Supplementary file 2: detailed description of selected studies employed non- sequential analysis

First author, year published	Setting and study period	Study design	Data source	Sample size	Study subjects	Vaccine studied	Adverse evets studied	Study purpose	Analyses method	Main finding
Baxter, 2016	USA, September 2005 - October 2006	Retrospective cohort with historical comparison and	Outpatient clinic, ED visits and inpatient data linked to immunization data	124,139 Tdap5	11 through 64 years old	Tdap5, new vaccine	All health outcomes up to 6 months following vaccination were captured and reviewed	Signal identification and verification	-Cox regression - Temporal cluster analysis	No increased risks were identified for any of the outcomes
Baxter, 2012	USA July 2006 through November 2007	Retrospective, SCRI design	Inpatient and ED visits linked with immunization data	29,010 individuals	60 years of age or older	Zoster vaccine (ZostavaxTM) , new vaccine	-All clinical events led to hospitalization or ED visits	Signal identification and verification	-Cox regression - Temporal cluster analysis	No increased risks were identified for any of the outcomes
Baxter, 2012	USA, October 2003 to March 2008	Retrospective cohort with concurrent comparison groups and SCRI designs	Inpatient and ED visits linked with immunization data	43,702 LAIV recipients	children aged 5–17 years	Ann Arbor strain live attenuated influenza vaccine	All medically attended adverse events	Signal identification and verification	Cox regression - Temporal cluster analysis	No increased risks were identified for any of the outcomes
Baxter, 2012	USA, October 2003 - March 2008	Retrospective cohort with concurrent comparison groups and SCRI designs	Outpatient visits, ED visits and inpatient data linked to immunization data	21,340 subjects	adults 18–49 years of age	Ann Arbor strain live attenuated influenza vaccine	All medically attended events Within 42 days of vaccination	Signal identification and verification	Cox regression - Temporal cluster analysis	No increased risks were identified for any of the outcomes
Chao, 2012	USA, August 2006 – March 2008	Retrospective cohort study with current vs. historical design	Outpatient visits, ED visits and inpatient data linked to immunization data	189 629 women who received at least 1 dose of HPV4	Women in the age range of 9–26 years	Quadrivalent human papillomavirus vaccine (HPV4) , new vaccine	Potential new-onset and 16 pre-specified autoimmune conditions	Signal identification and verification	Non-sequential analysis, but not clearly stated	No safety signal was found
Davis, 2004	USA, between 1 July 1997 and 31	Retrospective cohort study with both current vs.	Outpatient visits, ED visits and inpatient data	27,802 doses of COMVAX	All children 6 weeks to 36 months	COMVAX Combination vaccine, new	Adverse events resulting in medical utilization (hospitalizations,	Signal identification and	Exact binomial method	No safety signal was found

	December 2000	historical and Risk interval cohort)	linked to immunization data				ED visits and outpatient clinic visits	verification		
Donegan, 2014	UK, from 1 October 2012 to 31 March 2013	Prospective cohort study with current vs. historical, and Risk interval designs	Primary care general practice databases (CPRD)	20 074 pregnant women	Pregnant women who received any vaccine containing pertussis	Pertussis vaccine	Pre-specified events primarily stillbirth, but maternal and neonatal outcomes such as pre-eclampsia, eclampsia and low birth weight were included	Signal identification	Cox proportional hazard and Poisson regression	No safety signal was found
Duffy, 2017	USA, from 2008 to 2011	Retrospective cohort study with the self-controlled risk interval design	Outpatient visits, ED visits and inpatient data linked to immunization data (VSD)	12,354 LAIV	2 through 49 years old persons with asthma	Live attenuated influenza vaccine (LAIV)	Medically attended respiratory events in the 14 days after LAIV	Signal identification and evaluation	Poisson regression	No safety signal was found
France, 2004	USA, January 1, 1993, through December 31, 1999	Retrospective, case-crossover design	Outpatient visits, ED visits and inpatient data linked to immunization (VSD)	251600 children and 438167 vaccine dose	individual's younger than 18 years	Influenza vaccine (TIV)	All medically attended event	Signal identification and verification	Conditional logistic regression	No safety signal was found
Glanz, 2011	USA, between October 1, 2002, and March 31, 2006	Retrospective cohort study with self-controlled case series design	ED visits and inpatient data linked to immunization (VSD)	66 283 children aged 24 to 59 months	Children aged 24 to 59 months who received at least 1 TIV dose	trivalent inactivated influenza vaccine (TIV)	Pre-specified medically attended events in the 0-42 days' risk windows.	Signal identification and verification	Conditional Poisson regression	Signal for GIT symptoms (IRR, 1.18; 1.10-1.25), GIT disorders (7.70; 1.11-53.52), and fever (1.71; 1.64-1.80) are detected
Greene, 2012	USA, between August 2009 and April 2010	Retrospective study, self-controlled risk interval design	Outpatient visits, ED visits and inpatient data linked to immunization record (VSD)	1.48 million doses (MIV) and 1.72 million doses (TIV)	All age groups	MIV and seasonal TIV	GBS within 1–42 days following vaccination.	Signal identification and verification	Poisson regression, Temporal and Case-centred analysis	No statistically elevated risk of GBS observed

