



Anaphylaxis following H1N1 pandemic vaccines: Safety data in perspective[☆]

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ARTICLE INFO

Article history:

Received 21 January 2011

Received in revised form 5 April 2011

Accepted 8 April 2011

Available online 27 April 2011

Keywords:

Anaphylaxis

H1N1 pandemic vaccine

Safety

Postmarketing

Brighton Collaboration Case Definition

ABSTRACT

We present here a detailed analysis of anaphylaxis cases reported to GlaxoSmithKline safety database following vaccination with its H1N1 pandemic influenza vaccines, *Pandemrix*TM and *Arepanrix*TM. Cases were assessed according to the Brighton Collaboration Case Definition (BCCD) as either confirmed diagnosis (97/395, 24.6%), insufficient information to fulfil the minimal criteria of the case definition (117/395, 29.6%) or anaphylaxis excluded (181/395, 45.8%). There was no evidence that the rate of anaphylaxis following vaccination with *Pandemrix*TM or *Arepanrix*TM is increased with respect to the rates of anaphylaxis for other vaccines. Our analysis also highlighted the challenges of reliably determining the rate of anaphylaxis as an adverse event in the postmarketing setting following mass vaccination, as anaphylaxis was excluded in 45.8% of reported cases.

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1. Introduction

Anaphylaxis is an acute hypersensitivity reaction involving multiple organ systems that is triggered by the binding of a protein allergen to specific immunoglobulin (IgE). The presence of specific IgE indicates previous contact with the triggering substance or a cross-reactive allergen which induced a sensitizing response [1]. Anaphylaxis is a well-known adverse reaction to vaccines and a well-recognized adverse event following immunization (AEFI) [2]. Virtually all vaccines have the potential to trigger anaphylaxis [3]; however, the incidence of anaphylaxis is generally very low at approximately 1–10 cases per million doses of vaccine administered [1,2,4–6]. With such a low average rate for all vaccines, the likelihood that even the largest pre-licensure vaccine trials will identify a single case or provide a meaningful estimate of the incidence is extremely small [2]. Recent mass vaccination campaigns utilizing the GlaxoSmithKline (GSK) A/California/7/2009 H1N1 pandemic vaccines, adjuvanted with the oil-in-water emulsion-based Adjuvant System AS03 containing tocopherol, have allowed an assessment of anaphylaxis in the setting of millions of doses administered.

[☆] Notes: *Arepanrix*TM, *Pandemrix*TM, *Fluarix*TM and *FluLaval*TM are trademarks of the GlaxoSmithKline group of companies.

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In the context of vaccination, anaphylactic reactions have most often been reported following immunization with viral vaccines such as measles-containing vaccines, the yellow-fever vaccine, or polio vaccines [4,5], but also occur with bacterial vaccines such as pertussis [7]. Rates of anaphylaxis vary depending on the vaccine, for example recently reported incidence rates were 1.2 per million doses for conjugated meningococcal C vaccine, 0.9 per million doses for the diphtheria–tetanus–pertussis vaccine and 26 per million doses following quadrivalent human papillomavirus vaccine [7]. Symptoms occur rapidly after exposure to the allergen and identified cases of anaphylaxis tend to occur less than 1 h after vaccination [8]. With just a few minutes between vaccine exposure and onset of symptoms, there is often little question that vaccination was the cause of the event. Most life-threatening reactions begin within 10 min of immunization and therefore observation of vaccine recipients is recommended for at least 20 min after administration of the vaccine [9]. However, other frequent acute events may also occur fairly promptly after vaccination, including vasovagal reactions, psychogenic or conversion symptoms, and other non-specific symptoms such as rash [8], and these may sometimes confound the diagnosis.

