Vaccines for measles, mumps and rubella in children (Review)

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[Intervention Review]

Vaccines for measles, mumps and rubella in children

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ABSTRACT

Background

Mumps, measles and rubella (MMR) are serious diseases that can lead to potentially fatal illness, disability and death. However, public debate over the safety of the trivalent MMR vaccine and the resultant drop in vaccination coverage in several countries persists, despite its almost universal use and accepted effectiveness.

Objectives

To assess the effectiveness and adverse effects associated with the MMR vaccine in children up to 15 years of age.

Search methods

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, PubMed (July 2004 to May week 2, 2011) and Embase.com (July 2004 to May 2011).

Selection criteria

We used comparative prospective or retrospective trials assessing the effects of the MMR vaccine compared to placebo, do nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age.

Data collection and analysis

Two review authors independently extracted data and assessed methodological quality of the included studies. One review author arbitrated in case of disagreement.

Main results

We included five randomised controlled trials (RCTs), one controlled clinical trial (CCT), 27 cohort studies, 17 case-control studies, five time-series trials, one case cross-over trial, two ecological studies, six self controlled case series studies involving in all about 14,700,000 children and assessing effectiveness and safety of MMR vaccine. Based on the available evidence, one MMR vaccine dose is at least 95% effective in preventing clinical measles and 92% effective in preventing secondary cases among household contacts.

Effectiveness of at least one dose of MMR in preventing clinical mumps in children is estimated to be between 69% and 81% for the vaccine prepared with Jeryl Lynn mumps strain and between 70% and 75% for the vaccine containing the Urabe strain. Vaccination

with MMR containing the Urabe strain has demonstrated to be 73% effective in preventing secondary mumps cases. Effectiveness of Jeryl Lynn containing MMR in preventing laboratory-confirmed mumps cases in children and adolescents was estimated to be between 64% to 66% for one dose and 83% to 88% for two vaccine doses. We did not identify any studies assessing the effectiveness of MMR in preventing rubella.

The highest risk of association with aseptic meningitis was observed within the third week after immunisation with Urabe-containing MMR (risk ratio (RR) 14.28; 95% confidence interval (CI) from 7.93 to 25.71) and within the third (RR 22.5; 95% CI 11.8 to 42.9) or fifth (RR 15.6; 95% CI 10.3 to 24.2) weeks after immunisation with the vaccine prepared with the Leningrad-Zagreb strain. A significant risk of association with febrile seizures and MMR exposure during the two previous weeks (RR 1.10; 95% CI 1.05 to 1.15) was assessed in one large person-time cohort study involving 537,171 children aged between three months and five year of age. Increased risk of febrile seizure has also been observed in children aged between 12 to 23 months (relative incidence (RI) 4.09; 95% CI 3.1 to 5.33) and children aged 12 to 35 months (RI 5.68; 95% CI 2.31 to 13.97) within six to 11 days after exposure to MMR vaccine. An increased risk of thrombocytopenic purpura within six weeks after MMR immunisation in children aged 12 to 23 months was assessed in one case-control study (RR 6.3; 95% CI 1.3 to 30.1) and in one small self controlled case series (incidence rate ratio (IRR) 5.38; 95% CI 2.72 to 10.62). Increased risk of thrombocytopenic purpura within six weeks after MMR exposure was also assessed in one other case-control study involving 2311 children and adolescents between one month and 18 years (odds ratio (OR) 2.4; 95% CI 1.2 to 4.7). Exposure to the MMR vaccine was unlikely to be associated with autism, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, Crohn's disease, demyelinating diseases, bacterial or viral infections.

Authors' conclusions

The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation with the MMR vaccine cannot be separated from its role in preventing the target diseases.

PLAIN LANGUAGE SUMMARY

Using the combined vaccine for protection of children against measles, mumps and rubella

Measles, mumps and rubella (MMR) are three very dangerous infectious diseases which cause severe morbidity, disability and death in low-income countries.

Based on the evidence provided by three cohort studies (3104 participants), vaccination with one dose of MMR vaccine is at least 95% effective in preventing clinical measles among preschool children; in schoolchildren and adolescents at least one dose of MMR vaccine was 98% effective in preventing laboratory-confirmed measles cases; one or two MMR doses were respectively 92% and 95% effective in preventing secondary measles cases.

At least one dose of MMR vaccine is effective in preventing clinical mumps among children and adolescents when prepared with Jeryl Lynn strains (vaccine effectiveness = 69% to 81%, one cohort and one case-control study, 1656 participants), as well as when prepared with Urabe strain (vaccine effectiveness = 70% to 75%, one cohort and one case-control study, 1964 participants). Effectiveness against laboratory-confirmed mumps in children and adolescents was estimated to be between 64% to 66% for one and 83% to 88% for two doses of Jeryl Lynn MMR (two case-control studies, 1664 participants) and 87% for Urabe-containing MMR (one cohort study, 48 participants). Vaccination with Urabe MMR confers protection against secondary mumps infection (vaccine effectiveness = 73%, one cohort study, 147 participants).

We identified no studies assessing the effectiveness of MMR vaccine against clinical or laboratory-confirmed rubella.

Results from two very large case series studies involving about 1,500,000 children who were given the MMR vaccine containing Urabe or Leningrad-Zagreb strains show this vaccine to be associated with aseptic meningitis; whereas administration of the vaccine containing Moraten, Jeryl Lynn, Wistar RA, RIT 4385 strains is associated with febrile convulsion in children aged below five years (one person-time cohort study, 537,171 participants; two self controlled case series studies, 1001 participants). The MMR vaccine could also be associated with idiopathic thrombocytopaenic purpura (two case-controls, 2450 participants, one self controlled case series, 63 participants).

We could assess no significant association between MMR immunisation and the following conditions: autism, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, Crohn's disease, demyelinating diseases, or bacterial or viral infections. The methodological quality of many of the included studies made it difficult to generalise their results.

The glossary of study designs is available in the full-text review.

BACKGROUND

Description of the condition

Measles, mumps and rubella (MMR) are serious diseases that can lead to potentially fatal illnesses, disabilities and death. MMR are particularly prevalent in low-income countries where vaccination programmes are inconsistent and the mortality rate from disease is high. However, in high-income countries MMR are now rare, due to large-scale vaccination programmes.

Description of the intervention

The single component live attenuated vaccines of MMR have been licensed in the USA since the 1960s (Plotkin 1999a; Plotkin 1999b; Redd 1999). These single vaccines have been shown to be highly effective at reducing the morbidity and mortality rates associated with these childhood illnesses.

At least five MMR vaccines are known.

1. Triviraten Berna is a live virus vaccine containing 1000 TCID50 (50% tissue culture infectious doses) of Edmonston-Zagreb (EZ 19) measles strain, 5000 TCID50 of Rubini mumps strain and 1000 TCID50 of Wistar RA 27/3 rubella strain propagated on human diploid cells. The product contains lactose (14 mg), human albumin (8.8 mg), sodium bicarbonate (0.3 mg), medium 199 (5.7 mg) and distilled water as solvent.
2. M-M-R by Merck is a live virus vaccine. It is a sterile lyophilised preparation of 1000 TCID50 Enders' attenuated Edmonston measles strain propagated in chick embryo cell culture; mumps 20000 TCID50 Jeryl Lynn strain propagated in chick embryo cell culture; and rubella 1000 TCID50 Wistar RA 27/3 propagated on human diploid lung fibroblasts. The growth medium is medium 199 (5.7 mg) used with neomycin as stabiliser.
3. Morupar by Chiron is a live virus vaccine. It contains a sterile lyophilised preparation of 1000 TCID50 of Schwarz measles strain propagated in chick embryo cell culture; 1000 TCID50 Wistar RA 27/3 rubella strain propagated on human diploid lung fibroblasts; and 5000 TCID50 Urabe AM 9 mumps propagated in chick embryo cell culture, with neomycin as stabiliser.
4. Priorix vaccine, Glaxo SmithKline Beecham (GSK), is a lyophilised mixed preparation of the attenuated Schwarz measles CCID50 (50% cell culture infective dose) strain; RIT 4385 mumps CCID50 (derived from Jeryl Lynn strain); and CCID50 Wistar RA 27/3 rubella strain of viruses. These are separately obtained by propagation either in chick embryo tissue cultures (mumps and measles) or MRC5 human diploid cells (rubella). The vaccine also contains residual amounts of neomycin (25 µg per dose).
5. Trimovax by Pasteur-Merieux Serums and Vaccines contains live viruses: Schwarz measles strain, 1000 TCID50; Urabe Am 9 mumps strain, 5000 TCID50; and Wistar RA 27/3 rubella strain, 1000TCID50.

How the intervention might work

No national health policy recommends that the MMR vaccine be given as three separate vaccines. Combined live attenuated MMR vaccine was introduced in the USA in the 1970s (Redd 1999; Schwarz 1975). MMR is included in the World Health Organization's *Expanded Programme on Immunisation* and it is used in over 50 European countries, the USA, Canada, Australia and New Zealand; in total, over 90 countries around the world use the MMR vaccine. Accepted recommendations are that the first dose should be administered on or after the first birthday and the second dose of MMR at least 28 days later. In many European countries the second dose is administered at four to 10 years of age. Vaccination with MMR provides significant improvement in the efficiency of paediatric immunisation through the administration of three vaccines in a single injection, which is important in reducing costs while increasing immunisation coverage against the three diseases (Makino 1990). The incidence of MMR worldwide has been significantly reduced by MMR vaccination (WHO 1999).

Single-component measles vaccine (MV) is actually used in nearly all African WHO member states (44 out of 47 states); in the main cases vaccination schedules prescribe a single-dose administration at nine months of age. In only four African countries (Algeria, Lesotho, Republic of South Africa, Swaziland) a second MV dose is administered at 18 months or at six years of age (Algeria) (WHO 2011). The administration of the first dose of measles-containing vaccine at nine months of age is recommended in countries with ongoing transmission and with high risk of measles mortality among infants, in order to ensure adequate protection. The introduction of a second measles-containing vaccine dose to the immunisation schedule is recommended only when a coverage of at least 80% for the first dose of measles-containing vaccine has been reached for three consecutive years. It should be administered at 15 to 18 months of age (WHO 2009). Altogether, besides 44 African WHO member countries, an additional 24 countries have exclusively used MV in their vaccination schedule (among others the Russian Federation). Eleven countries have a single-dose MV administration at nine months of age (Bangladesh, Cambodia, Djibouti, Lao People's Democratic Republic, Malaysia, Nepal, Somalia, Sri Lanka, Timor Leste, Vanuatu and Vietnam).

The capability of MMR mass immunisation to eliminate the targeted disease has been demonstrated in a number of countries. The USA is the largest country to have ended endemic measles transmission (Strebel 2004), with interruption of indigenous transmission in 1993 (Watson 1998). In Finland, a national programme launched in 1982 reached measles elimination in 1996 and in 1999 the country was documented as free of indigenous mumps and rubella (Peltola 2000). These experiences demonstrate the possibility of achieving interruption of transmission in large geographic areas and suggest the feasibility of global eradication of measles. Therefore, it would be ethically unacceptable to conduct placebo-controlled trials to assess vaccine effects. Current research on the effectiveness of MMR vaccines focuses on comparison of vaccine strains and optimising protection by modifying the immunisation schedules; these topics are outside the scope of the present review.

A retrospective study (Kreidl 2003) reported data about MMR vaccination coverage for local areas in South Tyrol (North-East Italy) and reported cases of measles in the same areas. In all areas with complete vaccination coverage below 50%, an incidence of at least 333 cases per 100,000 was observed; whereas a very low incidence of the disease was registered in those areas where the highest immunisation coverage was achieved, despite their higher population density.

After the introduction of MMR vaccine in England in October 1988, the annual incidence of mumps declined sharply. The annual incidence rate fell from 160/100,000 in 1989 to 17/100,000 in 1995 (Gay 1997).

One retrospective observational study, which seemed to show an unexpectedly low clinical effectiveness (Vandermeulen 2004) was carried out on 1825 children aged between 15 months and 11 years. It examined the incidence of mumps in seven kindergartens and primary schools in Belgium during a mumps outbreak. This was assessed using questionnaires completed by parents and following evaluation of the reported data according to the Centers for Disease Control and Prevention (CDC) (CDC 1997) case definition. On average, 91.8% of the children had received at least one dose of MMR vaccine at any time before the outbreak occurred. In this group (N = 1641) mumps was diagnosed in 85 children whereas 20 out of the 139 non-immunised children developed mumps (45 children from both groups were excluded from the analysis because they had a history of mumps prior to the outbreak).

The components of monovalent vaccine containing MMR viruses, and subsequently combined MMR vaccine, are described below (Makino 1990; Plotkin 1999b). Numerous attenuated measles vaccines, mostly derived from the Edmonston strain, are currently produced worldwide. Four vaccines containing non-Edmonston derived strains are also in use, including Leningrad-16, Shanghai-191, CAM-70 and TD97. In most cases the virus is cultured in chick embryo cells. However, a few vaccines are attenuated in human diploid cells. The majority of vaccines contain small doses of antibiotics (for example 25 µg of neomycin per dose) but some do not. Sorbitol and gelatin are used as stabilisers (Schwarz 1975).

More than 10 mumps vaccine strains (Jeryl Lynn, Urabe, Hoshino, Rubini, Leningrad-3, L-Zagreb, Miyahara, Torii, NK M-46, S-12 and RIT 4385) have been used throughout the world (Redd 1999). Most vaccines also contain neomycin (25 µg of per dose). The Jeryl Lynn strain is widely used. Several manufacturers in Japan and Europe produce a live mumps vaccine containing the Urabe Am9 virus strain. Concerns about vaccine-associated meningitis have prompted some countries to stop using MMR with the mumps Urabe strain. Often the viruses are cultured in chick embryo fibroblasts (as with the Jeryl Lynn and Urabe strain-containing vaccines) but quail and human embryo fibroblasts are also used for some vaccines.

Most rubella vaccines used throughout the world contain the RA 27/3 virus strain (Plotkin 1965). The only exceptions are vaccines produced in Japan which use different virus strains: Matsuba, DCRB 19, Takahashi and TO- 336 are all produced using rabbit kidney cells; and Matsuura is produced using quail embryo fibroblasts. The RA 27/3 strain is used most often because of consistent immunogenicity, induction of resistance to re-infection and its low rate of side effects (Plotkin 1973). The live virus produces viraemia and pharyngeal excretion, but both are of low magnitude and are non-communicable (Plotkin 1999a).

Why it is important to do this review

Despite its worldwide use, no systematic reviews studying the effectiveness and safety of MMR vaccines are available.

OBJECTIVES

1. To review the existing evidence on the absolute effectiveness of the MMR vaccine in children (by the effect of the vaccine on the incidence of clinical cases of measles, mumps and rubella).

2. To assess the worldwide occurrence of adverse events, including those that are common, rare, short-term and long-term, following exposure to the MMR vaccine in children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), controlled clinical trials (CCTs), cohort studies, case-control studies, time-series studies, case cross-over studies, ecological studies, self controlled case series, mixed RCT and time-series (see Appendix 1).

Types of participants

Healthy children up to 15 years of age.

Types of interventions

Vaccination with any combined MMR vaccine given in any dose, preparation or time schedule compared with do nothing or placebo.

Types of outcome measures

Primary outcomes

1. Effectiveness: clinical and/or confirmed cases of measles, mumps or rubella.
2. Safety: serious systemic adverse events. All those which have been hypothesised so far (thrombocytopenic purpura, parotitis, joint and limb symptoms, Crohn's disease, ulcerative colitis, autism and aseptic meningitis), plus encephalitis/encephalopathy, febrile seizure, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, demyelinating diseases, bacterial or viral infection.

