Monitoring the safety of influenza A/H1N1 pandemic and seasonal vaccines in Morocco

Therapeutic Advances in Vaccines and Immunotherapy
2022, Vol. 10: 1–13
DOI: 10.1177/25151355221088157

Amina Tebaa, Raja Benkirane, Loubna Alj, Imad Cherkaoui and Rachida Soulaymani-Bencheikh

Abstract

Background: A vaccination campaign against pandemic influenza A/H1N1 was implemented in Morocco between November 2009 and April 2010. Overall, 705,883 subjects were vaccinated by *Pandemrix*, *Arepanrix*, and *Panenza*. The adverse events following immunization (AEFIs) data comparison was made with the 2014/2015 seasonal influenza vaccination campaign that was specifically investigated.

Aim: To evaluate the safety of the 2009 pandemic influenza A/H1N1 vaccine and to compare it to that of 2014 seasonal influenza vaccine.

Methods: During the pandemic vaccination campaign, the Morocco Pharmacovigilance Centre reinforced passive AEFI surveillance with an active and prospective monitoring programme of 1000 immunized people over 6 months at 10 randomly selected vaccination centres. For the 2014/2015 seasonal vaccination campaign, AEFI data were collected from spontaneous notifications.

Results: Active monitoring of 2009 pandemic collected 771 AEFI reports, corresponding to an AEFI incidence rate of 77.1% with vaccination by either *Pandemrix* or *Arepanrix* vaccine in 95% of cases. Reported AEFI were most frequently local (37.7%), general (29.5%), and neurological reactions (20.3%). Most of the AEFI (95.5%) were observed during the first 48 hours after vaccination, and the remainder within 2 weeks. None of the reported AEFI were serious case. The highest rate of notification was documented for health professionals, followed by patients with diabetes or chronic respiratory diseases. Concerning passive surveillance, the AEFI notification rate was significantly higher for the 2009/2010 pandemic vaccine (3.1 *vs* 1.2 per 10,000). However, there was no significant difference between pandemic and seasonal vaccination with regards to the serious adverse events (SAE) notification rate (0.3 *vs* 0.2 per 10,000).

Conclusion: Data analysis indicates that the vaccines used against 2009 pandemic influenza in Morocco have a satisfactory safety profile, similar to the seasonal influenza vaccine with the exception of local reactions as observed previously in other countries.

Keywords: Morocco, pandemic influenza, pharmacovigilance, seasonal influenza, vaccine safety

Received: 15 September 2021; revised manuscript accepted: 28 February 2022.

Correspondence to:
Amina Tebaa
Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM), Ministry of Health, Rue Lamfedel Cherkaoui, Rabat Instituts, Madinate Al Irfane, B.P. 6671, Rabat 10100, Morocco.
atebaa@yahoo.fr

Loubna Alj
Rachida Soulaymani-Bencheikh
Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM), Ministry of Health, Rabat, Morocco

Raja Benkirane
Ecole Nationale de Santé Publique (ENSP), Ministry of Health, Rabat, Morocco

Imad Cherkaoui
Direction de l'Epidemiologie et de Lutte contre les Maladies (DELM), Ministry of Health, Rabat, Morocco

Introduction

The World Health Organization (WHO) declared in June 2009 that the novel influenza strain A/H1N1 had met criteria for an influenza pandemic,[1] the first declared for four decades.[2] The emergence of this strain stimulated the development of specific vaccines in 2009 and prompted national and international health authorities to implement guidelines in order to limit transmission and mortality.

At this time, the available safety data of vaccines were derived from clinical trials, which collected data on the most common adverse events (AEs)

to be expected from each vaccine. However, it is essential to complete these trials with post-marketing surveillance studies in larger populations followed for longer periods of time. Such studies are designed to collect and analyse reports of rare and late adverse events following immunization (AEFIs). An AEFI is defined as 'any untoward medical occurrence which follows immunisation but which does not necessarily have a causal relationship with the usage of the vaccine.[3] The adverse event may be any unfavourable or unexpected sign, abnormal laboratory finding, symptom or disease'.[3]

Following the international alert on the influenza pandemic in 2009 and like most other countries, Morocco followed the recommendations and guidelines set out by the WHO and set up vaccination programmes against influenza virus for 'at-risk' populations, such as health professionals, people with chronic diseases or pregnant women. More specifically, the Moroccan vaccination programme recommends the use of two inactivated adjuvanted vaccines (*Pandemrix*™ and *Arepanrix*™ from GlaxoSmithKline Biologicals s.a.) and one inactivated non-adjuvanted vaccine (*Panenza*™ from Sanofi-Pasteur). These pandemic influenza vaccines were made available free of charge to 'at-risk' groups based on the following priorities: pilgrimage to Mecca, health professionals in direct contact with patients in emergency departments or intensive care units, adults with chronic diseases (diabetes, chronic respiratory diseases. and other chronic diseases), pregnant women, babies aged from 6 to 23 months and all individuals who wanted to be vaccinated among the general population. On the basis of vaccine producers and WHO recommendations and according to the Morocco Ministry of Health instructions (Ministerial Circular No. 190 DELM/36/DP/13 dated 7 December 2009), one dose (0.5 mL) and half a dose (0.25 mL) of vaccine were offered *via* the intramuscular route to respectively adults whatever their risk group and children aged from 6 to 23 months. Children did not receive a second dose of vaccine due to delayed vaccine delivery and logistical issues.

