Narcolepsy and H1N1 vaccination: a link?

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Purpose of review
A number of European countries have reported a dramatic increase in the rates of childhood narcolepsy with cataplexy in children immunized with a split-virion adjuvanted swine flu vaccine. Here, we review the strengths and weaknesses of these epidemiological studies and possible neuroimmunological mechanisms.

Recent findings
Initial concerns of a 13-fold increased relative risk of narcolepsy were raised by the Scandinavian health protection agencies in 2010. Subsequent retrospective studies support these findings in Canada, France, Ireland, England and Denmark. The cases are predominantly young children who present with severe and rapid onset of cataplexy as well as narcolepsy often within a few weeks of vaccination. The proposed mechanism for postvaccination narcolepsy is one in which an environmental trigger causes or enhances an antibody-mediated autoimmune response in patients with a preexisting genetic susceptibility. However, there have not yet been any reports of specific autoimmunity, either antibody or T-cell-mediated.

Summary
There is a strong association between narcolepsy and H1N1 vaccination. However, whether this reflects a true increase in affected individuals or a hastening of disease onset in individuals who would otherwise have developed narcolepsy later will become clear in the coming years. The pathological explanation of this association and narcolepsy is likely to be autoimmune, although supportive evidence is lacking.
Video abstract available: See the Video Supplementary Digital Content 1 (http://links.lww.com/COPM/A9).

Keywords
H1N1, immunization, narcolepsy, paediatrics, Pandemrix, sleep

INTRODUCTION

Perhaps the most startling recent development in vaccinology is the widely reported association between the ASO-3 adjuvanted swine flu (H1N1) vaccination (Pandemrix) and abrupt-onset narcolepsy with cataplexy in paediatric age groups. Although estimates vary, it is likely that more than 1000 children have been affected globally. Independent groups of researchers in several European countries have reported that children are around 14 times more likely to develop narcolepsy following the Pandemrix vaccination. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommends:

> 'In persons under 20 years of age Pandemrix is to be used only in the absence of seasonal trivalent influenza vaccines, following a link to very rare cases of narcolepsy in young people. Overall benefit-risk remains positive.'

In this review, we summarize the most recent epidemiological developments, and discuss these in the context of putative immunological mechanisms.

NARCOLEPSY: NATURE OR NURTURE?

Before exploring the role of this potential environmental trigger, an update of the clinical features and theories of narcolepsy pathogenesis is necessary. Narcolepsy is a lifelong sleep disorder of unknown cause, with onset typically in early adulthood. The prevalence of narcolepsy is widely reported to be around five per 100 000 [1], and patients experience excessive daytime sleepiness in conjunction with

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KEY POINTS

- Studies from several European countries have found that children are around 14 times more likely to develop narcolepsy following the Pandemrix vaccination.
- Cases of 'postvaccination' narcolepsy are typically described in young children with rapid onset of cataplexy symptoms.
- The presenting cataplexy symptoms are often the atypical positive and negative features described in young children, and can lead to diagnostic confusion.
- There is still no proven immunological mechanism that explains the epidemiological findings.

the pathognomonic symptom of cataplexy, which is a sudden bilateral loss of motor tone triggered by positive emotion (Tables 1 and 2) [2,3].

Central to narcolepsy is the loss of around 70 000 neurons secreting the neuropeptide orexin (hypocretin) in the lateral hypothalamus [4] with subsequent loss of orexin neuropeptide in the cerebrospinal fluid (CSF) [5]. These neurons play a pivotal role in sleep and energy homeostasis, and their selective death is thought to provide a pathological explanation for the condition.

Although the cause of narcolepsy remains unclear, epidemiological studies also provide some insight. Although first-degree relatives are at 10–40 times increased risk of developing narcolepsy, twin concordance rates are particularly low (25%), suggesting that environmental factors operate together with genetic susceptibility [6].

The prevailing hypothesis is that narcolepsy is an autoimmune condition, mainly because of the tight association with HLA DQB1*0602. T-cell immunity or antibody-mediated cytolytic attack on the orexin neurons is the most attractive hypothesis. The paradigm for autoantibodies directed against the surface of neurons in the central nervous system and causing neurological autoimmune disease, including conditions with marked sleep disturbance, is now well established [7], and could provide a particularly elegant explanation for the selective neuronal loss seen in narcolepsy. However, no causative autoantibodies or autoreactive T cells have yet been identified. Although antibodies directed against Tribbles homologue 2 (TRIB2) were recently implicated [8], this ubiquitous cytosolic kinase is an unlikely pathogenic target as it is an intracellular protein that would not be accessible to circulating antibodies. Moreover, TRIB2 antibodies are not common in narcoleptic patients, and are also found in other diseases [9–12].

