# Adverse Events with the Influenza A(H1N1) Vaccine Pandemrix® at Healthcare Professionals in Portugal

## Eventos Adversos com a Vacina Pandemrix® Contra o Vírus Influenza A(H1N1) em Profissionais de Saúde em Portugal

Joana Isabel MARQUES[1], Inês RIBEIRO VAZ[1,2], Cristina SANTOS[1,3], Jorge POLÓNIA[2]
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### ABSTRACT

**Introduction:** Healthcare professionals were a priority group for Pandemrix® vaccination. Surveying this particularly committed group for vaccination related side effects could help to get valuable information about vaccine safety profile. Our aim was to identify the adverse events following immunization with Pandemrix® among healthcare professionals.

**Material and Methods:** A questionnaire for active post-authorization monitoring of adverse events following immunization with the influenza vaccine A (H1N1) was designed and distributed to the vaccinated healthcare professionals working at 3 elected hospital centres in the Northern region, in the period from 26 October 2009 to 31 January 2010.

**Results:** From the 2358 vaccinated healthcare professionals that accepted to participate in this study, 864 (37%) returned back the fulfill questionnaire on time. Among these, 634 (73%) of healthcare professionals experienced at least one adverse event following immunization, but only 8% experienced an unexpected one. The adverse events most frequently reported were expected and very common: local reactions at the injection site (57%), myalgia (31%), fatigue (including asthenia) (24%) and headache (19%). No cases of major episodes, such as death or life-threatening events were reported. Female gender and existence of underlying conditions were independent risk factors to develop at least one adverse event following immunization to the pandemic vaccine.

**Conclusions:** Our work suggests an acceptable safety profile of this pandemic flu vaccine among healthcare professionals. Both frequency and severity of the observed adverse event following immunization do not seem to be higher than expected.


**Keywords:** Influenza Vaccines/adverse effects; Influenza A Virus, H1N1 Subtype; Health Personnel.


### RESUMO

**Introdução:** Os profissionais de saúde foram um grupo prioritário para vacinação contra a pandemia da Gripe A (H1N1), Pandemrix®. Assim, monitorizar os eventos adversos relacionados com esta vacina neste grupo específico poderá originar informação valiosa relacionada com o perfil de segurança da vacina. O nosso objetivo foi identificar os eventos adversos após imunização com a vacina Pandemrix® em profissionais de saúde.

**Material e Métodos:** Foi desenhado um questionário de monitorização dos eventos adversos ocorridos com a vacina Pandemrix®. O questionário foi distribuído aos profissionais de saúde a trabalhar em três centros hospitalares da região norte do País, vacinados no período de 26 de Outubro de 2009 a 31 de janeiro de 2009.

**Resultados:** Dos 2358 profissionais de saúde que aceitaram participar no estudo, 864 (37%) devolveram o questionário preenchido. Destes, 73% experienciaram pelo menos um evento adverso após imunização, mas só 8% experienciaram um evento inesperado. Os eventos adversos mais frequentemente reportados foram os esperados e muito comuns: reações locais no local de administração (57%), mialgia (31%), fadiga (incluindo astenia) (24%) e dor de cabeça (19%). Não foram reportados casos de eventos de maior gravidade para a saúde, tais como morte ou risco de vida. O género feminino e a existência de doença de base foram fatores de risco independentes para o desenvolvimento de pelo menos um evento adverso após imunização com a Pandemrix®.

**Conclusões:** O nosso trabalho sugere um perfil de segurança aceitável da vacina pandémica Pandermix® em profissionais de saúde. Tanto a frequência como a severidade dos eventos adversos não se verificaram superiores ao esperado.


**Palavras-chave:** Vacinas da Influenza / efeitos adversos; Vírus Influenza A Subtipo H1N1; Profissionais de Saúde.

## INTRODUCTION

The first alert to the pandemic virus A (H1N1) emerged from Mexico on 24 April 2009. The rapid dissemination of the new virus worldwide, fulfill the World Health Organization (WHO) criteria for the declaration of pandemic influenza in a few days after the first alert.[1] In Portugal, the first case was diagnosed at 29 April 2009 in a healthy young woman with an epidemiologic *link* to Mexico.[2]

The vaccines are the most important method to combat a pandemic flu, contributing to reduce the disease and mortality through the immunization against the virus.[3]

To minimize the risk of the disease, the Portuguese vaccination campaign started on 26 October of 2009. The acquisition of the pandemic vaccine was predicted on the National Contingency Plan of the Portuguese Health sector for the pandemic flu on the ambit of the strategic medicines reserve.[4]

