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Review

Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: What is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants☆

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ABSTRACT

The vaccine safety surveillance system effectively detected a very rare adverse event, narcolepsy, in subjects receiving AS03-adjuvanted A(H1N1) pandemic vaccine made using the European inactivation/purification protocol. The reports of increased cases of narcolepsy in non-vaccinated subjects infected with wild A(H1N1) pandemic influenza virus suggest a role for the viral antigen(s) in disease development. However, additional investigations are needed to better understand what factor(s) in wild influenza infection trigger(s) narcolepsy in susceptible hosts. An estimated 31 million doses of European AS03-adjuvanted A(H1N1) pandemic vaccine were used in more than 47 countries. The Canadian AS03-adjuvanted A(H1N1) pandemic vaccine was used with high coverage in Canada where an estimated 12 million doses were administered. As no similar narcolepsy association has been reported to date with the AS03-adjuvanted A(H1N1) pandemic vaccine made using the Canadian inactivation/purification protocol, this suggests that the AS03 adjuvant alone may not be responsible for the narcolepsy association. To date, no narcolepsy association has been reported with the MF59®-adjuvanted A(H1N1) pandemic vaccine. This review article provides a brief background on narcolepsy, outlines the different types of vaccine preparations including the ones for influenza, reviews the accumulated evidence for the safety of adjuvants, and explores the association between autoimmune diseases and natural infections. It concludes by assimilating the historical observations and recent clinical studies to formulate a feasible hypothesis on why vaccine-associated narcolepsy may not be solely linked to the AS03 adjuvant but more likely be linked to how the specific influenza antigen component of the European AS03-adjuvanted pandemic vaccine was prepared. Careful and long-term epidemiological studies of subjects who developed narcolepsy in association with AS03-adjuvanted A(H1N1) pandemic vaccine prepared with the European inactivation/purification protocol are needed.

1. Introduction

With the declaration of a global A(H1N1) influenza pandemic in June 2009, mass vaccination campaigns using newly developed monovalent A(H1N1) pandemic vaccines were initiated in a number of countries using a range of vaccines developed with different technologies [1]. In Europe, of the eight A(H1N1) pandemic vaccines licensed during the 2009 pandemic, three were authorized through the central procedure in the European Union (EU) under the European Medicines Agency (EMA) and the European Commission and included one adjuvanted with AS03, one adjuvanted with MF59®, and one without adjuvant [1]. In the United States, the Food and Drug Administration (FDA) authorized four non-adjuvanted and one live, attenuated vaccine [2]. In Canada, Health Canada authorized one AS03-adjuvanted A(H1N1) pandemic vaccine [3] and one non-adjuvanted A(H1N1) pandemic

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vaccine [4]. These vaccines are summarized in Table 1. The vaccine options offered and the final recommended target groups varied in different EU countries, in the United States, and in Canada with most following the recommendations of the World Health Organization. In the European Union and European Economic Area countries, more than 30.5 million doses of the AS03-adjuvanted A(H1N1) pandemic vaccine, more than 6.5 million doses of the MF59®-adjuvanted A(H1N1) pandemic vaccine, and more than 560,000 doses of nonadjuvanted A(H1N1) pandemic vaccine were sold and distributed [5]. Almost one year after their authorization, an increase in narcolepsy cases was associated with the European AS03-adjuvanted A(H1N1) pandemic vaccine raising major public concerns about the safety of adjuvanted vaccines.

Despite diligence in safety monitoring prior to authorization, the introduction of any new health intervention such as a drug, a vaccine, or a medical device cannot exclude the risk for a rare adverse event linked to the chemical/biological/mechanical components of the product, to genetic susceptibilities in certain subjects, or to environmental triggers. With very rare adverse events (defined as one in 10,000 vaccinations [1]), a signal may be detectable only after the product, a vaccine for example, is introduced into larger populations than those tested in pre-licensure trials. A major challenge with rare events is the determination of whether they are due to the product (e.g., vaccine) or just a coincidental occurrence in that population [6]. To help address this, the European Centre of Disease Prevention and Control (ECDC) funded in 2008 a network of researchers called the Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium to establish a European vaccine safety datalink in which rare adverse events could be aggregated to better investigate related safety concerns [7] similar to a model established across several US states [8]. VAESCO was to be used to develop age- and sex-specific background incidence data on rare and more common conditions in larger European populations which were anticipated to be of value in the setting of mass vaccination campaigns such as the influenza A(H1N1) pandemic virus in 2009 [9].

