Investigation of an increase in the incidence of narcolepsy in children and adolescents in 2009 and 2010

Final Report of National Narcolepsy Study Steering Committee

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1. Summary

In August 2010 the Swedish pharmacovigilance authority reported that it was investigating six cases of narcolepsy reported by health care professionals as a possible adverse event following the use of Pandemrix vaccine, used during the H1N1 2009 pandemic. This was followed shortly by reports from the Finnish National Institute for Health and Welfare (THL) noting there had been a more than expected number of cases of narcolepsy in children and adolescents that year. On 23rd September, the Committee on Human Medicinal Products (CHMP) of the EMA concluded in its initial review of available data that the available evidence did not confirm a link but that more research was needed.

By the end of March 2011 the IMB had received reports of two confirmed cases of narcolepsy following vaccination with pandemic vaccines. The Department of Health and the HSE agreed that the HSE Health Protection Surveillance Centre (HPSC) would work with the IMB and Irish clinical experts in narcolepsy to examine the Irish data and report back the findings.

In order to investigate the association of narcolepsy with the pandemic vaccination, a retrospective population-based cohort study was conducted. The incidence of narcolepsy in vaccinated and non-vaccinated individuals was compared.

Pandemic vaccination data was collected from different vaccination databases that are described hereafter. Narcolepsy cases were identified through active case finding by contacting all sleep clinics, neurologists, paediatricians, general practitioners, psychiatrists, psychologists and public health nurses in Ireland.

Medical and narcolepsy history was collected from the medical records and clinical charts of all cases of narcolepsy identified through the active case finding with a symptom onset from April 2009 (following their informed consent). Their vaccination status, date of vaccination and vaccine brand were also cross-checked in the vaccination databases.

Two experts (one adult and one paediatric neurologist) reviewed the clinical history of narcolepsy cases in order to confirm the diagnosis and classify them using the internationally agreed Brighton case definition for narcolepsy (Annex A). The reviewers were blinded to the vaccination status of the cases. Neither of the independent experts were involved with the diagnosis or management of the cases included in the study.

A total of 32 cases of narcolepsy meeting the case definition (Appendix A) with a symptom onset from April 2009 were reported through the active case finding and the evaluation of their clinical history. Twenty eight of these cases occurred in children/adolescents aged 5-19 years. Based on the first contact with health care because of narcolepsy symptoms, the

incidence of narcolepsy during the primary follow-up time (01/04/2009 to 31/12/2010) was 5.8 [95% CI: 3.5-9.0] per 100,000 person years in the vaccinated and 0.5 [95% CI: 0.2-1.0] per 100,000 person years in the unvaccinated individuals. There was a significant 13-fold higher risk of narcolepsy in vaccinated compared to unvaccinated individuals and the absolute increased risk associated with the vaccine was five narcolepsy cases per 100,000 vaccinated children and adolescents. These results are similar to those found in Finland and other Scandinavian countries such as Sweden and Norway.

In adults, the number of patients discharged with a primary diagnosis of narcolepsy and cataplexy remained stable over the period 1997-2009. We identified very few narcolepsy cases in adults with new onset of narcolepsy symptoms from April 2009 through our case finding and it limited the analysis of the risk of narcolepsy associated with pandemic vaccination. Although the RR point estimate for Pandemrix was relatively high, the wide confidence interval around the estimate impedes drawing any conclusion in those aged over 20 years.

The median delay between the vaccination and the first symptom of narcolepsy was 2.2 months (min: 2 weeks; max: 12.8 months). The median delay between the vaccination and the first health care contact for narcolepsy symptom was 4.1 months (min: 1.8 months; max: 16.8 months).

A source of potential bias in case selection may have been introduced by the extensive media attention in Finland and Sweden as cases may have be more likely to be reported if the patients were vaccinated. Although we cannot exclude any selection or confounding bias which might have overestimated the risk of narcolepsy linked to Pandemrix vaccination, we believe that the association was so high that it is unlikely to be explained by any possible bias. We estimate that we would need to diagnose an additional 33 cases in the unvaccinated cohort of young people between 5-19 years old in order for there not to be a significant increased risk in the vaccinated children. Similarly we estimate that we would need to diagnose an additional 55 cases in the unvaccinated cohort of young people to obtain a similar risk in both groups (RR=1). Extensive case finding was undertaken in Ireland over the last 6 months and it is unlikely that 33 – 55 cases in the unvaccinated cohort of 5-19 year olds are awaiting presentation to primary care and/or investigation in secondary care. The committee therefore considers the finding of an increased risk in vaccinated young people with Pandemrix to reflect a true increased risk in those aged 5-19 years vaccinated with Pandemrix.

Following an increased number of reports of narcolepsy in Finland and Sweden, the European Medicines Agency (EMA) initiated a review of Pandemrix and narcolepsy at the request of the European Commission under Article 20 of Regulation (EC) No 726/2004 in August 2010. At the completion of this review in July 2011 the EMA recommended that in persons under 20 years of age Pandemrix may only be used if the recommended seasonal

trivalent influenza vaccine was not available and if immunisation against H1N1 was still needed (e.g. those in the at risk groups). The EMA also confirmed that the overall benefit-risk balance of Pandemrix remained positive. The EMA considered that the results of the epidemiological studies relating to Pandemrix in Finland and Sweden showed an association between Pandemrix vaccination and narcolepsy in children and adolescents in those countries. A similar risk has not been confirmed but couldn't be ruled out in other countries.

The EMA also 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. They stressed that further research was necessary. Several initiatives are currently underway across the EU to further investigate this association.

The results of these further studies (e.g. the VAESCO study) that will consider possible confounders and facilitate better understanding of the interaction of other infections such as H1N1 with pandemic vaccine as a possible cause for the increase in narcolepsy in young people are awaited.

The committee recommended that a new single national immunisation information system be developed for all vaccination programmes which would facilitate investigation of possible vaccine adverse events.

2. Background and Mandate

In August 2010 the Swedish pharmacovigilance authority reported that it was investigating six cases of narcolepsy reported by health care professionals as a possible adverse event following the use of Pandemrix vaccine, used during the H1N1 2009 pandemic. This was followed shortly by reports from the Finnish National Institute for Health and Welfare (THL) noting there had been a more than expected number of cases of narcolepsy in children and adolescents that year. On the 26th August 2010 the European Medicines Agency (EMA) announced that it was conducting a review of the safety of Pandemrix. The Irish Medicines Board (IMB) participated in this review as the Irish pharmacovigilance authority. On 23rd September, the Committee on Human Medicinal Products (CHMP) of the EMA concluded in its initial review of available data that the available evidence did not confirm a link but that more research was needed.

In December 2010, the European Centre for Disease Control (ECDC) contracted the Vaccine Adverse Event Surveillance & Communication (VAESCO) consortium to undertake a study to examine the association between narcolepsy and the use of pandemic vaccine and also to examine other possible associations including between narcolepsy and pandemic influenza and other infections / vaccines.

In February 2011 THL issued a statement indicating an increased rate of narcolepsy was observed among children and adolescents aged 4 -19 years of age who had been vaccinated with Pandemrix (9 fold increase). The EMA CHMP in its review of the new data concluded that the new evidence added to the concern but that the data were still insufficient to establish a causal relationship between Pandemrix and narcolepsy. At the end of March 2011 the Swedish Pharmacovigilance authority published results from a registry study in four Swedish counties comparing the risk of narcolepsy in vaccinated versus unvaccinated individuals from October 2009 through December 2010. The Swedish study found an increased relative risk of 4.19 in vaccinated children and adolescents below 20 years of age. No increase was seen in adults.

By the end of March 2011 the IMB had received reports of two confirmed cases of narcolepsy following vaccination with pandemic vaccines. The Department of Health and the HSE agreed that the HSE Health Protection Surveillance Centre (HPSC) would work with the IMB and Irish clinical experts in narcolepsy to examine the Irish data.

The steering committee for the national narcolepsy study consisted of the following:

Dr. Darina O 'Flanagan, Director Health Protection Surveillance Centre (HPSC-HSE)
Dr Colette Bonner, Deputy Chief Medical Officer, Department of Health and Children (DoHC)
Dr. Catherine Crowe, Consultant Physician Sleep Disorders, Mater Private Hospital
Dr. Bryan Lynch, Consultant paediatric neurologist, Children's University Hospital Temple Street
Dr. Brian Sweeney, Consultant neurologist, Cork University Hospital
Dr. Joan Gilvarry, Director of Human Products Monitoring Department
Irish Medicines Board
Dr. Howard Johnson, Specialist in Public Health Medicine, Health Intelligence, Health Service Executive (HSE)
Dr. Suzanne Cotter, Specialist in Public Health Medicine (HPSC -HSE)
Ms. Anne-Sophie Barret, Fellow European Programme Intervention Epidemiology HPSC-HSE

Validation of cases according to internationally agreed criteria: Dr. Brian Sweeney and Dr. Blathnaid McCoy (consultant paediatric neurologist Our Lady's Hospital Crumlin Dublin).

3. Prevalence of narcolepsy and clinical picture in Ireland

3.1. Epidemiology of narcolepsy

Narcolepsy is a rare sleep disorder that causes a person to fall asleep suddenly and unexpectedly. Its precise cause is unknown, but it is generally considered to be triggered by a combination of genetic and environmental factors. Narcolepsy is characterized by excessive daytime sleepiness (EDS) and is often associated with cataplexy (episodic muscle weakness) and other rapid-eye movements (REM) sleep phenomena, such as sleep paralysis and hypnagogic hallucinations. Nocturnal sleep is characterized by sleep fragmentation and an inability to remain asleep.

Cataplexy is the only symptom specific to narcolepsy. It is defined as sudden and transient episodes of bilateral loss of muscle tone of brief duration (less than two minutes) triggered by emotions such as laughter or anger. Cataplexy is present in about 70% of patients with narcolepsy. Especially in children, cataplexy occurs typically on the face (change of facial expression, opening of the mouth, pushing the tongue out of the mouth, nodding of the head, double vision, etc.). Bending of the knees, weakness of lower limbs, or falling down because of loss of muscular tone is also common. Sleep paralysis is a transient, generalized inability to move or to speak during the transition between sleep and wakefulness. Hypnagogic hallucinations are vivid perceptual experiences occurring at sleep onset and include visual, tactile, kinetic and auditory phenomena. Other symptoms may occur such as weight gain and obesity due to a disturbed eating pattern, deterioration in school performance, poor concentration and emotional lability.

In the absence of documented abnormalities in the cerebrospinal fluid (CSF), formal sleep studies are mandatory for the diagnosis of narcolepsy. This typically consists of an overnight polysomnography followed by a multiple sleep latency test (MSLT). For a diagnosis of narcolepsy the mean sleep latency on MSLT is less than 8 minutes in adults or less than 12 minutes in children under 16 years and two or more sleep-onset rapid-eye movement periods (SOREMPs) are observed following sufficient nocturnal sleep during the night prior to the test. The Brighton case definition is attached in Appendix A.

Narcolepsy results from a loss of the neuropeptides orexin A and orexin B (also known as hypocretin 1 and 2). This loss is caused by destruction of the orexin/hypocretin producing cells in the hypothalamus in the brain. Hypocretin-1 measurement in the cerebro-spinal fluid (CSF) is a newly developed diagnostic tool as the majority of patients with narcolepsy-cataplexy are hypocretin-1 deficient. The test has a high sensitivity and specificity in patients with typical cataplexy. However the hypocretin-1 concentration in the CSF can be normal in narcolepsy without cataplexy.