According to a Portuguese Ministry Council resolution, it was authorized the purchase of 6 000 000 doses to vaccinate 30% of the resident population following the requirements of the WHO, confirmed by European Medicines Agency (EMA). With the aim to protect the most vulnerable persons, to reduce the morbidity and mortality, to maintain in function fundamental services and to reduce rapid spread of the disease, priority groups were defined. The first

1. Centre for Research in Health Technologies and Information Systems (CINTESIS). Faculty of Medicine. University of Porto. Porto. Portugal.
2. Northern Pharmacovigilance Centre. Faculty of Medicine. University of Porto. Porto. Portugal.
3. Health Information and Decision Sciences Department. Faculty of Medicine. University of Porto. Porto. Portugal.
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group comprised healthcare professionals, pregnant after 3 months of pregnancy with underlying conditions and workers with essential functions.[5]

After the beginning of the pandemic flu, two vaccines were authorized by a *mock-up* approaching, the unique against pandemic vaccines. Because it was not known in advance which strain of influenza A virus could give rise to a pandemic, the vaccines were previously prepared using one different influenza strain. These *mock-up vaccines* contain the H5N1 influenza strain, which can also cause pandemic and, apparently, no one were exposed until that time.[6,7] Once identified the new strain of the pandemic virus A (H1N1) by the World Health Organization (WHO), it was possible to the manufacturers to obtain the final vaccines substituting the *mock-up* strain A/Vietnam 1194/2004 H5N1 by the pandemic strain H1N1.[8,9]

Based on a recommendation of EMA, the European Commission authorized three vaccines (Focetria®, Pandemrix® and Celvapan®) according to a centralized process.[10] The vaccine acquired in Portugal was Pandemrix® (GlaxoSmithkline), authorized on 29 September 2009. This vaccine contains the viral surface fragmented and inactivated antigen A/California/7/2009 (H1N1)v-like strain (X-179A).[11] This vaccine, propagated in eggs, contains 3.75 µg haemaglutinin and adjuvant with AS03, a squalene based emulsion.[12]

Decades of evidence with seasonal influenza vaccines suggests that the inclusion of a new strain or the substitution by other strain doesn´t modify significantly the safety profile of vaccines. Besides, the authorization of the pandemic vaccines was made according to the quality, safety, immunogenicity, and clinical trials information available that predict a positive benefit-risk relationship.[13]

As well as to all new medicines, only limited data on safety and immunogenicity of influenza A/H1N1 vaccines will be available when Member States start using them at large scale. Active post-authorization monitoring of the vaccines was need to detect and assess rare adverse events following immunization (AEFI) and to measure severity and frequency of them in order to monitor the effectiveness and to act in case of a safety problem.[14]

The imperative of a rapid authorization of the pandemic vaccine and its excipients, the media explanation and the misinformation of some healthcare professionals caused general concerns about effectiveness and, especially, about safety of this pandemic vaccine. However, some studies showed that the tolerance of the pandemic vaccine appeared acceptable.[15-17] The results of a Slovene study also suggested that the risk-benefit balance for pandemic vaccine remained favorable.[18]

Although spontaneous reporting rate is usually higher after a pandemic vaccination than after the seasonal vaccines, it is important to monitoring adverse events following immunization actively. In fact, surveying a particular priority group of vaccination with knowledge about signs and symptoms involved could help to get valuable information about vaccine safety profile.

This work aims to describe the AEFI among healthcare professionals.

## METHODS

We designed a questionnaire for active post-authorization monitoring of AEFI with influenza vaccine A (H1N1) distributed in Portugal.

### Selection and Description of participants

This questionnaire was delivery immediately after the vaccination with Pandemrix®, by the nurses that administered this vaccine to the healthcare professionals working at 3 hospital centres in the Northern region, in the period from 26 October 2009 to 31 January 2010. The hospital centres were selected by convenience. According to the National Institute of Statistics the Northern Region consists in an area of 21 278 $Km^2$, with a population of 3 689 682 inhabitants.

All the participants were adult and received only one dose of the vaccine, according to the EMA scientific considerations[19] (There were no immunocompromised patients in our study).

All healthcare professionals vaccinated in the three elected hospital centres were informed about the aim of the study and asked to sign a written informed consent before the delivery of the self-assessment questionnaire to report the experienced AEFI. Data were collected from 26 October 2009 until 31 October 2010, and were validated and analyzed by the Portuguese Northern Pharmacovigilance Centre (UFN, in the original abbreviation).

The sample for this study consists in 2358 adult participants that perform the criteria for this study.

