Drug Saf (2013) 36:259–266
DOI 10.1007/s40264-013-0037-7

ORIGINAL RESEARCH ARTICLE

Incidence of Adverse Events Among Healthcare Workers Following H1N1 Mass Immunization in Ghana

A Prospective Study

Daniel N. A. Ankrah · Aukje K. Mantel-Teeuwisse · Marie L. De Bruin · Philip K. Amoo · Charles N. Ofei-Palm · Irene Agyepong · Hubert G. M. Leufkens

Published online: 19 March 2013

Abstract

Background Cases of the A(H1N1) 2009 influenza were first recorded in Ghana in July 2009. In June 2010 when prioritized vaccination against the novel A(H1N1) 2009 influenza virus started in the country, health workers were among the selected groups to receive the vaccination.

Objective The aim of this study was to determine the distribution and types of adverse events reported following immunization of healthcare workers at the Korle-Bu Teaching Hospital from the day vaccination started until 1 week after the end of vaccination.

Methods Safety data collected during the A(H1N1) 2009 influenza vaccination of health workers at the Korle-Bu Teaching Hospital (Accra, Ghana) were used for this study. All workers aged 18 years and over were eligible for vaccination. For uniformity, 0.5 mL of Pandemrix® (equivalent to 3.75 μg of hemagglutinin antigen) was administered intramuscularly into the deltoid muscle of the left arm. Each vaccinee was issued with a card and was advised to report any adverse events following immunization (AEFI) to designated health workers for follow-up. Incidence rates of adverse events were estimated and compared with the Pandemrix® Summary of Product Characteristics (SPC)

Results A total of 5870 people (64.9 % females) with a mean age of 34.0 years were vaccinated. In total, 140 vaccinees reported adverse events. The mean age among vaccinees reporting adverse events was 36.1 years. The overall incidence of vaccinees reporting adverse events and the overall incidence of adverse events was 232 (95 % CI 199–320) per 10,000 people and 930 (95 % CI 820–1070) per 10,000 people, respectively. In particular, we found no difference in the way males reported AEFI compared with females (Chi-squared [χ^2] = 0.59; $p > 0.2$), and we did not find any association between age as a categorical variable and vaccine adverse event reporting ($\chi^2 = 5.24$; $p > 0.1$). There were only three serious cases that led to hospitalization. All three cases occurred within 24 hours of receiving the vaccine. The incidence rates for the various reported events were all lower compared with those in the Pandemrix® SPC, but while injection-site pain was the most frequent in the SPC and other foreign studies, we recorded headache as the most frequent. Even fatigue, muscle/joint aches and fever had higher incidence rates compared with injection-site pain. Tachycardia (n = 6), tinnitus (n = 1) and decreased appetite (n = 4) were reported although were not included in the SPC.

Conclusion The most prominent adverse events reported were headaches, dizziness, muscle and joint aches, weakness, fever and injection-site pain. Although similar events were reported in other studies, the incidence was different and there were a few differences in the most frequently reported events. More studies of a similar nature should be encouraged in low- and medium-income countries to bridge the information gap with the developed world.

D. N. A. Ankrah (✉) · P. K. Amoo · C. N. Ofei-Palm
Korle-Bu Teaching Hospital, P. O. Box 77,
Korle-Bu, Accra, Ghana
e-mail: danielankrah45@hotmail.com

D. N. A. Ankrah · A. K. Mantel-Teeuwisse · M. L. De Bruin · H. G. M. Leufkens
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences,
Utrecht, The Netherlands

I. Agyepong
Greater Accra Regional Health Directorate,
Ghana Heath Service, Accra, Ghana

1 Introduction

Safety reporting of marketed medicines has always been an issue of global importance. In low and emerging economies in particular it may be difficult to get information on medicine safety because of non-existent or weak monitoring structures. For most results obtained, this has been through the process of spontaneous reporting. However, in recent times, cohort event monitoring (CEM; also called prescription event monitoring) is advocated as a tool in low- and middle-income countries because of its strengths in signal generation, and also because it is prospective [1, 2], leading to précised estimation of event rates.

So far, the CEM methodology has been proposed and used for malaria [1] and HIV [2] medications, but this or a similar tool may be applied to safety monitoring of vaccines such as the H1N1 vaccine. The use of healthcare workers as a special group for research has been very helpful in the past. Doll and Hill [3] investigated the effect of smoking on lung cancer among British doctors; the Nurses Health Study cohort [4] and the Health Professional Study cohort [5] are important special group examples that can be cited. Logistically, using such defined groups is advantageous because problems with follow-up [6] are minimal.