The *Centre Anti Poison et de Pharmacovigilance du Maroc* (CAPM) developed a reinforced surveillance protocol in order to evaluate the safety of the vaccines used during the 2009 vaccination campaign. This was based on a spontaneous reporting system and on an active case-finding approach using intensive monitoring to follow-up people who had been vaccinated.

After the 2009 influenza pandemic, patient concerns about the safety of influenza vaccines continue to be a barrier to vaccine uptake despite the WHO statement that side effects of pandemic influenza A/H1N1 2009 vaccine are similar to those observed with seasonal influenza vaccine. To date, no comparative review of reports of AEs following pandemic influenza A/H1N1 2009 and seasonal influenza vaccinations in the Moroccan population has been published. In November 2014, Morocco received a donation of 123,310 doses of Southern hemisphere formulation (same formulation as Northern hemisphere 2014–15) Green Cross™ trivalent inactivated and unadjuvanted influenza vaccine from the Partnership for Influenza Vaccine Introduction (PIVI) and Task Force for Global Health (TFGH) through a cooperative agreement on influenza vaccination between the US Centres for Disease Control and Prevention (US CDC) and the Morocco Ministry of Health. This donation allowed the Ministry of Health to expand their current target populations for seasonal influenza vaccine (health care professionals and health professions students) to include diabetics and elderly institutionalized persons. The vaccine campaign was completed by early January 2015 and 62.5% of doses were successfully administered to target populations. Monitoring for AEFIs was done by CAPM based on both routine basis and active monitoring.

The objectives of this study were to document the safety of the influenza A/H1N1 vaccines used in 2009 in Morocco and to compare the notification rate of AEs following pandemic influenza vaccination with that of seasonal influenza vaccination.

Material and methods

These were national observational studies performed in Morocco during the 6-month reference period of vaccination against pandemic influenza in the 2009–2010 seasons (from 1 November 2009 to 16 April 2010) and during the 2-month follow-up of the 2014–2015 seasonal influenza

campaign (from 14 November 2014 to 14 January 2015).

Study population

These two studies were conducted in different sites according to the context of vaccination:

For pandemic influenza vaccination campaign (2009/2010). Ten randomly selected centres were considered. Each centre represented one region of the country and was invited to enrol 100 subjects vaccinated against pandemic influenza. The population eligible for vaccination corresponded to a predefined 'at-risk' population, which included health professionals, patient with diabetes, with chronic respiratory diseases, or other chronic diseases, pregnant women (second quarter to third quarter), babies aged from 6 to 23 months old and others. In addition, we decided to include vaccinated healthy subjects in order to complete the target sample of 100 subjects in the centre.

A total sample of 1000 vaccinated subjects was targeted and constituted the national cohort involved in the study. Oral informed consent was obtained from all participating subjects.

For seasonal influenza vaccination campaign (2014/2015). Of the 123,310 doses of influenza vaccine donated, 110,092 were received on vaccination site, and 65,018 doses were actually administered corresponding to a vaccine uptake of 59.1%.

Study procedure

For pandemic influenza vaccination campaign (2009/2010). Vaccination was performed using the three vaccines for pandemic A/H1N1 influenza authorized in Morocco at this time: two inactivated adjuvanted vaccine (*Pandemrix* and *Arepanrix*) and the non-adjuvanted vaccine (*Panenza*). The adjuvanted vaccines were administered on 1 November and 1 December and the non-adjuvanted vaccine on 20 December. Only *Panenza* was administered to pregnant women and to infants of 6–23 months old. One dose of each vaccine was administered and considered in this study.

Each vaccinated subject was followed up closely during the following 6 months, except for pregnant women who were followed-up until the delivery.

For seasonal influenza vaccination campaign (2014/2015). Vaccination was performed using the Southern hemisphere formulation (same formulation as Northern hemisphere 2014–15) Green Cross trivalent inactivated and unadjuvanted influenza vaccine. The CAPM was actively engaged in planning and monitoring the 2014/2015 vaccine campaign. A circular was disseminated to all 83 provinces instructing them to strengthen the existing passive AEFI surveillance system. Any AEFI was spontaneously recorded by local health personal and thereafter reported to provincial, regional, and central levels during or after the campaign according to routine pharmacovigilance monitoring processes in force.

Data collection

For pandemic influenza vaccination campaign (2009/2010). During the study period (from 1 November 2009 to 16 April 2010), two sources of information were used to monitor the safety of administered vaccines, namely spontaneous notification and active surveillance.

Spontaneous notification. Spontaneous notifications considered in this study were reported only by health professionals following their own experience of AEFI or following a declaration of their patients or vaccinated subjects. Spontaneous notification of AEFIs declared by health professionals were documented as part of routine pharmacovigilance monitoring. Health professionals have no legal obligation to report AEFIs spontaneously. However, a national programme was implemented in order to raise awareness of health professionals about the AEFI and in order to encourage them to notify each AEFI spontaneously. Caution is required when interpreting the AEFI data provided by spontaneous notification. Like all passive surveillance data, AEFI data are subject to under-reporting. The AEFI notification rates cannot be interpreted as true incidence rates.

