| **Evidence Table 5. Postmarketing studies: Mixed population** | | | | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, Year, Study Design** | **Population studied** | **Vaccines included** | **Selection Bias** | **Attrition, non-response** | **Participation bias** | **Ascertainment of vaccination status** | **Ascertainment of health outcome** | **Analysis conducted** | **Adjusted for these potential confounders** | **Period data collected** | **Study funder** | **Primary results regarding vaccine** | **Any risk factor findings** | **Comment** |
| Baxter, et al. 2013,[55](#_ENREF_55) Case-centered and cohort | N=415 cases;  Location=California;  Age=48.5 years (mean), 5-87 years (range);  Setting=Kaiser Permanente Northern California (KPNC) | Influenza (TIV), 23-valent pneumococcal polysaccharide, IPV, Tdap, I-typhoid, Hepatitis A, Hepatitis B, Td | Medical reviewer aware of study hypothesis, may have influenced case selection | Of the 892 potential cases for which medical records were available, 114 were rejected by the MRAs, and 242 were rejected by the reviewing neurologist, either as incompatible with GBS or because of not enough information or no weakness found in chart review. Of the 550 confirmed cases, 415 were incident within the study period, and patients were KPNC members at the time of GBS onset, so were eligible for inclusion in the analysis | Not discussed | Medical record review | Medical record review | Case-centered: Logistic regression model with a case-centered specification  Cohort: Poisson regression | Case-centered: Age and sex matching for expected odds  Cohort: age | 1995-2006 | This work was supported by a subcontract with America's Health Insurance Plans under contract 200-2002-00732 from the CDC, as a part of the Vaccine Safety Datalink. | Table 2. Odds Ratio of Vaccination in a 6- or 10-Week Risk Interval Before Onset of Guillain-Barre Syndrome, Using a Case-Centered Analysis Design  OR, 95% CI, p=value  6-week Risk Interval  IPV: 7.19 (0.18-281.03), 0.245  Tdap: None (0.16 to NE), 0.249  PPV-23: 0.72 (0.11-2.87), 0.722  Hep A: 2.22 (0.30-10.63), 0.36  Hep B: 0.43 (0.02-2.56), 0.455  Td: 1.43 (0.33-4.56), 0.558  TIV: 1.11 (0.39-3.08), 0.83  10-week Risk Interval  IPV: 4.15 (0.11-163.38), 0.39  Tdap: None (.09 to NE), 0.377  PPV-23: 0.44 (0.07-1.72), 0.281  Hep A: 2.00 (0.39-8.74), 0.366  Hep B: 0.24 (0.01-1.46), 0.15  Td: 1.14 (0.32-3.29), 0.783  TIV: 0.99 (0.33-2.70), 0.991  Table 3. Number of Guillain-Barre Syndrome Cases and Crude Rates per 100 000 Person-Years (Cohort analysis)  Relative rate, 95% CI, p=value  1.3, (0.75-2.26), 0.35 | None |  |
| Crawford, et al., 2012[59](#_ENREF_59), Self-controlled case series | N=44  Location=Victoria, Australia  Age=48 (median); 7-95 years (range)  Setting=An active surveillance system for GBS  was established in 10 hospitals in Victoria | Monovalent H1N1 vaccine  (Panvax, CSL Limited)  TIV (Fluvax, CSL Limited; Vaxigrip, Sanofi Pasteur; Influvac, Abbott) | GBS cases only | Sixty-six cases of probable GBS were identified in the 12-month study period. Three cases were excluded, leaving 63 GBS episodes in  62 individuals. Of these, nine were excluded, as on review they did not meet diagnostic criteria for GBS. Four further confirmed cases were excluded, as the date of onset of symptoms predated the availability of  the monovalent H1N1 vaccine. In six cases, data were only available from  the hospital medical record (ie, neither the patient nor primary care physician were available). These cases  with incomplete immunisation histories were excluded from the primary  analysis, leaving 44 cases. | Not discussed | Research assistants obtained  informed consent once “possible” GBS cases were identified. A detailed  immunisation history was then obtained from study participants and their primary health care physician (following  patient consent) |  | Standard and pseudolikelihood methods | None, self-controlled design | September 30, 2009 to September 30, 2010 | This study was funded by CSL Ltd as part of postmarketing surveillance, with