

Did narcolepsy occur following administration of AS03- adjuvanted A(H1N1) pandemic vaccine in Ontario, Canada? A review of post-marketing safety surveillance data

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A vaccine safety signal and association between new onset of narcolepsy and AS03-adjuvanted pandemic influenza A(H1N1) vaccine (Pandemrix, GlaxoSmithKline) in children and young adults has been reported in several European countries. In Ontario, Canada, AS03-adjuvanted pandemic A(H1N1) vaccine (Arepanrix, GlaxoSmithKline) was the primary vaccine administered in 2009/10, with 4.8 million doses distributed. We assessed post-marketing safety surveillance data by extracting adverse events following immunisation (AEFIs) associated with this vaccine from the integrated Public Health Information System. Reports were screened for key terms related to narcolepsy and further limited to children and young adults four to 29 years of age. Of 1,604 AEFIs reported in Ontario, 53 reports met the search criteria. Individual assessment by a nurse consultant for additional context suggestive of narcolepsy yielded five reports for secondary medical review. None of the five reports proved consistent with a possible narcolepsy diagnosis based on the available information. We present the first post-marketing assessment from Canada of narcolepsy reports following receipt of Arepanrix. Continued investigation of differences between Arepanrix and Pandemrix and subsequent risk of narcolepsy is indicated. In light of the limitations of passive surveillance to detect a signal in this instance, validation using other data sources is prudent.

Introduction

Narcolepsy is a chronic neurological disorder characterised by excessive daytime sleepiness and sudden daytime sleep attacks, cataplexy, hypnagogic hallucination and sleep paralysis [1]. The prevalence is estimated to be between 25 and 50 per 100,000 [2]. Onset can occur at any age; however, peak onset has been observed in those aged 10 to 19 years [3]. Narcolepsy

has been associated with a strong genetic predisposition, specifically with the human leukocyte antigen (HLA) DQB1*0602, an allele that is approximately twice as common in northern as in southern Europe [4].

A vaccine safety signal involving new onset of narcolepsy associated with AS03-adjuvanted influenza A(H1N1) pandemic vaccine Pandemrix (GlaxoSmithKline, Rixensart, Belgium) was first reported by Sweden and Finland in August 2010 [5,6]. Subsequent post-marketing safety assessments in these and other European countries have reported an increased risk of narcolepsy among children and young adults following receipt of this vaccine [4,7-9].

The Global Advisory Committee on Vaccine Safety (GACVS) reviewed the available evidence in December 2012. At that time, an association between abrupt juvenile narcolepsy and Pandemrix had been confirmed in four countries with high vaccine uptake among children and adolescents: Finland, Ireland, Norway and Sweden. The GACVS noted that while absolute risk was low, the relative risk was significantly raised, ranging from 6.6 per 100,000 (95% confidence interval (CI): 3.1-14.5) in Sweden to 13.0 per 100,000 (95% CI: 4.8-34.7) in Ireland [10].

In February 2013, a similar association in England was found by Miller et al. who reported an odds ratio of 14.4 (95% CI: 4.3-48.5) for vaccination with AS03-adjuvanted pandemic vaccine at any time before onset of narcolepsy among four to 18 year-olds [11], reinforcing the signal detected in the other countries [4,7-11]. An updated GACVS review in June 2013 acknowledges the findings suggesting a possible risk of narcolepsy among young adults and reiterates the urgency of continued research given the threat of emergence of new

pandemics and the expected future need for pandemic vaccines [12].

In Canada, the AS₀₃-adjuvanted influenza A(H₁N₁) pandemic vaccine Arepanrix (GlaxoSmithKline Inc.) was authorised for use in October 2009 and was the primary vaccine administered during the influenza A(H₁N₁) pandemic of 2009/10 in addition to a limited quantity of unadjuvanted influenza A(H₁N₁) pandemic vaccine (Panvax) for pregnant women. In Ontario, Canada's largest province (13.2 million population in 2010), approximately 4.8 million doses of AS₀₃-adjuvanted pandemic vaccine were distributed between October 2009 and March 2010 (T. Scott, Ontario Ministry of Health and Long-Term Care, personal communication, July 2014). The entire population older than six months was eligible for vaccination; however, the date the vaccine was made available varied by risk group and age [13].