Hambidge, 2006	USA, between January 1, 1991, and May 31, 2003	Retrospective study with self-control risk interval, case-crossover and SCCS designs	Outpatient clinic, ED and inpatient data linked to immunization record (VSD)	45 356 children received 69 359 influenza vaccinations doses	All children 6 to 23 months old who received TIV	Trivalent inactivated Influenza Vaccine (TIV)	Medically Attended Events 0-42 days after vaccination.	Signal identification and verification	-Conditional Poisson and logistic regression	No safety signal was found
Hanson, 2016	USA, From October 1, 2008 through July 31, 2010	Retrospective study with self-control risk interval and concurrent cohort designs	Outpatient clinic, ED and inpatient data linked to immunization record (KPNC)	14,042 infants who received at least one dose	All 2-month-old infants	DTaP-IPV/Hib vaccine administered routinely as part of clinical care	All ED and hospital visits and selected outpatient outcomes during days 0–30 post-vaccination	Signal identification and verification	Non-sequential analysis, not clearly stated	No safety signal was found
Jackson, 2006	USA, January 1996 through November 2002	Retrospective study with Risk-interval design	Outpatient clinic, ED and inpatient data linked to immunization record (VSD)	316,995 adults received least one first dose of a PPV	Persons >= 50 years old	3rd dose of pneumococcal polysaccharide vaccine (PPV)	An injection site reaction within two weeks following vaccination.	Signal identification and verification	Fisher's exact test, logistic regression	No safety signal was found
Jackson, 2009	USA, December 31,2004 to 2006	Retrospective cohort study	Outpatient clinic an ED data linked to immunization record (VSD)	128,297 Td, Tdap, and MCV4 vaccinations	Adolescents and young adults (9 to 26 years old)	Td, Tdap, and MCV4 vaccinations Concomitant or sequential administration	Medically attended local reactions within six days following the vaccination	Signal identification and verification	Poisson regression	No safety signal was found
Kharbanda, 2013	USA, from June 1, 2002, to July 31, 2009	Retrospective cohort compare who did and did not receive TIV	Outpatient clinic, ED and inpatient data linked to immunization record (VSD)	74,292 vaccinated And 144,597 unvaccinated	All pregnant females aged 14–49 years	Trivalent inactivated influenza vaccine	All potential adverse obstetric events were identified	signal identification and verification	Poisson regression	No safety signal was found
Kharbanda, 2016	USA, between January 1, 2007 and November 15, 2013	Retrospective cohort with matched concurrent comparisons	Outpatient clinic, ED and inpatient data linked to immunization record (VSD)	53,885 vaccinated and 109,253 matched unvaccinated	Pregnant women	Combined tetanus toxoid, reduced diphtheria toxoid, acellular pertussis	Medically attended acute adverse events within 3 days of vaccination AND medically attended neurologic events	Signal identification and refinement	Poisson regression	No safety signal was found

