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Review

The narcolepsy-pandemic influenza story: Can the truth ever be unraveled?

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ABSTRACT

A safety signal around Pandemrix, an AS03 adjuvanted influenza A(H1N1) pdm09 vaccine potentially causing narcolepsy in children and adolescents became public in August 2010, long after cessation of the influenza A(H1N1) pdm09 campaigns in Europe. The signal originated from Finland and Sweden, two countries with school based pandemic vaccination campaigns, with high vaccine coverage, and vaccinations being provided at the peak of the circulating wild virus. Since the announcement awareness grew in Europe, with extensive public media dissemination and regulatory actions. This resulted in a steep increase in the spontaneous reports of exposed cases, a decrease in diagnostic lag times of this rare, underdiagnosed disease and finally victim compensation. The signaling countries conducted rapid risk assessment studies to quantify the signal to the best of their abilities, in the midst of the public awareness, most of which could not distinguish between a vaccine and an awareness effect. Due to the strong but variable associations from the epidemiological studies, the search for biological mechanisms started. Currently it is not yet understood how Pandemrix might cause narcolepsy, and whether it would be specific to Pandemrix. The paper describes the current evidence and puts forward the questions that remain to be answered, which are relevant for future pandemic preparedness when adjuvants may be used for dose sparing.

1. Pandemic influenza vaccines in Europe

In the 2009–2010 season millions of persons around the world were vaccinated with one of the influenza A(H1N1)pdm09 vaccines, which were licensed through fast track procedures to protect populations against 2009 (H1N1) pandemic influenza. Non-adjuvanted monovalent vaccines, containing split influenza virus or only hemagglutinin and neuraminidase surface structure, were mainly used in the USA and Australia [1,2]. In Europe adjuvanted influenza vaccines were most widely used. Two types of adjuvanted vaccines were licensed rapidly in the EU, both containing squalene based adjuvants: Focetria® (Novartis) with the MF59 adjuvant, plus Pandemrix® (GSK) and Arepanrix® (GSKl) both containing AS03. The split-virion antigens contained in these two AS03-adjuvanted vaccines may differ as a consequence of site-specific splitting/purification procedures that were used (Dresden-protocol for the European made Pandemrix and Quebec-protocol for Canadian made Arepanrix®). The Quebec protocol inactivated the influenza virus by ultraviolet irradiation followed by formaldehyde, then purified by centrifugation, followed by disruption with deoxycholate. In the Dresden protocol, the virus was concentrated, purified, detergent-treated, diafiltrated, and then inactivated by deoxycholate and formaldehyde [1].

Recommendations whom to target in the European Union came from the SAGE Committee of the World Health Organization (WHO) and the EU Health Security Committee, but there was large variation on implementation of these recommendations in the different countries in Europe leading to extensive heterogeneity in overall exposure rates ranging from a low of 0.4% in Slovakia to a high of 59% in Sweden [2]. Pandemrix® was the most frequently used vaccine in Europe, the European Medicines Agency (EMA) estimated that as of 8 August 2010, at least 38.6 million people in EU/EEA countries had been vaccinated: >30.5 million with Pandemrix®, >560,000 with Celvapan® and >6.5 million with Focetria® [3]. An estimated total of 12 million doses of Arepanrix were used, mostly in Canada [1]. An estimated total of 25 million patients were vaccinated with Focetria, globally [1]. The monovalent influenza A(H1N1)pdm09 vaccines were hardly used after the new seasonal trivalent influenza vaccines became available in the summer-fall of 2010.

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2. Safety of pandemic influenza vaccines

Due to the rapid licensure procedures very little was known about the safety of these vaccines and extensive passive and active surveillance programs were set up both in Europe as well as globally. Efforts focused on establishment of background rates of conditions of special interest such anaphylaxis, encephalitis, Guillain–Barré Syndrome (GBS), Bell's palsy, neuritis, convulsion, vasculitis, demyelinization, transverse myelitis, autoimmune hepatitis, thrombocytopenia, and sudden death. Background rates were assessed to facilitate signal detection based on spontaneous case reports [4,5]. Prospective hypothesis testing studies were established in the USA and Europe to study the association between influenza A(H1N1)pdm09 vaccines and Guillain–Barré Syndrome (GBS) as this was an a-priori concern due to the 1976 safety signal on swine flu vaccination and GBS in the USA. A multi-country study funded by ECDC showed that GBS was not associated with adjuvanted vaccines in Europe after adjusting for time and/or influenza like illness [6,7]. Low level associations between unadjuvanted pdm09(A)H1N1 influenza vaccines and GBS were observed in the USA [7,8], possibly due to lower effectiveness of the non-adjuvanted vaccines, as influenza itself was a strong risk factor for GBS [7]. A global proof of concept study, which pooled cases across the world in a self-controlled case series design confirmed the difference between adjuvanted and non-adjuvanted influenza A(H1N1)pdm09 vaccines in their association with GBS [9].

