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## Review article

# Adjuvanted AH1N1 influenza vaccine precipitating the appearance of narcolepsy<sup>☆</sup>



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## ABSTRACT

The vaccination against influenza A-H1N1 applied during the pandemic of 2009 demonstrated a positive association with the appearance of narcolepsy and/or concomitant cataplexy. Narcolepsy is a hypersomnia that affects greatly quality life of people that suffer from it. The present manuscript is an updated literature review regarding scientific evidence in this field. Reviewed scientific literature shows a positive relation between A-H1N1 vaccine and appearance of narcolepsy cases, however, etiopathogenic aspects are still unknown, so more studies are necessary, especially in the current moment, were some authors stipulate that a vaccine against SARS COVID-19 could cause similar effects that is crucial to minimize them.

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## Vacuna frente a influenza H1N1 con adyuvante AS03 y su efecto desencadenante de narcolepsia

## RESUMEN

La vacunación frente a la epidemia de influenza A-H1N1 que se aplicó durante la pandemia de 2009 ha demostrado tener una asociación positiva con la aparición de narcolepsia y/o cataplejía concomitante. La narcolepsia es una hipersomnia que afecta de manera importante la calidad de vida de quien la padece. El presente trabajo es una revisión bibliográfica actualizada acerca de la evidencia disponible en este sentido. La literatura revisada demuestra una relación positiva entre la vacuna frente a la influenza A-H1N1 y la aparición de narcolepsia, si bien el mecanismo etiopatogénico es aún desconocido, por lo que se hacen necesarios más estudios, especialmente en el momento actual, en que algunos autores apuntan a que la vacuna frente a SARS COVID-19 podría causar efectos similares que es necesario minimizar.

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## Palabras clave:

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## Introduction

Vaccination yields significant health benefits; however, fear surround the possible negative side effects has discouraged many people from getting vaccinated, which has led to the resurgence of diseases that until now, had been controlled, such as measles, pertussis, and diphtheria. This fear has been amplified even further by numerous epidemiological studies that confirmed the link between an anti-pandemic, AS03-adjuvanted flu vaccine used in Europe during the H1N1 2009 A (H1N1) flu pandemic with the side effect of narcolepsy development in children and adolescents.<sup>1</sup> It is important to highlight that adjuvants, such as AS03, act by augmenting vaccine immunogenicity, making them more attractive for use in developing future vaccines.<sup>2</sup>

Narcolepsy is a chronic hypersomnia syndrome characterized by excessive daytime sleepiness [EDS], an altered sleep pattern, and parasomnias during REM sleep, such as hypnagogic hallucinations and sleep paralysis. According to the International Classification of Sleep Disorders (ICSD-3), the illness can be divided into two distinct subcategories: narcolepsy type 1 and type 2. Narcolepsy type 1 (NT1) is probably an immunomediated disease caused by the destruction of orexin-producing neurons in the lateral hypothalamus, resulting in a deficit of that hormone in central nervous system. More than 98% of patients with NT1 have a predisposing genetic background, are positive for the HLA DQB1\*06:02 allele, and cataplexy (sudden loss of muscle tone triggered by emotion). In narcolepsy type 2 (NT2), orexin levels are normal and cataplexy is absent. Within the aetiology of NT1, various studies show an association with influenza H1N1 vaccination. La aetiology of NT2 is currently unknown.<sup>3</sup>

Narcolepsy is a rare disease that affects some 20–50/100,000 people.<sup>4</sup> However, during the first year following H1N1 vaccination, the relative risk of narcolepsy appears to increase.

## Background

The most recent pandemic (prior to the current COVID-19 pandemic) was the so-called «swine flu», caused by a regrouped type A influenza H1N1 virus. It first appeared in Mexico and the United States in March 2009. The number of laboratory-confirmed cases rapidly increased and the virus spread to many other countries. In June 2009, the WHO had already declared that a new pandemic had begun.

In 2009, an observational study in Mexico pointed out that 6.5% out of 900 patients hospitalized with H1N1 infection were seriously ill and, of them, 41% died. Mortality rates were particularly high in children, young adults, and pregnant women. Consequently, this first pandemic of the XXI century appeared to be very serious and there was considerable need to develop an effective vaccine against the pandemic very quickly.<sup>3</sup>

## Administration of the H1N1 vaccine

Eight different anti-pandemic vaccines were administered in Europe to a total of at least 46 million people. Five of these vaccines were not adjuvanted, whereas 2 included MF59 as

an adjuvant and other vaccines, specifically Pandemrix® and Arepanrix®, contained AS03 as an adjuvant.

