LÄKEMEDELSVERKET
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Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations
- Results of a case inventory study by the MPA in Sweden during 2009-2010

ABSTRACT

In Sweden, an unexpectedly large number of reports of narcolepsy in children and adolescents after vaccination with Pandemrix were received by the Medical Products Agency (MPA) from the summer of 2010. As reported in March 2011, a registry based study of four counties/regions, comprising 57 percent of the Swedish population, showed a four-fold higher risk of having narcolepsy diagnosed in vaccinated versus non-vaccinated subjects.

This report describes the Case Inventory Study which was undertaken by the MPA to study narcolepsy with cataplexy in children/adolescents 19 years and younger, specifically to measure the incidence of narcolepsy with cataplexy over time, to calculate risk in relation to vaccine exposure, and to describe case characteristics.

Information on all established and suspected cases of narcolepsy from 2009-2010 was collected from relevant clinical departments and sleep laboratories. Medical records were scrutinized by two clinical experts to classify the diagnosis according to the American Academy of Sleep Medicine criteria for narcolepsy with cataplexy, to estimate the time of onset of first narcolepsy symptoms, and to describe clinical features. In case of disagreement a third expert made an independent review, and consensus was sought.

81 cases of narcolepsy with cataplexy with an onset of symptoms during the study period January 1st 2009-December 31st 2010 were ascertained, of whom 69 (85%) had been vaccinated with Pandemrix before symptom onset. The population incidence rates peaked during the last quartile of 2009 and first quartile of 2010 to a highest level of 6.58/100 000 - in parallel with the H1N1 pandemic activity and the population wide vaccination campaign – thereafter declining successively.

A retrospective cohort study of vaccinated and non-vaccinated children/adolescents followed subjects from the beginning of the pandemic period October 1st 2009 until the end of 2010; it revealed an almost seven-fold higher incidence of narcolepsy with cataplexy in those vaccinated compared to those who were not vaccinated. The incidence rates were measured to be 4.2 per 100 000 in the vaccinated cohort, compared to 0.64 per 100 000 in the non-vaccinated cohort, yielding a relative risk of 6.6 (95% CI 3.1-14.5) and an absolute risk of 3.6 additional cases per 100 000 vaccinated subjects. The incidence was substantially higher within 3 months of the vaccination, 14.1/100 000 compared to 1.3/100 000 in the later time window.

Cases that occurred after vaccination had a higher prevalence of cataplexy as one of the initial symptoms (43% versus 8%, $p = 0.02$), and of greater than two initial symptoms (46% versus 17%, $p = 0.05$).

These new data from Sweden provide strengthened evidence that vaccination with Pandemrix is associated with an increased risk for narcolepsy with cataplexy in children and adolescents. Further cross-disciplinary and long-term follow-up research is urgently needed to explain possible causative mechanisms.

Introduction

In Sweden, a population vaccination campaign was carried out with the H1N1 pandemic vaccine Pandemrix from mid-October 2009 through March 2010. There was an estimated participation of over 6 million people, corresponding to a vaccine coverage of about 60 percent. Enhanced pharmacovigilance activities were enforced during and after this period in Sweden as in many other EU countries. This included stimulated ADR reporting and epidemiological follow-up studies.

The first cases of narcolepsy in children were reported to the MPA in the spring of 2010. Shortly after a newspaper report about a case of narcolepsy after Pandemrix vaccination was published that summer, an escalating number of reports of cases of narcolepsy in children/adolescents were received by the MPA, around the same time, there were an increasing number of reports being noted also in Finland. A similarly strong signal had not been previously reported from any other country where Pandemrix had been used.

The signal in Sweden stimulated reviews with participation of national experts, epidemiological studies, and sharing information to the public. In March 2011, the MPA presented results from a registry study showing a four-fold increased risk among vaccinated versus non-vaccinated children/adolescents, but no change of the risk in adults (1). This cohort study, performed in collaboration with health care authorities in four counties/regions and the Karolinska Institute, utilized *ad hoc* vaccination registration and outcome data from their local health databases. In Finland, a population based registry study provided evidence of a nine-fold increased risk of narcolepsy in vaccinated versus non-vaccinated children/adolescents with an age of 19 years or younger (2). On the basis of these signals in Sweden and Finland, an EU safety referral for Pandemrix was started in September 2010.

Another initiative by the MPA was the current narcolepsy Case Inventory Study. This 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 January 1st 2009 – December 31st 2010 and to ascertain which of those cases had onset of first symptoms within the study period, with the objectives to:

- 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;

- 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.

In the planning phase of the study, experts advised that there should be a focus on cases of narcolepsy *with cataplexy* as it is the most severe and most readily defined form of narcolepsy (as classified from criteria by the American Academy of Sleep). Further, since there was no evidence of an increased risk for narcolepsy in adults in the previous studies, it was decided to focus on children/adolescents.

Material and methods

Case ascertainment involved contact with clinical departments at hospitals in Sweden that were involved in the review and diagnosis of cases of narcolepsy (e.g. departments of neurology, paediatrics, paediatric neurology, or paediatric psychiatry) as well as sleep laboratories and laboratories of clinical physiology, which perform multiple sleep latency tests (MSLT), An additional source was the MPA database on spontaneous ADR reports on narcolepsy. Medical records were collected for cases which had been diagnosed or were under review during 2009 through 2010.

Two external clinical experts in neurology/sleep disorders were commissioned by the MPA to review the medical records of all the collected cases focusing specifically on cases of narcolepsy *with* cataplexy. The main objectives of the review were to classify the diagnosis according to the American Academy of Sleep Medicine criteria for narcolepsy with cataplexy (3, Appendix 1) and to assess the onset of the narcolepsy disease through dating of the first symptom of narcolepsy. The two experts made their assessments independently of each other.

For cases where the two reviewers came to different conclusions regarding the diagnostic classification of narcolepsy with or without cataplexy, a *third review* was performed by an external expert in paediatric neurology. The third reviewer also scrutinized cases for which there were discrepant estimates of the date of onset of narcolepsy disease. Thereafter, a discussion was held among the three reviewers in order to arrive at a consensus. Figure 1 shows the final results of this review.