Secondary outcomes

1. Local reactions (for example, soreness and redness at the site of inoculation) and systemic reactions (for example, fever, rash, vomiting and diarrhoea) following MMR vaccination.

Search methods for identification of studies

Electronic searches

For effectiveness

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, EMBASE (July 2004 to May 2011) and PubMed (July 2004 to May week 2, 2011). We used the following search terms for CENTRAL and PubMed.

1 explode 'Vaccines-Combined' / all subheadings
2 explode 'Vaccines-Attenuated' / all subheadings
3 #1 or #2
4 trivalen* or combin* or simultan* or tripl* or trebl*
5 vaccin* or immuni* or inoculat*
6 # 4 and # 5
7 # 3 or # 6
8 explode 'Measles-' / all subheadings
9 explode 'Mumps-' / all subheadings
10 explode 'Rubella-' / all subheadings
11 measles and mumps and rubella
12 #8 or #9 or #10 or #11
13 #7 and #12
14 explode 'Measles-Vaccine'
15 explode 'Mumps-Vaccine'
16 explode 'Rubella-Vaccine'
17 explode 'Measles-Mumps-Rubella-Vaccine' / all subheadings
18 measles mumps rubella or MMR
19 #14 or #15 or #16 or #17 or #18
20 #13 or #19

We adapted these subject terms for EMBASE (see Appendix 2). We conducted all searches during the second week of May, 2011. We also considered the Cochrane Database of Systematic Reviews (CDSR) and the NHS Database of Abstracts of Reviews of Effects (DARE) for published reviews. For search strategies used in the previous version of the review see Appendix 3.

For safety

Again, for this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, EMBASE (July 2004 to May 2011) and PubMed (July 2004 to May week 2 2011). We used the following search terms for CENTRAL and PubMed.

1 Vaccines-Combined [mesh word (mh)]
2 Vaccines-Attenuated
3 ((trivalen*[text word (tw)] or combin* (tw) or simultan* (tw) or tripl* (tw) or trebl* (tw) and (vaccin* (tw) or immuni* (tw) or inoculat* (tw)))
4 or/1-3
5 measles (tw) and mumps (tw) and rubella (tw)
6 4 and 5
7 Measles-Vaccine(mh) and Mumps-Vaccine (mh) and Rubella-Vaccine (mh)
8 MMR [title, abstract (ti,ab)]
9 (measles (tw) and mumps (tw) and rubella (tw) and (vaccin* (tw) or immuni* (tw) or inoculat* (tw))
10 or/6-9
11 adverse events [floating sub-heading (fs)] or chemically induced

(fs) or complications (fs) or contraindications (fs) or toxicity (fs) or poisoning (fs) or drug effects (fs)
12 ((adverse (tw) and (effect* (tw) or event* (tw)) or side effect* (tw) or hypersensitiv* (tw) or sensitiv* (tw) or safe* (tw) or pharmacovigil* (tw)
13 explode Product-Surveillance-Postmarketing (mh) or Drug-Monitoring (mh) or Drug-Evaluation (mh) or explode Risk (mh) or Odds-Ratio (mh) or explode Causality (mh)
14 relative risk (tw) or risk (tw) or causation (tw) or causal (tw) or odds ratio (tw) or etiol* (tw) or aetiol* (tw) or etiology (fs) or epidemiology (fs)
15 or/11-14
16 10 and 15
As before, we adapted this filter for searching EMBASE (see Appendix 2).

Searching other resources

For effectiveness trials, we searched bibliographies of all relevant articles obtained and any published reviews for additional studies. We also searched the following sources for unpublished, prospectively registered trials: http://www.clinicaltrials.gov/ and http://www.controlled-trials.com/. In addition, we contacted vaccine manufacturers, companies that market vaccines, the leading or corresponding authors of studies evaluated and researchers or experts in the field, where appropriate, to identify any unpublished studies. We imposed no language restrictions.
For safety trials, we assessed bibliographies of all relevant articles and any published reviews for additional studies. We imposed no language restrictions.

Data collection and analysis

See Appendix 1 for study design definitions (based on: Farrington 2004; Jefferson 1999; Last 2001).

Selection of studies

Two review authors (MGD, CDP) independently applied the inclusion criteria to all identified and retrieved articles. A third review author (VD) arbitrated in case of disagreements about eligibility of a study.

Data extraction and management

Three review authors (AR, MGD, CDP) independently performed data extraction using a data extraction form (Appendix 4). One review author (VD) checked data extractions and arbitrated in case of disagreements.

Assessment of risk of bias in included studies

Three review authors (AR, MGD, CDP) independently assessed the methodological quality of the included studies. We assessed the quality of RCTs and quasi-RCTs using the criteria adapted from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the quality of non-RCTs in relation to the presence of potential confounders which could make interpretation of the results difficult. However, because there was insufficient empirical evidence to demonstrate the validity of the non-randomised quality assessment screens, these studies were used for the purposes of qualitative analysis only.
We evaluated the quality of case-control (prospective and retrospective) and cohort studies using the appropriate Newcastle-Ottawa Scales (NOS) (Wells 2000). We applied quality control assessment grids, based on those developed by The University of York, NHS Centre for Reviews and Dissemination (Khan 2001), to historical controlled trials (HCTs), interrupted time-series and case cross-over studies and ecological studies (see Appendix 4). We used a classification and methodological quality checklist (unpublished) for case-only design studies, especially developed by CP Farrington and TO Jefferson and adapted from a paper by CP Farrington (Farrington 2004).

Measures of treatment effect

This is a descriptive review.

Unit of analysis issues

This is a descriptive review.

Dealing with missing data

We did not use any strategies to impute missing outcome data.

Assessment of heterogeneity

We firstly assessed included studies for clinical homogeneity. As we found diversity of exposure, outcomes and length of follow-up, we decided against pooling data and carried out a descriptive review.

Assessment of reporting biases

Not performed.

Data synthesis

We classified and discussed included studies according to the type of outcomes for which they provided evidence, i.e. effectiveness, possible association with harms or local and systemic adverse effects. We illustrated study characteristics, design, population, outcomes definitions, methods used and results in the Effects of interventions section and in the Additional tables.

Subgroup analysis and investigation of heterogeneity

This is a descriptive review.

Sensitivity analysis

This is a descriptive review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

We updated the searches in May 2011 and identified 3371 articles for screening. We identified and retrieved 96 papers after reviewing the titles and abstracts. Out of these, we included 33 in the update. Our original searches identified 4889 articles for screening, a large number of studies because of the deliberately broad search design. After screening, we retrieved 139 studies possibly fulfilling our inclusion criteria; 108 studies did not meet all inclusion criteria and were excluded, while 31 were included in this review. In this 2011 update, we included a total of 64 studies.

Included studies

We included the following studies.

- Five randomised controlled trials (RCTs) (Bloom 1975; Edees 1991; Lerman 1981; Peltola 1986; Schwarz 1975).
- One controlled clinical trial (CCT) (Ceyhan 2001).
- Twenty-seven cohort studies (Ahlgren 2009a; Beck 1989; Benjamin 1992; DeStefano 2002; Chamot 1998; Dunlop 1989; Fombonne 2001; Hviid 2004; Hviid 2008; Lopez Hernandez 2000; Madsen 2002; Makela 2002; Makino 1990; Marin 2006; Marolla 1998; McKeever 2004; Miller 1989; Ong 2005; Ong 2007; Robertson 1988; Schlegel 1999; Sharma 2010; Stokes 1971; Swartz 1974; Uchiyama 2007; Vestergaard 2004; Weibel 1980).
- Seventeen case-control studies (Ahlgren 2009b; Bertuola 2010; Black 1997; Black 2003; Bremner 2005; Bremner 2007; Castilla 2009a; Davis 2001; DeStefano 2004; Giovanetti 2002; Goncalves 1998; Harling 2005; Ma 2005; Mackenzie 2006; Mrozek-Budzyn 2010; Ray 2006; Smeeth 2004).
- Five time-series studies (da Cunha 2002; Dourado 2000; Fombonne 2006; Freeman 1993; Honda 2005).
- One case cross-over trial (Park 2004).
- Two ecological studies (Jonville-Bera 1996; Seagroatt 2005).
- Six self controlled case series (France 2008; Miller 2005; Miller 2007; Stowe 2009; Taylor 1999; Ward 2007).

One study (Freeman 1993) had a mixed RCT and time-series design and we classified it as the latter because adverse event data comparison was carried out on outcomes in children before and after vaccination. We classified studies reported as 'field trials' or 'controlled trials' as cohort studies when randomisation was not mentioned.

Twelve studies included effectiveness data against measles or mumps diseases: seven cohorts (Chamot 1998; Lopez Hernandez 2000; Marin 2006; Marolla 1998; Ong 2005; Ong 2007; Schlegel 1999) and five case-control studies (Castilla 2009a; Giovanetti 2002; Goncalves 1998; Harling 2005; Mackenzie 2006).

Seventeen reported on short-term side effects: five RCTs (Bloom 1975; Edees 1991; Lerman 1981; Peltola 1986; Schwarz 1975); one CCT (Ceyhan 2001); 10 cohort studies (Beck 1989; Benjamin 1992; Dunlop 1989; Makino 1990; Miller 1989; Robertson 1988; Sharma 2010; Stokes 1971; Swartz 1974; Weibel 1980) and one time-series study (Freeman 1993).

Important safety harms had been investigated in 35 studies: nine cohort studies (Ahlgren 2009a; DeStefano 2002; Fombonne 2001; Hviid 2004; Hviid 2008; Madsen 2002; McKeever 2004; Uchiyama 2007; Vestergaard 2004); 12 case-control studies (Ahlgren 2009b; Bertuola 2010; Black 1997; Black 2003; Bremner 2005; Bremner 2007; Davis 2001; DeStefano 2004; Ma 2005; Mrozek-Budzyn 2010; Ray 2006; Smeeth 2004); four time-series studies (da Cunha 2002; Dourado 2000; Fombonne 2006; Honda 2005); one case cross-over trial (Park 2004); two ecological studies (Jonville-Bera 1996; Seagroatt 2005) and seven self controlled case series (France 2008; Makela 2002; Miller 2005; Miller 2007; Stowe 2009; Taylor 1999; Ward 2007).

Excluded studies

Out of the 96 papers identified and retrieved for this update, we excluded 50 because they were not comparative, considered vaccines other than MMR, or did not present original data. (See Characteristics of excluded studies table for detailed information regarding reasons for exclusion). We classified a further 13 studies as pending, as some important details were not available in the papers (see Characteristics of studies awaiting classification table).

Risk of bias in included studies

Studies evaluating vaccine effectiveness

Out of the 12 cohorts and case-control studies assessing effectiveness of MMR vaccines in preventing measles or mumps, only three had a moderate bias risk. The remaining nine were characterised by poor methodological quality due to poor reporting or missing information about comparability between exposed or non-exposed groups; the composition of MMR vaccine is sometimes not reported (Table 1 Table 2 and Table 3).

Studies evaluating short-term side effects

Seventeen trials reported on short-term side effects: five RCTs; one CCT; 10 cohort studies and one time-series study (Table 4). We assessed the risk of bias in the RCTs and CCT to be of low risk of bias in two trials (Lerman 1981; Peltola 1986); moderate/unknown risk of bias in two trials (Ceyhan 2001; Edees 1991); and high risk of bias in two trials (Bloom 1975; Schwarz 1975).

Allocation

Out of the five RCTs and one CCT assessing short-term side effects, only two studies (Lerman 1981; Peltola 1986) had adequate concealment.

Blinding

Out of the five RCTs and one CCT assessing short-term side effects, three trials were double-blind (Lerman 1981; Peltola 1986; Schwarz 1975), one single-blind (Edees 1991), whereas the remaining two (Bloom 1975; Ceyhan 2001) were not blinded.

Incomplete outcome data

In the Ceyhan 2001 and Lerman 1981 trials, the selection of paediatric practices involved in the recruitment of children was not explained and the number and assessment of non-responders were not reported. Similarly in the Edees 1991 trial there are few details on the refusal and response rate during the recruitment phase and a lack of demographic information from the two UK areas where the trial was conducted. We considered the Ceyhan 2001 and Edees 1991 trials to have a moderate risk of detection bias affecting the outcomes.

Selective reporting

In the two trials we assessed as being at high risk of reporting bias (Bloom 1975; Schwarz 1975), we reported adverse effects for only 60% and 39% of participants, respectively.

Other potential sources of bias

Not known.

Cohort studies

- Low risk of bias: no studies.
- Moderate/unknown risk of bias: two studies (Benjamin 1992; Robertson 1988).
- High risk of bias: eight studies (Beck 1989; Dunlop 1989; Makino 1990; Miller 1989; Sharma 2010; Stokes 1971; Swartz 1974; Weibel 1980).

There was a lack of adequate description of exposure (vaccine content and schedules) in all cohort studies. Another recurring problem was the failure of any study to provide descriptions of all outcomes monitored. A lack of clarity in reporting and systematic bias made comparability across studies and quantitative synthesis of data impossible.

Time-series studies

The only time-series study (Freeman 1993) was evaluated to be affected by a high degree of risk of bias. The number of completed weekly diaries varied over the eight-week study period, with no indication of whether the losses occurred pre or postvaccination. In addition, there was an overall attrition rate of 33%.

Studies evaluating safety harms

The association between MMR and serious harms was investigated in 35 studies (nine cohorts, 12 case-control studies, four time-series studies, one case-cross over, two ecological studies, seven self controlled case series). Results of risk of bias assessment in the following is split by study design.

Cohort studies

- Low risk of bias: two studies (Hviid 2004; Vestergaard 2004).
- Moderate/unknown risk of bias: three studies (DeStefano 2002; Hviid 2008; Madsen 2002).
- High risk of bias: four studies (Ahlgren 2009a; Fombonne 2001; McKeever 2004; Uchiyama 2007).

In Fombonne 2001 the number and possible impact of bias was so high that interpretation of the results was difficult. The cohort study of Uchiyama 2007 was potentially affected by a different type of bias, considering that the participants were from a private clinic and that definitions of applied Autistic Spectrum Disorders (ASD) diagnosis and of methods used for ASD regression ascertainment were not clearly reported. Estimates from McKeever 2004 (although significant) are strongly affected by ascertainment bias, as children who are not taken to the doctor are less likely to be vaccinated and also have fewer opportunities to have diagnoses of allergic diseases recorded.

Case-control studies

- Low risk of bias: two studies (Black 1997; Davis 2001).
- Moderate/unknown risk of bias: eight studies (Black 2003; Bremner 2005; Bremner 2007; DeStefano 2004; Ma 2005; Mrozek-Budzyn 2010; Ray 2006; Smeeth 2004).
- High risk of bias: two studies (Ahlgren 2009b; Bertuola 2010).

In Black 1997 there was a moderate likelihood of selection bias because of missing cases and their records (up to 27%) but the study and its methods were well reported. Lack of clarity over the vaccine exposure status of the controls made the results of the Black 2003 study difficult to interpret. In Bertuola 2010, cases and controls were apparently not matched. Ascertainment of exposure was performed only with questionnaires to parents. Investigators were probably not blinded to the case or control status of the participants. In Ma 2005, refusal to participate in the study or inability to locate the participants and controls could have introduced a moderate risk of selection bias. Exclusion of participants without completed questionnaires and of those who did not attend the sixth grade at school within the study area could have introduced a relevant selection bias in the Ahlgren 2009b case-control study.

