral for MSLT, date of diagnosis, date of onset of EDS and the date of cataplexy, ordered for adults and children/adolescents being vaccinated with the influenza A(H1N1)pdm09 vaccine.

Figure 6.5.1 Distribution of index dates, vaccination date and cataplexy date for all cases in Denmark



The graph shows that all the dates for MSLT referral spread evenly over the study period, both for adults and children/adolescents. Cases with diagnoses up till May 2011 were included.

6.5.3 Cases and controls for primary and sensitivity analyses: Denmark

Table 6.5. Cases and controls in the primary and sensitivity analyses for Denmark

Period	Analysis	Cases	Controls
Sensitivity index date primary period	EDS April 09–June 2010	2	10
Sensitivity index date secondary period	EDS April 09–latest	3	15
Primary index date primary period	MSLT referral April 09–June 2010	15	75
Primary index date secondary period	MSLT referral April 09–latest	24	120
Sensitivity index date primary period	Diagnosis April 09–June 2010	5	25
Sensitivity index date secondary period	Diagnosis April 09–latest	19	95

MSLT: Sleeping test referral, EDS: onset excessive daytime sleepiness.

6.5.4 Lag times and recruitment Denmark

To assess whether the delays between MSLT referral and diagnosis have changed upon 'knowledge' about a potential signal, the delay times were calculated prior to July 2010 and after 30 June 2010.

The tables show the lag times between date of diagnosis and MSLT referral for cases with MSLT referral between April 2009 and June 2010. The lag time differed significantly between adults and children/adolescents prior to 30 June 2010, with adults having a much longer lag time

Table 6.5.1 Lag time between MSLT referral and diagnosis for cases with MSLT referral between April 2009 and June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	8	411.2	196.7	385.5	121	745
Children/adolescents	5	153.8	57.9	132.	93	217
Total	13	312.2	201.7	236	93	745

**2 cases with missing dates of diagnosis*

The 75th percentile was 215 days for children/adolescents and 563 for adults.

Table 6.5.2 Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010

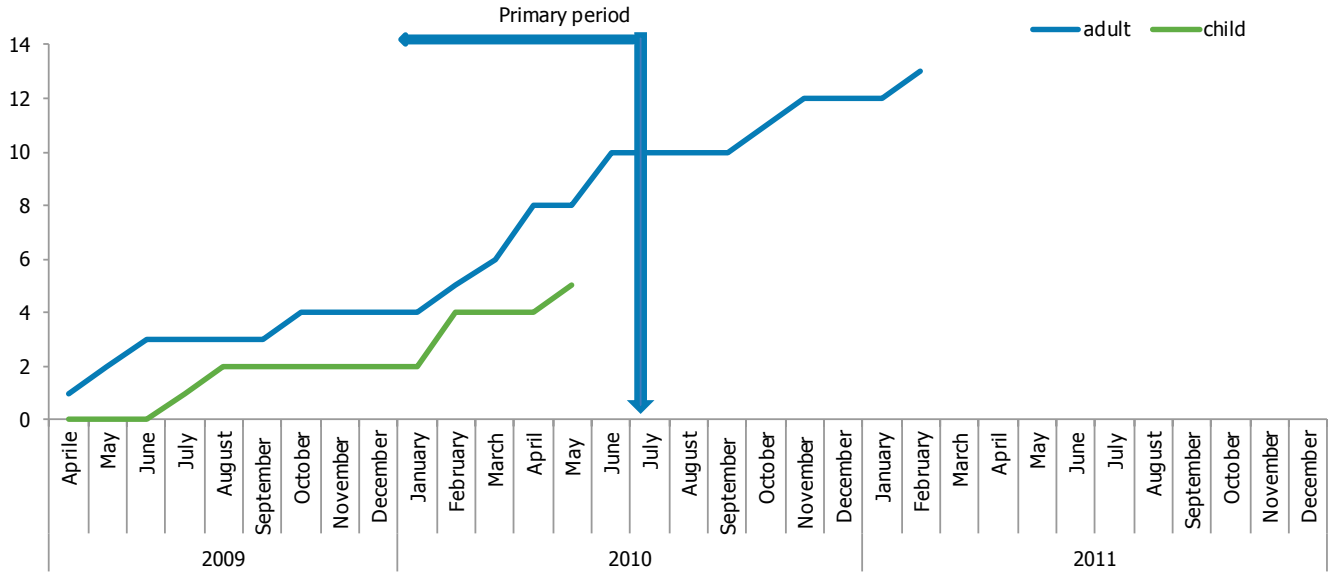
	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	3	-391	889.5	7	-1410	230
Total	3	-391	889.5	7	-1410	230

Table 6.5.3 Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010 by influenza A(H1N1)pdm09 vaccination

	Exposed [a)]	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	No	2	-590	1159	-590	-1410	230
	Yes	1	7	.	7	7	7
	Total	3	-391	889	7	-1410	230
Total	No	2	-590	1159	-590	-1410	230
	Yes	1	7	.	7	7	7
	Total	3	-391	889	7	-1410	230

[a)] *Influenza A(H1N1)pdm09 vaccine*

Figure 6.5.2 Cumulative graph of case recruitment by date of referral for MSLT



6.5.5 Descriptives (primary analysis: date of MSLT in primary study period): Denmark

Table 6.5.4. Case characteristics

		Child or adolescent		Adult	
		N	*%*	*N*	*%*
Age	6–12 yrs	1	20.0		
	13–18 yrs	4	80.0		
	19–59 yrs			13	100.0
Sex	F	3	60.0	5	38.5
	M	2	40.0	8	61.5
Brighton classification of diagnostic certainty (1–4)	1	4	80.0	3	23.1
	2	1	20.0	6	46.2
	3			3	23.1
	Unknown			1	7.7
Cataplexy reported	No			3	23.1
	Yes	5	100.0	10	76.9
Epworth sleep scale reported	5.00			1	20.0
	12.00	1	25.0	1	20.0
	15.00	1	25.0	1	20.0
	17.00			1	20.0
	18.00	1	25.0		
	19.00	1	25.0		
	24.00			1	20.0
Paediatric sleep scale reported	Empty	3	60.0	13	100.0
	Unknown	2	40.0		
Behaviourally insufficient sleep reported	No	5	100.0	13	100.0
Circadian rhythm disorder reported	No	5	100.0	13	100.0
CSF Hypocretin levels reported	No			4	30.8
	Unknown			1	7.7
	Yes	5	100.0	8	61.5
CSF Leukocytes reported	Empty			5	38.5
	No			2	15.4
	Yes	5	100.0	6	46.2
CSF Protein reported	Empty			5	38.5
	No			2	15.4
	Yes	5	100.0	6	46.2
Sleep latency reported	Yes	5	100.0	13	100.0
Sleep latency reported	No			3	23.1
	Yes	5	100.0	10	76.9
HLA type reported	No	4	80.0	12	92.3
	Unknown	1	20.0		
	Yes			1	7.7

Table 6.5.5. Case and control characteristics: morbidity Denmark

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
ILI in last year	No	5	100.0	25	100.0	10	100.0	50	100.0
URI in last year	No	5	100.0	25	100.0	10	100.0	50	100.0
ILI or URI in last year	No	5	100.0	25	100.0	10	100.0	50	100.0
Epilepsy	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Depression	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Pregnancy	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Diabetes	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Asthma	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Migraine	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Immuno-compromised	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Autoimmune disease	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Epstein Barr Virus	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Bacteremia/Sepsis	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Streptococcal infection	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		
Antibiotics	Empty	5	100.0	25	100.0	9	90.0	50	100.0
	Unknown					1	10.0		

Denmark did not supply data on co-variates.

Table 6.5.6. Case and control characteristics: vaccinations

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
Influenza A(H1N1)pdm09 vaccine	No	5	100.0	25	100.0	10	100.0	49	98.0
	Yes							1	2.0
Time since last pandemic vaccination	Not vaccinated	5	100.0	25	100.0	10	100.0	49	98.0
	43-180 days							1	2.0
Brand	Not vaccinated	5	100.0	25	100.0	10	100.0	49	98.0
	Pandemrix							1	2.0
Dose	Not vaccinated	5	100.0	25	100.0	10	100.0	49	98.0
	1 dose							1	2.0
Seasonal vaccination 2009/2010	No	5	100.0	25	100.0	10	100.0	50	100.0
HPV vaccination	No	5	100.0	25	100.0	10	100.0	50	100.0

6.5.6 Associations (crude) primary analysis: Denmark

Table 6.5.7. Association between influenza A(H1N1)pdm09 vaccination and narcolepsy (MSLT referral in primary period)

	Children and adolescents [a]			Adults			All		
	OR	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]
Influenza A(H1N1)pdm09 vaccination	NA			5**	0	195	5**	0	195

*[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact) ** Median unbiased estimates (exact odds ratio)*

6.5.7 Sensitivity analyses: Denmark

Table 6.5.8. Sensitivity analyses: associations between influenza A(H1N1)pdm09 vaccination and narcolepsy

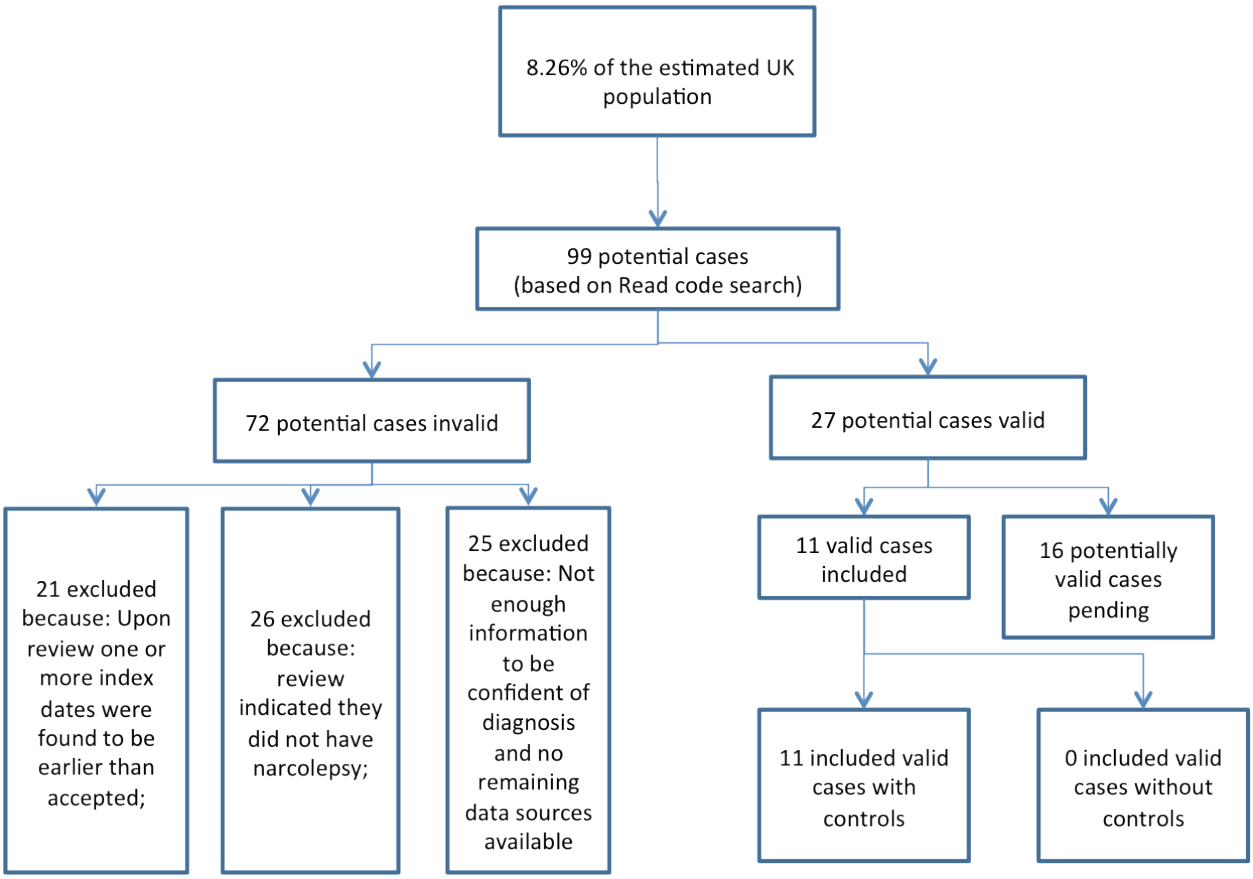
	Children and adolescents [a]			Adults		
	OR	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]
Date of MSLT as index date						
Primary period	NA			NA		
Secondary period	NA			5**	0	195
Date of EDS as index date						
Primary period	NA			NA		
Secondary period	NA			5**	0	195
Date of diagnosis as index						
Primary period	NA			NA		
Secondary period	NA			5**	0.7	37.3

*[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact); **Median unbiased estimate. NA=not assessable*

6.6 United Kingdom

In the UK, the GPRD was used to identify cases. Initially 99 potential cases were identified, of which 72 were considered invalid or lacked information. The electronic medical record including the free text fields were reviewed, and subsequently GPs were asked to supply all specialist information in order to validate it. For the analysis only 11 cases could be included.

Figure 6.6. Case attrition diagram for UK



6.6.1 Distribution of index dates: United Kingdom

Figure 6.6.1 Distribution of index dates, vaccination date and cataplexy date for cases in the UK

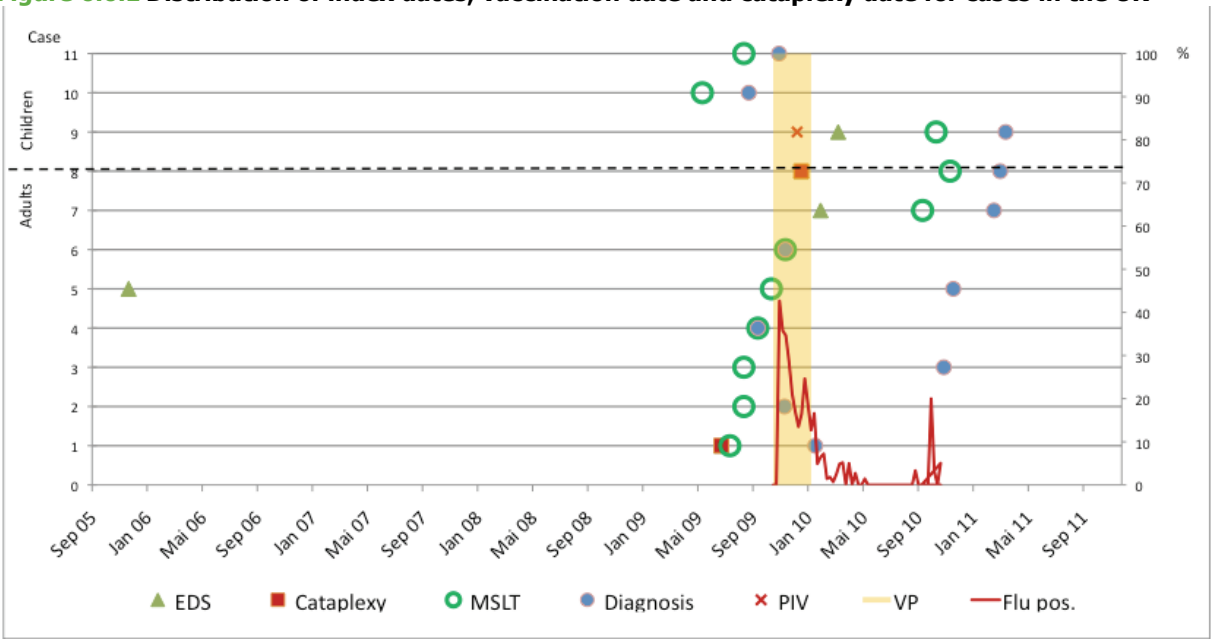


Figure 6.6.1 shows the distribution of the dates of vaccination, date of referral for MSLT, date of diagnosis, date of onset of EDS and the date of cataplexy, ordered for adults and children/adolescents being vaccinated with the influenza A(H1N1)pdm09 vaccine.

The graph shows that all the dates for MSLT referral spread evenly over the study period, both for adults and children/adolescents. Cases with diagnoses up until August 2011 were included in the study, although not all GPs may have had updates until that point in time.

6.6.3 Cases and controls for primary and sensitivity analyses the UK

Table 6.6. Cases and controls in the primary and sensitivity analyses for UK

Period	Analysis	Cases	Controls
Sensitivity index date primary period	EDS April 09–June 2010	4	85
Sensitivity index date secondary period	EDS April 09–latest	5	110
Primary index date primary period	MSLT referral April 09–June 2010	8	171
Primary index date secondary period	MSLT referral April 09–latest	11	271
Sensitivity index date primary period	Diagnosis April 09–June 2010	4	85
Sensitivity index date secondary period	Diagnosis April 09–latest	9	210

MSLT: Sleeping test referral, EDS: onset excessive daytime sleepiness.

6.6.4 Lag times and recruitment UK

To assess whether the delays between MSLT referral and diagnosis have changed upon 'knowledge' about a potential signal, the delay times were calculated prior to July 2010 and after 30 June 2010.

The tables show the lag times between date of diagnosis and MSLT referral for cases with MSLT referral between April 2009 and June 2010. The lag time differs between adults and children/adolescents but not significantly.

Table 6.6.1 Lag time between MSLT referral and diagnosis for cases with MSLT referral between April 2009 and June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	4	281.25	169.3	296	90	443
Children/Adolescents	2	90.5	17.7	90.5	78	103
Total	6	217.7	164.2	146	78	443

**two cases with missing diagnosis date*

The 90th percentile could not be calculated.

