



## Meeting report narcolepsy and pandemic influenza vaccination: What we know and what we need to know before the next pandemic? A report from the 2nd IABS meeting

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### ABSTRACT

A group of scientific and public health experts and key stakeholders convened to discuss the state of knowledge on the relationship between adjuvanted monovalent inactivated 2009 influenza A H1N1 vaccines used during the 2009 influenza pandemic and narcolepsy. There was consensus that an increased risk of narcolepsy was consistently observed after Pandemrix (AS03-adjuvanted) vaccine, but similar associations following Arepanrix (AS03-adjuvanted) or Focetria (MF59-adjuvanted) vaccines were not observed. Whether the differences are due to vaccine composition or other factors such as the timing of large-scale vaccination programs relative to H1N1pdm09 wild-type virus circulation in different geographic regions is not clear. The limitations of retrospective observational methodologies could also be contributing to some of the differences across studies. More basic and epidemiologic research is needed to further elucidate the association between adjuvanted influenza vaccine and narcolepsy and its mechanism and to inform planning and preparation for vaccination programs in advance of the next influenza pandemic.

### 1. Objective of meeting

The overall objective of this 2nd International Alliance of Biological Science (IABS) meeting was to review the status of the current knowledge regarding the relationship between narcolepsy and the administration of the adjuvanted pandemic influenza vaccines, especially Pandemrix, with the goal of being prepared for the next influenza pandemic. The meeting was organized by IABS in collaboration with the Belgian Federal Agency for Medicines and Health Products (FAMHP) and took place in Brussels, Belgium on March 26–27, 2018. Participants included experts in epidemiology, surveillance, vaccine safety, immunology, neurology, and regulatory affairs, as well as representatives from the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), NIBSC (UK), WHO, CDC, US Food and Drug Administration (FDA), Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services, GlaxoSmithKline (GSK), IABS, and patient organizations for Narcolepsy in Sweden and Ireland.

An initial IABS meeting had been held in Geneva in October 2015 and the results of that deliberation have been published [1].

The following questions were addressed during the meeting:

1. What are the latest data on the risk of narcolepsy following exposure to the 2009 pandemic vaccines?
2. Which scientific data are available and which data are lacking to explain the phenomenon seen in 2009–2010?
3. What evidence is there for an association of narcolepsy with wild type influenza infection?
4. What additional work is needed to prepare for the potential use of adjuvanted vaccines during a possible future pandemic?

The expected outcomes were: An improved understanding of the relationship between narcolepsy and adjuvanted influenza vaccines and preparation for the potential use of adjuvanted vaccines if needed

during another pandemic.

### 2. Background

Beginning in Mexico in April 2009, the 2009 H1N1 A/California pandemic influenza strain rapidly spread globally [2,3]. As part of a WHO coordinated pandemic response, manufacturers developed several monovalent adjuvanted influenza vaccines [4]. Pandemrix, a vaccine adjuvanted with Antigen System 03 (AS03), was utilized primarily in Europe and approximately 31 million patient doses were administered to populations in Finland, France, Germany, Ireland, Norway, Sweden and United Kingdom (ref) [5]. Arepanrix, a similar AS03 adjuvanted vaccine, although authorised in the European Union, was primarily utilized primarily in Canada, while also Focetria, an MF59 adjuvanted vaccine was utilized in Europe, with approximately 6.5 million doses mainly administered to populations in Italy, Netherlands and Spain, and globally.

The first official report of a possible increased risk of narcolepsy following receipt of Pandemrix vaccine was announced in August 2010 by the Swedish Medical Products Agency [6,7]. Soon thereafter, a similar increase was reported by the authorities in Finland [8,9]. Both countries offered Pandemrix to more than 50% of their population with vaccination coverage in the school-based programs above 60%.

After the initial safety signals, several epidemiological studies were conducted to evaluate this association in Europe to ensure that all three adjuvanted vaccines were studied [10–18]. To better understand the available epidemiological data and associated laboratory studies a meeting was held in Brussels in March 2018 attended by key stakeholders. The objective of the meeting was to identify and formulate outstanding research questions that should be addressed in further studies in order to prepare for the potential use of adjuvanted pandemic vaccines in a future pandemic.