Studies of the prevalence and incidence of narcolepsy are difficult to compare and interpret due to differences in narcolepsy case definition, method of confirming the diagnosis, study populations and other factors. The prevalence of narcolepsy with cataplexy is estimated at 25-50 per 100,000 population in Western countries. The incidence has been estimated at 0.74 cases per 100,000 person-years for narcolepsy with cataplexy and 1.37 per 100,000 person years for narcolepsy with or without cataplexy. There is not enough evidence to support gender difference but there seems to be a slight male predominance. In most cases age at onset lies between 15 and 40 years. One study conducted in two independent populations of patients with narcolepsy found a bimodal distribution in the age at onset, with the biggest peak around 15 years and a second peak around 36 years (1).

Symptoms usually develop gradually. It may take several years for each subsequent symptom to occur and the disease often goes unrecognized and undiagnosed until adulthood. EDS is usually the first symptom to appear, with cataplexy appearing either simultaneously or with a delay of 1 to 30 years.

The aetiology of narcolepsy is not completely understood. A multifactorial aetiology has been suggested, involving a genetic predisposition in combination with environmental risk factors. Possible risk factors include: streptococcal infections and viral infections. Studies have consistently shown associations between narcolepsy and obesity but this may reflect a consequence rather than a cause of the disease.

One of the most important predisposing genetic factors is a specific human leukocyte antigen (HLA), the HLA DQB1*-0602. Patients with narcolepsy-cataplexy carry the allele DQB1*0602 in 85-95% of cases, compared to about 30% of the normal population. Based on this association with HLA DQB1*-0602, researchers have suggested an autoimmune mechanism as a trigger for the selective loss of hypothalamic hypocretin producing neurons involved in REM-sleep regulation. When the majority of hypocretin cells have disappeared, narcoleptic symptoms would start to occur and the severity of symptoms will augment with an increasing number of degenerating hypocretin cells (2). This genetic factor is found in approximately 28% of the Finnish population. In the Northern European populations, this genetic risk for narcolepsy can be found in approximately 25-28% of the population, while in Southern Europe, the genetic risk is lower, occurring in 4-13% of the population (3).

3.2. Narcolepsy in Ireland

In Ireland, there is very little information on the epidemiology of narcolepsy. The prevalence rate of narcolepsy was estimated at 5 per 100,000 population in a study conducted in 2009 amongst all respiratory physicians, neurologists, paediatricians with an interest in neurology, and psychiatrists known to have an interest in sleep disorders. According to respondents, most reported patients belonged to the 13-19 years old age group. Although the authors did not rule out a low prevalence rate due to Irish unique ethnicity, they thought that narcolepsy prevalence rates were largely underestimated. They suggested that the condition was probably under-recognised due to various factors: the possible misinterpretation of reported symptoms of EDS, the unclear care management of patients with suspected narcolepsy, the possibility of false negative PSG or MSLT results and the financial and logistical constraints of hypocretin-1 testing (4).

A study of frequencies of HLA class I and II alleles and haplotypes of 250 Irish unrelated bone marrow donors found that the HLA DQB1*0602 was present in 35% of this population (5).

The Hospital Inpatient Enquiry (HIPE) scheme captures demographic, clinical and discharge data from acute hospitals in Ireland. The HIPE system was mined for all discharges with a primary diagnosis of 'Narcolepsy and Cataplexy' using the International Classification of Diseases (ICD)-9 code 347 (1997-2004) and ICD-10 code G47.4 (2005-2011). The HIPE cases shown in Figure 1 refer to hospitals which have public funding only. As not all cases are admitted, the HIPE inpatient data system does not include all cases of narcolepsy.

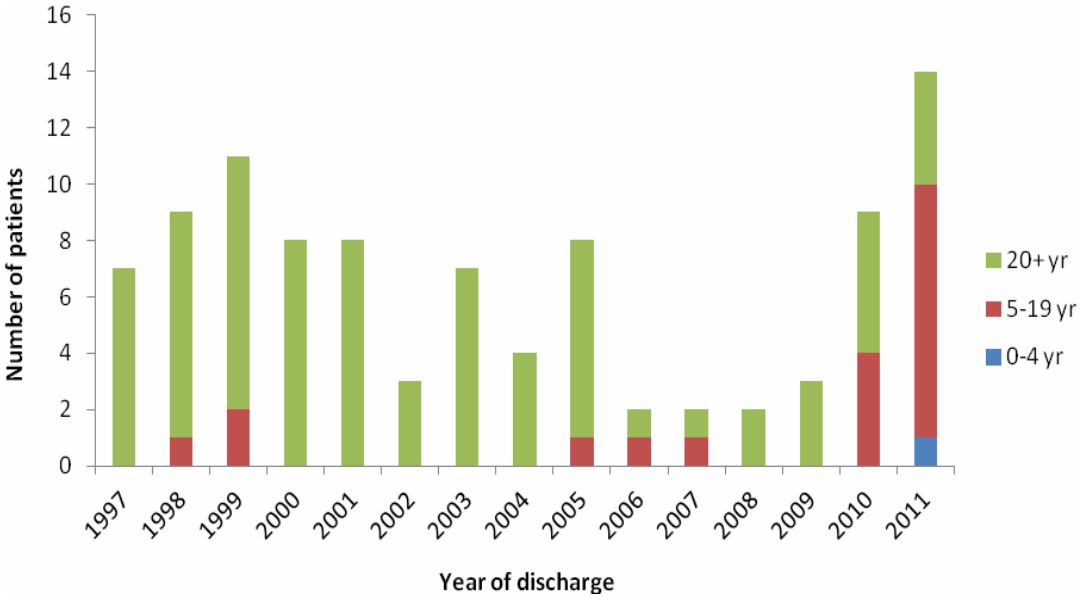


Figure 1: Numbers of cases with a primary diagnosis of narcolepsy from 2000 to 2011 in Ireland

(*Source: HIPE data - The 2011 data is provisional and incomplete - data up to November 2011)*

4. Vaccines used during the H1N1 2009 pandemic

In Ireland, two pandemic vaccine brands were used during the 2009/2010 pandemic influenza vaccination campaign: Pandemrix (GlaxoSmithKline) and Celvapan (Baxter). The Baxter vaccine was a whole cell killed vaccine produced on a Vero cell line and did not contain any adjuvant. Pandemrix was an inactivated split influenza virus vaccine produced in eggs. It contained the adjuvant ASO3. Both vaccines were used in several other European countries. Pandemrix was used in the Scandinavian countries, United Kingdom, Germany, France, the Netherlands and Spain. The same vaccine marketed as Arepanrix was used in Canada.

HSE provided the pandemic vaccine to the population in a phased manner between November 2009 and March 2010 (Table 1). Individuals at highest risk of influenza disease and its complications were provided the vaccine in the early stages, with those at less risk of severe disease vaccinated at later dates. The mass vaccine programme concluded on 31st March 2010 as the numbers contracting pandemic influenza declined significantly. However, pandemic vaccine continued to be provided to those individuals at highest risk of complications over the summer.

The vaccines were administered to the population at a variety of sites: GP surgeries, HSE mass vaccine clinics, HSE led school vaccination clinics, hospitals (vaccine clinics, wards, out-patient departments, occupational health departments). Information on vaccinated individuals was collected (personal identification, vaccine used, dates of administration, priority group and risk factors). Most vaccination information was collated using one of two nationally available computerised information systems. For individuals administered vaccine at GP surgeries, vaccination records were entered into the Primary Care Reimbursement Service (PCRS) either directly at the GP surgery site (on-line) or by the PCRS following receipt of GP paper claims. For HSE mass vaccine clinics, school clinics, hospitals, a specific information system was developed by the HSE, the Pandemic Data Management System (PDMS). This was used to collate information on individuals vaccinated at these sites (data entry at vaccination site, or at later date) and other non-GP sites.

The National Immunisation Office reported that approximately 6% of pandemic vaccine Pandemrix were distributed to sites other that GP or Mass Vaccination Clinics for administration to a mixture of staff and at risk patients. These included sites such as Public and Private Hospitals, non acute and community hospitals, nursing homes, occupational health facilities with the majority going to Public Hospitals. Administration of these doses would normally have been recorded locally by the administering site and therefore would

not necessarily have formed part of either of the two available databases which were used in the report i.e. H1N1Pandemic System PDMS or the PCRS H1N1 database.

During the 2010/2011 influenza vaccination campaign, the pandemic H1N1 strain was included in the seasonal vaccine. However, Pandemrix was still administered for a few weeks because of a shortage of the seasonal vaccine. General practitioners were advised to prioritise the available seasonal influenza vaccine for pregnant women and children aged 6 months – 18 years in the medically at risk groups.

Table 1: Pandemic vaccine programme in Ireland

Group order	Priority group	Vaccine delivery*	Official start date
Group 1	• At-risk groups aged 6 months up to 65 years of age[a] • Pregnant women in the 2nd and 3rd trimester and up to 6 weeks post partum or in the1st trimester with an additional risk factor • Immunosuppressed individuals and household contacts of individuals with immunosuppression • Residents of disability units regardless of whether they are in one of the medically at risk groups • Individuals with significant physical or intellectual disability (including neurodevelopment conditions)	GP/MVC[b]/ maternity hospitals	02/11/2009 (Vaccine delivered from 19/10/2009 so some vaccines given before start date)
Group 2	Healthcare staff	Occupational Health Services	09/11/2009
Group 3	• Children aged 6 months – 5 years	School vaccination clinics / MVC / GP	09/11/2009
	• Household contacts of children aged less than 6 months		30/11/2009
	• Children aged 5 – 18 years		30/11/2009
Group 4	Adults aged 65 years and over	MVC / GP	30/11/2009
Group 5	All others	MVC / GP	01/02/2010

[a] Detailed at-risk chronic illnesses as listed in the Immunisation Guidelines for Ireland (Chapter 10a)

[b] MVC: Mass Vaccination Clinics

*minority of vaccines delivered at other sites (e.g. acute and non-acute hospitals, nursing homes for patients, clients, staff)

Note: Please see Annex C for recommended dosage of Pandemrix and Celvapan in Ireland and changes to the recommendations (November 2009-January 2010)

5. Studies to establish the causal relationship of vaccination with pandemic vaccine and narcolepsy

5.1. Epidemiological studies in Ireland

In order to investigate the association of narcolepsy with the pandemic vaccination, a retrospective population-based cohort study was conducted. The incidence of narcolepsy in vaccinated and non-vaccinated individuals was compared.

Pandemic vaccination data was collected from the PCRS and PDMS databases that are described above. Narcolepsy cases were identified through an active case finding by contacting all sleep clinics, neurologists, paediatricians, general practitioners, psychiatrists, psychologists and public health nurses in Ireland. It was emphasised to investigating neurologists and sleep clinics that cases should be reported regardless of exposure history.