The incidence of anaphylactic reactions following vaccination appears to have declined over the last 50 years. This may be due to the improvements in vaccine manufacturing processes leading to fewer impurities in vaccines, or alternatively to more stringent definitions of anaphylaxis [5]. While the immunizing antigen itself can be the trigger for anaphylaxis, vaccine process residuals or excipients, exemplified by egg protein or gelatine respectively, may also be implicated [2]. The levels of ovalbumin in most seasonal

influenza vaccines have been demonstrated to be considerably less than the maximum content stated by the manufacturers [10,11], suggesting that they may be safe to administer to persons with egg allergy. However, known allergy to vaccine components, including egg proteins, is a contraindication to vaccination with *Pandemrix*TM or *Arepanrix*TM.

The actual rates of anaphylaxis may be greater than those determined by vaccine safety surveillance systems. This may be due to several factors, including the type of surveillance system involved (passive vs. active surveillance [3]), the type of vaccine employed (for example, reports based on one influenza vaccine cannot necessarily predict responses to another influenza vaccine) and the population being vaccinated (for instance young vs. old populations, different ethnic groups) [7]. GSK closely monitors reports of anaphylaxis following the administration of the GSK A/California/7/2009 (H1N1) pandemic vaccines (*Pandemrix*TM or *Arepanrix*TM; GSK Biologicals). During the H1N1 pandemic, enhanced pharmacovigilance activities included continual case review, weekly observed-to/expected analyses, weekly disproportionality analyses, and use of targeted follow-up questionnaires to obtain detailed information from case reporters.

We present here a detailed analysis of the anaphylaxis cases reported to GSK following vaccination with its pandemic influenza vaccines, *Pandemrix*TM and *Arepanrix*TM. These cases are discussed in light of the Brighton Collaboration Case Definition (BCCD) [1] which is designed to “define the level of diagnostic certainty of the reported event” [12]. Reporting rates of anaphylaxis following vaccination with *Pandemrix*TM or *Arepanrix*TM are subsequently compared to the rates observed with other vaccines. This analysis highlights the challenges of reliably determining the rate of anaphylaxis as an AEFI from a very large vaccinated population.

2. Materials and method

2.1. Vaccine

The GSK H1N1 pandemic influenza vaccines *Pandemrix*TM (manufactured in Dresden, Germany) and *Arepanrix*TM (manufactured in Québec, Canada) are monovalent inactivated split-virion pandemic influenza vaccines containing 3.75 µg of haemagglutinin per dose with the GSK Biologicals proprietary oil-in-water emulsion-based Adjuvant System AS03, containing tocopherol [13]. *Pandemrix*TM was first supplied in Denmark on 07 October 2009 and *Arepanrix*TM was first supplied in Canada on 21 October 2009. GSK followed the recommendations of health authorities when selecting the viral strain, A/California/7/2009 (H1N1) vaccine, for the vaccine formulation [14]. For the development of these novel A(H1N1) vaccines, GSK Biologicals utilized and largely relied on the extensive clinical experience acquired during the development of its registered H5N1 pandemic vaccine candidates [15–18]. The antigen components (split inactivated virus) of the vaccines were produced according to standard procedures already applied to the commercially available trivalent inactivated split virion seasonal influenza vaccines *Fluarix*TM (for *Pandemrix*TM) and *FluLaval*TM (for *Arepanrix*TM).

2.2. Exposure to *Pandemrix*TM and *Arepanrix*TM vaccines

The exact number of pandemic influenza vaccine doses administered is difficult to estimate, because vaccination programs are conducted by the individual countries and dosing recommendations vary by country. Therefore we used, as a denominator for the calculation of the reporting rates, either the known number of doses distributed (upper limit) or an estimate of the number of doses administered based on data from public health authorities and the

Table 1

List of Preferred Terms (PTs) that defined the narrow Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Query (SMQ) ‘Anaphylactic Reaction’ used in this study.

Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Circulatory collapse
First use syndrome
Kounis syndrome
Shock
Type I hypersensitivity

official website of countries in which *Pandemrix*TM and *Arepanrix*TM were administered (lower limit).