### Technical Information

Adverse events were defined according to the Medical Dictionary for Regulatory Activities (MedDRA terminology), and we adopted the International ICH E2A[20] criteria for classifying seriousness of the case and expectancy of the AEFI, which are the classifications used by the Portuguese Regulatory Authority. Accordingly, we classified AEFI as expected very common, expected common, expected uncommon and unexpected. Expected is an AEFI of which the nature, severity or outcome is consistent with the Summary of Product Characteristics (SPC). Unexpected is an AEFI of which the nature, severity or outcome is not consistent with the SPC. A serious adverse event is any untoward medical occurrence that at any dose*:* results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event. According to the frequency, we used the classification adopted by the Council for International Organizations of Medical Sciences (CIOMS)/ World Health Organization (WHO): very common, which occurs in a frequency more than 10%; common, which occurs in a frequency between 1% and 10% and uncommon, which occurs in a frequency > 0.1% and < 1%.

The self-assessment questionnaires collected data on:

- Personal data: individual professional number, gender, pregnancy, underlying conditions and medication usually taken, telephone number and/or e-mail.
- Vaccine: date of vaccination, batch number of the vaccine
- AEFI: fever, local reaction, generalized rash, seizures, myalgia, fatigue, sweating/chills/feeling cold, ganglion reaction, and a place to fulfill other events experienced. This section also contains information about the date of the experienced AEFI and the need of hospital and medical help, pharmacological treatment and absents to work
- Seasonal vaccine 2009 - 2010: information about the date of vaccination (if any) and AEFI experienced with this seasonal vaccine.

### Statistics

The answers to self-assessment questionnaires were analyzed and described with absolute frequencies and percentages using the SPSS 18. We compared the proportion of each type of AEFI between genders and the presence or not of underlying conditions with Chi-square or Fisher exact test.

We calculated the odds ratios and respective 95% confidence intervals to identify the risk factors associated with at least one adverse events following immunization by using simple and multivariate logistic regression. In multivariate logistic regression the independent variables were gender, seasonal flu vaccine and underlying conditions. A significant level of 5% was used.

## RESULTS

### Sample description

From the 2358 vaccinated healthcare professionals of our sample, 864 (37%) returned back the fulfill questionnaire on time. Seventy one percent of the respondents are females of whom 3% (*n* = 21) were pregnant. Among the 864 respondents, 19% (*n* = 192) (reported to suffer any underlying abnormal health conditions. The most frequent underlying conditions were asthma (*n* = 39), allergy (*n* = 24), rhinitis (*n* = 19), hypertension (*n* = 18), thyroid disease (*n* = 12), dyslipidaemia (*n* = 6) and cardiovascular disease (*n* = 6). Some other less frequent conditions, were history of pneumonia (*n* = 1) and history of tuberculosis (*n* = 3).

Seventy three percent of the respondents were vaccinated with one of all seasonal vaccines commercialized in Portugal during the period of the study, at least one week before the vaccination with the Pandemrix® (this information was missed in 24 respondents). Among the respondents vaccinated with the seasonal vaccine, 40 didn´t answer the question about adverse reactions to seasonal vaccine and 84 (15%) experienced at least one AEFI.

No statistical differences were found on the proportion of the reported AEFI among the three studied hospital centres.

Table 1- AFI experienced by the 17 respondents who needed medical care.

| | AEFI experienced: |
|---|---|
| 1 | Local (injection site) |
| 2 | Myalgia, headache, fatigue and sweating increased |
| 3 | Tremors, headache, sweating increased and adenopathy |
| 4 | Fever, myalgia; headache and fatigue |
| 5 | Myalgia, headache and fatigue |
| 6 | Local (injection site), myalgia, headache, fatigue and sweating increased |
| 7 | Local (injection site), tremors, myalgia, headache, fatigue and sweating increased |
| 8 | Fever and myalgia (H1N1 infection confirmed) |
| 9 | Viral conjunctivitis |
| 10 | Local (injection site), myalgia, fatigue and acute sinusitis |
| 11 | Asthmatic crisis |
| 12 | Fever, dyspnoea and cough |
| 13 | Local (injection site), tremors, myalgia, headache, fatigue, sweating increased, adenophathy, pain in arm and nasal congestion |
| 14 | Local (injection site), myalgia, fatigue, oropharyngitis and nasopharyngitis |
| 15 | Local (injection site), sweating increased, dizziness and allergic reaction |
| 16 | Fever, local (injection site), tremors, rash, myalgia, headache, fatigue, sweating increased, adenophathy and gastrointestinal symptoms |
| 17 | Local (injection site), tremors, myalgia; headache, fatigue; sweating increased and gastrointestinal symptoms |