5.1.1. Pandemic vaccination coverage

Figure 2 shows the number of doses distributed over weeks. Table 2a and 2b show the number of first shot vaccination and the population vaccine uptake by age group and by vaccine brand. Celvapan represented a minor proportion of administered vaccines. For example, in those aged 5-19, the vaccine uptake for Pandemrix was 39.8% whereas the vaccine uptake for Celvapan was 2.7%. The vaccine uptake for Pandemrix was greater in children and adolescents than in adults. The vaccine uptake by HSE areas is presented in figure 3.

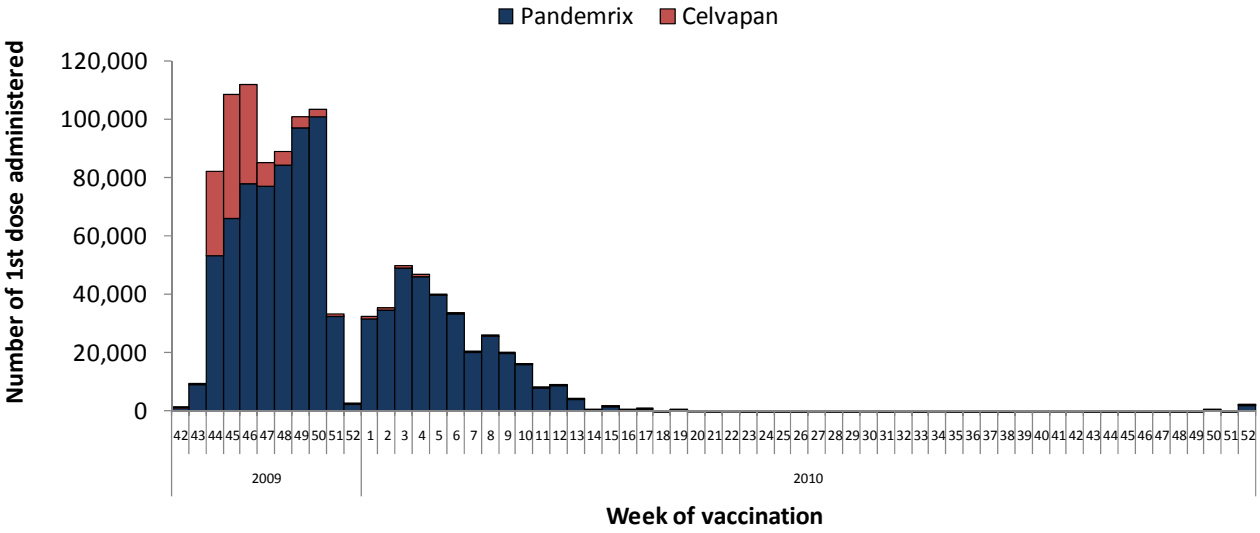


Figure 2: Number of first shot vaccination administered by vaccine brand, 2009/2010, Ireland (*Source: PCRS/PDMS -)*

Table 2a: Number of first shot vaccination with Pandemrix and population vaccine uptake by age group, 2009/2010 influenza vaccination campaign, Ireland (*Source: PCRS/PDMS)*

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

*Excluding half of those aged <1 year

Table 2b: Number of first shot vaccination with Celvapan and population vaccine uptake by age group, 2009/2010 influenza vaccination campaign, Ireland (*Source: PCRS/PDMS)*

Age group	Population of Ireland* (*Census 2006*)	Number of first shot vaccination with Celvapan	Population vaccine uptake (Celvapan)
0-4	271,714	22,452	8.3%
5-19	852,454	22,700	2.7%
20+	3,085,412	85,193	2.8%
Unknown	-	38	-
Total	4,209,310	130,383	3.1%

*Excluding half of those aged <1 year

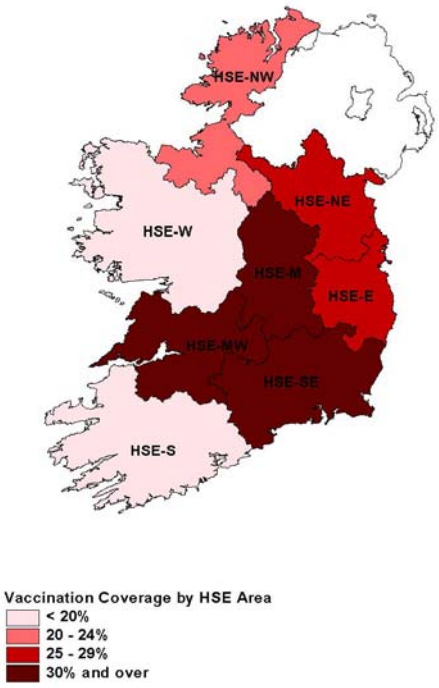


Figure 3: Vaccine uptake (first shot vaccination – all brands) by HSE area

5.1.2. Analysis plan and methods

The primary follow-up time was defined from 01/04/2009 to 31/12/2010. This period was defined to include all cases with a possible exposure to pandemic influenza infection and/or vaccination.

Two other study periods were defined in the sensitivity analysis:

- Period 2 : 01/04/2009 to 15/08/2010 (before the increased media attention in Sweden and Finland
- Period 3: 01/10/2009 (after the pandemic vaccine became available in Ireland) up to 31/12/2010

The onset of symptoms was determined from the GP notes with first documented history of symptoms such as excessive fatigue, sleep attacks, symptoms suggestive of cataplexy etc. As the date of onset of narcolepsy is exposed to uncertainty and the date of diagnosis may be delayed different dates were used to estimate the onset:

1) Time when the child/adolescent or his/her parents remembered that EDS symptoms or cataplexy had started (as recorded in the medical records)
2) Date of first health care contact due to narcolepsy symptoms (as recorded in the medical records)
3) Date of referral to a specialist for a sleep test
4) Date of sleep test

Of these four definitions for the time of onset, the time of 2) was used in the main analysis for determination of the onset time of narcolepsy. The other times were considered in sensitivity analysis to study any care-seeking bias linked to:

- an increased media attention in narcolepsy that occurred in Sweden/Finland at the end of August 2010;
- an increased awareness about narcolepsy among hospital clinicians and general practitioners (GP) in Ireland linked to a letter sent by the HSE in March 2011.

Based on international literature on the possible association between pandemic vaccination and narcolepsy, three cohorts were defined for the study: individuals born in 2006-2010 (aged 0-4 at the end of the study period), individuals born in 1991-2005 (aged 5-19) and adults born before 1991 (aged 20 years and over). However, no narcolepsy cases were reported in individuals born in 2006-2010 in Ireland. Therefore the analysis was performed for the two other cohorts, i.e. children/adolescents born in 1991-2005 and adults born before 1991.

The 2006 census data by single year of age was used to estimate the number of individuals in each age group, assuming that the change in the population from 2006 to 2009 was so small that it would not distort the result.

An incident case of narcolepsy was defined as having had a first contact with health care for narcolepsy symptoms during the study period. In the sensitivity analysis, other index dates were used to define incident cases (reported date of first symptom of narcolepsy, date of referral for a sleep test or date of MSLT within the study period).

In all analysis, an incident exposed case was defined as having received one or more dose of a pandemic vaccine before the reported date of first symptom of narcolepsy.

The incidence of narcolepsy was calculated by dividing the number of cases by the follow-up time. The analysis was stratified by vaccine brand. In the study, 852,454 children and adolescents born in 1991–2005 and 3,085,142 adults born before 1991 were followed. The risk time (person-years) in vaccinated individuals was calculated from the week of first vaccination until the end of the study period. The risk time in unvaccinated individuals was calculated from 01/04/2009 until the end of the study period for unvaccinated individuals, added to the time from 01/04/2009 to the week of vaccination for vaccinated individuals.

The relative risk (RR) was calculated as the ratio of the incidence rates and the absolute attributable risk (AAR) was calculated as the difference in the incidence rates. Poisson regression was used in Stata to calculate the 95% confidence intervals around the RR.

5.1.3. Description of narcolepsy cases identified in Ireland

- **Narcolepsy cases**

The active case finding identified 54 cases of narcolepsy reported from fifteen clinicians. Of these cases, 24 (44%) met the case definition (Annex A) with a symptom onset from April 2009. An additional 8 cases were subsequently reported by the two main clinicians identified by the HSE to manage referrals.

Informed consent was received from 32 of these cases. Medical and narcolepsy history was collected from their medical records and clinical charts. Their vaccination status, date of vaccination and vaccine brand were also cross-checked in the PCRS and PDMS databases.

Two experts (one adult and one paediatric neurologist) reviewed the clinical history of narcolepsy cases in order to confirm the diagnosis and classify them using the internationally agreed Brighton case definition for narcolepsy (Annex A). The reviewers were blinded to the vaccination status of the cases and neither of the independent experts was involved with the diagnosis or management of any of the cases included in the study.

There was a 100% concordance between the two evaluators when classifying the cases according the Brighton case definition. Of these 32 cases, 15 (47%) were classified as Level 1, 12 (37%) as Level 2 and 5 (16%) as Level 3. There were 22 females and 10 males. The age distribution of the 32 cases is shown in Figure 4.

The incidence rate was 0.4/100,000 person-years overall age group, 1.9/100,000 person-years in the 5-19 age group, and 0.1/100,000 person-years in those aged 20 and over.

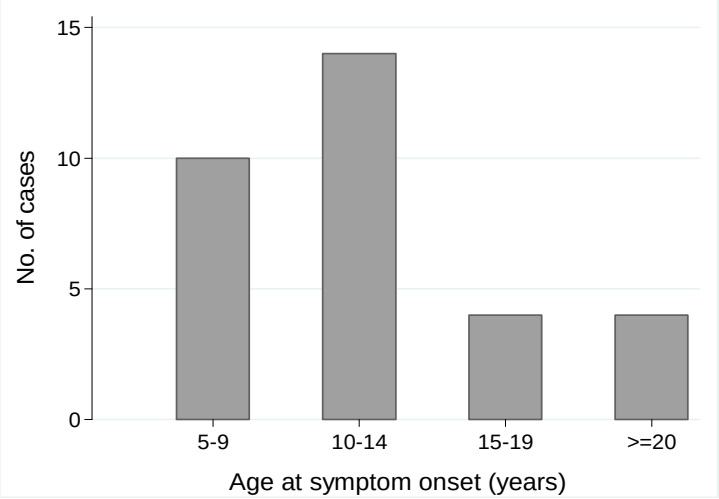


Figure 4: Age distribution of the cases of narcolepsy (N=32), 01/04/2009-31/12/2010, Ireland

Figure 5 shows the incidence rate per 100,000 person-years of narcolepsy by HSE area. For a visual comparison, Annex B shows the geographical distribution of narcolepsy, 2009/2010 pandemic vaccine uptake and different indicators of the 2009/2010 pandemic influenza outbreak.

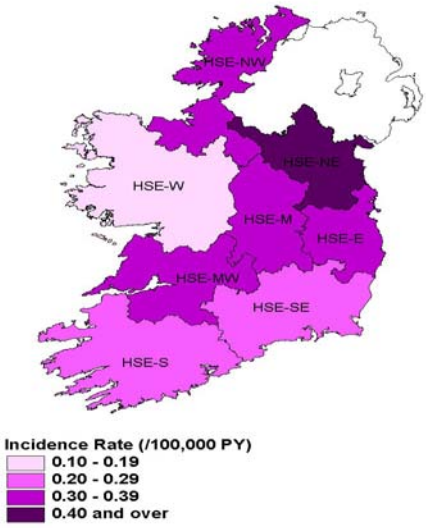


Figure 5: Incidence rate of narcolepsy by HSE area

Cataplexy occurred in 22 (69%) cases. In three cases, cataplexy appeared before the onset of EDS. In the 19 cases with cataplexy occurring at the same time or after EDS, the median time between the onsets of EDS and cataplexy was 2 months (min: 0 – max: 12).