financial support for study nurses at each site. | Table 3: Pandemic (H1N1) 2009 influenza A immunisation and Guillain-Barré syndrome: relative incidence (RI) estimates from the self-controlled case series with a 42-day postvaccination risk window  Base: 3.41 (0.78–14.97)  No seasonal trivalent influenza vaccine: 3.39 (0.77–14.91)  No period adjustment: 2.92 (0.75–11.31)  Three 2-week periods  0–13 days: 3.74 (0.41–34.05)  14–27 days: 3.35 (0.38–29.64)  28–41 days: 3.19 (0.35–28.67)  Only Brighton level 1–2 cases: 3.99 (0.82–19.55)  Include unconfirmed cases: 2.71 (0.62–11.85)  Include incomplete vaccine history: 3.25 (0.75–14.21)  Include incomplete vaccine history and second episode: 3.34 (0.76–14.59)  Include all: 2.25 (0.54–9.37) | None |  |
| Irving, et al. 2013,[236](#_ENREF_236)Case-control | N=486 (243 cases, 243 controls);  Location=US;  Age=18-44 years;  Setting=six health care organizations in the Vaccine Safety Datalink | Influenza (TIV) | No data on possible case ascertainment or vaccine administration differences across health plans | Three hundred eighty-six potential cases of spontaneous abortion were identified electronically; 255 cases were confirmed by medical record review and matched to control group participants. After excluding six pairs with unknown vaccination status, one pair with an invalid LMP, and five pairs with fetal demise at less than 5 weeks of gestation, 243 pairs were included in the final analysis. | Not discussed | Medical record review | Medical record review | Conditional logistic regression | Maternal age, health care utilization, maternal diabetes, parity | Autumn of 2005 or 2006 | Funded through a subcontract with America’s Health Insurance Plans (AHIP) under contract 200-2002-00732, from the Centers for Disease Control and Prevention (CDC). | Table 3. Odds of Influenza Vaccination in Cases of Early Pregnancy Loss in Varying Exposure Windows as Compared With Control Group Participants  Adjusted ORs, 95% CI, p-value  Primary analysis  Exposed 1-28 d before reference date:  1.23 (0.53-2.89), 0.63  Exposed more than 28 d before reference date:  1.24 (0.54-2.86), 0.61  Secondary analysis  Exposed while pregnant  0.80 (0.36-1.78), 0.58  Exposed before pregnant  2.34 (0.86-6.33), 0.10 | None |  |
| Isai et al., 2012[61](#_ENREF_61), cross-sectional in that both exposure and outcome are ascertained at the same time , but outcomes are ascertained following vaccination in EudraVigilance database | N=50,221 adverse events;  Location=European Union;  Age=Unknown;  Setting=EudraVigilance database | Flu vaccines: Cantgrip, Celtura, Celvapan, Fluval, Focetria, Pandemrix, Panenza | Unsure if EudraViligance contains AEs from all authorized medicines | Not discussed | Not discussed | Database review | Database review | No statistical comparisons | None | October 1, 2009 to 31 December 31, 2010 | Not reported | Analysis 1 included all cases as reported.  Analysis 2 used cases assessed as certain, probable or possible according to WHO Causality assessment and available Brighton Collaboration definitions  Using analysis 1, the reporting ratio calculated as the percentage of autoimmune ADRs amongst all reported ADRs shows comparable results for nonadjuvanted (0.94% [0.64–1.24]) and adjuvanted (0.60% [0.53–0.67]) vaccines.  The calculation using analysis 2 (restricted analysis) included 15 cases of autoimmune disorders for nonadjuvanted vaccines and121 cases for adjuvanted ones. The reporting ratio was 0.37% (0.18–0.56) and 0.26% (0.22–0.31), respectively.  For the calculation of reporting rates using the estimated number of vaccinees as the denominator, analysis 1 resulted in a reporting rate of 9.98 (6.81–13.16) per million for nonadjuvanted vaccines and of 6.87 (6.06–7.68) per million for adjuvanted vaccines.  Using analysis 2, the reporting rates were respectively 3.94 (1.95–5.94) and 3.01 (2.47–3.55) per million. | None |  |