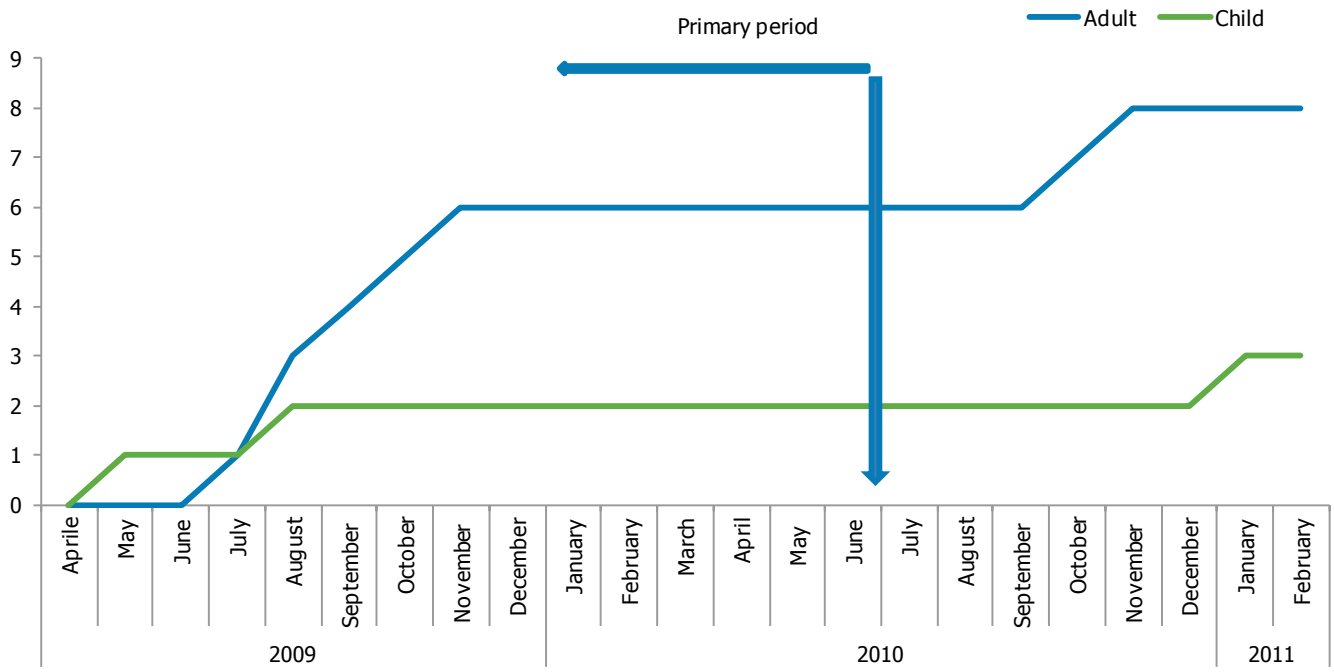
Table 6.6.2 Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	2	132.5	30.4	132.5	111	154
Children/Adolescents	1	169	.	169	169	169
Total	3	144.7	30.1	154	111	169

Table 6.6.3 Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010 by influenza A(H1N1)pdm09 vaccination

	Exposed [a)]	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	No	1	111	.	111	111	111
	Yes	1	154	.	154	154	154
	Total	2	132.5	30.4	132.5	111	154
Children/Adolescents	No	1	169	.	169	169	169
	Total	1	169	.	169	169	169
Total	No	2	140	41.0	140	111	169
	Yes	1	154	.	154	154	154
	Total	3	144.7	30.1	154	111	169

Figure 6.6.2 Cumulative graph of case recruitment by date of referral for MSLT



6.6.5 Descriptives (primary analysis: date of MSLT in primary study period) UK

Table 6.6.4. Case characteristics

		Child or adolescent		Adult	
		N	*%*	*N*	*%*
Age	13–18 yrs	2	100.0		
	19–59 yrs			6	100.0
Sex	F			3	50.0
	M	2	100.0	3	50.0
Brighton classification of diagnostic certainty (1–4)	2	1	50.0	1	16.7
	4A	1	50.0	3	50.0
	4B			2	33.3
Cataplexy reported	No			1	16.7
	Unknown			3	50.0
	YES	2	100.0	2	33.3
Epward sleep scale reported	11			2	33.3
	15			1	16.7
	18	1	50.0		
	21			1	16.7
	23	1	50.0		
	Unknown			2	33.3
Paediatric sleep scale reported	Empty	1	50.0	6	100.0
	Unknown	1	50.0		
Behaviourally insufficient sleep reported	No	1	50.0		
	Unknown	1	50.0	6	100.0
Circadian rhythm disorder reported	No	1	50.0		
	Unknown	1	50.0	6	100.0
CSF Hypocretin levels reported	No	1	50.0		
	Unknown	1	50.0	6	100.0
CSF Leukocytes results reported	No	1	50.0		
	Unknown	1	50.0	6	100.0
CSF Protein results reported	No	1	50.0		
	Unknown	1	50.0	6	100.0
Sleep latency reported	No	1	50.0	1	16.7
	Unknown			1	16.7
	Yes	1	50.0	4	66.7
Sleep latency REM reported	No	1	50.0	2	33.3
	Yes	1	50.0	4	66.7
HLA type reported	No	1	50.0		
	Unknown			5	83.3
	Yes	1	50.0	1	16.7

Table 6.6.5. Case and control characteristics: morbidity UK

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
ILI in last year	No	2	100.0	50	100.0	6	100.0	116	95.9
	Yes							5	4.1
URI in last year	No	1	50.0	34	91.9	3	60.0	59	71.1
	Yes	1	50.0	3	8.1	2	40.0	24	28.9
ILI or URI in last year	No	1	50.0	47	94.0	4	66.7	92	76.0
	Yes	1	50.0	3	6.0	2	33.3	29	24.0
Epilepsy	No	2	100.0	50	100.0	6	100.0	118	97.5
	Yes							3	2.5
Depression	No	2	100.0	49	98.0	5	83.3	92	76.0
	Yes			1	2.0	1	16.7	29	24.0
Pregnancy	No	2	100.0	50	100.0	6	100.0	88	72.7
	Unknown							1	.8
	Unknown date							4	3.3
	Yes							28	23.1
Diabetes	No	2	100.0	50	100.0	6	100.0	117	96.7
	Yes							4	3.3
Asthma	No	1	50.0	40	80.0	6	100.0	111	91.7
	Yes	1	50.0	10	20.0			10	8.3
Migraine	No	2	100.0	48	96.0	5	83.3	116	95.9
	Yes			2	4.0	1	16.7	5	4.1
Immuno-compromised	No	2	100.0	50	100.0	6	100.0	121	100.0
Autoimmune disease	No	2	100.0	49	98.0	5	83.3	106	87.6
	Yes			1	2.0	1	16.7	15	12.4
Epstein Barr Virus	No	2	100.0	50	100.0	6	100.0	120	99.2
	Yes							1	.8
Bacteremia/Sepsis	No	2	100.0	50	100.0	6	100.0	121	100.0
Streptococcal infection	No	2	100.0	49	98.0	6	100.0	121	100.0
	Yes			1	2.0				
Antibiotics	No	1	50.0	30	60.0	2	33.3	61	50.4
	Unknown			10	20.0	2	33.3	27	22.3
	Yes	1	50.0	10	20.0	2	33.3	33	27.3

Table 6.6.6 Case and control characteristics: vaccinations

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Influenza A(H1N1)pdm09 vaccine	Not vaccinated	2	100.0	50	100.0	6	100.0	121	100.0
Time since last influenza A(H1N1)pdm09	Not vaccinated	2	100.0	50	100.0	6	100.0	121	100.0
Brand	Not vaccinated	2	100.0	50	100.0	6	100.0	121	100.0
Dose	Not vaccinated	2	100.0	50	100.0	6	100.0	121	100.0
Seasonal vaccination 2009/2010	No	2	100.0	50	100.0	6	100.0	119	98.3
	Yes							2	1.7
HPV vaccination	Not vaccinated	2	100.0	50	100.0	6	100.0	121	100.0

6.6.6 Association: UK

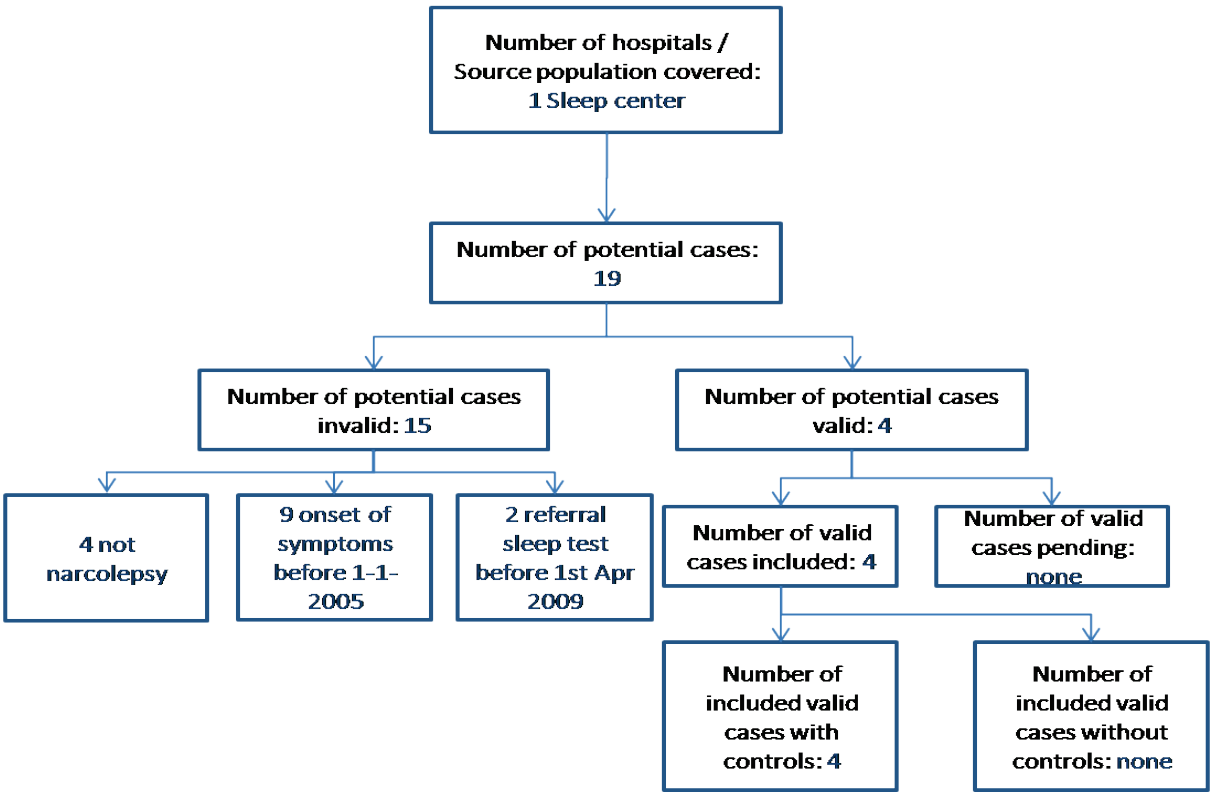
There was no exposure in the UK and the association could not be estimated.

6.7 Italy

6.7.1 Case attrition flow chart: Italy

In Italy, cases were identified from the files of the University Hospital Bologna. Of the 19 potential cases, 15 cases were excluded, mostly because symptom onset was prior to 1 January 2005. Charts were reviewed by the narcolepsy experts in the hospital and the CRF was completed in hospital. All patients provided consent.

Figure 6.7. Case attrition diagram for Italy – Emilia Romagna



6.7.2 Distribution of index dates Italy

Figure 6.7.1. Distribution of index dates, vaccination date and cataplexy date for cases in Italy

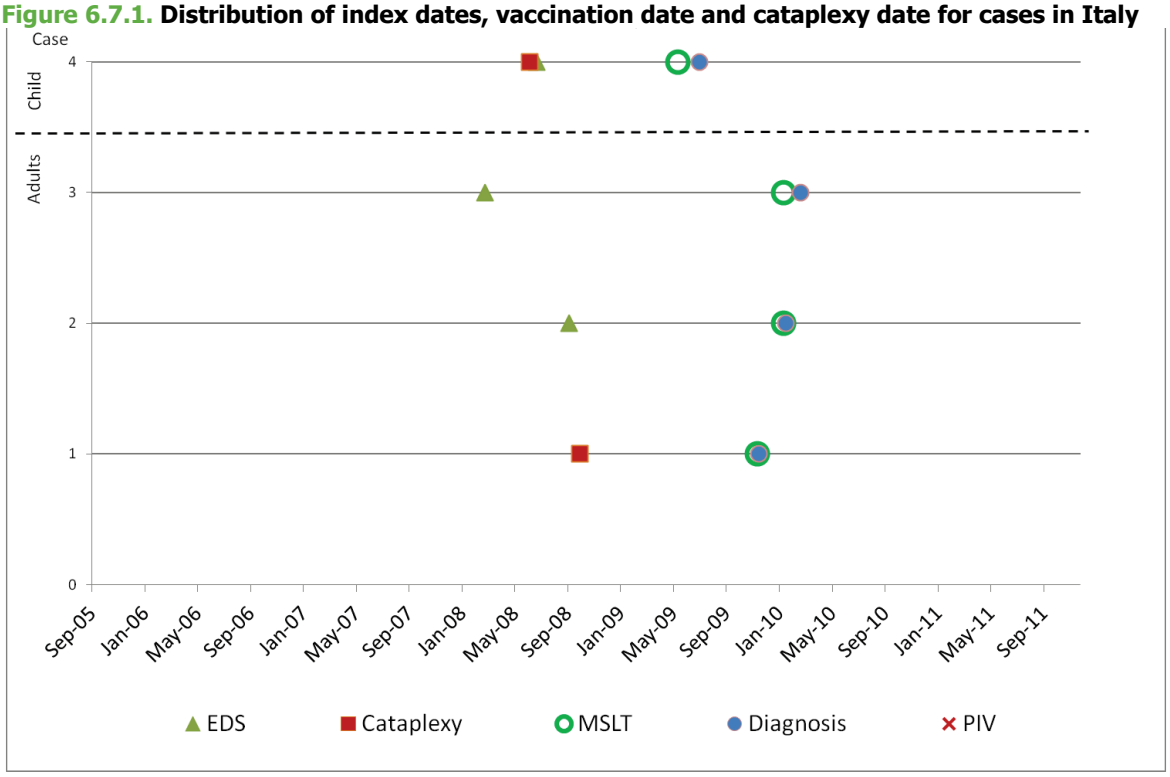


Figure 6.7.1 shows the distribution of the dates of vaccination, date of referral for MSLT, date of diagnosis, date of onset of EDS and the date of cataplexy, ordered for adults and children/adolescents being vaccinated with the influenza A(H1N1)pdm09 vaccine.

6.7.3 Cases and controls for primary and sensitivity analyses: Italy

Table 6.7. Cases and controls in the primary and sensitivity analyses for Italy

Period	Analysis	Cases	Controls
Sensitivity index date primary period	EDS April 09–June 2010	0	0
Sensitivity index date secondary period	EDS April 09–latest	0	0
Primary index date primary period	MSLT referral April 09–June 2010	4	16
Primary index date secondary period	MSLT referral April 09–latest	4	16
Sensitivity index date primary period	Diagnosis April 09–June 2010	4	16
Sensitivity index date secondary period	Diagnosis April 09–latest	4	16

MSLT: Sleeping test referral, EDS: onset excessive daytime sleepiness.

6.7.4 Lag times and recruitment Italy

To assess whether the delays between MSLT referral and diagnosis have changed upon 'knowledge' about a potential signal the delay times were calculated prior to July 2010 and after 30 June 2010.

The tables show the lag times between date of diagnosis and MSLT referral for cases with MSLT referral between April 2009 and June 2010. The lag time does not differ between adults and children/adolescents.

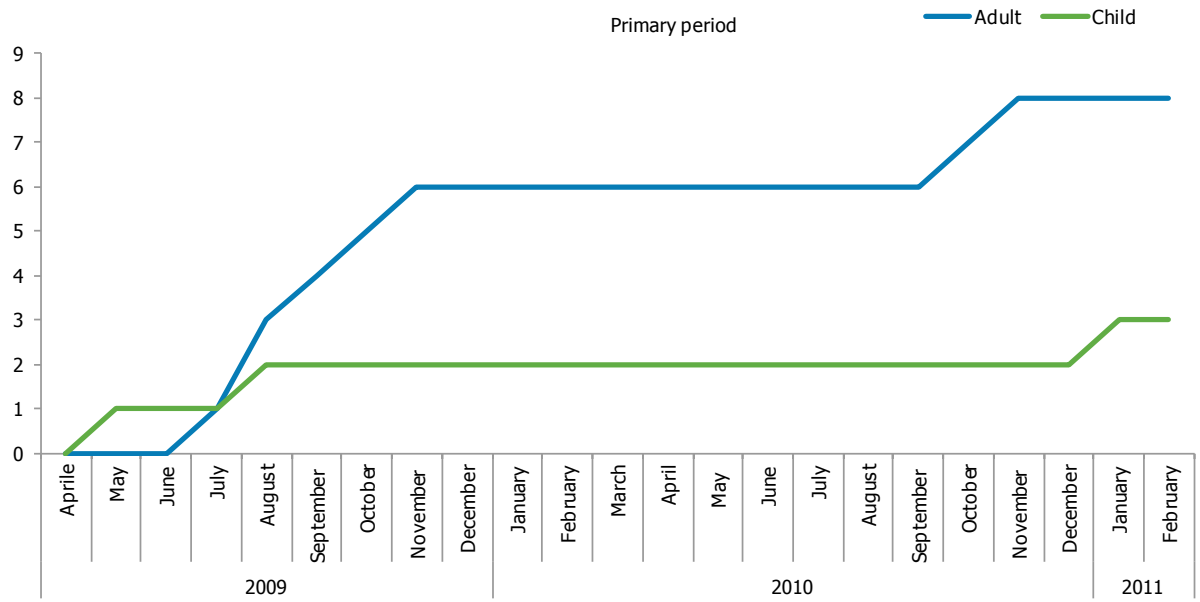
Table 6.7.1. Lag time between MSLT referral and diagnosis for cases with MSLT referral between April 2009 and June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	3	15.3	19.6	4	4	38
Children/Adolescents	1	50	.	50	50	50
Total	4	24	23.6	21	4	50

The lag time was very short in Italy.

There were no cases with MSLT after 30 June 2010 in Italy.

Figure 6.7.2. Cumulative graph of case recruitment by date of referral for MSLT



In Italy, case recruitment was very low, it continued until November 2010 as per protocol, but very few cases were observed.

6.7.5 Descriptives (primary analysis) Italy

Table 6.7.2. Case characteristics in Italy

		Child or adolescent		Adult	
		N	*%*	*N*	*%*
Age	6–12 yrs	1	100.0		
	19–59 yrs			3	100.0
Sex	M	1	100.0	3	100.0
Brighton classification of diagnostic certainty (1–4)	1.00	1	100.0	1	33.3
	3.00			2	66.7
Cataplexy reported	No			2	66.7
	Yes	1	100.0	1	33.3
Epworth sleep scale reported	13			2	66.7
	7			1	33.3
	Empty	1	100.0		
Paediatric sleep scale reported	14	1	100.0		
	Empty			3	100.0
Behaviourally insufficient sleep reported	No	1	100.0	3	100.0
Circadian rhythm disorder reported	No	1	100.0	3	100.0
CSF Hypocretin levels reported	Yes	1	100.0	3	100.0
CSF Leukocytes results reported	Unknown			1	33.3
	Yes	1	100.0	2	66.7
CSF Protein results reported	Yes	1	100.0	3	100.0
Sleep latency reported	Yes	1	100.0	3	100.0
Sleep latency REM reported	Yes	1	100.0	3	100.0
HLA type reported	Unknown			2	66.7
	Yes	1	100.0	1	33.3

Table 6.7.3. Case and control characteristics: morbidity Italy

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
ILI in last year	No			2	50.0			1	16.7
	Yes			2	50.0	1	100.0	5	83.3
URI in last year	No	1	100.0	3	100.0	2	100.0	8	100.0
ILI or URI in last year	No					1	33.3	2	16.7
	Yes	1	100.0	4	100.0	2	66.7	10	83.3
Epilepsy	No	1	100.0	4	100.0	3	100.0	12	100.0
Depression	No	1	100.0	4	100.0	3	100.0	11	91.7
	Yes							1	8.3
Pregnancy	Empty							1	8.3
	No	1	100.0	4	100.0	3	100.0	11	91.7
Diabetes	No	1	100.0	4	100.0	3	100.0	12	100.0
Asthma	No	1	100.0	4	100.0	3	100.0	8	66.7
	Yes							4	33.3
Migraine	No	1	100.0			3	100.0	6	50.0
	Yes			4	100.0			6	50.0
Immuno-compromised	No	1	100.0	4	100.0	3	100.0	12	100.0
Autoimmune disease	No	1	100.0	4	100.0	3	100.0	11	91.7
	Yes							1	8.3
Epstein Barr Virus	No	1	100.0	4	100.0	3	100.0	11	91.7
	Yes							1	8.3
Bacteremia/Sepsis	No	1	100.0	4	100.0	3	100.0	12	100.0
Streptococcal infection	No	1	100.0	4	100.0	3	100.0	12	100.0
Antibiotics	No			1	25.0	3	100.0	7	58.3
	Yes	1	100.0	3	75.0			5	41.7

Table 6.7.4 Case and control characteristics: vaccinations

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
Influenza A(H1N1)pdm09 vaccine	Not vaccinated	1	100.0	4	100.0	3	100.0	12	100.0
Time since last influenza A(H1N1)pdm09	Not vaccinated	1	100.0	4	100.0	3	100.0	12	100.0
Brand	Not vaccinated	1	100.0	4	100.0	3	100.0	12	100.0
Dose	Not vaccinated	1	100.0	4	100.0	3	100.0	12	100.0
Seasonal vaccination 2009/2010	No	1	100.0	3	75.0	3	100.0	12	100.0
	Yes			1	25.0				
HPV vaccination	Not vaccinated	1	100.0	4	100.0	3	100.0	12	100.0

6.7.6 Associations (crude) primary analysis Italy

There was no exposure in Italy and the association could not be estimated.