Pandemrix and Arepanrix are manufactured at different locations. The products contain the same adjuvant (AS₀₃) but the antigen is produced using different manufacturing steps, resulting in several differences between the vaccines. An assessment by the European Medicines Agency (EMA) notes that the biological mechanism for the association between Pandemrix and narcolepsy is not yet known and should continue to be evaluated [14]. A difference in the immune response to Pandemrix and Arepanrix has been hypothesised; however, an assessment by the EMA has indicated that there is not at present any evidence of this [7,14].

In Canada, a possible signal of narcolepsy was initially observed in 2010 by Montplaisir et al. at the Sleep Disorder Centre (Sacré-Coeur Hospital) in Montreal, Canada [15], and an evaluation of the risk of narcolepsy following administration of Arepanrix in the province of Quebec has been completed but not yet published [16]. To date there has been no signal of narcolepsy reported by the Public Health Agency of Canada (PHAC) from adverse events following immunisation (AEFIs) reported by the provinces and territories to the Canadian Adverse Event Surveillance System (CAEFISS). The objective of this report is to summarise a review of passive vaccine safety surveillance data for possible reports of narcolepsy following administration of Arepanrix in Ontario, Canada.

Methods

In Ontario, reporting of AEFIs by immunisers (physicians, registered nurses and pharmacists) is mandated by provincial public health legislation; however, vaccine recipients or their parents may also voluntarily report an AEFI. Initial reports of AEFIs are received by the local public health unit where they are reviewed and investigated; recommendations may be made to the vaccine recipient or provider by the local Medical Officer of Health (MOH) regarding additional follow-up and receipt of further doses of vaccine. AEFI reports are entered into the integrated Public Health Information

System (iPHIS), the passive electronic reporting system for reportable diseases and AEFIs in Ontario. Provincially reported AEFIs are not further validated or assessed using any other source of information beyond what is available in the iPHIS application.

For this review, we included all AEFI reports associated with administration of AS₀₃-adjuvanted A(H₁N₁) pandemic vaccine (Arepanrix) and reported in iPHIS starting October 2009. Data were extracted from iPHIS on 25 April 2013.

Narcolepsy was not specifically described in provincial AEFI reporting criteria during the reporting period. Although this review is not limited to specific types of events, it is assumed that reports which included possible signs and symptoms of narcolepsy would probably have been classified as 'Other severe/unusual events' which was defined during this reporting period as 'any adverse event believed to be temporally related to immunisation that does not fit any of the categories listed above and for which no other cause is clearly established. Report events of clinical interest which require medical attention, and particularly events that are (i) fatal, (ii) life-threatening, (iii) require hospitalisation, or (iv) result in residual disability' [17].

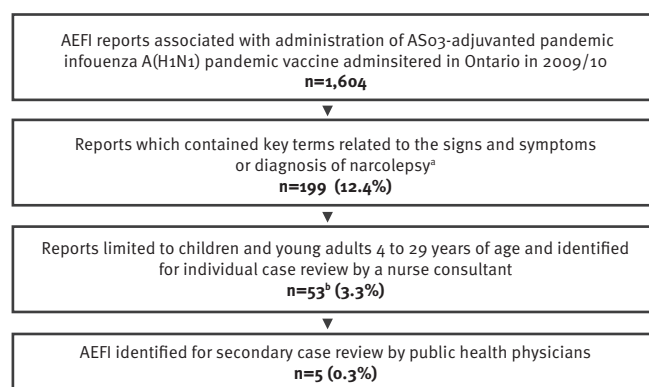
In order to further identify AEFI reports for review we executed a search on key all text fields within the data output that contained narrative case notes. We used key terms related to the signs and symptoms or to the diagnosis of narcolepsy including: cataplexy, muscle weakness, muscle tone, slurred, slurring (speech), sleepiness, sleepy, sleep disturbance(s), sleep paralysis, hallucination(s), dream(s), night terror(s), neurology and neurologist [18]. Reports were then further limited to children and young adults four to 29 years of age, which is consistent with the association previously noted in the literature. The identified reports were individually assessed by a nurse consultant at Public Health Ontario (PHO) for additional context suggestive of signs and symptoms of narcolepsy and, based upon this assessment, identified for secondary medical review. Secondary medical review was completed by two public health physicians at PHO who independently assessed reported AEFI case information. No specific case definition was applied to AEFI reports for this assessment.

