| **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 specificationCohort: Poisson regression | Case-centered: Age and sex matching for expected oddsCohort: 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 DesignOR, 95% CI, p=value6-week Risk IntervalIPV: 7.19 (0.18-281.03), 0.245Tdap: None (0.16 to NE), 0.249PPV-23: 0.72 (0.11-2.87), 0.722Hep A: 2.22 (0.30-10.63), 0.36Hep B: 0.43 (0.02-2.56), 0.455Td: 1.43 (0.33-4.56), 0.558TIV: 1.11 (0.39-3.08), 0.83 10-week Risk IntervalIPV: 4.15 (0.11-163.38), 0.39Tdap: None (.09 to NE), 0.377PPV-23: 0.44 (0.07-1.72), 0.281Hep A: 2.00 (0.39-8.74), 0.366Hep B: 0.24 (0.01-1.46), 0.15Td: 1.14 (0.32-3.29), 0.783TIV: 0.99 (0.33-2.70), 0.991Table 3. Number of Guillain-Barre Syndrome Cases and Crude Rates per 100 000 Person-Years (Cohort analysis)Relative rate, 95% CI, p=value1.3, (0.75-2.26), 0.35 | None |  |
| Crawford, et al., 2012[59](#_ENREF_59), Self-controlled case series | N=44Location=Victoria, AustraliaAge=48 (median); 7-95 years (range)Setting=An active surveillance system for GBSwas 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 in62 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 ofthe monovalent H1N1 vaccine. In six cases, data were only available fromthe hospital medical record (ie, neither the patient nor primary care physician were available). These caseswith incomplete immunisation histories were excluded from the primaryanalysis, leaving 44 cases. | Not discussed | Research assistants obtainedinformed consent once “possible” GBS cases were identified. A detailedimmunisation history was then obtained from study participants and their primary health care physician (followingpatient 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 windowBase: 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 periods0–13 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 ParticipantsAdjusted ORs, 95% CI, p-valuePrimary analysisExposed 1-28 d before reference date: 1.23 (0.53-2.89), 0.63Exposed more than 28 d before reference date:1.24 (0.54-2.86), 0.61Secondary analysisExposed while pregnant0.80 (0.36-1.78), 0.58Exposed before pregnant2.34 (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 definitionsUsing 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 CombinedViral 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 behaviordisordersDays 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 organsDays 1-60 Risk Interval: 1.0 (0.9-1.1) Days 1-14 Risk Interval: 1.2 (1.0-1.3)Ear conditionsDays 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 systemDays 1-60 Risk Interval: 2.1 (1.0-4.2)Days 1-14 Risk Interval: 2.1 (0.8-5.7)Diseases of circulatory systemDays 1-60 Risk Interval: 1.1 (1-1.3) Days 1-14 Risk Interval: 1.2 (1.0-1.5)Diseases of heartDays 1-60 Risk Interval: 1.1 (0.1-1.3) Days 1-14 Risk Interval: 1.3 (1.0-1.6)COPD and bronchiectasisDays 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 tissueDays 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 infectionsDays 1-60 Risk Interval: 1.1 (0.9-1.4) Days 1-14 Risk Interval: 1.8 (1.3-2.4)Cellulitis and abscessDays 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 connectivetissueDays 1-60 Risk Interval: 1.1 (1-1.2) Days 1-14 Risk Interval: 1.2 (1.0-1.4)Spondylosis, disc intervertebral disorders, backproblemsDays 1-60 Risk