The distribution of the 32 cases by different index dates is shown in figure 6, as well as the different study periods and the right-censored cases for each period. Twenty-seven cases had their first contact with health care for narcolepsy symptoms within the study period and 24 of these had a date of first contact prior to 15/08/2010.

The number of referral and MSLT tests did not increase after 15/08/2010 but they did increase from March 2011. In total, 17/31 (55%) and 21/32 (66%) cases were respectively referred and diagnosed after 01/03/2011.

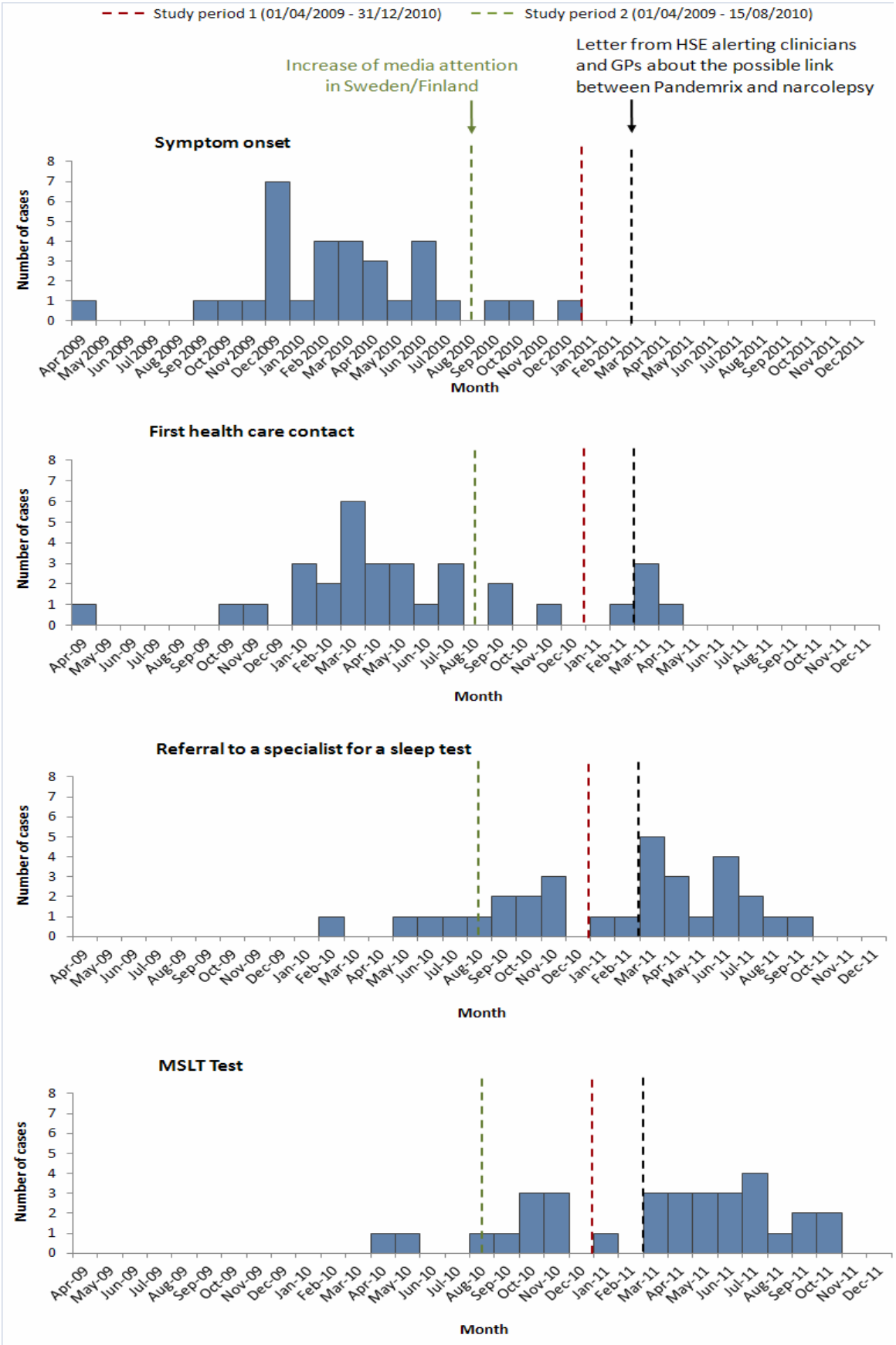


Figure 6: Distribution of narcolepsy cases according to their index dates (n=32) – *One case is not included in the third graph (missing date of referral for a sleep test)*

The median delays between the recalled symptom onset and the first health care contact, the first referral to a specialist for a sleep test, and the date of MSLT were respectively 1.6 months (min: 0 – max: 15.6), 12.5 months (min: 3.0 – max: 18.2) and 12.5 months (min: 3.9 - max: 19.3). The distribution of these timeframes is presented in Figure 7.

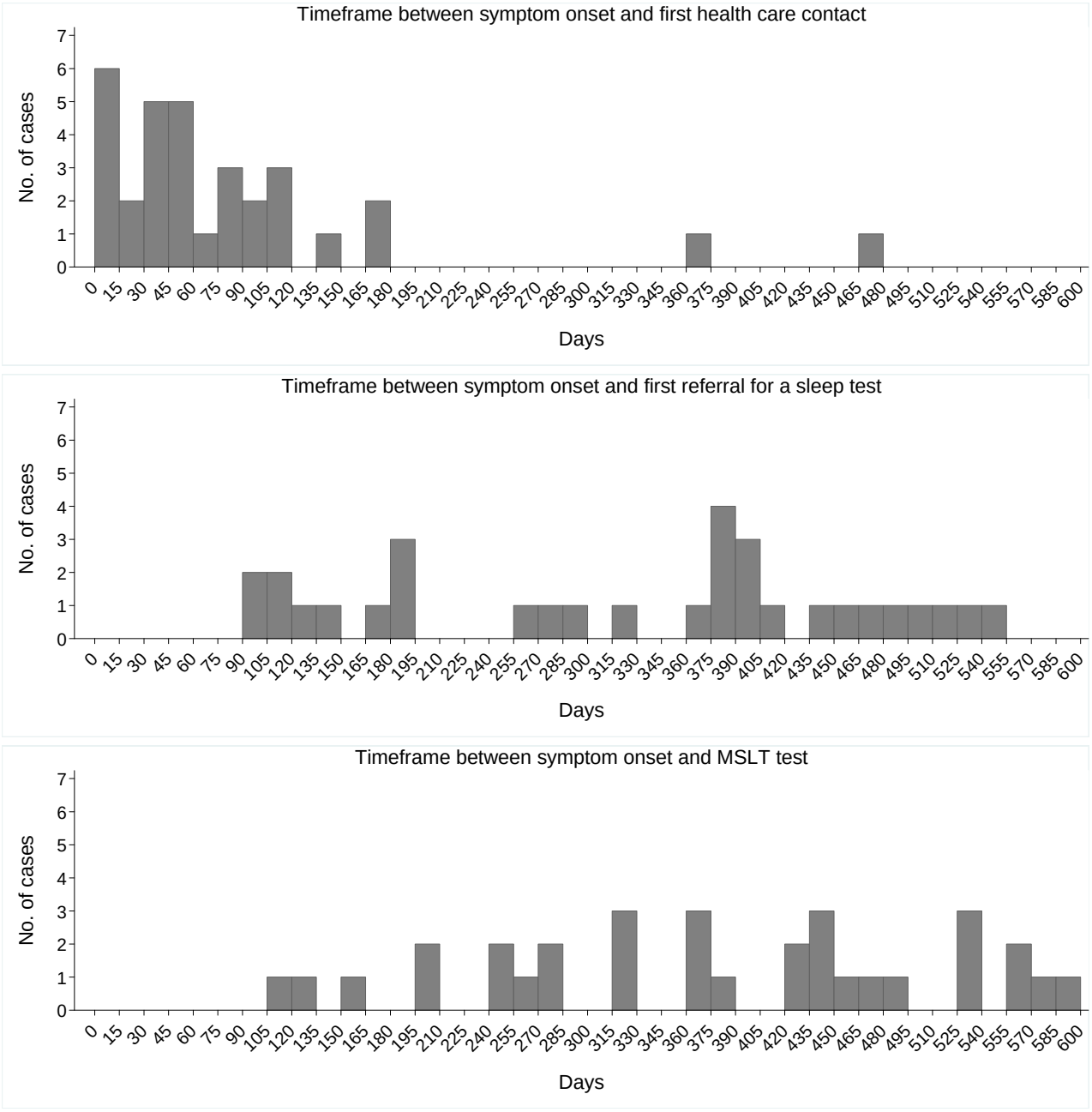


Figure 7: Timeframe between the recalled symptom onset and the other index dates
NB1: When the exact date of symptom onset was unknown, it was approximated to the 15th of the reported month
NB 2: *One case is not included in the third graph (missing date of referral for a sleep test)*

- **Narcolepsy cases vaccinated against pandemic influenza in 2009/2010**

Of the 32 cases with symptom onset from April 2009, 30 cases had been vaccinated against pandemic influenza. Vaccination status was independently verified by accessing the PCRS and PDMS databases. Twenty of the cases were recorded on the mass vaccination database (PDMS) and six were recorded on the GP database (PCRS). The vaccination status of four of the 30 cases were not found on either of the databases but were verified by retrieval of treatment record sheet from the GP or the mass vaccine clinic.

Of 30 vaccinated cases, 25 had received a pandemic vaccination before the recalled onset of the first narcolepsy symptom (24 with Pandemrix and 1 with Celvapan). Five cases had received pandemic vaccination after the first symptom onset and were considered as unvaccinated in the analysis. All but one of the vaccinated cases had received one dose of vaccine. The batch numbers of the vaccines received are included in Annex D. There was no association with any particular batch number and although 9 of the cases had received a particular batch it was the most common batch number reported on the databases.

The median delay between the vaccination and the first symptom of narcolepsy was 2.2 months (min: 2 weeks; max: 12.8 months). The median delay between the vaccination and the first health care contact for narcolepsy symptom was 4.1 months (min: 1.8 months; max: 16.8 months). The distributions of delay between vaccination and symptom onset/first health care contact are shown in Figure 8.

Of 27 cases with a first contact with health care within the study period, 21 had received a pandemic vaccination before the first symptom onset and 6 were classified as unvaccinated (1 case did not receive any vaccination at all and 5 cases were vaccinated after the first symptom onset). All 21 vaccinated cases had been vaccinated with Pandemrix. The only narcolepsy case who had received Celvapan had the first contact with health care after 31/12/2010 and was therefore not included in the analysis of the risk of narcolepsy.