**Abbreviations**

ADVANCE	Accelerated development of vaccine benefit-risk collaboration in Europe
AS03	Antigen System 03
BARDA	Biomedical Advanced Research and Development Authority
CDC	CDC: Centers for Disease Control and Prevention
ECDC	European Centre for Disease Prevention and Control
EMA	the European Medicines Agency
FDA	US Food and Drug Administration

GSK	GlaxoSmithKline;
H1N1pdm09	influenza A H1N1 strain from the 2009 pandemic
HLA	human leukocyte antigen
IABS	International Alliance for Biological Standardization
MSLT	multiple sleep latency testing
NS1	non-structural protein 1
PBMC	peripheral blood mononuclear cells
SAE	severe adverse events
SOMNIA	Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment
WHO	World Health Organization

**3. The influenza pandemic**

Influenza pandemics occur when a new influenza strain evolves and circulates in humans not previously exposed to this strain, spreading on a worldwide scale. This frequently leads to widespread disease, causing excessive morbidity and mortality. At the onset of a pandemic it is not possible to predict the ultimate severity of the outbreak. Faced with a pandemic, the public health community, working with vaccine manufacturers, seeks to rapidly produce and administer, to as much of the population as possible, vaccines directed against the pandemic strain. At the onset of the 2009 H1N1 pandemic several vaccines were rapidly pursued. Ultimately, there were eight pandemic vaccines licensed in Europe [19], including three with adjuvants to enhance the immune responses and to provide antigen sparing allowing for a larger population being vaccinated when vaccine antigen is limited [20]. Unfortunately, due to the limitations of influenza vaccine manufacturing techniques, there was a five-month lag period between the identification of the pandemic strain and the availability of the pandemic vaccines.<sup>2</sup> Thus, wild type H1N1pdm09 circulation preceded vaccine administration in many countries, which means that a part of the population had already been infected by wild type H1N1pdm09 strain before receiving the pandemic vaccine [21].

As mentioned earlier several adjuvanted vaccines were developed in response to the pandemic. Pandemrix, produced by GlaxoSmithKline (GSK) in Dresden, Germany, contained the adjuvant AS03, which is a mix of squalene and  $\alpha$ -tocopherol [22]. This same AS03 adjuvant had been previously included in avian influenza H5 and H7 vaccines where its safety and immunogenicity had been tested in adults but with relatively small sample sizes [22–24]. When AS03 was included in those avian strain vaccines, it markedly enhanced the immune responses and provided dose-sparing (i.e. less antigen needed to produce an adequate immune response). Pandemrix was widely distributed in Europe with an estimated 30.8 million patient doses administered in line with national procurement procedures [5]. In several European countries, including Sweden and Finland, Pandemrix was the only pandemic vaccine available for the vaccine campaigns. A similar AS03 adjuvanted pandemic vaccine, called Arepanrix (ID Biomedical Corp., a subsidiary of GSK Biologicals) produced at a manufacturing site in Quebec using a slightly different manufacturing process, was licensed for use in Canada [25]. The third adjuvanted vaccine, Focetria (Novartis Vaccines and Diagnostics), contained a different squalene based adjuvant, MF59, and was used in some countries in Europe in line with national procurement procedures, but far fewer doses were distributed, i.e. 6.5 million [26].

The effectiveness of the adjuvanted vaccine in preventing laboratory confirmed influenza was reported to be high. In a systematic review and meta-analysis of the effectiveness of the 2009 pandemic influenza H1N1 vaccines, Lansbury et al. reported pooled adjusted vaccine effectiveness against laboratory confirmed H1N1pdm09 infections with adjuvanted and unadjuvanted vaccines of 80% (95% confidence

**Table 1**

Identified questions that could be addressed in retrospective and prospective epidemiological studies in populations with natural influenza infection and/or exposure to adjuvanted pandemic vaccines.

- Is there seasonality in narcolepsy related to influenza and does this exist every year or are there some years that are more prominent than others? Are all population equally affected?
- What was the risk window following Pandemrix vaccination for developing narcolepsy and cataplexy, respectively? Any difference observed by age groups?
- Could a “dual-hit” with vaccination before or after a natural influenza A H1N1pdm09 infection in European and non-European settings explain development of narcolepsy/cataplexy following use of Pandemrix and other adjuvanted pandemic vaccines?
- Could analyses be stratified by different outcomes, exposures and case characteristics, e.g. confirmed diagnosis of narcolepsy, natural H1N1 infections, different time lags between vaccination and narcolepsy, and age?
- Could a compensatory drop in narcolepsy incidence be observed following the increase in incidence be observed?
- Could associations of vaccine administration or wild type influenza infection be assessed in additional populations/countries/years via case-control or cohort studies? Were there narcolepsy clusters following the previous pandemics including 1918–1920 with H1N1, in 1957–1958 with H2N2, and in 1968–1969 with H3N2?
- Could large health care database research be utilized to evaluate retrospective or real-time pandemic vaccine safety and effectiveness by vaccine brand during the 2009 pandemic and future pandemics?
- How could studies on vaccine safety and effectiveness involving all stakeholders be facilitated and adequately funded in the next pandemic?

