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The reporting completeness of a passive safety surveillance system for pandemic (H1N1) 2009 vaccines: A capture–recapture analysis

Wan-Ting Huang[a,*], Wei-I Huang[b], Yu-Wen Huang[c,d], Chien-Wen Hsu[c], Jen-Hsiang Chuang[a]

[a] Epidemic Intelligence Center, Taiwan Centers for Disease Control, Taipei, Taiwan
[b] Division of Drug Safety, Taiwan Drug Relief Foundation, Taipei, Taiwan
[c] Division of Drugs and New Biotechnology Products, Taiwan Food and Drug Administration, Taipei, Taiwan
[d] Institute of Biotechnology, College of Bioresources and Agriculture, National Taiwan University, Taipei, Taiwan

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ABSTRACT

Adverse events following pandemic (H1N1) 2009 vaccines ("2009 H1N1 vaccines") in Taiwan were passively reported to the National Adverse Drug Reaction Reporting System. To evaluate the completeness of spontaneous reporting, cases of death, Guillain–Barré syndrome (GBS), convulsion, Bell's palsy, and idiopathic thrombocytopenic purpura (ITP) after 2009 H1N1 vaccination that occurred between November 1, 2009 and August 31, 2010 were selected from the National Adverse Drug Reaction Reporting System (NADRRS) database and an additionally constructed nationwide large-linked database (LLDB), and matched on a unique personal identifier, date of vaccination (within ±7 days), and date of diagnosis (within ±7 days). Overall, matches occurred between the two data sources included 21 for death, 5 for GBS, 19 for convulsion, 22 for Bell's palsy, and 5 for ITP. The Chapman capture–recapture estimated spontaneous reporting completeness within 0–42 days of vaccination was 4% for death, 71% for GBS, 3% for convulsion, 9% for Bell's palsy, and 15% for ITP. For the interval ≥43 days after vaccination, reporting completeness was 0.1% for death, 14% for GBS, 0.1% for convulsion, <0.1% for Bell's palsy, and 0% for ITP. The estimated-to-expected ratio for Bell's palsy in the interval 0–42 days after vaccination was 1.48 (95% CI 1.11–1.98). Reporting completeness was higher for GBS than other adverse events after 2009 H1N1 vaccination. Linking the NADRRS to existing data sources in a capture–recapture analysis can be considered as an alternative to enhance Taiwan's postlicensure safety assessment of other routine vaccines. Nevertheless, the possibility of an increased risk for Bell's palsy detected by capture–recapture analyses needs further evaluation by controlled studies.

1. Introduction

On November 1, 2009, Taiwan began a nationwide pandemic (H1N1) 2009 vaccination ("2009 H1N1 vaccine") program using an inactivated vaccine without adjuvant (Adimmune Corporation, Taichung, Taiwan) and an MF59®-adjuvanted vaccine (Novartis Vaccines and Diagnostics, Sovicille, Italy). The government concurrently implemented a multifaceted postlicensure surveillance strategy to facilitate early detection of any safety problems. Part of the safety monitoring activities had relied on passive surveillance systems to detect unexpected or clinically significant adverse events after 2009 H1N1 vaccination [1].

Although passive surveillance systems can detect rare adverse events in a cost-effective and timely manner [2], underreporting of adverse events following immunization occurs and the magnitude varies depending on the severity of the event, temporal proximity to vaccination, and awareness of and obligation to report particular adverse events [3–5]. Published studies from the U.S. Vaccine Adverse Event Reporting System have suggested that reporting completeness can range from less than 1% for rash after measles, mumps, and rubella vaccine, 47% for intussusception after RotaShield® vaccine (Wyeth Laboratories, Marietta, PA), to 68% for vaccine-associated polio after oral poliovirus vaccine [3,4]. Therefore, information on reporting completeness is essential to evaluate an association between a vaccine and a reported adverse event, but this data is not routinely available [6].

The capture–recapture method has been applied in epidemiology to estimate the size of a population when a census is not feasible or impossible to conduct [7–9]. The validity of the estimates relied on four basic assumptions: the population being estimated is closed, the individuals can be accurately matched, the sources

* Corresponding author at: Epidemic Intelligence Center, Taiwan Centers for Disease Control, 2F, 6 Linsen S. Road, Taipei 10050, Taiwan.
Tel.: +886 2 2395 9825x3693; fax: +886 2 3393 6044.
E-mail addresses: muagi@cdc.gov.tw, huangwt@ntu.edu.tw (W.-T. Huang).

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should be independent, and all individuals should have the same probability of being ascertained by a capturing source [7,8]. We used the capture–recapture method to (1) assess the reporting completeness of Taiwan's passive safety surveillance system for selected adverse events after 2009 H1N1 vaccines; and (2) evaluate the risks of these events for the biologically plausible postvaccination risk intervals.

2. Material and methods

2.1. Passive safety surveillance system for 2009 H1N1 vaccines

The national passive safety surveillance in concert with the 2009 H1N1 vaccination program was collaboratively managed by Taiwan Centers for Disease Control (TCDC) and Taiwan Food and Drug Administration [1]. Patients or their parents, healthcare providers, manufacturers, and others were encouraged to report any health event that occurs at any time interval to the National Adverse Drug Reaction Reporting System [10], regardless of causality. Medical records were sought and reviewed for reports coded as serious by regulatory definitions [10], reports suggestive of adverse events of special interest (AESIs), and reports involving pregnancy-specific adverse events. The AESIs included Guillain–Barré syndrome (GBS), convulsion, Bell's palsy, idiopathic thrombocytopenia (ITP), and other outcomes [11]. We used the Brighton Collaboration case definition to verify the diagnoses for reports suggestive of GBS [12].