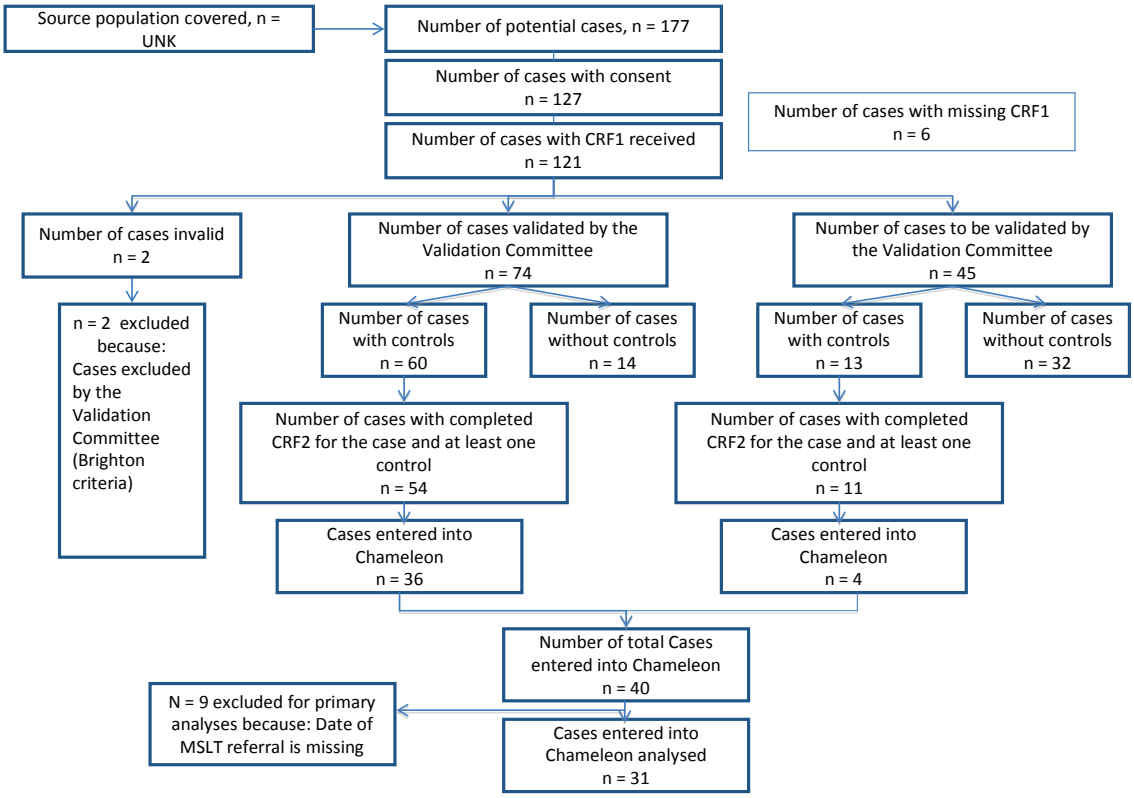
6.8 France

French investigators have experienced a delay in reporting and were only able to submit their final data gathered under this agreement to the VAESCO Consortium analysis team after the dataset had been established for the analyses in this manuscript. Those French data are also the subject of a separate report. Further analyses will now be conducted by the Consortium analysis team and updated results, including the French data are expected in October 2012. The updated overall VAESCO results including the French data will be published in a scientific article.

6.8.1 Case attrition diagram: France

In France, several sleep centres and specialised academic centres who are able to diagnose narcolepsy were identified. The neurologists asked cases for participation per hospital and once consent was obtained they were enrolled in the study. The study was presented as a study regarding risk factors for narcolepsy. In France nine cases were excluded from the primary analysis because of data lacking on the referral for MSLT. Since the study started late (many approvals required) many cases were pending. Many of the pending adult cases were not vaccinated, whereas the pending paediatric/adolescent cases were vaccinated more, however these occurred after 30 June 2010. This lack of completeness of cases may constitute a selection bias, which would result potentially in a higher risk for the adults in the primary analysis. The existence of a potential bias was verified with the investigators who presented the following explanations:

Figure 6.8: Case attrition diagram for France (April 2009–April 2011)



Reasons for selection bias as reported by the French investigators

Exploration of potential selection bias: comparison of included and not yet included/not matched subjects among patients eligible for the MSLT analysis

Description of patients included in Chameleon, according to study period, age category, and vaccination status:

Primary study period (MSLT referral April 2009–30 June 2010)

- Children/adolescents
  - Cases: five vaccinated/eight not vaccinated
  - Controls: five vaccinated/15 not vaccinated

- Adults
  - Cases: four vaccinated/eight not vaccinated
  - Controls: two vaccinated (one matched to a vaccinated case, one matched to a not vaccinated case)/26 not vaccinated

Period MSLT referral date after June 2010

- Children/adolescents:
  - Cases: four vaccinated/one not vaccinated
  - Controls: three vaccinated/nine not vaccinated
- Adults:
  - Cases: one vaccinated/none not vaccinated
  - Controls: one vaccinated/none not vaccinated

Description of patients not included in Chameleon yet, according to study period, age category, and vaccination status

Primary study period (MSLT referral April 2009-30 June 2010)

- Children/adolescents:
  - Cases: none vaccinated/one not vaccinated
  - Controls: none vaccinated/one not vaccinated
- Adults:
  - Cases: none vaccinated/two not vaccinated
  - Controls: none vaccinated/two not vaccinated/one who don't know

Period MSLT referral date after June 2010

- Children/adolescents:
  - Cases: eight vaccinated (one with unknown date of vaccination)/one not vaccinated
  - Controls: one vaccinated/ten not vaccinated
- Adults:
  - Cases: five vaccinated/ten not vaccinated
  - Controls: five vaccinated (one with unknown date of vaccination)/35 not vaccinated

1. Description of cases without controls, according to study period, age category, and vaccination status

Primary study period (MSLT referral April 2009–30 June 2010)

- Children/adolescents: six vaccinated/ten not vaccinated (15 with no controls, one (vaccinated) with information on control pending)
- Adults: none vaccinated five not vaccinated (four with no controls, one with information on control pending)

Period MSLT referral date after June 2010

- Children/adolescents: seven vaccinated/five not vaccinated (+one pending)
- Adults: two vaccinated/six not vaccinated

Table 6.8. Odds of vaccination in patients, according to study period, age category, and status (included in Chameleon, not included yet, not matched)

	Included (n exposed/n non-exposed)	Not included yet (pending) (n exposed/n non-exposed)	Not matched with controls (n exposed/n non-exposed)
Primary study period (MSLT referral April 2009–30 June 2010)			
Children/Adolescents or			
Cases	5/8	0/1	6/10
Controls	5/15	0/1	-
Adults			
Cases	4/8	0/2	0/5
Controls	2/26	0/2*	-
Period MSLT referral date after June 2010			
Children/Adolescents or			
Cases	4/1	8/1	7/5**
Controls	3/9	1/10	-
Adults			
Cases	1/0	5/10	2/6
Controls	1/0	5/35	-

**: 1 patient without knowledge on vaccination; **: 1 patient with pending information*

Preliminary conclusion

- potential unconservative bias in matching for adults in primary study period
- potential unconservative bias in matching for children/adolescents after primary study period
- no specific reason has been found for this potential selection (see above presented exploration of potential selection).

Potential explanations:

None found for adults

- unmatched cases were included all over the study period with no reason to believe that a later date of inclusion could have decreased the probability of matching
- they were included in different centres with no apparent selection bias:
  - two in centre A*: this centre included in total two adult cases with matched controls, all cases are not vaccinated,
  - one in centre B: no other case included in the study for this period
  - one in centre C: this centre included in total two adult cases with matched controls, all cases are not vaccinated,
  - one in centre D: no other case included in the study for this period.

** the centre name have been made anonymous in order not to ease potential identification of study participants*

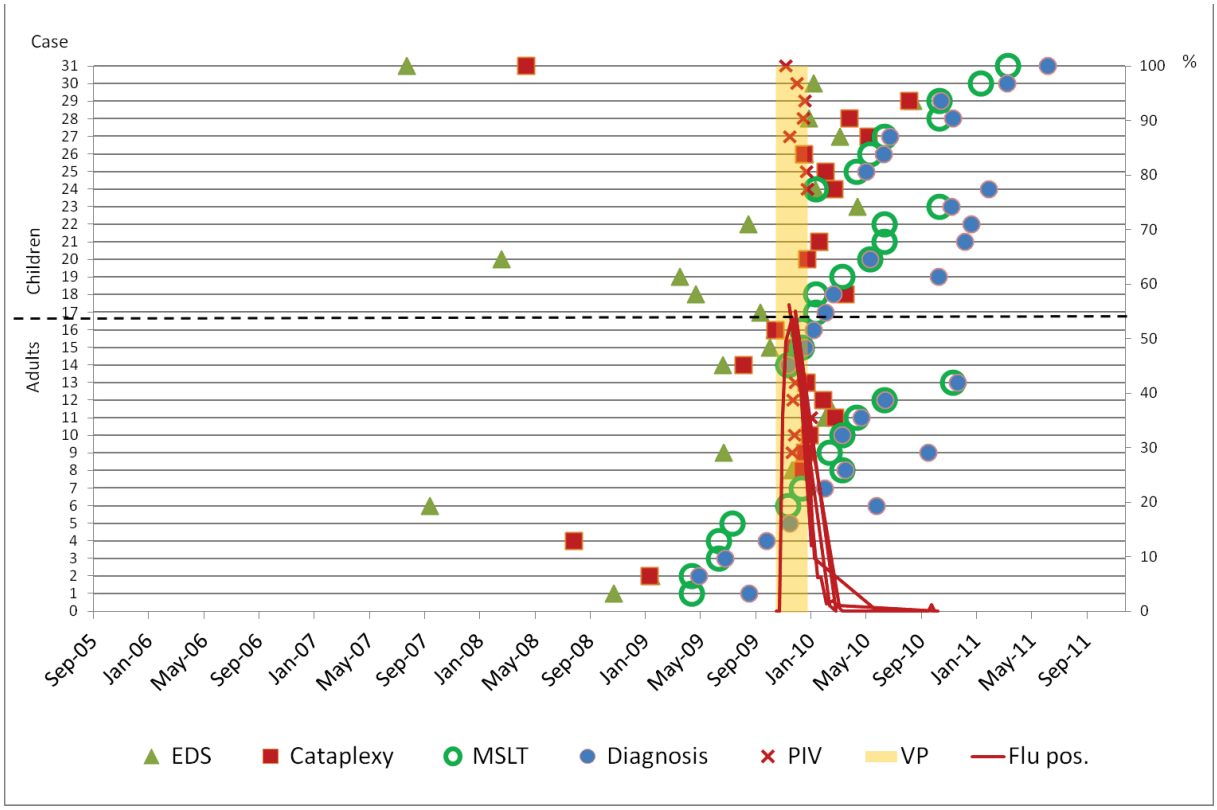
None found for children/adolescents

- unmatched cases were included all over the study period with no reason to believe that a later date of inclusion could have decreased the probability of matching
- they were included in different centres, with no apparent selection bias:
  - one in centre E (vaccinated): no other case included in the study for this period actually (but: six more that can be included: five vaccinated and one not vaccinated)
  - two in centre F (one vaccinated, one not vaccinated): no other case included in the study for this period
  - three in centre A (two vaccinated, one not vaccinated): one other included case (vaccinated) for this study period
  - one in centre D (not vaccinated): no other case included in the study for this period
  - one in centre G (vaccinated): one other case included in the study, also vaccinated
  - two in centre H (vaccinated): no other case included in the study for this period
  - one in centre I (not vaccinated): no other case included in the study for this period
  - one in centre B (not vaccinated): no other case included in the study for this period

6.8.2 Distribution of index dates: France

Figure 6.8.1 shows the distribution of the dates of vaccination, date of referral for MSLT, date of diagnosis, date of onset of EDS and the date of cataplexy, ordered for adults and children/adolescents being vaccinated with the influenza A(H1N1)pdm09 vaccine.

Figure 6.8.1 Distribution of index dates, vaccination date and cataplexy date for cases in France.



The graph shows that all the dates for MSLT referral spread evenly over the study period, both for adults and children/adolescents, although children/adolescents tended to have MSLT referral dates after October 2009. Cases are continuing to be included but last date of diagnosis for included cases in this analysis is June 2011.

6.8.3 Cases and controls for primary and sensitivity analyses: France

Table 6.8.1. Cases and controls in the primary and sensitivity analyses for France

Period	Analysis	Cases	Controls
Sensitivity index date primary period	EDS April 09–June 2010	26	54
Sensitivity index date secondary period	EDS April 09–latest	28	58
Primary index date primary period	MSLT referral April 09–June 2010	25	47
Primary index date secondary period	MSLT referral April 09–latest	31	60
Sensitivity index date primary period	Diagnosis April 09–June 2010	24	52
Sensitivity index date secondary period	Diagnosis April 09–latest	40	86

*MSLT: Sleeping test referral, EDS: onset excessive daytime sleepiness. * Currently one control is missing in the analysis set.*

6.8.4 Lag times and recruitment: France

To assess whether the delays between MSLT referral and diagnosis have changed upon 'knowledge' about a potential signal, the delay times were calculated prior to July 2010 and after 30 June 2010.

The tables show the lag times between date of diagnosis and MSLT referral for cases with MSLT referral between April 2009 and June 2010. The lag time did not differ between adults and children/adolescents.

Table 6.8.2. Lag time between MSLT referral and diagnosis for cases with MSLT referral between April 2009 and June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	12	72.6	78.9	33	.00	218
Children/Adolescents	13	86.6	118.2	27	.00	383
Total	25	79.9	99.5	27	.00	383

The 90th percentile was 315 days for children and 211 for adults.

Table 6.8.3. Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adult	1	10	.	10	10	10
Child/adolescent	5	41.2	32.6	30	3	88
Total	6	36	31.8	28.5	3	88

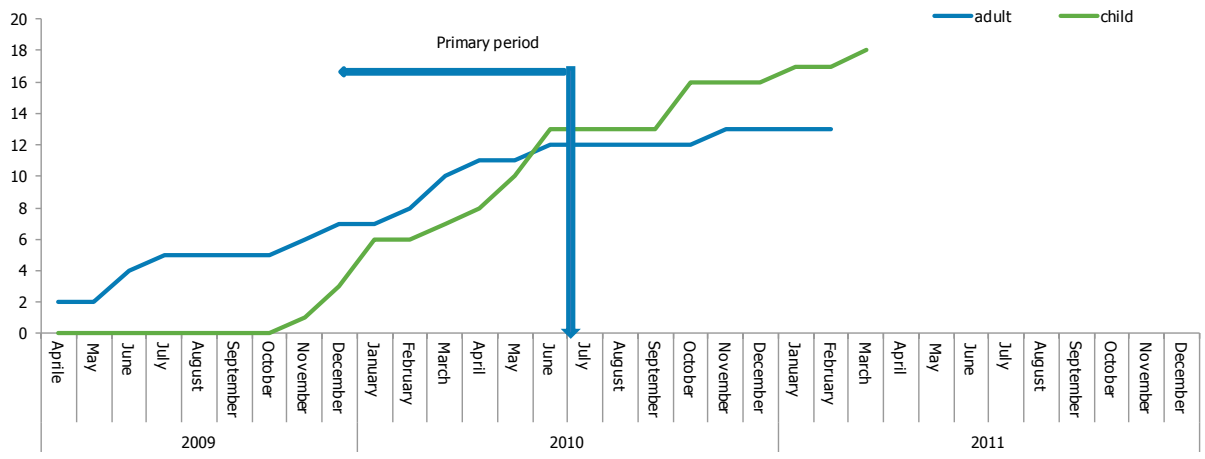
Table 6.8.4. Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010 by influenza A(H1N1)pdm09 vaccination in France

	Exposed [a)]	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	Yes	1	10	.	10	10	10
	Total	1	10	.	10	10	10
Children/Adolescents	No	1	27	.	27	27	27
	Yes	4	44.7	36.5	44	3	88
	Total	5	41.2	32.6	30	3	88
Total	No	1	27	.	27	27	27
	Yes	5	37.8	35.3	30	3	88
	Total	6	36	31.8	28.5	3	88

[a)] *Influenza A(H1N1)pdm09 vaccine*

There was no statistical association between exposure to influenza A(H1N1)pdm09 vaccine and the lag time in children/adolescents or adults or overall, but this is based on very few cases.

Figure 6.8.2 Cumulative graph of recruited cases based on date of MSLT referral



Based on the explanations made above we know there is potential for selection bias in France.