FROM CASE REPORT TO EUROPE-WIDE EPIDEMIOLOGICAL STUDY

Authorized by the European Medicines Agency in September 2009, Pandemrix is an ASO3-conjugated (containing squaline) split-virion vaccine. Worldwide, the vaccine was used in at least 47 countries, with over 30 million vaccinated individuals in Europe, and particularly high coverage rates in Finland, Sweden, Norway, Iceland and Ireland [13]. A similar ASO-3 conjugated vaccine (Arepanrix) was used in Canada. Although previously untested in paediatric age groups, Pandemrix was chosen because the novel ASO3 adjuvant was thought to enhance H1N1 immunogenicity at a time when the seriousness of the pandemic was overestimated globally [14].

Swedish and Finnish pharmacovigilance authorities first raised the alarm in August 2010 when they announced that they were respectively investigating six cases of narcolepsy reported by the healthcare professionals as a possible adverse event following the use of Pandemrix vaccine used during the H1N1 2009 pandemic [15,16]. A subsequent multicentre study reported an additional 14 post-vaccination cases of strikingly abrupt narcolepsy

Table 1. International Classification of Sleep Disorders-2 diagnostic criteria for narcolepsy-cataplexy, 2005

A	Symptoms of EDS for more than 3 months
B	Definite history of cataplexy: episodes of sudden, transient loss of muscle tone precipitated by emotion
C	Confirmation by CSF orexin-A measurement which should be less than or equal to 110 pg/ml
	OR
	Confirmation by multiple sleep latency testing following nocturnal polysomnography: following a minimum of 6-h sleep, mean sleep latency should be less than 8 min, and at least 2 SOMREMPs should be observed, defined as the electroencephalographic appearance of REM sleep within 40 min of sleep onset
D	The hypersomnia is not better explained by another cause, including other sleep disorders, neurological or psychiatric disorders, medication or substance misuse

CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; REM, rapid eye movement; SOMREMPs, sleep onset REM periods.

Table 2. Sensitivity and specificity of tests for narcolepsy-cataplexy

Test	Sensitivity	Specificity
HLA DQB*0602	89.3% (822/1291)	76 (1291)
CSF orexin <110 pg/ml	83.3% (233/182)	>99%
MSLT	87.9% (964/1095)	96.9% (1095)

CSF, cerebrospinal fluid; MSLT, Multiple Sleep Latency Test. (Adapted from Mignot [3]).

onset in atypical age groups [11]. Since these initial reports, robust epidemiological studies from, Finland [17▪,18▪▪], Sweden [19], Ireland [20▪], France [21▪] and England [22▪] have found strikingly similar results of around a 14-fold increased risk (Fig. 1: timeline and summary). To date, it would seem that all cases of narcolepsy appearing following vaccination share the susceptibility gene of HLA DQB0602.

Study designs to date have either compared incidence rates pre and postintroduction of the vaccine, or incidence rates in vaccinated versus unvaccinated individuals. The methodologies and findings of the main studies comparing vaccinated and unvaccinated groups is summarized in Table 3.

Intriguingly, the study led by the European Medicine's Agency's European Centre for Disease Prevention and Control (ECDC), better known as the VAESCO report, only confirmed an increase in narcolepsy diagnoses in the original Scandinavian countries [23▪]. There were, however, important methodological limitations including that the study was highly dependent on pooled incidence estimates from automated databases with differences in case capture, a factor which likely accounts for much of the variation in data between countries. Furthermore, Ireland, Iceland and Germany, which had high vaccination coverage rates, were not able to participate, and in the case of the United Kingdom, France, Sweden and Norway, case ascertainment could not be completed prior to the ending of the project.

IS H1N1 VACCINATION A CAUSE OF NARCOLEPSY?

A time-honored approach for establishing likely causation is the application of the criteria set out by Austin Bradford Hill [24]. In relation to the reported association between narcolepsy and H1N1 vaccination, evidence can be assessed in terms of strength, consistency, specificity, temporality, biological gradient (dose response), plausibility, coherence with laboratory findings, experiment and analogy to similar vaccines.

Strength

The stronger the association, the more likely it is that the relation between Pandemrix vaccination and narcolepsy is causal. Although the gross numbers of affected children may be relatively small, in a disease as rare as narcolepsy, a 14-fold increased risk is important. Although the quoted confidence intervals may be wide they still remain positive, even after careful adjustments for possible causes of bias [18▪▪,19].

