



International collaboration to assess the risk of Guillain Barré Syndrome following Influenza A (H1N1) 2009 monovalent vaccines[☆]



Caitlin N. Dodd^{a,*}, Silvana A. Romio^b, Steven Black^c, Claudia Vellozzi^d, Nick Andrews^e, Miriam Sturkenboom^b, Patrick Zuber^f, Wei Hua^g, Jan Bonhoeffer^{h,i}, Jim Buttery^j, Nigel Crawford^k, Genevieve Deceuninck^l, Corinne de Vries^m, Philippe De Wals¹, M. Victoria Gutierrez-Gimenoⁿ, Harald Heijbel^o, Hayley Hughes^p, Kwan Hur^q, Anders Hviid^r, Jeffrey Kelman^s, Tehri Kilpi^t, S.K. Chuang^u, Kristine Macartney^v, Melisa Rett^w, Vesta Richardson Lopez-Callada^x, Daniel Salmon^{y,z}, Francisco Gimenez Sanchez^{aa}, Nuria Sanz^{bb}, Barbara Silverman^{cc}, Jann Storsaeter^{dd}, Umapathi Thirugnanam^{ee}, Noline van der Maas^{ff}, Katherine Yih^w, Tao Zhang^{gg}, Hector Izurieta^g, the Global H1N1 GBS Consortium¹

^a Department of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

^b Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands

^c Department of Global Child Health, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

^d Centers for Disease Control and Prevention, Atlanta, GA, United States

^e Health Protection Agency, London, United Kingdom

^f Department of Immunizations, Vaccines and Biologicals (IVB), World Health Organization, Genève, Switzerland

^g Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD, United States

^h Brighton Collaboration Foundation, Basel, Switzerland

ⁱ University Children's Hospital, Basel, Switzerland

^j Murdoch Children's Research Institute, Dept of Paediatrics, Monash University, Victoria, Australia

^k The Department of Paediatrics, University of Melbourne, Melbourne, Australia

^l Public Health Research Unit, Quebec University Hospital Research Centre, Quebec City, Quebec, Canada

^m Department of Pharmacy & Pharmacology, University of Bath, Bath, United Kingdom

ⁿ Vaccine Department, Centre of Public Health Research (CSISP-FISABIO), Valencia, Spain

^o Swedish Institute for Infectious Disease Control, Lund, Sweden

^p Department of Defense, Washington, DC, United States

^q Center for Medication Safety, Pharmacy Benefit Management Services, Hines Veterans Affairs Hospital, Hines, IL, United States

^r Department of Epidemiology Research, Statens Serum Institute, Copenhagen, Denmark

^s Center for Drug and Health Plan Choice, Centers for Medicare and Medicaid Services, Baltimore, MD, United States

^t National Institute for Health and Welfare, Helsinki, Finland

^u Centre for Health Protection, Department of Health, Hong Kong

^v Children's Hospital at Westmead, Westmead, New South Wales, Australia

^w Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, United States

^x National Center for Child and Adolescent Health, Mexico City, Mexico, Mexico

^y National Vaccine Program Office, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services, Washington, DC, United States

^z Department of International Health and Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

^{aa} Pediatrics Department, Torrecárdenas Hospital, Almería, Spain

^{bb} Hospital Clinic i Provincial de Barcelona (SCReN), Barcelona, Spain

^{cc} Maccabi Healthcare Services, Tel Aviv, Israel

^{dd} Norwegian Institute of Public Health, Oslo, Norway

^{ee} National Neuroscience Institute, Singapore

^{ff} RIVM, Bilthoven, The Netherlands

^{gg} Department of Epidemiology, School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Shanghai, PR China

Abbreviations: CSF, cerebrospinal fluid; GP, general practitioner; MCRI, Murdoch Children's Research Institute; Maccabi, Maccabi Health Maintenance Organization; ICPI, Integrated Primary Care Information Database; NNI/CGH, National Neuroscience Institute Singapore General Hospital; NNI/TTSH, National Neuroscience Institute Tan Tock Seng Hospital; CPRD, Clinical Practice Research Datalink; DoD, Department of Defense; PRISM, Post-Licensure Rapid Immunization Safety Monitoring; VA, Department of Veterans Affairs; VAESCO, Vaccine Adverse Event Surveillance and Communication Consortium; VSD, Vaccine Safety Datalink.

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* Corresponding author. Tel.: +31645574714; fax: +31107044722.

E-mail addresses: c.dodd@erasmusmc.nl, caitlindodd@gmail.com (C.N. Dodd).

¹ See [Appendix A](#) for the group of Global H1N1 GBS Consortium.

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ABSTRACT

Background: The global spread of the 2009 novel pandemic influenza A (H1N1) virus led to the accelerated production and distribution of monovalent 2009 Influenza A (H1N1) vaccines (pH1N1). This pandemic provided the opportunity to evaluate the risk of Guillain–Barré syndrome (GBS), which has been an influenza vaccine safety concern since the swine flu pandemic of 1976, using a common protocol among high and middle-income countries. The primary objective of this project was to demonstrate the feasibility and utility of global collaboration in the assessment of vaccine safety, including countries both with and without an established infrastructure for vaccine active safety surveillance. A second objective, included *a priori*, was to assess the risk of GBS following pH1N1 vaccination.

Methods: The primary analysis used the self-controlled case series (SCCS) design to estimate the relative incidence (RI) of GBS in the 42 days following vaccination with pH1N1 vaccine in a pooled analysis across databases and in analysis using a meta-analytic approach.

Results: We found a relative incidence of GBS of 2.42 (95% CI 1.58–3.72) in the 42 days following exposure to pH1N1 vaccine in analysis of pooled data and 2.09 (95% CI 1.28–3.42) using the meta-analytic approach.

Conclusions: This study demonstrates that international collaboration to evaluate serious outcomes using a common protocol is feasible. The significance and consistency of our findings support a conclusion of an association between 2009 H1N1 vaccination and GBS. Given the rarity of the event the relative incidence found does not provide evidence in contradiction to international recommendations for the continued use of influenza vaccines.

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1. Introduction

Assessment of vaccine safety post-licensure requires well-designed epidemiological studies, which can be challenging for many countries due to scarcity of available data. Therefore, spontaneous reporting systems are more commonly used for post-marketing safety monitoring [1]. Traditionally, vaccines have been manufactured and introduced in the United States (US) and Europe before introduction in other countries, hence US and European vaccine safety monitoring capacity has served the global need to evaluate the safety of new vaccines [1]. However, vaccines are now being manufactured and introduced in several countries outside the US and Europe [2], requiring the development of vaccine safety monitoring systems globally to assure the safety of the world's vaccine supply and maintain trust in immunization programs. International vaccine safety collaborations can help build vaccine safety monitoring infrastructure and capacity and provide a means to assess rare adverse events following immunization (AEFI) in countries that now have limited capacity [3].