Active surveillance. Active surveillance was limited to the national cohort of 1000 'at-risk' subjects. Investigators from the CAPM contacted immunized subjects by telephone at specific times 48 hours, 21 days, and 6 months after immuni-

zation and invited to specify any potential AEFI. The self-assessment questionnaire collected data on gender, date of birth, vaccine name, date of vaccination, batch number, the manufacturer of the vaccine and the notification of AEs with the date of onset and resolution. Each individual questionnaire corresponds to one or many notifications included one or many AEs.

All AEFIs were notified and reported to the CAPM who classified them according to the *Preferred Term* (PT) and *System Organ Class* (SOC) in the WHO Adverse Reaction Terminology[4] and entered them into a specific study register. The AEFIs were considered serious if they resulted in death, required hospitalization or prolonged the hospitalization, were life-threatening, resulted in persistent disability, congenital anomalies or birth defects, or other medically important condition. The relationship between immunization and the appearance of any serious adverse events (SAEs) was assessed by the pharmacovigilance centre. Active surveillance and *ad hoc* studies (Global Manual on surveillance of AEFIs. WHO, 2014, https://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf) are usually conducted in order to further expand passive AEFIs surveillance activities and provide true incidence rates estimation.

For seasonal influenza vaccination campaign (2014/2015). All vaccination sites (health units, NGOs, institutional living facilities) used existing (or were provided by) registers to spontaneously record any AEs following the influenza campaign. Each vaccine recipient was also to receive a vaccine card after vaccination. Reports were taken using the standard triplicate pharmacovigilance form deployed throughout all Moroccan health care facilities and reported to the provincial and regional levels. A central team contacted by telephone focal points at provincial and regional levels to activate the AEFIs notification process.

Statistic analysis

The presentation of the results is principally descriptive. Most of the results are presented as frequency counts and percentages, with their 95% confidence intervals in term of AEFI (spontaneous) notification rate for passive surveillance and AEFI (true) incidence for active surveillance. A chi-square test was performed in order to compare frequency distributions when appropriate.

Results

Study participants

For pandemic influenza vaccination campaign (2009/2010). During the Moroccan vaccination campaign of 2009, 705,883 subjects were vaccinated around the country. Of those, 525,049 received an adjuvanted vaccine, corresponding to 74.4% of all subjects. These subjects provided the source population for spontaneous AE reporting.

With respect to the national pharmacovigiliance survey, a total of 1000 subjects were enrolled. All potential AEs possibly related to immunization with adjuvanted vaccine (*Pandemrix* and *Arepanrix*) and non-adjuvanted vaccine (*Panenza*) were documented. The largest 'at-risk' groups represented in the survey were health professionals and individuals with diabetes accounting for respectively 400 and 449 subjects, both corresponding to 84.9% of 1000 sujects. On another side, subjects with other chronic diseases, healthy subjects, pregnant women, and children from 6 to 23 months accounted for 77, 68, 67, and 20 subjects, respectively, corresponding together to only 23.2% of 1000 sujects. Males predominated among health professionals (63.2%) and healthy subjects (57.4 %), whereas females predominated among individuals with diabetes (52.8 %) or with other chronic diseases (54.5 %) and children from 6 to 23 months (60.0%; Table 1). The median age of the study participants was 40.25 years (10 months–80 years).

The majority of subjects ($n = 908$; 90.8%) received one dose of an adjuvanted vaccine ($n = 549$; 54.9% for *Arepanrix* and $n = 359$; 35.9% for *Pandemrix*) and the rest ($n = 92$; 9.2%) received one dose of a non-adjuvanted vaccine (*Panenza*).

For seasonal influenza vaccination campaign (2014/2015). Of the 83 provinces of Morocco, 65 returned data to the central level as of March 23, 2015. In these provinces, 104,023 persons were to be vaccinated in the selected target population. These provinces indicated they received 110,092 doses of Green Cross trivalent inactivated influenza vaccine and of these, 65,018 (62.5%) were successfully administered. Vaccine uptake was

Table 1. Reasons for immunization by sex in the study population during the 2009/2010 national pharmacovigilance survey.

Sex Target population (*)	Male (% by sex)	Female (% by sex)	*N* (% among 1000 subjects)
Healthcare workers	253 (63.2%)	147 (36.8%)	400 (40.0%)
Subjects with diabetic	211 (46.9%)	237 (52.8%)	449 (44.9%)
Subjects with chronic respiratory diseases	20 (52.6%)	18 (47.4%)	38 (3.8%)
Subjects with other chronic diseases	14 (35.9%)	24 (61.5%)	39 (3.9%)
Pregnant women	0 (0.0%)	67 (100.0%)	67 (6.7%)
Children from 6 to 23 months	8 (40.0%)	12 (60.0%)	20 (2.0%)
Healthy subjects	39 (57.4%)	29 (42.6%)	68 (6.8%)

(*) The categories are not mutually exclusive.

highest among diabetics among whom 37,761 (68.2%) were vaccinated, followed by health professionals with 17,186 (54.8%) vaccinated. Uptake among health students varied by type of institution due to the coincidence with the school examinations period with 564 (5.2%) vaccinations for students in medical and dental faculties and 4307 (60.5%) vaccinations for those in nurse institutes. Finally, uptake among elderly was extremely high with 5200 vaccinations (98.1%), most likely reflecting easier logistic issues of vaccine delivery to a residential population. Redeployment numbers represent influenza vaccine originally designated for one target population that was redirected to another facility or target population in the province. Overall, 12.3% of vaccine was redeployed to maximize the use of vaccine, although these data were not consistently recorded by all provinces.