| Klein, et al. 2012,[203](#_ENREF_203),Retrospective cohort | N=189,629;  Location=California;  Age=9-26 years;  Setting=Kaiser Permanente in California | Quadrivalent human papillomavirus vaccine (HPV4) | Entire population | Not discussed | Not discussed | Electronic medical record review | Electronic medical record review | Conditional logistic regression | None | 2006-2008 | This study was funded by Merck & Co. | Table 2. Summary of HCUP Categories With Elevated ORs Following HPV4 Vaccination in the Combined ED/Hospital Setting, All Doses Combined  Viral infection  Days 1-60 Risk Interval: 1.1 (0.9-1.3)  Days 1-14 Risk Interval: 1.5 (1.2-2.0)  Attention-deficit, conduct, and disruptive behavior  disorders  Days 1-60 Risk Interval: 1.5 (1.2-2.0)  Days 1-14 Risk Interval: 1.5 (1.0-2.3)  Disease of nervous system and sense organs  Days 1-60 Risk Interval: 1.0 (0.9-1.1)  Days 1-14 Risk Interval: 1.2 (1.0-1.3)  Ear conditions  Days 1-60 Risk Interval: 1.2 (1.0-1.5)  Days 1-14 Risk Interval: 1.5 (1.1-1.9)  Disorders of peripheral nervous system  Days 1-60 Risk Interval: 2.1 (1.0-4.2)  Days 1-14 Risk Interval: 2.1 (0.8-5.7)  Diseases of circulatory system  Days 1-60 Risk Interval: 1.1 (1-1.3)  Days 1-14 Risk Interval: 1.2 (1.0-1.5)  Diseases of heart  Days 1-60 Risk Interval: 1.1 (0.1-1.3)  Days 1-14 Risk Interval: 1.3 (1.0-1.6)  COPD and bronchiectasis  Days 1-60 Risk Interval: 1.5 (1-2.2)  Days 1-14 Risk Interval: 1.8 (1.1-3.2)  Asthma  Days 1-60 Risk Interval: 1.2 (1.1-1.4)  Days 1-14 Risk Interval: 1.21 (1-1.47)  Disease of skin and subcutaneous tissue  Days 1-60 Risk Interval: 1.0 (0.8-1.1)  Days 1-14 Risk Interval: 1.5 (1.2-1.9)  Skin and subcutaneous tissue infections  Days 1-60 Risk Interval: 1.1 (0.9-1.4)  Days 1-14 Risk Interval: 1.8 (1.3-2.4)  Cellulitis and abscess  Days 1-60 Risk Interval: 1.1 (0.8-1.4)  Days 1-14 Risk Interval: 1.6 (1.2-2.3)  Diseases of musculoskeletal system and connective  tissue  Days 1-60 Risk Interval: 1.1 (1-1.2)  Days 1-14 Risk Interval: 1.2 (1.0-1.4)  Spondylosis, disc intervertebral disorders, back  problems  Days 1-60 Risk Interval: 1.1 (0.9-1.3)  Days 1-14 Risk Interval: 1.4 (1.0-1.8)  Congenital anomalies  Days 1-60 Risk Interval: 1.6 (1.1-2.3)  Days 1-14 Risk Interval: 2.5 (1.6-4.0)  Other congenital anomalies  Days 1-60 Risk Interval: 1.8 (1.1-3.0)  Days 1-14 Risk Interval: 3.6 (2.0-6.3)  Fever of unknown origin  Days 1-60 Risk Interval: 1.1 (0.9-1.4)  Days 1-14 Risk Interval: 1.5 (1.0-2.1)  Lymphadenitis  Days 1-60 Risk Interval: 1.0 (0.6-1.8)  Days 1-14 Risk Interval: 2.3 (1.2-4.4)  Diabetes mellitus  Days 1-60 Risk Interval: 2.2 (1.1-4.4)  Days 1-14 Risk Interval: 2.5 (1.0-6.4)  Attention-deficit disorder  Days 1-60 Risk Interval: 1.7 (1.1-2.8)  Days 1-14 Risk Interval: 2.1 (1.1-4.1)  Personality disorders  Days 1-60 Risk Interval: 1.8 (0.9-3.4)  Days 1-14 Risk Interval: 2.8 (1.3-6.4)  Disorders of teeth and jaw  Days 1-60 Risk Interval: 1.1 (0.6-2.1)  Days 1-14 Risk Interval: 2.6 (1.2-5.6)  Congenital anomalies  Days 1-60 Risk Interval: 1.7 (1.0-2.8)  Days 1-14 Risk Interval: 2.7 (1.4-5.3)  Other congenital anomalies  Days 1-60 Risk Interval: 2.3 (1.1-5.0)  Days 1-14 Risk Interval: 5.1 (2.2-11.9) | None |  |
| Lee et al. 2011, Self-controlled design or a current versus historical comparison[60](#_ENREF_60) | N=4,512,366 flu doses in eight U.S. managed care organizations;  Age=6 mos to >=65 years; | H1N1 monovalent inactivated (MIV) and live, attenuated (LAMV) vaccines separate from seasonal trivalent inactivated (TIV) and live, attenuated (LAIV) influenza vaccines | Comprehensive population group | Not discussed | Not discussed | Medical record review | Medical record review. For Guillain–Barrésyndrome (GBS), all cases were adjudicated by at least two neurologists | SCRI: maximized sequential probability ratio test (MaxSPRT) Current versus historical comparison: Either the Poisson-based MaxSPRT or the Poisson-based conditional MaxSPRT (CMaxSPRT) was used logistic regression | Case-centered logistic regression: case date, age group, gender, and site. | 2009-2010 | Centers for Disease Control | No significant associations were noted during sequential analyses for Guillain-Barré syndrome, most other neurologic outcomes, and allergic and cardiac events. For MIV, a statistical signal was observed for Bell's palsy for adults aged >=25 years on March 31, 2010, using the self-controlled approach. Subsequent analyses revealed no significant temporal cluster. Case-centered logistic regression adjusting for seasonality demonstrated an OR for Bell's palsy of 1.26 (95% CI=0.97, 1.63). | None |  |