interval [CI] 59–90%) and 66% (95% CI 47–78%), respectively [27]. Overall vaccine effectiveness for the prevention of influenza-associated hospitalization was 61% (CI 14–82%). Long-term effectiveness of the adjuvanted vaccines was found to be approximately 91%, at two years after vaccination [28]. Thus, pandemic vaccines were effective in preventing the 2009 pandemic influenza and a long-term effect was observed up to two years post-vaccination [27].

**4. Narcolepsy**

Narcolepsy is a rare sleep disorder that is characterized by excessive daytime sleepiness that persists life-long. There is also an associated disorder called cataplexy which is the abrupt loss of muscle tone in association with emotional situations. The diagnosis of narcolepsy-cataplexy is confirmed by polysomnography and multiple sleep latency testing (MSLT). It can also be confirmed with a cerebral spinal fluid determination of a hypocretin concentration of < 110 pg/ml. The incidence of the disorder is reported to be 1/100,000 in Europeans, however, the diagnosis is often delayed, making precise incidence calculations problematic. The peak age at onset is approximately 15 years and the syndrome is highly correlated with presence of the HLA DQB1\*0602 haplotype, with over 90% of the subjects with narcolepsy-cataplexy having that haplotype [29–31]. Genome wide association

<sup>2</sup> <https://www.cdc.gov/h1n1flu/cdresponse.htm>.

**Table 2**

Identified questions that could be addressed in epidemiological studies on the differences between Pandemrix and Arepanrix and the association with narcolepsy.

- Is there a difference in the background incidence of narcolepsy between the populations that received Pandemrix and Arepanrix that could explain the observed difference in vaccine associated narcolepsy?
- Is there a difference in the expression of the HLA-DQB1\*06:02 allele and other HLA types in the populations that received Pandemrix and Arepanrix?
- Was there a difference in the time window between vaccination and infection in populations receiving Pandemrix and Arepanrix?
- Could the risk be assessed at the individual level by comparing the risk of narcolepsy according to timing of vaccination relative to infection (before, same time, or after) and for each individual calculate recent exposure and interaction of the vaccine effect could be assessed?

**Table 3**

Preparedness data needed for informed decision making in the public health response to a potential pandemic threat.

- Public health communication plans should be developed in anticipation of future influenza pandemics. Content should include disease epidemiology, regulatory processes for licensure, the rationale for age- and risk- based vaccine recommendations, and how vaccine safety and effectiveness will be monitored. Information should also be effectively transferred from national and regional levels to local and community levels and ultimately to the provider and patient levels.
- Large linked database systems should be built to conduct near real-time active vaccine safety and effectiveness monitoring during a global influenza pandemic vaccination campaign.
- Vaccine registries should be established, either within monitoring systems or at the national, regional, or state/provincial levels. There would optimally be bi-directional communication capability between registries and the large linked database systems to enhance capture of vaccine exposure for safety and effectiveness monitoring.
- Methods, outcomes, and risk and control intervals for adverse events should be standardized and surveillance systems should incorporate procedures for rapid chart access and data sharing to evaluate potential safety signals.
- Clinical trials and licensure of adjuvanted pre-pandemic (i.e., pandemic candidate) vaccines should be encouraged in advance of a pandemic. These should give consideration to the inclusion of children, the elderly, those with chronic illnesses, pregnant women, and include sufficient racial and ethnic minorities to be representative of the general population. It was however recognized that the ethics including vulnerable groups in such trials in the absence of a pandemic would require careful consideration.
- Modeling should be used to evaluate the benefit-risk balance when limited data are available.
- The roles, responsibilities, and authority of international, European, national, state/provincial, and local public officials should be clarified in advance of a pandemic influenza response and continuously reinforced and communicated to stakeholders and the public during the actual pandemic.
- National and when relevant international committees to investigate and promptly review vaccine adverse events of importance should be constituted during a pandemic influenza campaign.
- Compensation policies should be developed at the national level in advance of a future pandemic for individuals or parents who believe they or their children have suffered an injury from receipt of a recommended pandemic influenza vaccine. The process for developing policies should be transparent and preferably would include consideration of wide stakeholder input (public, healthcare providers, public health officials, etc.).

studies indicate that the cause of the disorder is likely autoimmune in nature [32].