To demonstrate that international collaboration is feasible for vaccine safety studies to investigate rare, serious and clinically complex AEFI, a group of vaccine safety researchers conducted a proof of concept collaborative vaccine safety study using a standard protocol [4–6]. A steering group² from the World Health Organization (WHO), United States Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), European CDC, Erasmus Medical Center, Cincinnati Children's Hospital, and the Brighton Collaboration [7], provided standardized methods and definitions for a study that included investigators from Australia, Canada, China, Denmark, Finland, France, Israel, Mexico, The Netherlands, Norway, Singapore, Spain, Sweden, the United Kingdom, and the United States.

The global spread of the 2009 novel pandemic influenza A (H1N1) virus [8] led to the accelerated production of monovalent 2009 Influenza A (H1N1) vaccines (pH1N1) by manufacturers in the Americas, Europe, and Asia [9]. Rapid and extensive vaccine administration was implemented worldwide. This pandemic provided the opportunity to evaluate the risk of Guillain–Barré syndrome (GBS), an acute polyradiculoneuropathy, following receipt of these vaccines using a common protocol among high and middle-income

countries and to assess the feasibility of this collaborative effort [10]. Several factors contributed to choosing this vaccine and this adverse event (GBS) to test the new consortium: First, GBS has been an influenza vaccine safety concern since 1976, when an elevated risk of GBS was identified following the “swine-flu” influenza vaccine [11]; second, case definitions and classifications for GBS are available, providing a tool for standardized assessment across sites [12]; third, since almost all GBS cases are hospitalized, unbiased case ascertainment could be achieved using hospital databases; and finally, since GBS is rare, assessment of risk would benefit from the increased sample size and statistical power that could result from an international collaboration.

The primary objective of this project was to demonstrate the feasibility and utility of global collaboration in the assessment of vaccine safety, including countries both with and without an established infrastructure for vaccine safety active surveillance. A second objective, included *a priori*, was to assess the relative risk of GBS following pH1N1 vaccination.

2. Methods

We chose the self-controlled case series (SCCS) design [13] to estimate the relative incidence (RI) of GBS in the 42 days following vaccination with pH1N1 vaccine. We chose this case-only analytic approach because it can be implemented in populations with varying levels of infrastructure for conducting epidemiologic studies; specifically, it does not require the availability of accurate population denominators which are difficult to obtain in many countries [9,10]. The case series approach includes only individuals who experienced the event of interest (GBS) in the analysis. Each individual's person-time during follow-up is divided into predefined vaccine exposed and non-exposed periods. Each GBS case then falls into a risk or non-risk window and contributes exposed and non-exposed time. Unvaccinated GBS cases contribute to the estimation of other time-varying covariates such as seasonality. Data are analyzed by conditional Poisson regression. The SCCS design requires that cases be ascertained completely and in an unbiased manner and that the probability of exposure is not affected by occurrence of the event of interest. Apart from its intrinsic resource efficiency, this design also controls for measured or unmeasured within-person non-time dependent confounding characteristics, including demographics and chronic co-morbid conditions, genetic susceptibility, and others [10].

² Steven Black, Caitlin Dodd (Cincinnati Children's Hospital), Hector Izurieta (FDA), Patrick Zuber (WHO).

Table 1
Database inclusion and exclusion in primary and sensitivity analyses by Country.

Country	Database	Criteria for exclusion	
Excluded databases			
France		Patient Consent Required (potential bias)	
Israel	Maccabi	Brighton Collaboration criteria not provided	
Mexico	Mexico City Mexican States	Relative incidence found to be an outlier compared to all other study site relative incidence findings Data were obtained solely from a specialist network (potential bias)	
Norway		Data were obtained solely from a specialist network (potential bias)	
Sweden		Patient consent required with potential bias	
Country	Database	Analyses in which database is included	Criteria for exclusion where applicable
Included databases			
Australia	Adelaide	– Primary analysis – All sensitivity analyses	
	MCRI ^a	– Primary analysis – All sensitivity analyses	
	Sydney	– Primary analysis – All sensitivity analyses	
Canada	Quebec	– Primary analysis – All sensitivity analyses	
China	Hong Kong	– Primary analysis – All sensitivity analyses	
	Shanghai	– Analyses through Brighton 4A – Primary analysis – All sensitivity analyses	All reported cases were Brighton level 4 or 4A
Denmark		– Primary analysis – All sensitivity analyses	
Finland		– Primary analysis – All sensitivity analyses	
The Netherlands	IPCI ^a	– Primary analysis – All sensitivity analyses	
Singapore	NNI/CGH ^a	– Primary analysis – All sensitivity analyses	
Spain	NNI/TTSH ^a	– Analyses through Brighton 4A	All reported cases were Brighton level 4 or 4A
	Almeria	– Analyses through Brighton 4A	All reported cases were Brighton level 4 or 4A
	Barcelona	– Primary analysis – All sensitivity analyses	
	Valencia	– Primary analysis – All sensitivity analyses	
The United Kingdom	CPRD ^a	– Analyses through Brighton 4A	All reported cases were Brighton level 4 or 4A
The United States	DoD ^a	– Primary analysis – All sensitivity analyses	
	Medicare	– Vaccinated-cases only analysis, excluded from all others	Database contained only cases post-vaccination
	PRISM ^a	– Vaccinated-cases only analysis, excluded from all others	Database contained only cases post-vaccination
	VA ^a	– Vaccinated-cases only analysis, excluded from all others	Database contained only cases post-vaccination
	VSD ^a	– Vaccinated-cases only analysis, excluded from all others	Database contained only cases post-vaccination

^a Murdoch Children's Research Institute (MCRI), Maccabi Health Maintenance Organization (Maccabi), Integrated Primary Care Information Database (IPCI), National Neuroscience Institute Singapore General Hospital (NNI/CGH), National Neuroscience Institute Tan Tock Seng Hospital (NNI/TTSH), CPRD (Clinical Practice Research Datalink), Department of Defense (DoD), Post-Licensure Rapid Immunization Safety Monitoring (PRISM), Department of Veterans Affairs (VA), Vaccine Safety Datalink (VSD).