As of 15 April 2010, approximately 142 million doses of *Pandemrix*TM had been distributed to 42 countries and approximately 137 million doses of *Arepanrix*TM had been distributed to 24 countries. Based on exposure data obtained from official websites of individual countries and directly from public health authorities, GSK estimates *Pandemrix*TM and *Arepanrix*TM exposures at that time to have been 40 and 12 million doses respectively. However, as not all countries had systems in place to track exposure data or do not make these data public, these numbers are difficult to calculate and may be imprecise. *Arepanrix*TM was mainly used in Canada while *Pandemrix*TM was mainly used in Europe with more than half of the doses of *Pandemrix*TM administered in the UK, Germany, France and Sweden. Our estimates are similar to those reported by the European Medicines Agency (EMA): as of the 11th April 2010, at least 131 million doses of *Pandemrix*TM were distributed and at least 30.1 million patients were estimated to have been vaccinated in the European Economic Area [19]. The final estimates from the EMA, as of 22nd August 2010, are close to those reported in April: at least 131.8 million doses distributed and at least 30.8 million people vaccinated [20].

2.3. Retrieval of spontaneous cases of Anaphylaxis from GSK worldwide safety database

GSK collects all adverse drug reactions spontaneously reported by health care providers, regulatory authorities and consumers in a worldwide GSK safety database. To retrieve all potential cases of anaphylaxis reported to GSK following vaccination with *Pandemrix*TM or *Arepanrix*TM, we searched the GSK worldwide safety database for all spontaneous reports identified using the narrow Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query ‘Anaphylactic reaction’ and received as of 15 April 2010. Standardised MedDRA Queries (SMQs) were developed as a common approach to facilitate retrieval of MedDRA-coded data to investigate drug safety issues in pharmacovigilance and clinical development [21]. SMQs are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level, that relate to a defined medical condition or area of interest and which are intended to aid in case identification. We selected the narrow SMQ ‘Anaphylactic reaction’, to allow more sensitivity in identifying cases that are highly likely to represent cases of anaphylaxis. Any case reported to GSK in association with *Pandemrix*TM or *Arepanrix*TM until the 15 April 2010 with one of terms composing the narrow SMQ ‘Anaphylactic reaction’ (Table 1) was retrieved by the search.

2.4. Identification of confirmed cases of Anaphylaxis

Each case retrieved by the SMQ was assessed by medically qualified staff according to the Brighton Collaboration Case Definition of anaphylaxis [1]. The Brighton Collaboration

Table 2Number of cases of anaphylaxis reported with *Pandemrix*TM and *Arepanrix*TM and diagnosis certainty according to the Brighton Collaboration case definition.

Cases	Total	Anaphylaxis			Not anaphylaxis
		Levels 1–3	Level 4	Levels 1–4	
Brighton Level ^a	Levels 1–5				Level 5
<i>Pandemrix</i> TM	323	73	76	149	174
<i>Arepanrix</i> TM	72	24	41	65	7
Total	395	97	117	214	181

^a Brighton Levels 1, 2, 3: meet the case definition; Brighton Level 4: Reported anaphylaxis with insufficient evidence to meet the case definition; Brighton Level 5: Not a case of anaphylaxis.

(<http://www.brightoncollaboration.org>) is “an international voluntary collaboration with the primary goal of facilitating the development, evaluation, and dissemination of information about AEFI for vaccines used in human populations” [22]. This is done through the development of standardized case definitions of AEFI with corresponding guidelines for standardized data collection, analysis, and presentation [23–27]. The Brighton Collaboration Case Definitions (BCCDs) are intended to increase the comparability of AEFI data across surveillance systems or research studies for retrospective analyses, and through standardized prospective data collection in a variety of geographic settings. Each case definition (see Appendix A) provides three levels of diagnostic certainty (Levels 1–3), incorporating the variable completeness of information associated with retrospective data collection. Level 4 is applied to cases reported without sufficient information to conclude on diagnostic certainty. Cases for which the diagnosis of anaphylaxis was excluded based on the BCCD were defined as Level 5. In order to be conservative in our approach, the analysis was performed both on cases fulfilling levels 1–3 of diagnostic certainty and on cases fulfilling Levels 1–4 of diagnostic certainty, assuming that Level 4 cases were all in fact confirmed cases of anaphylaxis.