Adjuvants bolster the immunogenicity of antigens, which makes it possible to use smaller amounts of immunogenes in vaccines for an efficient induction of protective immunity. Pandemrix® was the most widely used vaccine in Europe with more than 30.5 million doses administered.<sup>5</sup>

## Precipitating factors of narcolepsy

In 2013, Thebault et al.<sup>6</sup> reported a dramatic rise in narcolepsy rates in children from different European countries after being vaccinated with adjuvanted vaccines and concluded that there is a strong association between narcolepsy and H1N1 vaccination. However, other studies have yielded more ambiguous results.

One study carried out in Taiwan analyzed narcolepsy following H1N1 vaccines without adjuvant AS03 or with a different adjuvant. The authors detected no substantial association between the adjuvant and the onset of vaccine-induced narcolepsy. They pointed toward the virus itself as precipitating this narcolepsy.<sup>7</sup> In this same regard, Weibel et al.<sup>2</sup> conducted an extensive retrospective, observational study in 6 different countries (Argentina, Canada, Spain, Switzerland, Taiwan, and The Netherlands) and concluded that the incidence of narcolepsy had increased only in Sweden and in Taiwan, albeit, in the latter, the rise had taken place prior to vaccination; hence, the cause of its onset would have to be found elsewhere. A study similar to that by Kim et al.<sup>8</sup> performed in South Korea examined the cases of narcolepsy after administration of H1N1 vaccines that contained the adjuvant MF59. The authors found no increase in the cases of narcolepsy following the vaccination campaign. Tesoriero et al.<sup>9</sup> intranasally infected mice with the influenza A (H1N1) virus and observed that 4 weeks post-infection, their sleep-wake cycle was altered, opening the door to the possibility that the infection gave rise to neuronal disturbances that caused the narcolepsy. For their part, Haba-Rubio et al.<sup>10</sup> talk about narcolepsy as an autoimmune disease, the onset of which might be facilitated by the H1N1 vaccination in susceptible individuals.

Furthermore, Montplaisir et al.<sup>11</sup> analyzed the incidence of narcolepsy in the population of Quebec by means of a retrospective study. They concluded that there was an increased risk in people who received an AS03-adjuvanted vaccine, although their conclusions were weak and further investigation along this line was needed.

Thus, there are several studies around the world that have examine the possible action of the H1N1 vaccine as precipitating narcolepsy, although more studies must be carried out that can yield more accurate conclusions.

In the present day situation of the SARS COVID-19 pandemic, various teams are attempting to find a vaccine that protects people. Given the background of the possible association of narcolepsy with the H1N1 vaccine, it has become more compelling than ever before to ascertain whether the vaccines and/ or their adjuvants induce the narcolepsy, or if it is the virus itself that causes its onset in individuals genetically predisposed.<sup>12</sup>

## Treatment

The symptomatic treatment for narcolepsy associated with the administration of AS03-adjuvanted vaccines is the same as treatment for idiopathic narcolepsy; i.e., the administration of modafinil, methylphenidate, and sodium oxybate, amongst others. Immunomodulating therapy has failed to demonstrate that it is effective.<sup>3</sup>

A recent report by Viste et al. suggested that early immunotherapy combined with methylprednisolone and intravenous immunoglobulin (IVIg) can bring about a positive result in alleviating the symptoms, albeit the results must be taken with caution, as the natural evolution of narcolepsy is highly disparate.<sup>13</sup>

Dauvilliers et al. observed that orexin levels normalized and both the sleepiness and cataplexy remitted after treating a patient with IVIg. The authors' findings point toward the importance of getting an early diagnosis of narcolepsy, inasmuch as early or immediate treatment can reverse or prevent the permanent deficit of orexin, although the long-term prognosis with and without IVIg remains to be documented.<sup>14</sup>

For their part, Lecendreux et al.<sup>15</sup> concluded that, generally speaking, the symptoms of narcolepsy did not get significantly better thanks to IVIg. Nonetheless, in patients with high baseline symptoms, a subset of patients treated with IVIg achieved remission more quickly than control patients. Likewise, the study by Sarkanen et al. establishes that treatment with IVIg produced no benefit in individuals who developed narcolepsy subsequent to being vaccinated with Pandemrix®.<sup>3</sup>

Given the disability that narcolepsy causes in the people who suffer it and the frequency of multiple vaccinations that exist worldwide and, even more, bearing in mind that we are currently facing the SARS COVID-19 pandemic and in light of the different research groups that are searching for a vaccine, this work was envisioned with the aim of conducting a systematic review of the cases of H1N1 vaccine-induced narcolepsy.