Interval: 1.1 (0.9-1.3) Days 1-14 Risk Interval: 1.4 (1.0-1.8)Congenital anomaliesDays 1-60 Risk Interval: 1.6 (1.1-2.3)Days 1-14 Risk Interval: 2.5 (1.6-4.0)Other congenital anomaliesDays 1-60 Risk Interval: 1.8 (1.1-3.0)Days 1-14 Risk Interval: 3.6 (2.0-6.3)Fever of unknown originDays 1-60 Risk Interval: 1.1 (0.9-1.4) Days 1-14 Risk Interval: 1.5 (1.0-2.1)LymphadenitisDays 1-60 Risk Interval: 1.0 (0.6-1.8) Days 1-14 Risk Interval: 2.3 (1.2-4.4)Diabetes mellitusDays 1-60 Risk Interval: 2.2 (1.1-4.4)Days 1-14 Risk Interval: 2.5 (1.0-6.4)Attention-deficit disorderDays 1-60 Risk Interval: 1.7 (1.1-2.8)Days 1-14 Risk Interval: 2.1 (1.1-4.1)Personality disordersDays 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 jawDays 1-60 Risk Interval: 1.1 (0.6-2.1) Days 1-14 Risk Interval: 2.6 (1.2-5.6)Congenital anomaliesDays 1-60 Risk Interval: 1.7 (1.0-2.8) Days 1-14 Risk Interval: 2.7 (1.4-5.3)Other congenital anomaliesDays 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 usedlogistic regression | Case-centered logistic regression: case date, age group, gender, andsite. | 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 basedon questionnaire data collected in 1968 andfollow-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 relativerisks while adjusting for confounders. Cox regression was used toestimate 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 orderand social class in 1968. The Cox model withasthma onset after the age of 21 yrs as theoutcome 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 theintroduction 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 theirchildren 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, duringwhich 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 ofbacterial infection, parental smoking, parental asthma, history of viral infection, birth order and history of pneumoniaAsthma after 13 years: Sex, parental asthmaEczema after 7 years: Age 7 years asthma status, sex,parental asthma, parentalsmokingFood allergy after 7 years: Age 7 years asthma status, sex, parental smokingHay 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 AsthmaFoundation 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 yearsDiphtheria: 1.33 (1.06-1.68), p=0.01Tetanus: 1.16 (0.94-1.43), p=0.16Pertussis: 1.19 (0.96-1.47), p=0.11Polio: 1.05 (0.83-1.32), p=0.69OR (95% CI) for asthma by age 13 yearsDiphtheria: 1.28 (0.98-1.66), p=0.07Tetanus: 1.18 (0.89-1.55), p=0.24Pertussis: 1.11 (0.91-1.37), p=0.31Polio: 1.03 (0.79-1.35), p=0.84OR (95% CI) for eczema by age 7 yearsDiphtheria: 1.53 (1.13-2.07), p=0.01Tetanus: 1.53 (1.15- 2.04), p=0.01Pertussis: 1.46 (1.10-1.93), p=0.01Polio: 1.36 (1.00-1.87), p=0.05OR (95% CI) for food allergy by age 7 yearsDiphtheria: 1.47 (1.04-2.07), p=0.03Tetanus: 1.26 (0.93-1.71), p=0.14Pertussis: 1.39 (1.01-1.91), p=0.04Polio: 1.44 (1.00-2.07), p=0.05OR (95% CI) for hay fever by age 7 yearsDiphtheria: 1.20 (0.94-1.53), p=0.15Tetanus: 1.05 (0.84-1.31), p=0.67Pertussis: 1.10 (0.88-1.38), p=0.42Polio: 0.88 (0.69-1.12), p=0.30OR (95% CI) for asthma after age 13 yearsDiphtheria: 0.58 (0.26-1.27), p=0.17 Tetanus: 0.79 (0.32-1.96), p=0.61Pertussis: 0.57 (0.30-1.09), p=0.09Polio: 0.50 (0.22-1.10), p=0.08OR (95% CI) for eczema after age 7 yearsDiphtheria: 0.68 (0.36-1.29), p=0.24 Tetanus: 0.76 (0.38-1.52), p=0.44Pertussis: 