2.1. Study population

As shown in Table 1, 15 countries with available data and willingness to participate contributed data for this study: cases that met inclusion criteria for this study from Australia, Canada, China, Israel, Mexico, Singapore, Spain, and the United States and from the European Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium [14] (<http://vaesco.net>) (Denmark, Finland, France, The Netherlands, Norway, Sweden, and the United Kingdom) were included. Australian data were provided by hospitals in the state of Victoria (including Melbourne), Sydney, Perth, and Adelaide. Canadian data were provided from the entire province of Quebec; Chinese cases were contributed by sentinel hospitals in Hong Kong and Shanghai. Israeli data were provided by Maccabi, a national health maintenance organization (HMO) and Mexican data were contributed from Mexico City and surrounding rural areas. Singapore data were provided from one rural and one central hospital. Spanish data were provided by hospitals in Almeria, Barcelona, and Valencia. US data were contributed from the Department of Defense (DoD), the Department Veterans Affairs (VA), the Vaccine Safety Datalink (combined hospitalization and vaccination data from a collaboration of 8 health care organizations),

Medicare, and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program [15,16].

2.2. Case ascertainment and classification

The specific method of case ascertainment varied from country to country with some countries identifying potential cases through administrative databases whereas other countries reviewed hospital discharge logs manually (Table 2). Databases from all US sites other than the DoD contained only vaccinated cases and were limited to post-vaccination follow up time. Each site independently defined an observation period, ranging from 4 to 18 months, during which cases were obtained. The number of medical records requested and reviewed was not reported by the participating sites. Countries that did not identify and classify cases using a procedure compatible with the common protocol were excluded from this study (Table 1). For countries in which cases were ascertained through active surveillance, only those cases with verified hospital admission were included.

Diagnostic codes for GBS (ICD-9 code of 357.0, ICD-10 code of G61.0, or Read codes F370*) were used to identify potential cases for review. Cases identified exclusively through specialty

Table 2
Characteristics of databases included in primary or sensitivity analyses by country.

Country	Database	Dates of observation	Number of cases	Case ascertainment	Vaccination status ascertainment
Australia	Adelaide	9/30/2009–9/30/2010	1	Administrative database, active prospective surveillance	Vaccine Registry, Self-Report, Outpatient Chart Review
	MCRI ^a	9/30/2009–9/30/2010	54	Administrative database, active prospective surveillance	Vaccine Registry, Self-Report, Outpatient Chart Review
	Sydney	9/30/2009–9/30/2010	5	Administrative database, active prospective surveillance	Vaccine Registry, Self-Report, Outpatient Chart Review
Canada	Quebec	10/13/2009–3/31/2010	80	Administrative database, active prospective surveillance	Vaccine registry
China	Hong Kong	12/21/2009–6/30/2010	20	Hospital log review	Outpatient Chart Review, Self-Report
Denmark	Shanghai	1/1/2009–7/1/2010	22	Administrative database	Outpatient Chart Review
		11/1/2009–11/1/2010	31	National Patient Register using primary discharge diagnoses	Vaccine Registry
Finland		11/1/2009–11/1/2010	29	Hospital discharge and hospital outpatient records, primary diagnoses	Vaccine registry
The Netherlands	IPCI ^a	11/1/2009–11/1/2010	80	Identified prospectively through neurologists Completeness verified retrospectively against claims codes in each hospital.	GP ^b medical record
Singapore	NNI/CGH ^a	11/5/2009–8/31/2010	6	Administrative Database	Outpatient Chart Review, Self-Report
Spain	NNI/TTSH ^a	11/5/2009–8/31/2010	13	Administrative Database	Hospital Medical Records
	Almeria	11/1/2009–4/30/2010	8	Administrative Database	Outpatient Chart Review
	Barcelona	11/1/2009–4/30/2010	14	Administrative Database	Outpatient Chart Review
	Valencia	11/1/2009–4/30/2010	10	Administrative Database	Vaccine Registry
The United Kingdom	CPRD ^a	11/1/2009–11/1/2010	40	Automated GP records	GP ^b records
The United States	DoD ^a	11/1/2009–4/30/2010	6	Administrative Database	Vaccine Registry
	Medicare	11/1/2009–4/30/2010	39	Electronic Medical Records Administrative Database Chart Review	Administrative Database
	PRISM ^a	10/22/2009–8/7/2010	8	Vaccine Registries and Claims Databases	Electronic Medical Claims
	VA ^a	11/1/2009–4/30/2010	2	Administrative Database Electronic Medical Records	Vaccine Registry and Administrative database
	VSD ^a	8/1/2009–4/30/2010	11	Administrative Database Electronic Medical Records	Vaccine Registry and Administrative database.

^a Murdoch Children's Research Institute (MCRI), Integrated Primary Care Information Database (ICPI), National Neuroscience Institute Singapore General Hospital (NNI/CGH), National Neuroscience Institute Tan Tock Seng Hospital (NNI/TTSH), CPRD (Clinical Practice Research Datalink), Department of Defense (DoD), Post-Licensure Rapid Immunization Safety Monitoring (PRISM), Department of Veterans Affairs (VA), Vaccine Safety Datalink (VSD)

^b General practitioner.

network reporting or through other passive reporting method were excluded. The specific method of case ascertainment used and number of cases identified are shown in [Table 2](#).

All cases were classified locally according to Brighton Collaboration criteria [12] ([Table 3](#)). All cases meeting Brighton level 1, 2, 3 were considered confirmed and included in the primary analysis. A secondary analysis also included Brighton categories 4 and 4A. Category 4A was specifically defined for this international study and included cases diagnosed by a neurologist but for whom the medical chart did not provide sufficient information for the study reviewers to classify the case according to Brighton Collaboration criteria ([Table 3](#)).

Table 3
Brighton collaboration case definition for Guillain-Barré Syndrome [12].^a

Level	Requirements
1	Clinical, electrophysiological, AND cerebrospinal fluid (CSF) data
2	Clinical, data and electrophysiological OR cerebrospinal fluid (CSF) data
3	Clinical data
4	Information available is insufficient for levels 1–3, but no other diagnosis is apparent or warranted.
4A	Diagnosis was made by a neurologist, insufficient diagnostic data available in the medical chart (adopted specifically for this study)

^a Levels 1–3 only used in the primary analysis, levels 1–4A used in sensitivity analyses.

2.3. Vaccination status

Vaccination status was obtained through automated immunization registries or databases when available or through a review of the patient's vaccination record where it was not. In some cases, receipt of vaccine was obtained through self-report and subsequently verified in the vaccination record. The method used for each participating site is shown in [Table 2](#). All subjects had presence or absence of pH1N1 vaccine recorded with the date of exposure. Patients for whom no record of seasonal influenza vaccination were available were considered unexposed to the seasonal vaccine [Table 4](#).