## 5. Association between narcolepsy and pandemic influenza vaccines or influenza infection

With the announcement from the Swedish Medical Products Agency, the Finnish National Institute for Health and Welfare assessed their country's situation and launched a retrospective cohort study. That study estimated the relative risk for narcolepsy after Pandemrix in children 4–19 years of age at 12.7 (95% CI 6.1–30.8) [13]. In addition, many other European countries conducted studies to assess the

**Table 4**

Identified questions that could be addressed in laboratory studies in populations after natural influenza infections and/or vaccination with adjuvanted pandemic vaccines.

- What are the kinetics of the decay of NS1 antibodies following a natural influenza infection?
- Is there a difference in the immune response to a natural influenza infection or influenza vaccination in individuals expressing the HLA-DQB1\*06:02 allele compared to other HLA types?
- Is the HLA-DQB1\*06:02 allele linked to both vaccine or wild type virus associated narcolepsy?
- Is there a difference in the immune response to an adjuvanted vs a non-adjuvanted influenza vaccination in individuals expressing the HLA-DQB1\*06:02 allele compared to other HLA types?
- Could questions about the HLA relationship be assessed using peripheral blood mononuclear cells (PBMC) stimulated with various pandemic strains and measurement of T-cell responses based on HLA status?
- Could bio-banked sera and PBMC from confirmed natural H1N1 infections be analyzed based on HLA status and could new clinical studies with PBMC stimulation or antibody measurements following vaccination be assessed based on HLA status?
- What was the role of the different vaccine components for pathogenesis of narcolepsy/cataplexy?
- What differences in the antigen content and related immune response was observed following vaccination with Pandemrix and Arepanrix?

association between pandemic vaccines and narcolepsy, both in children and adults. The results of studies conducted in Europe (Finland, Germany, Ireland, England, France, the Netherlands, Norway and Sweden [10,12–16,18]) were recently reviewed by Sarkanen et al. who performed meta-analyses of their results [33]. During the first year after vaccination, the relative risk of narcolepsy was increased 5–14-fold in children and adolescents and 3–8-fold in adults, depending on the index date used. Similar elevated risk estimates were found for analyses using onset of symptoms as the key index date, with an overall risk of 14.32 (95% CI 8.92–22.99). The review concluded that a significantly elevated risk was only associated with Pandemrix [33]. The attributable risk for narcolepsy was estimated at 1 additional case per 18,400 doses administered in children and adolescents [33]. The risk of narcolepsy was also higher in cases with shorter delays between vaccination and onset date. No other pandemic vaccines except Pandemrix demonstrated clear associations with narcolepsy [33].

As there was considerable circulation of the pandemic virus in many countries before the vaccine was introduced, it was difficult to sort out whether immunized subjects had previously been infected with the wild type H1N1pdm09 strain, either asymptotically or symptomatically. This was particularly important to assess in those vaccinated individuals who ultimately developed narcolepsy. A study from the Finland National Institute of Health and Welfare assessed whether patients who fell ill with narcolepsy after vaccination with Pandemrix had specific antibody responses to the non-structural protein 1 (NS1) from the H1N1pdm09 virus, which was not a component of Pandemrix vaccine [34]. Using quantitative Western blot analysis, only two of the 45 (4.4%) narcoleptic patients vaccinated with Pandemrix showed specific antibody responses against the NS1 protein from the H1N1pdm09 virus, suggesting that few had previously been infected with the wild type H1N1pdm09 virus [34]. In contrast, acute and convalescent sera (14–21 days later) from patients who had laboratory confirmed H1N1pdm09 infection, showed high levels of H1N1pdm virus NS1-specific antibodies [34]. The study concluded that “it is unlikely that H1N1pdm09 virus infection contributed to a sudden increase in the incidence of childhood narcolepsy observed in Finland in 2010 after AS03-adjuvanted Pandemrix vaccination”. However, the serologic studies were performed on the subjects with narcolepsy two years after the pandemic, while the samples on the controls were obtained contemporaneously.