| Matheson et al. 2010, Prospective cohort[247](#_ENREF_247) | N=5,556 members of  Tasmanian Longitudinal Health Study, Age=7 to 44 yrs; | Diphtheria, Tetanus, Pertussis, Polio, Smallpox | Representative sample of Tasmania residents | At this follow-up, 88.1% (n = 7,562) were traced. A postal survey was sent to all traced participants and a response rate of 78.4% (n = 5,729) was achieved. This analysis is based on questionnaire data collected in 1968 and follow-up in 2004. School medical record data were available for 5,556 (97%) of 5,729. | Not discussed | School medical records which contained parent reported immunization history | Questionnaire - self-report | Multivariable regression models were used to estimate relative risks while adjusting for confounders. Cox regression was used to estimate the association between childhood immunizations and asthma developing after the age of 7 yrs | Multivariate: Sex, birthplace and history of bacterial infection, parental smoking, and parental asthma, history of viral infection, birth order and social class in 2004. We also investigated any eﬀect modiﬁcation related to having childhood asthma by age 7 yrs.  Cox: sex, bacterial infections, birth order and social class in 1968. The Cox model with asthma onset after the age of 21 yrs as the outcome was also adjusted for adult smoking, and socio-economic status in adult life | 2004 | National Health and Medical Research Council of Australia, Cliﬀord Craig Foundation of Tasmania and Victorian & Tasmanian Asthma Foundations | Associations with immunization (Adjusted RR) Current asthma at age 44  Diphtheria: 0.93 (0.71, 1.22) Tetanus: 1.05 (0.81, 1.38) Pertussis: 0.87 (0.68, 1.12) Polio: 0.92 (0.69, 1.24) DTP: 0.92 (0.73, 1.16) Eczema by age 44  Diphtheria: 1.05 (0.92, 1.20) Tetanus: 1.07 (0.94, 1.21) Pertussis: 0.99 (0.88, 1.12) Polio: 1.03 (0.89, 1.18) DTP: 1.04 (0.93, 1.16) Food allergy by age 44  Diphtheria: 1.09 (0.81, 1.47) Tetanus: 1.03 (0.78, 1.35) Pertussis: 1.11 (0.84, 1.47) Polio: 1.11 (0.80, 1.53) DTP: 1.02 (0.80, 1.30) Hay fever by age 44  Diphtheria: 1.02 (0.92, 1.12) Tetanus: 1.03 (0.94, 1.13) Pertussis: 1.03 (0.93, 1.13) Polio: 1.04 (0.93, 1.16) DTP: 1.05 (0.97, 1.15)  Association between immunization and incident asthma from age 8 to age 44 (Adjusted HR, 8-44 years) Diphtheria: 1.07 (0.83,1.39) Tetanus: 1.13 (0.88,1.45) Pertussis: 1.04 (0.82,1.32) Polio: 1.19 (0.89,1.60) DTP: 1.05 (0.85,1.31) | None | Giles GG, Lickiss N, Gibson HB. Respiratory symptoms in Tasmanian adolescents: a follow up of the 1961 birth cohort. Aust N Z J Med 1984: 14: 631–7.  Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. BMJ 1994: 309: 90–3. |
| Nakajima et al. 2007, Prospective cohort[248](#_ENREF_248) | N=8443; Location=Tasmania; Age=7-30 years; Setting=Primary schools (Tasmanian Asthma Study, a prospective population-based cohort study which started in 1968) | Diphtheria, tetanus, pertussis, polio (Study notes in Australia, there were two forms of polio vaccine—the Salk (injected polio vaccine) which was commonly used before the introduction of Sabin (oral polio vaccine) in 1966. | Children born in the UK, US, New Zealand, Canada or South Africa were more likely to have been immunized against diphtheria, pertussis and polio than those born in Tasmania.  Study notes parental health attitudes might have affected both seeking a diagnosis of an atopic condition and having their children vaccinated, which might have contributed to the risk of atopic conditions being associated with vaccination. Such a detection bias is more likely with eczema, given that eczema is more likely to develop in early childhood, during which timeframe childhood immunizations are given. The observed associations may also suggest that there is a higher likelihood of childhood immunizations in those already at greater risk of atopic disease. However the authors did not believe this to be the case.  