Time-series studies

- Low risk of bias: no studies.
- Moderate/unknown risk of bias: three studies (da Cunha 2002; Dourado 2000; Honda 2005).
- High risk of bias: one study (Fombonne 2006).

Limited error could have been introduced by using population data from a prior census (as estimation of the denominator) in Dourado 2000, so as by using the number of doses administered (as opposed to supplied) in the mass vaccination programme. Assessment of Pervasive Development Disorders (PDD) cases in Fombonne 2006 was made on the basis of administrative codes only: diagnosis could have been imprecise and did not allow us to consider PDD subtypes or regression.

Case cross-over studies

- Low risk of bias: no studies.
- Moderate/unknown risk of bias in one study (Park 2004).
- High risk of bias: no studies.

In Park 2004 there was a moderate likelihood of selection bias due to missing cases and their records (up to 27%).

Ecological studies

- Low risk of bias: no studies.
- Moderate/unknown risk of bias: one study (Jonville-Bera 1996).
- High risk of bias: one study (Seagroatt 2005).

Self controlled case series studies

- Low risk of bias: two studies (France 2008; Ward 2007).
- Moderate/unknown risk of bias: four studies (Makela 2002; Miller 2005; Miller 2007; Taylor 1999).
- High risk of bias: one study (Stowe 2009).

The study by Makela 2002 was weakened by the loss of 14% of the original birth cohorts and the effects of the rather long-term follow-up. What the impact of either of these factors was in terms of confounders is open to debate. It should be taken into account that autism does not often involve hospitalisation and data about outpatients visits were not available. The long follow-up for autism could be due to the lack of a properly constructed causal hypothesis. Again, the study of Taylor 1999 demonstrates the difficulties of drawing inferences in the absence of a non-exposed population or a clearly defined causal hypothesis. The exclusive use of discharge diagnoses for identification of cases in Miller 2007 could have introduced a noteworthy selection bias.

Effects of interventions

Studies reporting effectiveness findings

Eight cohorts and five case-control studies investigated effectiveness outcomes.

Measles

Evidence from cohort studies

Effectiveness against measles was investigated in three cohort studies (Marin 2006; Marolla 1998; Ong 2007).

One cohort study (Marolla 1998) evaluated the effectiveness of MMR vaccination in preventing clinical cases of measles in children aged 18 to 90 months from several local health agencies in Rome, Italy (n = 2745). Vaccination was performed with three different commercial MMR vaccines, two containing both Schwarz strain (Pluserix and Morupar) and one other prepared with Edmonston-Zagreb strain (Triviraten). Vaccines effectiveness was calculated by using the following formula [1-(measles incidence among vaccinated/measles incidence among unvaccinated) x 100]. Effectiveness (one dose) was estimated to be 97% (95% confidence interval (CI) 88 to 99) in the Morupar study arm, whereas no measles cases were found among Pluserix recipients. Effectiveness was comparably high (95%; 95% CI 90 to 98) when Triviraten was administered.

One other cohort study (Ong 2007) investigated the effectiveness of MMR immunisation (composition not reported by authors) in children aged between eight and 14 years in preventing measles cases with laboratory confirmation. Two laboratory-confirmed measles cases occurred among the 171 vaccinated children (one dose), whereas seven were observed in the unvaccinated group (n = 13). Vaccine effectiveness (VE = 97%) was calculated in Orenstein 1985, [(attack rate among unvaccinated-attack rate among vaccinated/attack rate among unvaccinated) x 100].

Effectiveness of MMR vaccination in preventing secondary measles cases was assessed in the Marin 2006 study. Vaccination with one or two doses of MMR vaccine (composition unknown) was highly effective in preventing secondary cases among contacts. Estimate VE (Orenstein 1985) was 92% (95% CI 67 to 98) after one dose and 95% (95% CI 82 to 98) after two doses.

Mumps

Effectiveness of the MMR vaccine against clinical mumps disease was assessed in five cohort and five case-control studies.

Evidence from cohort studies

In three cohort studies (Marolla 1998; Ong 2005; Schlegel 1999) occurrence of clinical mumps cases during outbreaks was retrospectively evaluated by comparing the incidence of disease among children who had been immunised with MMR vaccines containing different mumps strains (Jeryl Lynn, Urabe, Rubini) with that observed among non-immunised children.

In Ong 2005, carried out in childcare centres and primary schools in Singapore (n = 5072, aged five to 12) and Schlegel 1999, performed on children (n = 163, aged five to 13 years) from a small rural village in Switzerland, preventive effectiveness for Jeryl Lynn, Urabe or Rubini strains was compared with no immunisation.

Preventive effectiveness estimates (Orenstein 1985) for at least one dose of the Jeryl Lynn strain-containing MMR vaccine were similar in both studies, with statistically relevant significance: VE 80.7%; 95% CI 57.8 to 90.8 (Ong 2005) and 78% (95% CI 64 to 82) (Schlegel 1999).

Effectiveness of MMR Urabe vaccine (at least one dose) has been estimated to be highly effective (VE 87%; 95% CI 76 to 94) in Schlegel 1999, whereas the estimate from the Ong 2005 study did not reach statistical relevance (VE 54%; 95% CI -16.2 to 81.7).

The Rubini strain-containing MMR vaccine was highly ineffective in preventing clinical mumps cases in the Ong 2005 study (VE -55.3%; 95% CI -121.8 to -8.8); the estimate from the Schlegel 1999 study was not statistically relevant (VE -4%; 95% CI 218 to 15).

In Marolla 1998 effectiveness against mumps was similar for both Urabe-containing MMR vaccines (VE 75%; 95% CI 65 to 83 for Pluserix and VE 73%; 95% CI 59 to 82 for Morupar). The Rubini strain was much less effective (VE 23%; 95% CI 6 to 37).

The cohort of Lopez Hernandez 2000 estimated MMR vaccination effectiveness in preventing clinical mumps on male children aged between three and 15 years, attending a scholastic institute in Granada, Spain during an outbreak. Occurrence of clinical mumps cases was compared between children who received at least one dose of MMR vaccine (investigators were not able to determine the vaccine composition) and those who did not receive the MMR vaccine. The effectiveness estimate was 49% (P = 0.047) (Orenstein 1985).

One other cohort study (Chamot 1998) investigated the occurrence of clinical mumps in MMR vaccinated and non-vaccinated household contacts aged up to 16 years (secondary cases) of primary mumps cases (with clinical or laboratory confirmation). Urabe-containing MMR vaccine showed a protective effect against secondary case onset in comparison with no vaccination: vaccine effectiveness as ([1-(attack rate in vaccinated/attack rate in not vaccinated)] x 100) was 73.1%; 95% CI 41.8 to 87.6. Protection afforded by both Jeryl Lynn and Rubini-containing MMR vaccines was instead not statistically relevant (VE 61.6%; 95% CI -0.9 to 85.4 and VE 6.3%; 95% CI -45.9 to 39.8, respectively).

Evidence from case-control studies

Five case-control studies assessed the effectiveness of MMR vaccination against mumps (Castilla 2009a; Giovanetti 2002; Goncalves 1998; Harling 2005; Mackenzie 2006).

One case-control study (Harling 2005) assessed effectiveness of immunisation with one or two doses of Jeryl Lynn-containing MMR vaccine in the prevention of clinical and laboratory-confirmed mumps cases. Cases (n = 156) and controls (n = 175) were children and adolescents (aged one to 18 years) living in a religious community in North-East London, where a mumps outbreak was observed (June 1998 to May 1999). Effectiveness estimates (expressed as VE = [(1-Odds Ratio) x 100] for one or two doses were similar against clinical (VE 69%; 95% CI 41 to 84) and laboratory-confirmed mumps (VE 65%; 95% CI 25 to 84). Two doses were more effective (VE 88%; 95% CI 62 to 96) than one (VE 64%; 95% CI 40 to 78) against clinical mumps.

The following three case-control studies used surveillance systems with the aim of identifying mumps cases in the study population.

Goncalves 1998 assessed the effectiveness of at least one dose of MMR vaccines prepared with either the Urabe or Rubini strain in prevention of clinical mumps cases during an epidemic on a population of children and adolescents (189 cases and 378 controls, aged 15 months to 16 years). Significant protection was conferred by the Urabe strain-containing MMR vaccine (VE= [1-Odds Ratio (OR)] x 100 = 70%; 95% CI 25 to 88), and not by the Rubini strain-containing MMR (VE 1%; 95% CI -108 to 53).

In Giovanetti 2002 field effectiveness of MMR vaccination (at least one dose, unknown composition) in preventing clinical mumps on a population of children and adolescents (139 cases and controls) was 53.7% (95% CI 20.3 to 73.0 ; VE = [1-OR] x 100).

In Castilla 2009a, case definition considers clinical mumps with laboratory or epidemiological confirmation (Table 3), occurring during an outbreak in the Navarre region (Northern Spain) between August 2006 and June 2008 in children and adolescents

(241 cases and 1205 matched controls). Vaccine effectiveness of MMR vaccine prepared with Jeryl Lynn mumps strain (VE = [1-OR] x 100), calculated by means of conditional logistic regression analysis, was 72% (95% CI 39% to 87%, P = 0.0013) for any dose, 66% (95% CI 25% to 85%, P = 0.0075) for one dose and 83% (95% CI 54% to 94%, P = 0.0005) for two doses. The authors hypothesised a higher risk of having mumps when the first MMR dose is administered after the 36th month of age (OR 3.11; 95% CI 1.15 to 8.43, P = 0.0254) or when the two MMR doses are administered more than 36 months apart (OR 10.19; 95% CI 1.47 to 70.73, P = 0.0189).

Mackenzie 2006 attempted to estimate effectiveness of MMR vaccination against virological-confirmed mumps on pupils (aged 13 to 17 years) attending a boarding school in Scotland (20 cases and 40 matched controls). The numerical size of the study was not large enough to reach statistical relevance (OR for any MMR dose = 0.66; 95% CI 0.22 to 2.00).

Rubella

We found no studies assessing the effectiveness of MMR vaccine against clinical rubella.

Short-term side effects

CCTs and RCTs

MMR vaccines were compared with monovalent measles vaccine (Ceyhan 2001; Edees 1991; Lerman 1981), two types of monovalent mumps and rubella vaccines (Lerman 1981) or placebo (Bloom 1975; Lerman 1981; Peltola 1986; Schwarz 1975). One trial (Peltola 1986) carried out in twins, reported a possible protective effect of the MMR vaccine with a lower incidence of respiratory symptoms, nausea and vomiting, and no difference in the incidence of other unintended side effects compared with placebo, with the exception of irritability. Another trial concluded that there was no increased clinical reactivity with a MMR vaccine containing two strains of rubella (Lerman 1981).

The trial by Edees concluded that there was no significant difference between the numbers of children developing symptoms after MMR or measles vaccination (Edees 1991). The trials by Bloom and Schwarz concluded that the incidence of raised temperature, rash, lymphadenopathy, coryza, rhinitis, cough, local reactions or limb and joint symptoms were not significantly different from placebo (Bloom 1975; Schwarz 1975).

All RCTs and CCTs reported a wide range of outcomes and used different terms, often with no definition. For example, body temperature higher than 38 °C was measured or reported in 16 ways. When reported, different temperature increments, recording methods, observation periods and incidence made comparisons between trials and pooling of data impossible (Table 5).

Cohort studies

Occurrence of short-term side effects was assessed in 10 cohort studies altogether. They compared the MMR vaccine with single measles vaccine (Dunlop 1989; Makino 1990; Miller 1989; Robertson 1988), mumps-rubella vaccine (Swartz 1974), single mumps vaccine (Makino 1990), single rubella vaccine (Swartz 1974; Weibel 1980), placebo (Beck 1989) or no intervention (Benjamin 1992; Sharma 2010; Stokes 1971).

The study by Benjamin found that the MMR vaccine was associated with an increased risk of episodes of joint and limb symptoms in girls less than five years of age (Benjamin 1992).

There was no difference in the incidence of common outcomes such as fever, rash, cough, lymphadenopathy, arthralgia, myalgia and anorexia between the MMR vaccine and rubella vaccine (Makino 1990; Swartz 1974; Weibel 1980), mumps-rubella vaccine (Swartz 1974), single mumps vaccine (Makino 1990) or measles vaccine (Dunlop 1989; Makino 1990). Two studies (Miller 1989; Robertson 1988) found that symptoms were similar following MMR and measles vaccination except for a higher incidence of parotitis following MMR vaccination (Miller 1989). Makino reported a higher incidence of diarrhoea in the MMR vaccines arm compared to the single measles or rubella vaccines arms (Makino 1990). The studies by Beck and Stokes reported no difference in the incidence of rash and lymphadenopathy between MMR vaccination and placebo (Beck 1989) or do nothing (Stokes 1971). However, Stokes 1971 reported an increase in the incidence of fever in the period Day 5 to Day 12 postvaccination but Beck 1989 reported no difference.

Considering the cohort of Sharma 2010 only within the subgroup of younger children (16 to 24 months of age), fever during the 42 days postvaccination had been reported more frequently among individuals immunised with MMR than among unvaccinated individuals. This trend appeared to be different when the older population was considered; fever had been reported with slightly higher frequency among unvaccinated children.

Time-series

In the Freeman 1993 study, conducted by 22 family physicians, occurrence of common symptoms following MMR immunisation (type not described) was assessed by means of weekly diaries in participants immunised at 13 and 15 months of age, comparing their incidence during the four weeks before with that observed four weeks after immunisation. The incidence of rash, lymphadenopathy and nasal discharge was found to be higher after exposure to MMR immunisation.

Severe harms

Possible association of MMR immunisation with severe harms has been tested in several observational studies.

Neurological diseases

1. Encephalitis - encephalopathy

Association between MMR immunisation and occurrence of encephalopathies was investigated in three studies: one case-control study (Ray 2006) and two self controlled case series studies (Makela 2002; Ward 2007).

The case-control study of Ray 2006 tested if hospitalisations due to encephalopathy, Reyes syndrome or encephalitis (Table 6) occurring in children aged zero to six years could be linked to MMR vaccine administration. Different time intervals between MMR exposure and date of hospitalisation have been considered: seven to 14 days, zero to 14 days, zero to 30 days, zero to 60 days and zero to 90 days. Four hundred and fifty-two cases together with their 1280 matched controls were included in the analysis. In none of the considered time intervals was exposure to the MMR vaccine statistically different among the cases and controls.

Makela 2002 was based on a surveillance study by the National Public Health Institute that began after the introduction of MMR vaccination in Finland for children aged 14 to 18 months and six years (1982). Participants aged one to seven years (n = 535,544) who received the MMR II vaccine between November 1982 and June 1986 were considered in the study (this population corresponds to 86% of all children scheduled for MMR vaccination in Finland). Risk association was evaluated by comparing the number of hospitalisations for encephalitis or encephalopathy (see Table 6 for outcome definition) within three months after vaccination with those occurring during the subsequent seven three-month intervals. Out of the 199 hospitalisations for encephalitis or encephalopathy, nine occurred within three months after MMR vaccination, 110 occurred more than three months after vaccination (88 in an interval between three and 24 months), whereas 80 occurred before the vaccine was administered. Trial authors stated that no hospitalisation excess for encephalitis or encephalopathy was observed during the three months post-immunisation (P = 0.28).