In Ghana, when the Ministry of Health decided to vaccinate Ghanaians against the influenza, healthcare workers were among the first to be vaccinated after the first reports of A(H1N1) 2009 influenza in July 2009 [7]. For most developing countries, including Ghana, vaccines were supplied by the WHO. Because of the nature of vaccine technology, it was evident that in the early stages of the pandemic, available vaccines would not be enough to cater for everyone [8]. To mitigate such anticipated shortfalls, the Strategic Advisory Group of Experts on Immunization (SAGE) of the WHO identified three different objectives that countries could adopt as part of their pandemic vaccination strategy [9]. These were: "(i) protecting the integrity of the healthcare system and the country's critical infrastructure; (ii) reducing morbidity and mortality; and (iii) reducing transmission of the pandemic virus within communities". SAGE also recommended immunization strategies that should be used by countries depending on their epidemiological trends, resources and ease of access to vaccines [9].

The National Technical Coordinating Committee (NTCC) of the Ministry of Health, Ghana, decided that vaccination should be prioritized [10] because Ghana received vaccines equivalent to approximately 10 % of the population. Health workers, national security personnel, pregnant women (after first trimester) and other high-risk people (asthmatics, cardiovascular disease patients, diabetic patients, international travellers, etc.), in that order, were scheduled to be vaccinated depending on the availability of vaccines [10]. People below 18 years of age were not vaccinated. Vaccine deployment was under the auspices of the Vaccine Deployment Sub-Committee of the NTCC and the disease surveillance departments; the National Program on Immunisation and the Food and Drugs Board of Ghana were responsible for safety surveillance.

Previous studies evaluated the safety of the H1N1 vaccine in daily practice. After using about 82 million doses of A(H1N1) 2009 influenza vaccines in the US, safety reports from the Vaccine Adverse Event Reporting System (VAERS) showed that about 93 % (9359/10085) of all such reports were not serious [11]. During monitoring of safety of vaccines and antivirals against the pandemic A(H1N1) 2009 influenza in France, 3855 events were recorded after using 4.1 million doses of the Pandemrix® vaccine [12] (GlaxoSmithKline Biologicals s.a., Rixensart, Belgium). Only 5 % of these were serious, with the rest being non-serious and expected. The profile of adverse events reported during monitoring following mass immunization of various age groups in The Netherlands was comparable to that indicated in the summary of product characteristics (SPC) [13].

However, Ghana is a Sub-Saharan country located in the tropics where seasonal influenza is not endemic and nobody receives seasonal flu vaccination. According to reports [10], the last time an outbreak of this nature (the Spanish flu) occurred in Ghana (then the Gold Coast) was in 1918 when the death toll was about 11,600. The population at the time was about 2 million [14] compared with the current population of about 24 million. Therefore, adverse events occurring after vaccination in the Ghanaian population may differ from other populations.

This article therefore reports on the distribution and types of adverse events following immunization (AEFI) of healthcare workers in a health institution in a tropical country devoid of seasonal influenza, after receiving a single dose of the monovalent Pandemrix® A(H1N1) 2009 influenza vaccine.

2 Materials and Methods

2.1 Setting

The Korle-Bu Teaching Hospital is a tertiary health institution with 2000 beds. It shares its premises with the University of Ghana Medical School and the School of Allied Health Sciences, the School of Nursing and the School of Pharmacy, and students of these education institutions use the hospital for their practical training. All healthcare workers of the Teaching Hospital aged 18 years

and older were eligible for vaccination. Those who had previously had the infection and had been treated were excluded. Each participant received one dose of 0.5 mL of Pandemrix® A(H1N1) 2009 influenza vaccine with batch number A81CA656A. This was a monovalent, split virion, inactivated and adjuvanted vaccine propagated in eggs [15]. The seed virus was derived from A/California/07/2009 (H1N1) strain (where A is the virus type, followed by the geographical region, then the strain number, the year of isolation and, lastly, the strain type [16]). It is administered as a single dose of 0.5 mL, which is equivalent to 3.75 μg of hemagglutinin antigen.

For uniformity, the injection was administered intramuscularly into the deltoid muscle of the left arm. Trained Community Health Nurses from the Ghana Health Service were used for the immunization programme. At the Korle-Bu Teaching Hospital, five immunization centres were set up at strategic locations to improve accessibility. Immunization was done from 14–18 June 2010. All those who were vaccinated were issued with an immunization card.