2.4. Covariates

Presence or absence of risk factors for GBS, including preceding gastrointestinal infections and respiratory infections, were collected for the 30 days prior to diagnosis through chart review or recall by the subject when chart review was not possible. While a standard abstraction form was not used, a standard case report form was used to record all data used in analysis. Since presence or absence of the potential infective episodes in the 30 days preceding GBS rather than exact dates of the episodes was collected, these infections could not be controlled for in the analysis but could be studied as potential effect modifiers. To control for circulation of the pandemic influenza virus we used seasonality as a proxy.

Table 4
Number and characteristics of Guillain–Barré syndrome cases and relative incidence following pH1N1 vaccination by database from ten countries.^a

Country	Database	Number of cases	Number of pH1N1 ^b exposed cases	Number of cases meeting Brighton Criteria 1–4A	Number of exposed cases meeting Brighton Criteria 1–4A	Age (mean, SD) ^c	Sex = M (frequency, %)	Database-specific GBS ^d RI ^e (CI) ^f , Brighton Levels 1–4A	
Australia	Adelaide	1	0	1	0	4 (NA ^g)	1 (100%)	NA	
	MCRI ^h	54	10	54	10	49.2 (23.9)	30 (56%)	2.10 (0.40, 11.05)	
	Sydney	5	0	5	0	5.8 (4.7)	3 (60%)	NA	
Canada	Quebec	80	43	80	43	49.5 (21.9)	55 (69%)	1.45 (0.70, 3.00)	
China	Hong Kong	20	5	20	5	57.8 (13.3)	12 (60%)	0.88 (0.07, 11.32)	
	Shanghai	22	0	22	0	42.0 (18.1)	15 (68%)	NA	
Denmark		31	4	31	4	49.2 (20.2)	14 (45.2)	4.08 (0.48, 34.83)	
Finland		29	13	29	13	54.4 (20.8)	12 (41.4)	2.59 (0.77, 8.68)	
The Netherlands	ICPI ^h	80	29	79	28	45.0 (20.8)	32 (40.0)	2.81 (1.07, 7.34)	
Singapore	NNI/CGH ^h	6	1	6	1	36.3 (16.9)	5 (83%)	3.60 × 10 ⁹ (0, infinity)	
	NNI/TTSH ^h	13	2	13	2	54.9 (16.7)	9 (69%)	3.60 × 10 ⁹ (0, infinity)	
Spain	Almeria	8	1	8	1	45.9 (20.3)	5 (63%)	1.27 × 10 ⁹ (0, infinity)	
	Barcelona	14	0	14	0	38.9 (23.7)	8 (57%)	NA	
	Valencia	10	0	10	0	47.8 (22.8)	6 (60%)	NA	
The United Kingdom	CPRD ^h	40	3	40	3	45.4 (20.4)	17 (42.5)	10.92 (0.92, 130.13)	
The United States	DoD ^h	6	6	6	6	28.8 (6.8)	6 (100%)	8.39 (0.73, 97.00)	
	<i>Databases with vaccinated cases only</i>								
	Medicare	39	39	35	35	72.8 (8.5)	25 (64%)	2.04 (0.99, 4.20)	
	PRISM ^h	8	8	7	7	48 (33.5)	4 (50%)	2.27 (0.44, 11.77)	
	VA ^h	2	2	1	1	60 (12.7)	2 (100%)	NA	
	VSD ^h	11	11	11	11	51.5 (24.2)	4 (36%)	3.78 (0.92, 15.61)	

^a Descriptive statistics are for all cases regardless of Brighton Collaboration Criteria unless otherwise specified.

^b monovalent 2009 (H1N1) A vaccines.

^c Standard deviation.

^d Guillain–Barré syndrome.

^e Relative incidence.

^f Confidence interval.

^g Not applicable.

^h Murdoch Children's Research Institute (MCRI), Integrated Primary Care Information Database (ICPI), National Neuroscience Institute Singapore General Hospital (NNI/CGH), National Neuroscience Institute Tan Tock Seng Hospital (NNI/TTSH), CPRD (Clinical Practice Research Datalink), Department of Defense (DoD), Post-Licensure Rapid Immunization Safety Monitoring (PRISM), Department of Veterans Affairs (VA), Vaccine Safety Datalink (VSD).

This was accomplished by defining the peak of influenza season for each site as the period during which >15% of all surveillance influenza laboratory tests were positive, and estimating the relative incidence of GBS in this peak season. This produced time periods for each site defined either as “high influenza circulation” or “low influenza circulation”. Although the seasonality of GBS is not strictly related to influenza infection, influenza surveillance data provided an efficient means by which to uniformly define seasonal periods across continents and hemispheres. This formulation allowed for a peak influenza season specific to each site while also allowing for a common estimate of the effect of seasonality across sites. Data to determine these periods of influenza circulation were obtained from publicly available governmental influenza surveillance, where available. For some sites, it was necessary to obtain these data from influenza surveillance conducted at the site.

2.5. Data collection and sharing

All data, with the exception of data from the VAESCO consortium, were uploaded to a secure WHO workspace where it was checked for quality and completeness by study group statisticians; VAESCO data were maintained by the VAESCO data management center at Erasmus Medical Center. All data was de-identified prior to submission. Institutional Review Board approval was obtained for those sites at which the study was not considered exempt. Inclusion and exclusion criteria as well as protocol and statistical analysis considerations were discussed on bi-weekly telephone conferences with all sites beginning in January, 2010.

2.6. Analysis and statistical methods

Data were analyzed using the SCCS method to investigate whether pH1N1 vaccination was associated with an increased risk of GBS during the pre-specified high-risk time window of days 1–42 post vaccination. This period of increased risk was chosen because of evidence from previous published studies [11]. We conducted two co-primary analyses: an analysis pooling all individuals across sites and an analysis using a meta-analytic approach in which estimates of rate ratios from each database were weighted based upon within and between-study errors and subsequently merged. While the pooled analysis provides more power, the meta-analytic approach is more conservative in its estimation as it weighs results from sites with less variability more heavily, thus providing greater assurance that outlying observations or sites with highly variable data will not bias the overall RI estimate. All analyses using the standard SCCS approach excluded the two weeks preceding vaccination from the background period to account for a possible healthy vaccinee effect [17], and controlled for seasonality as defined by periods of circulating influenza.

