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LETTER TO THE EDITORS

Safety surveillance of influenza A(H1N1)v monovalent vaccines during the 2009–2010 mass vaccination campaign in France

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In June 2009, the World Health Organization declared a pandemic due to A(H1N1)v 2009 influenza virus. In France, a mass vaccination campaign started following European Medicines Agency (EMA) recommendations, and a Pharmacovigilance plan was launched. The aim of this study was to describe safety data collected from 21 October 2009 to 15 June 2010 for Pandemrix® (ASO3 adjuvant vaccine, indicated in adults and children >9 years) and Panenza® (a nonadjuvant vaccine primarily administered to children <9 years old and pregnant women), the two most frequently used vaccines in France.

The French Pharmacovigilance system consists of a network of 31 regional centres and is based on mandatory spontaneous reports of "serious" and/or "unexpected" adverse events (AEs) [1]. However, it is well known that spontaneous notifications suffer from underreporting, the magnitude of which varies between 82% and 98% [2]. For the 2009–2010 vaccination campaign, French health authorities heightened awareness to extensive notifications with online health practitioner and patient reports via the regional centre concerned. All

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reports were reviewed daily, analysed and input into the French Pharmacovigilance database. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) [3]. An AE was considered "serious" if it was life threatening or resulted in death, permanent disability, congenital anomaly, hospitalization or prolonged hospitalisation [4]. An event was ranked "medically serious" when it requires medical intervention or hospitalisation <24 h to prevent one of the outcomes listed in the serious AE definition [4]. Particular attention was given to AEs of special interest (AESIs) as defined by EMA [5], mainly demyelinating disorders and Guillain-Barré syndrome (GBS). GBS was defined according to Asbury criteria [6], and multiple sclerosis (MS) was defined following McDonald's criteria [7]. Data reported in our study does not include AEs in pregnant women.

During the campaign, 4.1 million doses of Pandemrix® and 1.6 million doses of Panenza® were administered (French Health Authorities data). Among the 4,746 declarations received (Pandemrix® plus Panenza®), 3,740 (78.8%) came from health practitioners and 1,006 (21.2%) from patients. Following Pandemrix®, 4,180 AEs were reported (reporting rate102 :100,000 vaccine doses) including 334 "medically serious" and 193 "serious". The main "nonserious" AEs were "general and local disorders" (65.9%, mainly influenza-like illness, pain and site reactions) followed by "neurological disorders" (17.6%, mainly paresthesia and headaches). Concerning Panenza®, 566 AEs were reported (reporting rate35:100,000), including 61 "medically serious" and 70 "serious". The main "nonserious" AEs were "general and local disorders" (47.0%, mainly influenza-like illness, pain and malaises) and "allergic reactions" (16.3%, mainly cutaneous reactions). The most frequently reported "serious" AEs were neurological for both Pandemrix® (38.9%) and Panenza® (28.9%). Isolated ascending paresthesia (without any other neurological symptom and complication) were the most frequent AEs, with Pandemrix® in adults, and febrile convulsions being the most common neurological AEs with Panenza® in children (Table 1).

Table 1 Adverse events (AEs) reported with A(H1N1)v vaccines [Pandemrix® (PX) and Panenza® (PZ)] to the French System of Pharmacovigilance between 21 October 2009 and 15 June 2010: *n* (%)

AE[a]	Serious		Medically serious		Nonserious		Total		Reporting rate[b]	
Vaccine	PX	PZ	PX	PZ	PX	PZ	PX	PZ	PX	PZ
Local reaction[c]	1 (0)	0	32 (1)	3 (10)	2405 (99)	27 (90)	2438	30	59.5	1.9
Influenza like illness[d]	10 (1)	4 (1)	45 (2)	10 (4)	1,920 (97)	267 (95)	1,975	281	48.2	17.6
Pain	5 (0)	3 (4)	41 (3)	8 (10)	1,194 (96)	67 (86)	1,240	78	30.2	4.9
Malaise	9 (4)	1 (3)	26 (12)	6 (15)	177 (83)	33 (83)	212	40	5.2	2.5
Headache	2 (0)	0	9 (1)	0	835(99)	39 (100)	846	39	20.6	2.4
Paresthesia	20 (3)	1 (2)	57 (8)	2 (4)	607 (89)	49 (94)	684	52	16.7	3.3
Dizziness	2 (1)	0	7 (3)	2 (13)	203 (96)	14 (88)	212	16	5.2	1.0
Seizures[e]	7 (39)	13 (68)	8 (44)	5 (26)	3 (17)	1 (5)	18	19	0.4	1.2
Guillain-Barré syndrome	8 (100)	5 (100)	0	0	0	0	8	5	0.2	0.3
Demyelinating disorders[f]	11 (100)	4 (100)	0	0	0	0	11	4	0.3	0.3
Gastro-intestinal disorders[(g)]	1 (0)	3 (3)	13 (2)	0	628 (98)	113 (97)	642	116	15.7	7.3
Hypersensitivity reactions[(h)]	10 (2)	2 (1)	27 (5)	4 (2)	510 (93)	158 (96)	547	164	13.3	10.3
Deaths	17 (100)	5 (100)	0	0	0	0	17	5	0.4	0.3

The table shows the most common "serious", "non serious" and "medically serious" AEs, as well as three AEs of special interest (AESIs): seizures, Guillain-Barré syndrome and demyelinating disorders. Values are number of reports. For each AE, value between brackets indicates percentage of AE concerned according to the "seriousness".

[(a)] Using MedDRA terms. More than 1 code could be assigned to a single report.

[(b)] Reports per 100,000 doses administered.

[(c)] Local injection site reaction term includes pain, warmth, haematoma, indurations, inflammation, erythema, eczema, oedema and ecchymosis site reactions.

[(d)] Influenza like illness term includes influenza like illness, chills, fever and asthenia.

[(e)] Seizures term includes febrile convulsion, epileptic seizure and status epilepticus.

[(f)] Demyelinating disorders term includes multiple sclerosis relapse and primary multiple sclerosis.

[(g)] Gastrointestinal disorders term includes nausea, abdominal pain, vomiting and diarrhoea.

[(h)] Hypersensitivity reactions term includes anaphylactic shock, hypersensitivity, urticaria, angioedema.

Among the 75 AESIs, 13 GB cases were reported, with a delay of 4 days to 4 months after vaccination. Eight of these 13 patients had a viral infection during the weeks before. Fifteen cases of demyelinating disorders occurred from 1 to 61 days after injection. Seven of these 15 patients suffered from MS relapse, whereas the other eight occurred in patients without any history of MS. In all reported deaths (n=22) causes other than recent A(H1N1)v vaccination were described. No report of narcolepsy was made during the study period. Cases with cataplexy or narcolepsy were been reported later – from August 2010 forward.

This review summarises surveillance data from 5.7 millions doses of vaccine administered in France. For the first time, patient reporting was formally introduced in France, reaching 21.2% of the collected reports. Most reports were considered "nonserious". Injection site reactions appeared to be more frequent with the adjuvant vaccine and allergic AE with the nonadjubant vaccine. For both types of vaccine, neurological AEs were among the most frequently reported "serious" AEs, with 13 reports of confirmed GBS and 15 reports of demyelinating disorders. However, no causal relationship has been established between these AEs and vaccination. Finally, despite limits of this survey based on spontaneous reporting (especially underreporting, which remains difficult to quantify [1] and background rates of diseases [8]), the study did not detect any safety issues, at least within the 8-month follow-up.

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