For all cases included in the study, information on the vaccination with Pandemrix (date of dose 1 and 2, and batch numbers) was obtained from vaccination records in the respective regional vaccinating health care units.

- Analyses of population incidence trends

For the descriptive analysis, the numbers of cases by gender and age groups (0-4, 5-9, 10–14, 15–19), from the six health care regions of Sweden, were analyzed during different time periods over the study period. The first analysis looked at the distribution of cases over yearly quartiles (3 month intervals, 8 periods). The second analysis looked at the distribution of cases over time intervals defined in relation to the pandemic: Jan 1, 2009 - Sept 30 2009 ('pre-pandemic' period), October 1, 2009 – March 31, 2010 'pandemic/vaccination' period, and April 1, 2010 –31 December 2010 as 'post pandemic/vaccination period'). The number of cases was related to the general population figures (person-time) to calculate the corresponding population incidence rates. The Confidence Limits were based on the 95% Poisson variation of the number of cases.

- Comparison of incidence rates in vaccinated and non-vaccinated cohorts

Cases of narcolepsy with cataplexy, defined by date of onset of disease (first symptom), were related to person-years of observation in vaccine exposed versus un-exposed children/adolescents, both overall and in defined age groups (≤ 9, 10 – 14, 15 – 19). In this analysis, *incident exposed cases* were defined as having the date of vaccination before the date of first symptom of narcolepsy.

The person-year experience at risk in the target population was extrapolated from the previous registry study which was performed in the populations of four counties/regions in Sweden (Stockholm county, Västra Götaland region, Östergötland county and Skåne region), comprising 5.3 million inhabitants (57 % of the Swedish population) (1). In these areas all vaccinated individuals had been included in vaccination registers which enabled definition of cohorts of vaccinated and non-vaccinated cohorts and their person-time and in local databases with registration of hospital admissions and specialist care which provided diagnoses of narcolepsy cases in the cohorts.

The risk time (person-years) in vaccinated subjects was calculated from the date of the first vaccination until the end of the study period (December 31, 2010). The risk time in non vaccinated subjects was counted from October 1, 2009 until the end of the study period or the date at which they were vaccinated.

Vaccine coverage in the four-county registry study population younger than 20 years (1.25 million subjects) was 67.1%. This was deemed to be representative of the whole Swedish population for this age group. The risk time was extrapolated from the registry study to the current study of the entire Swedish population. The basis for calculations of person-years is given in Appendix 2.

The incidence rates were calculated by dividing the numbers of incident cases by the estimated person-years of observation, comparing the rates of narcolepsy in those who were exposed to the rates in those who were non-exposed. The ratio of the incidence rates was the relative risk (RR) and the difference in incidence rates was the absolute risk; 95 percent confidence intervals (CFI) were calculated on the basis of Poisson regression.

In addition to the overall analysis of narcolepsy incidence with cataplexy, analysis was also made for *time windows* after vaccination, i.e. up through 3 months, and beyond.
Also, a sensitivity analysis was performed after reclassifying the five cases with exposure to vaccination during the same month as onset of symptoms as exposed.

- Comparison of characteristics for vaccinated and non-vaccinated cases
Data on the cases were tabulated and compared by vaccination status regarding age, gender, first registered symptom, number of symptoms registered during the first month, proportions with positive Multiple Sleep Latency Test (MSLT), levels of hypocretin, proportions with 2 specific HLA haplotypes, normal Magnetic Resonance Tomography (MRT) or Computerized Tomography (CT) and with abnormal weight gain.

Results

Overview of data collection

132 medical records of the 135 cases identified for review were retrieved for the study period (Figure 1).

87 cases of narcolepsy with cataplexy were confirmed.

There were 18 cases that were determined not to have a diagnosis of narcolepsy, and there were 8 cases which had insufficient data to make the diagnosis.

There were 10 cases for which the two reviewers had discrepant views regarding the diagnosis of narcolepsy. In none of these 10 cases was cataplexy deemed to be present.

Narcolepsy *without cataplexy* was observed in 9 cases, of whom 4 had been vaccinated. These cases are *not* further analyzed in this report.

I: Occurrence and incidence of narcolepsy with cataplexy in the entire Swedish population and *during the two-year study period* January 1st, 2009 – December 31st, 2010.

Overall, 87 cases of narcolepsy with cataplexy were ascertained for the whole study period (*Figures 1, 2*). Among them 69 had been vaccinated before onset of the first symptom. There were 13 cases with symptom onset before vaccination or who had not been vaccinated; 6 of these had

symptom onset before January 1st 2009. These 6 cases were excluded from the analyses, leaving 7 non-vaccinated cases during the study period. Five cases had symptom onset during the same month as the vaccination; for the main analysis, these were classified as non-exposed. The detailed analysis in this study therefore includes a total of *81 cases*; 69 vaccinated and 12 cases classified as non-vaccinated (7 non-vaccinated cases plus 5 cases with symptom onset in the same month) (Figure 2).

Table 1a and Figure 3 show the distribution of cases by quartiles of the two study years, both overall and by age groups. The numbers of cases by age groups corresponded to the following incidence *rates* (per 100 000 person-years): 0.18 (0-4 year age group), 2.18 (5-9 years), 3.52 (10-14 years) and 1.72 (15-19 years). In the first three quartiles of 2009, 5 cases were observed; in quartile 4 of 2009 and quartiles 1 and 2 of 2010, there were 27, 36 and 11 cases, respectively; and in quartiles 3 and 4 of 2010, there were 2 cases. The overall incidence rate was 1.85 per 100 000; the rates in the three high-risk quarters were considerably higher, 4.94, 6.58, and 2.0, respectively, compared to the nine months prior to the pandemic period (0.18, 0.37) and the last six months of 2010 (0.18)

Data were also compiled for the three defined periods. In the *pre-pandemic* period of January 1st through September 2009, 5 cases were ascertained, corresponding to an incidence rate (per 100 000 person-years) of 0.31; in the subsequent *pandemic-vaccination* period October 1st, 2009-March 31st, 2010, there were 63 cases, yielding an incidence rate of 5.78; and in the *post-pandemic -vaccination* period April 1st - December 31st, 2010, there were 13 cases with an incidence of 0.79 (data not otherwise shown).