Potential recall biases and differential misclassification of exposure | Subjects were lost to follow-up at each stage of the study. In 1968 99% response rate; In 1974 87.2% response rate; In 1991 74.7% response rate | Not discussed | School medical records filled out by parents | Parental report | Multiple logistic regression | Sex, birthplace, history of bacterial infection, parental smoking, parental asthma, history of viral infection, birth order and history of pneumonia  Asthma after 13 years: Sex, parental asthma  Eczema after 7 years: Age 7 years asthma status, sex, parental asthma, parental smoking  Food allergy after 7 years: Age 7 years asthma status, sex, parental smoking  Hay fever after 7 years: Age 7 years asthma status, sex, parental smoking, feeding in 1st 3 months | Authors collected information from the 1968 survey and the 1974 and 1991 follow-up studies. | The 1968 and 1974 studies were funded by the Tasmanian Asthma Foundation and the 1991 study was funded by the National Health Medical Research Council. Computerization of the 1974 study was funded by the Victorian Asthma Foundation. | OR (95% CI) for asthma by age 7 years Diphtheria: 1.33 (1.06-1.68), p=0.01 Tetanus: 1.16 (0.94-1.43), p=0.16 Pertussis: 1.19 (0.96-1.47), p=0.11 Polio: 1.05 (0.83-1.32), p=0.69  OR (95% CI) for asthma by age 13 years Diphtheria: 1.28 (0.98-1.66), p=0.07 Tetanus: 1.18 (0.89-1.55), p=0.24 Pertussis: 1.11 (0.91-1.37), p=0.31 Polio: 1.03 (0.79-1.35), p=0.84  OR (95% CI) for eczema by age 7 years Diphtheria: 1.53 (1.13-2.07), p=0.01 Tetanus: 1.53 (1.15- 2.04), p=0.01 Pertussis: 1.46 (1.10-1.93), p=0.01 Polio: 1.36 (1.00-1.87), p=0.05  OR (95% CI) for food allergy by age 7 years Diphtheria: 1.47 (1.04-2.07), p=0.03 Tetanus: 1.26 (0.93-1.71), p=0.14 Pertussis: 1.39 (1.01-1.91), p=0.04 Polio: 1.44 (1.00-2.07), p=0.05 OR (95% CI) for hay fever by age 7 years Diphtheria: 1.20 (0.94-1.53), p=0.15 Tetanus: 1.05 (0.84-1.31), p=0.67 Pertussis: 1.10 (0.88-1.38), p=0.42 Polio: 0.88 (0.69-1.12), p=0.30 OR (95% CI) for asthma after age 13 years Diphtheria: 0.58 (0.26-1.27), p=0.17  Tetanus: 0.79 (0.32-1.96), p=0.61 Pertussis: 0.57 (0.30-1.09), p=0.09 Polio: 0.50 (0.22-1.10), p=0.08 OR (95% CI) for eczema after age 7 years Diphtheria: 0.68 (0.36-1.29), p=0.24  Tetanus: 0.76 (0.38-1.52), p=0.44 Pertussis: 0.57 (0.35-0.93), p=0.03 Polio: 0.76 (0.39-1.48), p=0.43 OR (95% CI) for food allergy after age 7 years Diphtheria: 1.50 (0.81-2.79), p=0.20 Tetanus: 0.98 (0.54-1.75), p=0.94  Pertussis: 0.88 (0.57-1.35), p=0.55 Polio: 1.02 (0.57-1.83), p=0.94 OR (95% CI) for hay fever after age 7 years Diphtheria: 1.19 (0.75-1.89), p=0.45  Tetanus: 1.09 (0.67-1.78), p=0.72 Pertussis: 0.96 (0.67-1.38), p=0.83 Polio: 0.78 (0.47-1.28), p=0.32 | Not reported |  |
| Ray et al. 2011, Prospective cohort and case-control[249](#_ENREF_249) | N=1,660 (415 Rheumatoid arthritis cases, 1245 controls) Location=CA; Age=15-59 years; Setting=Kaiser Permanente Northern CA members | Hepatitis B, influenza | Cases and controls from the same HMO population. Cases more likely to be African American or Latino than controls. Controls more likely to have missing data for race. | None noted | Not discussed | Database record review and medical record review | Medical record review | Cohort study: Poisson regression.  Case control: conditional logistic regression | Cohort study: adjusted for age, sex, race, number of health care visits within 1 year  Case-control: sex, race, number of utilization visits. Matched on age and utilization | 1997 to 1999 | Centers for Disease Control and Prevention Vaccine Safety Datalink Project | RR from cohort study 90 Day Exposure Interval Hepatitis B: 1.44 (0.46, 4.51), p=0.53 Influenza: 0.72 (0.45, 114), p=0.16 180 Day Exposure Interval Hepatitis B: 1.67 (0.74, 3.77), p=0.22 Influenza: 1.36 (1.03, 1.80), p=0.03 365 Day Exposure Interval Hepatitis B: 1.23 (0.58, 2.63), p=0.59 Influenza: 1.34 (1.06, 1.69), p=0.01 OR from case-control study 90 Day Exposure Interval Hepatitis B: 1.5 (0.4, 5.2), p=0.55 Influenza: 0.7 (0.4, 1.2), p=0.14 180 Day Exposure Interval Hepatitis B: 2.0 (0.8, 5.1), p=0.14 Influenza: 1.1 (0.8, 1.6), p=0.57 365 Day Exposure Interval Hepatitis B: 1.4 (0.6, 3.1), p=0.39 Influenza: 1.1 (0.9, 1.5), p=0.43 730 Day Exposure Interval Hepatitis B: 1.0 (0.5, 2.1), p=0.91 Influenza: 1.1 (0.8, 1.4), p=0.59 | Not reported |  |