AEFIs notification

For pandemic influenza vaccination campaign (2009/2010)

Spontaneous notification. Among the source population of 705,883 subjects vaccinated, a total of 222 individuals spontaneously notified AEFIs during the study period. This corresponds to a (spontaneous) notification rate of 3.1 per 10,000 immunized subjects in the country (95% CI: 2.7–3.6 per 10,000; Table 2).

The highest spontaneous notification rate was recorded from health professionals themselves (39.5 per 10,000 immunized subjects) followed by those declared, *via* health professionals, by healthy subjects and subjects with diabetes or respiratory diseases). In this group, data on demographics were available for 126 subjects, of whom 84 (66.7%) were women and 121 (96.0%) were adults.

Active surveillance cohort. Among the thousand subjects involved in the national intensive pharmacovigilance survey, 771 reported experiencing AEFIs corresponding to a (true) incidence of 77.1% of the immunized population involved in this survey (95% CI: 74.5–79.7 %). Data on demographics of this population were available for 746 subjects, of whom 336 (41.7%) were women, 738 (99.0%) were adults (of whom 20 were aged >65 years) and eight (1.0%) were children (data were missing for 27 subjects).

For seasonal influenza vaccination campaign (2014/2015). Among the source population of 65,018 subjects vaccinated, a total of eight AEFI cases were reported from 15 out of 16 regions during the study period. This corresponds to a (spontaneous) notification rate of 1.2 per 10,000 immunized subjects (95% CI: 0.4–2.1 per 10,000) during the 2014/2015 season. The (spontaneous) notification rate of AEFIs (3.1 per 10 000) (95% CI: 2.7–3.6 per 10,000) for 2009/2010 pandemic vaccine was significantly higher than that observed for 2014/2015 seasonal vaccine ($p=0.002$, Fisher's exact test; Table 2).

Table 2. Notification rate and incidence of AEFIs among the study population during 2009/2010 inflenza pandemic and 2014/2015 influenza season.

Study period	2009/2010 inflenza pandemic								2014/2015 influenza season			
Type of AEFI surveillance	National pharmacovigilance survey				Spontaneous reporting				Spontaneous reporting			
	No. of vaccinated subjects	No. of subjects reporting AEFIs	Incidence rate (%)	95% CI (%)	No. of vaccinated subjects	No. of subjects reporting AEFIs	Notification rate (/10,000 subjects)	95% CI (/10,000)	No. of vaccinated subjects	No. of subjects reporting AEFIs	Notification rate (/10,000 subjects)	95% CI (/10,000)
Health professionals	400	350	87.5	84.3–90.7	9874	39	39.5	27.1–51.9	17,186	–	–	–
Health students	–	–	–	–	–	–	–		4871	–	–	–
Pilgrims	–	–	–	–	39,206	2	0.5	0.0–1.2	–	–	–	–
Subjects with diabetes or respiratory diseases	449	300	66.8	62.5–71.2	221,730	104	4.7	3.8–5.6	37,761	–	–	–
Subjects with other chronic diseases	77	38	49.4	38.2–60.5	222,536	22	1.0	0.6–1.4	–	–	–	–
Pregnant women	67	36	53.7	41.8–65.7	167,870	3	0.2	0.0–0.4	–	–	–	–
Children 6–23 months	20	4	20.0	2.5–37.5	11,658	–	–		–	–	–	–
Elderly people in close institutions	–	–	–	–	–	–	–		5200	–	–	–
Subjects working in close institutions	–	–	–	–	6932	–	–		–	–	–	–
Healthy subjects	68	43	63.2	51.8–74.7	26,077	14	5.3	2.6–8.2	–	–	–	–
Not specified	–	–	–	–	–	38	–		–	–	–	–
Total (*)	1000	771	77.1	74.5–79.7	705,883	222	3.1	2.7–3.6	65,018	8	1.2	0.4 - 2.1

AEFI, adverse events following immunization.
(*) The difference between the two (spontaneous) notification rates of AEFI is statistically significant (Fisher's exact test = 0.002).

Information on the vaccine type was only available systematically for the subjects followed in the national intensive pharmacovigilance survey. The incidence rate of AEFIs for adjuvanted vaccines (82.1%) (95% CI: 78.7% - 85.1%) for *Arepanrix* and (78.3%) (95% CI: 73.7% - 82.2%) for *Pandemrix*) was significantly higher than that observed for the non-adjuvanted vaccine (42.4%) (95% CI: 32.8%–52.6%); ($p < 0.0001$, chi-square test); Table 3).

Table 3. Incidence of AEFIs according to the used vaccine during the active reporting survey.