In Ward 2007, in order to evaluate the association between encephalitis (see Table 6 for case definitions) and MMR vaccination, cases (n = 107) diagnosed at the age of 12 to 35 months were considered (children aged 12 to 15 months were scheduled for MMR vaccination in Britain and Ireland). The risk period for encephalitis was considered to be the time between 15 and 35 days following MMR immunisation. The incidence of disease within the risk period was compared with that outside it (the control period). The incidence of encephalitis in the risk period (15 to 35 days) was not statistically different from that of the control period (relative incidence = 1.34 ; 95% CI 0.52 to 3.47). This estimate does not change in the presence or absence of primary HHV-6 or HHV-7 infections.

2. Aseptic meningitis

The association of the MMR vaccine with aseptic meningitis was evaluated in the following studies.

Case-control studies

In Black 1997, MMR vaccination within defined intervals before the index date (zero to 14 days, zero to 30 days, eight to 14 days) was assessed in cases and controls to assess its association with aseptic meningitis (see Table 7 for outcome definitions). Exposure to the MMR vaccine was not statistically different between cases and controls in any of the considered time intervals.

Cross-over studies

In Park 2004 the risk association of MMR vaccination with aseptic meningitis (see Table 7 for outcome definitions) has been evaluated by means of a cross-over design. Thirty-nine participants aged 13 to 29 months of both sexes were included. Risk estimation was calculated considering whether MMR vaccine exposure occurred during a time window of 42 days before disease onset or before (from 43 to 365 days before): 11 out of the 39 participants received MMR vaccination during the risk period and 28 outside of it. Mantel-Haenszel OR estimate indicates a positive association (3.0; 95% CI 1.5 to 6.1).

Self-controlled case-series study

In the study of Makela 2002, the risk association of MMR II vaccine (Enders-Edmonston, Jeryl Lynn ,Wistar RA 27/3) exposure was assessed as for encephalitis, by comparing the number of hospitalisations within three months after vaccination with those occurring during the subsequent seven three-month intervals. Ten hospitalisations for aseptic meningitis occurred within three months after MMR immunisation, whereas there were 110 thereafter (54 between three and 24 months) and 41 were vaccinated after hospitalisation. No significant increase in aseptic meningitis was observed during the three months following immunisation (P = 0.57).

Time-series studies

Dourado 2000 compared the incidence of aseptic meningitis hospitalisation (see Table 7 for definitions) before and after a mass immunisation campaign (Pluserix) carried out in Salvador city (State of Bahia, NE Brazil, population about 2.2 million in 1996) and having as target population children aged one to 11 years (452,334 based on the 1996 census). The incidence of aseptic meningitis hospitalisation was significantly higher during the third (18 cases

risk ratio (RR) 14.28; 95% CI 7.93 to 25.71), fourth (15 cases RR 11.90; 95% CI 6.38 to 22.19), fifth (nine cases, RR 7.14; 95% CI 3.38 to 15.08) and sixth (four cases, RR 3.17; 95% CI 1.12 to 9.02) weeks following the start of the immunisation campaign when compared with that observed during the 23 pre-immunisation weeks (reference period). Risk association was moreover estimated by case series method, including in analysis only the 37 aseptic meningitis cases with known vaccination status and date occurring during the epidemiological weeks 36 to 39 (about 15 to 35 days after immunisation). Authors attributed 32 of the 37 cases to be due to Urabe-containing MMR vaccine Pluserix (one in about 14,000 doses).
The study of da Cunha 2002 had an analogous design and was carried out in two other Brazilian states, Mato Grosso (MT) and Mato Grosso do Sul (MS). As before, the target population were children aged one to 11 years (estimated 580,587 in MS and 473,718 in MT). The incidence of aseptic meningitis in MS became significantly higher than in the pre-immunisation time from two weeks after the start of the campaign (four cases, RR 5.6; 95% CI 1.3 to 14.1), which peaked at three weeks (16 cases, RR 22.5; 95% CI 11.8 to 42.9) and four weeks after the start of the campaign (15 cases, RR 21.1; 95% CI 11.0 to 40.7) and returned to the average after week 39. A similar trend was observed in MT, where the incidence of cases became significantly higher during the third week (40) after the start of the campaign (five cases, RR 2.6; 95% CI 1.1 to 6.5) which peaked in week 42 (30 cases, RR 15.6; 95% CI 10.3 to 24.2) and week 43 (23 cases, RR 12.0; 95% CI 7.6 to 19.4) and returned to the average from week 46 onwards.

3. Febrile seizure

Person-time cohort studies

The study of Vestergaard 2004 is a person-time cohort assessing the risk of febrile seizure (Table 8) after the introduction of routine MMR vaccination in Denmark in 1987. The study population consisted of the birth cohorts 1991 to 1998 (n = 537,171). Globally, the risk of febrile seizure was significantly higher among the vaccinated (RR 1.10; 95% CI 1.05 to 1.15). When different time frames after vaccination are considered, the RR was at the highest point within two weeks after immunisation (RR 2.75; 95% CI 2.55 to 2.97), did not differ significantly in weeks three to six and became slightly less than one in weeks seven, eight, nine to 26 and 27 to 52. The RR was not different to the unvaccinated after week 53. For evaluation of long-term prognosis, the number of recurrent episodes of febrile seizure and the cases of epilepsy observed in children who received MMR vaccination within 14 days before their first febrile seizure episode and in those who were vaccinated more than 14 days before their first febrile seizure episode, were compared with those who were not vaccinated at the time of their first febrile seizure episode. A significant risk association was found only for recurrent febrile seizure episodes in children who were immunised with MMR within 14 days before the first episode (RR 1.19; 95% CI 1.10 to 1.41, adjusted for age, calendar period, age at first febrile seizure and current vaccination status).

Self controlled case series study

In Ward 2007 (already described in the section 'Encephalitis - encephalopathy'), the risk of severe illness with fever and convulsion following MMR immunisation was also investigated. The considered risk period was the time between six and 11 days following immunisation. As before, disease incidence within the risk period was compared with that outside it (the control period). Episodes of severe illness with fever and convulsion were more frequent within six to 11 days after MMR immunisation (relative incidence (RI) 5.68; 95% CI 2.31 to 13.97).
In Miller 2007 children aged 12 to 23 months (n = 894) with a discharge diagnosis of febrile convulsion (Table 8) and who received one MMR vaccine dose were included in the analysis. The incidence of disease during two "at risk" periods (between six to 11 and 15 to 35 days after immunisation) was compared with that determined for the background period. During the time between six and 11 days following MMR vaccination (of all types) a significantly higher relative incidence (RI) of febrile convulsion had been observed (RI 4.09; 95% CI 3.1 to 5.33). On the contrary, RI of febrile convulsions did not differ significantly from the background period during the 15 to 35 days following MMR immunisation (RI 1.13; 95% CI 0.87 to 1.48). The risk incidence of febrile convulsion was also analysed considering a "more specific" definition (Table 9). Considering all MMR vaccine types, the risk incidence remains higher in the six to 11 days following vaccination (RI 4.27; 95% CI 3.17 to 5.76), whereas the time between 15 to 35 days following vaccination it remains of borderline significance (RI 1.33; 95% CI 1.00 to 1.77).

Thrombocytopaenic purpura

Case-control studies

In Black 2003 cases (n = 23) and matched controls (n = 116) were selected within data contained in the General Practice Research Database (GPRD). Relative risk of developing idiopathic thrombocytopaenic purpura (ITP) (see Table 10) within six weeks after MMR immunisation was estimated to be 6.3 (95% CI 1.3 to 30.1) with an estimate attributable risk of 1 case/25,000 doses. Risk would be not statistically different from reference groups for the time between 7 and 26 weeks after vaccination.
Also Bertuola 2010 tested the association between acute immune thrombocytopaenia (AIT) and MMR vaccination by means of a case-control design in children and adolescents (aged one month

to 18 years). The risk estimate was calculated considering the exposure to the MMR vaccine (strain composition not reported) during the six weeks preceding hospitalisation in cases and controls (see definitions Table 10). Fourteen out of the 387 cases and 27 out of the 1924 controls received the MMR vaccine within six weeks before hospitalisation (OR 2.4; 95% CI 1.2 to 4.7, adjusted for age and use of drugs by multiple logistic regression).

Self controlled case series and risk interval studies

The study by France 2008 is based on data contained in the Vaccines Safety Datalink project for the years 1991 to 2000, covering eight managed care organisations (MCO) across the USA. By consulting the database, 63 cases aged 12 to 23 months who met the definition (Table 10) could be identified. The 42 days following immunisation was considered as the exposed period, whereas the time before and after this was considered the not exposed period, with the exclusion of a six-week time interval before vaccination. Twenty cases had been classified as exposed and 43 as not exposed. The incidence rate ratio (IRR) between the exposed and unexposed time was calculated by using two different analytical methods: the self controlled case series (SCCS) and the "risk interval" (i.e. person-time cohort) method. By the SCCS method, conditional Poisson regression was used to calculate the IRR, controlled by age and excluding fixed covariate from the model (gender, MCO, MMR dose number). By the "risk interval" method, the Poisson regression model controlled for age, MMR dose number, MCO site and gender was used to calculate IRR. Estimates were respectively 5.38 (95% CI 2.72 to 10.62) and 3.94 (95% CI 2.01 to 7.69). Considering the analysis included only children aged 12 to 15 months (the age at which about 80% of MMR vaccinations were administered), the IRR estimates were 7.06 (95% CI 1.95 to 25.88) and 7.10 (95% CI 2.03 to 25.03) for SCCS and "risk time", respectively. The attributable risk was estimated to be about 1 ITP case per 40,000 administered MMR doses.

Ecological studies

The evidence of association between MMR, or any of its component vaccines, and the onset of thrombocytopenic purpura (TP) was also assessed in one ecological study (Jonville-Bera 1996). The study concluded that the evidence favoured an association but in all cases TP appeared to be a benign, self limiting condition not distinguishable from its idiopathic counterpart or from TP occurring after natural infection with measles, mumps or rubella. The study discussed the weakness of relying on the passive reporting system for the identification of cases and acknowledged a possible under-reporting of cases of TP.

Autism

Cohort studies

Three retrospective cohort studies investigated the risk of autism and pervasive development disorders (PDD) following MMR immunisation (Fombonne 2001; Madsen 2002; Uchiyama 2007) (Table 9).

The study by Madsen 2002 was conducted in Denmark and included all Danish children born between January 1991 and December 1998. The authors linked vaccination data reported in the National Board of Health with a diagnosis of autism (Table 9) from the Danish Psychiatric Central Register. After adjustment for confounders, the RR for autism is 0.92 (95% CI 0.68 to 1.24) and 0.83 (95% CI 0.65 to 1.07) for other autistic spectrum disorders. No association between age at vaccination, time since vaccination or date of vaccination and development of autism was found.

The retrospective cohort study by Fombonne 2001 tested several causal hypotheses and mechanisms of association between exposure to MMR vaccination and pervasive development disorders (PDDs, Table 9). The population was made up of three cohorts of participants; one was of older children acting as the control (pre-MMR vaccination introduction). The authors concluded that there was no evidence that PDDs had become more frequent, the mean age at parental concern had not moved closer to the date of exposure to MMR vaccination, there was no evidence that regression with autism had become more common, parents of autistic children with regression did not become concerned about their child in a different time frame from that of children without regression and children with regressive autism did not have different profiles or severity to those in the control group. Nor was there evidence that regressive autism was associated with inflammatory bowel disorders.

The retrospective cohort study by Uchiyama 2007 assessed the association between exposure to MMR vaccination and regression in autistic spectrum disorders (ASD). Participants were children with an ASD diagnosis (Table 9) from a private paediatric psychiatric clinic located in Yokohama city, Japan (Yokohama Psycho-Developmental Clinic, YPCD), that has become recognised as a centre for ASD. For study purposes, cases of ASD in patients born between 1976 and 1999 were considered (n = 904). They were classified according to the chance of having received the MMR vaccine as follows.

1. Pre-MMR vaccine generation: born between January 1976 and December 1984, n = 113.
2. MMR vaccine generation: born between January 1985 and December 1991, n = 292.
3. Post-MMR vaccine generation with an age of one to three years old after 1993 when the MMR vaccination programme was terminated, n = 499.

For 325 out of the 904 identified ASD cases, a regression in ASD could be assessed. Data were analysed in different ways.

Within the MMR vaccine generation group, OR estimates were calculated considering the cases of deterioration observed in children who received the MMR vaccine from the MCH handbook

(15/54) and the number of regression observed among participants who did not receive the MMR vaccine (45/132), after exclusion of those with unknown vaccination status (89). Authors reported an OR of 0.74 (95% CI 0.35 to 1.52, P = 0.49) in patients who received the MMR vaccine versus no MMR vaccination in the MMR period.

Furthermore, the OR estimate was calculated considering as the control group (not MMR vaccinated) also both pre- and post-MMR generation groups. Estimates were again not significant (OR 0.626; 95% CI 0.323 to 1.200). Comparison of regression cases observed within the MMR generation group (independent from documented vaccination status) with that observed in pre-MMR, post-MMR and pre- plus post-MMR groups did not provide statistically significant OR estimates.

Case-control studies

The risk of an association between the MMR vaccine and autism was investigated in three case-control studies (DeStefano 2004; Mrozek-Budzyn 2010; Smeeth 2004).

The study by Smeeth 2004 assessed the association between exposure to the MMR vaccine and the onset of autism and other PDDs (Table 9). The study was based on data from the UK's General Practice Research Database (GPRD) which was set up on 1 June 1987. The authors concluded that their study added to the evidence that MMR vaccination was not associated with an increased risk of PDDs. The OR for the association between MMR vaccination and PDDs was 0.78 (95% CI 0.62 to 0.97) for the non-practice matched control group and 0.86 (95% CI 0.68 to 1.09) for the practice matched control group. The findings were similar when analysis was restricted to children with a diagnosis of autism only, to MMR vaccination before their third birthday, or to the period prior to media coverage of the hypothesis linking MMR vaccination with autism.

DeStefano 2004 compared the distribution of ages at first MMR vaccination in children with autism (cases, Table 9) and controls, divided into three age strata: up to 18, 24 and 36 months. The authors concluded that there was no significant difference between cases and controls in the age at first vaccination up to 18 months (adjusted OR 0.94; 95% CI 0.65 to 1.38) and 24 months (adjusted OR 1.01; 95% CI 0.61 to 1.67); but more cases received MMR vaccination before 36 months (adjusted OR 1.23; 95% CI 0.64 to 2.36; unadjusted OR 1.49; 95% CI 1.04 to 2.14), possibly reflecting the immunisation needs of children in a surveillance programme.

In the study by Mrozek-Budzyn 2010 cases of autism in children aged between two and 15 years were identified by means of general practitioners' records from Małopolska Province in southern Poland (Table 9). For each case, two controls matching for birth year, gender and practice were selected. A total of 92 cases with childhood or atypical autism and 192 matched controls were included. Estimate OR were calculated considering vaccine exposure (MMR or monovalent measles) before autism diagnosis or before symptoms onset separately in univariate and multivariate analysis (this latter balanced for mother age ≥ 35 years, gestation time ≤ 38 weeks, medication during pregnancy, perinatal injuries and five-minute Apgar score). In multivariate analysis, administration of MMR vaccine before the diagnosis was associated with a relevant reduced risk of autism (OR 0.17; 95% CI 0.06 to 0.52; P = 0.002); this association was not confirmed when exposure before symptom onset was considered (OR 0.42; 95% CI 0.15 to 1.16). Risk of autism was significantly lower for MMR vaccinated children when compared with children immunised with single component measles vaccine, both before diagnosis (OR 0.47; 95% CI 0.22 to 0.99) and symptom onset (OR 0.44; 95% CI 0.22 to 0.91).