Figure 3 demonstrates the peak in incidence of narcolepsy with cataplexy in the 9 months of the pandemic period and a marked decline in the last 6 months of the study period.

Table 1 b and Figure 4 display the incidence rates per 100 000 person-years in the six health care regions in Sweden. The rates seem to vary with the latitude of the region. The most southern regions (South, South-East and West) showed the highest rates of 2.99, 2.14, 2.31, the middle regions (Uppsala/Örebro and Stockholm) somewhat lower rates of 1.88 and 0.99, and the northern region (North) the lowest rate of 0.25.

II. Comparison of incidence for narcolepsy with cataplexy in vaccinated and non-vaccinated children/ adolescents *during the pandemic period from October 1st, 2009*.

Total incident cases of narcolepsy with cataplexy among vaccinated subjects, with onset of narcolepsy symptoms after the date of vaccination, was 69. For comparison, cases classified as non-exposed, i.e. cases that occurred *during the pandemic period* (i.e. from October 1st 2009) and where there was no exposure to vaccination or where vaccination had occurred after onset of symptoms or during the same month as onset of symptoms, was 7.

Since there is no nationwide vaccination register, it was not possible to calculate the risk time directly for the total vaccinated and non-vaccinated cohorts in all of Sweden. However, risk time was extrapolated from the previous registry study (1) in four counties/regions of Sweden where vaccination registration was applied, as described in the material and methods section.

Calculations of incidence rates for all ages up through 19 years, and in the three age groups 0-9 years, 10-14 years and 15-19 years, are presented in table 2. 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 person-years, yielding a relative risk of 6.6 (95% Confidence Interval 3.1-14.5) and an absolute risk of 3.6 additional cases (95% Confidence Interval 2.5-4.7) per 100 000 vaccinated subjects.

Among the age groups in the vaccinated cohort, the incidence rates were numerically the highest in the 10-14 year age group, 6.2 per 100 000, followed by the 15-19 and ≤ 9 year groups, 5.7 and 2.6 per 100 000, respectively. In the non-vaccinated cohort, estimates by age groups were uncertain due to the small numbers.

Of the 69 cases, 53 cases (76.8%) had onset of symptom within three months after the date of vaccination, and 16 cases (23.2%) had onset of symptom later than three months after vaccination. The overall incidence during the first three months of follow-up was 14.1 per 100 000 and in the later time window 1.28, per 100 000 person-years. In relation to the incidence in the unexposed cohort, the rate for the early three-month window corresponded to a relative risk of 22.0 (95% Confidence Interval 10.0-43.4) and for the later window a relative risk of 2.0 (95% Confidence Interval 0.8-4.9).

As a sensitivity analysis, the five cases with vaccination and first symptom during the same month were reclassified as exposed, leading to overall incidence rates of 4.6 and 0.18 per 100 000 in the exposed versus non-exposed cohorts, respectively, implying an higher relative risk estimate than in the main analysis.

III. Some characteristics of the cases, by vaccination status

In Table 3a gender, age and symptoms, were compared by vaccination status. There were no significant differences between vaccinated (69) and non-vaccinated (12) cases with regard to gender and age distributions. Median ages of the vaccinated (range 3-19 years) and non-vaccinated (range 6-17 years) cases were 13 and 12 years, respectively. It is of note that among the vaccinated cases there was one child 3 years and another 4 years of age.

Virtually all cases started with daytime sleepiness, whereas cataplexy in the month of onset was more frequent in vaccinated cases, 43%, than in non-vaccinated, 8% (p =0.02). Also hypnagogic hallucinations, disturbed night time sleep and sleep paralysis were more frequently described in those who were vaccinated, but the differences were non-significant. The presence of two or more simultaneous symptoms during the first month was more frequent in vaccinated versus non-vaccinated cases, 46% versus 17% (p =0.05).

As to laboratory findings, Table 3b, data were available for all cases regarding the MSLT test variable, which was confirmed positive for 88% of the vaccinated and 75% of the non-vaccinated cases. Hypocretin levels, available for 35% of the vaccinated and for 42% of the non-vaccinated cases, showed no statistically significant differences. It is noteworthy that in the exposed cases 75% of the subjects had levels below 41.5 pg/ml, and that both exposed and unexposed cases had median values below the detection limit (10 pg/ml). Genotype data were available for less than one third of the vaccinated cases; in those tested the two genotypes HLA DQB1*0602 and HLA DRB2 (DRB1*1501) were positive in virtually all vaccinated cases (96% and 94%, respectively). For the non-vaccinated cases, only a few tested cases were available, precluding interpretation of numerical differences. Magnetic Resonance Tomography (MRT)/ Computerized Tomography (CT) had been performed in 57% and 75% of the cases with normal findings in almost all cases.

Data on abnormal weight gain was present in more than 70% of the cases, showing a higher (non-significant) prevalence in the vaccinated cases as compared to the non-vaccinated, 65% and 33%, respectively (p = 0.08).

Discussion

This case inventory study identified 81 cases of narcolepsy with cataplexy (85% being vaccinated with Pandemrix) of ages 19 and younger that had an onset of first symptom of narcolepsy during the two-year study period January 1st through December 31st 2010. Analysis of these cases yielded the following key findings.

Firstly, a peak in the incidence of narcolepsy with cataplexy following the H1N1 activity and pandemic vaccinations was observed (*Table 1a, Fig. 3*). The overall incidence was low before the pandemic period, 0.2-0.4/100 000 person-years. From the third quartile of 2009, when the H1N1 pandemic escalated and the pandemic vaccinations were performed on a population wide level, the incidence rose steeply to a level of 4.94/100 000, and further to 6.58/100 000 in the first quartile of 2010 when the pandemic was waning and the vaccination campaign ending. From the second quartile of 2010 the incidence declined to a level of 2.0/100 000 and further to a low level of 0.2/100 000 in the last two quartiles of 2010.

The incidence rates varied by age, being around 2/100 000 in the 0-9 year age group, 3.5 in the 10-14 year age group and 1.7 in the 15-19 year age group.

Also, there seemed to be a pattern in the incidence with latitude (Table 1b, Figure 4). In the three health care regions in the southern part of Sweden the rates ranged from 2.14 to 2.99/100 000, in the two regions in the mid-part from 0.99 to 1.88/100 000, whereas in the northern region the rate was the lowest, 0.25/100 000.