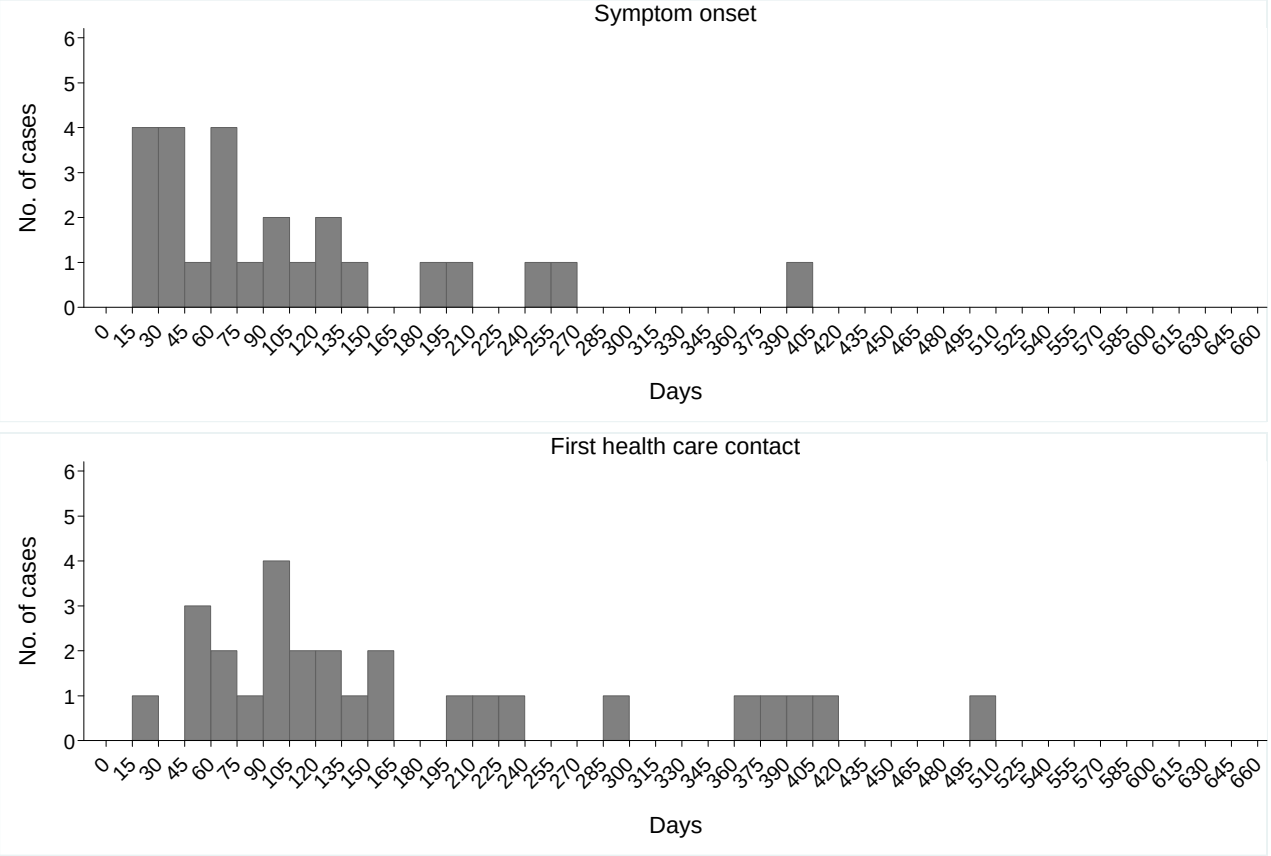


Figure 8: Delay between vaccination and symptom onset or date of first health care contact in vaccinated narcolepsy cases (N=25)
NB: When the exact date of symptom onset was unknown, it was approximated to the 15th of the reported month

- **Comparison of vaccinated and unvaccinated narcolepsy cases**

Table 3 shows the cases' characteristics by vaccination status. There was no significant difference between the distribution of vaccinated and unvaccinated cases by age and sex. There was a significant difference in the Brighton case definition, with vaccinated cases being more frequently classified as level 1 than unvaccinated cases. The two cases who had never received a pandemic vaccine were classified as Level 2 (n=1) and Level 3 (n=1).

Vaccinated cases were more frequently affected with cataplexy but the difference with unvaccinated cases was not statistically significant. In those with cataplexy occurring at the same time or after the EDS onset, the median delay between the EDS onset and the cataplexy onset was 2.0 months (min: 0 – max: 12) in vaccinated individuals and 5.5 months

(min: 3.0 – max: 8.0) in unvaccinated individuals. This difference was not statistically significant.

The timeframes between the date of onset of first symptom and other index dates (first contact with health care, referral for a sleep test and MSLT test) were not significantly different between vaccinated and unvaccinated cases.

Table 3: Characteristics of narcolepsy cases by vaccination status (N=32), 01/04/2009-31/12/2010, Ireland

Characteristics	**Vaccinated cases (N=25)** n (%)	**Unvaccinated cases (N=7)*** n (%)	**P value** (Fisher exact test)
Age at onset			1
5-19	22 (88)	6 (86)	
≥20	3 (12)	1 (14)	
Sex			1
Male	8 (32)	2 (29)	
Female	17 (68)	5 (71)	
Brighton case definition			0.04
Level 1	14 (56)	1 (14)	
Level 2	9 (36)	3 (43)	
Level 3	2 (8)	3 (43)	
Presence of cataplexy	18 (72)	4(57)	0.65

* Five cases had a reported date of symptoms onset prior to the date of vaccination and were considered as unvaccinated

5.1.4. Risk of narcolepsy in children and adolescents

Of 28 cases of narcolepsy reported among children/adolescents, 24 had their first contact with health care because of narcolepsy symptoms within the primary study period. Of these, 19 had received a pandemic vaccine before their reported symptom onset. All of them had received Pandemrix so the results are reported here for Pandemrix only.

Based on the first contact with health care because of narcolepsy symptom, the incidence of narcolepsy during the primary follow-up time (01/04/2009 to 31/12/2010) was 5.8 [95% CI: 3.5-9.0] per 100,000 person years in the vaccinated and 0.5 [95% CI: 0.2-1.0] per 100,000 person years in the unvaccinated individuals. There was a significant 13-fold higher risk of narcolepsy in vaccinated compared to unvaccinated individuals and the absolute increased risk associated with the vaccine was five narcolepsy cases per 100,000 vaccinated children and adolescents (Table 4).

Table 4: Relative risk of narcolepsy in vaccinated/unvaccinated children and adolescents (date of first contact with health care for narcolepsy symptom between 01/04/2009 and 31/12/2010 and exposure defined as vaccination with Pandemrix)

Study period	Narcolepsy cases		Follow up years		Relative Risk			AAR/100,000 vaccinated individuals
	Vacc	Not vacc	Vacc	Not Vacc	RR	Lower CI	Upper CI	
01/04/2009 -31/12/2010	19	5	330,904.5	1,128,441.3	13.0	4.8	34.7	5.3
01/04/2009 -15/08/2010	16	5	200,580.1	907,979.2	14.5	5.3	39.5	7.4

The sensitivity analysis based on different index dates and study periods is shown in figure 9. Using the primary study period, the RR varied with the index dates but it remained consistently higher than 1.

Using the study period 2 (01/04/2009-15/08/2010), the RR remained similar using the date of first symptom of narcolepsy or the date of first contact with health care. The RR dropped to 2.3 using the date of referral for a sleep test and was not significantly different from 1 anymore. However this analysis was only based on one vaccinated case and two unvaccinated cases since 25 cases were referred after 15/08/2010.

Using the study period 3 (01/10/2009-31/12/2010), the RR were similar to the study period 1.

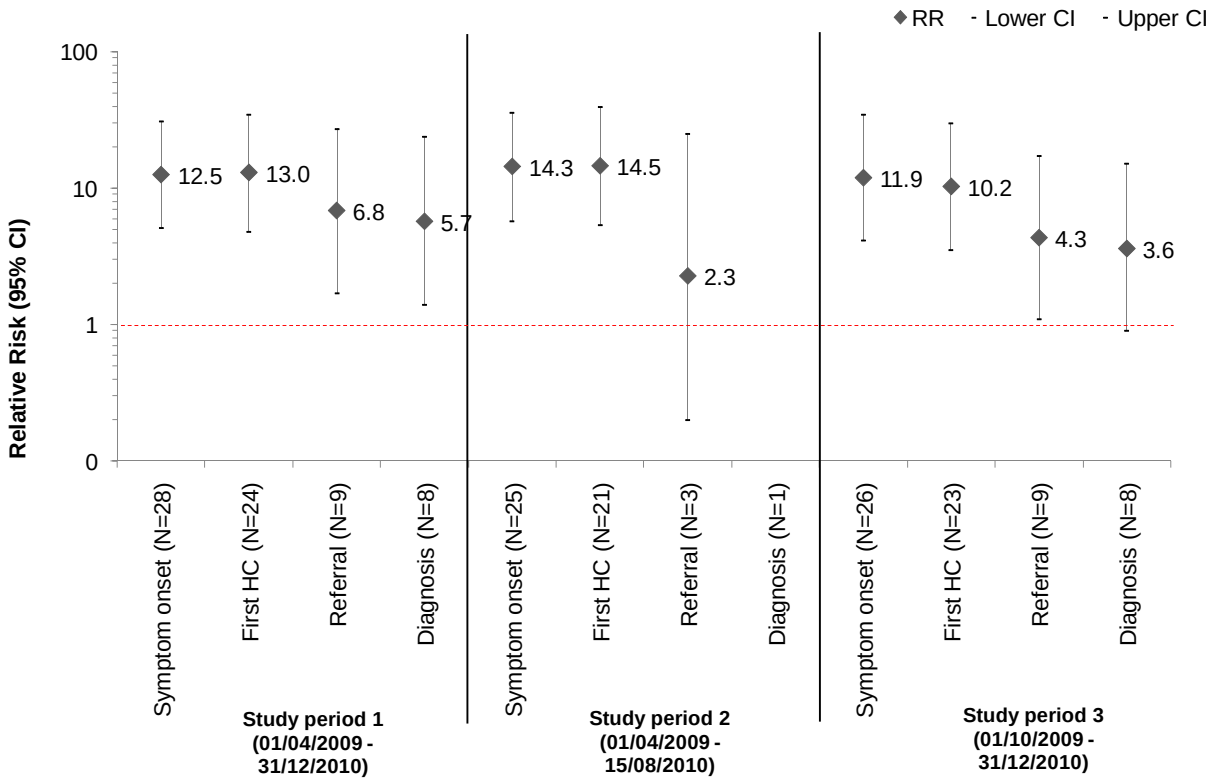


Figure 9: Relative risk of narcolepsy in vaccinated compared to unvaccinated children and adolescents using different index dates and study periods

The RR based on the first contact with health care would become non-significant only if there were still an additional 33 unvaccinated cases to be diagnosed in the 5-19 year olds in Ireland (RR=1.70, 95% CI: 0.98-2.96). The RR point estimate would get towards 1 only if there were still an additional 55 unvaccinated cases to be diagnosed in the 5-19 years old (RR=1.1, 95% CI: 0.6-1.8).

5.1.5. Risk of narcolepsy in adults

Of four cases of narcolepsy reported among adults, three had their first contact with health care because of narcolepsy symptoms within the primary study period. Of these, two had received a pandemic vaccine before their reported symptom onset. They both had been vaccinated with Pandemrix so the results are reported here for Pandemrix only.