The hypothesis of the potential impact of a “dual hit” was also raised by meeting participants, suggesting that both vaccine

administration and wild type H1N1pdm09 infection in combination could increase the risk of narcolepsy [35]. The Norway study also indicated that the combined exposure to influenza and vaccination increased the risk ratio for narcolepsy, compared to the exposure of influenza infection alone or vaccination alone, suggesting a synergy [16]. However, the role of influenza should be viewed with caution due to underreporting of influenza disease. This hypothesis could also explain the presence of an association in Finland, Sweden and Norway, where the H1N1pdm09 circulation coincided with the vaccination programmes [35].

The SOMNIA study conducted a multi-country study in 13 different study sites located in nine countries [36]. This was a retrospective cohort analysis using electronic health databases to assess narcolepsy incidence rates before and during H1N1pdm09 virus circulation, and after vaccination campaigns in Canada, Denmark, Spain, Sweden, Taiwan, the Netherlands, and the United Kingdom. That analysis concluded that there was no overall change in incidence rates of narcolepsy after vaccination using any of the adjuvanted pandemic vaccines in any of the study sites, except Sweden and Taiwan [36]. In Sweden, narcolepsy incidence rate increased significantly after the start of the H1N1pdm09 vaccination with Pandemrix, particularly in children (incidence rate ratio 9.0; 95% CI 6.9–11.8) [36]. In Taiwan there was an increased rate of narcolepsy during the circulation of the wild type H1N1pdm09 virus in both children and adults prior to the vaccination campaign, with incidence rate ratio at 3.4 (95%CI 2.1–5.5) and 2.9 (95%CI 1.6–5.0) in the age groups in 5–18 and 19–59 years, respectively, but no increased risk following vaccination with Focetria [37]. In Canada there was no overall increased risk of narcolepsy, despite widespread use of the AS03-adjuvanted Arepanrix. A case control analysis was also conducted in Argentina, Canada, Spain, Switzerland, Taiwan, and the Netherlands, and identified 360 cases (150 cases in children and 210 cases in adults) and the analysis did not reveal an increased risk of narcolepsy in either children or adults following Arepanrix or Focetria [36].

The Taiwan Centers for Disease Control also conducted a case control analysis to investigate the relationship between narcolepsy and wild type H1N1pdm09 exposure, using patients recruited from sleep centers [37]. They identified 137 narcolepsy cases who met the MSLT criteria for narcolepsy (including 64 cases that were HLA DQB1\*0602 positive). They matched each case to 10 population-based controls and noted a significant risk of narcolepsy associated with influenza-like illness in children ( $p = 0.014$ ). Similar studies conducted in China have reported narcolepsy peaking several months after wild type influenza circulation with a more pronounced peak in 2010, although laboratory confirmation of influenza infection was not performed [38,39].

Two other studies conducted in countries where only non-adjuvanted or MF59-adjuvanted A (H1N1) pdm09 vaccines were used, did not detect an association with narcolepsy and vaccine administration. One was conducted in the Vaccine Safety Datalink in the United States [40] and the other, an ecologic study, conducted in South Korea [11]. However, this lack of association may be true or due to the longer lag time in these countries between the onset of symptoms and the conduct of the diagnostic MSLT test, often being months to years. In contrast in China and Taiwan, the lag time between symptom onset and diagnosis is very short, a few weeks to months. Longer lag times make it more difficult to observe a temporal association between vaccine administration and narcolepsy. Partinen et al. have also suggested that a shorter lag time is also associated with more severe manifestations such as cataplexy which approximately 90% of Pandemrix vaccinated children in Finland were reported to exhibit [8]. The onset of narcolepsy appears more explosive in school-age children, while cases in adults are diagnosed later or can be more easily missed. These two factors might contribute to some of the differences in the observed association across age groups and for different time windows between vaccination and disease onset.

## 6. What is the potential pathogenesis?

An understanding of the pathogenesis of narcolepsy associated with Pandemrix has been sought and many important questions have been raised. What actually causes the damage to hypocretin-secreting neurons? Is this damage vaccine enhanced, wild type virus related, or is it a combination of both vaccine and wild type influenza infection? Is this an autoimmune process? What is the level of evidence? What is the significance of the association with a specific HLA type? Several speakers discussed this issue and provided insights.