## Material and methods

The following question was posed to perform this bibliographic review: Does the AS03-adjuvanted influenza A (H1N1) vaccine induce the onset of narcolepsy, in comparison with individuals who have not been vaccinated or who have received an unadjuvanted vaccine?

### Inclusion criteria

- Type of study: populational studies and both prospective and retrospective observational studies.
- Language: articles published in the English language.
- Year of publication: articles published in the last 10 years.
- Subject matter: articles that reported populational analyses of individuals who required preventive immunization against influenza A (H1N1) in whom narcolepsy and possible concomitant cataplexy had appeared.

### Exclusion criteria

- Duplicate articles.

- Articles published in a language other than English.
- Articles more than 10 years old.
- Case reports.
- Bibliographic reviews.
- Animal studies.

### Search strategy

A bibliographic search was performed of the Medline and Embase databases in January 2020. The following Mesh descriptors were used: «*influenza vaccines*», «*narcolepsy*». The descriptors and key words were combined with each other by means of the AND operator. Furthermore, a manual search was carried out in an attempt to locate the odd publication related to the subject of the study.

### Data synthesis

Table 1 summarizes the main data from the articles that were analyzed: the first author and year of publication, country where the study was conducted, the vaccine administered, the population to whom the vaccine was administered, cases of narcolepsy reported, onset of cataplexy concomitant to narcolepsy, and the most salient conclusions of each study.

## Results

The initial search yielded 147 results. After applying the inclusion and exclusion criteria and after the both authors conducted a thorough screening of the abstracts, the full text of seven articles was finally analyzed and included in this review, inasmuch as they focused on evaluating the onset of narcolepsy and their possible causal relationship with immunization against H1N1 influenza with vaccines that included the AS03 adjuvant. All the studies included in the review were studies that examined data specifically focused on one country. The studies that encompassed and/or summarized data from several countries were not included in this review. Five of the studies incorporated examined the association between narcolepsy and vaccination against influenza A (H1N1) in Europe (the United Kingdom, Finland, Ireland, France, and Norway) and 2 in Canada.

A total of 398 cases of narcolepsy were reported by the studies included in this systematic review regarding narcolepsy induced by vaccination against influenza A (H1N1), of which 191 presented cataplexy concomitant to narcolepsy (Table 1), which accounted for 47.98% of the sample of cases with narcolepsy.

All of the European studies and one of the studies performed in Canada found a positive association between the administration of Pandemrix® and onset of narcolepsy. The only study included in this review that does not confirm a single case of narcolepsy, despite finding 53 individuals with clinical manifestations suggestive of this syndrome, was carried out in Canada and Arepanrix® was administered to the study sample (Table 1).

Table 1 – Synthesis of the main data provided by the studies included in this systematic review.

| Author and year          | Country        | Individuals  | Vaccine administered    | Cases of narcolepsy            | Age of onset   | Concomitant cataplexy | Main conclusions  |
|--------------------------|----------------|--------------|-------------------------|--------------------------------|--|-----------------------|---|
| Nohynek et al., 2012     | Finland        | 2.76 million | Pandemrix® AS03         | 71                             | 4–19 years   | 51 (71.8%)            | 12.7 times greater risk of narcolepsy in the 8 months following vaccination with Pandemrix® compared to unvaccinated individuals  |
| Dauvilliers et al., 2013 | France         | 4.1 million  | Pandemrix® AS03         | 85                             | Mean age 15.3 years (5–51 years); 35 (56.5%) were <18 years of age | Not specified         | H1N1 vaccination was strongly associated with a higher risk of narcolepsy-cataplexy in children and adults.   |
| Heier et al., 2013       | Norway         | 470,000      | Pandemrix® AS03         | 58                             | 4–19 years   | 44 (75.8%)            | During the 3 years following vaccination, significantly higher risk of narcolepsy with cataplexy ( $P < .0001$ ) and lower orexin levels in CSF in vaccinated individuals |
| O'Flanagan et al., 2014  | Ireland        | 946,795      | Pandemrix® AS03         | 32                             | Children/adolescents aged 5–19 and adults                          | 24 (75%)              | Confirms association between Pandemrix® and narcolepsy. More studies are needed to explore the immunogenic mechanism of narcolepsy  |
| Harris et al., 2014      | Canada         | 1604         | Arepanrix® AS03         | 53 with symptoms of narcolepsy | 4–29 years   | 0                     | The authors conclude that none of the cases can be considered narcolepsy  |
| Montplaisir et al., 2014 | Canada         | –            | AS03-adjuvanted vaccine | 24                             | Mean age 24 years  | 16                    | Higher risk of narcolepsy in vaccinated individuals <20 years of age  |
| Winstone et al., 2014    | United Kingdom | 363,004      | Pandemrix® AS03         | 75                             | 4 to 18 years  | 56 (74.66%)           | Some symptoms of narcolepsy, including cataplexy, were more frequently reported in vaccinated vs. non-vaccinated patients   |