Based on the first contact with health care because of narcolepsy symptoms, the incidence of narcolepsy during the primary follow-up time (01/04/2009 to 31/12/2010) was 0.39 [95% CI: 0.05-1.42] per 100,000 person years in the vaccinated adults and 0.02 [95% CI: 0.001-0.12] per 100,000 person years in the unvaccinated adults. The RR was 18.8 [95% CI: 1.7-207.4] and the absolute increased risk associated with the vaccine was 0.4 narcolepsy cases per 100,000 vaccinated adults (Table 5). Given the small number of cases in adults, the sensitivity analysis using different index dates or study periods could not be done.

Table 5: Relative risk of narcolepsy in vaccinated/unvaccinated adults (censoring based on the first reported symptom onset and exposure defined as vaccination with Pandemrix)

Study period	Narcolepsy cases		Follow up years		Relative Risk			AAR/100,000 vaccinated individuals
	Vacc	Not vacc	Vacc	Not Vacc	RR	Lower CI	Upper CI	
01/04/2009 -31/12/2010	2	1	507,197.2	4,769,922.7	18.8	1.7	207.4	0.4

5.2. Immunogenetic studies

As part of the clinical management of narcolepsy, some narcolepsy cases were sampled for HLA typing. Seventeen had the DQB1*-0602 allele which is known to be frequently associated with narcolepsy-cataplexy. Fourteen of these cases were affected with cataplexy. The remaining cases were either not tested for HLA typing or the HLA results were not available at the time of chart retrieval.

5.3. Identification of further cases

HPSC is aware of 18 further cases that are at various stages of investigation.). Of these, 5 have been diagnosed with narcolepsy but consent is still outstanding (n=2), consent was not received in time to be included in study (n=2) or consent was refused (n=1)

The other cases may or may not meet the case definition. It is possible that further cases will come to light over the next months.

5.4. Epidemiological studies in other countries

5.4.1. Finland

Following a number of notifications of suspect adverse events of narcolepsy linked to vaccination with Pandemrix, the National Institute of Health and Welfare (THL) conducted a retrospective population-based cohort study following children/adolescents born in 1991-2005. By 24th August 2011, 98 cases of narcolepsy following vaccination with Pandemrix had been notified to the THL, of whom 79 were aged 4-19 years at the time of vaccination.

The final results of the study confirmed that vaccination with Pandemrix contributed to the increased incidence of narcolepsy observed in those aged 4-19 years old. Using the date of first contact with heath care because of narcolepsy symptom, the RR in this age group for the study period 01/01/2009-15/08/2010 was 12.7 [95%CI: 6.1-30.8] and the absolute increased risk associated with the vaccine was 6 cases of narcolepsy per 100,000 vaccinated individuals. No increased incidence of narcolepsy was noted in children aged less than 4 years and in the adults over 19 years (6).

5.4.2. Sweden

In Sweden, the Medical Products Agency also conducted some epidemiological investigations following an unexpected large number of reports of narcolepsy in children and adolescents after vaccination with Pandemrix.

In a first study, the investigators compared the incidence rates of narcolepsy in vaccinated and unvaccinated individuals from October 2009 to December 2010. The RR was 4.2 [95%CI: 1.8-12.1] in children and adolescents. No increase in the incidence of narcolepsy was noted in adults (7).

In a second study, the investigators restricted the case definition to narcolepsy with cataplexy in children and adolescents from October 2009 to December 2010. They found a RR of 6.6 [95% CI: 3.1-14.5] and an absolute attributable risk of 3.6 cases per 100,000 vaccinated children and adolescents. The incidence of narcolepsy was substantially higher within the 3 months of the vaccination (8).

5.4.3. Norway

The Norwegian authorities have presented data on 20 cases of narcolepsy during the period September 2009 until July 2010, 19 of whom were vaccinated. They estimated an excess risk

of narcolepsy in 3/100,000 vaccinated children and adolescents similar to the Swedish results (9).

5.4.4. VAESCO case-control study

The European Centre for Disease Prevention and Control (ECDC) undertook a study within the framework of the Vaccine Adverse Events Surveillance and Communications (VAESCO). The study was conducted in nine European countries and aimed to estimate the background rate of narcolepsy, to assess a potential change in narcolepsy rates after April 2009 and October 2009, and to study the risk factors for narcolepsy (including influenza infection and vaccination).

Background rates were estimated through a retrospective cohort study while risk factors for narcolepsy were studied through a retrospective case-control study. Final VAESCO results are expected later this year.

6. EU authority measures and conclusions

Following an increased number of reports of narcolepsy in Finland and Sweden, the European Medicines Agency (EMA) initiated a review of Pandemrix and narcolepsy at the request of the European Commission under Article 20 of Regulation (EC) No 726/2004 in August 2010.

At the completion of this review in July 2011 the EMA recommended that in persons under 20 years of age Pandemrix may only be used if the recommended seasonal trivalent influenza vaccine was not available and if immunisation against H1N1 was still needed (e.g. those in the at risk groups). The EMA also confirmed that the overall benefit-risk balance of Pandemrix remained positive.

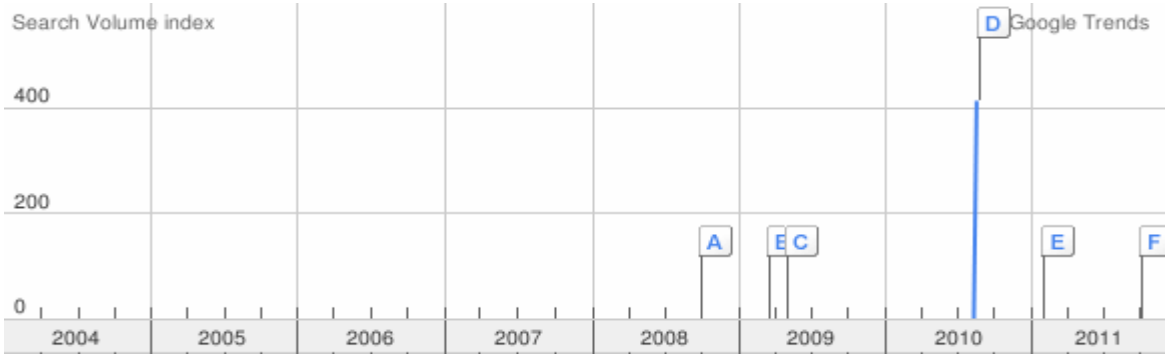
The EMA considered that the results of the epidemiological studies relating to Pandemrix in Finland and Sweden showed an association between Pandemrix vaccination and narcolepsy in children and adolescents in those countries. A similar risk has not been confirmed but couldn’t be ruled out in other countries.

The EMA also 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. They stressed that further research was necessary. Several initiatives are currently underway across the EU to further investigate this association.

7. Impact of Media on case identification

As a proxy for the effect of media attention in the population, we also looked at trends in searches for the keyword “narcolepsy” in Google (Figure 10). It suggests that concerns about narcolepsy in the Irish population started to rise in September 2011 (as opposed to August 2010 in Finland).

Finland



Ireland

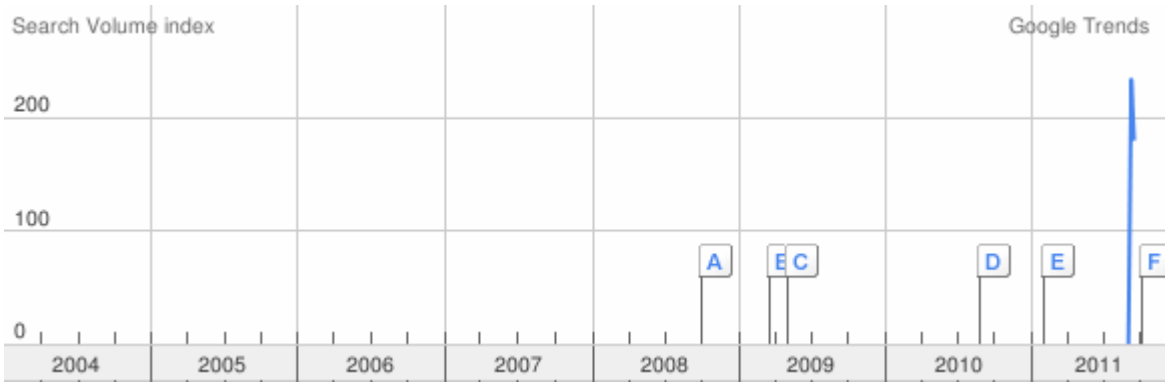


Figure 10: Trends in searches for the keyword “narcolepsy” in Google

Legend figure 10.

- A Japan experts find genetic clues to narcolepsy. ABC Science Online - Sep 29 2008
- B Narcolepsy Drug Might Be Addictive. U.S. News & World Report - Mar 17 2009
- C Researcher IDs Narcolepsy as Autoimmune Disease. Forbes - May 4 2009
- D Europe probes swine flu shot, narcolepsy link. Seattle Times - Aug 27 2010
- E Finland: link between swine flu shot, narcolepsy. Washington Post - Feb 1 2011
- F Finland vows care for narcolepsy kids who had swine flu shot AFP - Oct 5 2011

8. Timing of cases relative to Pandemic Influenza wave in 2009

In Ireland, children and adolescents were the most affected by the 2009/2010 pandemic influenza outbreak. In the 5-14 year olds, the influenza-like illness incidence rate peaked in week 43, i.e. one week before the pandemic influenza vaccination campaign was officially launched (Figure 11).