Time-series studies

Fombonne 2006 analysed the trend of pervasive developmental disorders (PDDs) prevalence in cohorts born from 1987 to 1998 attending a school board in the south and west parts of Montreal (n = 27,749 on 1 October 2003). The relationship between PDD prevalence trends and MMR vaccination coverage through each birth cohort was assessed. Children with PDDs (n = 180) were identified from a special list that was filled with data of children identified by code 51 (autism) and by code 50 (autism spectrum disorder) to allow the schools to receive incremental funding. The authors reported that while a significant trend toward a decrease in MMR uptake through birth cohorts from 1988 to 1998 (X^2 for trend = 80.7; *df* = 1; P < 0.001) could be assessed, a significant increase in rates of PDDs from 1987 to 1998 was found (OR 1.10; 95% CI 1.05 to 1.16; P < 0.001). By comparing the rate of increase in PDDs prevalence between the one-dose and two-dose period, no statistically significant differences were detected.

A Japanese study (Honda 2005) assessed the trend of autistic spectrum disorders (ASDs) incidence among birth cohorts from 1988 to 1996 (Yokohama city, Central Japan) up to seven years of age, in relation to the decline of MMR vaccination coverage in the same birth cohorts, i.e. before and after termination of MMR vaccination programmes in children (1993). Through examination of risk factor analysis with conditional regression, a significant increase in cumulative incidence of all ASDs through birth cohorts from 1988 to 1996 has been observed (χ^2 = 45.17, df = 8, P < 0.0001). This trend was different before and after the 1992 birth cohort: considering the 1996 birth cohort as a reference, incidence of all ASDs was significantly lower until 1992 and was not different after 1993. A significant increased incidence could be assessed also when outcomes definition of childhood autism (χ^2 = 31.86, df = 8, P < 0.0001) or other ASD (χ^2 = 19.25, df = 8, P = 0.01) were considered. The authors concluded that causal hypothesis involving the MMR vaccine as a risk factor was not supported by the evidence because the ASD incidence continued to increase even if the MMR vaccination programme was terminated.

Self controlled case series

In the study by Makela 2002, already described in the section relative to neurological diseases (see above), an attempt to evaluate the association between MMR vaccination and hospitalisation for autism was made (Table 9). Unlike encephalitis and aseptic meningitis, instead of a risk period, changes in the overall number of hospitalisations for autism after MMR vaccination, including only the first hospital visit during the study period, were considered. Times between immunisation and hospitalisation observed among the 309 hospitalisations for autism following MMR immunisation were very wide (range three days to 12 years and five months), their numbers remained relatively steady during the first three years and then decreased gradually. No cluster intervals from vaccination could be identified. Authors concluded that there was no evidence of association, but did not report statistical data supporting this conclusion.

One other self controlled case series study (Taylor 1999) assessed clustering of cases of autism by post-exposure periods in a cohort of 498 (with 293 confirmed cases) children. The authors reported a significant increase in onset of parental concern at six months post-vaccination, but no significant clustering of interval to diagnosis or regression was found within any of the considered time periods (two, four, six, 12, 24 months).

Asthma

Cohort studies

The cohort study by McKeever 2004 used an historical birth cohort of children (1988 to 1999) consisting of 29,238 children of both sexes aged between 0 and 11 years and identified through the West Midlands General Practice Research Database (GPRD), to investigate the association between MMR and diphtheria, polio, pertussis and tetanus (DPPT) vaccination and asthma or eczema (Table 11). Incident diagnoses of asthma/wheeze and eczema (Table 11) were identified using the relevant Oxford Medical Information System (OMIS, derived from ICD-8) and Read codes (a hierarchical code used in GP practices in England). Association with MMR vaccine exposure and risk of asthma and eczema has been assessed by univariate analysis. Correspondent crude hazard ratios (HR) were 3.51 (95% CI 2.42 to 5.11) and 4.61 (95% CI 3.15 to 6.74) for asthma and eczema, respectively. Stratifying for GP consultation frequency in the first 18 months, HR estimates remain significant only for the subgroup with lower consulting frequency (zero to six times in the first 18 months) and not for the other subgroups (seven to 10 times, 11 to 16 times and more than 16 times): HR 7.18 (95% CI 2.95 to 17.49) for association between MMR vaccination and asthma; HR 10.4 (95% CI 4.61 to 23.29) for association between MMR vaccination and eczema, respectively.

One other cohort study (DeStefano 2002) used data from the Vaccine Safety Datalink (VSD) project in order to detect a possible association between asthma and some infant vaccines, among which was MMR (Table 11). For the study, a population of children who were enrolled in four Health Maintenance Organisations (HMOs) from birth until at least 18 months of age (to a maximum of six years) between 1991 and 1997 was considered (n = 167,240). Asthma cases (n = 18,407) were identified by reviewing computerised databases maintained at each HMO (see Table 11 for case definition). Ascertainment of vaccine exposure was performed by using computerised immunisation tracking systems maintained by each of the HMOs. Out of the 167,240 included participants 12,426 were not immunised with the MMR vaccine. Proportional hazard regression does not show a significant association between asthma and MMR vaccination (RR 0.97; 95% CI 0.91 to 1.04).

Person-time cohort studies

Association between asthma hospitalisation, anti-asthma medications (Table 11) and MMR vaccine exposure was tested on Danish birth cohorts from 1991 to 2003 in the Hviid 2008 study, by using the Danish Civil Registration System. Each participant recorded in the register had an identification number, that allowed a link to data contained in other national registers (Danish National Hospital Register, Danish Prescription Drug Database and National Board of Health). MMR vaccination status was considered as a time-varying variable and individuals could contribute to person-time as both unvaccinated and vaccinated participants. MMR vaccination is protective against all asthma hospitalisation (RR 0.75; 95% CI 0.73 to 0.78); the protective effect of vaccination was greater in younger children (no more significant when the vaccine was administered after 18 months of age), in those with the longest time spent at the hospital (18 days to one year), in girls, in low birth-weight children, in children with one older sibling and in those living in rural areas. The vaccination was also protective against hospitalisation for severe asthma (RR 0.63; 95% CI 0.49 to 0.82), even if estimates were not significant within the following stratifications: age three or four years; fully immunised children; low hospitalisation propensity; male sex; birth weight below 2499 g or above 4000 g; birth order >/= three; birth in the capital or in a rural area. Total use of anti-asthma medications was less frequent among participants immunised with MMR (RR 0.92; 95% CI 0.91 to 0.92). No reduction in use (all medications) was observed for participants vaccinated at ages between 23 and 26 months (RR 1.00; 95% CI 0.98 to 1.01) or at 27 months or later (RR 1.01; 95% CI 0.99 to 1.03). Considering single classes of medication in the unstratified study population, these data were confirmed with the exception for systemic b2-agonists, for which reduction in use could not be observed (RR 1.02; 95% CI 1.01 to 1.02). Considering only the first use of any anti-asthma medication in the unstratified population, the RR was 0.93; 95% CI 0.92 to 0.94.

Leukaemia

The case-control study of Ma 2005 was realised within the Northern California Childhood Leukaemia Study (NCCLS) and assessed whether vaccination with MMR (and other vaccines) plays a role in the aetiology of leukaemia. In NCCLS (active since 1995) incident cases of newly diagnosed leukaemia in children aged between 0 and 14 years and ascertained from major paediatric clinical centres within 72 hours after diagnosis were collected (Table 12). Analyses had been carried out for both total leukaemia cases and control (323 and 409, respectively) and for acute lymphoblastic leukaemia (ALL) subset (282 cases and 360 controls). Considering leukaemia as case definition, OR estimates for any MMR dose before the reference date in all populations was 1.06 (95% CI 0.69 to 1.63). Considering ALL as case definition the OR estimate for any MMR dose before the reference date in all populations was 0.87 (95% CI 0.55 to 1.37).

Hay fever

Two case-control studies (Bremner 2005; Bremner 2007) investigated the risk of hay fever in MMR-vaccinated children in the UK (using the same data source).

Bremner 2005 focused particular attention on the timing of MMR vaccination to identify a critical period for MMR immunisation and hay fever risk (see Table 13 for definition). The nested case-control study was conducted within two large databases, the General Practice Database (GPRD) and Doctors' Independent Network (DIN) and involved 7098 hay fever cases and controls. After performing a conditional logistic regression the authors reported that infants who received MMR vaccination did not have a greater or lesser risk of developing hay fever than unvaccinated children. MMR unvaccinated children compared with vaccinated in month 14 (base group) had an OR of 0.79 (95% CI 0.78 to 1.08). A reduced risk of hay fever was noted after completing MMR after two years of age (OR 0.62; 95% CI 0.48 to 0.80).

Bremner 2007 specifically investigated if exposure to MMR vaccination during the first grass pollen season of life influences the risk of hay fever more than any other time of the year. The study was conducted within GPRD and DIN Databases and involved 7098 hay fever cases matched with controls. The risk of later hay fever following exposure to MMR vaccine within the first grass pollen season of life was not statistically different from that observed when MMR administration occurred outside of it (OR 1.05; 95% CI 0.94 to 1.18; P = 0.38).

Type 1 diabetes

Hviid 2004 was a retrospective cohort study carried out in Denmark aiming to evaluate if there was an association between childhood vaccinations and the onset of type 1 diabetes. A cohort of children born from 1 January 1990 to 31 December 2000 from the Danish Civil Registration System was individuated. The Danish Civil Registration System identified with a unique number all people living in Denmark. This number made it possible to obtain linked information on vaccination, diagnosis of type 1 diabetes (Table 14), the presence or absence of siblings with type 1 diabetes and potential confounding factors. The vaccination data were obtained from the National Board of Health, where the General Practitioners reported data. The results of this study do not sustain the hypothesis that there is a link between vaccinations and type 1 diabetes (measles, mumps and rubella (all children): rate ratio 1.14; 95% CI 0.90 to 1.45).

Gait disturbance

Association between MMR vaccination and gait disturbance was assessed by means of a self controlled case series study (Miller 2005) and considered as cases hospital admissions or general practice consultations in children within the Thames regions of England. Hospital admission cases were obtained from hospital computerised records for the period April 1995 to June 2001, considered those relative to children aged 12 to 24 months with ICD-10 diagnoses related to acute gait disorder (G111, G112, G25, R26, R27, R29, H55 and F984). Cases were validated by reviewing hospital case notes and grouped into five categories (Table 15). Vaccination history of cases was obtained from immunisation records. In all, 127 cases with available immunisation status were identified. Out of these, 65 belonged to category 4 (i.e. non-ataxic, non-viral origin) and were excluded from analysis. No cases corresponding to category 1 definition were found. Relative incidence (RI) within and outside post-vaccination time risk (0 to 30 and 31 to 60 days) was calculated after age stratification in one-month intervals. RI estimates for pooled two, three and five categories were not statistically relevant (RI 0.83; 95% CI 0.24 to 2.84 for 0 to 30 days risk time and RI 0.20; 95% CI 0.03 to 1.47 for 31 to 60 days risk time).

As gait disturbance does not require hospitalisation, authors carried out a further analysis based on cases observed in General Practices using the General Practice Research Database (GPRD) as the source, and considered children aged 12 to 24 months, born between 1988 and 1997. Read and OXMIS codes indicating a possible consult for gait disturbance were identified in GPRD by mapping ICD-9 codes and by searching keywords 'ataxia', 'gait', 'coordination', 'mobility' and 'movement'. Diagnoses were grouped into six categories (Table 15). Vaccination history was obtained from prescription records. In all, 1398 children with diagnoses A-F and known immunisation history were included. Since, in the authors' opinion, a vaccine-specific effect would appear one week after immunisation (an excess of B and C diagnoses was observed on vaccination day) the risk period zero to day five was separately considered. In any other considered risk periods (six to 30, 31 to 60 and six to 60 days after MMR immunisation) RI did not have a statistically relevant increased incidence. Early administration of thiomersal-containing DTP/DT vaccine did not influence this estimate.

Crohn's disease and inflammatory bowel disease

Two studies (Davis 2001; Seagroatt 2005) considered the hypothesis of an association between MMR vaccination and Crohn's disease (CD) or inflammatory bowel disease and ulcerative colitis (Table 16).

One case-control study (Davis 2001) was conducted in the United States using data from the Vaccine Safety Datalink (VSD) to evaluate if MMR and measles-containing vaccines increased the risk for inflammatory bowel disease (IBD). Medical records were reviewed and cases were classified according to the type of disease (CD, ulcerative colitis/proctitis or IBD). The authors concluded that exposure to the MMR vaccine was not associated with an increase risk of CD (OR 0.4; 95% CI 0.08 to 2.0), ulcerative colitis (OR 0.80; 95% CI 0.18 to 3.56) and all IBD (OR 0.59; 95% CI 0.21 to 1.69).

One ecological study (Seagroatt 2005) investigated a possible association between the MMR vaccine and CD. Using English national data on emergency admissions, the authors compared admissions for CD in populations with a vaccination coverage of $\geq$ 84% with populations with a MMR vaccination coverage of $\geq$ 7%. The estimated rate ratio for the MMR vaccination programme was 0.95 (95% CI 0.84 to 1.08). Even if age-specific rates of emergency admission for CD increased during the time considered in the study (April 1991 to March 2003), this trend seems not to have been influenced by the introduction of the MMR vaccine. The introduction of the MMR vaccination programme in England did not increase the risk of CD.

Demyelinating diseases

The possible association between the MMR vaccine and demyelinating diseases was assessed in two studies, using the same population data set.

Ahlgren 2009a is a cohort study carried out in the Gothenburg area (Swedish west coast, 731,592 residents on 31 December 2000). Cases of multiple sclerosis (MS) and clinically isolated syndrome (CIS) in participants born between 1959 and 1990 with onset at ages between 10 and 39 years before July 1984 among Gothenburg residents were considered, corresponding to a total of 5.9 million person-years of observation (Table 17). The incidence of probable or definite MS (Poser criteria) and CIS (372 and 162 cases, respectively) was analysed in corresponding measles, mumps and rubella vaccination programmes, by selecting four birth cohorts corresponding to the first years of a specific vaccination programme.

- Birth cohorts 1962 to 1966 (102 MS cases): administration of the monovalent rubella vaccine to 12-year old girls in 1974.
- Birth cohorts 1970 to 1973 (62 MS cases): administration of the MMR vaccine at 12 years of age (1982).
- Birth cohorts 1974 to 1978 (37 MS cases): administration of monovalent measles vaccine in pre-school children. (It was already introduced in 1971, thus adequate coverage was reached only for those born in 1974 and onwards). About 90% of subjects from these birth cohorts received the MMR vaccine at 12 years of age.
- Born between July 1981 and June 1984 (five MS cases): administration of the MMR vaccine at 18 months and at 12 years of age.

The incidence of MS and CIS within each birth cohort was compared to that calculated for the preceding ones, including that of 1959 to 1961, corresponding to the pre-vaccine era. No significant changes in age and gender-specific incidence of MS between selected and preceding selected cohorts has been observed.

Authors use the same population incidence data in order to assess an association between MMR exposure and MS onset by means of a case-control design (Ahlgren 2009b). Similar to the cohort study, case definitions included MS or CIS according to Poser's criteria, residence in Gothenburg, birth date between 1959 and 1986, and disease onset from the age of 10 years onwards. For analysis of vaccine exposure, only cases and controls who attended the sixth grade in school (12 years) within the study area, for whom CHSH records were available (206 cases and 888 controls) were included. Estimates (OR) were calculated by using a logistic model including sex and year of birth, using MMR vaccine exposure as a dependent variable. Exposure to the MMR vaccine (in all) was not statistically different among cases and controls (OR 1.13; 95% CI 0.62 to 2.05).