## Discussion

More than 1300 cases of narcolepsy associated with the H1N1 vaccine have been reported across the globe in the last decade. This first signs of the increase in the number of cases of narcolepsy subsequent to H1N1 flu vaccination campaigns were observed in Finland, Sweden, and France. A higher incidence of narcolepsy was later found in Norway, United Kingdom, Ireland, and Germany.

Between October 2009 and January 2010, approximately 470,000 children and adolescents in Norway, aged 4–19 years, were immunized against influenza A (subtype H1N1) with Pandemrix®. Some 50% of the population in this age group was covered by the vaccination.<sup>16</sup> In Finland, the immunization coverage reached 75% of the population.<sup>17</sup>

The rise in the incidence of narcolepsy has been linked to the AS03 adjuvant of the vaccine manufactured in Europe, which was distributed to more than 30.5 million people.<sup>1</sup> The narcolepsy-vaccine association was seen for the first time in children and adolescents and later, in young adults as well.<sup>5</sup>

The immunogenetic mechanism of narcolepsy and how the Pandemrix® vaccine contributes to its development remains unclear and requires an in-depth study in order to be fully understood. Various studies in European countries have proven an increase in cases of narcolepsy and its relationship with the Pandemrix vaccine®, but not with the Arepanrix® vaccine by the same laboratory, making further investigation necessary in order to understand the pathological process that affects the precipitation of narcolepsy.<sup>18</sup> In this regard, Harris et al.<sup>19</sup> analyzed the data from the Ontario population to assess the relationship between the Arepanrix® vaccine and the subsequent onset of narcolepsy. A total of 1604 vaccines were administered between 2009 and 2010. There were 53 individuals who met several factors to be considered to suffer episodes of narcolepsy; they were all aged 4–29. However, the authors indicated that only one of these cases appeared to be linked to the administration of the vaccine and ended up concluding that none of the reported cases were diagnosed as narcolepsy. The authors concluded that further research is needed with respect to the vaccine and a possible subsequent development of narcolepsy.

Heier et al.<sup>16</sup> analyzed 470,000 Norwegian children and adolescents with ages between 4 and 19 years who received the Pandemrix® influenza A (subtype H1N1) vaccine between October 2009 and January 2010. They diagnosed 58 cases of narcolepsy among the individuals vaccinated. All of the cases displayed EDS and 46 of them presented cataplexy; 37 cases were positive for HLA-DQB1\*0602; this allele turned out to be a susceptibility factor to narcolepsy. Moreover, 10 cases of narcolepsy appeared in unvaccinated individuals. The authors concluded that the vaccine increases the risk of narcolepsy with cataplexy and that this increase was statistically significant ( $P < .0001$ ). This coincides with the results of Harris et al., who established that the onset of narcolepsy following the administration of the vaccine appears to be due to an immunomodulating effect of the vaccine and to the close connection between narcolepsy and the HLA-DQB1\*0602 allele. Los authors concluded that this allele is twice as common



in individuals from Northern Europe compared to Southern Europe.<sup>19</sup>

With the continuous development of sophisticated computer technologies and tools, the capacity to identify cross-reactive epitopes in vaccines that lead to rare adverse events in susceptible individuals will improve. This will enable greater refinement of these vaccines to prevent potential risks like narcolepsy and maximize the benefits offered by immunization. In the case of the flu vaccine (where a cross-reacting epitope has been identified from an influenza nucleoprotein with high similarity to the human orexin receptor involved in narcolepsy), this cross-reacting epitope could be eliminated by applying purification passes of subunits known to effectively minimize the total amount of the influenza nucleoprotein that is transferred to the final vaccine.<sup>1</sup>

Nohynek et al.<sup>17</sup> performed a study of the Finnish population by means of a national vaccination registry to analyze its relationship to the cases of narcolepsy that occurred between 2009 and 2010. Of the 2.76 million vaccines administered during the study period, 1000 individuals were randomly selected. Sixty-seven (67) new cases of narcolepsy were detected in individuals aged from 4 to 19. The authors discovered a ratio of 9:100,000 in vaccinated individuals compared to 0.7:100,000 in non-vaccinated people. According to the authors, the vaccine is not the only causal factor of narcolepsy, although it does act as a risk factor, increasing its onset, together with other environmental, psychological, or social factors.