Temporal relationship

The very premise that Pandemrix might be a causal factor of narcolepsy relies on the fact that affected individuals had a preceding vaccination. This implicitly holds true for all of the studies, which used retrospective case identification. This is the only absolutely essential criterion and is fulfilled by all reported studies.

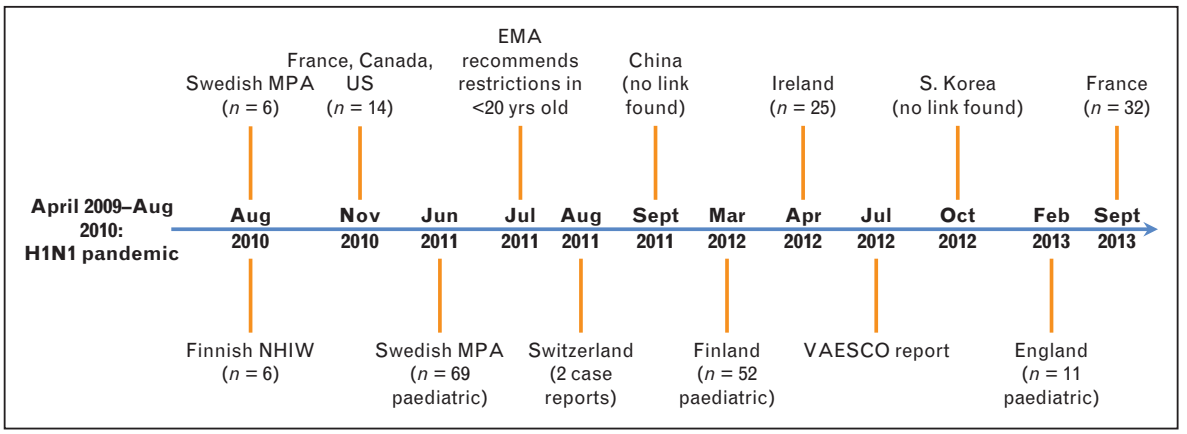

FIGURE 1. Reports of post-H1N1 vaccination narcolepsy. EMA,European Medicines Agency; MPA, Medical Products Agency; NIHW, National Institute of Health and Welfare; VAESCO, Vaccine Adverse Event Surveillance and Communication.

Table 3. Summary of European studies of expert-confirmed narcolepsy rates in vaccinated and unvaccinated groups

Country	Date	Authors	Design	Study period	Vaccine uptake	No. post-vaccination cases	Age at Diagnosis	Lag time vaccinatio n-diagnosis	Risk of narcolepsy in vaccinated groups
Sweden	Jun 2011	Medical Products Agency [19]	Retrospective cohort vaccinated vs. unvaccinated in those aged<19	01/01/09–31/12/10	67.1% of under 20 year olds	69	Median 13		RR 6.6 (3.1–14.5) paediatric narcolepsy post vaccination Abs.R 3.6/100,000 vaccinations
Finland	Mar 2012	Nohynek *et al.* [18▪▪]	Retrospective cohort vaccinated vs. unvaccinated in those aged 4–19yrs	01/01/10–31/12/10	75% in 5–20 year olds, >80% in 5–14 year olds	50	Mean 11.6 (SD 3.1)	44 weeks	RR 12.7 (6.1–30.8) paediatric narcolepsy post vaccination Atrib.R:1:16,000 (13–21,000) vaccinations
Ireland	April 2012	Irish National Narcolepsy Steering Committee [20▪]	Retrospective cohort vaccinated vs. unvaccinated	01/04/09–31/12/10	41.7% of <19 year olds 22.5% general population	25 (19 children/ adoles cents)	Modal age group 10–14	31.5 weeks	RR 13 paediatric narcolepsy post vaccination; Abs.R 5/100000 absolute risk in this age group
England	Feb 2013	Miller *et al.* [22▪]	Retrospective case coverage method	01/01/08–10/02/13	8.4% of 2–18 year olds	11	Modal age group 4–8	<6 months in 64%	9.9x RR; Atrib.R 1/52–57,500
France	Sept 2013	Dauvilliers *et al.* [21▪]	Retrospective case-control vaccinated versus unvaccinated	01/10/09–30/04/11	8.8%	37 26 >19 yrs	Median 14.8 (IQR 13.3–24.4	49.4 weeks	<18 age group: OR 6.5 [2.1–19.9] >18: OR: 4.7 [1.6–13.9]