6.8.5 Descriptives (primary analysis) France

Table 6.8.5. Case characteristics

		Child or adolescent		Adult	
		N	*%*	*N*	*%*
Age	0–5 yrs	1	7.7		
	6–12 yrs	3	23.1		
	13–18 yrs	9	69.2		
	19–59 yrs			12	100.0
Sex	F	5	38.5	6	50.0
	M	8	61.5	6	50.0
Brighton classification of diagnostic certainty (1–4)	1	7	53.8	4	33.3
	2	5	38.5	1	8.3
	3	1	7.7	5	41.7
	Empty			2	16.7
Cataplexy reported	No	2	15.4	5	41.7
	Yes	11	84.6	7	58.3
Epworth sleep scale reported	12	1	10.0		
	13	1	10.0	1	8.3
	14	1	10.0	1	8.3
	15			2	16.7
	16	1	10.0	1	8.3
	17	1	10.0	2	16.7
	18	3	30.0	1	8.3
	19	1	10.0	2	16.7
	20			1	8.3
	21			1	8.3
	22	1	10.0		
	Empty	3			
Paediatric sleep scale reported	12	1	7.7		
	13	1	7.7		
	15	1	7.7		
	17	1	7.7		
	18	2	15.4		
	19	1	7.7		
	Empty	5	38.5	12	100.0
	Unknown	1	7.7		
Behaviourally insufficient sleep reported	No	13	100.0	12	100.0
Circadian rhythm disorder reported	No	13	100.0	12	100.0
CSF Hypocretin levels reported	No	5	38.5	6	50.0
	Yes	8	61.5	6	50.0
CSF Leukocytes results reported	Empty	5	38.5	6	50.0
	Unknown	8	61.5	6	50.0
CSF Protein results reported	Empty	5	38.5	6	50.0
	Unknown	8	61.5	6	50.0
Sleep latency reported	Yes	13	100.0	12	100.0
Sleep latency REM reported	Yes	13	100.0	12	100.0
HLA type reported	Empty	1	7.7	1	8.3
	Yes	12	92.3	11	91.7

Table 6.8.6. Case and control characteristics: morbidity in France

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
ILI in last year	No	8	66.7	12	80.0	3	60.0	14	73.7
	Yes	4	33.3	3	20.0	2	40.0	5	26.3
URI in last year	No	1	12.5	4	25.0	1	16.7		
	Yes	7	87.5	12	75.0	5	83.3	21	100.0
ILI or URI in last year	No	3	23.1	7	35.0	6	50.0	5	18.5
	Yes	10	76.9	13	65.0	6	50.0	22	81.5
Epilepsy	No	12	92.3	19	95.0	11	91.7	23	85.2
	Yes	1	7.7	1	5.0	1	8.3	4	14.8
Depression	No	13	100.0	19	95.0	12	100.0	23	85.2
	Yes			1	5.0			4	14.8
Pregnancy	Empty	7	53.8	10	50.0	6	50.0	15	55.6
	No	6	46.2	10	50.0	5	41.7	7	25.9
	Unknown date							1	3.7
	Yes					1	8.3	4	14.8
Diabetes	No	13	100.0	20	100.0	12	100.0	27	100.0
Asthma	No	11	84.6	14	70.0	10	83.3	23	85.2
	Unknown					1	8.3		
	Unknown date							1	3.7
	Yes	2	15.4	6	30.0	1	8.3	3	11.1
Migraine	No	11	84.6	18	90.0	9	75.0	18	66.7
	Unknown date					1	8.3	3	11.1
	Yes	2	15.4	2	10.0	2	16.7	6	22.2
Immuno compromised	No	13	100.0	20	100.0	12	100.0	27	100.0
Autoimmune disease	No	9	69.2	11	55.0	6	50.0	17	63.0
	Yes	4	30.8	9	45.0	6	50.0	10	37.0
Epstein Barr Virus	No	10	76.9	20	100.0	12	100.0	26	96.3
	Unknown							1	3.7
	Unknown date	1	7.7						
	Yes	2	15.4						
Bacteremia/Sepsis	No	13	100.0	20	100.0	12	100.0	27	100.0
Streptococcal infection	No	11	84.6	18	90.0	12	100.0	25	92.6
	Unknown	2	15.4	1	5.0			2	7.4
	Yes			1	5.0				
Antibiotics	No	13	100.0	17	85.0	8	66.7	20	74.1
	Unknown date			1	5.0	2	16.7	2	7.4
	Yes			2	10.0	2	16.7	5	18.5

**Note: one control missing in French case control study*

Table 6.8.7 Case and control characteristics: vaccinations

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
Influenza A(H1N1)pdm09 vaccine	No	9	69.2	15	75.0	8	66.7	26	96.3
	Yes	4	30.8	5	25.0	4	33.3	1	3.7
Time since last influenza A(H1N1)pdm09 vaccination	Not vaccinated	9	69.2	15	75.0	8	66.7	26	96.3
	8-42 days	1	7.7	2	10.0				
	43-180 days	2	15.4			3	25.0	1	3.7
	>180 days	1	7.7	3	15.0	1	8.3		
Brand	Not vaccinated	9	69.2	15	75.0	8	66.7	26	96.3
	Pandemrix	2	15.4	3	15.0	4	33.3	1	3.7
	Panenza	2	15.4						
	Unknown			2	10.0				
Dose	Not vaccinated	9	69.2	15	75.0	8	66.7	26	96.3
	1 or more doses	4	30.8	5	25.0	4	33.3	1	3.7
Seasonal vaccination 2009/2010	No	13	100.0	18	90.0	12	100.0	24	88.9
	Yes			2	10.0			3	11.1
HPV vaccination	No	12	92.3	18	90.0	12	100.0	27	100.0
	Yes	1	7.7	2	10.0				

6.8.6 Associations (crude) primary analysis: France

Table 6.8.8. Sensitivity analyses: associations between influenza A(H1N1)pdm09 vaccination and narcolepsy

	Children and adolescents [a]			Adults			All		
	OR	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]
Influenza A(H1N1)pdm09 vaccination	1.3	0.2	10.3	11.2	1.4	Inf [d]	3.8	0.8	24.1

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact);

6.8.7 Sensitivity analyses France

Table 6.8.9. Sensitivity analyses: associations between influenza A(H1N1)pdm09 vaccination and narcolepsy

	Children and adolescents [a]			Adults			All		
	OR	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]	*OR*	*LL* [b]	*UL* [c]
Date of MSLT as index date									
Primary period	1.3	0.2	10.3	11.2	1.4	Infinity	3.8	0.8	24.1
Secondary period	2.4	0.6	11.4	11.2	1.4	Infinity	4.3	1.2	19
Date of EDS as index date									
Primary period	2.9	0.6	18.9	12.7**	1.7	Infinity	6.0	1.5	34.2
Secondary period	7.2	1.9	40.6	16.9	2.4	Infinity	7.2	1.9	40.6
Date of diagnosis as index									
Primary period									
Secondary period	2.3	0.6	11.4	15.7	2.0	709.8			

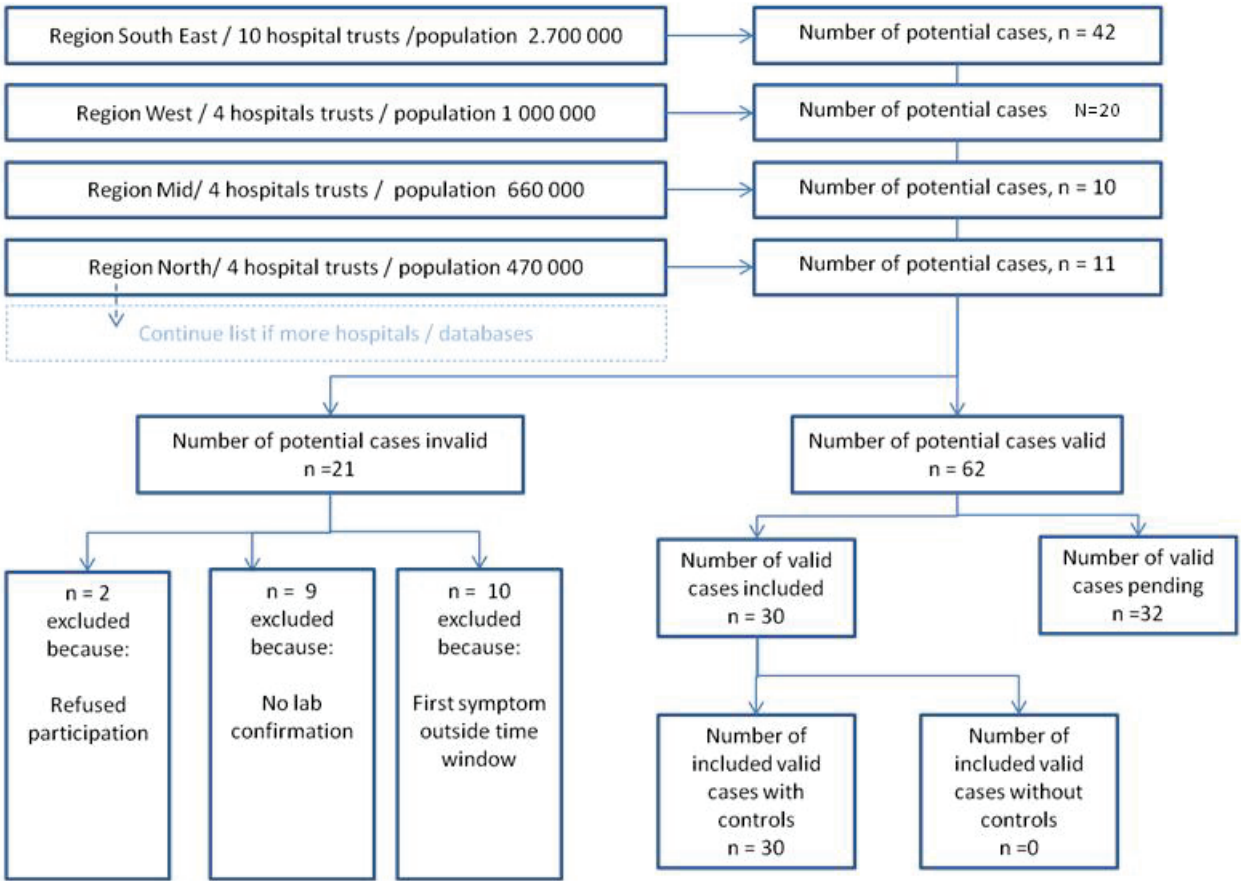
*[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact)** median unbiased estimate*

6.9 Norway

6.9.1 Case attrition diagram Norway

In Norway, specific sleep centres and specialised academic centres which are able to diagnose narcolepsy were identified. The neurologists asked cases for participation per hospital, and once consent was obtained they were enrolled in the study. Pending/refusing adult cases had a slightly lower prevalence of exposure, whereas the pending paediatric cases were vaccinated similarly as the included cases. This means that based on the currently available data there may be a potential overestimation in adults.

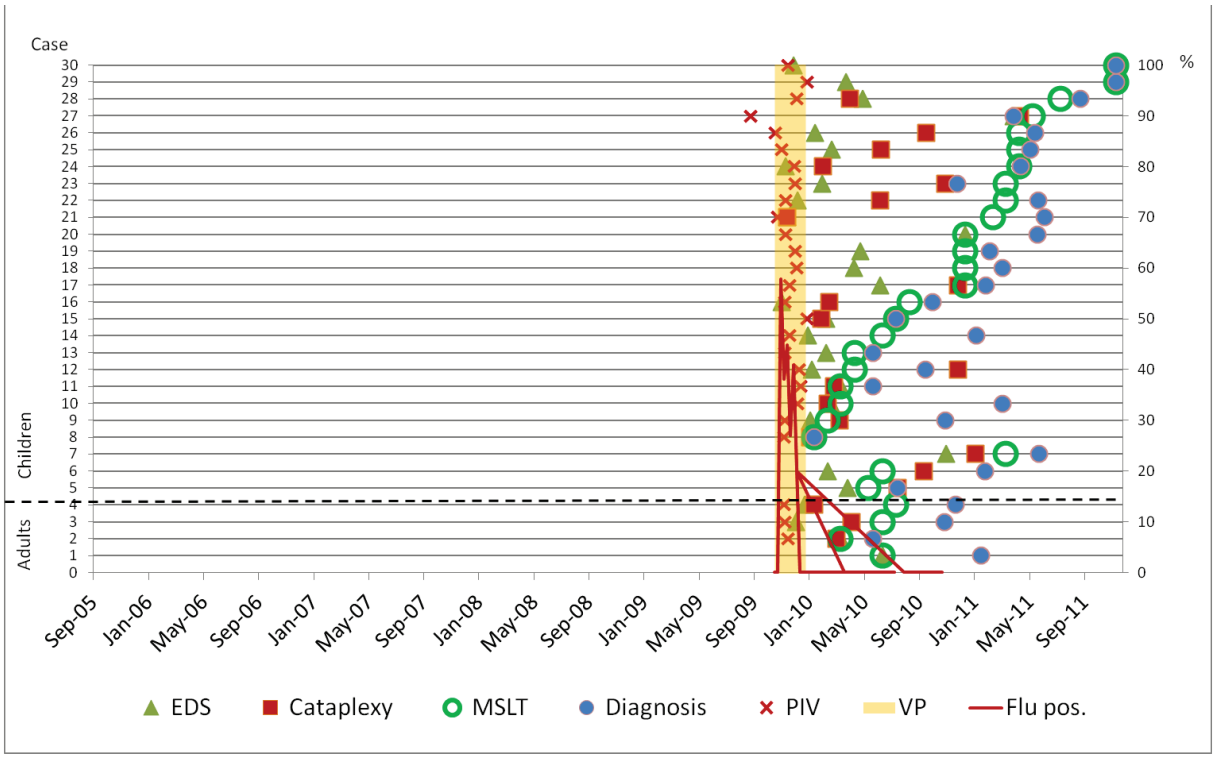
Figure 6.9.1.: Case attrition diagram for Norway



6.9.2 Distribution of index dates Norway

Figure 6.9.2 shows the distribution of the dates of vaccination, date of referral for MSLT, date of diagnosis, date of onset of EDS and the date of cataplexy, ordered for adults and children/adolescents being vaccinated with the influenza A(H1N1)pdm09 vaccine.

Figure 6.9.2 Distribution of index dates, vaccination date and cataplexy date for cases in Norway



The graph shows that all the dates for MSLT referral occur after the start of the vaccination campaign. Cases were included until September 2011.

6.9.3 Cases and controls for primary and sensitivity analyses: Norway

Table 6.9. Cases and controls in the primary and sensitivity analyses for Norway

Period	Analysis	Cases	Controls
Sensitivity index date primary period	EDS April 09–June 2010	24	88
Sensitivity index date secondary period	EDS April 09–latest	26	96
Primary index date primary period	MSLT referral April 09–June 2010	12	44
Primary index date secondary period	MSLT referral April 09–latest	30	110
Sensitivity index date primary period	Diagnosis April 09–June 2010	4	13
Sensitivity index date secondary period	Diagnosis April 09–latest	30	110

MSLT: Sleeping test referral, EDS: onset excessive daytime sleepiness.

6.9.4 Lag times and recruitment: Norway

To assess whether the delays between MSLT referral and diagnosis have changed upon 'knowledge' about a potential signal, the delay times were calculated prior to July 2010 and after 30 June 2010.

The tables show the lag times between date of diagnosis and MSLT referral for cases with MSLT referral between April 2009 and June 2010. The lag time did not differ between adults and children/adolescents.

Table 6.9.1. Lag time between MSLT referral and diagnosis for cases with MSLT referral between April 2009 and June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	3	142.6	74.1	138	71	219
Children/Adolescents	9	154.4	118.3	157	1	358
Total	12	151.5	105.9	147.5	1	358

The 90th percentile was 315 days for children/adolescents and 211 for adults

Table 6.9.2. Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	1	133	.	133	133	133
Children/Adolescents	17	36.2	60.9	44	-107	161
Total	18	41.6	63.4	45	-107	161

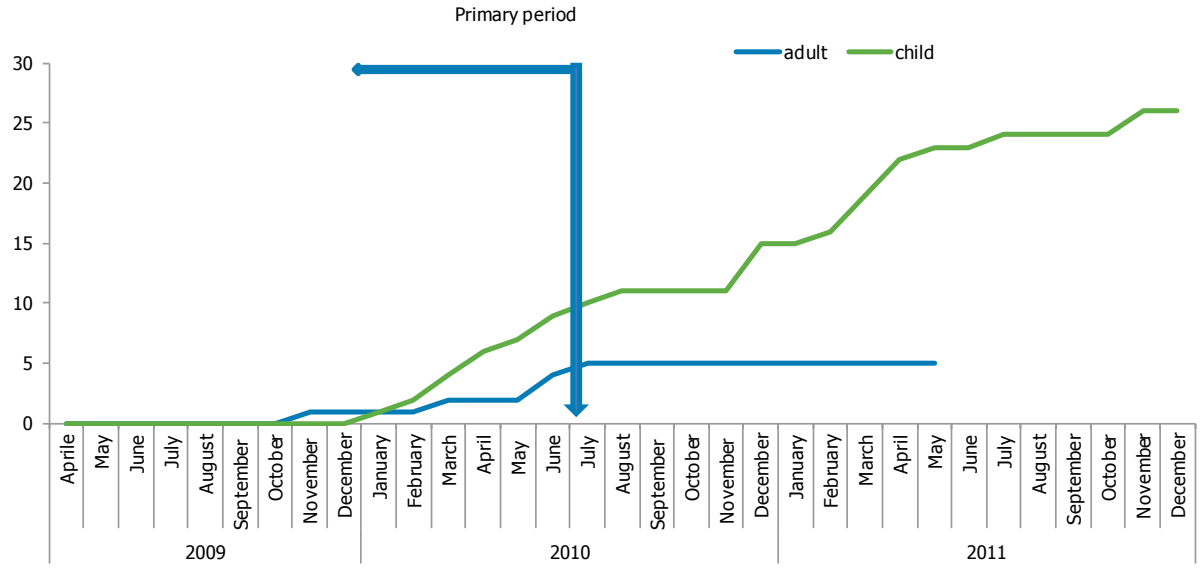
Table 6.9.3. Lag time between MSLT referral and diagnosis for cases with MSLT referral after June 2010 by influenza A(H1N1)pdm09 vaccination in Norway

	Exposed [a)]	N	Mean	Std. Deviation	Median	Minimum	Maximum
Adults	Yes	1	133	.	133	133	133
	Total	1	133	.	133	133	133
Children/Adolescents	No	1	75	.	75	75	75
	Yes	16	33.8	62.0	39.5	-107	161
	Total	17	36.2	60.9	44	-107	161
Total	No	1	75	.	75	75	75
	Yes	17	39.6	64.7	44	-107	161
	Total	18	41.6	63.3	45	-107	161

[a)] *Influenza A(H1N1)pdm09 vaccine*

There was no statistical association between exposure to influenza A(H1N1)pdm09 vaccine and the lag time in children/adolescents or adults or overall, but this is based on very few cases.

Figure 6.9.3. Cumulative graph of recruited cases based on date of MSLT referral



Based on the explanations made above we know there is potential for some selection bias in Norway, especially in the adult group.