O'Flanagan et al.<sup>18</sup> explored the risk of narcolepsy in an Irish population who underwent pandemic immunization [sic] between November 2009 and March 2010 in comparison with those who did not receive the vaccine. The people analyzing the suspected cases of narcolepsy were unaware of whether the individual had been previously vaccinated or not. Thirty-two (32) cases of narcolepsy were identified. All of the individuals exhibited the HLA DQB1\*0602 allele. The mean time between the vaccine and the onset of the first symptom was 4.1 months. The authors concluded that there is a significant risk of developing narcolepsy in children and adolescents who have received Pandemrix<sup>®</sup> versus those who did not receive said vaccine, in a proportion of 5:100,000; these results are similar to those attained in other European studies.<sup>17</sup>

A study by Dauvilliers et al.<sup>14</sup> analyzed the data from 14 French sites. The authors found a positive association between the administration of the vaccine and the onset of narcolepsy with cataplexy, with an odds ratio of 6.5 for individuals <18 years and 4.7 for those over the age of 18 years.

Winstone et al.<sup>20</sup> detected an incidence of 0.42:100,000 in the English population, although the estimations of risk attributable to the vaccine are 1:16,000 according to Finnish studies (7). For the Norwegian authors,<sup>13</sup> the populational risk was estimated at 1.1 for every 100,000 subjects. Montplaisir et al.<sup>11</sup> reported an incidence of 1.5 per million individuals; i.e., much less than the incidence reported in Europe. The authors pointed out the need to examine, not only the effect of the AS03 adjuvant, but other possible risk factors, such as the increased autoimmune response. Other authors, such as Han et al.,<sup>7</sup> have found that the rise in cases of narcolepsy and their association with immunization against H1N1 to be unlikely poco probable.

In 2010, influenza A (H1N1) vaccine-induced narcolepsy was fairly unheard of by most parents and even by primary care physicians and there was a fair degree of hesitation to believe that there was a relationship between them.<sup>17</sup> Since then, studies several have evinced this relationship, although the period of time for a higher risk is unclear. In this regard, Finnish and Swedish studies have reported that the window of time of greatest risk of onset of narcolepsy is up to 2 years post vaccination with Pandemrix<sup>®</sup>. The relative risk of narcolepsy during the first year after vaccination ranged from 2 to 25 in children and adolescents and from 2 to 9 in adults.

A recent meta-analysis by Sarkanen et al.<sup>5</sup> found a 5- to 14-fold risk of narcolepsy associated with Pandemrix<sup>®</sup> in children and adolescents, and a 2- to 7-fold risk in adults. The existing studies suggest that Pandemrix<sup>®</sup> may have accelerated a process that the individual already had «at baseline».<sup>17</sup>

Research carried out by Duffy et al.<sup>21</sup> in the United States with vaccines without adjuvants, yielded a very low incidence of narcolepsy. The authors suggest that there may be a dual explanation. On the one hand, unadjuvanted vaccines were used in their study. Furthermore, the authors refer to the fact that more Caucasian individuals exhibit the HLA DQB1\*0602 allele, which has a strong link to the onset of narcolepsy, which could explain the higher incidence of narcolepsy among European individuals.

Based on the literature reviewed, further research is needed into the etiopathogenic mechanisms of narcolepsy. Likewise, on-going collaboration between researchers, vaccine manufacturers, and regulatory bodies would be welcomed in order to maintain the public's trust in vaccine safety.

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## Conclusions

The literature reviewed appears to evince a possible effect of AS03-adjuvanted vaccination against influenza A (H1N1) as a promoter or accelerator of the onset of narcolepsy. Nevertheless, certain aspects have yet to be elucidated, which is why there is a compelling need for an in-depth analysis of this relationship, as well as its etiopathogenic and immunological mechanism, with the aim of establishing preventive and treatment protocols to deal with such a disabling sleep disorder.

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## Conflict of interests

The authors have no conflict of interests to declare.

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