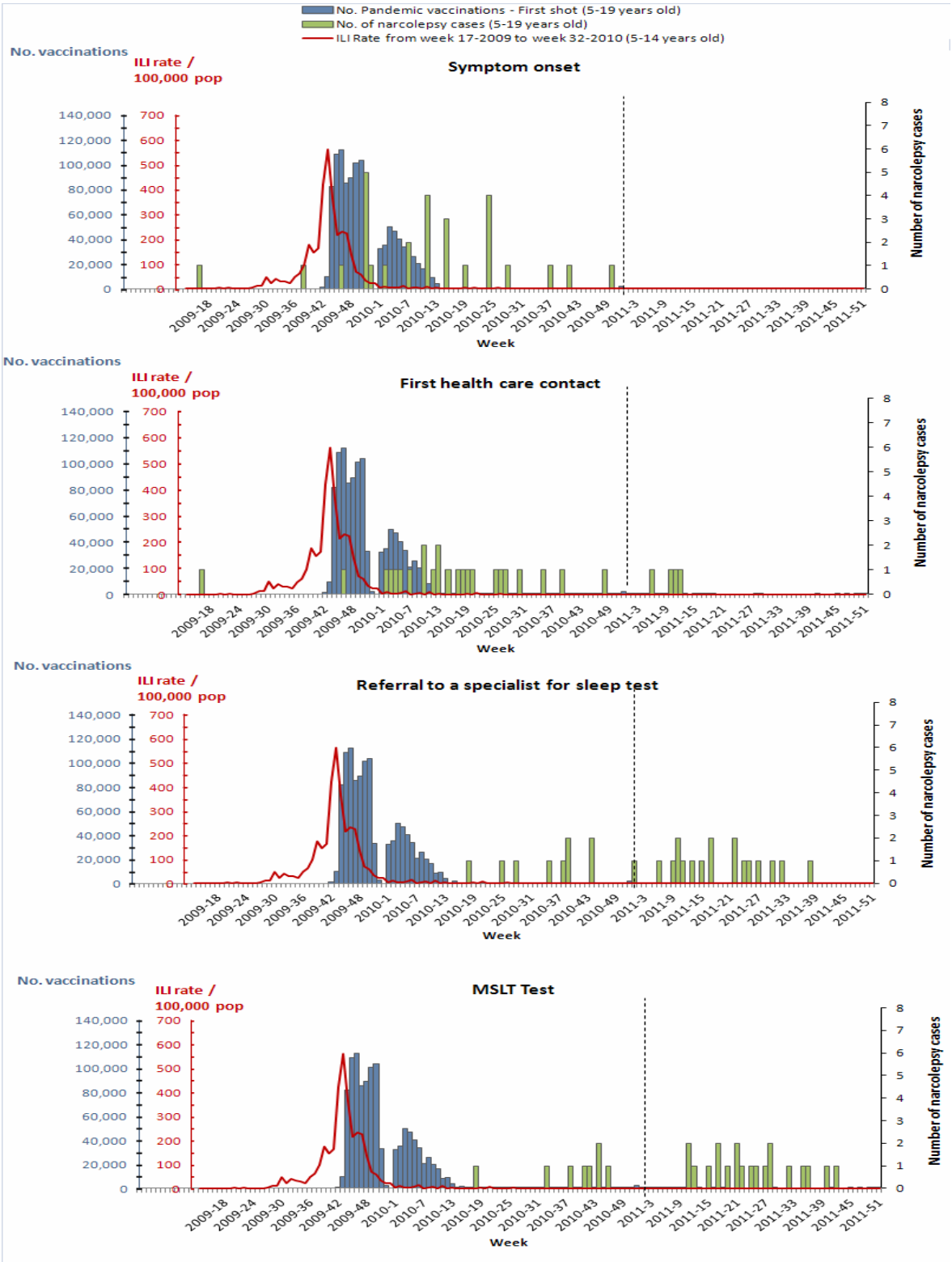


Figure 11: ILI rate from week 17-2009 to 32-210 (5-14 years old), number of pandemic vaccinations (5-19 years old) and number of narcolepsy cases (5-19 years old) by week
NB 1: When the exact date of symptom onset was unknown, it was approximated to the 15th of the reported month

9. Discussion

An increase in the incidence of narcolepsy was observed from 2009 in children and adolescents in Ireland.

As of 16th December 2011, 28 cases of narcolepsy with a symptom onset since April 2009 have been identified in children and adolescents in Ireland, and 22 (78.6%) of them had received a pandemic vaccine before symptom onset. Using as the index date their first contact with health care for narcolepsy symptoms, 24 cases were included in the analysis and 19 (79.2%) of them had received a pandemic vaccine before symptom onset.

Based on the primary study period (01/04/2009 to 31/12/2010) and the first health care contact because of narcolepsy symptom, we found a significant 13-fold higher risk of narcolepsy in children/adolescents vaccinated with Pandemrix compared with unvaccinated children/adolescents. The absolute number of narcolepsy cases attributable to Pandemrix vaccination was 5 per 100,000 vaccinated children/adolescents. These findings are remarkably similar to the results found in the retrospective population-based cohort study conducted in Finland.

The primary study period (01/04/2009 to 31/12/2010) was defined to include all cases with a possible exposure to both pandemic influenza infection and vaccination. The end of the study period was chosen to exclude any case that might have been identified because of an increase of GP and clinicians awareness about narcolepsy from March 2011 or because of the media attention in March 2011 (leading to a possible overestimation of the RR). However, when considering different index dates in the sensitivity analysis (excluding the cases that sought health care or were referred or had a MSLT test after 31/12/2010), the RR remained consistently and significantly greater than 1. We obtained similar results when restricting the study period from October 2010 when the pandemic vaccine was made available to the Irish population.

In another sensitivity analysis, we studied the possible effect of an increase of media attention in Finland at the end of August 2010. Using the date of first health care contact, the RR was significantly greater than 1. The result obtained using the date of referral for specialised sleep testing (MSLT) is difficult to interpret because of the small number of cases (25 of 28 cases were excluded because they were referred after 15/08/2010).

The health seeking behaviour, referral for a sleep test or diagnosis of cases did not seem to have changed following the increase of media attention in Finland. Looking at the index dates of the cases of narcolepsy, we did not find any particular increase in health care seeking, referral nor diagnosis after August 2010. On the other hand, a substantial number

of cases were referred and diagnosed from March 2011 onwards. This coincided with communication to general practitioners and hospital clinicians in March and April. As a proxy for the effect of media attention in the population, we also looked at trends in searches for the keyword "narcolepsy" in Google (Figure 10). It suggests that concerns about narcolepsy in the Irish population started to rise in September 2011 (as opposed to August 2010 in Finland).

A source of potential bias in case selection may have been introduced by the extensive media attention in Finland and Sweden as cases may be more likely to be reported if the patients were vaccinated. This is acknowledged to be a potential source of bias in the study. Both GPs and hospital clinicians were made aware of the reason for the study. The clinicians were requested to investigate vaccinated and unvaccinated in a similar fashion. However it is likely that vaccinated cases were more likely to undergo invasive procedures such as measurement of hypocretin in the CSF. However this would mainly effect their classification into Level 1 or level 2 and the study did not exclude cases who did not have their hypocretin measured

Although the case finding was performed irrespective of the cases' exposure status, it may be possible that vaccinated cases were more likely to have been identified and we cannot rule out that some unvaccinated cases have not yet been diagnosed or reported at the time of the report. However, the RR based on the first contact with health care would become non-significant only if there were still an additional 33 unvaccinated cases to be diagnosed in the 5-19 year olds in Ireland (RR=1.70, 95% CI: 0.98-2.96). The RR point estimate would get towards 1 only if there were still an additional 55 unvaccinated cases to be diagnosed in the 5-19 years old (RR=1.1, 95% CI: 0.6-1.8). It is possible that GPs were more likely to refer vaccinated cases who had more subtle symptoms that those unvaccinated with subtle symptoms. However we believe that GPs would refer those with severe symptoms of narcolepsy and cataplexy regardless of exposure history. The RR that we found in this study might have been overestimated but it is not likely that the positive association would disappear even if further unvaccinated cases are reported in the coming months

As noted above it is likely that more cases will be confirmed over the next few months. We think it is unlikely that these new cases will alter the findings described in this report.

In adults, the number of patients discharged with a primary diagnosis of narcolepsy and cataplexy remained stable over the period 1997-2009. We identified very few narcolepsy cases in adults through our case finding and it limited the analysis of the risk of narcolepsy associated with pandemic vaccination. Although the RR point estimate for Pandemrix was relatively high, the wide confidence interval around the estimate impedes drawing any conclusion in those aged over 20 years.

Only one case had received Celvapan (adult case). This case had the first contact with health care after 31/12/2010 and was therefore excluded from the analysis.

Because of the small number of cases, we had a very low power for testing the difference of characteristics between vaccinated and unvaccinated cases. The age and sex and distribution were similar between both groups. However there was an overall predominance of females in both the vaccinated and unvaccinated groups. Twenty two of the thirty two cases studied were female. Vaccinated cases were more likely to be classified as Level 1 of the Brighton case definition and to present with cataplexy (although this latter finding was not statistically significant). The delay between EDS onset and cataplexy onset was also shorter in vaccinated cases compared to unvaccinated cases (although not statistically significant). These results might suggest a clearer clinical picture of narcolepsy in vaccinated cases and a possible quicker development of symptoms as compared with the classical presentation.

In this study, we could not adjust the analysis for possible confounding factors such as previous infections or other vaccinations. Upper air-way infections, including the 2009/10 pandemic or *Streptococcus pyogenes* infections have been suggested as possible triggering factors for narcolepsy (10). In Ireland, children and adolescents were the most affected by the 2009/2010 pandemic influenza outbreak. In the 5-14 year olds, the influenza-like illness incidence rate peaked in week 43, i.e. one week before the pandemic influenza vaccination campaign was officially launched (11). The combination of pandemic influenza infection and vaccination might have initiated the development of narcolepsy. Further studies are needed to explore other triggering factors and possible interactions.

It is noteworthy that a high number (all of those for whom results were available) of cases had the HLA allele DQB1*-0602. The immunogenetic mechanism of narcolepsy and how Pandemrix vaccination contributed to its development need to be further studied and understood.

A limitation of the study is that not all pandemic vaccinations delivered during the pandemic are included in the 2 databases that were reviewed. As described above, the national immunisation office reported that 6% of pandemrix vaccines were supplied to sites such as public and private hospitals, community hospitals, nursing homes for the elderly and occupational health facilities. Some of these facilities provided information to the central databases and some recorded the information locally. However only a very small subset of these doses would have been delivered to young people in the relevant age group of 5- 19 years and therefore the committee does not consider that this alters the main findings of the report. It does however highlight the need for a national immunisation information system that would facilitate vaccine safety enquiries.

10. Conclusion

Through a retrospective population-based cohort study, we demonstrated that the increased incidence of narcolepsy in children/adolescents in Ireland from 2009 was associated with vaccination with Pandemrix. All cases who were tested and results available at time of chart retrieval (n=17) occurred in those who are genetically susceptible. The association could not be assessed accurately in adults because of the small number of cases reported. Our results were very similar to the findings reported from Finland and other Scandinavian countries.

Although we cannot exclude any selection or confounding bias which might have overestimated the risk of narcolepsy linked to Pandemrix vaccination, we believe that the association was so high that it is unlikely to be explained by any possible bias. Extensive case finding was undertaken in Ireland over the last 6 months and it unlikely that 33 – 55 cases in the unvaccinated cohort of 5-19 year olds are awaiting presentation to primary care and or investigation in secondary care.

Further studies are awaited (e.g. the VAESCO study) that will consider possible confounders and facilitate better understanding of the interaction of other infections such as H1N1 with pandemic vaccine.

11. Acknowledgements

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

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Annex A: Brighton case definition for Narcolepsy

General note:

In rare cases, a suspected narcolepsy case may not be classifiable according to the levels below (e.g. when there is cataplexy, no sleepiness, and hypocretin-1 levels are unavailable). In these instances, the case definition committee will examine the clinical data and decide whether or not the patient can be classified as having narcolepsy, and if yes, at which level.

Level 1

In the *presence* of:

criterion 1: Excessive daytime sleepiness[a] and/or suspected cataplexy AND

criterion 2: CSF hypocretin-1 deficiency[c]

Level 2

In the *presence* of:

criterion 1: Excessive daytime sleepiness[a] AND

criterion 2: Definite cataplexy[b] AND

criterion 3: Level 1 or 2 MSLT abnormalities[d]

Note: criterion 3 has only been added to add some form of 'objectivity' (without sacrificing sensitivity)

Level 3

In the *presence* of:

criterion 1: Excessive daytime sleepiness[a] AND

criterion 2: Level 1 MSLT abnormalities[d]

In the *absence* of:

criterion a: Other mimicking disorders, see [e]

[a] Excessive Daytime Sleepiness

Definition in adults (>= 16 years):

An acquired condition, characterized by:

- Involuntary sleep episodes during the day;
- Present almost daily for at least one month.