Secondly, an increase in the *overall* relative risk and absolute risk for narcolepsy with cataplexy in association with pandemic vaccinations was found (*Table 2*). The rate was 4.2/100 000 in the vaccinated cohort and 0.64/100 000 in the non-vaccinated cohort, yielding a relative risk of 6.6 (95% Confidence interval 3.1-14.5) and an absolute risk (incidence rate difference) of 3.6 cases per 100' (95% Confidence Interval 2.5-4.7). In the vaccinated cohort, the incidence rates varied by age, being the highest in the 10-14 and 15-19 year age groups, 6.2 and 5.7, as compared to 2.6/100 000 in the 0-9 year age group.

When reclassifying, for the purpose of a sensitivity analysis, those 5 cases with vaccination and symptom onset during the same month in the unexposed cohort to the exposed cohort, the relative risk estimate increased further but was imprecise due to the presence of only two cases in the non-vaccinated cohort.

In an early 3-month *time window* after the vaccination, the incidence was higher than in the window beyond three months, the incidence rates being 14.1 and 1.3 per 100 000 person-years, respectively. In relation to the non-vaccinated cohort, the relative risk was 22.0 (95% CFI 10.0-48.3) in the 3-month window and 2.0 (95% Confidence interval 0.8-4.9) in the later window.

Thirdly, cases occurring after vaccination seemed to be different from those non-vaccinated regarding some characteristics described in the medical records. The vaccinated cases appeared more likely than non-vaccinated cases to present with cataplexy during the month of onset, (43% versus 8%), and with two or more simultaneous symptoms, 46 % versus 17 % (Table 3a). As to laboratory results, no differences could be identified but results are uncertain due to limited availability of data.

In summary, there was an increase in the incidence of narcolepsy with cataplexy in children/adolescents during and shortly after the H1N1 pandemic period. There was an increased risk of almost seven-fold for diagnosis of narcolepsy with cataplexy in those who received vaccination with Pandemrix, with the highest risk noted within months of the exposure. Cases

occurring after vaccination may have a different phenotype than non-vaccinated cases, given the characteristics of presenting more often with cataplexy as a first symptom and with more than two simultaneous symptoms.

Several strengths of the present study should be acknowledged. Medical records were scrutinized by two independent clinical experts and upon disagreement through consensus with a third expert, which enabled criteria based classification of cases, description of case characteristics, and determination of the date of disease onset. Even though there was no national vaccination registry during the pandemic period, risk time experience from the previous registry study could be used and extrapolated to the national level for this study. The classification of disease onset from medical records was important, since this time definition is deemed to be less sensitive to bias than time of diagnosis, as discussed in the previous registry study (1). The approach used was to catch *all potential* cases through both clinical departments and sleep laboratories, irrespective of vaccination status. Vaccination status was determined from vaccination records.

Also, some weaknesses should be taken into account. There is at present, pending national statistics on narcolepsy occurrence for 2010, no reference to assess the completeness of case enrolment through the inventory approach. Due to the extensive efforts to identify the relevant various clinical and laboratory departments and to remind responsible clinicians to respond to the requests, it is deemed that the enrolment was fairly complete. Furthermore, the inventory, which was independent of the MPA ADR reporting system, should have covered cases irrespective of vaccination status. Nevertheless, the yield of cases from the case inventory study needs to be compared to national statistics for 2010 as soon as they become available.

The possibility for stimulated and selective information from patients/parents and prescribers/physicians and possible biased detection are other important issues. The fact that all the studied cases had narcolepsy *with cataplexy*, which is a severe and specific symptom, should reduce the possibility for detection bias.

It is possible that the first 6 reported cases after Pandemrix vaccination to the MPA from the Skåne region in the spring and summer of 2010 spurred awareness among professionals. However, it was not until August 2010 that the potential narcolepsy-vaccination association became known to the public due to a tabloid paper article on a paediatric case. The date of disease onset was used in relation to both the pandemic period and the vaccination activities to characterize the relationship between exposure and outcome more accurately and thereby reduce the possible bias. It is noteworthy that of the 81 studied cases, 79 (98%) had onset of symptoms before July 1st, 2010

The approach to extrapolate vaccine exposure risk time from another study, performed in part of the population (57%), may entail errors. However, it is likely that the vaccination activities in the four counties/regions, with a vaccine coverage of 67.1% for the targeted age groups, represented the experience for all of Sweden. This conclusion is supported by information from three other counties in Sweden in which vaccine coverage was of similar magnitude overall and in age groups. Differences in time of start for the vaccination campaigns between counties, influencing risk time, are likely to be small, since the vaccinations were performed within a few months time after the vaccine became available in mid-October 2009.

There was no access to data on possible confounders. Confounding is not likely to be a major problem for the interpretation of the results. First, the target group is children/adolescents in whom little co-morbidity (that could theoretically be related to both the risk of narcolepsy and likelihood of vaccine exposure) is expected. Second, risk factors for narcolepsy are not well characterized.

Currently, there are only two other reports from epidemiological studies on the risk of narcolepsy in relation to the H1N1 pandemic and pandemic vaccination, i.e. the report from the National Institute for Health and Welfare in Finland in February 2011 (2) and from Medical Products Agency in Sweden March 2011 (1). Results from the VAESCO case-control study in several European countries are pending. The present case inventory study contributes new and more extensive information for the Swedish setting. It examines cases with a *validated* diagnosis of narcolepsy with cataplexy and with a defined date of onset, shows patterns of incidence for the *whole* country as well as between vaccine exposed and unexposed cohorts over different time periods and windows, and characterises some phenotype differences between vaccinated and non-vaccinated cases. One important advantage with the present study is that date of onset of symptoms could be related to time of exposure, reducing the problem of detection bias which was a concern in the registry study using date of diagnosis.

These new results provide strengthened evidence for an increase in the risk of narcolepsy with cataplexy, which is greatest within a few months after the vaccination with Pandemrix. A remaining question is whether the incidence returns to baseline rates or below over time. Even if the relative risk was high, the overall absolute risk over the study period was rather low, 3.6 additional cases per 100 000 vaccinated subjects.