There are no data that pathogenic auto-antibodies in pregnant women with narcolepsy have been transmitted to their infants, since all their infants have been born without narcolepsy [41]. Some have demonstrated the presence of tissue-specific autoantibodies or activated T-cells in patients with narcolepsy, but there has been no demonstrated pathogenicity. There is a strong relationship between narcolepsy and HLA-DQB1 alleles, but there is evidence that the same HLA alleles are also associated with enhanced immune response responsiveness to influenza vaccines [42].

The role of wild type virus infection in narcolepsy has also been assessed as a high proportion of the vaccinated population was infected by the H1N1pdm09 virus before being vaccinated. One study, using results of published and unpublished H1N1pdm09 seroepidemiological studies, suggested that 47% of children aged 5–19 years of age were infected during the pandemic [43]. In Europe, the peak of the pandemic immediately preceded or coincided with the mass vaccination program and in Norway, over half of the school children were infected before vaccination [44].

It is known that influenza viruses can infect the olfactory receptor neurons and move from the olfactory bulb with anterograde axonal transport into the brain. In immunodeficient mice, experimental intranasal administration of H1N1pdm09 was shown to infect the lateral hypothalamus and the hypocretin-producing neurons [45].

An alternative hypothesis is that after an immune response to a natural H1N1pdm09? Infection, CD8 T-cells are generated that can spread to the brain and attack the hypocretin neurons that are expressing H1N1pdm09 hemagglutinin [46]. Using a mouse model one group demonstrated that CD8 T-cells could destroy neurons in the hypothalamus with this loss causing manifestations similar to human narcolepsy [46]. Another group proposed that narcolepsy resulted from specific-antigen-associated molecular mimicry coupled with non-specific immunostimulation [47]. They reported that antibodies to influenza nucleoprotein cross-reacted to human hypocretin receptor 2 and shared motifs between influenza virus nucleoprotein and human hypocretin receptor 2. They also demonstrated that sera from narcoleptic patients who received Pandemrix had anti-hypocretin receptor 2 antibodies that cross-reacted to influenza nucleoprotein.

Another study presented data that autoreactive memory CD4 and CD8 positive T-cells specific for self-antigens expressed by hypocretin producing neurons were identified in narcolepsy patients and rarely in healthy controls [48]. The autoreactive memory CD4 response was polyclonal and recognized exogenous peptides but failed to recognize whole proteins. Rare autoreactive CD8 T-cell clones were also present in the cerebrospinal fluid of the narcoleptic patients. However, they did not identify hypocretin specific T-cells in narcolepsy patients.

## 7. Parental and patient perspective

The patient perspective was presented by representatives of two national narcolepsy organizations, one from Ireland and one from Sweden. Patient organizations also have been formed in other countries. Narcolepsy has had a major impact on the lives of the affected individuals. They require more time to complete their schooling and experience difficulties in obtaining and keeping employment, with many only able to work part-time.

A European patient organization, the Pandemrix narcolepsy alliance



was formed in 2013 with patients and their affected families from Finland, Ireland, Norway, Sweden and the UK. They have met with the European Commissioners on Health and Consumption in 2014 and 2016 to discuss opportunities for research support for better treatments and vaccine injury compensation systems [49]. Finally, it was noted that vaccine injury compensation systems vary significantly among the countries that offered Pandemrix in large vaccination campaigns with Finland, France, Norway, Sweden and United Kingdom having a compensation system in place while Ireland did not. In Ireland patients or their families had to file their claims for compensation in civil court. Several other countries had insufficient vaccine injury compensation systems for such a severe injury.

## 8. Research challenges and proposals for further research

Following a series of presentations on the state of the art of the association between development of narcolepsy and Pandemrix vaccination, the meeting participants were divided into five working groups to address research challenges and proposals for further studies. The groups included; epidemiologic studies, the association of narcolepsy with natural wild type influenza infection, the potential mechanisms of pathogenesis, the differences between Arepanrix and Pandemrix, and the public health responses needed before another pandemic. Each of these will be discussed below.

### 8.1. Epidemiological studies

Although many large epidemiological studies assessed the risk of narcolepsy associated with Pandemrix, there are remaining questions. One question relates to the time windows between pandemic vaccine administration and narcolepsy onset that should be used in epidemiological studies. The relative risk for narcolepsy is higher for shorter windows. The participants also questioned whether earlier recognition of narcolepsy would result in a spike in the incidence, which would be followed by a compensatory drop and a subsequent return to baseline incidence. Studies from Finland and England are completed but additional studies in Sweden, Norway, Ireland, Germany and Canada could be useful to assess the impact of different time windows.