Table 2 - Frequency (%) of at least one adverse event following immunization (AEFI) with the 2009 pandemic vaccine A (H1N1) Pandemrix® per gender

| | | Gender | | |
|---|---|---|---|---|
| Adverse Events | **Total *n* (%)** | Male *n* (%) | Female *n* (%) | *p* |
| Expected – Very Common | | | | |
| Local (injection site) | **488 (57)** | 106 (44) | 382 (62) | <0.001 |
| Myalgia | **267 (31)** | 60 (25) | 207 (33) | 0.011 |
| Fatigue (including asthenia) | **209 (24)** | 50 (21) | 159(26) | 0.110 |
| Headache | **162 (19)** | 30 (12) | 132 (21) | 0.002 |
| Fever | **60 (7)** | 12 (5) | 48 (8) | 0.141 |
| Pain in arm (including arthralgia) | **24 (3)** | 4 (2) | 20 (3) | 0.201 |
| Expected - Common | | | | |
| Sweating increased | **134 (16)** | 19 (8) | 115 (19) | <0.001 |
| Adenopathy | **31 (4)** | 3 (1) | 28 (5) | 0.019 |
| Influenza like illness (ILI) | **8 (1)** | 4 (2) | 4 (1) | 0.232 |
| Expected – Uncommon | | | | |
| Gastrointestinal symptoms* | **18 (2)** | 2 (1) | 16 (3) | 0.103 |
| Rash | **15 (2)** | 0 (0) | 15 (2) | 0.009 |
| Malaise | **5 (1)** | 1 (0) | 4 (1) | 1.000 |
| Dizziness | **4 (1)** | 1 (0) | 3 (1) | 1.000 |
| Somnolence | **3 (1)** | 1 (0) | 2 (0) | 1.000 |
| Unexpected | | | | |
| Tremors | **68 (8)** | 15 (6) | 53 (9) | 0.237 |
| Other unexpected | **22 (3)** | 5 (2) | 17 (3) | 0.560 |

*such as diarrhea, vomiting, abdominal pain, nausea

Table 3 - Frequency (%) of at least one adverse event following immunization with the 2009 pandemic vaccine A (H1N1)v Pandemrix® per presence or not of underlying conditions.

| | | underlying conditions | | |
|---|---|---|---|---|
| Adverse Events | **Total *n* (%)** | No *n* (%) | Yes *n* (%) | *p* |
| Expected – Very Common | | | | |
| Local (injection site) | **488 (57)** | 382 (55) | 106 (65) | 0.013 |
| Myalgia | **267 (31)** | 205 (29) | 62 (38) | 0.027 |
| Fatigue (including asthenia) | **209 (24)** | 157 (22) | 52 (32) | 0.010 |
| Headache | **162 (19)** | 122 (17) | 40 (25) | 0.034 |
| Fever | **60 (7)** | 46 (7) | 14 (9) | 0.353 |
| Pain in arm (including arthralgia) | **24 (3)** | 17 (2) | 7 (4) | 0.188 |
| Expected - Common | | | | |
| Sweating increased | **134 (16)** | 97 (14) | 37 (23) | 0.005 |
| Adenopathy | **31 (4)** | 23 (3) | 8 (5) | 0.310 |
| Influenza like illness (ILI) | **8 (1)** | 6 (1) | 2 (1) | 0.649 |
| Expected – Uncommon | | | | |
| Gastrointestinal symptoms* | **18 (2)** | 10 (1) | 8 (5) | 0.011 |
| Rash | **15 (2)** | 11 (2) | 4 (3) | 0.501 |
| Malaise | **5 (1)** | 5 (1) | 0 (0) | 0.590 |
| Dizziness | **4 (1)** | 3 (1) | 1 (1) | 0.566 |
| Somnolence | **3 (1)** | 3 (1) | 0 (0) | 1.000 |
| Unexpected | | | | |
| Tremors | **68 (8)** | 46 (7) | 22 (13) | 0.003 |
| Other unexpected | **22 (3)** | 16 (2) | 6 (4) | 0.279 |

*such as diarrhea, vomiting, abdominal pain, nausea

**Adverse Events Following Immunization (AEFI)**

Among the 864 respondents, 73% (*n* = 634) (experienced at least one AEFI. From those 44% (*n* = 282), experienced only one AEFI, 19% (*n* = 118) experienced two types of AEFI, and 37% (*n* = 93) experienced three or more types of AEFI.