						vaccine (Tdap)	within 0–42 days following vaccination			
Jacobsen, 2009	USA, February 2006–June 2007	Retrospective, self-controlled risk interval and current vs. historical	Outpatient clinic, ED and inpatient data linked to immunization record (KPSC)	31,298 children	Children ages 12–60 months	MMRV, new combination vaccine	Pre-defined outcome, febrile convulsion during the 30 days' post-vaccination	Signal detection and refinement	Cox regression, Poisson regression	Febrile convulsion in days 5–12 following vaccination (RR = 2.20, 95% CI = 1.04, 4.65)
Klein, 2012	USA, August 2006 and March 2008.	retrospective, observational cohort study (risk interval design)	Kaiser Permanente in California	189 629 females (346 972 HPV4 Doses)	all females who received at least 1 dose of HPV4	Quadrivalent human papillomavirus vaccine (HPV4), new vaccine	Emergency Department visits and hospitalizations grouped into predefined diagnostic categories from days 1 to 60 days	Signal detection and refinement	Conditional logistic regression	No safety signal was found
Klein, 2012	USA, from January 2000 - October 2008	Retrospective cohort with historical comparison	VSD	86 750 for MMRV and 67 438 for MMR + V	children aged 48 to 83 months	MMRV and MMR + V	Febrile seizure during the 42 days after.	Signal detection and refinement	Poisson regressions	No safety signal for febrile seizure was found
Klein, 2015	USA, from January 2000 - June 2012	Retrospective study with self-controlled risk interval design	8 VSD sites	123 200 MMRV and 584 987 MMR + V doses	children were aged 12 to 23 months	Comparing MMRV with MMR + V,	Anaphylaxis, ataxia, arthritis, meningitis/ encephalitis, acute disseminated encephalomyelitis, Kawasaki disease, seizure, and fever	Signal detection and refinement	Exact binomial tests, logistic regression	No safety signal was found
Nordin, 2014	USA, between June 1, 2002, and July 31, 2009	Retrospective matched cohort study and	Outpatient clinic, ED and inpatient data linked to immunization record (VSD	92 440 unvaccinated and 57 649 vaccinated.	Pregnant women, those aged 14-49 years	Trivalent inactivated influenza vaccine (TIIV)	Preterm and small for gestational age births	Signal detection and evaluation	Conditional logistic regression	No increased signal was found
Nordin, 2014	USA 2008–2009 and2009–2010 seasons,	Retrospective, multisite matched observational cohort study	Outpatient clinic, ED and inpatient data linked to immunization record (VSD	9349 women receiving MIV and 17,491 unvaccinated	Pregnant women	Monovalent H1N1 inactivated influenza (MIV)	Pre specified medically attended adverse events within 42 days of vaccination	Signal detection	Poisson regression	No increased signal detected