Only cases meeting Brighton Collaboration criteria level 1–3 [12] from databases which included pre and post-vaccination time were included in the primary analysis, which also included a time-varying covariate to assess the effect of seasonality. The date of diagnosis or hospitalization was used as the index date for GBS.

The standard SCCS method is only valid if the occurrence of an event (GBS in this case) does not alter the probability of subsequent exposure. This assumption may be violated since knowledge on the part of practitioners and patients regarding the *a priori* association between GBS and swine flu vaccine [11] may influence vaccination practices, and patients may forego or delay vaccination after GBS diagnosis [18]. For this reason, we also evaluated GBS risk using modifications of the standard SCCS approach to analyze data in which the event-dependent exposures assumption may have been violated. The first of these is the vaccinees-only approach, in which only vaccinated subjects are included and the observation window begins at the date of vaccination. The removal

of non-vaccinated cases reduces power to estimate the effect of time-varying covariates such as seasonality [19]. The second modification is the pseudo-likelihood approach, a novel method which considers all cases (vaccinated or not) included in the analysis [20]. In this extension to the standard SCCS, we estimated risk under a counterfactual in which every vaccine exposure is treated as the last possible exposure for that subject. The inclusion of all cases during the entire observation period retains optimal power for the estimation of time-varying covariates [20]. The pseudo-likelihood approach was used to estimate the effect of pH1N1 vaccine with adjustment for seasonality. The vaccinated-cases only and pseudo-likelihood approaches are equivalent when only one exposure is considered and no time-dependent covariates are included in the analysis. Because there was less than 20% difference between the pH1N1 vaccine-associated relative incidence estimates from the standard and pseudo-likelihood approaches (the difference decided *a priori* as evidence of bias from contraindication), all subsequent analyses were conducted using the standard approach.

A series of sensitivity analyses were conducted. To assess the effect of seasonal influenza vaccination, the exposure dates were included when known and subjects with missing data were assumed to be non-recipients of seasonal vaccine. We also assessed the risk window in more detail using days 1–7, 8–21, and 22–42 and estimated risks for each different window simultaneously within the same model. Subsequently, cases meeting Brighton criteria through level 4 and 4A were included and an analysis using the date of onset rather than the date of diagnosis was conducted. An analysis limited to Brighton criteria levels 1 and 2 was also conducted. To understand possible effect modifiers and confounders, analyses stratified by sex, age category (<5, 5–9, 10–18, 19–49, 50–64, and 65+ years), history of GBS, and presence of recent infections were also performed. To capitalize on the diversity of vaccine types and manufacturers in the data set, we also stratified by adjuvanted and non-adjuvanted vaccines.

In the meta-analytic approach, we adjusted for seasonality using month-long periods rather than seasonal peaks since, as data were not being pooled across databases, a common measure of seasonality was not necessary. Estimates of the exposure to pH1N1 vaccine in each database, considering only first dose as exposure of interest, were subsequently combined using a meta-analytic approach with a random effects model in which the estimate from each site is weighted by the inverse of its variance plus the variance of estimates between databases [21]. All analyses were conducted using SAS 9.2 (SAS Institute, Cary NC).

3. Results

3.1. Pooled data analysis

In the primary analysis of pooled data limited to Brighton Collaboration criteria levels 1–3 (Table 5), we found a RI of 2.86 (95% CI 1.88–4.34). In country-specific analyses for the meta-analytic approach, analysis of the data contributed by the Mexico City database was found to have a very high RI of 39.19 (3.74, 410.41). When we excluded Mexican cases from the primary analysis, the estimate of the RI for the primary analysis decreased to 2.42 (1.58, 3.72) (Table 5). Based upon these results, cases from Mexico were excluded from all analyses along with cases from those databases with potential ascertainment bias, resulting in 10 countries contributing cases to the analysis data set (Table 1).

The vaccinated cases only approach produced an estimated RI of 2.37 (1.47, 3.85). The pseudo-likelihood approach produced a similar point estimate of 2.23 (1.42, 3.52) (Table 5).

In sensitivity analyses, inclusion of cases through Brighton criteria levels 4 and 4A increased the RI estimate from the

Table 5
Relative incidence of GBS following pH1N1 vaccination in data pooled across twenty databases from ten countries.

Analysis	Risk window(s)	Exclusions	Brighton criteria levels	Relative incidence	Confidence interval
Primary analysis					
Standard self-controlled case series (SCCS)	Days 1–42	• Databases (DBs) with vaccinated cases only	1–3	2.42	(1.58, 3.72)
Sensitivity analyses					
Standard SCCS	Days 1–42	• DBs with vaccinated cases only	1–4A	2.83	(1.91, 4.19)
Standard SCCS	Days 1–42	• DBs with vaccinated cases only	1–2	2.34	(1.48, 3.70)
Standard SCCS	Days 1–42	• DBs with vaccinated cases only • Cases with reported URI or ILL in the 30 days before diagnosis	1–3	2.88	(1.79, 4.65)
Standard SCCS	Days 1–42	• DBs with vaccinated cases only • Cases with reported GI in the 30 days before diagnosis	1–3	2.73	(1.75, 4.26)
Pseudo-likelihood	Days 1–42	• DBs with vaccinated cases only	1–3	2.23	(1.42, 3.52)
Pseudo-likelihood	Days 1–42	• DBs with vaccinated cases only	1–4A	2.59	(1.72, 3.90)
Vaccinated cases only	Days 1–42	• Unvaccinated cases • Cases vaccinated after diagnosis	1–3	2.37	(1.47, 3.85)
Standard SCCS	Days 1–7*	• DBs with vaccinated cases Only	1–3	2.61	(1.17, 5.84)
	8–21*			3.11	(1.77, 5.47)
	22–42*			1.91	(1.07, 3.42)
	*Modeled Simultaneously				
Vaccinated cases only adjuvanted	Days 1–42	• Unvaccinated cases • Cases vaccinated after diagnosis • Non-adjuvanted vaccine recipients	1–3	1.88	(1.04, 3.41)
Vaccinated cases only Non-adjuvanted	Days 1–42	• Unvaccinated cases • Cases vaccinated after diagnosis • Adjuvanted vaccine recipients	1–3	2.97	(1.13, 7.84)