| Siberry et al. 2010,[250](#_ENREF_250) Phase I/II open label safety and immunogenicity trial with no control group | N=305 HIV positive adolescents; Age=11–24 years; Setting=27 US sites of the IMPAACT network | MCV4 | Eligibility criteria for were: (1) age of 11 to 24 years; (2) on stable antiretroviral therapy (ART) or not receiving ART for at least 90 days prior to vaccination; (3) no personal or family history of Guillain–BarréSyndrome (GBS); and (4) no meningococcal polysaccharide vaccine within last 2 years and no MCV4 at any time | 324 original participants, 305 final | Subjects included in the immunogenicity analysis (n = 305) were similar to those not included except that those not included were less likely to be receiving HAART | Vaccines were administered by authors | Observation and self-report | Multivariable logistic regression | Not reported | Between July and October of 2007 | National Institute of Allergy and Infectious Diseases cooperative agreement #5 U01 AI41110 with the Pediatric AIDS Clinical Trials Group (PACTG) and #1 U01 AI068616 with the IMPAACT Group | No subjects had GBS. Two subjects had AEs grade >= 3 or higher. Authors ruled out any possible association with MCV4 vaccine. | Lower CD4 count more likely to experience AEs. |  |
| Tokars et al. 2012, Self-controlled analyses[251](#_ENREF_251) | N= 379 Guillain-Barré Syndrome (GBS) patients; Location=10 US states/metro areas; Age=1-84 years;  From Centers for Disease Control and Prevention Emerging Infections Program active, population-based surveillance dataset | H1N1 vaccines | Biases if cases differed from the general population in terms of for example being more likely to be vaccinated | None | Not reported | Self-report or medical record | Active ascertainment through network of neurologists, hospital discharge data and review of medical charts | Conditional Poisson regression | Tested interactions: age group, sex, mode of administration (injected, intra-nasal, or unknown), whether seasonal influenza vaccine had been received in the 42 days prior to H1N1 vaccine receipt, and the EIP site reporting the data | 2009-2010 | Not reported | Relative risk Overall: 2.1 (1.2, 3.5) | RRs Age (years) 0.5–24: 3.0 (1.0, 9.1) 25–49: 2.0 (0.7, 5.5) 50–64: 2.1 (0.8, 5.6)  ≥65: 1.5 (0.5, 4.3)  Sex  Male: 2.3 (1.2, 4.7) Female: 1.8 (0.8, 3.9)  Vaccine type Inactivated: 2.2 (1.3, 3.9) Live attenuated: 1.3 (0.1, 14.1) Unknown: 1.4 (0.2, 9.0)  Seasonal vaccine within 42 days before H1N1 vaccine No: 2.4 (1.3, 4.5) Yes: 1.6 (0.6, 4.0) |  |
| Velentgas et al. 2012,[223](#_ENREF_223) Retrospective cohort study | N=12.6 million;  Location=U.S.;  Age=11- to 21-year-olds;  Setting:Five US health plans | Meningococcal conjugate vaccine (MCV4); meningococcal polysaccharide vaccine (MPSV4), tetanus–diphtheria–acellular–pertussis vaccine (Tdap), tetanus and diphtheria vaccine (Td), tetanus, hepatitis B (HepB), human papillomavirus (HPV), and inﬂuenza vaccination | Entire population | Not discussed | Not discussed | Automated claims and enrollment data were used to identify vaccinations. Authors identiﬁed MCV4 (ACYW-135-D, Menactra W  ), meningococcal polysaccharide vaccine (MPSV4), tetanus–diphtheria–acellular–pertussis vaccine (Tdap), tetanus and diphtheria vaccine (Td), tetanus, hepatitis B (HepB), human papillomavirus (HPV), and inﬂuenza vaccinations and their associated dates of administration using Current Procedural Terminology, Healthcare Common Procedure Coding System, or ICD-9 procedure codes as present in the medical claims