Results

We identified a total of 1,604 AEFI reports associated with administration of Arepanrix in 2009 and 2010 in Ontario (no Arepanrix was administered after 2010). The Figure summarises the results of the sequential review process to identify possible reports of narcolepsy. There were 53 reports which contained one or more key terms possibly related to the signs and symptoms or diagnosis of narcolepsy and were within the pre-specified age range (4–29 years of age).

FIGURE

Identification of possible reports of narcolepsy through sequential review of all reports on adverse events following immunisation associated with administration of AS03-adjuvanted influenza A(H1N1) pandemic vaccine (Arepanrix) in Ontario, Canada, 2009/10 (n=1,064)



AEFI: adverse event following immunisation.

- ^a Key terms related to the signs and symptoms / diagnosis of narcolepsy included: cataplexy, muscle weakness, muscle tone, slurred, slurring (speech), sleepiness, sleepy, sleep disturbance(s), sleep paralysis, hallucination(s), dream(s), night terror(s), neurology and neurologist.
- ^b Two reports could not be further reviewed due to lack of further information in the original report.

Individual assessment of reports by a nurse consultant yielded five reports for secondary medical review (Table). Upon this review, it was determined that none of the five reports were consistent with a possible narcolepsy diagnosis based on the available information.

TABLE

Reports identified for secondary medical review for possible narcolepsy associated with administration of AS03-adjuvanted A(H1N1) pandemic vaccine (Arepanrix) in four to 29 year-olds in Ontario, Canada, 2009/10 (n=5)

Age range (years)	Reported adverse event category	Signs and symptoms	Time to onset / duration	Outcome
15–19	Other severe/unusual events	Fatigue, disorientation, low grade fever, paraesthesia in lower extremities	1 day/ unresolved as of day 3 following immunisation	Outcome unknown
10–14	Other severe/unusual events	Auditory hallucinations for three nights following receipt of vaccine	6 hours/ 3 days	Symptoms spontaneously resolved, no recurrence as of two months following receipt of vaccine
10–14	Other severe/unusual events	Immediately fell asleep and unable to rouse, unresponsive to pain	15 minutes/ 15 minutes	Blood tests and EEG normal, no recurrence after initial episode
4–9	Encephalopathy/ encephalitis: depressed level of consciousness	Confusion, disorientation, shortness of breath, headache, dizziness, malaise	1 day/ 2 hours	Outcome unknown
4–9	Other severe/unusual events	Daytime sleepiness, night-time hallucinations	<1 day / 1 day	Normal medical examination, spontaneous resolution of symptoms; no recurrence as of two months following receipt of vaccine

AEFI: adverse event following immunization; EEG: electroencephalography.

Discussion

This review process did not identify any potential reports of narcolepsy in individuals 29 years and younger following administration of Arepanrix and thus, no safety signal was noted in passively reported AEFI surveillance data in Ontario, Canada. Of note, subsequent to this review, one case of narcolepsy associated with Arepanrix was reported through the AEFI reporting system in Ontario. However, this case was older than the pre-specified age range of four to 29 years of age for this review and subsequent investigation determined that onset of symptoms pre-dated receipt of the vaccine (data not shown).

Spontaneously reported narcolepsy following AS03-adjuvanted influenza A(H1N1) pandemic vaccine among four to 19 year-olds from seven countries (Canada, Finland, Germany, Iceland, Norway, Sweden, United Kingdom) varied widely [19]. The highest incidences, that also exceeded expected background rates, were seen in Iceland, Sweden and Finland (4.9–9.4 per 100,000 vaccinated cases), whereas Canada reported the lowest incidence (0.1 per 100,000 vaccinated cases), which did not exceed the expected background [19].