Bacterial and viral infections

The incidence of viral and bacterial infection following MMR administration was investigated by means of a self controlled case series design by Stowe 2009. Episodes of hospitalisation for bacterial or viral infections occurring in children aged between 12 and 23 months, were identified by consultation of computerised hospital admission records from North, East and South London, Essex, East Anglia, Sussex and Kent using ICD-9 or ICD-10 codes and covering the time between 1 April 1995 and 1 May 2005 (2077 admission in 2025 children).

Bacterial infections were characterised as lobar pneumonia or invasive bacterial infection, whereas those of viral aetiology were encephalitis/meningitis, herpes, pneumonia, varicella zoster or miscellaneous virus (Table 18). Admissions were linked to date of MMR (and meningococcal) immunisation resulting from records held on child health systems. 'At risk' time periods were considered the intervals of 0 to 30, 31 to 60 and 61 to 90 days after immunisation. Admissions for lobar pneumonia were less frequent in the time between 0 and 30 days after MMR immunisation (RI 0.65; 95% CI 0.48 to 0.86) or during the 90 days following immunisation (RI 0.77; 95% CI 0.64 to 0.93). No significant differences were found comparing incidence of invasive bacterial diseases in risk periods with that of background period. Regarding viral infections, a significantly lower incidence of varicella zoster was assessed within 30 days after MMR immunisation (RI 0.58; 95% CI 0.34

to 0.99). However, RI estimates were not statistically relevant for the 31 to 60, 61 to 90 and the whole 0 to 90 days risk periods. On the contrary, the risk of hospitalisation due to herpes infection was higher in the risk time interval between 31 and 60 days after MMR vaccine administration (RI 1.69; 95% CI 1.06 to 2.70) but this risk was not significant considering the other risk periods. Hospitalisation risk for encephalitis/meningitis, viral pneumonia and miscellaneous viral infections, did not reach statistical significance in any of the considered risk time intervals. No significant risk of both bacterial and viral infection has been detected following concomitant administration of MMR and meningococcal C vaccine.

DISCUSSION

Summary of main results

MMR vaccination would be highly effective ($\geq$ 95%) in preventing clinical measles cases in preschool children and estimates were similar for each of the two measles strains with which participants had been immunised (Schwarz or Edmonston-Zagreb, one cohort study, n = 2745). The MMR vaccine (unspecified composition) is also about 98% effective in preventing laboratory-confirmed cases in children and adolescents (one cohort study, n = 184). Effectiveness in preventing secondary measles cases among household contacts was 92% for one and 95% for two vaccine doses (one cohort study, n = 175).

Effectiveness of at least one dose of a Jeryl Lynn-containing MMR vaccine in preventing clinical mumps cases in children and adolescents has been estimated between 69% and 81% (one cohort and one case-control study, n = 1656). Effectiveness of Jeryl Lynn containing MMR in preventing laboratory-confirmed mumps cases in children and adolescents was estimated to be between 64% to 66% for one and 83% to 88% for two vaccine doses (two case-control studies, n = 1664). At least one dose of Urabe strain-containing MMR is 70% to 75% effective in preventing clinical mumps (one cohort and one case-control study, n = 1964) and 87% effective against laboratory-confirmed mumps (this last estimate was provided from only one small cohort study with high bias risk, n = 48). Vaccination with MMR prepared with Urabe strain has demonstrated to be 73% effective in preventing secondary mumps cases (one cohort study, n = 147). In any case, there was an acceptably high effectiveness of the vaccine prepared only with Urabe or Jeryl Lynn strain but not so for that containing Rubini strain.

We found no studies assessing effectiveness of MMR against rubella.

Association with aseptic meningitis is confirmed for MMR vaccines containing Urabe and Leningrad-Zagreb mumps strains on the basis of two very large time-series studies with moderate risk of bias and carried out on about 1,500,000 children aged one to 11 years, assessing a significant increased risk in the time between one and 10 weeks after immunisation, peaking within the third or fifth week. Association was not significant for vaccines prepared with mumps Jeryl Lynn strains, as it results from one cohort and one self controlled case series studies.

Due to the results of a well conducted, very large person-time cohort study involving 537,171 children between three months and five year of age, febrile seizure (as first or as recurrent episode) has been found to be associated with MMR vaccine (prepared with Moraten, Jeryl Lynn and Wistar RA) within two weeks after administration in preschool Danish children.

In children aged 12 to 23 months, association with febrile convulsion six to 11 days after immunisation, would have been assessed for MMR containing both Jeryl Lynn or RIT 4385 mumps strains in a self controlled case series study with moderate bias risk (n = 894).

Increased risk of severe illness with fever and convulsions in children aged 12 to 35 months within six to 11 days after MMR exposure was assessed in one further self controlled case series study in which the vaccine strain composition was not reported (n = 107).

Association with acute or idiopathic thrombocytopaenic purpura within six weeks from immunisation was assessed in four studies (two case-controls, n = 2450, one self controlled case series, n = 63) but vaccine composition was not described in any of the studies.

Based on the identified studies, no significant association could be assessed between MMR immunisation and the following conditions: autism, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, Crohn's disease, demyelinating diseases, bacterial or viral infections.

Overall completeness and applicability of evidence

External validity of included studies was also low. Descriptions of the study populations, response rates (particularly in non-randomised studies), vaccine content and exposure (all important indicators of generalisability) were poorly and inconsistently reported. In addition, inadequate and inconsistent descriptions of reported outcomes (a well-known problem (Kohl 2001)), variable observation periods and selective reporting of results contributed to our decision not to attempt pooling data by study design.

Quality of the evidence

We found problematic internal validity in some included studies and the biases present in the studies (selection, performance, attrition, detection and reporting) influenced our confidence in their findings. The most common type of bias was selection bias. We analysed reasons presented by the papers to justify missing data. Despite accepting as 'adequate' explanations such as 'non-response to questionnaire' and 'medical records unavailable', not all reports offered adequate explanations for missing data.

Potential biases in the review process

There are some weaknesses in our review. The age limit of participants, although substantially justified by public health concerns about the effects of vaccination on the developing child, did lead us to exclude some studies only on this basis. Additionally, the methodological quality tools used to assess the ecological, time-series and case-only designs have not to our knowledge been empirically tested. We believe this to have had minimal impact on our findings given the size and nature of the biases present in the design and reporting of the included studies.

The range of differing study designs used by authors is partly a reflection on the lack of control children not exposed to MMR, due to the population nature of vaccination programmes. As MMR vaccine is universally recommended, recent studies are constrained by the lack of a non-exposed control group. This is a methodologically difficulty which is likely to be encountered in all comparative studies of established childhood vaccines. We were unable to include a majority of the retrieved studies because a comparable, clearly-defined control group or risk period was not available. The exclusion may be a limitation of our review or may reflect a more fundamental methodological dilemma: how to carry out meaningful studies in the absence of a representative population not exposed to a vaccine that is universally used in public health programmes. Whichever view is chosen, we believe that meaningful inferences from individual studies lacking a non-exposed control group are difficult to make.

The hypothesis that secondary vaccine failure (waning immunity) could occur and increase over the years after the last immunisation, has been considered in some studies but it needs to be better elucidated. Two studies (Briss 1994; Hersh 1991) carried out in the USA during mumps epidemics on high school student populations having high vaccination coverage (over 97% received at least one mumps-containing vaccine dose before the outbreak), showed that risk of acquiring mumps was higher in participants who were vaccinated at least three (Briss 1994) or five years (Hersh 1991) before the outbreak, than in those who were more recently vaccinated, thus this estimate was not statistically relevant. Linear regression analysis demonstrated no significant trend for increasing mumps attack rates by years, since last vaccination neither after one nor after two mumps-containing vaccine doses (Schaffzin 2007). A Belgian study carried out on pupils from seven kindergartens and primary schools in Bruges city (age range three to 12 years) during a mumps epidemic in 1995 to 1996 (Vandermeulen 2004) estimated that odds of developing mumps increased 27% per one-year increase, from one year after the last MMR immunisation onwards. A case-cohort study (Cortese 2008) carried out at a University in Kansas (USA) during the 2006 outbreak showed that case patients were more likely than their roommates without mumps to have received the second MMR dose more than 10 years before (odds ratio (OR) 2.50; 95% confidence interval (CI) 1.28 to 5.00). Waning immunity may be secondary to a lack of natural exposure (Cortese 2008; Dayan 2008a). The group with the highest mumps incidence during the 2006 outbreak in the USA were college-age youths (18 to 24 years) born during the 1980s, when the spread of mumps was so low that many of them were never exposed to the disease. They probably received a second dose in the early 1990s, when opportunities for booster shots against exposure to wild viruses became increasingly rare (Dayan 2008a). Moreover, the risk of the contracting mumps virus from abroad should be considered, because in several countries, mumps vaccination was not routinely administered (Cohen 2007; Dayan 2008a). Apart from waning immunity it must be taken in account that mumps strains used in vaccine preparation differed phylogenically from those isolated during recent mumps outbreaks (Dayan 2008a; Dayan 2008b). These facts could explain, at least in part, the vaccine failure observed during some mumps outbreaks.

Agreements and disagreements with other studies or reviews

Currently, this is the only review covering both effectiveness and safety issues of MMR vaccines. In agreement with results from other studies and reviews a significant association between autism and MMR exposure was not found. The study of Wakefield (Wakefield 1998), linking MMR vaccination with autism, has been recently fully retracted (The Editors of The Lancet 2010) as Dr. Wakefield has been found guilty of ethical, medical and scientific misconduct in the publication of the paper; many other authors have moreover demonstrated that his data were fraudulent (Flaherty 2011). A formal retraction of the interpretation that there was a causal link between MMR vaccine and autism has already been issued in year 2004 by 10 out of the 12 original co-authors (Murch 2004). At that time (1998) an excessive and unjustified media coverage of this small study had disastrous consequences (Flaherty 2011; Hilton 2007; Offit 2003; Smith 2008), such as distrust of public health vaccination programmes, suspicion about vaccine safety, with a consequential significant decrease in MMR-vaccine coverage and re-emergence of measles in the UK.

AUTHORS' CONCLUSIONS

Implications for practice

Existing evidence on the safety and effectiveness of MMR vaccine supports current policies of mass immunisation aimed at global measles eradication and in order to reduce morbidity and mortality associated with mumps and rubella.

Implications for research

The design and reporting of safety outcomes in MMR vaccine studies, both pre and post-marketing, need to be improved and standardised definitions of adverse events should be adopted. More evidence assessing whether the protective effect of MMR could wane with the time since immunisation should be addressed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahlgren 2009a

Methods	Cohort study	
Participants	Participants residents in the great Gothenburg area (Sweden) born between 1959 and 1990	
Interventions	Different vaccination programmes carried out from 1971 with different vaccines (single-component measle, mumps and rubella vaccine so as with MMR vaccine) having as target population children of different ages	
Outcomes	Incidence of multiple sclerosis (MS, 4 Poser's criteria) and Clinically Isolated Syndrome (CIS) with onset between 10 and 39 years of age was assessed in birth cohorts immunised within 4 vaccination programmes	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Ahlgren 2009b

Methods	Case-control study
Participants	Cases: participants with multiple sclerosis (MS) or clinically isolated syndrome (CIS) born between 1959 and 1986 and disease onset at age $\geq$10 years, resident in Gothenburg area (Sweden) Cases: participants from the same area as the cases (randomly selected from General Population Register) born in the same year as cases
Interventions	MMR vaccination (vaccination with single-component vaccines has been also considered)
Outcomes	Risk of MS associated with MMR exposure
Notes	Same population as for Ahlgren 2009a
Risk of bias	

Ahlgren 2009b (*Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Beck 1989

Methods	Prospective cohort
Participants	196 children aged 12 to 14 months
Interventions	MMR containing 4.1 TCID50 of mumps strain L -Zagreb (information about measles and rubella employed strains not reported, n = 103) versus Placebo (composition unknown, n = 93) No information about doses given and route of immunisation
Outcomes	- Local reactions (redness, swelling, tenderness, 30 days follow-up) - Temperature > 37.5 °C - Catarrhal symptoms - Parotid swelling
Notes	The study is reported with minimal details (no population description, no details given on how the groups are selected, how they are assigned, the total population, how measurements are made)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Benjamin 1992

Methods	Retrospective cohort comparing incidence of joint and limb symptoms in MMR vaccinated children versus non-vaccinated
Participants	5017 children between 1 and 5 years
Interventions	MMR vaccine (strains and doses not specified, 1588 participants included in analysis) versus No treatment (1242 participants included in analysis)
Outcomes	- Joint complaints, all episodes (arthralgia, possible/probable arthritis) - Joint complaints 1st ever episodes (arthralgia, arthritis possible or probable, joint total first ever, limb/joint complaint episodes, hospital admission, GP consultation, sore eyes, convulsion, coryza, parotitis, temperature, rash) Within 6 weeks after immunisation. Data based on a 6-week parental recall questionnaire and clinician home visit
Notes	Low response rate in non-immunised group

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Bertuola 2010

Methods	Case-control study
Participants	Cases (n = 387): children aged between 1 month and 18 years of age with acute immune thrombocytopaenia (AIT, defined as platelets count < 100,000/l at admission) recorded between November 1999 and September 2007 Controls (n = 1924): children of the same age, hospitalised during the same period as cases with acute neurological disorders and endoscopically confirmed gastroduodenal lesions were considered as controls
Interventions	MMR vaccine exposure (strain composition not reported)
Outcomes	Risk of AIT during the 6 weeks following MMR immunisation
Notes	

Risk of bias

Bertuola 2010 (*Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Black 1997

Methods	Case-control study
Participants	Children 12 to 23 months old from the Vaccine Safety Datalink project. Cases: children with confirmed aseptic meningitis (hospital record, discharge diagnosis and cerebrospinal fluid white blood cell count, n = 59) Controls: children matching cases by age, sex, HMO membership status (n = 188)
Interventions	Vaccination with MMR (Jeryl Lynn strain only), data from medical records
Outcomes	Risk of AM within 14 days, 30 days, 8 to 14 days of vaccination
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Black 2003

Methods	Retrospective case-control
Participants	Cases: children enrolled in the General Practice Research Database (GPRD), aged less than 6 years with idiopathic thrombocytopaenic purpura (ITP) (n = 23) Cases: children matched with controls by age at index date, practice and sex
Interventions	MMR vaccine (from GPRD records)
Outcomes	Exposure to MMR within 6 weeks or 7 to 26 weeks

Black 2003 *(Continued)*

Notes	Controls are not described very well (for example, we do not know from which population they are drawn)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Bloom 1975

Methods	RCT, double-blind
Participants	282 children
Interventions	Three lots of MMR vaccine (lot 1, 2, 3 prepared from Schwarz live attenuated measles virus, Jeryl Lynn live attenuated measles virus, and Cenedehill live attenuated measles virus) versus Placebo Vaccines contained at least 1000 TCID50 for measles and rubella and 5000 for mumps
Outcomes	Observations for intercurrent illness and vaccine reactions made approximately 3 times/ child between 7 to 21 days post - Temperature elevation above normal 1.5 °F - Rash - Lymphadenopathy - Coryza - Rhinitis - Cough - Other - Local reaction - Limb and joint symptoms
Notes	The study does not say if all children were observed at least once