data. | Inpatient and outpatient medical claims were searched to identify instances of the ICD-9 code 357.0 (i.e. GBS). Medical charts for potential GBS cases were requested  by the health plans from the hospital of treatment or  other provider, such as a neurologist, rehabilitation  hospital, or primary care provider. Photocopies of relevant sections of the medical record were obtained for adjudication review. GBS case adjudication was performed by a panel of three neurologists under the oversight of one of the  authors (A.A.A.). | Incidence rate estimation | None | 2005-2008 | This study was funded by a contract from Sanoﬁ-Pasteur  to Harvard Pilgrim Health Care. | . Risk and attributable risk of GBS after vaccination, according to vaccine type  MCV4  Cumulative incidence; one sided upper CI: 0; 2.09  Attributable risk: 0; 1.46  MPSV4  Cumulative incidence; one sided upper CI: 7.79; 37.00  Attributable risk: 7.16; 36.37  Tdap  Cumulative incidence; one sided upper CI: 0; 2.49  Attributable risk: 0; 1.86  Td  Cumulative incidence; one sided upper CI: 0; 8.02  Attributable risk: 0; 7.39  Tetanus  Cumulative incidence; one sided upper CI: 0; 106.20  Attributable risk: 0; 105.57  Inﬂuenza  Cumulative incidence; one sided upper CI: 3.49; 11.00 Attributable risk: 2.86; 10.37  HepB  Cumulative incidence; one sided upper CI: 8.04; 38.10 Attributable risk: 7.40; 37.47  HPV  Cumulative incidence; one sided upper CI: 3.42; 10.80 Attributable risk: 2.79; 10.17 | None |  |
| Wise et al. 2012, Retrospective cohort[252](#_ENREF_252) | N=408 Guillain–Barrésyndrome (GBS) cases; Location=US; Age=0-65+ (no average measures given); Setting=10 sites of the Emerging Infections Program (EIP): California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee | Inactivated and live attenuated inﬂuenza A (H1N1) 2009 monovalent vaccines (in study referred to collectively as pH1N1 vaccine) | No details on recruitment for EIP, but study focused on entire population  Possible misclassification of exposure and outcome | 707 suspected GBS cases 282 did not meet Brighton criteria (40%) Of the remaining 425, 14 were excluded due to GBS onset prior to 10/1/09 Medical records reviewed for 411 GBS cases 408 vaccinated | Not discussed | Dates of receipt of pH1N1 vaccine and 2009–2010 seasonal inﬂuenza vaccine (hereafter referred to as seasonal vaccine) were recorded from vaccination cards, vaccine registries, or providers administering the vaccine, or via self-report (as recorded in the medical record or telephone interview) if a documented source was not available | Active, population-based surveillance for GBS cases. Trained surveillance ofﬁcers reviewed medical records to gather standardized information on patient characteristics, clinical presentation, and medical history for every suspected GBS case. | Estimation of incidence rate ratios using Mantel-Haenszel method | Age (stratification)  Age specific RR were adjusted for sex | October 1, 2009, and May 31, 2010 | Not reported | RR (95% CI) of GBS (confirmed and probable)  pH1N1 vaccine <25: 1.67 (0.58-3.22) 25+: 1.54 (0.90-2.25) Overall: 1.57 (1.02-2.21)  Seasonal vaccine <25: 1.78 (0.59-3.48) 25+: 1.36 (0.84-1.91) Total: 1.43 (0.94-1.89) | Not reported |  |
| Yih et al. 2012,[253](#_ENREF_253) Self-controlled risk interval, case-centered, and current-vs.-historical comparison.  For GBS and most other outcomes, the SCRI design was used. Case-centered approach was used to adjust for seasonality. For selected rare outcomes, current vs.-historical comparison methods were used | N=3,040,363 doses; Location=US; Age=2–49 years; Setting=Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system. Five health insurance and associated companies with 38 million members and 9 state/city immunization registries contributed records | Monovalent pandemic 2009 H1N1 influenza vaccine | Comprehensive set of data from health insurance companies. No control group | To avoid bias related to time lag in the accrual of health insurance claims data, authors used outcome data only for vaccinations given up to dates in January or February, ensuring nearly complete follow-up through both the risk and control periods. | Not discussed | Insurance company records | Data on outcomes came from insurance claims. For GBS, there was GBS medical record review by experts | SCRI: conditional Poisson regression  Case-centered method for GBS: Logistic regression  Current-vs.