Definition in children (< 16 years):

An acquired condition, characterized by:

- Clear increase in daytime sleep episodes;
- Usually in combination with feelings of subjective sleepiness and impaired concentration;
- Present almost daily for at least one month.

[b] Definite cataplexy

Definition in adults (>= 16 years):

Presence of all of the following criteria (*before* initiation of treatment):

- Episodes of muscle weakness;
- With preserved consciousness;
- At least 2 attacks with a clear trigger;
- Majority of attacks lasting < 30 seconds.

Episode with documented reversible areflexia will also qualify as definite cataplexy, regardless of the above criteria.

Definition in children (< 16 years):

Children may present with cataplectic episodes that fulfil the criteria for adult cataplexy.

There may also be another phenotype that is restricted to children, with the following criteria:

- Acute-onset movement disorder, characterized by:
    - Falls to the ground (i.e. while walking or running), and/or
    - Generalized hypotonia, and/or
    - Head drops and/or
    - Prominent facial involvement resulting in “cataplectic facies”, with ptosis, mouth opening, tongue protrusion, remarkable facial weakness, grimaces.
- Preserved consciousness
    - Triggered by possible ‘emotional’ circumstances, such as when watching funny cartoons, eating certain food, playing games.
- Emotional triggers can be absent in the first weeks after onset
    - Duration of a few seconds to several minutes, but often present in protracted clusters due to continuing emotional triggers;
    - Episodes can be clearly distinguished from epileptic seizures or neuromuscular disorder.

[c] Hypocretin-1 deficiency

Hypocretin-1 concentration below 110 pg/ml using the Phoenix radioimmunoassay in crude, unextracted CSF. Performed in a laboratory according to published guidelines, using the Stanford reference sample[i]

[d] Multiple Sleep Latency Test Criteria

4 or 5 nap MSLT performed according to the AASM protocol[ii]

A. Mean sleep latency of less than 8 minutes (adults) or less than 12 minutes (children <16 years)[iii iv]
B. At least 2 sleep-onset REM periods

Level 1: A AND B
Level 2: A OR B

Note: "level 2 MSLT" has only been added to have a certain form of 'objectivity' without sacrificing sensitivity.

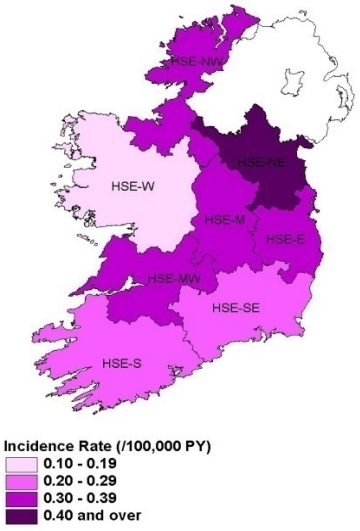
[e] to be excluded

The following conditions should be excluded:

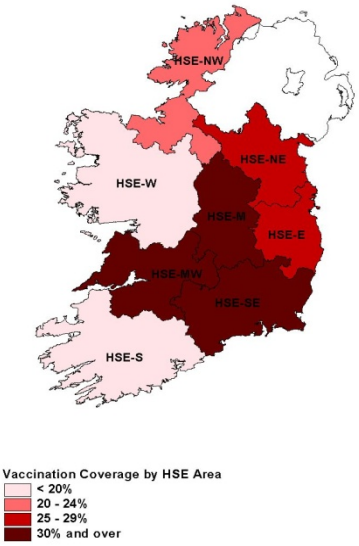
- Other sleep disorders, according to ICSD-2 criteria:
  - Sleep disordered breathing
  - Behaviourally Induced Insufficient Sleep
  - Circadian Rhythm Disorders
  - Recurrent hypersomnias
  - Hypersomnias secondary to medical or psychiatric conditions
- Use of sedating medication
- Focal cerebral lesions, indicated by neurological examination and/or brain imaging

[i] Lin et al. Guidelines for the appropriate use of CSF measurements to diagnoste narcolepsy and accrediation of measurement sites. In: Narcolepsy and Hypersomnia, 1st edition, 2006. Edited by Bassetti, Billiard and Mignot.
[ii] Littner et al. Practice parameters for clinical use of the multiple sleep latency test and maintenance of wakefulness test. Sleep 2005; 28:113-121
[iii] Guilleminault et al. Narcolepsy in children: a practical guide to its diagnosis, treatment and follow-up. Pediatr Drugs 2000;2:1-9
[iv] Serra L, et al. Cataplexy features in childhood narcolepsy. Mov Disord. 2008 Apr 30;23(6):858-65.

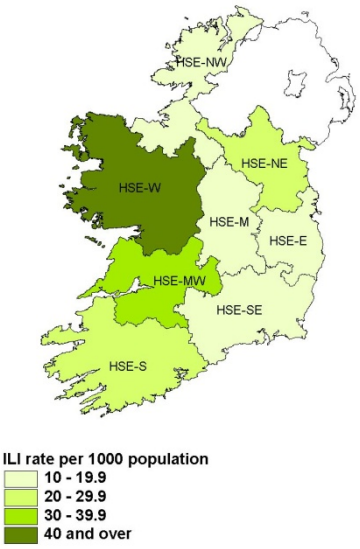
Annex B: Geographical distribution of narcolepsy incidence, 2009/10 pandemic vaccine uptake and indicators of pandemic influenza activity in 2009/10



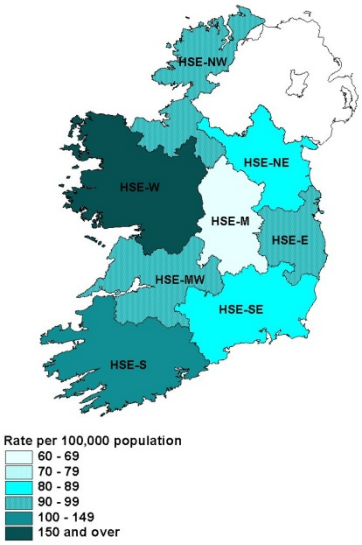
Incidence rate of narcolepsy (01/04/2009 – 31/12/2010)



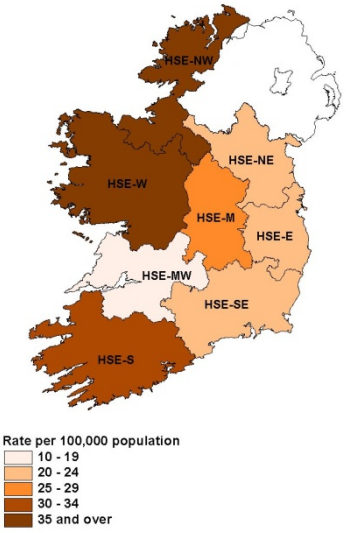
Pandemic vaccine uptake (all age groups and all vaccine brands) in 2009/2010



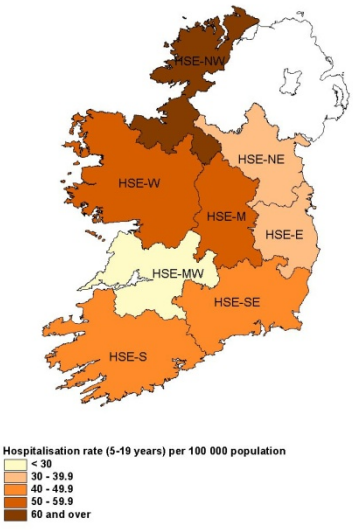
Cumulative incidence of influenza-like illness (week 17-2009 to 32-2010)



Cumulative incidence of laboratory confirmed influenza (week 17-2009 to 32-2010)



Cumulative incidence of hospitalisation for influenza (all age groups, week 17-2009 to 32-2010)



Cumulative incidence of hospitalisation for influenza (5-19 years old, week 17-2009 to 32-2010)

Annex C: Recommended dosage of Pandemrix and Celvapan in Ireland and changes to the recommendations (November 2009-January 2010)

Date Recommendation Communicated via NIO Bulletin	Category	Pandemrix		Celvapan	
		Number of Doses	Dosage (mls)	Number of Doses	Dosage (mls)
11/11/2009	Children 6 months to 12 years (up to 13th birthday)	2	0.25	2	0.5
	All those 13 years and over who are immunocompromised (due to disease or on immunosuppressive treatment)	2	0.5	2	0.5
	All those 13 years and over (including HCWs) who are NOT immunocompromised	1	0.5	2	0.5
	Pregnant women and up to 6 weeks post partum	1	0.5	2	0.5
27/11/2009*	Children 6 months to 9 years (up to 10th birthday)	2	0.25	2	0.5
	All those 10 years and over who are immunocompromised (due to disease or on immunosuppressive treatment)	2	0.5	2	0.5
	All those 10 years and over (including HCWs) who are NOT immunocompromised	1	0.5	2	0.5
	Pregnant women and up to 6 weeks post partum	1	0.5	2	0.5
03/12/2009	Children 6 months to 9 years (up to 10th birthday)	1	0.25	2	0.5
	Children 6 months to 9 years (up to 10th birthday) who are immunocompromised (due to disease or on immunosuppressive treatment)	2	0.25	2	0.5
	All those 10 years and over who are immunocompromised (due to disease or on immunosuppressive treatment)	2	0.5	2	0.5
	All those 10 years and over (including HCWs) who are NOT immunocompromised	1	0.5	2	0.5
	Pregnant women and up to 6 weeks post partum	1	0.5	2	0.5

All those requiring a 2nd dose of Pandemrix offered this at least three weeks after first dose
Everyone vaccinated with Celvapan recommended two doses (0.5ml) at least three weeks apart
From 27/11/2009 Pandemrix was recommended for all those requiring pandemic vaccine (unless they had an egg allergy) to maximise vaccine usage as most only need one dose and children under 10 years only require half a dose
*Children aged 10-12 years (up to 13th birthday) who already received one dose (0.25ml) of Pandemrix were recommended a second dose (0.25ml) of Pandemrix at least three weeks after the first
**Children aged 10-12 years (up to 13th birthday) who already received one dose (0.25ml) of Pandemrix were not recommended any further doses of Pandemrix (except those who are immunocompromised who require a second half adult (0.25ml) dose at least three weeks after the first dose) HCWs=Health Care Workers

Annex D: Pandemrix distribution, batch numbers and dates of distribution (November 2009-January 2010)

Vaccine	Batch Number	No. patients in receipt of batch	No persons in receipt of batch by first dose	Delivery dates			
				Oct-09	Nov-09	Dec-09	Jan-10
Pandemrix	A81CA047D	1	15031	√			
	A81CA067A	2	77139	√			
	A81CA070A	0	47081	√			
	A81CA084A	1	74693	√			
	A81CA105A	1	87475	√			
	A81CA137A	0	57696		√		
	A81CA149A	2	91061		√		
	A81CA180A	9	165752		√		
	A81CA227A	2	150286			√	
	A81CA228A	2	42834			√	
	A81CA293A	5	59349			√	
	A81CA377A	1	5334			√	
	A81CA379A	3	70944			√	
	A81CA380A	0	322			√	
	A81CA403A	0	82				√
	A81CA445A	0	159				√
Celvapen	VNV9J007A	1		√			
Grand Total		**30**		**6**	**3**	**6**	**3**