For more detailed information of the individual studies, readers are directed to the individual studies.
RR, relative risks (the probability that a member of an exposed group will develop disease relative to the probability that a member of an unexposed group will develop the same disease).
Abs R, absolute risk (the observed or calculated probability of an event in the population under study).
Atrib R, attributable risk (assuming a factor is the cause of a disease, attributable risk is the amount of risk that is because of that factor)
OR, odds ratio (measure of effect size describing the strength of an association between two binary values)
Definitions taken from http://www.medicine.ox.ac.uk/bandolier/glossary.html

It remains to be seen whether the rate of paediatric narcolepsy will return to preswine flu levels now that Pandemrix vaccination is uncommon. One possibility is that the unusually early onset of postvaccination narcolepsy simply represents an accelerated disease course in individuals who may have otherwise gone on to develop the condition several years later. The incidence of narcolepsy, therefore, might now start to fall below that of preswine flu levels in older children and younger adults, if potential cases have been 'triggered' earlier.

Dose–response relationship

Given the fixed-dosing regimes used, at the individual case level this criterion is not applicable.

Consistency

A causal relationship is likely to be consistently reported in different study populations by studies with different designs. This can be said for several of the European studies which, as previously outlined, found similarly increased incidences in different countries, ether comparing pre versus postvaccination cases or vaccinated versus unvaccinated cases. The exception was the ECDC (VAESCO) study [23▪] that, as mentioned above, had methodological limitations. In China, a retrospective self-report analysis of Beijing narcolepsy onset concluded that a three-fold increase in narcolepsy onset following the 2009 H1N1 pandemic was unlikely to be explained by the increased vaccination, as only eight of 142 (5.6%) patients recalled receiving Pandemrix vaccination [25]. In South Korea, where three quarters of children were vaccinated, an ecological study of incidence rates pre, during and post Pandemrix found no increase in cases [26]. In both of these cases, criticism can be made of the lack of case verification, but it is still interesting that associations have not thus far been found outside of Europe, even in countries with high vaccine uptake rates.

Plausibility and coherence

As previously outlined, the prevalent aetiological hypothesis is of an autoimmune destruction of orexin neurons. The paradigm for vaccine-triggered neurological autoimmune diseases is a well recognized concept, for example as in the case of Guillain–Barré. A plausible mechanism would involve cross-reactivity of T-cell clones and/or antibodies with H1N1 vaccine components and the orexin neurons. This, however, fails to acknowledge the possible significance of the strong immune reaction as a result of the ASO3 adjuvant (a chemical mixed with the vaccine deliberately intended to heighten the body's immune stimulation). For instance, the split virion might be irrelevant, with the immune response induced by the adjuvant nonspecifically enhancing preexisting immunity, and thereby lowering the threshold for brain inflammation and destruction of the orexin neurons in susceptible HLA DQB0602 positive individuals.

It is widely reported that streptococcal infection is associated with narcolepsy onset [27]. Furthermore, elevated streptococcal titres have also been detected in a large proportion of postvaccination cases [10]; it is possible that the interaction between H1N1 vaccination and recent streptococcal infection may provide excessive immune activation that leads to autoimmunity against the orexin neurons in susceptible individuals.

Consideration of alternate explanations

In judging whether a reported association is causal, it is necessary to determine the extent to which researchers have taken other possible explanations into account and have effectively ruled out such alternative explanations. Could it simply be that the early Finnish reports rapidly raised awareness of narcolepsy, and therefore just prompted quicker case ascertainment? In diseases with usually a long lag time such as narcolepsy there are a large pool of existing cases waiting to be 'diagnosed'. If these were diagnosed faster following greater awareness of the condition, narcolepsy would appear to be more common, and this could have been preferentially for the vaccinated young people.

The cited studies attempted to take this into account by restricting analyses to patients with a diagnosis by July 2011, when reports from Finland and Sweden had not generated media or public interest, and before the first spike in Internet searches for 'narcolepsy' (which occurred in December 2011). Many went further and modelled the extra numbers of cases they would have to have missed if such bias existed. None of these adjustments, however, altered their conclusions.

Experiment

A formal randomized controlled trial will of course never take place. Trials of intravenous immunoglobulins, used extensively to treat antibody-mediated autoimmune diseases, have yielded conflicting results, neither confirming nor disproving efficacy

[28,29]. As all reported cases are HLA DQ06 positive, it could be helpful to determine HLA type prior to vaccination and question its use in those children who are positive [11]. This has not yet been performed and, as this particular vaccine is not being used currently, is unlikely to take place in the near future.