Of interest is the observation of different incidence rates in different parts of the country, the higher rates in the more southern parts. Even though such a gradient has not been statistically verified, different reasons may be considered. One reason may be different detection rates in different parts of the country. This is unlikely due to the focus on narcolepsy with cataplexy, the extended study period during which such cases should have been captured and the approach for collecting data through clinical departments in all parts of the country. If real, however, the time dynamics of the H1N1 influenza and of vaccination activities in different parts of the country may have been of importance. It would be of interest to collect such region specific data and to explore ecological patterns that could give clues on possible joint effects between the vaccine and the H1N1 influenza.

The risk estimates in this study were somewhat higher than in the previous registry study, which may be explained by a number of aspects, e.g. a more complete ascertainment of cases from the health care system, a more careful case classification, the focus on narcolepsy with cataplexy and a more precise definition of vaccine exposure and disease onset.

These results can be compared with the first and preliminary results of the Finnish registry study (2). On the basis of 52 vaccinated and 8 non-vaccinated cases of 'confirmed narcolepsy' (according to Brighton criteria) in children and adolescents 19 years and younger, about a 9-fold increase in the risk was found after 8 months of observation, while in the Swedish study the risk increase was almost seven-fold and peaked within three months after the vaccination. Some features differing between the Swedish and Finnish studies may be worth noting; the Finnish study included 'confirmed' cases, not only those with cataplexy as in the Swedish study; the observation period in the Finnish study was ended on August 16, 2010, in order to minimize bias due to media attention; and onset of disease in the Finnish study was defined as the first health care visit due to sleep disturbance. Even though the designs of the Finnish registry study and the present case inventory study are similar, the different methodological approaches, in addition to random variation, may explain the differences in magnitude of the excess risks between the two studies.

Thus, there is evidence from epidemiological studies of an association between Pandemrix vaccination and narcolepsy in both Sweden and Finland. These findings raise new issues for research. What is the role of this particular vaccine, e.g. the adjuvant? Is this risk relationship present only in Sweden and Finland? If so, can other factors act jointly with the vaccine to cause

narcolepsy? Can the H1N1 influenza *per se* or together with the vaccine be causative? Are there specific susceptibility factors? What could be the mechanisms of causation?

In order to better understand how the increased risk has occurred, knowledge from further epidemiological studies during an extended follow-up and through a multi-national case-control study, and from genetic and immunological studies, now in the pipeline, will be of crucial importance.

Conclusion

The incidence of narcolepsy with cataplexy in children/adolescents in the Swedish population increased during the pandemic and vaccination period, with a rapid decline in incidence during the post pandemic period. Subjects who had been vaccinated with Pandemrix were at a 6.6-fold increased risk to develop narcolepsy with cataplexy compared to those who had not been vaccinated. Cases of narcolepsy with cataplexy with onset after vaccination had a higher prevalence of cataplexy as a first symptom and of two or more simultaneous symptoms as compared with non-vaccinated cases.

These new results provide strengthened evidence that vaccination with Pandemrix during the pandemic period was associated with an increase in the risk for narcolepsy with cataplexy in children/adolescents 19 years and younger. Further research is urgently needed to explain the possible causative mechanisms.

References

1. A registry based comparative cohort study in four Swedish counties of the risk for narcolepsy after vaccination with Pandemrix - A first and preliminary report, by the Medical Products Agency, March 28, 2011, www.mpa.se

2. National Narcolepsy Task Force Interim Report, 31 January 2011, National Institute for Health and welfare (THL), www.thl.fi

3. American Academy of Sleep Medicine. The International Classification of Sleep Disorders: diagnostic and coding manual. 2nd ed. Chicago, IL: AASM, 2005

Table 1a. Numbers of narcolepsy (with cataplexy) cases with symptom onset January 1st 2009-Deecember 31st 2010, in subjects born after 1990, overall and by age groups. Population based Incidence Rates per 100 000 person-years, 95% Confidence Limits (CFL).
Description of age relation and time trends by quartiles of years.

		Quartiles, 2009 – 2010								All
		09-Q1	09-Q2	09-Q3	09-Q4	10-Q1	10-Q2	10-Q3	10-Q4	
		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)

*one 3 year and one 4 year old child

Table 1b. Numbers of narcolepsy (cataplexy) cases with symptom onset January 1st 2009-December 31st 2010, in subjects born after 1990, overall in the six health care regions of Sweden. Population based Incidence Rates per 100 000 person-years, 95 % CFL.

	Health Care Region						All
	Uppsala-Örebro	South	South-East	West	Stockholm	North	
	N	N	N	N	N	N	N
All	17	26	10	17	10	1	81
Incidence rates (100') 95 % Confidence Limits	1.88 (1.00, 2.88)	2.99 (1.95, 4.13)	2.14 (0.86, 3.64)	2.32 (1.23, 3.54)	0.99 (0.40, 1.69)	0.25 (0.00, 0.76)	1.85 (1.46, 2.26)

Table 2: Incidence rates in vaccinated versus non-vaccinated subjects; Incidence Rate Ratios (Relative Risk, RR), Incidence Rate Difference (Absolute risk, AR), 95 % Confidence Interval (CFI)

	Vaccinated	Non-vaccinated	Vaccinated vs non-vaccinated
	# cases, Person-years[1], Incidence rates/100'	# cases, Person-years[1,2], Incidence rates/100'	RR, AR, 95% CFI
All	69 / 1624'= 4.2	7 / 1093' = 0.64	RR= 6.6 (3.1-14.5) AR= 3.6 (2.5-4.7)
≤ 9	21 / 815'= 2.6	3 / 486' = 0.62	
10-14	27 / 439' = 6.2	4 / 155' = 2.5	
15-19	21 / 370' = 5.7	0 / 236' = 0	

[1/] Risk time, person-years of observation was derived and extrapolated from a population-based comparative registry-based cohort study of Pandemrix and narcolepsy diagnoses in four counties/regions of Sweden covering 5.3 million inhabitants (57 % of the population) (1). See appendix 2.

[2/] Cases and person-years for the non-vaccinated cohort were derived from the pandemic period, i.e. from October 1st 2009.