0.57 (0.35-0.93), p=0.03Polio: 0.76 (0.39-1.48), p=0.43OR (95% CI) for food allergy after age 7 yearsDiphtheria: 1.50 (0.81-2.79), p=0.20Tetanus: 0.98 (0.54-1.75), p=0.94 Pertussis: 0.88 (0.57-1.35), p=0.55Polio: 1.02 (0.57-1.83), p=0.94OR (95% CI) for hay fever after age 7 yearsDiphtheria: 1.19 (0.75-1.89), p=0.45 Tetanus: 1.09 (0.67-1.78), p=0.72Pertussis: 0.96 (0.67-1.38), p=0.83Polio: 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 yearCase-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 study90 Day Exposure IntervalHepatitis B: 1.44 (0.46, 4.51), p=0.53Influenza: 0.72 (0.45, 114), p=0.16180 Day Exposure IntervalHepatitis B: 1.67 (0.74, 3.77), p=0.22Influenza: 1.36 (1.03, 1.80), p=0.03365 Day Exposure IntervalHepatitis B: 1.23 (0.58, 2.63), p=0.59Influenza: 1.34 (1.06, 1.69), p=0.01OR from case-control study90 Day Exposure IntervalHepatitis B: 1.5 (0.4, 5.2), p=0.55Influenza: 0.7 (0.4, 1.2), p=0.14180 Day Exposure IntervalHepatitis B: 2.0 (0.8, 5.1), p=0.14Influenza: 1.1 (0.8, 1.6), p=0.57365 Day Exposure IntervalHepatitis B: 1.4 (0.6, 3.1), p=0.39Influenza: 1.1 (0.9, 1.5), p=0.43730 Day Exposure IntervalHepatitis B: 1.0 (0.5, 2.1), p=0.91Influenza: 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 riskOverall: 2.1 (1.2, 3.5) | RRsAge (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 typeInactivated: 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 vaccineNo: 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 requestedby the health plans from the hospital of treatment orother provider, such as a neurologist, rehabilitationhospital, 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 theauthors (A.A.A.). | Incidence rate estimation | None | 2005-2008 | This study was funded by a contract from Sanoﬁ-Pasteurto Harvard Pilgrim Health Care. | . Risk and attributable risk of GBS after vaccination, according to vaccine typeMCV4 Cumulative incidence; one sided upper CI: 0; 2.09 Attributable risk: 0; 1.46MPSV4 Cumulative incidence; one sided upper CI: 7.79; 37.00 Attributable risk: 7.16; 36.37TdapCumulative incidence; one sided upper CI: 0; 2.49 Attributable risk: 0; 1.86Td Cumulative incidence; one sided upper CI: 0; 8.02 Attributable risk: 0; 7.39Tetanus Cumulative incidence; one sided upper CI: 0; 106.20 Attributable risk: 0; 105.57Inﬂuenza Cumulative incidence; one sided upper CI: 3.49; 11.00 Attributable risk: 2.86; 10.37HepB Cumulative incidence; one sided upper CI: 8.04; 38.10 Attributable risk: 7.40; 37.47HPV 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 populationPossible misclassification of exposure and outcome | 707 suspected GBS cases282 did not meet Brighton criteria (40%)Of the remaining 425, 14 were excluded due to GBS onset prior to 10/1/09Medical records reviewed for 411 GBS cases408 vaccinated | Not discussed | Dates of receipt ofpH1N1 vaccine and 2009–2010 seasonal inﬂuenza vaccine (hereafter referred to as seasonal vaccine) were recorded from vaccination cards, vaccine registries, or providersadministering 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 informationon 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, ensuringnearly 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 regressionCase-centered method for GBS: Logistic regressionCurrent-vs.