2.2 Safety Assessment

One week prior to initiation of immunization, letters were sent to all clinical departments to sensitize workers. Copies of the special adverse events reporting forms designed for the exercise (using the Vaccine Incident Report Form from the North Yorkshire Health Protection Unit and North Yorkshire and York NHS Primary Care Trust as a guide [17]) were attached to these letters so that workers were familiar with the form. All vaccinees at the vaccination centres were verbally informed of the risks associated with the vaccine and were advised to report suspected adverse events to designated members of the Public Health Unit to complete the reporting form. The Public Health Unit was made up of two doctors and a pharmacist. Their role (among others) was to ensure that all those reporting had received the Pandemrix® vaccine previously. Those with serious AEFI were referred to standby physicians at the Surgical/Medical Emergency Unit for monitoring. A serious adverse event was defined as "death, a life threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered to be serious adverse drug experiences when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition [21 C.F.R. § 312.32(a)]" [18].

Adverse event data were collected from the first day of immunization until 1 week after the end of the immunization period. An AEFI in this study was defined as any untoward medical occurrence in a vaccine which follows immunization and which does not necessarily have a causal relationship with the administration of the vaccine [19]; therefore, no causality assessment was carried out.

2.3 Data Analysis

Data on collected adverse events were entered by two separate national service persons using Microsoft Excel version 2007 (Microsoft Corporation, Redmond, WA, USA). These were validated and transferred to Stata intercooled version 9 (StataCorp LP, College Station, TX, USA) for analysis. Collected AEFIs were recoded using the Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class codes version 11.1. MedDRA® terminology is the medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Those vaccinated were compared with the cases of adverse events collected using age (categorized in four bands) and sex. Using Pearson's Chi-squared (χ^2) test, we explored associations between adverse event reporting and age as well as sex. Incidence reporting rates were calculated per 10,000 patients/doses of the Pandemrix® vaccine administered, and 95 % confidence intervals (CIs) were calculated. Incidences of specific AEFIs reported were compared to classification in the SPC [15] of Pandemrix®. There were four missing values on age which were excluded from the final analysis.

2.4 Ethical Clearance

Ethical clearance to use the collected data for the study was given by the Ethical and Protocol Review Committee of the University of Ghana Medical School, Accra, Ghana.

3 Results

A total of 5870 people (64.9 % females) were vaccinated (see Table 1). Nearly half of the healthcare workers vaccinated were less than 30 years of age and mean age among vaccinees was 34.0 years. Vaccination of females outnumbered males in all age groups with the exception of those aged 40–49 years who were almost equal in number.

A total of 140 vaccinees reported suspected adverse events, 94 (67.1 %) of whom were women. The mean age of vaccinees reporting adverse events was 36.1 years. There were four missing values for age (three males and one female) among those who reported. These were excluded from any age-related analysis.

Table 1 Distribution of number of people vaccinated and vaccinees reporting adverse events following immunization by sex and age group

Sex	Age group (years)				
	<30	30–39	40–49	≥50	Total
Number of healthcare workers vaccinated (N = 5870)					
Male (%)	849 (29.8)	494 (39.9)	407 (50.1)	361 (37.1)	2,111 (35.1)
Female (%)	1,999 (70.2)	743 (60.1)	406 (49.9)	611 (62.9)	3,759 (64.9)
Total (%)	2,848 (100)	1,237 (100)	813 (100)	972 (100)	5,870 (100)
Vaccinees reporting adverse events following immunization (N = 136[a])					
Male (r)	17 (0.020)	10 (0.020)	10 (0.025)	6 (0.017)	43 (0.020)
Female (r)	39 (0.020)	20 (0.027)	17 (0.042)	17 (0.028)	93 (0.025)
Total (r)	56 (0.02)	30 (0.024)	27 (0.033)	23 (0.024)	136 (0.023)

r Age-specific incidence rate

[a] There were four missing values (three males and one female) for age that were excluded

The total number of adverse events reported was 544, with most of the vaccinees reporting multiple events. The mean number of adverse events reported was four. Figure 1 shows the distribution of adverse events reported, ranging from 1 to 8 events per reporting vaccinee.

The overall incidence of vaccinees reporting adverse events and the overall incidence of adverse events was 232 per 10,000 people (95 % CI 199–320) and 930 per 10,000 people (95 % CI 820–1070), respectively. Table 1 shows the incidence distribution by sex and age group.

Apart from the incidence for females aged 40–49 years per 10,000 people, all the other incidences were rather similar (see Fig. 2). In particular, we found no difference in the way males reported AEFI compared with females ($\chi^2 = 0.59$; $p > 0.2$) and we did not find any association between age as a categorical variable and vaccine adverse event reporting ($\chi^2 = 5.24$; $p > 0.1$).