	National pharmacovigilance survey		
	No. of immunized subjects (*N* = 1000)	**No. of subjects reporting AEFIs (*N* = 771)**	**Incidence (%)**
Adjuvanted vaccine			
Arepanrix	549	451	82.1
Pandemrix	359	281	78.3
Non-adjuvanted vaccine			
Panenza	92	39	42.4

Classification of the reported AEFIs according to the SOC

Overall, 1249 AEFIs were reported by the concerned population ($n = 993$ subjects) in pandemic influenza vaccination campaign (2009/2010). The majority of these AEFIs (77.9%; $n = 973$) AEFIs were documented during the national intensive pharmacovigilance survey. The AEFIs were classified by PT and SOC (Table 4). During the intensive pharmacovigilance survey, application site disorder was the most reported SOC. During this phase, the most frequently reported AEFI was pain (211 cases; 21.7%) followed by fever (162 cases; 16.6%), headache, and injection site reactions (94 cases; 9.7% for each). During the spontaneous reports phase, the most often cited SOC was neurological disorder and the most frequent AEFI documented was fever (61 cases; 22.1%). No case of narcolepsy was reported during the study period.

During the national intensive pharmacovigilance survey, the immunized subjects were followed-up during three reference periods: 48 hours, 21 days, and 6 months after immunization. The majority ($n = 803$; 82.5%) of AEs were reported during the first follow-up period (48 hours after immunization) and the rest ($n = 170$; 17.5%) were reported during the second follow-up period (21 days following immunization). No AEs were reported during the last follow-up (6 months after immunization).

SAEs reported

For pandemic influenza vaccination campaign (2009/2010). No SAEs were reported in the national intensive pharmacovigilance survey. From spontaneous reporting, 21 (9.5%) subjects reported an event classified as an SAE. These involved nine patients (42.8%) who were hospitalized, for hemiparalysis (6 cases), for convulsions (2 cases) and Sweet's syndrome (1 case). There were five cases (23.8%) of medication overdose, four cases of life-threatening AEs and three deaths. The corresponding SAE notification rate was 0.3 per 10,000 doses administered (95% CI: 0.2–0.4 per 10,000). All these cases were reported in subjects with diabetes (15 cases) or chronic respiratory diseases (6 cases). The causal relationship between immunization and SAEs was assessed and considered absent in 8 (38.1%) cases, possible in 11 (52.4%) cases and unlikely in 2 (9.5%) cases (Table 5). All serious cases were observed following vaccination with adjuvanted vaccine.

Three persons died during the study. No causal relationship between immunization and the deaths was suspected. Two deaths were due to autopsy-confirmed bowel obstruction which occurred concurrently with the vaccination and the third concerned a very old subject suffering from two chronic diseases (diabetes and hypertension).

For seasonal influenza vaccination campaign (2014/2015). Among the eight AEFI cases, seven were mild and one was a case of Guillain–Barré Syndrome (GBS) and therefore classified as an SAE. An investigation was conducted at the provincial level and the GBS case recovered successfully. The corresponding SAE notification rate was 0.15 per 10,000 doses administered (95% CI: 0.0–0.5 per 10,000). The (spontaneous) notification rate of SAE (0.3 per 10,000; 95% CI:

Table 4. Reported AEs during the study.

Reported adverse event	Number of AEs (*n*, %)		
(System organ class)	**Active reporting (*N* = 973)**	**Spontaneous reporting (*n* = 276)**	***p* value**
Application site disorders	**367 (37.7%)**	85 (30.8%)	0.017
Pain	211 (21.7%)	46 (16.7%)	
Injection site reaction	94 (9.7%)	14 (5.1%)	
Tumefaction	22 (2.3%)	20 (7.2%)	
Oedema	20 (2.0%)	2 (0.7%)	
Induration	20 (2.0%)	3 (1.1%)	
General disorder	288 (29.5%)	83 (30.1%)	NS
Fever	162 (16.6%)	61 (22.1%)	
Shivering	59 (6.1%)	15 (5.4%)	
Asthenia	40 (1.4%)	5 (1.8%)	
Fatigue	20 (2.0%)	2 (0.7%)	
Ache	7 (0.7%)	0 (0.0%)	
Central and peripheral nervous system disorders	198 (20.3%)	**134 (48.6%)**	<0.0001
Headache	94 (9.7%)	39 (14.1%)	
Influenza syndrome	45 (4.6%)	45 (16.3%)	
Vertigo	31 (3.2%)	41 (14.8%)	
Paraesthesia	20 (2.0%)	8 (2.9%)	
Sleep disorders	8 (0.8%)	1 (0.4%)	
Discomfort	5 (0.5%)	0 (0.0%)	
Musculoskeletal system disorders	58 (6.0%)	33 (12.0%)	0.0004
Myalgia	22 (2.3%)	28 (10.1%)	
Athralgia	19 (1.9%)	3 (1.1%)	
Musculoskeletal pain	14 (1.4%)	0 (0.0%)	
Others	3 (0.3%)	2 (0.7%)	
Gastrointestinal system disorders	26 (2.6%)	31 (11.2%)	<0.0001
Abdominal pain	2 (0.2%)	4 (1.4%)	
Diarrhoea	8 (0.8%)	12 (4.3%)	
Nausea	14 (1.4%)	0 (0.0%)	
Vomiting	2 (0.2%)	15 (5.4%)	