3. Results

3.1. Cases of Anaphylaxis reported following vaccination with *Pandemrix*TM or *Arepanrix*TM.

Three hundred and ninety-five cases were retrieved from the GSK worldwide safety database by the narrow SMQ Anaphylactic reaction: 323 associated with *Pandemrix*TM and 72 associated with *Arepanrix*TM. (Table 2). Through assessment against the Brighton Collaboration Case Definition of anaphylaxis, we identified 41 cases (10%) at Level 1, 45 cases (11%) at Level 2, 11 cases (3%) at Level 3, 117 cases (30%) at Level 4 and 181 cases (46%) at Level 5. Level 5 cases mainly described events of syncope or vasovagal reactions (115/181). Most of the case reports retrieved for *Arepanrix*TM were from Canada (62/72) where the majority of doses of *Arepanrix*TM were administered. The majority of cases (272/323) reported in recipients of *Pandemrix*TM were from Germany (105), Sweden (62), United Kingdom (55), Switzerland (26) and Norway (24). Most of the cases with diagnostic certainty of Levels 1–3 occurred in women (84%) and the median age of the subjects was 30 years (Table 3).

The time to onset was specified in 94 out of 97 reports. All these cases presented within 24 h after vaccination, of which 73 (78%) occurred within an hour. All were classified as serious according to the ICH regulatory definition [28]. Forty three percent of

Table 3

Age and gender of subjects with confirmed cases of anaphylaxis (Levels 1–3).

Vaccine	Gender (N)		Age (Years)
	Female	Male	
<i>Pandemrix</i> TM	63	10	30 [2–80]
<i>Arepanrix</i> TM	18	6	34 [1–81]
Total	81	16	30 [1–81]

the subjects (42/97) had a history of allergies, atopic diseases or asthma. The event resolved or improved after treatment with adrenaline, corticosteroids and/or antihistamines in 76% of these subjects (74/97), in 23% (22/97) the outcome was unknown or unresolved at the time of reporting and one 81 year-old male subject with a medical history of chronic obstructive pulmonary disease and lung neoplasm, experienced signs and symptoms that were suggestive of anaphylactic reaction 85 min following vaccination and died 8 days later due to renal failure.

3.2. Reporting rates of Anaphylaxis

Reporting rates of anaphylaxis were calculated per million doses distributed or administered, per vaccine or globally (Table 4). As a sensitivity analysis, the reporting rates were also calculated assuming that all cases assessed as Level 4 of diagnostic certainty were confirmed cases of Anaphylaxis. For both *Pandemrix*TM and *Arepanrix*TM, the reporting rates for confirmed cases of anaphylaxis (Levels 1–3) increased when the analysis included cases of anaphylaxis from Levels 1 to 4 (Table 4). For combined analysis of *Pandemrix*TM and *Arepanrix*TM, the reporting rates for cases of anaphylaxis from Levels 1 to 4 were 0.8 and 4.1 per million doses distributed and administered respectively.

The cumulative proportion of anaphylaxis reports received with respect to the total number of adverse events reports for *Pandemrix*TM and *Arepanrix*TM is presented in Fig. 1. Overall, very few adverse event reports were received in the weeks after the vaccination campaigns started, and there was an apparent high ratio of anaphylaxis reports compared to other adverse events reported for *Pandemrix*TM, while no reports of anaphylaxis were received for *Arepanrix*TM. However, these ratios stabilized in the following weeks and the cumulative proportion of anaphylaxis reports received for *Pandemrix*TM and *Arepanrix*TM remained stable overtime and was below 10% for both vaccines (analysis based on bi-weekly calculation of the cumulative proportion of cases retrieved with the narrow Standardised MedDRA Query – ‘Anaphylactic reaction’ with respect to the total number of adverse events reports received with these vaccines).