Among the respondents that experienced at least one AEFI, 34% (*n* = 206) needed pharmacological treatment, 3% (*n* = 19) motivated absence to work, 3% (*n* = 17) needed medical care and 2% (*n* = 13) appealed to hospital. No case of death due to the vaccination against pandemic influenza vaccine was reported.

The 17 respondents, who needed medical care, experienced the AEFIs described in table 1.

Seventy two percent of the respondents experienced at least one expected very common AEFI, 18% experienced at least one expected common AEFI, 5% experienced at least one expected uncommon AEFI and 8% experienced an unexpected AEFI (tremors).

The AEFI most frequently reported were expected and very common: 57% local reactions at the injection site with a median time between the vaccination and the AEFI onset of 0 days (minimum = 0, maximum = 7); 31% myalgia with a median time between the vaccination and the AEFI onset of 1 days (minimum = 0, maximum = 16); 24% fatigue, including asthenia, with a median time between the vaccination and the AEFI onset of 1 days (minimum = 0, maximum = 16) and 19% headache with a median time between the vaccination and the AEFI onset of 1 days (minimum = 0, maximum = 16). We found a higher frequency of all type of AEFI in female gender and health care professionals with underlying conditions (tables 2 and 3).

In tables 2 and 3, the category *other unexpected* refers to less frequent AEFI reports, like conjunctivitis, corize, asthma crises, herpes, confirmed H1N1 flu, etc.

The results of a multivariate analysis showed that female gender and existence of underlying conditions are independent risk factors to developing at least one AEFI to the pandemic flu vaccine (table 4).

## DISCUSSION

In the present study, although the great majority of healthcare professionals experienced at least one AEFI, only 8% of them were considered as unexpected and only 3% needed medical care. The time between the vaccination and the AEFI onset was short. Nevertheless, the maximum time between the vaccination and the AEFI development could range from 0 to 16 days in some cases.

Moreover, no cases of *major* episodes, such as death or life-threatening events were reported whereas the most frequent AEFI reports were *expected* and *very common* local reactions at injection site. According to CIOMS/WHO, these reactions are typically classified as non serious clinical manifestations.

Consequently, our results suggest that the benefit-risk relationship was favourable to the H1N1 pandemic vaccine as described in other countries and other groups.[16,17] Our results are also consistent with the spontaneously Adverse Drug Reaction reported to the Portuguese Pharmacovigilance System involving Pandemrix®, in the same period.[21]

As expected and in agreement to data from others,[22] underlying conditions and female gender were identified as risk factors for experiencing AEFI after pandemic influenza vaccination.

It is plausible that our data may have been influenced by the fact that healthcare professionals are a population more conscious about the issues related to the safety of medicines and so they are more aware of signs and symptoms that better describe an AEFI. In this particular case, because of their working place and their clinical knowledge they may have paid exceptional attention to the potential risks of the pandemic vaccination. As so, a possible limitation of this study is that we may have underestimated the absence to work or the request of formal medical or hospital

Table 4 - *Odds Ratios* (OR) for adverse event following immunization (AEFI) with the 2009 pandemic vaccine A (H1N1) Pandemrix® and respective 95% confidence intervals (CI)

| | **At least one AEFI** *n* (%) | **Crude OR** | **95% CI** | **Adjusted OR** | **95% CI** |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Male | 151 (62) | - | | - | |
| Female | 483 (78) | 2.20 | [1.59, 3.03] | 2.18 | [1.38, 3.59] |
| **Seasonal vaccine** | | | | | |
| No | 163 (71) | - | | - | |
| Yes | 457 (75) | 1.22 | [0.87, 1.72] | 1.11 | [0.78,1.57] |
| **Underlying conditions** | | | | | |
| No | 497 (71) | - | | - | |
| Yes | 137 (85) | 2.23 | [1.41, 3.52] | 2.22 | [1.56,3.03] |

*adjusted for gender, existence of underlying conditions and seasonal vaccine

care, since the population of this study work in a hospital. On the other hand, we may overestimated the needed of medical care and the appealed to hospital because of the facilitated access to the hospital services by this specific population.

In a consequence of those limitations stated before, we couldn't be able to classify with effectiveness the seriousness of the AEFIs, but we could pronounce that healthcare professionals are the population more used to describe and report adverse events to the authorities.

## CONCLUSIONS

Our work clearly indicates that this pandemic flu vaccine has an acceptable safety profile among healthcare professionals. Also, in that population, both the frequency and severity of the AEFI observed were the ones that were expected from the experience of other similar vaccines.

## CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest in concern to this article.

## FINANCIAL SOURCES

No financial external sources contributed to the elaboration of this article.

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