Table 3a: Case characteristics: gender, age and symptoms, by vaccination status

	Vaccinated (69 cases)	**Non-vaccinated (12 cases)**	**Difference (p value)**
Sex: - Male - Female	 32 (46%) 37 (54%)	 4 (33%) 8 (67%)	P= 0.4013
Age - median - range	 13 years 3-19 years	 12 years 6-17 years	
First symptom: (%) - Daytime sleepiness - Cataplexy - Hypnagogic hallucination - Disturbed night time sleep - Sleep paralysis	 67 (97%) 30 (43%) 6 (9%) 7 (10%) 3 (4%)	 12 (100%) 1 (8%) 0 1 (8%) 0	 P= 0.0208
# symptoms 1st month: (%) - One - Two, or more	 37 (54%) 32 (46%)	 10 (83%) 2 (17%)	 P= 0.0543

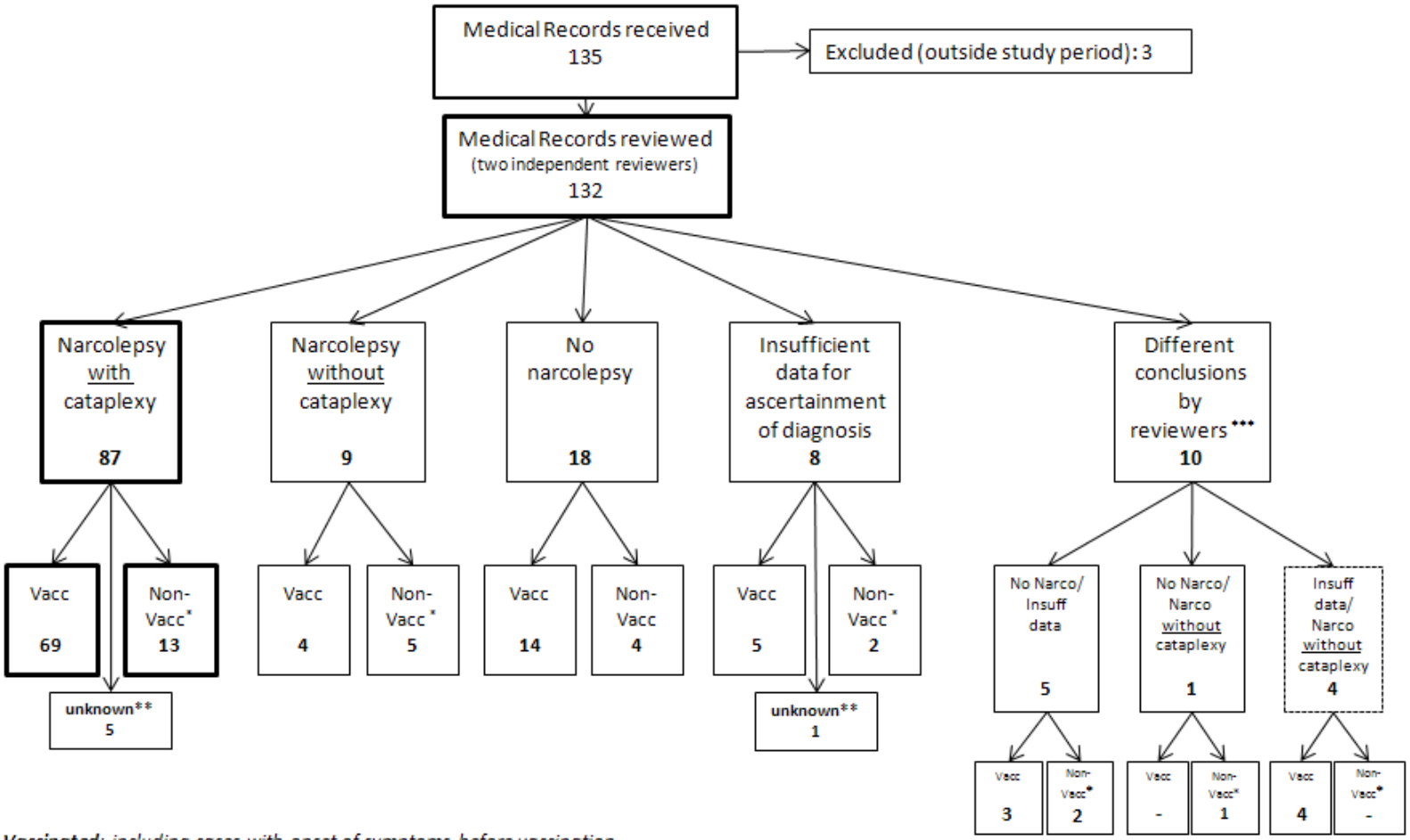
Table 3b: Case characteristics: laboratory findings, by vaccination status

	Vaccinated (69)	Non-vaccinated (12)	Difference (p value)
Hypocretin - Data available - Level: pg/ml*	 24/69 (35%) Min: <10 Median: <10 Mean: 26 Max: 131 Std: 39.8 Q1: <10 Q3: 41,5	 5/12 (42%) Min: <10 Median: <10 Mean: <10 Max: 24 Std: 11.7	
MSLT - Data available - Positive** (%)	 69/69 (100%) 61/69 (88%)	 12/12 (100%) 9/12 (75%)	
HLA DQB1*0602 - Data available - % Positive	 27/69 (39%) 26/27 (96%)	 7/12 (58%) 7/7 (100%)	
HLA DRB2 - Data available - % Positive	 18/69 (26%) 17/18 (94%)	 3/12 (25%) 3/3 (100%)	
MRT/CT normal - Data available - % Normal - % Abnormal	 39/69 (57%) 35/39 (90%) 4/39 (10%)	 9/12 (75%) 9/9 (100%) -	
Abnormal weight gain, Y/N - Data available - % Yes	 48/69 (70%) 31/48 (65%)	 9/12 (75%) 3/9 (33%)	 p=0.0795