Table 4Reporting rates of Anaphylaxis following vaccination with *Pandemrix*TM and *Arepanrix*TM.

Cases	Total	Anaphylaxis	
		Levels 1–3	Levels 1–4
Brighton Level ^a	Levels 1–5		
Per million doses distributed			
<i>Pandemrix</i> TM	2.3	0.5	1.0
<i>Arepanrix</i> TM	0.5	0.2	0.5
Total	1.4	0.3	0.8
Per million doses administered			
<i>Pandemrix</i> TM	8.1	1.8	3.7
<i>Arepanrix</i> TM	6.0	2.0	5.4
Total	7.6	1.9	4.1

^a Brighton Levels 1, 2, 3: meet the case definition; Brighton Level 4: Reported anaphylaxis with insufficient evidence to meet the case definition; Brighton Level 5: Not a case of anaphylaxis.

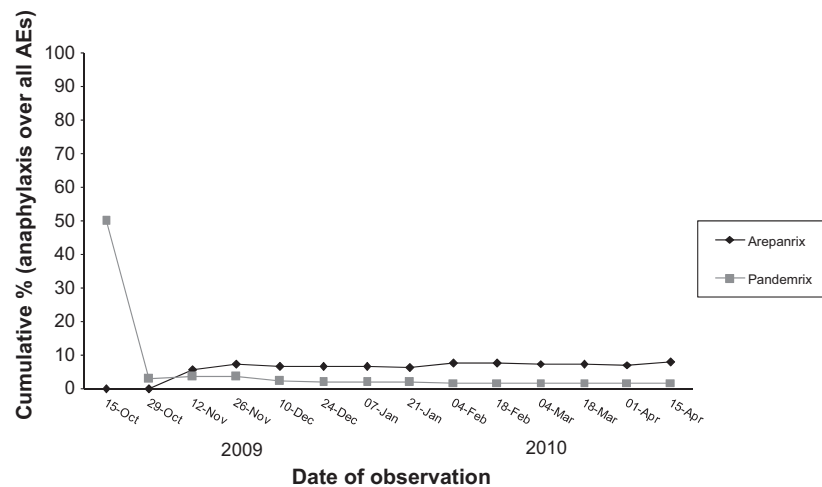


Fig. 1. Reporting of anaphylaxis cases following vaccination with the H1N1 pandemic influenza vaccines (October 15, 2009 to April 15, 2010). The anaphylaxis reports were based on the narrow Standardised Medical Dictionary of Regulatory Activities Query – ‘Anaphylactic reaction’. The data are expressed as the cumulative proportion of anaphylaxis reports with respect to the total number of adverse events reports received following mass-vaccination with *Pandemrix*TM and *Arepanrix*TM.

4. Discussion

This report provides an analysis of the anaphylaxis cases reported to GSK following vaccination with the pandemic influenza vaccines, *Pandemrix*TM and *Arepanrix*TM. Only a quarter of the cases could be confirmed to be cases of anaphylaxis according to the Brighton Collaboration Case Definition [1]. Furthermore, in almost half of the cases reported the diagnosis of anaphylaxis was excluded (Level 5). The reporting rates for confirmed cases of anaphylaxis were 0.5 and 1.8 per million doses distributed and administered for *Pandemrix*TM, 0.2 and 2.0 for *Arepanrix*TM, and 0.3 and 1.9 per million doses distributed and administered for the combined analysis of *Pandemrix*TM and *Arepanrix*TM. These reporting rates observed following vaccination with the GSK adjuvanted pandemic influenza vaccines are comparable with the rates reported in the literature for anaphylaxis following vaccination with other vaccines in postmarketing setting (1–10 cases per million doses of vaccine [1,2,4–6]). Even by adopting a conservative approach that includes Level 4 cases and using the lowest estimation of the exposure, the observed reporting rates remain within the range of expected reporting rates.