-historical: logistic regression | Case-centered: data partner, sex, and age groupCurrent v historical: data partner, sex, and age group | 2009-2010 | Food and Drug Administration through America’s Health Insurance Plans underCenters 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 testingSCRI analysisDemyelinating disease: 1.01 (0.86-1.20), 0.84Peripheral nervous system disorders 6 months–24 years: 1.17 (0.84-1.63), 0.24>=25 years: 0.99 (0.92-1.05), 0.61Bell’s palsy 6 months–24 years: 1.21 (0.54-2.69), 0.54>=25 years: 1.23 (0.88-1.73), 0.12Other cranial nerve disorders >=25 years: 1.07 (0.89-1.28), 0.35Allergic reactions >=6 months: 1.17 (0.92-1.49), 0.10Hemorrhagic stroke 6 months–24 years: 1.13 (0.46-2.82), 0.72>=25 years: 0.85 (0.62-1.16), 0.18Ischemic stroke 6 months–24 years: 2.17 (0.61-7.73), 0.12>=25 years: 0.92 (0.77-1.10), 0.23Seizures 6 months–24 years: 0.55 (0.22-1.37), 0.09>=25 years: 0.50 (0.15-1.65), 0.13Current-vs.-historical analysisDemyelinating disease 6 months–24 years: 0.95 (0.54-1.68), 0.82Encephalitis/myelitis/encephalomyelitis >=6 months: 0.85 (0.28-2.54), 0.69Other cranial nerve disorders 6 months–24 years: 0.85 (0.55-1.32), 0.35Ataxia >=6 months: 0.72 (0.41-1.28), 0.14Anaphylaxis >= 6 months: 0.75 (0.29-1.90), 0.542009 H1N1 Vaccines Without Proximate Seasonal Inﬂuenza VaccineSCRI analysisDemyelinating disease >=25 years: 1.00 (0.79-1.28), 0.98Peripheral nervous system disorders 6 months–24 years: 0.88 (0.50-1.55), 0.57 >=25 years: 1.12 (1.01-1.23), 0.003Bell’s palsy 6 months–24 years: 1.25 (0.37-4.24), 0.64 >=25 years: 1.65 (1.03-2.64), 0.006Other cranial nerve disorders >=25 years: 1.07 (0.82-1.40), 0.51Allergic reactions >=6 months: 1.06 (0.71-1.60), 0.69Hemorrhagic stroke 6 months–24 years: 1.00 (0.23-4.42), 1.00 >=25 years: 0.93 (0.59-1.45), 0.66Ischemic stroke 6 months–24 years: 2.50 (0.29-21.6), 0.27 >=25 years: 0.88 (0.69-1.13), 0.18Seizures 6 months–24 years: 0.25 (0.03-1.92), 0.08>= 25 years: 0.44 (0.09-2.09), 0.18Current-vs.-historical analysisDemyelinating disease 6 months–24 years: 0.82 (0.40-1.68), 0.47Encephalitis/myelitis/encephalomyelitis >= 6 months: 0.62 (0.15-2.49), 0.37Other cranial nerve disorders 6 months–24 years: 0.87 (0.51-1.49), 0.52Ataxia >=6 months: 0.67 (0.35-1.29), 0.12Anaphylaxis >=6 months: 0.67 (0.22-2.00), 0.472009 H1N1 Vaccines With Concomitantly Administered Seasonal Inﬂuenza VaccineSCRI analysisDemyelinating disease >=25 years: 1.48 (0.80-2.72), 0.10Peripheral nervous system disorders 6 months–24 years: 1.50 (0.56-4.01), 0.29 >=25 years: 1.12 (0.88-1.43), 0.22Bell’s palsy 6 months–24 years: 4.00 (0.22-71.2), 0.21 >=25 years: 1.33 (0.43-4.15), 0.51Other cranial nerve disorders >=25 years: 1.72 (0.97-3.07), 0.02Allergic reactions >= 6 months: 2.41 (1.15-5.07), 0.002Hemorrhagic stroke 6 months–24 years: 2.00 (0.21-18.6), 0.42 >=25 years: 1.13 (0.32-3.93), 0.81Ischemic stroke 6 months–24 years: 2.00 (0.09-46.9), 0.57 >=25 years: 1.05 (0.49-2.25), 0.88Seizures 6 months–24 years: 1.00 (0.12-8.19), 1.00Current-vs.-historical analysisDemyelinating disease 6 months–24 years: 1.04 (0.31-3.45), 0.93Encephalitis/myelitis/encephalomyelitis >=6 months: 3.45 (0.70-17.0), 0.05Other cranial nerve disorders 6 months–24 years: 0.86 (0.32-2.34), 0.70Ataxia >= 6 months: 1.01 (0.22-4.60), 0.98Anaphylaxis >=6 months: 1.20 (0.16-9.04), 0.86 | None |  |