6.9.5 Descriptives (primary analysis): Norway

Table 6.9.4. Case characteristics Norway

		Child or adolescent		Adults	
		N	%	N	%
Age	0–5 yrs	1	3.8		
	6–12 yrs	17	65.4		
	13–18 yrs	8	30.8		
	19–59 yrs			4	100.0
Sex	F	14	53.8	3	75.0
	M	12	46.2	1	25.0
Brighton classification (1–4	1	17	65.4	3	75.0
	2	4	15.4		
	3	2	7.7		
	4A	1	3.8	1	25.0
	Unknown	2	7.7		
Cataplexy reported	Empty			1	25.0
	No	3	11.5		
	Unknown	2	7.7		
	Yes	21	80.8	3	75.0
Epworth sleep scale reported	10	1	3.8		
	11	1	3.8		
	15	1	3.8		
	18	1	3.8		
	19	1	3.8		
	20	1	3.8	1	25.0
	22	1	3.8		
	23			1	25.0
	7	1	3.8		
	Empty	8	30.8	1	25.0
	Unknown	10	38.5	1	25.0
Paediatric sleep scale reported	Empty	22	84.6	4	100.0
	Unknown	4	15.4		
Behaviourally insufficient sleep reported	No	21	80.8	2	50.0
	Unknown	4	15.4	2	50.0
	Yes	1	3.8		
Circadian rhythm disorder reported	No	24	92.3	2	50.0
	Unknown	2	7.7	2	50.0
CSF Hypocretin levels reported	No	6	23.1		
	Unknown	1	3.8		
	Yes	19	73.1	4	100.0
CSF Leukocyte results reported	Empty	4	15.4	1	25.0
	No	4	15.4		
	Unknown	13	50.0	1	25.0
	Yes	5	19.2	2	50.0
CSF Protein results reported	Empty	3	11.5	1	25.0
	No	5	19.2		
	Unknown	13	50.0	1	25.0
	Yes	5	19.2	2	50.0
Sleep latency reported	No	3	11.5		
	Unknown	1	3.8	1	25.0
	Yes	22	84.6	3	75.0
HLA type reported	No	2	7.7	1	25.0
	Unknown	3	11.5	1	25.0
	Yes	21	80.8	2	50.0

Table 6.9.5. Case and control characteristics: morbidity in Norway

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
ILI in last year	No	7	87.5	24	85.7	1	100.0	9	90.0
	Yes	1	12.5	4	14.3			1	10.0
URI in last year	No	7	100.0	26	100.0	3	100.0	10	100.0
ILI or URI in last year	No	8	88.9	28	87.5	3	100.0	11	91.7
	Yes	1	11.1	4	12.5			1	8.3
Epilepsy	No	9	100.0	32	100.0	2	66.7	12	100.0
	Unknown					1	33.3		
Depression	No	9	100.0	31	96.9	2	66.7	12	100.0
	Unknown					1	33.3		
	Yes			1	3.1				
Pregnancy	No	9	100.0	31	96.9	1	33.3	7	58.3
	Unknown					1	33.3		
	Unknown date			1	3.1				
	Yes					1	33.3	5	41.7
Diabetes	No	9	100.0	31	96.9	2	66.7	11	91.7
	Unknown					1	33.3		
	Yes			1	3.1			1	8.3
Asthma	No	9	100.0	30	93.8	2	66.7	12	100.0
	Unknown					1	33.3		
	Yes			2	6.3				
Migraine	No	8	88.9	30	93.8	2	66.7	12	100.0
	Unknown					1	33.3		
	Yes	1	11.1	2	6.3				
Immuno-compromised	No	9	100.0	32	100.0	2	66.7	12	100.0
	Unknown					1	33.3		
Autoimmune disease	No	9	100.0	30	93.8	2	66.7	10	83.3
	Unknown					1	33.3		
	Unknown Date							1	8.3
	Yes			2	6.3			1	8.3
Epstein Barr Virus	No	9	100.0	31	96.9	2	66.7	11	91.7
	Unknown					1	33.3		
	Yes			1	3.1			1	8.3
Bacteremia/Sepsis	No	9	100.0	31	96.9	2	66.7	12	100.0
	Unknown			1	3.1	1	33.3		
Streptococcal infection	No	9	100.0	31	96.9	2	66.7	12	100.0
	Unknown			1	3.1	1	33.3		
Antibiotics	Empty	1	11.1						
	No	8	88.9	25	78.1	2	66.7	8	66.7
	Unknown			1	3.1	1	33.3		
	Unknown date			6	18.8			4	33.3

Table 6.9.5. Case and control characteristics: vaccinations in Norway

		Children and adolescents				Adults			
		Cases		Controls		Cases		Controls	
		N	%	N	%	N	%	N	%
Influenza A(H1N1)pdm09 vaccine	No	2	22.2	14	43.8	1	33.3	5	41.7
	Yes	7	77.8	18	56.3	2	66.7	7	58.3
Time since last influenza A(H1N1)pdm09 vaccination	Not vaccinated	2	22.2	14	43.8	1	33.3	5	41.7
	43-180 days	6	66.7	11	34.4	1	33.3	3	25.0
	>180 days	1	11.1	7	21.9	1	33.3	4	33.3
Brand	Not vaccinated	2	22.2	14	43.8	1	33.3	5	41.7
	Pandemrix	7	77.8	17	53.1	2	66.7	6	50.0
	Unknown			1	3.1			1	8.3
Dose	Not vaccinated	2	22.2	14	43.8	1	33.3	5	41.7
	1 dose	7	77.8	18	56.3	2	66.7	6	50.0
	2 doses							1	8.3
Seasonal vaccination 2009/2010	No	9	100.0	32	100.0	3	100.0	12	100.0
HPV vaccination	No	8	88.9	28	87.5	3	100.0	12	100.0
	Yes	1	11.1	4	12.5				

6.9.6 Associations (crude) primary analysis: Norway

Table 6.9.6 Associations between influenza A(H1N1)pdm09 influenza vaccination and narcolepsy

	Children and adolescents [a]			Adults			All		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Influenza A(H1N1)pdm09 vaccination	2.9	0.4	33.3	1.4	0.1	94.9	2.3	0.5	15.1

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact);

6.9.6 Sensitivity analyses Norway

Table 6.9.7. Sensitivity analyses: associations between influenza A(H1N1)pdm09 vaccination and narcolepsy

	Children and adolescents [a]			Adults		
	OR	LL [b]	UL [c]	OR	LL [b]	UL [c]
Date of MSLT as index date						
Primary period	2.9	0.4	33.3	1.4	0.1	94.9
Secondary period	4.1	1.1	23.7	1.4	0.1	94.9
Date of EDS as index date						
Primary period	5.6	1.3	33.7	NA		
Secondary period	3.8	1.0	17.9	NA		
Date of diagnosis as index						
Primary period	3.6	0.3	infinity	1.5	0.04	Infinity
Secondary period	4.1	1.1	23.7	1.4	0.1	17.4

[a] ≤ 18; [b] lower 95% confidence level (exact); [c] upper 95% confidence level (exact)

7 Discussion

This report, in the opinion of the consortium, represents an important milestone in the overall scientific investigation of the possible association of narcolepsy following influenza A(H1N1)pdm09 vaccination.

7.1 Background and incidence rates

Background rate data are useful to obtain quantitative measures of diagnostic rates and to provide rapid insight in changing epidemiologic patterns of disease diagnoses over time, by age, sex, and country [26]. The background rates of narcolepsy diagnosis were calculated in seven European countries as part of an evaluation of a signal that was observed in Sweden and Finland on the basis of narcolepsy case reports in patients immunised with Pandemrix. Data were made available in February 2011 to ECDC and EMA.

7.1.1 Main findings

The pooled incidence of narcolepsy diagnosis was found to be quite stable over time. The pooled incidence rate of diagnosed narcolepsy in seven EU/EEA countries in all age groups is around 1 per 100 000 person-years (0.93 per 100 000 PY 95%CI 0.90–0.97) during the period 2000–2010. The incidence rates for the age group 0–5 years was 0.13 (95%CI 0.07–0.20), the age group 5–19 years was 0.83 (95%CI 0.75–0.91) in the age group 20–59 it was 1.06 (95%CI 1.01–1.11) and in the elderly (60+) it was 0.88 (95%CI 0.81–0.95) per 100 000 person-years. Incidence rates were age-dependent with a peak between 15–30 years of age in women especially, and a smaller peak around 60 years of age. Overall a slightly higher incidence rate in women was found as compared to men. Significant (6–7 fold) increases in the diagnosis of narcolepsy in the 5–19 year age group in Finland and Sweden following the start of influenza A(H1N1)pdm09 vaccination campaigns were observed, underlining the reported signal. A significant, yet much smaller (< 2 fold), increase was also seen in the 5–19 and 20–59 year age groups Denmark, where an increase started already prior to the start of the vaccination campaign and in Finland in the over 60 year age group after September 2009.

7.1.2 Homogeneity of rates

A common protocol, common infrastructure for data sharing, standardised data elaboration and central data analysis were employed to avoid heterogeneity due to differences in study methods beyond the local data collection. Rates did differ between countries. Incidence rates were low in Italian regions, whilst rates for Denmark were at the upper end of the scale. Validated rates in the Netherlands-IPCI database were in the magnitude of the Italian rates. Also, specific age and sex patterns of narcolepsy incidence rates differed between countries. This may be explained by differences between the national healthcare databases, which varied between in- and outpatient claims and primary care medical record databases. Also, it is possible that differences in referral and diagnostic patterns exist between the countries and that these may change over time. Nevertheless, relative to the changes observed in 2010 in some countries, the resulting variability in incidence over time and across countries was within a narrow range. The limited impact may be explained merely by narcolepsy being a rare disease. The incidence rates of narcolepsy were very similar prior to the start of the vaccination campaigns between signalling and non-signalling countries (0.87 vs. 0.83 /100 000 PY)

In 2010, the homogeneity decreased as large increases in the incidence rate of narcolepsy in Finland and Sweden were observed. In Finland, an increase in the incidence rate of narcolepsy diagnoses after September 2009 in children and adolescents between 5–19 years of age was observed, and to a lesser extent in the elderly. In Sweden, an increase in the 5–19 year age group was observed after September 2009 as well. This is in line with the signal reported in these countries for Pandemrix. A similar pattern was not observed in the other countries during the period for which data could be analysed. In Denmark an increase in the incidence rate of narcolepsy was also observed after September 2010, however here only risk groups were targeted for influenza A(H1N1)pdm09 vaccination, and overall vaccine coverage was low. In the Netherlands, no increase in incidence was seen in the influenza A(H1N1)pdm09 vaccine targeted age groups. Also, in Italy and the UK no increase in incidence of narcolepsy was seen. In all of these countries the vaccination coverage was low in the 5–19 year age group. In Norway, where prevalent and incident narcolepsy cases could not be well differentiated, no change in narcolepsy diagnosis/visit rates were seen until the end of 2010 in spite of high coverage with Pandemrix in this country. Emerging data from Norway show that Pandemrix exposed cases started to be reported in 2011. Comparison of pooled rates after the start of the influenza A(H1N1)pdm09 vaccination campaign showed a significant difference in rates between the signalling and non-signalling countries (1.67 vs. 0.95 /100 000 PY).

The data show that the method is able to pick up signals of the extent as seen in Finland and Sweden. It also shows the added benefit of applying common methods and utilising a shared infrastructure for data sharing across European countries.

7.1.3 Accuracy (internal validity)

Because of the use of population-based systems, the denominators are accurately calculated. The accuracy of the numerators depends on the completeness of case identification, the validity of diagnosis and the ability to classify cases based on available information on diagnostic criteria in the medical record.

Within population-based databases, all diagnosed cases are generally captured. However, narcolepsy is known to be an under-diagnosed disease. Thus incompleteness was assumed due to under diagnosis. In the UK and the Netherlands, GP medical record databases were utilised to identify cases. In these countries the GPs receive information on all diagnoses made by specialists, however, this may be delayed. This could explain the reduction in the rates at the end of the study period in the UK. Although Italy used hospitalisation data, these should capture all cases since diagnosis of narcolepsy requires hospitalisation in Italy.

Unfortunately, narcolepsy diagnoses for background rates were only validated in the Netherlands. Here, 50% of initially identified cases had another diagnosis. In a quarter, available data were insufficient to confirm the clinical diagnosis. This exercise demonstrated that an initial observed increase of the rate in 2009 and 2010 disappeared upon validation. The numbers were too low to stratify the positive predictive value (PPV) by age.

Case validation has not yet been performed for the other participating databases. However the PPV of narcolepsy diagnosis was calculated for the cases included in the narcolepsy case control study for Denmark, the UK-GPRD and Finland using the BC narcolepsy case definition. The case control study applied different inclusion and exclusion criteria, and for Denmark different case identification methods were used. In Denmark cases for the case control study were identified from a specialised sleep centre that covers 70% of the country.

Due to these differences, PPVs stemming from the case control study cannot be directly applied to rates found in the background rates study. Nonetheless they are indicative for the value of the different case identification methods. For other countries, regions or databases the PPV remained below 50%. The PPV for the cases identified in UK-GPRD and Finland was 35% and 49% respectively (see section 6.2–6.6). This indicates that validation of the cases included in the background rate study could decrease the rates substantially and possibly also change age, time and gender patterns, as was the case for the Netherlands-IPCI rates.

7.1.4 Other epidemiological findings

Incidence rates were age dependent with a peak between 15–30 years of age in women especially, and a smaller peak around 60 years of age. Overall a slightly higher incidence rate was found in women as compared to men. The incidence data demonstrate an apparent seasonal effect. The lower rates observed in July are unlikely a function of disease, but rather reflective of a lower diagnosis rate of a chronic condition during the major holiday periods in Europe.

7.1.5 External validity

In most of the participating countries (Sweden, Finland, Denmark, Norway) data were obtained on a national level and therefore reflect the incidence of diagnosed narcolepsy in those countries. In the Netherlands and the UK, subsets of the total population were utilised, but these subpopulation are known to represent the age and sex distribution in the general population [27, 28]. In Italy, two regional databases were utilised, both in the centre of Italy and reflecting the populations in those regions, which are not representative of the entire Italian population.

Very few estimates of the incidence of narcolepsy or narcolepsy diagnosis have been published in the literature. A US-based study reported an incidence of narcolepsy with cataplexy of 0.74 (95%CI: 0.47–1.16) per 100 000 PY, and of narcolepsy with or without cataplexy of 1.37 (95%CI: 0.95–1.90) per 100 000 PY over a 30 year period [29]. In this study the incidence rate was higher in men than in women (1.72 vs. 1.05) and all except one case occurred between the ages of 10 and 39 years, with the highest incidence between 10 and 19 years of age. Incidence rates of narcolepsy diagnosis from this study are in the same magnitude as those found in the US-based study, yet validated rates from the Netherlands are substantially lower (0.2 per 100 000 PY), as are rates from the Italian regions. Similar to the findings by Silber et al the highest background incidence rate of narcolepsy diagnosis was seen between 15 and 30 years of age. However, incident rates outside this age period are relatively high compared to Silber *et al*. As this study's rates reflect diagnosis, this could indicate a long lag-time between onset of disease and diagnosis. In contrast to the study by Silber et al, a slightly higher incidence rate in women was detected in most centres. This was most marked between the ages of 15 and 30 years, coinciding broadly with the reproductive age. It cannot be determined whether this peak is a result of biological mechanisms or due to determinants of diagnosis.

In a recent study in China, Han et al found a seasonal pattern for narcolepsy, with onset of narcolepsy being least frequent in November and most frequent in April [30]. While this study's data also indicate a seasonal effect on incidence rates, the peaks and troughs are not during the same months. However, diagnoses of narcolepsy as the index date was considered in our study, while Han *et al*. used onset of disease.

Clearly, population-based background rate data cannot provide conclusive evidence on a potential association between influenza A(H1N1)pdm09 vaccination and narcolepsy diagnosis. However, the established infrastructure and methods allowed evaluation of the signal and its potential population impact.

The increases in diagnosis rates observed towards the end of 2009 and 2010 in Finland and Sweden coincide with a high influenza A(H1N1)pdm09 vaccination coverage and support the safety signal previously observed in those countries. In contrast, the lower increase in narcolepsy diagnosis rates in Denmark was observed amidst low influenza A(H1N1)pdm09 vaccination coverage and started prior to the start of the campaign, suggesting factors other than influenza A(H1N1)pdm09 vaccination may be associated with the increasing narcolepsy diagnosis rates. Further validation of identified cases is likely to impact the magnitude and patterns of narcolepsy diagnosis rates.

This observation provides some indication that factors other than influenza A(H1N1)pdm09 vaccination may also be associated with increasing incidence rates of narcolepsy diagnosis. Thus, additional factors that could explain an increase in incidence of diagnosis of narcolepsy in 2010 should be considered for formal hypothesis testing.

7.2 Case control study

This report provides important insights into the scientific question and represents the final report to the ECDC of the VAESCO narcolepsy study conducted under ECDC Specific Agreement No 4. It is however not the final answer to the question on whether and how much influenza A(H1N1)pdm09 vaccination is associated with narcolepsy, as several countries are still collecting data, and exploring the presence of potential biases. Also key issues, which are difficult to resolve at a European level are: the low coverage rates; the rarity of the disease; and the fact that regulatory/media and professional attention limits the time during which cases can be recruited, without having interference from that attention. The analyses were performed focusing on that period alone and faced limited power. This has an impact since the lag-time between disease onset and diagnosis may be quite extensive. Within the VAESCO participating countries additional information is being collected to complete the pending cases, therefore the presented results should be interpreted cautiously[5].

All countries worked from a common protocol and instructions but the implementation differed based on national requirements and availability of data. Key differences between countries are:

- inclusion of cases with diagnosis after 2010 (Italy and Finland included only cases with diagnosis dates prior to December 2010, most other countries included till beginning of 2011, Norway included cases diagnosed up until the end of 2011)
- incompleteness of case recruitment during the recruitment period (Sweden, Norway, France)
- incompleteness of ascertainment of recruited cases (UK, Norway, France, Sweden)
- need for informed patient consent from case and controls (Sweden, Norway, Italy, France)
- retrospective patient interview for exposure assessment instead of registries (Sweden, France)
- lack of co-variate data (Denmark, Finland); and unblinded review of cases (Finland, Norway).

These differences may impact on the country specific estimates.

7.2.1 Key findings of the primary analysis of the case control study are:

A total of 249 cases with MSLT referral dates (primary index date) were submitted (135 from non-signalling countries). A total of 152 cases entered into the primary analysis (MSLT referral date during April 2009– 30 June 2010) (signalling/non-signalling: 63/89). Of those 152 cases 88 were children/adolescents (signalling/non-signalling: 44/44) and 64 adults (signalling/non-signalling: 19/45). The overall exposure prevalence to influenza A(H1N1)pdm09 vaccine for primary analysis was 59% in children/adolescents (signalling/non-signalling: 93% / 25%) and 17% in adults (signalling/non-signalling: 26%/13%).

Mean age of the cases was 20 for cases with MLST referrals in the primary study period and 16.5 years for cases with MSLT referrals from April 2009 until the end of recruitment. The prevalence of cataplexy was high in most countries, in particular in children/adolescents both in signalling and non-signalling countries (91% in signalling countries and 81.6% in non-signalling), and in the exposed and non-exposed cases. In adults the prevalence of cataplexy was 63% in signalling countries and 66% in non-signalling. The BC narcolepsy criteria were applied in all countries, in signalling countries 70% of adults were classified as level 1–3, for the non-signalling countries the figure was 77%. In children/adolescents percentages of level 1–3 were 95% and 92% in signalling and non-signalling countries respectively.

[5] New final data from France was submitted to the VAESCO analysis team at the end of August and reanalysis of data has been initiated.

Clusters of MSLT referral dates were seen for exposed children/adolescents in the signalling countries in January-February 2010 (Finland) and after July 2010, coinciding with the time that one Finnish neurologist first discussed a potential association with colleagues (first peak) and the regulatory/media attention (second peak) [26]. Peaks in MSLT referral dates were not observed for children/adolescents nor adults in non-signalling countries. Children/adolescents who were exposed to influenza A(H1N1)pdm09 vaccine prior to MSLT referral showed a peak in EDS onset month in the beginning of 2010 both in the signalling and non-signalling countries. However the extent was more extreme in the signalling countries. The paediatric/adolescent cases that were not exposed to influenza A(H1N1)pdm09 vaccine prior to MSLT had a more regular pattern of EDS onset over time. Children/adolescents with MSLT referral dates from May 2011 onwards were exposed cases only, which could point to a potential selective recruitment. The pattern in adults was different. While there was a peak of MSLT referral dates in March and April 2010 there was no clear peak in August 2010. The period of MSLT referral dates was shorter for adults than children/adolescents, no adult cases with MSLT dates after February 2011 were included, whereas mostly only exposed children/adolescents with MSLT dates after that period were included from Norway.

The recruitment patterns show that calendar time is an important factor in this study as it is associated with case inclusion and exposure.

Cases could only be included in the study when they were diagnosed. Due to the lag time between onset and diagnosis there is always a certain period required to allow for persons to get diagnosed. If countries have shorter recruitment periods, not enough time may have passed to identify all newly occurring cases since these cases would not have had the time to be diagnosed.

In non-signalling countries the median lag time between EDS onset and MSLT referral was shorter for exposed than non-exposed children/adolescents and adults. In non-exposed it was around 11 months for children/adolescents and 15 months for adults. In the exposed it was seven months both for children/ adolescents and adults. The median lag time between EDS onset and diagnosis of narcolepsy was also shorter in exposed children/adolescents and adults than in non-exposed persons. In the non-signalling countries it was 13 months for non-exposed children/adolescents and 20 months for adults. In the exposed it was 10 months for children/adolescents and 11 months for adults. Median lag time between MSLT referral and diagnosis was below two and a half months in non-exposed children/adolescents, and one and a half months in exposed. In adults it was three and a half months and two weeks respectively.