The calculation of reporting rates for an adverse event requires correct identification of cases for determination of the numerator but also reliable exposure data for the denominator. GSK has accurate information only with regard to the number of vaccine doses distributed to countries using the vaccine and those doses returned to GSK. Although the number of doses of vaccine administered is not known, the number of doses of vaccine distributed can provide an estimation of the upper limit of vaccine exposure [29]. Estimating the number of doses actually administered depends on the existence of country-specific tracking systems for the vaccinated population. If available, this information may be kept confidential by the local health authorities or provided to GSK inconsistently. Moreover, this information is not always available as many countries do not have a reliable system in place to provide estimates of the number of persons vaccinated. These limitations can make estimates of actual exposure imprecise. We used an estimation based on available exposure data obtained from official websites or public health authorities of individual countries as the lower limit, which are likely an underestimation of the actual exposure.

There were differences in the reporting rates between countries. Most (72%) of the 395 case reports retrieved were from Germany (105), Canada (62), Sweden (62), and United Kingdom (55), where the majority of doses of *Arepanrix*TM or *Pandemrix*TM were administered. Whether this is simply related to better reporting systems in

these countries rather than real differences cannot be determined based on these data. It can be expected however, that in this setting of mass vaccination with a novel vaccine, close monitoring of immediate post-vaccination reaction is likely to have occurred worldwide. Health Canada and the European Medicines Agency have performed their own analyses and both concluded that, overall, the reporting rate of anaphylaxis following vaccination with the above pandemic vaccines was not different from the generally expected rate of 1–10 cases per million doses observed for other vaccines [20,30].

Anaphylaxis ascertainment obtained during a pandemic immunization campaign using a novel vaccine might be expected to have high reporting rates due to increased awareness of health care providers, the considerable public attention, the involvement of many first-time influenza vaccinees, as well as the implementation of enhanced passive adverse event surveillance systems. Furthermore, anaphylaxis-related events are more likely to be reported than others, because they are often serious and temporally closely linked to vaccination. However, potential underreporting in some countries, other reporting biases such as media influence, or incomplete case details are major limitations [31] and add complexity for the analysis and interpretation of spontaneous reports.

SMQs are useful for an objective and consistent selection of all potential cases of a predefined condition. However, for a comprehensive safety evaluation, subsequent assessment by medical staff of the cases retrieved is mandatory in order to identify the cases actually representing the condition being analysed. Identifying confirmed cases of anaphylaxis reported through post-marketing surveillance is a complex exercise due to the considerable variability in the clinical presentation, and also the generally limited quality of the information in spontaneous reports for all AEs [2,32]. The available details of spontaneous reports are not as complete as those documented in a clinical trial setting and therefore full clinical details were not available for all cases. In this analysis, the diagnosis of anaphylaxis was excluded (assessed as Level 5 of diagnostic certainty) in nearly 50% of the cases retrieved by the SMQ; this would have led to erroneous reporting rates had these cases been included in our calculations. The case reporters might have indeed mentioned one of the SMQ terms in the report while the detailed description of the event was more consistent with a diagnosis other than anaphylaxis. This is commonly the case, for example, with the SMQ terms ‘circulatory collapse’ or ‘shock’, which are not specific to anaphylaxis and are generally due to other causes. In addition, some non-specific events can be easily confused with anaphylaxis

[2]. Vasovagal reactions and syncope caused by the combination of injection pain and fear at the time of vaccination are commonly mistaken for anaphylaxis by reporters.