The “dual hit” hypothesis, which suggests that both exposure to natural H1N1pdm09 infection and to adjuvanted vaccine receipt would have a synergetic effect, should be further evaluated using existing sera collected from different populations. Pooling of data and conducting additional meta-analyses was debated. It would increase statistical power to detect associations, could include non-European countries and allow longer follow-up, but would reduce the number of covariates (due to missing data) and would hide the large heterogeneities across countries and populations.

Prospective studies collecting sera at different time points during and after the pandemic, from various age groups with low vaccine coverage and including subjects with confirmed natural influenza infection should be evaluated to determine the kinetics of the decay of NS1 antibodies. Investment in creating large linked databases would allow for rapid data sharing, and real-time monitoring of safety signals. These databases could also provide rapid and accurate information on population exposure to a pandemic vaccine by age, risk group and product type. Multinational data sharing systems could be used for signal generation and algorithms could be developed to identify pre-specified conditions of known interest (e.g., neurologic conditions such as Guillain-Barré syndrome and narcolepsy). However, since the vaccines used in the next pandemic could give rise to other completely unexpected severe adverse events (SAEs), artificial intelligence techniques and machine learning could be deployed to search databases and identify unique symptom clusters that could herald a new adverse event. Such systems could also generate expected rates for various conditions and ideally generate real-time vaccine effectiveness estimates to facilitate benefit/risk assessments of the vaccines.

Even if such infrastructure was established pre-pandemic with agreed upon protocols for multi-country data sharing and ground rules for conducting hypothesis testing studies, high quality country-specific studies would still be needed to investigate signals. These studies should incorporate local clinicians and epidemiologists who are best placed to understand the diagnostic pathways and potential biases and confounders that may be operative in their own local and country-level settings. Similarly, while machine learning, and symptom algorithms could be useful for signal generation, they would not obviate the need to ensure that clinicians are alert to the potential for novel unexpected adverse events and to report these promptly to regulatory or licensing authorities. Reporting clinicians should also be encouraged to take and store serum samples and potentially cells from cases of suspected SAEs to facilitate hypothesis testing if specific problems emerge. While both ECDC and EMA performed their own supra-national roles in the last pandemic, there is still room to improve collaboration in data sharing between the two entities. Also as a condition of licensure, EMA requires manufacturers to conduct their own post marketing safety and effectiveness studies. However, these studies can often only be done by public health institutes who have a similar responsibility for the acquisition of safety data. Vaccine manufacturers should also work to identify and report adverse events after immunization. Improved ways of collaborating between public funded and for-profit organizations should be in place before the next pandemic and could use the experience and protocols developed by the EU-funded ADVANCE (Accelerated development of vaccine benefit-risk collaboration in Europe) project as a model.

### 8.2. Association between narcolepsy and wild type influenza virus infection

Confirmation of an association of narcolepsy with wild type virus would further our understanding of the role of influenza antigens in the causation of narcolepsy and potentially impact studies of the mechanism of action of vaccine adjuvants. Several specific questions are summarized in Table 1.

### 8.3. Mechanisms of pathogenesis

Three key aspects were considered in discussing pathogenesis; the vaccine components, the wild type virus, and the time window between infection and vaccination. Participants proposed future studies including; DQ0602 restricted CD4<sup>+</sup> and CD8<sup>+</sup> T-cell influenza epitopes in in-vitro/ex-vivo analysis, binding of human T-cells to soluble HLA, comparative binding of epitopes to DQ002+, DQ0603+ (protective) and non-DQ 602 alleles, and screening responses to key influenza antigens (hemagglutinin, neuraminidase, nucleoprotein). In addition, responses to multiple seasonal and pandemic influenza viruses (H1N1pdm09, H3, H5, H7) and the antibody landscape to various influenza strains (H1 vs H3) in individuals with DQ 602+, DQ603+ and non-DQ 602 should be assessed. T-cell and antibody responses to H1N1 in patients with narcolepsy compared to controls should also be evaluated. Studies could be conducted on the influenza virus by elaborating a regional map of the influenza viruses that circulated in China in the geographic area where narcolepsy was detected and the tropism of that virus for the olfactory bulb and central nervous system in animal models. The time window between infection and vaccination in narcolepsy cases needs to be carefully assessed with the potential for ferret or other animal models to be pursued. Finally dissecting the differences in the immune-response to influenza infection and vaccination with both unadjuvanted and adjuvanted vaccines should be further pursued. See summaries in Tables 2 and 4.