primary analysis (Brighton criteria 1–3) using the standard SCCS and pseudo-likelihood approaches to 2.83 (1.91, 4.19) and 2.59 (1.72, 3.90), respectively. Limiting included cases to Brighton criteria levels 1 and 2 in analysis using the standard SCCS only slightly reduced the estimate to 2.34 (1.48, 3.70). Adjusting for seasonal influenza vaccine exposure led to no change in the pH1N1-associated estimate, 2.57 (1.68, 3.93) (p value vs. primary analysis $RI=0.85$) and found no increase in relative incidence associated with seasonal influenza vaccine exposure [0.77 (0.28, 2.14)]. Using recorded date of onset as opposed to the date of diagnosis as the index date produced almost no change, likely due to the fact that the risk interval is long (data not shown). The analyses for multiple risk periods following vaccination yielded estimates of 2.61 (1.27, 6.35), 3.11 (2.18, 6.46), and 1.91 (1.31, 3.98) for risk windows of 1–7, 8–21 and 22–42 days following vaccination, respectively. Excluding subjects with a reported history of GBS led to a slightly reduced estimate of 2.27 (1.47, 3.51). Excluding patients with reported influenza like illness or upper respiratory illness in the 30 days before onset of GBS slightly increased the pH1N1-associated estimate to 2.88 (1.79, 4.65). The exclusion of those with reported gastrointestinal illness also increased the vaccine-associated estimate to 2.73 (1.75, 4.26).

In age-stratified analyses, using the standard SCCS showed that the RI in days 1–42 following exposure increased with age: children age < 19 years, the RI was 0.73 (0.16, 3.46), adults age 19–49 years, $RI=1.56$ (0.51, 4.71), age 50–64 years, $RI=2.78$ (1.36, 5.68), and 4.30 (2.18, 8.50) in those 65 and older. These confidence intervals overlap, suggesting a trend rather than a statistically significant difference in relative incidence by age. In standard SCCS analysis stratified by sex, the estimated RI was slightly higher in males, 2.75 (1.65, 4.57) than in females, 2.34 (1.09, 5.04) although the difference was not statistically significant ($p=0.73$).

The estimate of adjuvanted vaccines, performed using the vaccinated cases only approach, yielded a RI estimate of 1.88 (1.03, 3.41) while the non-adjuvanted estimate was higher at 2.97 (1.13, 7.84). This difference was not statistically significant ($p=0.43$).

Because data on cases exposed to vaccines containing the MF-59 adjuvant were limited to one database, we were unable to reliably compare the RI associated with each of the two adjuvants.

3.2. Meta-analytic approach

Results from the meta-analytic approach were similar to those from the pooled analysis but the magnitude of the estimates was decreased (Table 6). The standard SCCS approach produced an estimate of 2.09 (1.28, 3.42) while the vaccinated cases only approach produced an estimate of 2.33 (1.5, 3.62). Analysis of adjuvanted and non-adjuvanted vaccines using the meta-analytic approach yielded RI estimates of 1.65 (0.86, 3.19) and 3.10 (1.70, 5.65), respectively. This difference between adjuvanted and non-adjuvanted exposures was not statistically significant ($p=0.16$).

4. Discussion

We have shown that international collaboration to evaluate serious rare outcomes using a common protocol is feasible and offers some advantages compared to single country or site analyses. Because GBS following vaccination is very rare with reported rates between 0.04 and 0.17 cases per 100,000 vaccinations [22], this combined analysis included a much larger number of cases than any published single country analysis and allowed inclusion of data from sites that did not have enough cases for a site-specific analysis. This provided both increased power to evaluate the outcome but also sufficient power to conduct sub-analyses by vaccine type. Secondly, the availability of data from several countries allowed us to identify a site (Mexico), which had a RI of GBS following pH1N1 vaccine much higher than that at any other site; had the analysis been conducted only in Mexico, conclusions regarding the risk of GBS following vaccination could have been inappropriately generalized to other populations.

We have found an increased risk of GBS following receipt of pH1N1 influenza vaccine. This risk is consistent with the level of risk reported by others. Estimates from single-country studies ranged from 1.05 to 4.70, the majority of which reported statistically significant increased risk [23–32]. Estimates were lower in studies of adjuvanted vaccines (1.05–3.04) [25,31] than in non-adjuvanted vaccines (1.57–4.70) [26–30,32].

Because we knew *a priori* that both adjuvanted and non-adjuvanted vaccines would be used within our study population,

Table 6
Relative incidence of GBS following pH1N1 vaccination in results from twenty databases in ten countries, pooled using a meta-analytic approach.

Analysis	Risk window(s)	Exclusions	Brighton criteria levels	Relative incidence	Confidence interval
Self-controlled case series (SCCS)	Days 1–42	• Databases (DBs) with vaccinated cases only	1–3	2.09	(1.28, 3.42)
Vaccinated cases only	Days 1–42	• Unvaccinated cases excluded • Cases vaccinated after diagnosis	1–3	2.33	(1.50, 3.62)
Vaccinated cases only adjuvanted	Days 1–42	• Unvaccinated cases • Cases vaccinated after diagnosis • Non-adjuvanted vaccine recipients	1–3	1.65	(0.86, 3.19)
Vaccinated cases only non-adjuvanted	Days 1–42	• Unvaccinated cases • Cases vaccinated after diagnosis • Adjuvanted vaccine recipients	1–3	3.10	(1.70, 5.65)

we included a comparative analysis in our analysis plan. In all our primary and sensitivity analyses, the risk of GBS following administration of non-adjuvanted vaccines was significantly elevated. The increased risk found for adjuvanted vaccines was not as consistent. It was significantly elevated in our pooled analyses but became non-significant in the meta-analysis. Moreover, the point estimates of the risk for adjuvanted vaccines were consistently lower than those for non-adjuvanted vaccines in all our analyses. This preliminary finding is reassuring, given general concerns regarding the use of adjuvanted vaccines for influenza, and the fact that these vaccines use less influenza antigen per dose, a useful advantage for pandemic situations during which the amount of available antigen for vaccine production may initially be limited. We hypothesize that one possible explanation for the apparent (non-significant) risk difference between adjuvanted and non-adjuvanted vaccines is the higher amount of influenza antigen in non-adjuvanted vaccines, although other factors could have contributed. Another possible explanation is increased protection from influenza in those who have received adjuvanted vaccines [33] and a subsequent reduction in GBS due to influenza infection, which may have confounded our results. The trend described was seen for both MF-59 and AS03 adjuvanted vaccine. However, only one country in the study (The Netherlands) used MF-59 adjuvanted vaccine, so our ability to compare adjuvants was limited. While we believe our results to be reassuring, they are by no means definitive. Although the difference between the RI estimates for adjuvanted and non-adjuvanted vaccines are not different in our pooled analysis ($p = 0.43$) or in our meta-analysis ($p = 0.16$), the finding warrants further investigation.