Feeling faint or fainting is a well-known symptom of anaphylactic reactions, but confirmed anaphylactic reactions are often much more dramatic than mere fainting. Nausea and hyperventilation are also common symptoms. The complaints of breathlessness experienced by a person who is hyperventilating may be incorrectly identified as dyspnoea and other symptoms such as tingling sensations in hands and feet and even convulsions often follow hyperventilation [5]. Other possible allergic-type manifestations, such as urticarial rash, can also be misdiagnosed as anaphylaxis. Without specific diagnostic procedures for allergy, it is indeed difficult to identify and differentiate IgE-mediated allergic and non-allergic vaccination-associated anaphylaxis symptoms [33]. As an example, a recent study using allergologic diagnostic procedures ruled out IgE-mediated allergic anaphylaxis to vaccine components in all 38 tested subjects that previously reported suspected vaccine-induced anaphylaxis [33].

In the present study, the proportion of anaphylaxis cases with diagnostic certainty of Levels 1–3 was higher in females compared to males (84% vs. 16%). Previous data from epidemiological studies have shown that the incidence of anaphylaxis is significantly higher in adult women, even though the disproportion between women and men observed in our study is unexpectedly high. However, the exact contribution of biological and behavioural differences associated to gender for this observation has not been clearly delineated so far [34,35].

We found the Brighton Collaboration Case Definition of anaphylaxis [32] of added value for consistency of case evaluation and diagnosis ascertainment. However, we considered it too detailed for screening of cases in the safety database. Post-marketing surveillance reports of adverse events following vaccination usually lack the necessary level of clinical detail to classify them within 1–3 levels of diagnostic certainty described in the case definition. For these adverse events of special interest following vaccination, we attempted to use standardized follow-up questionnaires to ensure that adequate detail was recorded to allow subsequent assessment using the Brighton case definition of anaphylaxis. However, despite the use of these questionnaires, we still found that 30% of cases were assessed as Level 4 because insufficient details were provided to fulfil the minimal criteria for the case definition for anaphylaxis. As described by Gold et al. [32], the BCCD for anaphylaxis is complex and of limited application in post-marketing setting. Reporters are unlikely to spontaneously report sufficient detail required for the Brighton classification, or might inconsistently use terms describing the anaphylactic reaction. To overcome these limitations, we calculated the reporting rates by taking into account the cases with insufficient detail for diagnosis (Brighton Level 4 cases).

5. Conclusion

Our analysis suggests that the reporting rates of anaphylaxis following vaccination with *Pandemrix*TM and *Arepanrix*TM, the GSK AS03-adjuvanted pandemic influenza A/H1N1 vaccines, is within the expected rates of anaphylaxis for vaccines in general (1–10 per 1,000,000 doses vaccine). In large-scale mass vaccination campaigns, confirmed cases of anaphylaxis may sometimes be difficult to differentiate from other acute events that may also occur after vaccination such as vasovagal reactions, psychogenic or conversion symptoms. This highlights the importance of recognising, managing and reporting of these events, particularly in a pandemic situation. In addition, it is important for staff vaccinating individuals to ensure that sufficient information and details are recorded and reported to allow subsequent classification and analysis using

the Brighton case definitions. Our results are in line with previous reports that anaphylaxis following vaccination is a rare event and should not restrict vaccination programs.

Acknowledgements

We address special thanks to Ziad Zeinoun and Thomas Verstraeten for critical reading of the manuscript and helpful suggestions. Finally we thank Claire Marie Seymour (XPE Pharma & Science) for writing assistance and Sophie Tambour (XPE Pharma & Science) for editorial assistance and manuscript coordination. *Contributors:* Each author significantly contributed to the interpretation of the data. All authors had full access to all the data in the analysis and had final responsibility for the decision to submit for publication. *Conflict of interest statement:* All authors are employees of GSK Biologicals. *Funding:* This analysis was funded by GSK Biologicals. GSK Biologicals was involved in all stages of study conduct and analysis, and also took in charge all costs associated with the development and the publishing of the present manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2011.04.026.

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