Specificity

Because outcomes such as narcolepsy are likely to have multiple factors influencing them, it is highly unlikely that we will find a one-to-one cause–effect relationship between vaccination and narcolepsy. In fact, there is some evidence for lack of specificity in that not only the vaccine but also H1N1 itself is associated with higher rates of narcolepsy [11]. Few of the published studies have managed to establish which vaccinated or unvaccinated children had also been exposed to, and contracted H1N1, which was in fact milder in many more cases than expected.

POSTVACCINATION NARCOLEPSY: A SPECIFIC PHENOTYPE?

The most striking clinical features of 'postvaccination' narcolepsy are the atypically young ages affected, and the particularly abrupt onset of cataplexy symptoms. In vaccinated children, the time between vaccination and onset of cataplexy, the defining feature of narcolepsy, ranged between 2 days and 20 weeks, with an average time of 7.4 weeks [11]. Moreover, there are many atypical features, some of which mimic other neurological disorders [30]. Negative motor features include hypotonia, ataxic gait and head drops; positive motor features include tongue protrusions, grimacing, stereotypies and dystonic/choreiform movements of arms. All features can be part of the initial presentation of the disease, often in very young children, and may be persistent and occur in the absence of clear emotional triggers. Perhaps the most plausible explanation of this is that, rather than representing an entirely new disease entity, post-vaccination narcolepsy is a greatly accelerated form of the disease in susceptible individuals.

Immunology

One of the major limitations of prior studies looking for serological clues of narcolepsy aetiology has been the challenge in collecting serum and CSF samples sufficiently close to disease onset. The putative causative agent, for instance orexin neuron-specific antibodies or T cells, may only be transiently present, which may explain the paucity of findings when investigating samples taken years after diagnosis. The abrupt and unequivocal onset of symptoms in postvaccination narcolepsy appears to provide an unusual opportunity to investigate such recent-onset samples, and may provide insight into aetiology of all cases of narcolepsy. A number of laboratories are currently investigating the samples from these children for evidence of autoantibodies, T cells or other immune mechanisms that could be causative. No results have been reported so far.

CONCLUSION

The association between Pandemrix vaccination and narcolepsy is arguably one of the most robust vaccine-associated neurological adverse events yet reported, in a field wherein such claims are often made, but usually unsubstantiated. The tantalizing prospect that this tragic occurrence would generate new information to help understand the pathogenesis of narcolepsy has not yet been realized. The CHMP has now recommended that:

'In persons under 20 years of age Pandemrix to be used only in the absence of seasonal trivalent influenza vaccines, following a link to very rare cases of narcolepsy in young people'.

SUGGESTIONS FOR FUTURE RESEARCH

(1) In countries where a postimmunization 'spike' has been observed, long-term follow-up of affected individuals is required to determine if there are any persistent differences in clinical phenotype including responses to treatments.
(2) Continued surveillance of narcolepsy incidence rates in those same countries to address questions about whether these were new cases, or cases 'waiting to happen' but brought forward by a vaccination 'trigger'.
(3) Investigations including ASO titres, CSF orexin and sera for immunological markers could be performed as soon as possible after onset of symptoms, and the samples stored for future investigations if a biomarker is identified.

Acknowledgements

None.

Conflicts of interest

P.G. has provided report as independent expert witness to a medicolegal case for children who developed narcolepsy soon after immunizations. His duty was to the court.

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This systematic analysis of the incidence rates of narcolepsy 2002–2010 identified a sudden increase in the incidence rates in 2010, corresponding to the use of Pandemrix. Most of these cases were paediatric and had experienced abrupt symptom onset.

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This was the first of the European retrospective cohort studies of 4–19 year olds, comparing rates of narcolepsy in vaccinated versus unvaccinated individuals, to be reported in a peer review journal. The authors reported around 13-fold rates of nacrolepsy in the vaccinated group.

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Athough not peer-reviewed, this apparently comprehensive retrospective study of Irish narcolepsy incidences in both children and adults found a 13-fold increased risk in vaccinated children. Authors also made substantial efforts to account for the potential bias of increased media attention, and concluded that although this may have contributed, it could not have explained all of additional cases seen.

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This is the most recently published European report, based on the French NarcoFlu report released in 2012. Most notably, in France, the higher rates of narcolepsy following vaccination were seen in adults as well as children (odds ratio 4.7 and 6.5 respectively).

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