There were only three serious cases that led to hospitalization. This amounted to a reporting rate of 5 (95 % CI 2–9) per 10,000 people vaccinated. Each of them reported more than one event, some of which were more severe (weakness, dizziness, breathing difficulty, fever, fast heart beat, and muscle and joint aches). All three cases occurred within 24 hours of receiving the Pandemrix® injection. Each case was detained overnight (for about 24 hours) and they all fully recovered.

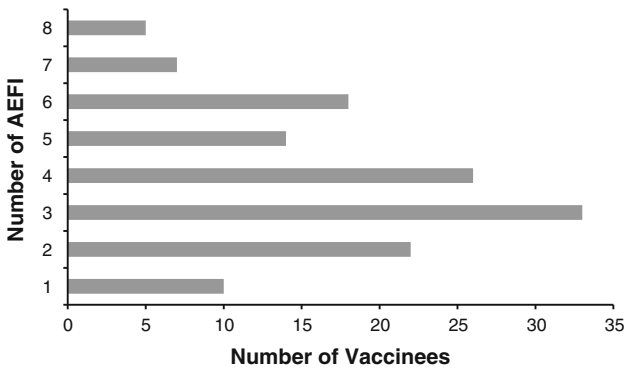

Fig. 1 Distribution of multiple events among vaccinees who reported AEFI. *AEFI* adverse events following immunization

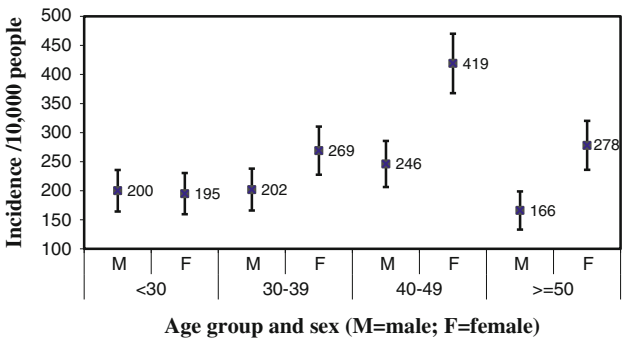

Fig. 2 Incidence rates of adverse events reported per 10,000 people with 95 % confidence interval

Table 2 shows that adverse events classified as general disorders and administrative site conditions or nervous system disorders were the two most frequently occurring adverse event categories. The incidence rate per 10,000 doses for headache (a nervous system disorder) was 162 (95 % CI 137–189). This was the most predominant adverse event that was reported. Other reported adverse events with high incidence rates in this study included body weakness (asthenia), muscle and joint aches (myalgia and arthralgia), fever, and pain/redness at the injection site. There were two reports of sleepiness (somnolence).

Most of the AEFIs reported were well established [15, 20]. However, events such as tachycardia, tinnitus and decreased appetite were not recorded in the SPC of the Pandemrix® A(H1N1) 2009 influenza vaccine.

Furthermore, Table 2 shows that all the events reported were either within or below the expected range when

Table 2 Types and distribution of adverse events following immunization using MedDRA® System Organ Class codes

Adverse event	MedDRA® PT	Frequency (N = 5870)	IRα/10,000	IRq/10,000 (N ~ 5000)
Blood and lymphatic system disorders				
Lymphadenopathy	Lymphadenopathy	2	3	≥100 to <1000
Metabolism and nutritional disorders				
Loss of appetite	Decreased appetite	4	7	–
Psychiatric disorders				
Change in behaviour	Abnormal behaviour	10	17	≥10 to <100
Nervous system disorders				
Dizziness	Dizziness	48	82	≥10 to <100
Sleepiness	Somnolence	2	3	≥10 to <100
Headache	Headache	95	162	≥1000
Eye Disorders				
Pain in the eyes	Eye pain	1	2	≥100 to <1000
Ear and labyrinth disorders				
Ringing sound in the ear	Tinnitus	1	2	–
Cardiac disorders				
Fast heart beat	Tachycardia	6	10	–
Vascular disorders				
Paleness	Pallor	1	2	≥100 to <1000
Respiratory, thoracic and mediastinal disorders				
Hoarseness	Dysphonia	7	12	≥100 to <1000
Breathing difficulty	Dyspnoea	2	3	≥100 to <1000
Runny nose	Rhinorrhoea	1	2	≥100 to <1000
Sore throat	Pharyngolaryngeal pain	1	2	≥100 to <1000
Sneezing	Sneezing	1	2	≥100 to <1000
Gastrointestinal disorders				
Abdominal pain	Abdominal pain	1	2	≥10 to <100
Nausea	Nausea	29	49	≥10 to <100
Vomiting	Vomiting	4	7	≥10 to <100
Skin and subcutaneous tissue disorders				
Hives	Urticaria	3	5	≥10 to <100
Itching	Pruritus	3	5	≥10 to <100
Musculoskeletal and connective tissue disorders				
Pain in the neck	Neck pain	1	2	≥100 to <1000
Muscle and joint aches	Myalgia/arthralgia	80	136	≥1000
General disorders and administrative site conditions				
Weakness	Asthenia	89	152	≥1000
Chills	Chills	2	3	≥100 to <1000
High/low fever	Pyrexia	76	129	≥1000
Pain/redness at injection site	Injection site pain	61	104	≥1000