Results obtained through the primary analysis (the standard self-controlled case series), the pseudo-likelihood approach, and vaccinated-cases only up to Brighton level 3 were very similar, indicating there was likely little bias introduced if a history of GBS impacted vaccination practices during the 2009–2010 season. Exclusion of Brighton level 3 cases produced very little change in the RI estimate, suggesting lack of a diagnostic bias in the absence of electrophysiological or cerebrospinal fluid data. Inclusion of cases meeting Brighton Criteria levels 4 and 4A increased the relative incidence estimate. Given that in these cases the diagnosis could not be reliably verified, it is unclear if this increase reflects a more complete capture of true GBS cases or the inclusion of non-true cases occurring near the date of vaccination because of diagnosis bias. Future studies in which the time and resources for centralized adjudication are available may be able to answer this question.

Inclusion of the reported date of seasonal influenza vaccination led to little change in the estimate. This could be attributed to minimal risk associated with seasonal influenza vaccine [34], or to under-reporting or confusion regarding whether seasonal or pandemic vaccine that was received leading to misclassification bias. In the analysis of multiple risk periods following vaccination, the increased incidence in the pre-specified high risk period including days 8–21 supports the 1976 finding of highest risk in weeks 2–3 following vaccination [11]. It has been hypothesized that the

risk peaks during this interval because this is when the humoral immune response to the vaccine is highest [35]. Previous findings of increased risk in males as well as increasing risk with increasing age were also supported in our analyses [36]. The background incidence of GBS has also been shown to be about 40% higher in males than in females and to increase with increasing age [37].

It is interesting to note that the exclusion of those subjects who experienced influenza-like illness or gastrointestinal illness resulted in small, non-significant increases in vaccination-associated relative incidence, with p values vs. primary analysis $RI = 0.59$ and 0.70 , respectively. While these non-significant findings appear to be inconsistent with those published by the VAESCO consortium [14] and other studies [27], it is important to note that the SCCS is a methodology based upon an underlying timeline. As we did not have data on dates of influenza-like illness or gastrointestinal illness and could not include these as time-varying covariates, exclusion of those with an infection in the 30 days before diagnosis likely excluded infection-induced cases which should have occurred at similar rates within and outside of the vaccine-associated risk window. This exclusion would therefore serve to increase the estimated relative incidence associated with pH1N1 vaccine exposure.

An additional finding in our study is the increased GBS risk following pH1N1 vaccination with the increased age of vaccine recipients. This may be the result of a lower immune response in older individuals [38] with consequent increased susceptibility to H1N1 infection and subsequent infection-induced GBS in this age group. It may also be related to higher pre-vaccination antibody titers in those previously exposed to H1N1-like viruses [39] potentially leading to greater immune response following vaccination. This possible age effect requires further investigation.

As we have indicated, database-specific analysis of the data contributed by Mexico City produced a very high RI associated with pH1N1 exposure. We hypothesize that this could be due to a longer period of H1N1 circulation in Mexico prior to vaccine introduction with a high likelihood of vaccinated individuals having already been exposed to the H1N1 wild type virus [40,41] which may have induced a greater immune response upon receipt of pH1N1 vaccine due to already elevated antibody titers. Additionally, cases of confirmed H1N1 infection in Mexico tended to have more severe clinical presentation and to result in death more frequently as compared to other countries, perhaps indicating greater virulence of the virus in the early stages of the pandemic [40]. However, control for seasonality in the Mexican database did not reduce the pH1N1 vaccine associated RI estimate. Further studies to elucidate the reason for this much higher risk level in Mexico are warranted.

The meta-analytic approach for pooling of database-specific relative incidences weights those databases with a large degree of variation less heavily than those with less variation. Therefore, databases with only one or two exposed cases and consequently with large standard errors, have much less weight in the combined estimate of 2.09 (1.28, 3.42). While this estimate is attenuated

through the weights applied in the meta-analysis, the relative incidence of GBS in the 42 days following vaccination remains significantly elevated with a confidence interval very similar to that of the pooled estimate of 2.42 (1.58, 3.72). Interestingly, results from stratification of adjuvanted and non-adjuvanted vaccines in the meta-analytic analyses produced a non-significant relative incidence for adjuvanted vaccines and an increased relative incidence for non-adjuvanted vaccines. This can be interpreted as evidence that the trend of increased risk in non-adjuvanted vaccines as opposed to adjuvanted vaccines is not being driven by a set of influential databases.

In this proof of concept, we have learned that international collaborative database studies to evaluate vaccine safety are feasible, even across continents. However, the requirement that participating sites have access to databases from which cases could be ascertained in an unbiased manner limited participation to high and middle income sites with existing infrastructure to conduct active surveillance. However, new vaccines are now being introduced either exclusively in the developing world or concurrently with their release in developed countries. In addition, some newer vaccines, such as the malaria vaccine currently in phase three trials in Africa [42], will mainly target the developing world. These changes indicate the need for improved vaccine safety assessment in low and middle income countries to ensure the safety of new vaccines.

Developing capacity outside of developed countries to evaluate vaccine safety signals that arise out of passive surveillance systems or from other sources is necessary both to assure the safety of the world's vaccine supply and also to prevent vaccine safety scares from undermining successful programs. The only low to middle income country (LMIC) remaining in the final analysis was China, evidencing a need to increase infrastructure in LMIC for ascertainment of vaccination status and adjudication of adverse events following vaccination. In addition, evaluation of very rare event can be facilitated by the increased statistical power that could be achieved through international collaboration.

Although the protocol was common among sites, the degree to which sites were able to review charts and ascertain important covariates such as infections varied from site to site. Future collaborative studies would benefit from centralized case adjudication, improved data quality control and closer supervision of data abstraction and case ascertainment.

This study had several limitations. While the results of the analyses stratified by presence or absence of an adjuvant are intriguing, the use of adjuvanted or non-adjuvanted vaccines was generally homogeneous within each country. Because of this homogeneity, it was not possible to estimate the difference between adjuvanted and non-adjuvanted vaccine associated relative incidence within the same population and it was not possible to separate the effect of the vaccine formulation from the unknown effect of the country and its associated characteristics. Also, the observed association may have been modified by infections, some of which are known to increase the risk of GBS. While we attempted to control for concomitant infections such as influenza like illness and gastrointestinal illness, it was not possible within the limitation of the current study to include these infections as time varying covariates, which would be the ideal approach in the self-controlled case series methodology. Controlling for such time varying covariates may have attenuated the observed associations, as shown in previous studies [43–45]. Additionally, the use of reported seasonal peaks of circulating influenza was a means of estimating seasonal effects across sites but may not have been as accurate as the standard approach of estimating fixed-length periods when analyzing data from one geographic location. Given budget and data-sharing constraints, case verification was performed by each site and quality control was performed on site; a pooled review by a single expert

group was not conducted. In spite of the use of common criteria provided by the Brighton Collaboration, the adjudication process may have varied from site to site.

