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

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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.

☆ *Disclaimer:* The findings, opinions and assertions contained in this document are those of the individual scientific professional participants. They do not necessarily represent the official position of any of the participant's organizations (e.g., government, university, or corporations).

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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.

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 group[2] 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].

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