*detection limit= 10 pg/ml

** MSLT results regarded as supportive of narcolepsy diagnosis by both reviewers

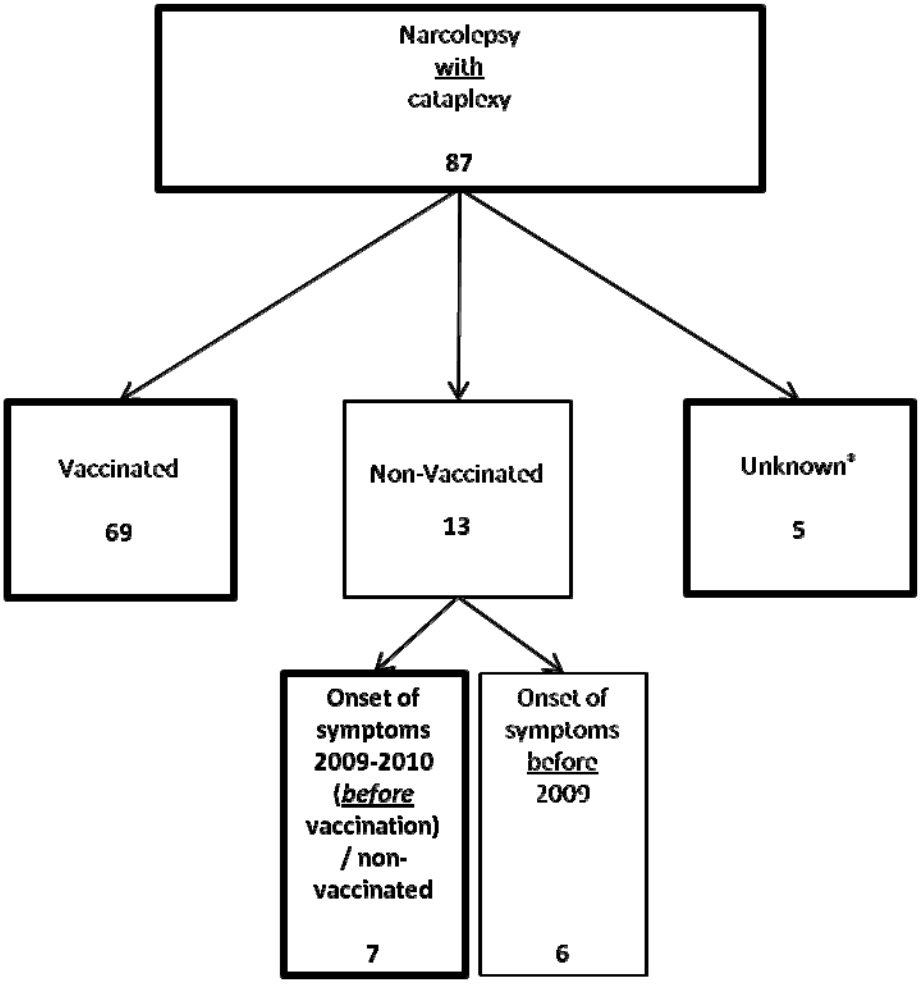
Fig 1. Overview - results of case inventory study in Sweden during 2009-2010
(children born 1990 or after)



* ***Non-Vaccinated***: *including cases with onset of symptoms before vaccination*
** ***Unknown***: *date of vaccination is during the month of onset of narcolepsy symptoms*

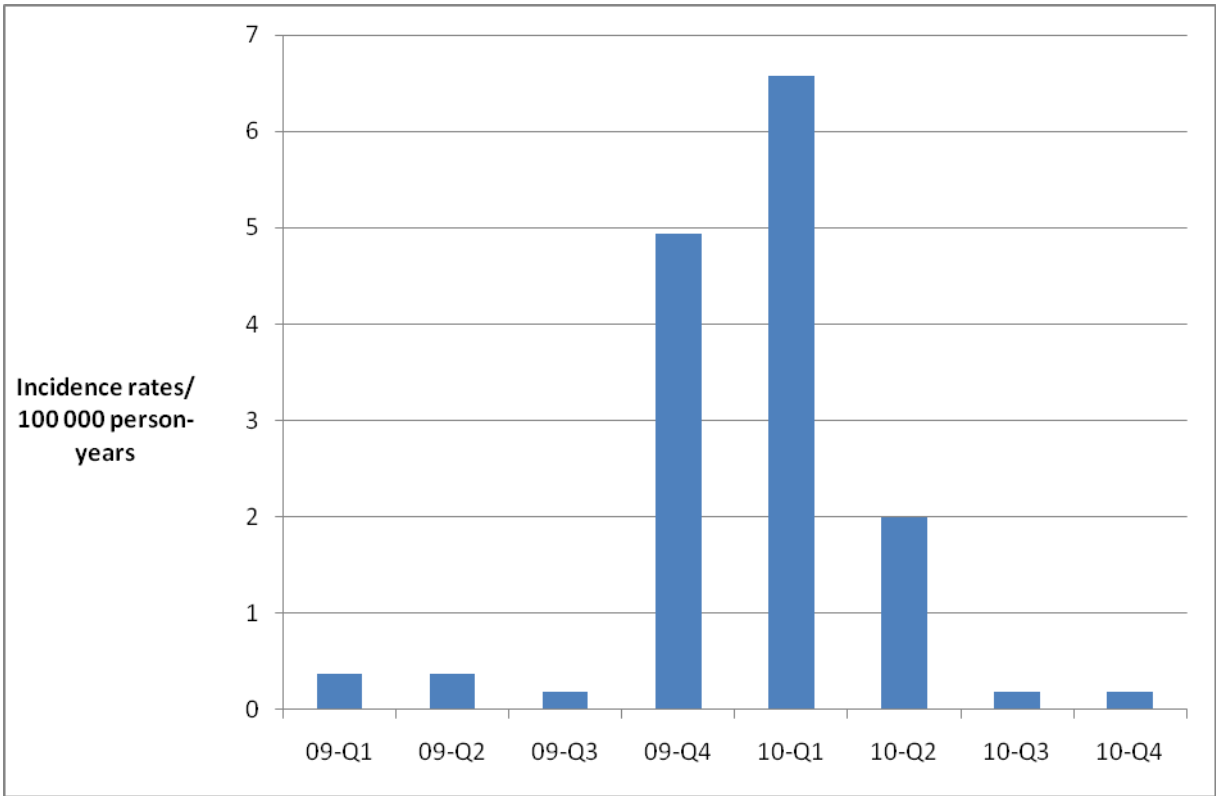
*** *NOTE: additional cases (13) which one reviewer concluded as "Narcolepsy with cataplexy" and the other reviewer came to a different conclusion have been reviewed by a 3rd reviewer for a final conclusion*

Fig 2. Overview - cases of Narcolepsy with cataplexy
(children born 1990 or after)



* ***Unknown***: *date of vaccination is during the month of onset of narcolepsy symptoms*

Fig 3: Population incidence rates by quartiles (3 months periods), 2009-2010.