2.2. Data linkage for 2009 H1N1 vaccine safety studies

An additional safety infrastructure that TCDC developed to evaluate the safety of 2009 H1N1 vaccines is the nationwide large-linked database (LLDB) on 2009 H1N1 vaccinations and selected health outcomes [1]. In Taiwan, medical institutions are required to report death through the National Death Certification System within 7 days after a death certificate is issued [13]. The government-organized National Health Insurance (NHI) enrolls more than 99% of the citizens and contracts with 92% of the healthcare facilities in the country [14]. Computerized data on all-cause mortality and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnoses of GBS (code 357.0), convulsion (codes 345*, 780.3, 780.31, 780.39), Bell's palsy (code 351.0), and ITP (codes 287.3, 287.31, 287.5) were prospectively collected from the National Death Certification System and NHI databases. The 2009 H1N1 vaccination data were collected from the NHI prescription database or manually computerized from paper records, depending on whether the vaccine was administered at provider offices or nontraditional settings [1]. The vaccine and outcome databases were linked by a unique identifier assigned to each Taiwan resident. As of August 31, 2010, this LLDB had recorded 3.5 million (62%) of the 2009 H1N1 vaccine doses administered to the Taiwan population (Appendix A).

2.3. Data matching and capture–recapture analysis

We selected all cases of death, GBS, convulsion, Bell's palsy, and ITP after 2009 H1N1 vaccination that occurred between November 1, 2009 and August 31, 2010 from the National Adverse Drug Reaction Reporting System (NADRRS) database and LLDB. Because persons less than 9 years of age may receive two vaccine doses and each vaccine recipient may experience the same AESI multiple times, we matched the two data sources on three variables: the unique personal identifier, date of vaccination, and date of disease onset/diagnosis/death. The dates of vaccination and onset/diagnosis/death in the two data sources were allowed to differ by up to 7 days to account for recall bias and time required from disease onset to diagnosis in the passive surveillance reports.

For each outcome, we estimated the total number of cases after 2009 H1N1 vaccination using the Chapman capture–recapture methods [15]. The Chapman estimates of the true number of cases (N) is calculated as $N = [(b+1)(c+1)/(a+1)] - 1$, in which a denotes the number of cases captured in both data sources, b denotes the number of cases captured in the NADRRS, and c denotes the number of cases captured in the LLDB. We further calculated variances for Chapman estimates ($Var[N]$) using the formula as $Var(N) = [(b+1)(c+1)(b-a)(c-a)]/[(a+1)^2(a+2)]$ [16], and obtained the 95% variance-based confidence intervals (CIs) of N by log-transformations. To evaluate the impact of the duration between 2009 vaccination and the event on disease ascertainment, we also recalculated the capture–recapture estimates of the total number of cases for the intervals 0–42 and ≥43 days after vaccination. Reporting completeness was calculated as the ratio of the number of NADRRS reports to the estimated true number of cases after vaccination.

2.4. Estimated versus expected analysis

The background incidence of GBS, convulsion, Bell's palsy, and ITP for the general population at 6 months to 17 years and ≥18 years of age in Taiwan had been published elsewhere [1,17]. The age-specific mortality rates for persons aged 0–6, 7–17, and ≥18 years were calculated using the 2010 mortality statistics data [18]. By applying these background incidence to the number of 2009 H1N1 vaccine doses administered to each age group (Appendices A and B), we calculated the number of coincident events that might be expected as background rate events for the intervals 0–2, 3–42, and 43–85 days (death); 0–7 days (convulsion); or 0–42 days (GBS, Bell's palsy, and ITP) after receipt of a 2009 H1N1 vaccine. The expected number of coincident events was compared with the Chapman capture–recapture estimated true number of cases that should have occurred within the same postvaccination risk interval.

All analyses were performed by using SAS, version 9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Chapman capture–recapture estimates

We identified 52 deaths from the NADRRS and 4544 deaths from the LLDB; 21 matches occurred between the two data sources (Table 1). The proportions of deaths that occurred in the first 0–42 days after vaccination differed between the NADRRS ($n = 36$, 69%) and LLDB ($n = 459$, 10%). The Chapman estimate of the total number of deaths after 2009 H1N1 vaccination was 10,948 (95% CI 8015–14,955). Completeness of spontaneous reporting for any death after vaccination was 4% and 0.1% for the intervals 0–42 and ≥43 days, respectively.

Six cases of GBS, 45 cases of convulsion, 48 cases of Bell's palsy, and 18 cases of ITP after vaccination were identified in the NADRRS and 13 cases of GBS, 4523 cases of convulsion, 1427 cases of Bell's palsy, and 237 cases of ITP were identified in the LLDB (Table 2). Case matches occurred between the two data sources included 5 for GBS, 19 for convulsion, 22 for Bell's palsy, and 5 for ITP. We estimated the total number of cases after 2009 H1N1 vaccination to be 15 (95% CI 12–19) for GBS, 10,404 (95% CI 7548–14,340) for convulsion, 3041 (95% CI 2278–4061) for Bell's palsy, and 753 (95% CI 411–1379) for ITP (Table 3). The spontaneous reporting completeness in the 0–42 days after vaccination was 71% for GBS, 3% for convulsion, 9% for Bell's palsy, and 15% for ITP. For the interval ≥43 days after vaccination, reporting completeness was 14% for GBS, 0.1% for convulsion, <0.1% for Bell's palsy, and 0% for ITP.