Unexpectedly 12 cases of narcolepsy occurring in children and adolescents following vaccination with Pandemrix® were publicly reported on 19 August 2010 by the Medicine Product Agency (MPA) in Sweden ($n = 6$) and on 24 August by the National Institute for Health and Welfare (THL) in Finland ($n = 6$), when vaccinations campaigns had long ceased in most countries. Both Sweden and Finland had used only Pandemrix® and had targeted the entire population resulting in high coverage rates [2]. In hindsight a suspicion of the association between Pandemrix® and narcolepsy in a child had already been noticed by Dr. Partinen in December 2009 and this association was discussed among neurologists in February 2010 in Finland [10]. The collection of narcolepsy cases were only notified to the public health and regulatory agencies when publicity started in August 2010 in Sweden.

The Pandemrix-narcolepsy signal in children and adolescents boosted a lot of media attention which was spreading from Scandinavia to the rest of Europe both through regular media and social media [3]. A referral procedure for Pandemrix® was requested by the European Commission on August 27 2010 under Article 2 of Regulation (EC) No. 726/2004 [11], which was announced by a press release. EMA asked countries to report all cases. In its subsequent meeting on September 17, 81 reports had already been received through the EUDRAVIGILANCE spontaneous reporting system. Of these, 34 reports came from Sweden, 30 from Finland, 10 from France, 6 from Norway and 1 from Portugal. Reports rapidly increased to 467 reports for Pandemrix received by December 2011 [3]. As of July 2014 more than 1000 reports are available in the EUDRAVIGILANCE database, many of which are duplicates due to different reporters (EUDRAVIGILANCE public access). Most reports concern children, and focus on Pandemrix®. Surprisingly, only very few reports were received for Arepanrix® which has the same antigen and adjuvant as Pandemrix® but Pandemrix® was shown to have more neuramidase and nucleoprotein than Arepanrix® [12,13], due to different production processes [1]. Arepanrix® was widely used in other parts of the world such as Canada and Latin America and spontaneous reports in these countries should have appeared in the EUDRAVIGILANCE database as the vaccine was licensed also in the EU.

No signals about narcolepsy following any of the adjuvanted or non-adjuvanted pdm(2009)H1N1 vaccination have occurred in other parts of the world. Very few reports concerned narcolepsy following Focetria® or Celvapan® [1,3]. Several conclusions may be drawn from this pattern of spontaneous reporting. First, the sudden increase in reporting of Pandemrix exposed narcolepsy cases showed that physicians were very aware about the potential association. Second, this awareness seemed to be totally focused on Pandemrix® and on children/adolescents.

2.1. How the narcolepsy signal was followed up

The European Center for Disease Control and prevention (ECDC) requested the VAESCO consortium to conduct a formal investigation into the association, leveraging the distributed European wide collaborative approach that was just established in investigating the potential GBS association [3,6,7,14]. In parallel, several Scandinavian countries (first Sweden and Finland later also Ireland and Norway) started their own rapid assessment studies, to be able to respond quickly to fierce political pressure and the public concerns, while being personally threatened by the public [15–20]. Most of these rapid assessment studies focused on children/adolescents as the signal had arisen in this group. While public health and regulatory agencies conducted these studies to the best of their abilities under extremely challenging circumstances, the results varied widely, across and within countries and designs (see Table 1). In spite of these highly variable results, the association is now generally accepted with wide scale compensation of Pandemrix® exposed victims in the Nordic countries and UK, which makes open scientific debate and proper follow-up studies difficult. Compensation of children refuelled the discussion amongst adults in the Nordic countries. Although initial studies did not show associations in Sweden (MPA cohort and Finland, a small association was subsequently shown in Finland. An ecological study was done in Korea [22] and a cohort study in USA [23], both did not show an association.

EMA requested the marketing authorization holder GSK to investigate the association between. Since all countries with high Pandemrix® exposure in Europe were engaged in the VAESCO study, and private co-funding or involvement was not allowed by ECDC, GSK conducted their post authorization safety commitment in the province of Quebec, where Arepanrix® had been used. The study in Quebec showed highly variable results based on the approach taken and the small number of cases, a final analysis with a test-negative case control design is still pending (see Table 1) [24].

During 2011 publicity around the association kept increasing and spreading to other countries, especially around appearance of the results of the first rapid assessment studies in Sweden (April 2011 results of cohort study and June 30, results of case inventory study) and Finland (Interim report of cohort studies January 31, 2011 and final report August 31 2011). Compensation of children/adolescent with narcolepsy after Pandemrix® was announced in July 2011 in Sweden and Finland, later followed by Norway, Ireland and the UK®. Narcolepsy patient organizations in other countries now seek to get compensation for exposed cases through class suits in Nordic countries (J. Lammers, personal communication). At the European Medicines Agency the association and new (interim) results were discussed almost at each monthly meeting of the Pharmacovigilance Working Party, and press releases were issued in September 2010, February 2011 (when Finnish and VAESCO interim results were discussed), April 2011 (recommending interim measures after availability of Swedish cohort data) and in July 2011 (restricting use of Pandemrix® to adults, after expert meeting).