(continued)

Table 4. (Continued)

Reported adverse event	Number of AEs (*n*, %)		
(System organ class)	**Active reporting (*N* = 973)**	**Spontaneous reporting (*n* = 276)**	***p* value**
Cardiovascular disorders	10 (1.0%)	5 (1.8%)	NS
Respiratory system disorders	10 (1.0%)	7 (2.5%)	0.028
Skin and appendages disorders	8 (0.8%)	21 (7.6%)	<0.0001
Vision disorders	3 (0.3%)	0 (0.0%)	NA
Reproductive disorders, female	2 (0.2%)	0 (0.0%)	NA
Psychiatric disorders	1 (0.1%)	1 (0.4%)	NA

NA, not applicable; NS, not significant.

Table 5. Serious adverse events reported spontaneously and their potential relationship with the immunization.

Study period	2009/2010 inflenza pandemic		2014/2015 influenza season	
Type of SAE	**Number of cases**	**Causal relationship**	**Number of cases**	**Causal relationship**
Guillain–Barré Syndrome	1	Absent (Hodgkin's disease)	1	Possible
Sweet's syndrome	1	Possible		
Hemiparesis	3	Absent (stroke)		
Limb paresis	3	Possible		
Seizures	2	Absent (epilepsy)		
Thrombocytopenic purpura	1	Possible		
Hyperglycaemia	1	Unlikely (diabetes)		
Gastrointestinal disorders	2	Possible		
Acute arteritis	1	Unlikely		
Vaso-vagal syncope	2	Possible		
Fatal acute abdominal disorder	2	Absent		
Asthma attack	2	Possible		
Total SAE	21		1	
No. of vaccinated subjects	705,883		65,018	
SAE notification rate (*) (/10,000 subjects)	0.3		0.2	
95% CI (/10,000 subjects)	0.2–0.4		0.0–0.5	

SAE, serious adverse events.
(*) The difference between the 2 SAE rates is not statistically significant (Fisher's exact test).

0.2–0.4 per 10,000) for 2009/2010 pandemic vaccine was not significantly higher than that observed for 2014/2015 seasonal vaccine ($p > 0.05$, Fisher's exact test; see Table 5).

Discussion

This article presents the safety data of influenza A/H1N1 vaccines, collected following the immunization campaign of 2009 in Morocco and compares the notification rate of AEs following pandemic influenza A (H1N1) 2009 with that of the 2014/2015 seasonal influenza vaccinations that was specifically investigated after a donation of 123,310 doses of trivalent inactivated and unadjuvanted influenza vaccine through a collaboration with the US CDC, PIVI, and TFGH. To date, no such comparative review has been published despite the fact that concerns of patients and health care workers regarding the safety of influenza vaccines continue to be a barrier to vaccine uptake in Morocco. During this campaign (1 November 2009 to 16 April 2010), a total of 705,883 subjects were vaccinated with two types of vaccines: adjuvanted and non-adjuvanted vaccines. This corresponds to a vaccination rate in Morocco of 2.4% of the general population. This rate was similar to the vaccination rate recommended by the WHO, who fixed as a first objective for the developing countries a vaccination rate of 2% of the general population during the period from November 2009 to February 2010.[5]

During the study, two sources of information were used to collect AEFIs. The first procedure consists on a spontaneous reporting of AEFIs, and the second procedure consists on a national active pharmacovigilance survey using a self-assessment questionnaire. A total of 222 spontaneous notifications were recorded during the immunization campaign. This corresponds to 3.2 notifications per 10,000 immunized subjects. This rate was intermediate between those reported in Ireland and United States (0.63 and 0.82, respectively, spontaneous notifications per 10,000 subjects)[6,7] and those reported in France and Denmark (9.4 and 17.9, respectively, spontaneous notifications per 10,000).[8,9] However, this (spontaneous) notification rate was significantly higher than that of 1.2 per 10,000 immunized subjects observed for 2014/2015 seasonal vaccine. Both clinical trials and active surveillance studies have shown that pandemic adjuvanted vaccines induce frequent local reactions[10–12] that were up to 30.8% with the spontaneous reporting in our study.

During the active pharmacovigilance survey, among the thousand subjects responding to the self-assessment questionnaire, 771 (77.1%) subjects notified AEs. This rate is very high compared to that of passive AEs surveillance. Like all passive surveillance data, AEFI data are subject to under-reporting, Thus the active notification rate observed in Morocco could be interpreted as true AEFI incidence rates but it seemed to be higher compared to the rate reported in Slovenia (29.2%)[10] or in Korea (6.3%)[11] for example. However, it should be noted that the direct comparison of the spontaneous or active notification rates between countries was difficult because many specific factors can influence these rates. It includes for example, the intra-individual specificity (such as age, community, and background conditions) and the reactogenicity of each subject to the type of vaccine used. The background rate of disease (such as multiple sclerosis or autoimmune disease) was an important aspect in the assessment of vaccine safety and should be considered in the determination of the AEFIs.[3] This aspect may help to distinguish between legitimate AEs and events that are associated with but not caused by vaccination.[13]

In general, the type of AEFIs observed in our study were comparable to those reported in the clinical trials and the post-marketing vaccine surveillance system as indicated in the summary of product characteristics (SPC) of each used vaccine at the time of study.[14–16]

Based on the *SOC*, *a*pplication site disorders such as pain and injection site reaction were reported by over one-third of subjects as evoked above, followed by general disorders such as fever. These results are consistent with several studies using the same or different influenza vaccine where around 50%–60% of subjects reported local site reactions.[10,12] Moreover, our study results are consistent with the information in the pandemic vaccines package insert. This information as we observed in Morocco (Table 4) is specifying that some local reactions such as pain at injection site or general disorders like fever or headache are expexted to be very common (more than 10%).