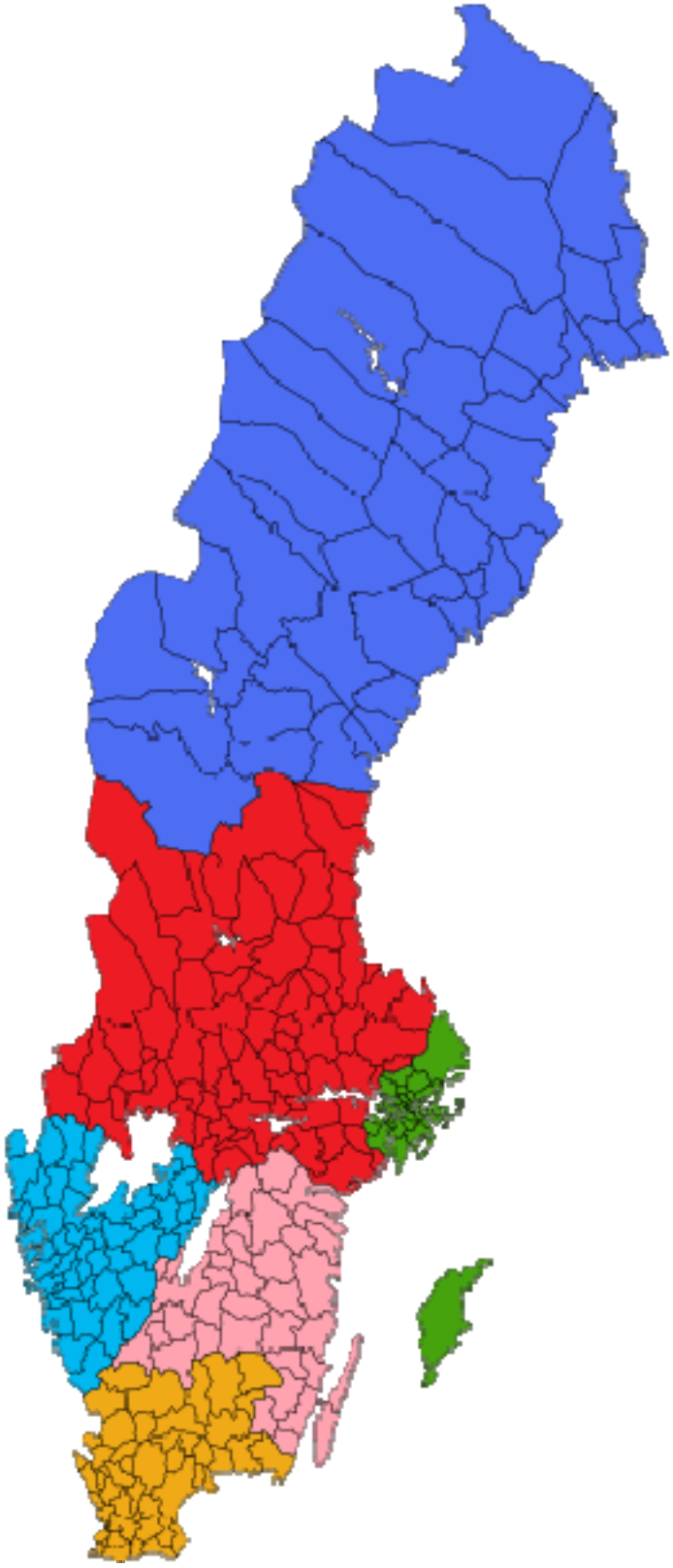


Fig4. Map of the six health care regions in Sweden; Incidence Rates per 100 000 person-years

North region (0.25)
Uppsala-Örebro region (1.88)
Stockholm region (0.99)
South-East region (2.14)
West region (2.31)
South region (2.99)

Appendix 1

Narcolepsy with cataplexy diagnostic criteria (Am Academy of Sleep Med)

1. Excessive daytime sleepiness occurring almost daily for at least 3 months.

2. Definite history of cataplexy, defined as sudden and transient (less than 2 minutes) episodes of loss of muscle tone, generally bilateral, trigged by emotions (usually laughing and joking).

3. Diagnosis should, whenever possible, be confirmed by nocturnal polysomnography (with a minimum of 6 h sleep) followed by a daytime MSLT:
    - Mean daytime sleep latency 8 minutes or shorter, with two or more sleep onset in REM periods (the time from sleep onset to REM sleep should be less than 15 minutes in at least two naps).
    - Alternatively, hypocretin-1 concentrations in the cerebrospinal fluid 110 pg/ml or lower, or a third of mean control values.

4. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Appendix 2

- Basis for extrapolation of risk time *overall* for the vaccinated and non-vaccinated cohorts:

Age groups	4-county population	Entire SE population	Factor for extrapolation	Vacc: P-years 4-county	Vacc: P-years in SE pop (extrapol)	Non-vacc: P-years 4-county	Non-vacc: P-years SE pop (extrapol)
Total	1 254 433	2 187975	0.57	935500	**1 624 197**	618800	**1 093 993**
≤ 9	644778	1 052 156	0.61	497 189	815064	296379	485867
10-14	278484	497286	0.56	245862	439039	86715	154846
15-19	331171	638533	0.52	192449	370094	235706	453280

- Basis for calculation of risk time for the *time windows* in the exposed cohort:

Risk time for the two time windows in the vaccinated cohort was approximated by multiplying the number of subjects in the vaccinated cohort - 2 187 975 subjects with the 67.1% coverage = 1 468 131 subjects - by 3/12 year for the early window, yielding 377 032 person-years, and for the late window by subtracting this figure from the total number of person-years for the vaccinated cohort, leaving 1 247 165 person-years.