IRα incidence rate per 10,000 people in this study, *IRq* incidence rate per 10,000 people from the Pandemrix® SPC [15], *MedDRA®* Medical Dictionary for Regulary Activities, *PT* Preferred Term, *SPC* Summary of Product Characteristics, – indicates not mentioned in the SPC

compared with information from the Pandemrix® SPC but the trends were not always the same. For example, the most predominantly reported adverse event in this study was headache but in the SPC injection-site pain was mentioned as the most frequently occurring adverse reaction.

4 Discussion

This study presents the results of adverse events reported following immunization of healthcare workers in a Teaching Hospital in Ghana. Out of a total of 5870 people

who were vaccinated, 140 reported adverse events. The overall incidence rate of reported cases was 239 per 10,000 people, and the highest number of adverse events reported per person was eight. Only 2.1 % (3/140) of reported AEFI were serious.

The large number of vaccinees under 30 years of age is representative of the population pyramid of Ghana, 66 % of whom are below age 30 years [21], which enhances generalizability of our results. The proportion of patients reporting serious adverse events among those reporting any event was lower in this study (2.1 %) than previously reported by Vellozzi et al. [11], who reported 7.2 % (726/10,085) after administering 82.4 million doses using the VAERS, and Liang et al. [22], who reported 8.8 % (711/8067) after using 89.6 million doses. However, this study involved a much smaller population size and used only the Pandemrix® vaccine, but the other two studies used different vaccines. Kung et al. [23], reported that 0.77 % of the study subjects in a clinical trial reported any events that affected daily activities requiring medical attention. All findings from clinical practice, including our study results, imply that serious reactions may be associated with an A(H1N1) 2009 influenza vaccine. On the contrary, Greenberg et al. [24], Vajo et al. [25] and Plennevaux et al. [26], in separate randomized trials, reported that no vaccine-related serious adverse events were recorded.

We did not find any difference in adverse event reporting rates between the sexes and there was no association between vaccine adverse event reporting and the various age groups vaccinated. This is consistent with the review from Vellozzi et al. [11].

Nervous system disorders, general disorders and administration site conditions, and musculoskeletal and connective tissue disorders accounted for most of the adverse events that occurred among cases. In particular, headache, pain at injection site, body weakness, pyrexia and myalgia/arthralgia occurred most frequently. This was also the situation with other studies [23–25, 27, 28]; however, some reported adverse events such as tachycardia, tinnitus and decreased appetite were not yet included in the SPC.

For vaccines used in different populations, comparability is essential for evidence-based understanding of safety concerns [29]. Case definitions may also differ depending on whether they were collected from clinical trials or passive postmarketing surveillance, or as a result of its origin, i.e. from a developed or developing country [30–35]. Incidence rates for the various reported events were all lower compared with those in the Pandemrix® SPC [15], but while injection-site pain was the most frequent in the Pandemrix® SPC and other studies [24, 28], we recorded headache as the most frequent. Even fatigue, muscle/joint aches and fever had higher incidence rates compared with injection-site pain. Ghana is hyperendemic for malaria [21] and infectious diseases are present. Headache, fever, muscle/joint aches and fatigue are characteristic symptoms of malaria. These high incidence rates could also be the result of background rates [36, 37] of such events being reported just because of their temporal association. Although temporality is essential, it is not sufficient to prove causality. It is well known that background rates could lead to over-ascertainment of an event and it is therefore necessary that these are accounted for during causality assessment of events. A selective increase in the number of reports following immunization could also have been possible because of notoriety bias [13].

Uncommon adverse events with relatively high incidence rates (dizziness, nausea and abnormal behaviour) per 10,000 doses may also be due to high background rates or as a result of co-medications. These would need to be further investigated in any future mass immunization activity. There were two reports of sleepiness (somnolence). Both cases were females and their ages were 36 years and 45 years. Nevertheless, there have been reports of a possible association between Pandemrix® and narcolepsy [38–42] involving vaccination against the A(H1N1) 2009 influenza virus among children and adolescents. After close monitoring of investigations, the Global Advisory Committee for Vaccine Safety (GACVS) [43] indicated that the situation was not a general worldwide phenomenon and current available information was inadequate to prove association. That notwithstanding, the GACVS agrees with the European Medicines Agency for Medicinal Products for Human use that Pandemrix® should only be used by people aged 20 years and older [44]. Vajo et al. [25] suggested the involvement of different ethnic groups in studies concerning the A(H1N) 2009 influenza vaccine. This is one such study and it is hoped that it would serve as a comparator for similar studies, especially those in Sub-Saharan Africa.