Also, others side effects as redness and swelling at the injection or shivering were found common (1–10%) as expected. However, some important side effects seems to be more commonly found (vertigo and paraesthesia) or less commonly found (fatigue) in our study comparatively to the vaccine package insert information. At last, gastrointestinal system disorders (diarrhoea, vomiting, and abdominal pain) expected to be uncommon (0.1–1%) were more commonly notifyed by spontaneous reporting of AEFIs probably due to the background rate of digestive diseases.

The adjuvanted vaccine was the most frequently vaccine used during the 2009 pandemic and seemed to be associated with higher rate of AEFIs compared to the non-adjuvanted vaccine ($p < 0.001$). This result was consistent with other founding of other studies and with the information available in the vaccines package insert. For example, a study describing the active surveillance of AEs in Slovenia showed that the adjuvanted vaccine was the most frequently used and mostly associated with occurrence of AEFIs.[10]

During the spontaneous reporting phase of the 2009 pandemic, 21 notifications were considered as serious. This corresponds to a rate of 0.3 notifications of SAEs per 10,000 immunized subjects, which was very close to the rate founded in France (0.4 per 10 000 subjects).[8] This (spontaneous) notification rate was not significantly higher than that observed for 2014/2015 seasonal vaccine suggesting that the 2009 pandemic vaccine seems to have a good safety profile, similar to seasonal influenza vaccine with the exception of local reactions.[17]

In addition, we observed in our study that among the 1222 analysable subjects, only one reported a GBS considering that this event is expected to be very rare (less than 0.01%) according to the vaccines package insert information. Nevertheless, no causal relationship between the occurrence of this SAE and the immunization was detected. In the literature, it was suggested that during a mass immunization with pandemic H1N1 influenza vaccines involving for example 10 millions subjects, it can be predicted that about 22 will develop GBS.[13]

Among the 'at-risk population', no new or unexpected events were observed in immunized pregnant women. However, subjects with diabetic reported the majority of SAEs (15/21 subjects). This result suggests that diabetic seems to be the most important risk factor to develop SAEs following immunization against H1N1.

It was noted in our study that the notification rate reported during the active pharmacovigilance phase was significantly higher than the rate found in the spontaneous reporting phase ($p < 0.0002$). This may be explained by under-reporting of passive surveillance as stated above but also by the fact that subjects in the active pharmacovigilance phase were pre-selected and identified as an 'at risk population', and are thus more 'susceptibles' to experience AEs. In addition, these subjects are followed during the study period which gives them the opportunity to report each AEs during the study course. Moreover, the spontaneous notifications may be associated with a loss of certain information. For example, subjects may forget to report a potential AE to their physicians because they do not associated it to the immunization or they believe that it was associated with their own disease. Many proposals are recommended especially by the WHO, to strenghten a rountine and passive AEFI notification system. Stimulated passive AEFI surveillance is a good example of such recommendations that have proven their relevance in the COVID-19 vaccination context. For this purpose, health staff should be trained, sensitized, and followed-up by a central AEFI monitoring centre *via* a network of focal points at local levels. Once an AEFI is detected, an agreed protocol is used for the patient care and management. In parallel, information and communication technology tools should be promoted to allow a more reactive transmission of reports with daily data review at different administrative levels to generate possible signals for adequate response.

This study has some limitations. First, the direct comparison between adjuvanted and non-adjuvanted vaccines was not robust because the background conditions of these two groups were different. Second, it is difficult to stress the causal relationship between the vaccination and the occurrence of AEs based on the information provided in our study. Additional methods such as the comparison of observed and expected AEs from the health databases or studies based on individual-level data on exposure and outcome

should be of particular interest. However, the combination of the active pharmacovigilance survey and the spontaneous reporting used in our study seems to be an adequate method to collect AEs in Morocco because the two methods are complementary and allow to build the health database in this country. Other methods were used around the world and were adapted according to local specificity of each country. For example, it was shown in United Kingdom that a real-time surveillance of AEFIs with H1N1 vaccines (based on a web reporting system (*Yellow Card Scheme*®) and on a paper reports) confronted to a mathematical computing events would be expected after immunization should be an optimal strategy for the assessment of vaccine safety.[18]

Conclusion

This study is the first report describing the monitoring of the safety of influenza A/H1N1 pandemic vaccine in Morocco and to compare it with that of the 2014/2015 seasonal influenza vaccine This article described the method and the results of the AEs monitoring during the 2009 pandemic which was based on two systems of collection of information; the spontaneous reporting and the active surveillance of AEFIs. This study shows that according to these sources of information, no new AEFIs (serious or not serious) with adjuvanted or non-adjuvanted vaccines were observed in Morocco from November 2009 to April 2010. This indicates that the 2009 pandemic influenza A/H1N1 vaccines used in Morocco seems to have a good safety profile similar to seasonal influenza vaccine with the exception of local reactions. Continuous monitoring of seasonal vaccines is necessary in order to ensure a long-term safety of these vaccines. In addition, other supplementary methods which detect and evaluate rare and late AEFIs should also be considered in the near future.