Narcolepsy associated with European AS03-adjuvanted A(H1N1) pandemic vaccine was a very rare event. This article provides a brief background on narcolepsy, outlines the different types of vaccine preparations including the ones for influenza, reviews the accumulated evidence for the safety of adjuvants, and explores the association between autoimmune diseases and natural infections. It concludes with a hypothesis on why vaccine-associated narcolepsy may not be solely linked to the AS03 adjuvant but more likely be linked to how the specific influenza antigen component of the European AS03-adjuvanted A(H1N1) pandemic vaccine was prepared.

Table 1
List of adjuvanted and non-adjuvanted 2009 A(H1N1) inactivated monovalent vaccines and live, attenuated vaccine approved by European Medicine Agency, Food and Drug Administration, and Health Canada.

Regulatory agency	Adjuvant	Product name (or manufacturer if no product name)
European Medicines Agency [1]	AS03[a]	Pandemrix® (GlaxoSmithKline Biologicals s.a.)
	–	Celvapan® (Baxter AG)
	MF59®[b]	Focetria® (Novartis Vaccines and Diagnostics S.r.l.)
Food and Drug Administration [2]	–	CSL Limited
	–	ID Biomedical Corporation of Quebec
	–	Novartis Vaccines and Diagnostics Limited
	–	Sanofi Pasteur, Inc.
	–	Medimmune LLC[c]
Health Canada [3,4]	AS03[a]	Arepanrix® (GlaxoSmithKline Inc)
	–	GlaxoSmithKline Inc

[a] AS03 = 11.86 mg DL α-tocopherol, 10.69 mg squalene, 4.86 mg polysorbate 80.
[b] MF59® = 1.175 mg sorbitan trioleate, 9.75 mg squalene, 1.175 mg polysorbate 80.
[c] Live, attenuated A(H1N1) 2009 pandemic vaccine.

2. Vaccine-associated narcolepsy: the challenge

2.1. Time-course

For the A(H1N1) pandemic, the sequence and timing of events (Fig. 1) illustrate the challenges facing health agencies in a pandemic: 1) Initially, there was the identification of a new circulating A(H1N1) influenza virus (April 15, 2009). Following identification, the potential threat was escalated to the level of a global pandemic due to its rapid and widespread transmission (June 11, 2009). 2) Vaccine manufacturers responded to the urgent need for a public vaccine by working with health agencies globally to identify, isolate, and mass-produce millions of A(H1N1) pandemic vaccine doses within a narrow window of time (April 24, 2009–November 29, 2009). The challenge of protecting large populations during a pandemic underlie the reasons adjuvants were utilized to boost vaccine efficacy and vaccine supply through dose-sparing. 3) Almost a year after the authorization of the pandemic vaccines in Europe (September 2009), an increase in cases of narcolepsy was detected with the European AS03-adjuvanted A(H1N1) pandemic vaccine (August 18, 2010).

2.2. Epidemiology of narcolepsy with European AS03-adjuvanted A(H1N1) pandemic vaccine

The first suggestion of an association of narcolepsy with an A(H1N1) pandemic vaccine was a case series released by the Swedish Medical Agency reporting six adolescents (age 12–16 years) who developed narcolepsy following immunization with European AS03-adjuvanted A(H1N1) pandemic vaccine [10]. Subsequently, Finland's National Institute of Health and Welfare detected an increased incidence of narcolepsy in children and adolescents four to 19 years of age [11,12] associated with the use

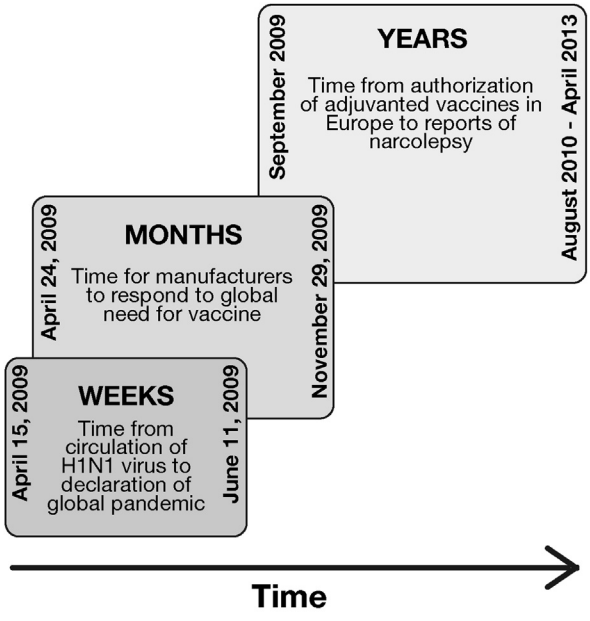

Fig. 1. Sequence of events during 2009 A(H1N1) pandemic. For the A(H1N1) pandemic, the sequence and timing of events illustrate the challenges facing health agencies in a pandemic, the reasons adjuvants were utilized, and when a very rare adverse event was detected.