There were potential limitations to this study that need to be mentioned. There is the propensity for underreporting, a characteristic of most passive surveillance studies that may lead to biased estimates of events [45, 46]. However, the use of healthcare workers may have resulted in better reporting response than would have been the case compared with the general population. The short surveillance period (which was done to avoid the reporting of extraneous events) may have prevented the capturing of events of long latency. We hope to improve upon this subsequently. Background rates of adverse events were not calculated, and may lead to over-ascertainment of some events. Such a system of adverse event reporting may only be used for signal generation [47]; it cannot prove causality. No diagnostic tests were done to confirm association of AEFI with the vaccine. This was because the focus was not on causality assessment.

Collection of data for this study was comparable to CEM in that it was observational and prospective [1, 2]; however, unlike CEM, there was no pre-treatment control period.

This study is concerned with vaccine adverse events collected after mass immunization of healthcare workers using the Pandemrix® A(H1N1) 2009 influenza vaccine. It has shown that monitoring of AEFI among healthcare workers can be a useful tool to study vaccine-related adverse events. Efforts should be made to determine the actual vaccine adverse event incidence rates because this can impact positively on vaccine uptake in future.

Immunization is a public good and the higher the extent of coverage the better the effect on the general population. It has been observed that vaccine adverse event reports during vaccination campaigns can be used to inform the general public on the expected benefit-risks that may be associated with the vaccine and this may improve immunization levels in future programmes [48]. Public health commitment to improve knowledge on vaccines should be encouraged and should focus on both risks and benefits.

Using data from healthcare workers for this study was helpful for many reasons. First of all, these are knowledgeable people who are likely to report events they experienced. Furthermore, should there be a need for follow-up enquiries, this may not be difficult because of the close proximity of reporters compared with the general population. For such programmes to be successful, prior notification of prospective vaccinees should be done well. Additionally, to forestall misguided publications, the press should be briefed. The estimated cost of operational activities of the vaccination programme in Ghana was $1,138,000.00 [10]. Irrespective of the limitations encountered in this study, the lesson learned for other countries, particularly those in low- and medium-income countries is that big studies are good if done well, but small studies, if carried out well, can also make a difference.

5 Conclusion

Among health workers at the Korle-Bu Teaching Hospital in Ghana, the most prominent adverse events reported were headaches, dizziness, muscle and joint aches, weakness, fever and injection site pain. The types of AEFI reported were similar to other studies but the frequency of occurrence did not follow the same pattern. The real benefits and risks of vaccines should be made known to the general public since this may improve uptake of immunization in future; however, this can only be achieved through more research on safety reporting.

Acknowledgments We thank the following people for their selfless contributions to this article: the Medical Superintendent, Mamprobi Polyclinic (MPC); Deputy Director Of Nursing Services, MPC; Mrs Allotey, Public Health Unit, MPC; Mr J. Addo, Disease Control Unit, Korle-Bu; Mr Stanley Diamenu, WHO office, Ghana; and Dr. J.O. Commey, Korle-Bu Teaching Hospital. We also thank Mr L. Dadzie and Mr E. Aktey, who designed and entered the data, and all members of the Public Health Unit (Korle-Bu Teaching Hospital). Finally, we would like to thank Dr. Richard O. Laing, WHO, for his review and advice on this paper.

Conflict of interest The Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, has received unrestricted funding from the Netherlands Organisation for Health Research and Development, the Dutch Health Care Insurance Board, the Royal Dutch Pharmacists Association, the private-public funded Top Institute Pharma (http://www.tipharma.nl, includes co-funding from universities, government and industry), the EU Innovative Medicines Initiative, EU 7th Framework Program, the Dutch Medicines Evaluation Board and the Dutch Ministry of Health and Industry (including GlaxoSmithKline, Pfizer and others)

Funding/support No sources of funding were used to conduct this study or prepare this manuscript.