### 8.4. Differences between Pandemrix and Arepanrix

The general consensus of the meeting was that there was an increased risk of narcolepsy consistently observed after Pandemrix.

However, the risk of narcolepsy after Arepanrix was considered from low to none. Only one small study from Quebec suggested an increased risk of narcolepsy after Arepanrix [50]. The differences either in the vaccine, in the populations in which vaccines were utilized or in the circulation of the wild type virus with respect to the timing of vaccination campaigns were considered as likely factors that might explain the differences between the two vaccines. These issues are summarized in Table 2.

#### 8.5. Data needed for informed decision making in the public health response to a potential pandemic threat

A successful public health response to an influenza pandemic requires coordinated efforts at the international, national, regional, state, and local levels. Furthermore, it requires input and coordination among the scientific and medical communities, public health and regulatory authorities, elected and appointed government officials, emergency responders, community organizations, and the public. A number of public health actions and responses were proposed for future pandemics. These are summarized in Table 3.

### 9. Conclusions and recommendations

The association between the receipt of Pandemrix and the development of narcolepsy has been consistent in the countries in which it has been studied. The observed risks differed somewhat across settings and the potential reasons for these differences include; individual country vaccination policies and vaccination coverage levels, total number of vaccines administered to the population, genetics, environmental factors, awareness and detection biases, case definitions and case finding. There are no clear associations observed between development of narcolepsy and the other pandemic adjuvanted vaccines.

Further epidemiological and fundamental basic research needs to continue and be supported. The laboratory studies that should be addressed are summarized in Table 4.

The public health response during a pandemic is critical. Communication needs to be enhanced and the medical and public health community need to rely on the lessons learned from this pandemic to prepare for the next. Preparedness should go beyond the concerns about narcolepsy. In particular:

Epidemiological research requires that international collaboration mechanisms, infrastructure, capacity for data sharing and large linked database systems with comparable data should be built;

The question of pooling past and future data needs further discussion for agreement; Sharing human samples should be explored but must be respectful of confidentiality and informed consent issues.

Finally, research on therapeutic options for patients with narcolepsy should be supported and clinicians skilled at dealing with narcolepsy should be available to affected patients.

#### Declaration of interest statement

Steve Black is a consultant to GSK, Takeda, SutroVax, and CEPI. Kathryn Edwards is a consultant to Sanofi, Moderna, IQVIA, and X4pharma. The other authors declare no conflict of interest.

The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the U.S. Food and Drug Administration. The use of product trade names is for identification purposes only.

#### Contributions

KE has written the meeting report with contributions from SB, PN, GH, KJ, HN, EMil and EMig. GH has adapted the report for this article. All authors have revised and approved the final version of the

manuscript.

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Kathryn Edwards\*

Medical Center North, Vanderbilt University School of Medicine, Nashville, TN, D7227, USA

E-mail address: [Kathryn.edwards@vumc.org](mailto:Kathryn.edwards@vumc.org).

Germaine Hanquet

Brussels, and Antwerp University, Universiteitsplein 1, 2610, Antwerp, Belgium

E-mail address: [ghanquet@skynet.be](mailto:ghanquet@skynet.be).

Steve Black

Cincinnati Children's Hospital, Cincinnati, OH, USA

Emmanuel Mignot

Stanford Center for Sleep Sciences and Medicine, Stanford University, Palo Alto, CA, USA

Christopher Jankosky<sup>1</sup>

Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

Tom Shimabukuro

Immunization Safety Office, Centers for Disease Control and Prevention (CDC), 1600, Clifton Road, Atlanta, GA, USA

E-mail address: [TShimabukuro@cdc.gov](mailto:TShimabukuro@cdc.gov).

Elizabeth Miller

Public Health England, London, United Kingdom

Hanna Nohynek

National Institute for Health and Welfare THL Department of Health Security, Infectious Disease Control and Vaccinations Unit Helsinki, Finland

Pieter Neels

IABS, Rue de la Vallée 3, 1204, Genève, Switzerland  
E-mail address: [pieter.neels@vaccine-vaccine.be](mailto:pieter.neels@vaccine-vaccine.be).

\* Corresponding author.

<sup>1</sup> The author did the work on the paper when he was at CBER/FDA and has since left the organization.