In signalling countries the median lag time between EDS onset and MSLT referral did not differ between exposed and non-exposed in children/adolescents (however there were only very few non-exposed) but it did in adults. Median lag time in non-exposed children/adolescents was around five months between EDS onset and MSLT referral and 10 months to diagnosis. In adults this was 15 and 20 months respectively. Median lag time between MSLT referral and diagnosis was five months in non-exposed children/ adolescents, and two and a half months in exposed. In adults it was four months and four months respectively.

Figure 7.1 attempts to graphically demonstrate the time issues encountered in the study, which create one of the major limitations and difficulties in studying this association.

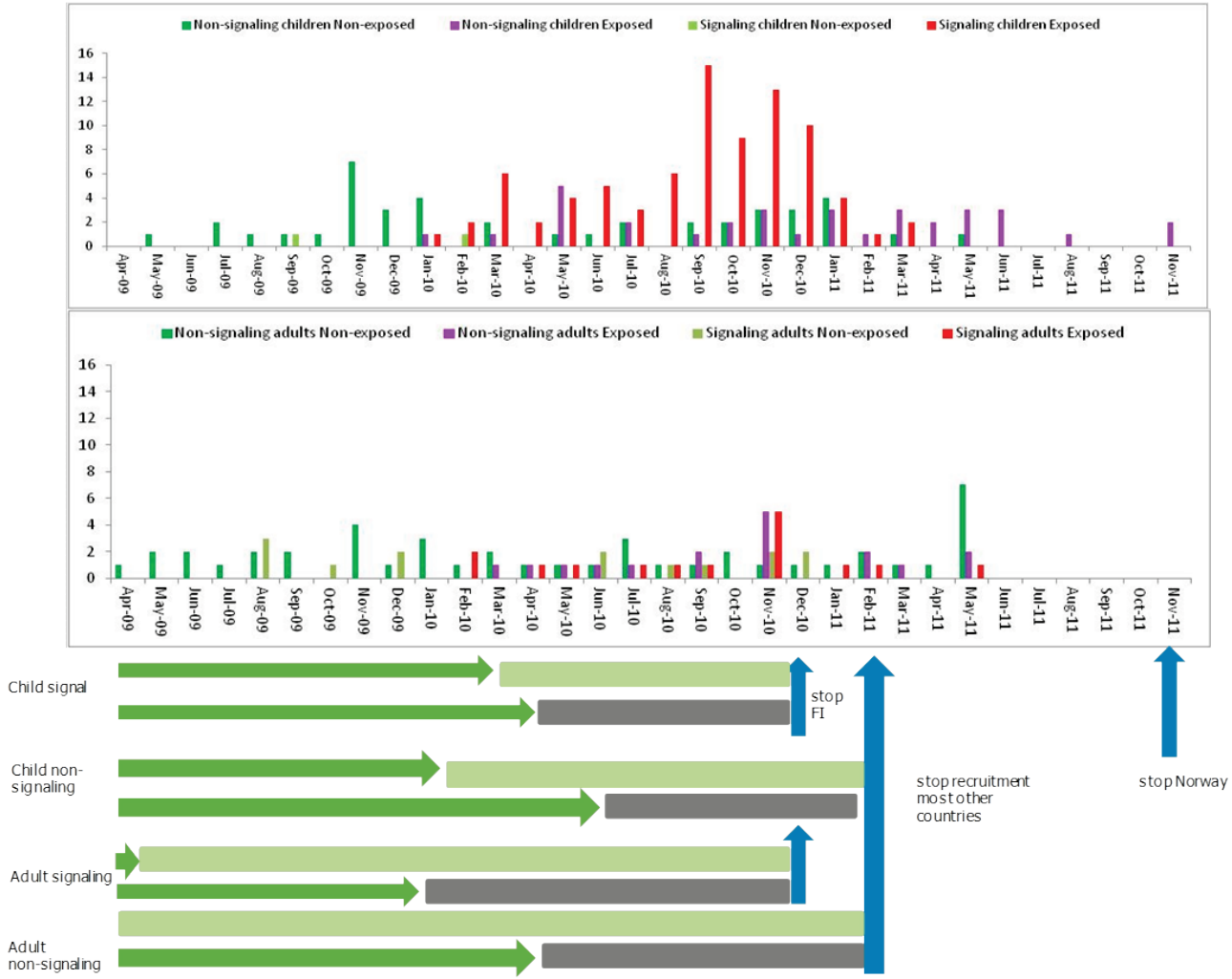
Due to differences in lag times between exposed/non-exposed, children/adolescents and adults and differences in recruitment periods, analyses based on the total recruitment period (secondary study period) may be affected by many issues. Restriction of the analysis to the primary study period has several advantages:

- some avoidance of potential regulatory/media attention effects (however complete avoidance would require not that only MSLT but also diagnosis was done prior to attention).
- less influence of selection issues due to insufficient recruitment period. The median lag time between MSLT referral and diagnosis was less than six months in most countries, which means that in most countries the recruitment extended sufficiently into the primary study period.

Using the date of MSLT as primary index date has an advantage over using the date of EDS for the following reasons

- In 10% of cases the EDS date was missing and in many others, imputation of the day and even month was necessary which leads to misclassification of exposure. Retrospective assessment of that index date, which is not easy to obtain runs the risk of being biased, especially if the vaccination status is known, or in countries where reimbursement is provided to cases of narcolepsy following use of Pandemrix.
- The lag time between EDS onset and diagnosis is much longer than the one between EDS and MSLT referral. The recruitment time in the VAESCO study would not have allowed for all cases with EDS onset in the primary risk period to be diagnosed by the end of the recruitment period. The EDS analysis is therefore more liable to selection issues, especially, if the delay is shorter for exposed subjects, as was the case in many countries. This may be one of the reasons why the most recently included children/adolescents were all exposed. The grey and red arrows below the graph demonstrate the period where there would not be complete inclusion until the end of recruitment, and the black arrows demonstrate the period of time to capture at least 50% of the cases.

Figure 7.1. Recruitment over time based on month of diagnosis of children/adolescents (upper) and adults (lower histogram)



Arrow blocks: the light green and grey blocks shows the median lag time between EDS date and diagnosis in exposed (light green bars) and non-exposed (grey bars) subjects, showing the difference in time. The dark green arrows show until which point in time at least 50% of the cases that would have occurred start of the study period could have been included given the recruitment period and the lag time. The difference in length of the green arrows for exposed and non-exposed shows the potential for differential inclusion based on the fact that the lag times differed between exposed and non-exposed.

7.2.2 Primary analysis:

In signalling countries (Finland and Sweden) there was a statistically significant association between influenza A(H1N1)pdm09 vaccination and narcolepsy. The odds ratio was higher in children/adolescents than in adults (14.2 (95%CI 2.5–infinity in children/adolescents vs. 1.2 (95%CI 0.2–9.1) in adults). The VAESCO case control study in Finland was based on the same cases as the Finnish cohort study and the estimate of association is nearly the same. Less than half of the eligible cases in Sweden could be included, and a potential selection bias cannot be excluded.

In non-signalling countries (France, Italy, Netherlands, United Kingdom, Denmark, Norway) influenza A(H1N1)pdm09 vaccination was not associated with a statistically significant increase in risk of narcolepsy following influenza A(H1N1)pdm09 vaccination (unadjusted OR=2.3, 95%CI 0.9-6.3). These estimates are not adjusted for other co-variates but matched on age, sex and country. Adjustment in countries where this was possible (all excluding Denmark) showed an increase in risk for children and a decrease of risk in adults.

There was no statistically significant difference in the association measure between adults and children in non-signalling countries (OR=3.7 for adults (95%CI 0.7–20.7) vs. 1.6 (95%CI 0.5–6.1) in children/adolescents), however the estimate in adults may be biased towards a higher risk because of evidence of higher inclusion of exposed adult cases especially in France and Norway. Pending cases in the primary study period seem to have a lower exposure prevalence to influenza A(H1N1)pdm09 vaccination in France, although the same could also be true for controls. Due to this potential bias in the adult estimate, results should be interpreted cautiously and separately for children/adolescents and adults in the non-signalling countries.

Analyses on the time since last vaccination showed that the risk estimates were highest in the 180 days following vaccination, however follow-up time was limited in the primary analyses and no reliable estimates for the effect after 180 days could be obtained.

The time since last vaccination and brand were analysed, however there was not enough heterogeneity in exposure to influenza A(H1N1)pdm09 vaccination to estimate the effect of Focetria or other pandemic vaccines reliably.

7.2.3 Sensitivity analyses

Extensive sensitivity analyses were done to look at the robustness of the estimates and the effects of potential biases that were anticipated in the protocol and statistical analysis plan.

Study period

The sensitivity analysis based on the secondary study period (from April 2009–end of recruitment), which includes the period after the start of regulatory/media attention) plus a variable recruitment calendar time for the different countries shows that the odds ratio for the association between influenza A(H1N1)pdm09 vaccination and narcolepsy increased in both age groups and in both signalling/non-signalling countries compared to the primary study period. Although the increase in risk estimates follows regulatory/media attention, it cannot prove nor reject a causal relation.

Another reason for the increase in estimates is the selective inclusion of exposed subjects towards the end of the recruitment period because lag times between onset /MSLT and diagnosis were shorter in exposed children, and because the right censoring were more likely to be included. The possibility that the period after the primary study period introduces bias because of the issues mentioned above cannot be excluded. Since the primary period is suffering less from these potential biases, it is recommended to interpret data from the secondary period with caution.

Restriction of the study period until February 2010 in Finland (tertiary period: to limit to the point in time when attention started), resulted in a substantial reduction of the association based on the MSLT referral date in children (from 11 till 5.8), yielding a non-significant association.

Index date

In principle, the EDS onset date would be the preferred index date as it would be closer to the start of the disease than the MSLT referral date and causal factors should act and be measured prior to start of the disease. In the design phase it was decided not to use EDS as primary index date since it often cannot be measured accurately. Indeed in the study in more than a quarter of the cases, the EDS date was either missing or imputed, in some countries patients were interviewed for EDS dates (Norway, Sweden) or EDS dates were obtained from schools (Finland). However, retrospective assessment of this index date carries a potential risk for bias. This is particularly so when media attention has already spread the news about an association, evaluators were not blinded to exposure, and in the signalling countries reimbursement is provided for exposed children with narcolepsy.

Sensitivity analyses on the index dates (using date of diagnosis or date of EDS onset) showed that the association between influenza A(H1N1)pdm09 vaccination and narcolepsy increased both in adults as well as in children/adolescents when based on onset of EDS as index date in the non-signalling countries. In the signalling countries the EDS date actually resulted in a lower but still increased estimate for children. The increased risk based on EDS date was consistent for the different countries and when pooled became statistically significant. Section 6.1.8 attempted to explore whether this effect observed in the EDS analysis could be explained by selection, misclassification of exposure and/or influences of specific countries. However this was not evident. The time recruitment issues (as explained in figure 7.1) and potential media effect could still not be ruled out as explanation for the EDS effect. The analysis presented in section 6.1.1 which restricted the cases to those with diagnosis dates prior to the start of media attention shows however that influenza A(H1N1)pdm09 vaccination is not associated with a significant risk of narcolepsy in children/adolescents when the cases were diagnosed prior to July 2010, and the index date is the EDS date. This analysis rules out the media effect but not the recruitment/lag time issues.

Other dates that could have been used would be the date of first health care contact, however, this date was not collected in the VAESCO study, but would be somewhere between the MSLT referral date and the EDS date.

Case validity

Restriction of the cases to those with cataplexy or BC levels 1–2 showed that the associations became stronger in the non-signalling countries but not in the signalling countries.

7.3 Data currently available on narcolepsy and influenza A(H1N1)pdm09 vaccination

Sweden and Finland are the countries where the signal of a potential association between influenza A(H1N1)pdm09 vaccination and narcolepsy first appeared. Both countries have undertaken several rapid assessment studies to further investigate the respective signals. These studies represent most of the evidence that is currently available and the Finnish data were recently published in a peer reviewed pape [25]. The VAESCO case control study was also conducted in these two signalling countries, and was based on the same (Finland) or partially the same cases (Sweden).

7.3.1 Inter-relationships between the Swedish and Finnish studies and the VAESCO study.

The Swedish Institute for Infectious Disease Control liaised with the Karolinska Institute to participate in the VAESCO case control study. The Swedish Medical Product Agency (MPA) conducted the initial cohort study and the case inventory studies, which have been described above. They retrieved access to data and case charts based on their public health mandate, which allowed them to bypass some ethical considerations that are required for research (i.e. they did not need to ask for patient consent). For the VAESCO study, medical ethical approval and patient consent was required, physicians needed to supply data *de novo* and therefore the study was delayed and not all cases could be included. The VAESCO study also required blinded evaluation of cases according to the Brighton criteria instead of the American Sleep Society criteria. In Sweden many cases will overlap between the VAESCO and Swedish MPA led studies, but recruitment and validation is done independently and therefore potentially different.

The Finnish cohort study in children (see section 7.2.1) was the basis for the VAESCO study, cases were identified and validated based on the cohort protocol, and according to the criteria of the cohort study, which differed slightly from the VAESCO study [25]. Since referral to a specialist (rather than for MSLT) was an index date in the cohort study, this was utilised for the VAESCO case control study instead of the referral date for MSLT. This means there is 100% overlap of the paediatric/adolescent cases between the THL cohort study and the VAESCO case control study. The cohort study could not adjust for age, time and gender, which were matching factors in the case control study, therefore the estimates may differ slightly [25]. The two studies cannot be considered to be independent.

7.4 Strengths and limitations of the VAESCO case control study

7.4.1 Strengths

Studying the association between influenza A(H1N1)pdm09 vaccination and narcolepsy was extremely difficult for the following reasons: 1) rarity of disease; 2) long delay between onset and diagnosis, which augments potential for bias; 3) large professional/regulatory/media attention about the association; 4) no clarity about the etiology of the disease.

The VAESCO study has the following strengths:

- The scale of investigation is unprecedented and allows for a wider European picture on an important unanticipated safety issue, which has been accomplished in little more than one year.
- The study shows the power of a collaborative effort across eight countries, with different stakeholders, to tackle an important vaccine safety issue. Collaboration proved to be possible and to add value to existing knowledge, in spite of the significant underfunding. This proves that there is great willingness to participate in these efforts.
- Flexibility in implementation of the study protocol has been provided, this allows for participation of countries that do not have large (national) linked databases, which may increase the power.
- The distributed data model, infrastructure and tools allowed for flexibility, homogeneity and high quality, which could be applied across countries with very different availability of resources and expertise.
- The case control design allowed for the study of additional risk factors, which contributed to a better understanding of the risk factors for the disease and explorations of confounding.
- A-priori the design tried to take care of many anticipated biases (e.g. diagnostic awareness, exposure, outcome misclassification).
- The study included adults from the beginning which allows for investigation of the entire age range and assessment of effect modification.
- Extensive sensitivity analyses were conducted to obtain a full appreciation of the potential association.

7.4.2 Limitations

The results of this case control study should be interpreted in the context of the limitations of observational studies in general. The study was initiated after extensive and broad media coverage and regulatory attention about a strong signal that Pandemrix might be associated with narcolepsy in children/adolescents. Regulatory attention led to stimulated reporting of cases as observed by the increase in case reports in EudraVigilance (see section 8).

The VAESCO study was designed in the context of a vaccine safety signal with a clear request from ECDC and EMA to not only study the association between influenza A(H1N1)pdm09 vaccination including Pandemrix and narcolepsy, but also to consider other potential explanations, such as infections and other vaccines. There were many scientific and political challenges to address this signal which originate from the facts that:

- Narcolepsy/cataplexy is very rare, has a long lag time, with unclear etiology and often goes undiagnosed.
- Vaccination coverage in the age range in which narcolepsy incidence is highest, was very low in many countries.
- The signal was originating from two of the VAESCO members who needed a rapid answer.
- The lack of adequate budget to address the signal appropriately under the circumstances. All centres contributed in kind to these investigations.
- Not all countries with high vaccination coverage were participating as they were unable to do so (e.g. Ireland, Iceland). Germany could not sign the VAESCO agreement and therefore did not join the European study but is conducting a national study in parallel.
- In the UK, data were used from GPRD which is a sample of the UK population that can be accessed rapidly. A nationwide study through sleep centre is conducted in parallel.
- Case inclusion is still on-going in some of the countries and further data will become available in a near future but therefore not available in this final report to ECDC.

The current study tried to address the challenges in the best possible way, however observational studies always have limitations which can be summarised as selection bias, information bias and confounding. They are discussed in this order below:

7.4.3 Selection bias

Selection bias in a case control study occurs if the inclusion of cases and controls is not complete and depends on exposure. There are many sources for a potential selection bias such as:

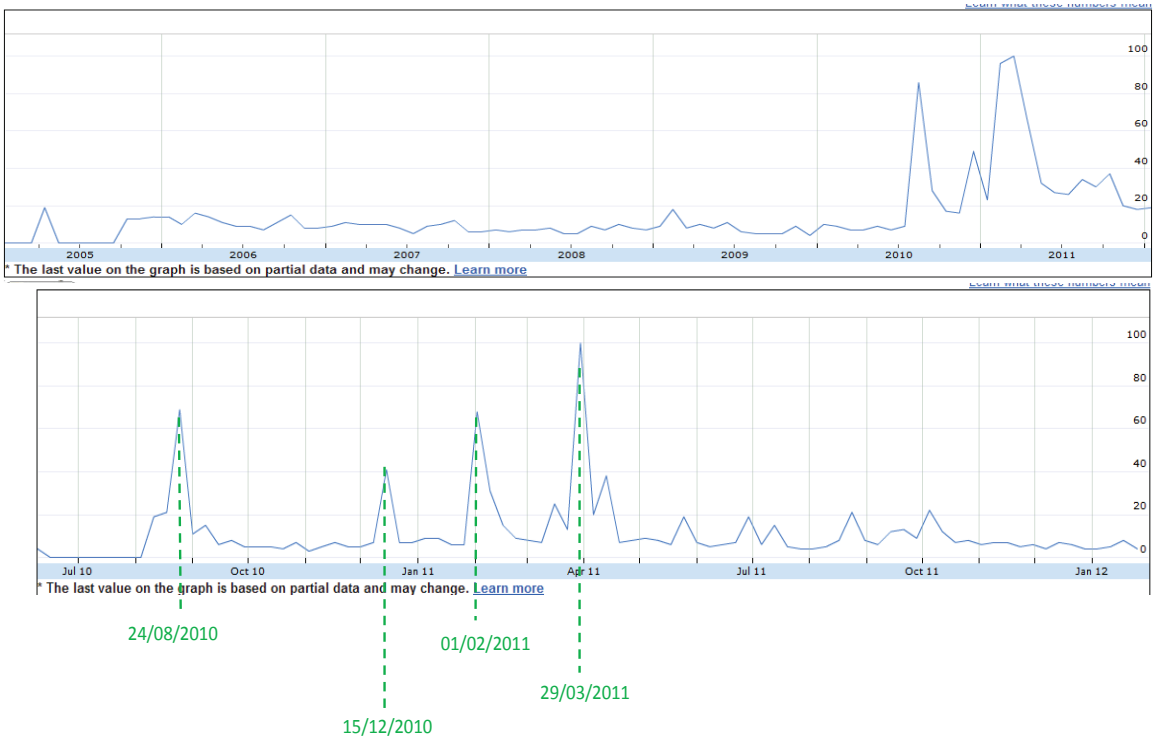
- Incomplete inclusion because a person does not provide informed consent if required: This does not necessarily need to be associated with exposure, but could occur if for example the invitation letter specifies the association of interest, if there is media attention around the association which makes the patients aware, or because exposure is related to social class which often is a strong determinant for participation. Interviewers/investigators were instructed not to mention the association in the invitation letter. However many ethical committees required this (e.g. Norway, Sweden). In the United Kingdom, Finland, Denmark and the Netherlands cases were obtained from diagnosis registries and consent was not required which limits the potential for this source of bias. Consent was required in Sweden, Norway, France and Italy. Since only the consenting cases can be asked for exposure it was not possible to exclude a potential selection bias in these countries.
- Incomplete inclusion because of lack of information: in several countries case ascertainment could not be finalised prior to the ending of the VAESCO narcolepsy project, and this was particularly so in the UK, France, Sweden and Norway. Lack of inclusion becomes a problem in a case control study if it is related to exposure, which was suggestive in France and Norway for adults. Although many cases were pending in the UK, this may not have a large impact on the power of the study since the exposure prevalence was very low. In the VAESCO study, physicians were requested to include all cases (independent of exposure) from a diagnosis list (rather than from memory). In Norway, Denmark, Sweden, France, Italy, France and Netherlands cases were obtained from sleep laboratories /centres. In the Netherlands, Denmark and Sweden inclusion was verified against objective diagnosis/claims lists. In Italy, France and Norway inclusion of cases relied on the retrieval mechanisms of the neurologists/specialists and it could not always be verified against an objective list of diagnosis/claims. In these countries a potential selection bias due to this reason cannot be excluded, even if physicians were instructed to include all cases.
- Higher probability of inclusion due to diagnostic awareness: A study on narcolepsy is prone to this bias since it is a disease with a very long lag time (time between onset and diagnosis). Changes in clinical practice that lead to a change in the lag time may be a source for selection bias, especially if this change in clinical practice is associated with exposure.

