



TECHNICAL REPORT

Narcolepsy in association with pandemic influenza vaccination

A multi-country European epidemiological investigation

In brief

Scope and purpose of the report

The ECDC technical report summarises results from two studies undertaken by ECDC and the Vaccine Adverse Event Surveillance and Communication (VAESCO) Consortium:

- One study on narcolepsy background incidence rates to establish baselines and detect changes in incidence over time; and
- A case-control study to determine risk factors.

Both studies concern the association between narcolepsy and specific influenza A(H1N1)pdm09 vaccines while at the same time considering other likely causes.

The studies involve eight countries: Denmark, Finland, France, Italy, the Netherlands, Norway, Sweden and the United Kingdom.

Main conclusions of this report

The case-control study found an association between vaccination with Pandemrix® and an increased risk of narcolepsy in children and adolescents (5 to 19 years of age) in Sweden and Finland – countries which reported the initial signal (signalling countries). Pandemrix® was the only pandemic vaccine used in these countries. No such association was found in adults in these countries.

The overall number of new cases of narcolepsy being reported after September 2009 was much higher in Sweden and Finland (significantly increased incidence rates) compared with the other countries participating in the study. In the Netherlands, the United Kingdom and Italy, no increase in narcolepsy incidence was noted. However, vaccination coverage among the reported affected age group (5–19 years of age) was low in all these other countries.

In the non-signalling countries (Denmark, France, Italy, the Netherlands, Norway and the UK), the strictest primary analysis, the kind of assessment designed to avoid most biases like media and diagnostic awareness biases, found no significant risk to children and adolescents.

However, sensitivity analyses that assess the robustness of the results from the primary analysis, have highlighted the importance of several time-related factors that affect the strength of association between influenza pandemic vaccines and narcolepsy. An example of a time-related factor shown to influence results is the length of the chosen study period, eg the inclusion of cases occurring before and after the period of media attention would give a different outcome.

One such sensitivity analysis was based on the date of onset of excessive daytime sleepiness before media attention. This identified an increased risk for narcolepsy for children and adolescents following influenza A(H1N1)pdm09 vaccination in both signalling and non-signalling countries.

A similar sensitivity analysis also addressed date of onset of excessive daytime sleepiness and showed an association in adults in non-signalling countries before awareness increased.

To further inform the regulatory actions and the public, the report recommends increasing the statistical power by:

- ensuring completeness of the case–control study through an exhaustive case inclusion in the primary study period before increased awareness in the countries that are currently part of the VAESCO study;
- including further European countries with significant vaccine coverage among the affected age groups that were unable to be part of the current study (e.g. Ireland);
- pooling all available data from national studies that were not included in VAESCO (Ireland, the United Kingdom (studies based in sleep centres) and Germany).

Another conclusion from the report is that it would be important to extend the investigation beyond Europe, where there was no regulatory or media attention. In particular, countries such as Canada and Brazil used AS03-adjuvanted Arepanrix®, a vaccine very similar to Pandemrix®. The experience of countries where children and adolescents were vaccinated with other pandemic vaccines (adjuvanted and unadjuvanted) is also very important.

Further information

The background and subsequent incidence rates study

- The background study used eight different large linked healthcare databases from seven countries (Denmark, Finland, Italy, the Netherlands, Norway, Sweden, and the United Kingdom).
- Prior to 2009 pandemic influenza vaccination campaigns, the background incidence of diagnosed narcolepsy, based on figures extracted from healthcare databases covering a 10-year period was stable (at around 0.85 diagnoses for every 100 000 people each year, with lower rates in children).

The case–control study

- Eight countries participated (Denmark, Finland, France, Italy, the Netherlands, Norway, Sweden, and the United Kingdom).
- The study applied a common protocol, common case report forms, a common Brighton Collaboration case definition (allowing case validation) and automated case classification (ABC) tool, and detailed instructions for data collection.

VAESCO

VAESCO (Vaccine Adverse Event Surveillance and Communication) is a European research network funded and directed by ECDC and coordinated for ECDC by the Brighton Collaboration. It includes researchers from public health institutes, regulatory agencies and universities. The long-term aim of the work is to create an independent infrastructure and epidemiological resource in support of vaccine safety monitoring and investigation in Europe that can respond to calls for investigations from bodies like the European Medicines Agency and the World Health Organization.

Most European countries already monitor the safety of human vaccines. However, the sensitivity and timeliness of the monitoring systems, the technical capacity for investigations and strategies for communication with health professionals and the general public vary across the region. With a view to making better use of valuable resources, VAESCO has addressed the lack of common objectives and standards. This work will make it easier to compare data between European countries and thus increase the reliability of national vaccine safety data.

Narcolepsy

Narcolepsy is a rare chronic neurological disorder caused by the brain's inability to regulate sleep–wake cycles normally. It is a disorder of excessive daytime sleepiness. Symptoms often begin in adolescence but the condition often remains unrecognised and undiagnosed until adulthood. The usual feature is repetitive episodes of profound sleepiness that may occur both at rest and during periods of activity (talking and eating). Sleep attacks may be very brief (microsleeps) resulting primarily in lapses in attention and in mood disturbances (patients may be initially misdiagnosed with attention deficit disorder (ADHD) or depression). The most severe cases experience cataplexy, which is a sudden loss of muscle tone causing collapse in response to an emotional stimulus like laughing. There are known genetic predispositions. There is no simple treatment but the symptoms of narcolepsy are sometimes helped with therapy such as sleep hygiene and psychosocial support, and with drugs that stimulate the central nervous system and with antidepressants, both of which can have serious side-effects.