5. Conclusion

We have demonstrated that multinational studies are feasible and can provide a useful platform to evaluate future vaccine safety concerns especially for rare, serious events. We look forward to the development of a sustainable global infrastructure in both developed and developing countries to meet global needs. The finding of much higher risk in Mexico and our ability to contrast this risk with that found in other countries using data submitted under a common protocol is a strength of this multinational study and supports the need for international collaboration in vaccine safety monitoring.

The significance and consistency of our findings support a conclusion of an association between 2009 (H1N1) vaccination and GBS. Nonetheless, given the rarity of the event the relative incidence found suggests that the vaccine would be responsible for very few excess GBS cases. Although we are not able to estimate attributable risk using the SCCS methodology, we know from other studies that the background risk of GBS is approximately 0.9 [46] cases per one million individuals and that the relative risk associated with the 1976–77 swine influenza vaccination campaign was 7.60 [11]. A relative incidence of 2–3 following vaccination would mean approximately 1–2 excess cases per one million vaccinees. Due to this minimal increase in incidence, our findings do not provide evidence in contradiction of international recommendations for the continued use of influenza vaccines.

This large collaborative multinational study has made possible the generation of a number of new hypotheses related to possible differences in risk of vaccine-associated GBS by age and by the use of adjuvants, which will require further investigation.

Role of the funding source

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Conflicts of Interest

Steven Black is a consultant for Novartis Vaccines and serves on Data and Safety Monitoring Boards for GlaxoSmithKline.

Nigel Crawford received CSL Ltd. support for the investigator-led study from which Australian data was contributed.

Philippe De Wals has received research grant support for other work from GlaxoSmithKline.

Tehri Kilpi has received research grant support for other work from GlaxoSmithKline.

Miriam Sturkenboom is the head of a research unit that occasionally conducts research for pharmaceutical industries, always with the full freedom to publish. These include: Novartis, Eli Lilly, Boehringer Ingelheim and Pfizer. There is no involvement of them in this paper.

Tao Zhang has received research grant support for other work from Pfizer.

All other authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

We further confirm that any aspect of the work covered in this manuscript that involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Appendix A. Global H1N1 GBS Consortium

GBS Working Group: Antonio Addis, Aysha Akhtar, Judith Cope, Robert Davis, Paul Gargiullo, Xavier Kurz, Barbara Law, Grace Lee, Isabelle Sahinovic, and Jerry Tokars.

Almeria (Spain): Pedro Serrano.

Australia: The Victoria – Australia GBS Active investigators: Allen Cheng, Nick Andrews, Pat Charles, Hazel Clothier, Bruce Day, Timothy Day, Peter Gates, Richard MacDonnell, Les Roberts, Victoria Rodriguez-Casero, Tissa Wijeratne, Lynette Kiers, and the Paediatric Active Enhanced Disease Surveillance (PAEDS) network investigators: Christopher Blyth, Robert Booy, Elizabeth Elliott, Michael Gold, Helen Marshall, Peter McIntyre, Peter Richmond, Jenny Royle, Nicholas Wood and Yvonne Zuryski.

Barcelona (Spain): Gonzalo Calvo, Magda Campins, Nuria Corominas, Ferran Torres, Josep Valls, and Anna Vilella.

Department of Defense (US): Donald Dutra, Angelia Eick-Cost, Henry M Jackson Foundation working in support of the Armed Forces Health Surveillance Center, Patrick Garman, Zheng Hu, Henry M Jackson Foundation working in support of the Armed Forces Health Surveillance Center, and Marianne Rigo, Health Care Resolution Services working in support of the Military Vaccine Agency.

Food and Drug Administration (US): Judith Badoo, David Cho, Laura L. Polakowski, Sukhminder K. Sandhu, and Guoying Sun.

Hong Kong: Hoi-Shan Sophelia Chan, Kwok-yin Chan, Raymond Cheung, Yuk-fai Cheung, Sharon Cherk, SK Chuang, Joshua Wai-ming Fok, Bun-hey Fung, Kwai-fu Ko, Ka Wing Lau, Kwok-kwong Lau, Patrick Li, Hui-tung Liu, Shao-haei Liu, Tina Mok, Joanna So, Winnie Wong, and Shun-ping Wu.

Medicare (US): Armen Avagyan, Robert Ball, Dale Burwen, Riley L. Franks, Jonathan M. Gibbs, Rebecca E. Kliman, Garner F. Kropp, Thomas E. MaCurdy, David B. Martin, Laura L. Polakowski, Sukhminder K. Sandhu, Guoying Sun, and Christopher M. Worrall.

Mexico: Dra. Elvira Fuentes Fuentes, Paola Carolina Ojeda González, Jesus Reyna, and Rosa Patricia Vidal Vázquez.

Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Network (US): Robert Ball, Martin Kulldorff, Grace Lee, Tracy A. Lieu, Richard Platt.

Quebec (Canada): Gaston De Serres.

Singapore: Kamilah Jabin, Bee Leng Sally Soh.

Vaccine Adverse Event Surveillance and Communication (VAESCO) Consortium (Europe): Lisen Arnheim-Dahlstrom, Anne Castot, Hester de Melker, Jeanne Dieleman, Jonal Hallgren, Bart Jacobs, Kari Johansen, Piotr Kramarz, Maryse Lapeyre, Tuija Leino, Ditte Molgaard-Nielsen, Mees Mosseveld, Henning K Olberg, Cormac Sammon, Christel Saussier, Martijn Schuemie, Agnes Sommet, Par Sparen, Henrik Svanstrom, Ann Vanrolleghem, and Daniel Weibel.

Valencia (Spain): Javier Diez Domingo (Vaccine Department, Center of Public Health Research (CSISP-FISABIO)), José Luís Micó Esparza (H. Arnau de Vilanova), Rafael M. Ortí Lucas (H. Clínico Universitario), Juan B. Mollar Maseras (H. Universitario La Fe), José Luís Alfonso Sánchez (Consorcio Hospital General Universitario), Mercedes Garcés Sánchez (H. De Manises), Vicente Zanón Viguier (H. Universitario Dr. Peset).

Department of Veterans Affairs (US): Francesca Cunningham, Bharat Thakkar, and Rongping Zhang.

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