In the VAESCO study it was observed that prior to the regulatory/media attention in August 2010, the lag times between referral for MSLT and diagnosis were substantial (varying from one week to ten months). After media attention these times shortened in general and in particular for exposed children. In Finland and Sweden, the signal resulted in compensation for children and a faster diagnostic workup. Due to these changes in clinical practice, exposed subjects may be diagnosed more rapidly. The effect of this is most pronounced when a study has a short case accrual period, so that non-exposed subjects do not have the time to be diagnosed and included. In the VAESCO study, countries had different lag times and different case accrual periods. In the country sections it was estimated whether the accrual period would allow for most cases to be entered given the recruitment period and the lag times (see figure 7.1). In some countries (Finland, Italy and Sweden) the recruitment period was not long enough to capture all the cases with onset of narcolepsy in the primary study period. Figure 7.1 shows that in the period after the study period, and mostly so at the end of the period, only exposed case was included. Exposed cases have much shorter lag times from EDS to diagnosis in most countries and therefore have a higher probability to be included at the end of the study where there is right censoring.

Bias due to diagnostic awareness will be most pronounced after media attention. That is why the primary analysis of the VAESCO study censored prior to the start of media attention. A sensitivity analysis was conducted that included the period after the media attention in August 2010, and in all groups the association measure went up, pointing towards the potential existence of such bias and bias due to incomplete (and selective) recruitment at the end of the period both in signaling and non-signaling countries.

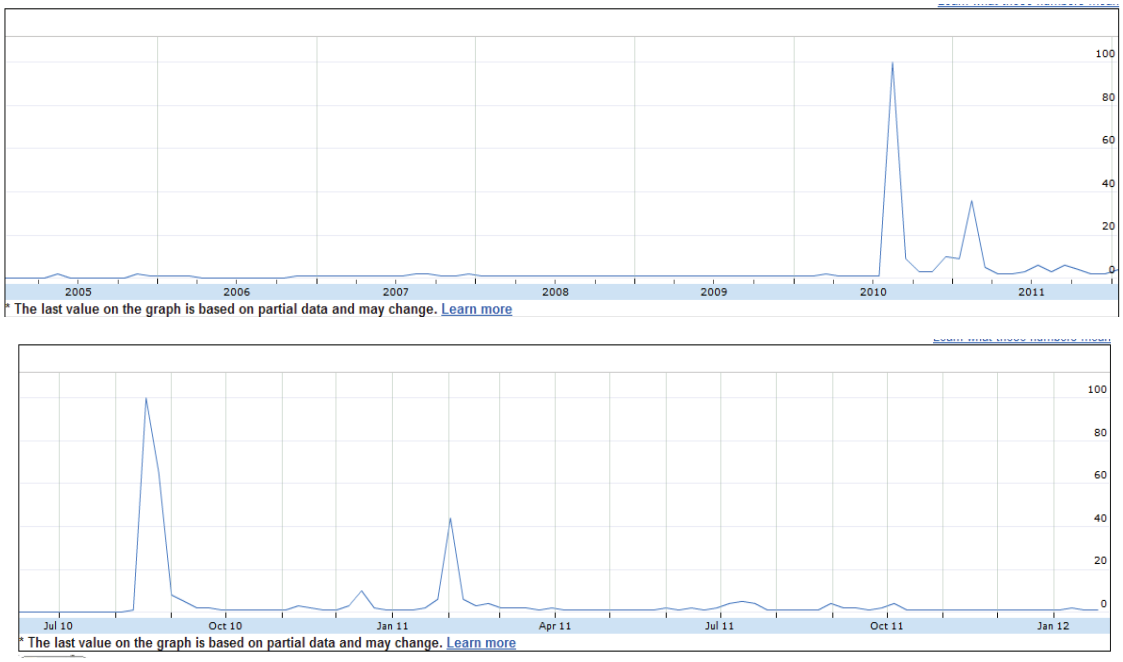
Figures 7.4–7.4.2 show the Google hits in Sweden and Finland as kindly supplied by ECDC.

Figure 7.4. Google hits on the term Narcolepsy between 2005 and 2012 (up) and June 2010 and January 2012*



** showing clear spikes that followed important publications or release of new information (reports) nationally and internationally: 24 August 2010 press release THL Finland; 1 February2010 release of Finnish cohort study interim analysis; 29 March2011 release of Swedish cohort study report.*

Figure 7.4.1. Google hits on the term Narcolepsy between 2005 and 2012 and June 2010 and January 2012*



** showing clear spikes that followed important publications or release of new information (reports) nationally and internationally. 24/8 2010: press release THL Finland, 1-2-2010: Release of Finnish cohort study interim*

7.4.4 Information bias

Outcome misclassification

Outcome misclassification was avoided as much as possible by using the ad hoc Brighton case definition for narcolepsy. Application of case classification algorithms results in more homogeneity. However, in this study, data were retrieved retrospectively, and therefore the ability to classify events depends on the level of detail of recorded medical information. In most countries the percentage of level 1–2 was very high, in particular in the children/adolescents category, which means that outcome misclassification is limited. In adults outcome misclassification may be more pronounced. Some countries had not yet the full information available for classification (e.g. Sweden), in the UK, information supplied by GPs (questionnaire/copies of specialists) was often insufficient to classify the case adequately.

Unblinded review of cases might lead to outcome and index date misclassification and potential bias if done differentially for exposed and non-exposed. This is even more relevant if the dates of onset/referrals need to be assessed, which might be based on more subjective information. The VAESCO protocol required blinded review of cases. However, in Finland reviewers were not blinded to exposure. In Norway, validation was done by the reporting neurologists without deleting exposure information, although most cases were exposed, the assessment of the onset of narcolepsy could be affected by the knowledge about exposure.

Ideally the analysis aiming to establish an association between exposure and outcome uses onset of symptoms as the primary index date. In the VAESCO study three index dates were investigated, the date of onset of EDS, the date of MSLT referral and the date of diagnosis of narcolepsy. The primary index date was defined as the date of referral for MSLT even though this may be later than the date of actual disease onset. This was done for the following reasons.

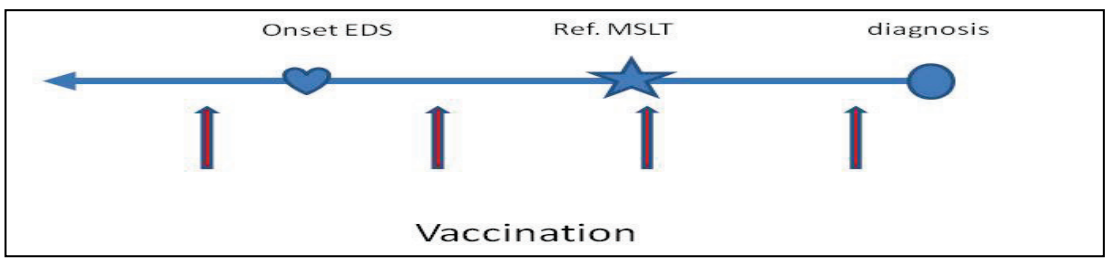
Exposure misclassification

Exposure misclassification to influenza A(H1N1)pdm09 vaccination is limited as it was explicitly requested to use information from automated registries regarding exposure. In Sweden and France, information was retrieved from patients by interview. In the Netherlands, exposure may be misclassified as GP records were used for assessment of exposure. However, children below the age of five, and parents of young children were vaccinated through the health agency and information would not be captured in the GP records. The extent of this misclassification was limited: there were no young children and verification of exposure of a sample of cases by the neurologists after finalisation of the study showed no misclassification.

The exposure prevalence in the controls in the primary analysis is lower than expected from the coverage rates because a substantial number of cases (plus controls) were retrieved prior to the start of the vaccination campaign. Restriction of the cases to those with index dates after the start of vaccination campaigns showed coverage rates as expected in their time matched controls.

- The date of EDS is difficult to assess objectively in retrospect (oral communication EU narcolepsy experts), especially if the vaccination status and the research question/concern are known. It was anticipated by the narcolepsy experts that this date will be missing or be difficult to assess.
- Date of MSLT referral as index date was chosen as the primary index date. Since the date of referral is later than onset, this may lead to misclassification of exposure (i.e. classifying wrongly subjects that were exposed after disease onset as subjects that were exposed in the risk period) (see figure second vaccination arrow), but as long as exposure is assessed in the same way between cases and controls, and the exposure probability does not alter upon symptoms, this bias should lead to an underestimation of the risk.
- The date of narcolepsy diagnosis is generally much later in time than the date of disease onset. Using this date as the index date might lead to even more misclassification of exposure. This is similar to the reasoning around the date for MSLT referral, the measure of association from the analysis using the date of diagnosis as index date should be lower than the estimate from the date of EDS onset or MSLT referral in case of a causal association.

Figure 7.4.2. Retrospective sequence of dates considered as potential index dates in the VAESCO narcolepsy study.*



**vaccination may occur at one of the red arrows*

7.4.5 Confounding

Confounding is addressed in different ways in the case control study: 1) by design due to matching; 2) through statistical adjustments.

In the VAESCO study matches were made on age, country, sex and index date. Matching has the disadvantage that power may be lost in conditional analyses, since it considers only strata with discordant information. In strata of high or low exposure, prevalence the concordance between case and controls may be high. This was the case both in the signalling and non-signalling countries.

In most countries, data on several co-variates were collected although very little is known about the risk factors for narcolepsy. Influenza and streptococcal infections have been recognised as risk factors for narcolepsy, these factors were not significantly associated with narcolepsy in this study [19, 31, 17]. Adjustment for co-morbidity, infections and other vaccines (HPV and seasonal vaccinatin) did not greatly alter the association in adults, but adjustment for influenza like illness and asthma had quite an impact in children/adolescents. It resulted in an increase of the estimate. Not all countries could provide co-variate data, therefore the effect of adjustment on the association between influenza A(H1N1)pdm09 vaccination and narcolepsy in children/adolescents in the signalling countries could not be estimated. Since very little is known about the risk factors for narcolepsy, residual confounding cannot be excluded.

7.4.6 Sample size/power

The main limitation of the VAESCO analysis is the lack of power due to:

- the low exposure prevalence in the age ranges of the reported narcolepsy cases in many countries
- the high correlation of exposure between matched cases and controls resulting in a reduced number of discordant pairs and less statistical power
- the fact that an association may only exist in children/adolescents
- the limited number of cases outside of the signalling countries
- the need and the decision to censor in July 2010, prior to regulatory and media attention.

In the final analysis power remained limited. High Pandemrix exposure countries in the EU include Iceland and Ireland. Although it was requested, these countries were not in the position to contribute to VAESCO.

8 Overall conclusion

Narcolepsy is an under diagnosed disease of widely unknown etiology. The availability of vaccines and the concern of narcolepsy being associated with influenza A(H1N1)pdm09 vaccination have triggered several investigations worldwide. ECDC has called on the VAESCO network to establish national and European background rates of narcolepsy and determine the strength of an association between influenza A(H1N1)pdm09 vaccine and narcolepsy.

An increase in incidence rates of narcolepsy following the start of influenza A(H1N1)pdm09 vaccination campaigns as well as a strong association were described in Finland and Sweden. The findings were published in various reports and recently in a peer reviewed journal.

The VAESCO studies confirm the increasing background incidence rates and strong associations in Finland and Sweden.

The primary analysis in the primary study period (30 June 2010) in the non-signalling VAESCO countries could not confirm the strength of the signal in Finland and Sweden. Extensive sensitivity analyses demonstrated that the association estimate is sensitive to changes in the time period and the index dates, and underline the difficulty to investigate this association in the presence of regulatory/media attention. Attempts to avoid a potential bias due to this attention led to a short primary study period which restricted the number of cases that could be included in this analysis. Our sensitivity analyses showed that the time between onset and diagnosis was much shorter in exposed subjects in most countries. This resulted in higher inclusion rates of exposed subjects at the end of the recruitment period. The effect of this was observed in all analyses regarding the secondary period, which could therefore potentially overestimate the association. Additional findings of the VAESCO study include the association observed in adults in the non-signalling countries. This does not differ from children/adolescents or was even higher in many sensitivity analyses. Given the longer lag times between onset of disease and diagnoses in adults, the low number of cases, and the influence of data from France on these analyses, these findings should be interpreted with caution and require further investigation.

9. Other studies /data

9.1 Sweden

Sweden was one of the countries that recommended vaccination of all persons with influenza A(H1N1)pdm09 vaccine. Sweden only supplied Pandemrix and overall uptake was 59%.

The first cases of narcolepsy in children/adolescents were reported to the Swedish MPA in the spring of 2010. In August 2010, the MPA announced a special investigation regarding narcolepsy following influenza A(H1N1)pdm09 vaccination and a press release was issued on August 17. Following a first newspaper report on a case of narcolepsy that occurred after Pandemrix vaccination in the summer of 2010, an increasing number of case reports in children/adolescents were received by the MPA [31]. There was substantial media attention in Sweden from August 2010 onwards.

9.1.1 Cohort study

In March 2011, the MPA reported results from a rapid assessment registry-based cohort study which showed a four-fold increased risk among vaccinated versus non-vaccinated children and adolescents, and no change in the risk of narcolepsy in adults [32]. The study utilised an *ad hoc* vaccination registration and outcome data from local healthcare databases. The cohort of all persons born in or after 1990 had a parallel design of vaccinated and unvaccinated individuals (children/adolescents). All cases of diagnosed narcolepsy (ICD–10 G47.4) reported to the healthcare databases in these four regions between 1 October 2009 and 31 December 2010 were linked to information in the regional vaccination databases.

Table 9. Overview of first reported cohort study in Sweden in children/adolescents (April 2011)

	Vaccinated				Unvaccinated				Vaccinated vs unvaccinated	
County	*#Events*	*Risk time**	*Rate*	*95% CI*	*#Events*	*Risk time**	*Rate*	*95% CI*	*RR*	*95% CI*
SLL	11	3.583	3.07	(1.53–5.49)	2	2.403	0.83	(0.10–3.01)	3.69	(0.80–34.2)
Skåne	10	1.928	5.19	(2.49–9.54)	2	1.848	1.08	(0.13–3.91)	4.79	(1.02–45.0)
VGL	16	3.005	5.33	(3.04–8.65)	2	1.549	1.29	(0.16–4.66)	4.12	(0.97–37.0)
ÖGL	1	0.840	1.19	(0.03–6.63)	0	0.388	0.00	(0.00–9.51)	∞	(0.01–∞)
ALL	**38**	**9.355**	**4.06**	**(2.87–**	**6**	**6.188**	**0.97**	**(0.36–2.11)**	**4.19**	**(1.76–12.1)**

In each of the counties, the relative risk of narcolepsy in the vaccinated was increased. This study showed a significant increase. However, the study suffered from several methodological limitations:

- cases were not validated and obtained based on ICD10 codes
- the index date was the date of diagnosis which might mean that onset was prior to influenza A(H1N1)pdm09 vaccination
- follow-up continued until December 2010, which includes the period with heightened awareness following media attention
- no adjustment for confounding factors.

9.1.2 Case inventory study

On 30 June 2011 the Swedish MPA published a second report based on a case inventory study [33].

The case inventory study was designed to capture and evaluate all cases of narcolepsy, i.e. irrespective of vaccination status, which were reviewed in the health care system during the two-year period 1 January 2009-31 December 2010 and to ascertain which of those cases had onset of first symptoms within the study period. The objectives were to:

1) measure and analyse the number of cases and incidence of narcolepsy with cataplexy in the entire Swedish population over time, i.e. during and after as compared with before the pandemic period;

2) compare the incidence of narcolepsy with cataplexy in subjects exposed to Pandemrix vaccination with those non-exposed during the pandemic period and thereafter; describe and compare some characteristics of exposed and non-exposed narcolepsy (with cataplexy) cases.

Medical records were collected for cases which had been diagnosed or were under review during 2009 through 2010. Medical records were reviewed by two independent experts to classify the disease (according to American criteria) and to assess onset of symptoms. Assessors were not blinded to influenza A(H1N1)pdm09 vaccination exposure.

Eighty-seven cases with cataplexy were identified, and nine narcolepsy cases without cataplexy. Overall, the incidence rate in those vaccinated was almost seven-fold higher than in the non-vaccinated subjects, 4.2 versus 0.64 per 100 000 PY, yielding a relative risk of 6.6 (95% CI:3.1–14.5) and an absolute risk of 3.6 additional cases (95% C 2.5–4.7) per 100 000 vaccinated subjects. The incidence rates (based on first symptoms) in the vaccinated were highest in Q4 of 2009 and Q1 of 2010 [32] (see table 9.1).

Table 9.1. Numbers of narcolepsy (with cataplexy) cases with symptom onset between 1 January 2009–31 December 2010, in subjects born after 1990 and population based incidence rates per 100 000 PY, 95% confidence limits (CFL) [32]

		Quartiles, 2009 – 2010								
		09-Q1	09-Q2	09-Q3	09-Q4	10-Q1	10-Q2	10-Q3	10-Q4	All
		N	N	N	N	N	N	N	N	N; Incidence Rates (100'), 95% CFL
	Age groups									
	0-4 years	-	-	-	1	-	1	-	-	2*; 0.18 (0.00,0.46)
	5-9 years	-	-	-	6	13	2	-	1	22; 2.18 (1.29, 3.18)
	10-14 years	1	2	1	16	9	5	1	-	35; 3.52 (2.41, 4.73)
	15-19 years	1	-	-	4	14	3	-	-	22; 1.72 (1.02, 2.51)
N; Incidence Rates (100'), 95% CFL		2; 0.37 (0, 0.91)	2; 0.37 (0, 0.91)	1; 0.18 (0, 0.55)	27; 4.94 (3.1, 6,95)	36; 6.58 (4.57, 8.78)	11; 2.01 (0.91, 3.29)	1; 0.18 (0, 0.55)	1; 0.18 (0, 0.55)	81; 1.85 (1.46, 2.26)

In summary, the study shows an increased risk of validated incident narcolepsy with cataplexy in children/adolescents during the immunization campaign and the three months thereafter.