Sukumaran, 2015	USA, betweenJanuary1,2007, and November 15, 2013	Retrospective cohort	Outpatient clinic, ED and inpatient data linked to immunization record (VSD)	29 155 pregnant women	women aged 14 through 49 years who received Tdap vaccine during pregnancy	tetanus, diphtheria, and acellular pertussis (Tdap) vaccine	Acute adverse events (fever, allergy, and local reactions) and adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight	Signal detection and evaluation	log-binomial regression	No increased risk observed
Sukumaran, 2015	USA, between January1,2007, and November 15, 2013	Retrospective cohort study	Outpatient clinic, ED and inpatient data linked to immunization record (VSD)	36,844 pregnant women	Pregnant women aged 14–49 years	Concomitant and sequential administration of Tdap and influenza vaccines	Medically attended acute events (fever, any acute reaction) and adverse birth outcomes (preterm delivery, low birth weight, small for gestational age	Signal detection	log-binomial regression	No increased risk observed
Tartof, 2017	USA, between September 2011 and September 2014	Retrospective observational safety study	Outpatient clinic, ED and inpatient data linked to immunization record (KPSC)	387 vaccinated children	Children 2–10 years	Quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) new vaccine	26 Pre-specified events of interests AND serious medically attended events up to 1 year after vaccination	Signal detection	Poisson distribution, descriptive in nature, no statistical tests were performed	The data did not suggest safety concerns
Tseng, 2012	USA. from1January2007to31December2008	Case-centred design and self-controlled case series design	Outpatient clinic, ED and inpatient data linked to immunization record (VSD)	193 083 adults aged 50 and older	All adults age >=50 years who received a zoster vaccine	Zoster vaccine	Pre-specified adverse events (Stroke, Cerebrovascular diseases, Cardiovascular diseases, Meningitis, encephalitis and encephalopathy etc)	Signal identification and evaluative	Binomial logistic regression, conditional Poisson regression and stratified analysis by age	The risk of allergic reaction was significantly increased within 1–7 days of vaccination (RR = 2.32, 1.85–2.91)
Tseng, 2017	USA, during September 30, 2011 to June 30, 2013	Cohort study with self-controlled case-series design	Outpatient clinic, ED and inpatient data linked to immunization record (KPSC)	48 899 vaccinated individuals	Aged 11 to 21 years , new vaccine	Quadrivalent meningococcal conjugate vaccine (MenACWYCRM)	Twenty-six pre-specified events of interest including neurologic, rheumatologic and hematologic, disease 1 year after vaccination	Signal identification and evaluative	Conditional Poisson regression adjusted for seasonality	Increased risk of Bell's palsy identified but not confirmed
Jackson, 2002	USA, January, 1997, and	Retrospective cohort	Outpatient clinic, ED and inpatient data linked to	76 133 doses of DTaP	Children less than7 years of age who	Diphtheria-tetanus toxoids-acellular	Pre-specified outcome (injection site reactions, seizures and allergic responses within 7	Signal identification	Descriptive, proportions were compared	-

	December, 2000		immunization record Group Health Cooperative, Seattle		received one or more doses of DTaP vaccine	pertussis (DTaP)	days of DTaP vaccination and febrile episodes within 3 days		with the chi square test with Yates correction	
Kharbanda, 2014	USA, between January 1, 2010, and November 15, 2012	Retrospective cohort study	Outpatient clinic and inpatient data linked to immunization record (KPNC and KPSCN)	26 000 women received Tdap compared to 97 265 not received	All pregnant women (singleton)	Maternal Tdap vaccination during pregnancy	Chorioamnionitis and hypertensive disorders of pregnancy preterm and small for-gestational-age (SGA) births	Signal identification AND evaluation	non sequential, one-time analysis logistic and Poisson regression	Marginal but statistically significant increased risk of chorioamnionitis diagnosis was observed (adjusted RR, 1.19; 95%CI, 1.13-1.26).
Nordin, 2013	USA, 1 June 2002 through 31 July 2009	Retrospective cohort study with matched concurrent comparison	Outpatient clinic, ED and inpatient data linked to immunization record (VSD)	75,906 vaccinated and 147,992 unvaccinated	Pregnant women	Trivalent inactivated influenza vaccine	medically attended events occurring within 42 days of receiving the vaccine,	Signal identification and evaluation	Poison regression, matched by age, site, and pregnancy start date	No signal identified
Nordin, 2013	USA, VSD cohort from 1991 -2006 and DoD cohort from 1999 -2007	Retrospective cohort study with matched concurrent comparison and risk-interval designs	VSD and US Department of Defence (DoD)	47,159 doses from VSD and 1.12 million doses from DoD	All yellow fever-vaccine-exposed individuals	Yellow fever vaccine	-Allergic and local reactions -Visceral events and neurologic events	Signal identification and evaluation	Conditional logistic Regression and Poisson regression. (Matched by age-, site-, and gender-matched unexposed subjects	No signal identified

COMVAX® (Haemophilus b conjugate vaccine (meningococcal protein conjugate) and hepatitis B vaccine (recombinant)); gastrointestinal tract (GIT); CPRD - *Clinical Practice Research Datalink;* KPSC- Kaiser Permanente Southern California health care program; KPNC Kaiser Permanente Northern California health care program