-historical: logistic regression | Case-centered: data partner, sex, and age group  Current v historical: data partner, sex, and age group | 2009-2010 | Food and Drug Administration through America’s Health Insurance Plans under Centers for Disease Control and Prevention contract | Risks of Health Outcomes of Interest Occurring After Receipt of a First Dose of Inactivated or Not-Otherwise-Speciﬁed 2009 H1N1 Inﬂuenza Vaccine: A 95% CI was used for anaphylaxis; 99% CIs were used for all other outcomes shown in the table, to account for multiple testing  SCRI analysis Demyelinating disease: 1.01 (0.86-1.20), 0.84 Peripheral nervous system disorders  6 months–24 years: 1.17 (0.84-1.63), 0.24 >=25 years: 0.99 (0.92-1.05), 0.61 Bell’s palsy  6 months–24 years: 1.21 (0.54-2.69), 0.54 >=25 years: 1.23 (0.88-1.73), 0.12 Other cranial nerve disorders  >=25 years: 1.07 (0.89-1.28), 0.35 Allergic reactions  >=6 months: 1.17 (0.92-1.49), 0.10 Hemorrhagic stroke  6 months–24 years: 1.13 (0.46-2.82), 0.72 >=25 years: 0.85 (0.62-1.16), 0.18 Ischemic stroke  6 months–24 years: 2.17 (0.61-7.73), 0.12 >=25 years: 0.92 (0.77-1.10), 0.23 Seizures  6 months–24 years: 0.55 (0.22-1.37), 0.09 >=25 years: 0.50 (0.15-1.65), 0.13 Current-vs.-historical analysis Demyelinating disease  6 months–24 years: 0.95 (0.54-1.68), 0.82 Encephalitis/myelitis/encephalomyelitis  >=6 months: 0.85 (0.28-2.54), 0.69  Other cranial nerve disorders  6 months–24 years: 0.85 (0.55-1.32), 0.35 Ataxia  >=6 months: 0.72 (0.41-1.28), 0.14 Anaphylaxis  >= 6 months: 0.75 (0.29-1.90), 0.54  2009 H1N1 Vaccines Without Proximate Seasonal Inﬂuenza Vaccine  SCRI analysis Demyelinating disease  >=25 years: 1.00 (0.79-1.28), 0.98 Peripheral nervous system disorders  6 months–24 years: 0.88 (0.50-1.55), 0.57  >=25 years: 1.12 (1.01-1.23), 0.003 Bell’s palsy  6 months–24 years: 1.25 (0.37-4.24), 0.64  >=25 years: 1.65 (1.03-2.64), 0.006 Other cranial nerve disorders  >=25 years: 1.07 (0.82-1.40), 0.51 Allergic reactions  >=6 months: 1.06 (0.71-1.60), 0.69 Hemorrhagic stroke  6 months–24 years: 1.00 (0.23-4.42), 1.00  >=25 years: 0.93 (0.59-1.45), 0.66 Ischemic stroke  6 months–24 years: 2.50 (0.29-21.6), 0.27  >=25 years: 0.88 (0.69-1.13), 0.18 Seizures  6 months–24 years: 0.25 (0.03-1.92), 0.08 >= 25 years: 0.44 (0.09-2.09), 0.18  Current-vs.-historical analysis Demyelinating disease  6 months–24 years: 0.82 (0.40-1.68), 0.47  Encephalitis/myelitis/encephalomyelitis  >= 6 months: 0.62 (0.15-2.49), 0.37 Other cranial nerve disorders  6 months–24 years: 0.87 (0.51-1.49), 0.52 Ataxia  >=6 months: 0.67 (0.35-1.29), 0.12 Anaphylaxis  >=6 months: 0.67 (0.22-2.00), 0.47   2009 H1N1 Vaccines With Concomitantly Administered Seasonal Inﬂuenza Vaccine  SCRI analysis Demyelinating disease  >=25 years: 1.48 (0.80-2.72), 0.10 Peripheral nervous system disorders  6 months–24 years: 1.50 (0.56-4.01), 0.29  >=25 years: 1.12 (0.88-1.43), 0.22 Bell’s palsy  6 months–24 years: 4.00 (0.22-71.2), 0.21  >=25 years: 1.33 (0.43-4.15), 0.51 Other cranial nerve disorders  >=25 years: 1.72 (0.97-3.07), 0.02 Allergic reactions  >= 6 months: 2.41 (1.15-5.07), 0.002 Hemorrhagic stroke  6 months–24 years: 2.00 (0.21-18.6), 0.42  >=25 years: 1.13 (0.32-3.93), 0.81 Ischemic stroke  6 months–24 years: 2.00 (0.09-46.9), 0.57  >=25 years: 1.05 (0.49-2.25), 0.88 Seizures  6 months–24 years: 1.00 (0.12-8.19), 1.00 Current-vs.-historical analysis Demyelinating disease  6 months–24 years: 1.04 (0.31-3.45), 0.93 Encephalitis/myelitis/encephalomyelitis  >=6 months: 3.45 (0.70-17.0), 0.05 Other cranial nerve disorders  6 months–24 years: 0.86 (0.32-2.34), 0.70 Ataxia  >= 6 months: 1.01 (0.22-4.60), 0.98 Anaphylaxis  >=6 months: 1.20 (0.16-9.04), 0.86 | None |  |