There are several limitations to this study which may potentially lead to an overestimation of the effect:

- use of cases reported through the ADR database may have led to selection bias (inclusion of exposed)
- unblinded assessment of the cases
- inclusion of the period of time after start of media attention for case inclusion which may have resulted in diagnostic bias
- lack of adjustment for confounding factors
- denominator for rate calculations not on person level basis but on extrapolations.

Over time the number of reported cases of narcolepsy after vaccination with Pandemrix has passed well over 100.

Based on the study findings and the CHMP decision in July 2011, Swedish parents of children who developed narcolepsy after vaccination with Pandemrix have started to receive compensation [34].

9.2 Finland

Finland recommended influenza A(H1N1)pdm09 vaccination for its entire population. Coverage was high, especially in children/adolescents, and only Pandemrix was used.

Dr. M Partinen, a narcolepsy expert noted that influenza A(H1N1)pdm09 vaccination (in Finland Pandemrix) could be associated with narcolepsy as he saw many more cases in his practice than expected. On 22 February 2010, he discussed this suspicion with colleagues in Finland, the first case report was notified to the National Institute for Health and Welfare (THL) in May 2010. Subsequently, reports began to accumulate. In August 2010 after the Swedish National Agency for Medicines published the observation of a cluster of narcolepsy cases temporally related to vaccination with Pandemrix on August 15, the National Advisory Committee on Vaccination in Finland (KRAR) and THL issued a statement on 24 August 2010 [35]. From August 2010 onwards there was repeated and substantial media attention.

9.2.1 Cohort study (interim)

On 31 January 2011 the task force in Finland released the interim report with the results from a rapid 'fixed' retrospective cohort study in all children/adolescents born at or after 1 January 1991. The study was conducted during the period 1 January 2009 and 31 December 2010 (primary analysis censored at August 2010) by using data from hospital discharge diagnoses (ICD-10 G47.4) and national vaccine exposure registries. All cases were reviewed by two narcolepsy experts of the task force who classified cases according to the ad hoc Brighton case definition. Experts were not blinded to the vaccination status of the children. The onset of symptoms (excessive daytime sleepiness and/or cataplexy) was based on the descriptions and dates noted in the medical records. For the purposes of the main analysis, the onset time was defined as accurately as possible. This was done using patient records from hospitals and primary care. The primary care source documents included records from school health, healthcare centres and private clinics. The onset time of narcolepsy was defined as that particular day when the patient was for the first time seen by the school nurse, other public health nurse or general practitioner because of the parental observation or own complaint of unusual day time sleepiness and fatigue, and this visit and/or contact was recorded by the health care personnel in the patient records. The risk of narcolepsy was nine-fold elevated in the primary analysis and increased in sensitivity analyses which changed the index date [35]. Interpretation of the results has to take the following strengths and limitations into account:

- review of cases (validation and assessment of index dates) was not blinded to influenza A(H1N1)pdm09 vaccination exposure which is important for re-assessment of the index dates
- diagnostic awareness raised since the potential association between Pandemric and narcolepsy was discussed among narcolepsy experts already in February 2010
- inability to adjust for confounding factors
- historic comparator group due to lack of unexposed cases in the parallel (unvaccinated cohort), in this period cases could be diagnosed differently and the time between EDS onset and diagnosis could also be different than in the cases that occur later in time.

The strength of the Finnish study was the speed with which the results were generated and communicated.

9.2.2 Cohort study (final)

On 31 August 2011 the final study report was released in Finnish, the final results were a follow-up of the interim data and based on the same design: retrospective cohort study [36]. Out of 71 persons in the hospital discharge registries, 67 were confirmed with a narcolepsy diagnosis. Using a retrospective cohort study 915 854 children and adolescents born from 1991–2005 were followed up between 1 January 2009 and15 August 2010. In this cohort 688 566 persons were immunised with Pandemrix. Time-dependent Poisson regression was used as the analytic method. Sixty-four incident narcolepsy cases were included in the analysis. Immunised people had a relative risk of 12.7 (95%CI 6.1–30.8) as compared to the non-immunised. Six cases per 100 000 could be attributed to immunisation. No increased risk was observed among adults. All patients with a sample taken for analysis (n=41) exhibited the HLA DQB1*0602 phenotype. No patients exhibited the protective *0603 phenotype. Contrary to previous studies, studies at THL suggest that squalene (AS03) produces an antibody response. Preliminary studies suggest that repeated immunisations in healthy subjects produce AS03 antibodies. Roughly 25% of narcolepsy cases (children) have antibodies against AS03. Studies on cell-mediated immunity among narcolepsy cases and controls are ongoing. No changes in incidence of coeliac disease or diabetes mellitus type 1DM1 have been identified using social security registry data. All cases have antibodies against A(H1N1)pdm09 components (which could be wildtype virus and/or vaccine). Antibodies against non-structural NS1 protein (which is not present in the vaccine) were seen in 10% of cases and 15% of controls.

Based on the study findings, and the CHMP decisions, Finnish children who developed narcolepsy after influenza A(H1N1)pdm09 vaccination get reimbursement from the Finnish Insurance Pool.

At the end of March 2012, the Finnish data were published by PlosONE. The Finnish cases were described along with the incidence [23], whereas THL reported on the cohort study [25]. Incidence rates and numbers of cases in the paper by Partinen et al. differ slightly from the cases and rates reported in the VAESCO study, although the same data sources were used.

9.3 France

On 4 April 2011 the French Medicines Agency issued a press release and report based on the French pharmacovigilance data [37]. At that point 23 cases of narcolepsy were reported after use of Pandemrix (on 4.1 million vaccinated) and two cases after use of the non-adjuvanted influenza A(H1N1)pdm09 vaccine Panenza (on 1.6 million vaccinated cases), 14 persons were older than 16 whereas 11 cases were between 8–15 years of age. The onset of symptoms started between two days and five months after vaccination. The total number of observed cases is less than expected, but in the age group 10–15 years of age, it was higher: nine observed whereas 2.1 were expected. France is investigating the signal by participating in the VAESCO study and with an extension afterwards.

9.4 Denmark

Based on the Swedish and Finnish data the Danish Medical Product Agency reviewed the narcolepsy issue. No cases were reported in Denmark, which used Pandemrix in persons at risk. Denmark had a low overall vaccine coverage rate (< 10%).

9.5 Ireland

Ireland is one of the high vaccine uptake countries which used Pandemrix. In Ireland a comparative cohort study was just released, comparing the rates of narcolepsy in exposed and non-exposed subjects (all ages). The rate was 5.8 per 100 000 PY in the vaccinated and 0.5/100 000 PY in the non-vaccinated, resulting in a 13-fold higher risk of narcolepsy in vaccinated compared to non-vaccinated in children/adolescents. No increased risk was found for adults. In Ireland all cases occurring up to 31 December2010 were included, which includes the period after the start of media attention. Only one case was diagnosed prior to start of the regulatory attention.

9.6 Germany

Germany is a low-uptake country for influenza A(H1N1)pdm09 vaccination (<10%), but has been using primarily Pandemrix. Following the media-attention of narcolepsy cases in Sweden and Finland, 18 cases reporting of narcolepsy following Pandemrix vaccination were reported to the Paul-Ehrlich Institute between October 2010 and June 2011. It concerned 13 children/adolescents and five adults [38]. The Paul Ehrlich Institute is conducting a case control study based on the VAESCO protocol together with Dr. Mayer.

9.7 United Kingdom

The UK is a low-uptake country for influenza A(H1N1)pdm09 vaccination (<10%), but has been using primarily Pandemrix. The UK participated in the VAESCO study by using data from the GPRD, and currently the Health Protection Agency is investigating the association independently by using a self controlled case series design.

9.8 World Health Organization

The Global Advisory Committee on Vaccine Safety (GACVS) issued press releases in, February, April and July and August 2011 on Pandemrix vaccine and narcolepsy. GACVS subscribes to the EMA recommendations.

9.9 US Centers for Disease Control and Prevention

The United States Centers for Disease Control and Prevention (CDC) released a statement in September 2010, following the signal in Europe. They reviewed the Vaccine Adverse Event Report System (VAERS) and found no signals or concerns suggesting an association between US licensed influenza A(H1N1)pdm09 or seasonal influenza vaccines and narcolepsy in the United States. The USA only used non-adjuvanted monovalent influenza A(H1N1)pdm09 vaccines [39].

9.10 European Centre for Disease Prevention and Control

ECDC requested a study proposal from the VAESCO consortium in August 2010, this proposal was discussed at CHMP in September 2010 and the study started officially in December 2010. Based on the Finnish report and Swedish data, ECDC issued a public health development on reports of cases of narcolepsy and cataplexy in children and adolescents in March 2011[6]. The view of ECDC was the same as that of the European Medicine's agency and WHO, noting especially the latter's position that, from the evidence gathered so far, countries currently vaccinating against influenza should continue preferential use of trivalent seasonal vaccines containing the influenza A(H1N1)2009 strain. In May 2011 an updated position statement was released [40].

[6]Available at: http://ecdc.europa.eu/en/healthtopics/pandemic_preparedness/2009_pandemic_vaccines/Pages/vaccine-safety.aspx

9.11 European Medicines Agency and data from spontaneous reports

The European Medicines Agency launched a press release on 27 August 2010 stating that a review of Pandemrix was started on request of the European Commission to investigate whether there is a link between cases of narcolepsy and vaccination with Pandemrix. The Agency had calculated that Pandemrix, which had been used since September 2009 for vaccination against H1N1 influenza was given to at least 30.8 million Europeans. The CHMP was charged to carefully look at all of the available data to determine whether there is evidence for a causal association. As part of this evaluation the Committee will also consider the so-called background rate for narcolepsy, i.e. the number of cases that would normally be expected to be diagnosed. The Agency announced that it was liaising with the ECDC, international regulatory partners and WHO [41].

In the EudraVigilance database only one single case was reported until media awareness rose (August 2010).

Figure 9. Reports to EudraVigilance database until August 2012

	Narcolepsy			Cataplexy			Total number of distinct cases		
Primary source country	Number of child cases	Number of adult cases	Number of unknown cases	Number of child cases	Number of adult cases	Number of unknown cases	Number of child cases	Number of adult cases	Number of unknown cases
2009									
EEA	1	0	0	1	0	0	1	0	0
Non-EEA	0	0	0	0	0	0	0	0	0
VAESCO	1	0	0	1	0	0	1	0	0
2010									
EEA	157	31	0	90	18	0	159	32	0
Non-EEA	2	0	0	2	0	0	2	0	0
VAESCO	143	28	0	77	15	0	143	29	0
2011									
EEA	273	63	2	115	36	1	276	64	2
Non-EEA	2	1	0	1	1	0	2	1	0
VAESCO	227	54	1	79	29	1	228	55	1
2012									
EEA	103	32	2	43	15	0	106	33	2
Non-EEA	0	0	0	0	0	0	0	0	0
VAESCO	93	26	0	39	9	0	96	27	0

In September, 2010 the CHMP discussed the safety concerns of Pandemrix and in particular the signal on narcolepsy, it reviewed the protocol of the VAESCO study and on the 23 September a press release was issued stating that additional studies are needed. They adopted the VAESCO case control study. In February 2011, PhWP and CHMP discussed Pandemrix again, after the release of the Finnish interim report [42]. The press release stated that a causal association was not yet established and the results of further studies were needed. After release of the Swedish data in April 2011, the topic was discussed again. This time the Swedish data, showing a relative risk of four, and a French report of some cases were considered, as well as an official request from ECDC to take measures. The CHMP recommended a label change stating that prescribers should take the potential risk of narcolepsy into account when prescribing Pandemrix to children/adolescents [43]. In July 2011 the European Medicines Agency convened an expert meeting to discuss the evidence and potential mechanisms, the experts advised the Pharmacovigilance Working Party and CHMP, who communicated the following decisions in July 2011.

European Medicines Agency recommends restricting use of Pandemrix (21 July 2011)

In persons under 20 years of age Pandemrix to be used only in the absence of seasonal trivalent influenza vaccines, following link to very rare cases of narcolepsy in young people. Overall benefit-risk remains positive.

Finalising its review of Pandemrix and narcolepsy the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that in persons under 20 years of age Pandemrix may only be used if the recommended seasonal trivalent influenza vaccine is not available and if immunisation against H1N1 is still needed (e.g. in persons at risk of the complications of infection). The CHMP confirmed that overall the benefit-risk balance of Pandemrix remains positive.

The review of Pandemrix was initiated to investigate a possible link between Pandemrix vaccination and narcolepsy, following an increased number of reported cases of narcolepsy among children and adolescents in Finland and Sweden. The reported cases of narcolepsy occurred following the H1N1 pandemic vaccination campaign in late 2009 and early 2010. The current review has been conducted in the context of seasonal use.

The CHMP considered all available data on the possible association between Pandemrix and narcolepsy and the impact on the overall benefit-risk balance of Pandemrix. These included the results of epidemiological studies carried out in Finland and Sweden, analysis of safety surveillance data performed in several Member States and case reports from across the European Union (EU). They also included the preliminary results of an epidemiological study of narcolepsy and pandemic vaccines in eight EU Member States, coordinated by the European Centre for Disease Prevention and Control (ECDC) through a network of research and public health institutions (VAESCO).

The CHMP also took advice from a specially convened meeting of experts in fields such as paediatric neurology, vaccinology, immunology, sleep disorders, infectious diseases, epidemiology, as well as experts from Health Canada, the World Health Organization (WHO) and the ECDC, to consider the latest available data regarding the possible link between Pandemrix and narcolepsy.

The CHMP considered that the epidemiological studies relating to Pandemrix in Finland and Sweden were well designed and the results show an association between Pandemrix vaccination and narcolepsy in children and adolescents in those countries. The results indicate a six- to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children and adolescents, corresponding to about an additional three to seven cases in every 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years). A similar risk has not been confirmed but cannot be ruled out in other countries.

The Committee noted that the vaccine is likely to have interacted with genetic or environmental factors which might raise the risk of narcolepsy, and that other factors may have contributed to the results. There are several initiatives being developed across the EU to further investigate this association.

The CHMP noted that similar epidemiological studies have not been completed in other countries. The preliminary results of the VAESCO study confirmed the signal in Finland. Results are still preliminary and do not allow conclusions in other countries (where vaccination coverage with Pandemrix was lower), but the final results of the VAESCO study are still awaited.

Exposure to specific infectious diseases (including H1N1) at different ages, particularly upper respiratory infections, may have contributed to the observations in the Nordic area. The CHMP considered that it would be helpful if ongoing epidemiological studies seek to address this question [44].

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Annex 1 Country-specific comments and disclaimers

Finland: National Institute for Health and Welfare

We are unable to subscribe to the conclusions presented in the VAESCO report. The details of this disclaimer are presented below.

The VAESCO narcolepsy study is an enormous and ambitious multinational effort for the investigation of the association between pandemic vaccination and narcolepsy. The study report describes extensively and in detail the background of the study, country-specific data sources, case and onset definitions, various sensitivity analyses, and the challenges in investigating such a rare disease. Challenges in pooling data from heterogeneous data sources are also highlighted. However, our position is that fundamental concerns related to pooling heterogeneous data are not reflected in the key findings nor in the overall conclusions of the study. In the following, we present our concerns related to standardisation and pooling. Our position is that unsubstantiated pooling of data may lead to misinformed interpretations regarding e.g. diagnostic bias and, subsequently, erroneous overall conclusions.

The focus of the study was to investigate the association between narcolepsy and pandemic vaccination in children and adolescents. This requires populations under study with sufficient genetic predisposition to narcolepsy, as well as sufficient amount of exposure to the vaccine in the age-group with the signal. This was not the case for most of the 'non-signalling' countries, where there were e.g. zero exposed cases in Netherlands, Denmark, UK and Italy during the primary follow-up period. However, the data from all these countries is pooled to draw inference from the 'non-signalling' countries, and misleadingly expressed as a representative result from six countries.

The study combined data from areas with well- and less well-defined source populations which e.g. resulted in highly variable selection methods for controls in e.g. Italy, Netherlands and France. This fundamental problem is highlighted by the disclaimer provided by the French investigators. After excluding countries with low or zero exposure, and the potentially biased data from France (based on the disclaimer), the only country with exposure similar to the 'signalling countries' (Finland and Sweden) is Norway. The key findings should more clearly state these inherent deficiencies in power and lack of data comparability from all other countries except Norway.

Based on Finnish data alone, there is clear distinction between children and adults in onset definitions: in adults, confirmed cases diagnosed in 2009-2010 had a median lag of 5 years between EDS onset and referral to specialist. However, in children the median lag from onset to referral was 5 months. This is likely explained by the sudden surge of cases in children with abrupt and severe symptoms in early 2010[1,2], which mainly occurred in an age group where the onset of narcolepsy has in previous years been virtually nonexistent (age group 5-15). Diagnostic workup is highly influenced by, among others, the local health care systems, abruptness of symptoms and age of the patient. This indicates that the primary onset definition (referral) lacks comparability even within country-specific data, and therefore most likely also between countries. Failure to account for the experience in local diagnostic practises in the report when interpreting different onsets is exemplified by the Norwegian disclaimer.

One of the reported key findings is that median times from onset to diagnosis are shorter in the exposed than in unexposed cases. This concern of accelerated diagnosis among vaccinated is highlighted as the most central challenge in the investigation of this association. This is also the rationale for restricting primary analysis to cases referred to MSLT prior July 2010. The drawback of this approach is that due to delays in diagnosis, the number of cases to be included in the primary analysis, and subsequently the power of the study is severely hampered.

The conclusions in the report highlight the importance of addressing the multitude of time-related biases. Furthermore, significant association in the majority of sensitivity analyses in children and adolescents based on Norwegian data is interpreted as supportive evidence of such bias. Since the diagnostic bias is highlighted as the most important challenge in the study, it is regrettable that this important issue is addressed simply by excluding majority of cases for the primary analysis: Based on Finnish data, this has been investigated by using different onset definitions, follow-up periods, and comparative age groups. All sensitivity analyses gave consistent results, suggesting that the observed association between narcolepsy and pandemic vaccination in children and adolescents was not solely due to diagnostic bias [3].

Furthermore, recent follow-up data from Finland show that further 50 confirmed cases have been diagnosed in 2011, 47/50 of them vaccinated [4]. Similarly, the data from Norway in the VAESCO report include cases up until 2011, so far without indication of increase in unvaccinated cases. Arguably, continuous follow-up provide more convincing evidence for or against bias due to accelerated diagnosis than median times between onset and diagnosis, which were derived in the VAESCO report by pooling data across countries with varying diagnostic practises.

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France: National Agency of Medicine and Health Product Safety

As underlined in the report, there is a possibility that the cases presently included in the analysis for adults for the primary period have higher rate of exposure than other eligible cases not presently taken into account because of absence of matched controls. At the time of the VAESCO study data lock, the recruitment of case and control was still ongoing in France. The results herein presented should therefore only be considered as preliminary. From that time, almost all French eligible cases have been matched with at least one control, which clearly decreases the possibility of the initially envisioned potential selection bias. Statistical analysis on the overall French data is currently being finalised. Data regarding additional French cases and matched controls will be integrated into further statistical analyses planned to be conducted by VAESCO for the publication of the pooled analysis results.

Norway: Norwegian Institute of Public Health

The Norwegian position is that the VAESCO primary analysis is hampered by too strict exclusion criteria and hence a lack of power. According to the Norwegian investigators the best way to understand the Norwegian data is to look at the total (secondary) study period.

Annex 2 Research groups

Study ID	VAESCO-Narcolepsy
Short title	Infections, vaccinations and narcolepsy
Protocol Version	4.2
Date of publication	September 2012
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