Acknowledgements

The authors wish to acknowledge the investigators of the Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM) for their sustained work on AEIV active and passive surveillance during the 2009 pandemic. We are grateful to Margaret McCarron, Sara Mirza, and Susan Chu for their support and supervision onsite of the 2014/2015 seasonal influenza vaccination campaign on behalf of the US Centres for Disease Control and Prevention.

Author contributions

Amina Tebaa: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Raja Benkirane: Investigation; Resources; Validation; Visualization.

Loubna Alj: Validation; Visualization.

Imad Cherkaoui: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Rachida Soulaymani-Bencheikh: Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Validation; Visualization.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The pandemic influenza vaccination campaign study has been funded by the Centre Anti Poison et de Pharmacovigilance du Maroc and the seasonal influenza vaccination campaign was supported by the US Centres for Disease Control and Prevention through its Cooperative Agreement with the Morocco Ministry of Health (grant number IP820).

ORCID iD

Amina Tebaa https://orcid.org/0000-0002-1976-1075

Disclaimer

The findings and conclusion of this paper are those of the authors and do not necessarily represent the official position of the US Centres for Disease Control and Prevention.

Ethics

The study was performed in the framework of the Declaration of Helsinki and relevant international and national legislation. No ethical approval was required for this study.

References

1. World Health Organization. New influenza A (H1N1) virus: global epidemiological situation, June 2009. *Weekly Epi Rec* 2009; 84: 249–260.
2. Girard MP, Tam JS, Assossou OM, *et al*. The 2009 A (H1N1) influenza virus pandemic: a review. *Vaccine* 2010; 28: 4895–4902.
3. World Health Organization. Adverse Events Following Immunization (AEFI). https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/aefi
4. World Health Organization. The WHO Adverse Reaction Terminology, 2005. https://who-umc.org/vigibase/vigibase-services/who-art/
5. World Health Organization. Pandemic influenza A (H1N1) 2009 virus vaccine – conclusions and recommendations from the October 2009 meeting of the immunization Strategic Advisory Group of Experts. *Weekly Epi Rec* 2009; 84: 505–516.
6. Irish Medicines Board. UPDATE on national monitoring experience with pandemic H1N1 vaccines, 18 March 2010, https://www.hpra.ie/docs/default-source/Safety-Notices/imb_h1n1_vaccines_update_1apr10.pdf?sfvrsn=0
7. Centers for Disease Control Prevention. Safety of Influenza A (H1N1) 2009 Monovalent Vaccines – United States, October 1–November 24, 2009. *MMWR* 2009; 58: 1351–1356.
8. Durrieu G, Caillet C, Lacroix I, *et al*. National campaign of vaccination against the flu A (H1N1) v: national follow-up of pharmacovigilance. *Therapie* 2011; 66: 527–540
9. Folkenberg M, Callreus T, Svanstrom H, *et al*. Spontaneous reporting of adverse events following immunisation against pandemic influenza in Denmark November 2009-March 2010. *Vaccine* 2011; 29: 1180–1184.
10. Kraigher A and Ucakar V. Surveillance of adverse events following immunization against pandemic influenza in Slovenia in season 2009/10. *Vaccine* 2010; 28: 5467–5472.
11. Choe YJ, Cho H, Song KM, *et al*. Active surveillance of adverse events following immunization against pandemic influenza A (H1N1) in Korea. *Jpn J Infect Dis* 2011; 64: 297–303.
12. Harmark L, van Hunsel F, Hak E, *et al*. Monitoring the safety of influenza A (H1N1) vaccine using web-based intensive monitoring. *Vaccine* 2011; 29: 1941–1947.
13. Black S, Eskola J, Siegrist CA, *et al*. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet* 2009; 374: 2115–2122.
14. Summary of Product Characteristics (SPC) Arepanrix, October 2011, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001201/WC500089737.pdf
15. Summary of Product Characteristics (SPC) Pandemrix, February 2012, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000832/WC500038121.pdf
16. Agence Francaise de Sécurité Sanitaire des Produits de Santé (Afssaps). Public assessment report – Scientific Discussion-Panenza-Pandemic influenza vaccine (H1N1), November 2009, http://afssaps-prd.afssaps.fr/html/par_eu/20091113_fr447_panenza_par.pdf
17. De Serres G, Gariépy M-C, Coleman B, *et al*. Short and long-term safety of the 2009 AS03-adjuvanted pandemic vaccine. *PLoS ONE* 2012; 7: e38563.
18. Bryan P, Seabroke S and Davies C. H1N1 vaccine safety: real-time surveillance in the UK. *Lancet* 2010; 376: 417–418.