In order to further evaluate our findings from a local perspective, we estimated the expected background number of narcolepsy cases in the population of four to 29 year-olds in Ontario using published estimates of the population-based incidence rate from the United States of 0.79 per 100,000 per year (all ages), as Canadian data were not available [3]. Between October 2009 and December 2010, we would have expected 44 new cases of narcolepsy, yet there were no reports to the passive AEFI reporting system during the same

time period in which the influenza A(H1N1) pandemic vaccine campaign also occurred. This number, based on the incidence across all ages, is likely to be an underestimate since peak onset is among the adolescent and young adults.

Expected cases notwithstanding, the lack of signal detected by our passive vaccine safety surveillance system may still not be surprising given a number of factors including the rarity of the disease, the lack of previous association between narcolepsy and vaccine, the delay from onset of symptoms to diagnosis and the decentralised nature of narcolepsy diagnosis in Ontario. In general, reports to the provincial surveillance system of neurological adverse events following any vaccine are rare with 3.5 reports per 1 million doses distributed [20]. With respect to the diagnosis of narcolepsy, referral to a sleep clinic is a common component of the diagnostic workup in Ontario; however, most clinics operate as independent health facilities which are regulated but not coordinated provincially. Within this decentralised model of care an overall increase in reports of narcolepsy may not necessarily be observed at the clinic level. Furthermore, health professionals involved in the diagnosis and treatment of narcolepsy are not routinely involved in the assessment and management of AEFIs and therefore may not necessarily recognise and report an adverse event, particularly one that has not been previously associated with any particular vaccine.

Other limitations of this assessment include those which are shared with other passive AEFI surveillance systems including under-reporting, inconsistent quality and completeness of AEFI reports and reporting bias [21]. In particular, the lack of outcome information was a key limitation to the identification of possible cases of narcolepsy. AEFI reports in iPHIS generally contain descriptions of signs and symptoms temporally associated with receipt of a vaccine, but not necessarily the results of specialist consultation and subsequent diagnosis which for narcolepsy can take several weeks to months following onset of symptoms. In addition, while the Brighton definition of narcolepsy [22] was used to inform this assessment, it was not formally used to classify reports due to the lack of detailed information available in provincial AEFI surveillance reports.

The limitations of passive reporting underscore the need for strengthened capacity and better systems to actively search large administrative databases, coupled with efficient international communication and rapid response when new signals emerge. The use of keyword searching (also referred to as 'text mining' or 'natural language processing') for signal generation has the potential to improve vaccine safety surveillance particularly for emerging or previously unrecognised events. However, subsequent evaluation including clinical case review can be labour-intensive depending on the number of signals generated and the frequency of the event assessed using this approach [23-25].

In addition to the already established association between Pandemrix and narcolepsy, the absence of a safety signal from passive surveillance of Arepanrix requires further study. The United Kingdom for example was not initially a country where a signal was identified; however, subsequent assessment demonstrated an increased risk of narcolepsy [9,11]. To this end, Ontario is also participating in an international study led by the Brighton Collaboration assessing the relationship between AS03-adjuvanted pandemic vaccine and narcolepsy in jurisdictions using Arepanrix compared with previous similar assessments of Pandemrix [26]. In addition, signals that have meanwhile been detected in older adults present a limitation of this current assessment which was limited to children and young adults four to 29 years of age [9,27].

Conclusions

This report represents the first published post-marketing assessment from Canada of reports to a passive AEFI surveillance system on narcolepsy following receipt of the AS03-adjuvanted influenza A(H1N1) pandemic vaccine Arepanrix. No reports of narcolepsy were identified. Given the lack of safety signal to date from Arepanrix, continued investigation of differences between Arepanrix and Pandemrix and subsequent risk of narcolepsy appears to be indicated. However, in light of the limitations of passive surveillance to detect a signal in this instance, validation using other data sources is prudent.

Conflict of interest

None declared.

Author contributions

TMH designed the study, conducted case-level review, contributed to the analysis of the data and drafted the manuscript. KW contributed to the design of the study, analysed the data and commented on the final version of the manuscript. LS conducted case-level review and critically commented on the manuscript. JF contributed to the design of the study and critically commented on the manuscript. NC contributed to the design of the study, conducted case-level review and critically commented on the manuscript. SLD supervised the conduct and report of the study, conducted case-level review and critically commented on the manuscript. TMH and KW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in interpretation of the results and approved the final version of a manuscript.

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