References

1. WHO. A practical handbook on the pharmacovigilance of malaria medicines. http://www.who.int/malaria/publications/atoz/malaria-pharmavigil.pdf. Accessed 6 Mar 2013.
2. WHO, Health Technology and Pharmaceuticals, Medicines Policy and Standards. Pharmacovigilance for antiretrovirals in resource-poor countries. http://www.who.int/medicines/publications/PhV_for_antiretrovirals.pdf. Accessed 6 Mar 2013.
3. Doll R, Hill AB. Smoking and carcinoma of the lung, preliminary report. BMJ. 1950;(ii):739–48.
4. Stampfer MJ, Willet WC, Colditz GA, et al. A prospective study of post-menopausal estrogen therapy and coronary heart disease. N Engl J Med. 1985;313:1044–9.
5. Ascherio A, Rim EB, Stampfer MJ, et al. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med. 1995;332:977–82.
6. Szklo M, Nieto FJ. Epidemiology beyond the basics. 2nd ed. Sudbury: Jones and Bartlett Publishers; 2007.
7. Update on current situation: pandemic influenza H1N1 in Ghana as at 12/08/2010. Accra: Ghana Health Service, 2010.
8. Nolan T, McVernon J, Skeljo M, Richmond P, Wadia U, Lambert S, et al. Immunogenicity of a monovalent 2009 influenza A (H1N1) vaccine in infants and children: a randomized trial. JAMA. 2010;303:37–46.
9. WHO. Weekly epidemiological record: Strategic Advisory Group of Experts on Immunization—report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic, 7 July 2009. http://www.who.int/wer/2009/wer8430.pdf. Accessed 21 Nov 2010.
10. Ministry of Health, Ghana. H1N1 vaccine deployment plan. Accra: Ministry of Health, 2010.
11. Vellozzi C, Broder KR, Haber P, Guh A, Nguyen N, et al. Adverse events following influenza A(H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting

System, United States, October 1, 2009-January 31, 2010. Vaccine. 2010;28:7248–55.
12. Jacquet A, Robine I, Durrieu G, Auriche P, Bidault I, Ouaret S, et al. Intensive pharmacovigilance monitoring for influenza vaccines and antiviral drugs used during the influenza A(H1N1)v pandemic: the French experience. Drug Safety. 2010;33(10): 909–10.
13. van Puijenbroek EP, Broos N, van Grootheest K. Monitoring adverse events of the vaccination campaign against influenza A(H1N1) in the Netherlands. Drug Saf. 2010;33(12):1097–108.
14. Ghana: historical demographic data of the whole country. http://www.populstat.info/Africa/ghanac.htm. Accessed 4 Jul 2011.
15. Pandemrix® suspension and emulsion for emulsion for injection: summary of product characteristics. Last updated on the eMC 23/09/2010. http://www.medicines.org.uk/EMC/medicine/22352/SPC/Pandemrix+suspension+and+emulsion+for+emulsion+for+injection/. Accessed 21 Nov 2010.
16. Ho T, Wang S, Lui C. Historical review of pandemic influenza A in Taiwan, 2009. Paediatr Neonatol. 2009;51(2):83–8.
17. North Yorkshire Health Protection Unit and North Yorkshire and York NHS Primary Care Trust. Vaccine incident reporting form. http://www.nyypct.nhs.uk/ClinicalCommunity/docs/PGD_VI/Vaccine%20Incident%20Report%20Form%20v2.pdf. Accessed 4 Jun 2010.
18. Beltuna JP. Legal basis—United States. In: Mann R, Andrews E, editors. Pharmacovigilance. 2nd ed. Chichester: Wiley; 2007. p. 25–34.
19. Public Health Agency of Canada. User guide: report of adverse events following immunization (AEFI). http://www.healthunit.org/professionals/Influenza/Resources/AEFI%20Form%20User%20Guide.pdf. Accessed 4 May 2012.
20. Pandemrix® patient information. Available from URL : http://www.guysandstthomasbrc.nihr.ac.uk/Resources/Infectionandimmunity/PDFpandemrixpatientinformationsheet.pdf. Accessed 6 Mar 2013.
21. Ghana Statistical Service, Ghana Health Service and ICF Macro. Ghana demography and health survey 2008. Accra: Ghana Statistical Service, Ghana Health Service and ICF Macro, 2009.
22. Liang X, Li L, Lui D, Li K, Wu W, Zhu B, et al. Safety of influenza A(H1N1) vaccine in post-marketing surveillance in China. N Engl J Med. 2011;364(7):638–47.
23. Kung H, Huang K, Kao T, Lee Y, Chang F, et al. A clinical study to assess the immunogenicity and safety of a monovalent 2009 influenza A (H1N1) vaccine in an area with low-level epidemics of pandemic influenza. Vaccine. 2010;28:7337–43.
24. Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, et al. Response to a monovalent 2009 influenza A(H1N1) vaccine. New Engl J Med. 2009;365(25):2405–13.
25. Vajo Z, Tamas F, Sinka L, Jankovics I. Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009–10 influenza season: a multicentre, randomized controlled trial. Lancet. 2010;375:49–55.
26. Plennevaux E, Sheldon E, Blatter M, Reeves-Hoché MK, Denis M. Immune response after a single vaccine against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. Lancet. 2010;375:41–8.
27. Roman F, Vaman T, Kafeja F, Hanon E, Damme PV. ASO3A-adjuvanted influenza A(H1N1) 2009 vaccine for adults up to 85 years of age. Clin Infect Dis. 2010;51(6):668–77.
28. Liang X, Wang H, Wang J, Fang H, Wu J, et al. Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double blind, randomised, placebo-controlled trial. Lancet. 2010;375:56–66.
29. Iskander JK, Gidudu J, Arboleda N, Huang W. Selected major issues in vaccine safety. Ann Nestlé [Engl]. 2008;66:93–103.
30. Kohl KS, Gidudu J, Bonhoeffer J, et al. The development of standardized case definitions for adverse events following immunization. Vaccine. 2007;25:5671–4.
31. Kohl KS, Bonhoeffer J, Braun MM, et al. The Brighton Collaboration: creating a global standard for case definitions (and guidelines) for adverse events following immunization. In: Henriksen K, Battles JB, Marks ES, Lewin DI, editors. Advances in patient safety: from research to implementation (volume 2, concepts and methodology). Rockville: Agency for Healthcare Research and Quality; 2005. p. 87–102.
32. Bonhoeffer J, Kohl KS, Chen RT, et al. The Brighton Collaboration: enhancing vaccine safety. Vaccine. 2004;22:2046.
33. Bonhoeffer J, Heininger U, Kohl KS, et al. Standardized case definitions of adverse events following immunizations (AEFI). Vaccine. 2004;22:547–50.
34. Kohl KS, Bonhoeffer J, Chen RT, et al. The Brighton Collaboration: enhancing comparability of vaccine safety data. ISPE commentary. Pharmacoepidemiol Drug Saf. 2003;12:335–40.
35. Bonhoeffer J, Kohl KS, Chen RT, et al. The Brighton Collaboration: addressing the need for standardized case definition of adverse events following immunization (AEFI). Vaccine. 2002; 21:298–302.
36. Black S, Eskola J, Siegrist C, Halsey N, MacDonald N, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet. 2009;374:2115–22.
37. Wang Y, Xiao Z, Wang W. Awareness of the background rates of sudden cardiac death during mass immunization with pandemic H1N1 influenza vaccines increases the intended vaccination rate. Prev Med. 2010;51:445–6.
38. Dauvilliers Y, Montplaisir J, Cochen V, Desautels A, Einen M, et al. Post-H1N1 narcolepsy-cataplexy. Sleep. 2010;33(11): 1428–30.
39. Caplan AL. Duty to warn? The ethics of disclosing information about possible risks associated with H1N1 vaccination. Sleep. 2010;33(11):1426–7.
40. Zarocosters J. WHO backs further probes into possible link between H1N1 vaccine and narcolepsy in children. BMJ. 2011; 342:d909.
41. Geoff W. New findings on H1N1 vaccine prompt revised prescribing advice (news). BMJ. 2011;342:d2524.
42. Montastruc J-L, Durrieu G, Rascol O. Pandemrix®, (H1N1)v influenza and reported cases of narcolepsy (letter). Vaccine. 2011;29(11):2010.
43. WHO. Statement on narcolepsy and Pandemrix. http://www.who.int/vaccine_safety/topic/influenza/pandemrix/h1n1_safety_assessing/narcolepsy_statement_Jul2011/en/. Accessed 10 Mar 2012.
44. European Medicines Agency. European Medicines Agency recommends restricting use of Pandemrix. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109182.pdf. Accessed 10 Mar 2011.
45. Varricchio F, Iskander J, DeStefano F, Ball R, Pless R, et al. Understanding vaccine safety information from the vaccine adverse reporting system. Pediatr Infect Dis J. 2004;23(4):287–94.
46. Ellenberg SS, Chen RT. The complicated task of monitoring vaccine safety. Public Health Rep. 1997;112(1):10–20.
47. Centers for Disease Control and Prevention. Surveillance for safety after immunization: vaccine adverse events reporting system (VAERS)—United States, 1991–2001. MMWR Surveil Summ. 2003;52:1–24.
48. Broos N, van Puijenbroek EP, van Grootheest K. Fever following immunization with influenza A(H1N1) vaccine in children: a survey based study in the Netherlands. Drug Saf. 2010;33(12): 1109–15.