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	Unclear risk	Unclear

Bloom 1975 *(Continued)*

Allocation concealment	Unclear risk	Unknown but decoding and tabulation done by computer
Blinding All outcomes	Unclear risk	Not mentioned
Incomplete outcome data addressed All outcomes	High risk	16% of possible total observations missing
Free of selective reporting	High risk	No explanation for excluding symptom reports are missing

Bremner 2005

Methods	Nested case-control studies carried out in United Kingdom (England, Wales, Scotland, Northern Ireland) using 2 large databases of primary care consultations
Participants	Case Certain (Definition I): a child with hay fever diagnosis before 24 months of age, and a second diagnosis of hay fever or a relevant therapy in a subsequent years and with a 3rd diagnosis or a relevant therapy in a further year Case Certain (Definition II):a child without first diagnosis before 24 months of age, but with a second diagnosis of hay fever or a relevant therapy in subsequent year Case Less certain (Definition I): a child as a case certain (Definition I) without 3rd diagnosis of hay fever or a relevant therapy in a further year Case Less certain (Definition II): a child with at least a hay fever diagnosis, even if there are not a second diagnosis or a relevant therapy in a subsequent year For GPRD Database 2115 Cases Certain and 2271 Cases Less Certain were selected. After exclusion of cases without a suitable control left (2.025 Cases certain and 2171 Cases Less Certain) For DIN Database 1480 Cases Certain and 1477 Cases Less Certain were selected. After exclusion of cases without a suitable control left 1459 Cases certain and 1443 Cases Less Certain Only codex synonymous with "allergic rhinitis" with seasonal variation in recording were permitted Description of controls: the controls were the children that had not allergic rhinitis or hay fever diagnosis. A suitable control matched a case (1:1) with a practice ID, age , sex and index date (date of a first diagnosis in a 'Less certain' case, or date of confirmatory diagnosis or therapy if a certain case)
Interventions	MMR II (first entries). The time categories for MMR immunisation were: 1st to 13th month, 14th, 15th, 16th, 17th, 18th-24th, 25th month or later The study considers also association with DTP and BCG vaccines
Outcomes	Risk of hay fever at different immunisation ages, using administration at 14 months of age as reference value
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable

Bremner 2005 *(Continued)*

Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Bremner 2007

Methods	Case-control study
Participants	Case of hay fever were children with diagnostic codes and/or treatment for hay fever (see Bremner 2005), after 2 years of age. Control was child that matched for general practice, sex, birth month and follow-up of control "to at least date of diagnosis case"
Interventions	MMR II
Outcomes	Incidence of hay fever following MMR exposure was compared inside versus outside the grass pollen season
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Castilla 2009a

Methods	Case-control study
Participants	Cases (n = 241): children aged 1 to 10 years with confirmed (laboratory or epidemiologically) mumps with symptoms of disease between August 2006 and June 2008 Controls (n = 1205): children matched for sex, municipality, district of residence and paediatrician
Interventions	MMR vaccine prepared with Jeryl Lynn mumps strain
Outcomes	Exposure to MMR vaccine at least 30 days before mumps onset
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Ceyhan 2001

Methods	CCT
Participants	1000 infants aged 38 to 40 months from 5 maternity and child health centres in Ankara, Turkey
Interventions	Measles vaccine (Rouvax, Schwarz measles strain, 1000 TCID50) administered at 9 months plus MMR administered at month 15 versus MMR (Trimovax, Schwarz measles strain, 1000 TCID50; AM 9 mumps strain, 5000 TCID50; Wistar RA/27/3 rubella strain, 1000 TCID 50) administered at months 12 only
Outcomes	- Fever 39.4 °C - Runny nose - Cough - Rash - Diarrhoea - Redness - Swelling Even if visits by midwife 7, 14, 28 days after vaccination to collect adverse reactions records from parents and every 3 months for 60 months phone call/visit for standard questionnaire were carried out, the time of observation for adverse events is not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Semi-randomised
Allocation concealment	Unclear risk	Not used
Blinding All outcomes	High risk	Not blinded

Ceyhan 2001 (*Continued)*

Incomplete outcome data addressed All outcomes	Unclear risk	10% (50/500) excluded from arm 2 because immunised with different vaccine batch
Free of selective reporting	Unclear risk	Adverse reactions does not specify the time of observations (7, 14 days) if cumulative, number of events or number of children

Chamot 1998

Methods	Retrospective cohort study
Participants	Family contacts (n = 265) aged up to 16 years of primary confirmed (n = 223) or probable (n = 60) mumps cases notified at Health Service Cantonal of Geneva from 01 February 1994 to 30 April 1996
Interventions	Immunisation with MMR containing different mumps strains: - MMR-II®, Merck Sharp & Dohme used in Switzerland since 1971 prepared with Jeryl Lynn B mumps strain - Pluserix®, SmithKline Beecham or Trimovax®, Mérieux, used in Switzerland since 1983 prepared with Urabe Am 9 mumps strain - Triviraten ®, Berna used in Switzerland since 1986 and prepared with Rubini mumps strain Unvaccinated contact acted as control group. The vaccination status was obtained from vaccination books
Outcomes	Clinical mumps cases among contacts: Secondary cases were those diagnosed from 10 to 30 days maximum after a index case Tertiary cases were those diagnosed from 10 to 30 days maximum after a secondary case
Notes	By participants recruiting paediatricians included the serious cases and excluded household with difficult access to Health Service

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

da Cunha 2002

Methods	Before/after study to see if there is increased risk of acute aseptic meningitis and mumps in children aged 1 to 11 years in 2 regions of Brazil, Mato Grosso do Sul and Mato Grosso (MS and MT)
Participants	About 845,000 children aged between 1 and 11 years
Interventions	MMR vaccine containing Leningrad-Zagreb mumps strain (Serum Institute of India Ltd)
Outcomes	Aseptic meningitis (clinical diagnosis or notification form). 31 (in MT) or 37 (in MS) weeks before and 10 weeks after vaccination campaign
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Davis 2001

Methods	Case-control study
Participants	Vaccine Safety Datalink Project (VSDP), children enrolled from the 6th month Cases: cases of definite IDB (VSDP, n = 142) Controls: children matched for sex, HMO and birth year (n = 432)
Interventions	Exposure to MMR or other measles containing vaccines (MCV)
Outcomes	Exposure to MMR or MCV considering any time, within 2 to 4 months, within 6 months
Notes	There are no details of vaccine type - manufacturer, strains, dosage etc

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

DeStefano 2002

Methods	Retrospective cohort (from the Vaccine Safety Datalink Project)
Participants	167,240 children between 18 months and 6 years
Interventions	Exposure to MMR vaccine (and other vaccines)
Outcomes	- Asthma (ICD -9 code 493)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

DeStefano 2004

Methods	Retrospective case-control
Participants	Cases: children with autism through the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP, n = 624) Controls: children matched with cases for age, gender and school attendance (n = 1824)
Interventions	Exposure to MMR vaccine (no better defined)
Outcomes	MMR exposure in cases and controls stratified for age groups
Notes	Probable bias in the enrolment in MADDSP and cases may not be representative of the rest of the autistic population of the city

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Dourado 2000

Methods	Before/after. Retrospective study of aseptic meningitis. Pre-mass vaccination campaign versus post cases are compared to determine the incidence of aseptic meningitis
Participants	452,344 children aged 1 to 11 years (from census)
Interventions	Immunisation with MMR vaccine Pluserix (Smith Klein Beecham, containing mumps strain Urabe)
Outcomes	Aseptic meningitis periods of 23 weeks pre-vaccination and 10 weeks post were compared
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Dunlop 1989

Methods	Prospective cohort
Participants	335 healthy children aged about 15 months
Interventions	MMR vaccine Trimovax (Mérieux, containing measles strain Schwarz 1000 TCID50, rubella RA 27/3 1000 TCID50, mumps Urabe Am/9 5000 TCID50) versus Measles vaccine Rouvax (Mérieux, containing measles strain Schwarz, 1000 TCID50) Single dose IM or sc administered
Outcomes	- Rash - Temperature - Cough - Pallor - Diarrhoea - Rash nappy - Injection site bruise - Earache - Parotitis - Lymphadenopathy - Hospitalisation Parental daily diary for 3 weeks and weekly for 3 more weeks
Notes	

Dunlop 1989 (*Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Edees 1991

Methods	RCT, single-blind
Participants	420 healthy children aged between 12 and 18 months
Interventions	MMR vaccine Trimovax (Schwarz measles strain, 1000 TCID50 ; Urabe AM/9 mumps strain, 5000 TCID50 ; RA/27/3 rubella strain, 1000 TCID 50) versus Measles vaccine Rouvax (Schwarz 100 TCID50) Administered both in upper arm or leg
Outcomes	- Local symptoms: erythema, induration, pain - General - specific symptoms: rash, parotitis, conjunctivitis, testicular swelling, arthralgia, arthritis, convulsions - General non-specific symptoms: temperature, adenopathy, nasopharyngeal disorders, gastrointestinal disorders, restlessness. Diary completed by parents daily for 3 weeks with a further 3 weekly observations
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	Unclear risk	No description
Allocation concealment	Unclear risk	Not used
Blinding All outcomes	High risk	Single-blind
Incomplete outcome data addressed All outcomes	Low risk	

Fombonne 2001

Methods	Retrospective cohort
Participants	283 children from 3 cohorts of children with pervasive development disorders (PDD)
Interventions	Testing several causal hypothesis between exposure to MMR and developing of PDD
Outcomes	All cases were accurately assessed by a multidisciplinary team and in most cases data were summarised and extracted on standard forms
Notes	The number and possible impact of biases in this study is so high that interpretation of the results is impossible

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Fombonne 2006

Methods	Time-series study
Participants	Birth cohorts 1988 to 1998 attending a school board in the south and west parts of Montreal area (N = 27,749 on October 1st, 2003), age 5 to 16
Interventions	MMR vaccination
Outcomes	Prevalence trend of Pervasive Development Disorders (PDD) was analysed in relation to MMR vaccination status
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

France 2008

Methods	Study based on Vaccine Safety Datalink (VSD) investigating association of immune thrombocytopaenic purpura (ITP) and MMR within 42 days after immunisation and assessing association risk by means of both self controlled case series and risk intervals (person-time cohort) methods
Participants	Children aged 12 to 23 months with ITP identified from VSD database for the years 1991 to 2000
Interventions	Exposure to MMR vaccine (composition not provided in the study report)
Outcomes	ITP diagnoses within 42 days from immunisation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Freeman 1993

Methods	Before/after. Children due to receive MMR (over a 1-year period) were assigned to receive the vaccine (MMR II) at either 13 or 15 months, depending on the random assignment of their family physician
Participants	Children receiving MMR
Interventions	MMR - MMRII (Merck Sharp & Dohme) administered at either 13 or 15 months
Outcomes	- Cough - Temperature - Rash - Eyes runny - Nose runny - Lymphadenopathy - Hospital admission Assessed by daily diaries (from 4 weeks before to 4 weeks post vaccination)
Notes	Only ~67% of the participants (253 out of 376) completed the study. It is not explained how delays in vaccination, for some participants, effect the 8-week diary

Risk of bias

Bias	Authors' judgement	Support for judgement

Freeman 1993 (*Continued)*

Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Giovanetti 2002

Methods	Case-control study
Participants	Children and adolescent aged 14 months to 15 years from an Italian Local Health Agency with 12, 880 residents of this age group Cases (n = 139): clinical mumps cases identified by national infectious diseases surveillance system within study area Controls (n = 139): randomly selected from immunisation registry, matched for birth year and address
Interventions	MMR vaccine exposure at least 30 days before disease onset (registry and phone interviews)
Outcomes	Association between MMR vaccine exposure and clinical measles within 30 days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Goncalves 1998

Methods	Case-control study
Participants	Children and adolescents (15 months to 16 years) from Oporto city (Portugal) *Before 1 November 1992 (immunisation with Urabe mumps strain)*: Cases (n = 73): clinical mumps cases reported by GPs or hospital doctors during the 1995 to 1996 mumps outbreak Controls (n = 169): 2 consecutive vaccination records of the same sex, month and birth year as the case, were selected *After 1 November 1992 (immunisation with Rubini mumps strain)*: Cases (n = 133): clinical mumps cases reported by GPs or hospital doctors during the 1995 to 1996

	mumps outbreak Controls (n = 236): 2 consecutive vaccination records of the same sex, month and birth year as the case, were selected	
Interventions	MMR vaccination. As in vaccination records strain was not reported, authors assume that until 1 November 1992 Urabe strain has been administered, whereas Rubini strain thereafter	
Outcomes	Association between MMR vaccine exposure and clinical measles	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Harling 2005

Methods	Case-control study carried out on children from a religious community in North East London, as a measles outbreak occurred (June 1998 to May 1999). The community was located in a quite small area, with own schools and amenities and was served by 2 GPs. MMR vaccination coverage in the community ranged between 67% and 86%
Participants	Cases (n = 161): clinical or laboratory mumps diagnoses with onset date between 18 June 1998 to 2 May 1999 observed in children aged from 1 to 18 years who belonged to the community, identified through mumps notification from the 2 GPs to the local Consultant Communicable Disease Control (CCDC), searching of the electronic practice list for diagnoses made using the terms "mumps" and successive checking, or verbal reports by community members. For notified cases, laboratory testing (oral fluid for IgM antibody and mumps RNA was made available (at the Enteric, Respiratory and Neurological Virus Laboratory, ERNVL). Altogether 161 mumps cases with onset during the outbreak were observed (142 notified by GPs, 12 through search in the electronic practice list, and 7 reported by parents). One case had no date of onset specified, but illness occurred in the outbreak period. Out of the 142 notified cases, 43 had also laboratory-confirm of infection by IgM radioimmuno assay, PCR detection of mumps RNA or both Controls (n = 192): controls were selected from children in the community registered with the 2 practices. They were chooses by random samples from electronic practices lists in order to match age and sex profile of the cases. Community membership was ascertained as by cases
Interventions	Vaccination status of cases and controls (together with clinical details of cases) was obtained from practice records and cross-checked with child health immunisation database of the local health authority. Laboratory records were obtained from ERNVL As vaccination status was available for 156 cases and 175 controls data analysis was carried out on

	this population. 79 cases and 134 controls received at least 1 dose of MMR vaccine at least 1 month before disease onset Even if authors did not report any descriptions of the MMR vaccine used for immunisation, it is assumed that mumps component was Jeryl Lynn strain, as it is in use in the UK at study time
Outcomes	Association between measles (clinical defined) and receiving of any doses, 1 or 2 doses of MMR vaccine at least 1 month before disease onset Association between laboratory-confirmed measles cases and receiving of any doses of MMR vaccine at least 1 month before disease onset
Notes	Composition and description of the administered vaccine was not provided, although it is stated that in UK at study time, MMR vaccine was prepared by using Jeryl Lynn strain Authors notes that the presence of controls who have had in the past mumps infection (i.e. could have developed immunity without vaccination) and the longer exposition to the outbreak for the cases, could have lead to underestimation of vaccine effectiveness. Other factors other than sex, age, and practices, could moreover have influenced the risk of infection and vaccination status of both cases and controls (e.g. if they were drawn from different residential areas or from groups with different levels of herd immunity and different behaviours)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Honda 2005

Methods	Time-series study
Participants	Birth cohorts from 1988 to 1996 (Yokohama city, Central Japan) up to 7 years of age (N = 31,426)
Interventions	MMR vaccine exposure
Outcomes	Autistic Spectrum Disorders (ASD) incidence before and after termination of MMR vaccination programme in children (1993)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable

Honda 2005 (*Continued)*

Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Hviid 2004

Methods	Person-time cohort study
Participants	Danish birth cohorts 1990 to 2000
Interventions	Vaccination with MMR and other vaccines (data from the National Board of Health)
Outcomes	Type 1 diabetes
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Hviid 2008

Methods	By using data from the Civil Registration System and considering all children born in Denmark between January 1st, 1991 and December 31st, 2003, the present study investigates the association between MMR immunisation and hospitalisation with asthma diagnosis and use of anti-asthma medication with a person-time cohort design
Participants	For the analysis of association between MMR vaccination and asthma hospitalisation all born in Denmark between 1 January 1991 and 31 December 2003, aged between 1 and 5 years, has been considered within the time period from 1 January 1992 and 31 December 2004 (N = 871,234) . Children contributed to person-time follow-up from 1 year of age until age of 5, or until 31 December 2004, death or disappearance/emigration. Follow-up resulted in 2,926,406 person-years. In consequence of several reasons, 15,914 children terminated their follow-up prematurely (5455 because of death, 10,159 emigrated and 300 disappeared) Follow-up length for the analysis of use of anti-asthma medication reached from 1 January 1996 to 31 December 2004 as data about medical prescription were available only from 1996. A total of 600,938 children contributed to follow-up, corresponding to 1,858,199 person-years. Follow-up was prematurely terminated for 12,552 children (for 4681 because of death, 7710 because of emigration, whereas 161 disappeared)

Hviid 2008 (*Continued*)

Interventions	Dates of MMR vaccination were obtained from the National Board of Health, NBH (in Denmark routine childhood vaccination could be administered by GPs only, who have to report them to the NBH). Used preparation contains strain Moraten measles strain, Jeryl Lynn mumps strain and Wistar RA 27/3 rubella strain. Authors report that 85% of the 871,234 subjects in the cohort for asthma hospitalisation and 84% of those considered for anti-asthma medication (n = 600,938) received MMR before follow-up end. MMR vaccination status was considered as time-varying variable and individuals could contribute to person-time as both unvaccinated and vaccinated subjects
Outcomes	Asthma hospitalisation (from the Danish National Hospital Register) Anti-asthma medication (from the Danish Prescription Drug Database)
Notes	There is no information about the time considered between vaccination and disease onset or use of medication (i.e. authors do not provide a definition of MMR vaccinated and not vaccinated status)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Jonville-Bera 1996

Methods	Ecological study to assess the association between MMR and the onset of thrombocytopenic purpura (TP)
Participants	Data from the French passive survey between 1984 and June 30th 1992. The 60 cases with outcome (TP) were mainly toddlers
Interventions	Immunisation with MMR (n = 4,396,645), measles (n = 860,938), mumps (n = 172,535), rubella DTP and ingle rubella (n = 2,295,307), measles/rubella (n = 1,480,058)
Outcomes	Cases of thrombocytopenic purpura diagnosed at one of the 30 survey centres after. All case within 45 days from vaccination. Over 8-year period of immunisation
Notes	The denominator is determined by the number of doses distributed

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable

Jonville-Bera 1996 (*Continued)*

Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Lerman 1981

Methods	RCT, double-blind
Participants	502 healthy children aged between 15 months and 5 years
Interventions	MMR vaccine (Merck Sharp & Dohme) with HPV - 77: DE - 5 rubella strain versus MMR vaccine (MMRII) with Wistar RA 27/3 rubella strain versus Measles vaccine (Merck Sharp & Dohme) VS Mumps vaccine (Merck Sharp & Dohme) versus Rubella vaccine HPV 77: CE - 5 versus Rubella vaccine Wistar RA 27/3 versus Placebo (vaccine diluent) One dose subcutaneously
Outcomes	- Local reactions (pain, redness or swelling at the injection site within 4 days after immunisation) - Temperature > 38 °C at 6 weeks - Respiratory symptoms (6 weeks) - Rash (6 weeks) - Lymphadenopathy (6 weeks) - Sore eyes (6 weeks) - Joint symptoms (6 weeks)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	Low risk	Adequate
Allocation concealment	Low risk	Adequate
Blinding All outcomes	Low risk	Double-blind

Lopez Hernandez 2000

Methods	Retrospective cohort study assessing effectiveness of MMR vaccination against clinical mumps on preschool and school children during an outbreak (March-November 1997)
Participants	Male children aged between 3 and 15 years attending one scholastic institute in the district of Cartuja y Almanjàyar (n = 775), that had the highest mumps attack rate in the district
Interventions	MMR immunisation (school, vaccination or register by the local Health Centre). Composition and strains not reported
Outcomes	Parotitis. Clinical defined by surveillance (case definition: unilateral or bilateral swelling of parotids or salivary glands, sensible to tasting, lasting more than 2 days, that appears without apparent cause or without contact with affected subjects)
Notes	It was not possible to assess mumps strain types administered to study population (in Spain Urabe Am 9 strain was used till 1993, it was replaced by Jeryl Lynn and Rubini after that year. Even if cases are those identified by surveillance, there is no description in the report of how it has been performed (e.g. active or passive surveillance ?). In any case, in the paragraph of case definition, authors declare that included cases are only those identified by surveillance and that real cases are unknown (underestimated)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Ma 2005

Methods	Case-control study
Participants	Cases (n = 323): newly diagnosed leukaemia in children aged between 0 and 14 years and ascertained from major paediatric clinical centres within 72 after diagnosis Controls (n = 409): for each case 1/2 controls matched for date of birth, gender, Hispanic status (either parent Hispanic), maternal race (white, African American, or other) and maternal county of residence
Interventions	MMR immunisation (no vaccine description) before index date
Outcomes	Association between MMR exposure and onset of leukaemia or acute lymphoblastic leukaemia (ALL)
Notes	

Ma 2005 (*Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Mackenzie 2006

Methods	Case-control study carried out in a private school in Lothian (Scotland) to evaluate effectiveness of 1 or 2 doses of MMR vaccine
Participants	Cases (n = 20): virologically confirmed mumps cases Controls (n = 40): participants matched to cases for age, sex, residential status and country source (UK or other)
Interventions	MMR immunisation with 1 or 2 vaccine doses (no description of composition)
Outcomes	Protective effectiveness of MMR immunisation against virological confirmed mumps
Notes	The size sample of cases employed was to small for reaching statistical significance, the poor accuracy in reporting vaccination status by parents of some children, the fact that controls had not virological test, the absolute lack information about vaccine composition (e.g. strain employed), the narration done by authors to have matched cases and controls for age, sex, residential status, country source without description of these variables in 2 groups make this study at high risk of bias

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Madsen 2002

Methods	Retrospective cohort
Participants	All Danish children born between January 1991 and December 1998: 537,303
Interventions	MMR vaccine (containing measles strain Moraten, mumps Jeryl Lynn, rubella Wistar RA 27/3) versus Pre-vaccination or non-vaccinated person-years
Outcomes	- Autism (ICD-10 code F84.0, DSM-IV code 299.00) - Autistic-spectrum disorder (ICD-10 codes F84.1 - F84.9, DSM-IV codes 299.10 - 299.80)
Notes	The follow-up of diagnostic records ends one year (31 Dec 1999) after the last day of admission to the cohort. Because of the length of time from birth to diagnosis, it becomes increasingly unlikely that those born later in the cohort could have a diagnosis

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Makela 2002

Methods	Person-time cohort study
Participants	561,089 children aged between 1 and 7 years at the time of vaccination
Interventions	Immunisation with MMR 2 vaccine (Merck, containing measles strain Enders Edmonston, mumps Jeryl Lynn and rubella Wistar RA 27) during a national immunisation campaign
Outcomes	- Encephalitis - Aseptic meningitis - Autism
Notes	Incidence of outcomes during the first 3 months after immunisation was compared with that in the following period (from 3 to 24 months after immunisation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable

Makela 2002 *(Continued)*

Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Makino 1990

Methods	Prospective cohort
Participants	1638 healthy children
Interventions	MMR vaccine MPR (Kitasato Institute, Japan containing measles AIK-C 5000 TCID50 , mumps Hoshino 15000 TCID50 and rubella Takahashi 32000 TCID50) versus Measles vaccine (Kitasato Institute, containing measles AIK-C 25000 TCID50) versus Mumps vaccine (Kitasato Institute, containing mumps Hoshino 10000 TCID50)
Outcomes	- Temperature, axillary (up to 37.5 °C or up to 39.0 °C) - Rash (mild, moderate or severe) - Lymphadenopathy - Parotitis - Cough - Vomiting - Diarrhoea Within 28 days after vaccination
Notes	Inadequate description of the cohorts

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Marin 2006

Methods	Retrospective cohort study carried out in Republic of the Marshall Islands (South Pacific) after a measles outbreak in 2003 to evaluate MMR vaccine effectiveness in contacts aged 6 months to 14 years with household secondary attack rate (SAR) method
Participants	72 households (a total of 857 participants) were selected by convenience sampling of measle cases reported in Majuro from 13 July to 7 November 2003. Contacts of these 72 primary cases aged between 6 months and 14 years with available MMR vaccination status were considered for effectiveness analysis (n = 219)
Interventions	MMR vaccine (composition not reported) in 1, 2, 3 or more doses administered A contact was considered vaccinated if documented record of measles vaccine administration > 4 days before the rash onset of primary case was available. An unvaccinated contact was a person without record of measles vaccination according to criteria in written or electronic records in a centralised electronic database. A person with unknown vaccination status had not immunisation card and his name was not in immunisation record (excluded from analysis)
Outcomes	Measles case defined as a subject who: 1) met the WHO clinical definition for measles (fever, generalised maculopapular rash and cough, coryza or conjunctivitis) or 2) had a positive test for measles IgM antibody by any serologic assay with the absence of vaccination 6 to 45 days before testing Primary case: first case of measles in household Secondary case: a contact (person that resided in household for at least 1 day through the infectious period of primary case - from 4 days before rash to 4 days after) with measles rash onset 7 to 18 days after primary case's rash onset Non-case: a contact with no clinically apparent disease within 18 days after primary case's rash onset Data were collected by a "standardized questionnaire" and interviews were conducted at home with household member
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Marolla 1998

Methods	Retrospective cohort study
Participants	Participants were children born between 1 January 1989 and 31 December 1994, whose parents requested an ambulatory visits by their family paediatricians between 15 May and 30 June 1996. 3050 were enrolled, corresponding to about 40% of the children population in the same age range in care by the 20 paediatricians who participated in the study
Interventions	During the time between 15 May and 30 June 1996 (period in which the visits has been performed) the 20 family paediatricians together with children's parents and by considering the content of medical records filled in a schedule, in which following information were collected: personal data, study titre of both parents, type of trivalent MMR vaccine, date of immunisation, practitioner who administered vaccine, onset of measles or mumps disease, eventual hospital admission, diagnostic criteria used and the practitioner who diagnosed the disease. For the cases when vaccination status could not be immediately assessed, parents were required to communicate as soon as possible the data contained in vaccination records During study time paediatricians received a questionnaire on vaccination modality and on how to store and administer it correctly Out of the 3050 initially enrolled children, 2099 were vaccinated with 1 of 3 MMR commercial preparations whereas 646 were not vaccinated. A total of 2745 were included in the effectiveness analysis The remaining 305 participants were excluded because of receiving monovalent vaccine (167), because schedule was compiled with insufficient detail (124), received vaccine after disease onset (6) , or contracted measles or mumps before the 15th month of age Out of the 2099 vaccinated, 1023 received Pluserix ®SKB, 747 Morupar® Biocine, and 329 Triviraten® Berna
Outcomes	Diseases under investigation has been defined as following: Measles: exanthema lasting for at least 3 days, with fever and/or coryza, and/or conjunctivitis, diagnosed at least 30 days after vaccine administration Mumps: parotid swelling lasting for at least 2 days diagnosed by a practitioner at least 30 days after vaccine administration Even if not described, paediatricians who conducted the study, considered as cases those corresponding to these definition from schedule data Altogether 124 measles cases (10 among vaccinated) and 457 mumps cases (251 among vaccinated) has been observed. 92 (74.2%) measles and 386 mumps cases (84.5%) occurred in the years 1995 to 1996
Notes	Diagnosis of measles and mumps disease was made only on clinical parameters and on the basis of data sampled during interviews and of those present in the medical records by paediatricians Results have been managed by paediatricians themselves, who were not blind to vaccination status of the children Mean age at enrolment was not statistical different between not vaccinated and pooled vaccinated groups (about 52 months), but authors do not provide these data (or age stratification) within each vaccine arm (considering age interval and visit time, follow-up time considered could range from 3 to 75 months). Administered vaccine types varied during the time considered for investigation: Pluserix (Schwarz/Urabe AM9) has been more used in the years between 1990 and 1991 and was withdrawn from the mark in 1992. Triviraten (Edmonston-Zagreb/Rubini) was of prevalent use in the years 1992, 1993 and 1994, Morupar (Schwarz/Urabe AM9) in 1995 and 1996. Exposition to disease and time since vaccination could be very different among subjects and this is not taken in account by evaluating effectiveness

Marolla 1998 (*Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

McKeever 2004

Methods	Cohort study assessing association between MMR and diphtheria, polio, pertussis and tetanus vaccination (DPPT) and asthma or eczema
Participants	Birth cohorts 1988 to 1999 identified through the West Midlands General Practice Research Database (GPRD; n = 16,470, aged from 20 months to 11 years, accounting for 69,602 person-years)
Interventions	MMR vaccination (data from GPRD; also data about other vaccination has been considered)
Outcomes	Incident diagnoses of asthma/wheeze and eczema were identified using the relevant Oxford Medical Information System (OXMIS, derived from ICD-8) and Read codes
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Miller 1989

Methods	Prospective cohort
Participants	12023 healthy children aged 1 to 2 years
Interventions	MMR vaccine (Immrawa or Pluserix, both containing measle strain Schwarz, rubella RA 27/3, mumps Urabe 9) versus

Miller 1989 (*Continued)*

	Measles vaccine (not described) Single dose	
Outcomes	- Temperature (2 or more days over 21 days) - Rash (2 or more days over 21 days) - Anorexia (2 or more days over 21 days) - Number of symptoms for 1 day only (Daily diary completed by parents)	
Notes	The study reports that 84% of diaries/questionnaires completed but only analysed 65%	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Miller 2005

Methods	Self controlled case series
Participants	Children hospitalised with gait disturbance between April 1995 and June 2001 (n = 127, age 12 to 24 months) Children with gait disturbance resulting from general practice visit (GPRD archive), born between 1988 and 1997 (n = 1398, age 12 to 24 months)
Interventions	MMR immunisation
Outcomes	Relative incidence of gait disturbance after MMR immunisation (considered risk periods 0 to 30 to 31 60 days)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable

Miller 2005 *(Continued)*

Blinding All outcomes	High risk	Not applicable

Miller 2007

Methods	Self controlled case series
Participants	Children aged 12 to 23 months (894) with discharge diagnosis of febrile convulsion (ICD-10 codes R560 or R568)
Interventions	MMR vaccination dose when on age of 12 to 23 months (immunisation records)
Outcomes	Incidence of disease during two at risk periods (between 6 to 11 and 15 to 35 days after immunisation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Mrozek-Budzyn 2010

Methods	Case-control study
Participants	Cases: 96 children with childhood or atypical autism diagnosis aged between 2 and 15 years from Ma łopolska Province (southern Poland) Controls: 192 children matched for birth year, gender and practice to the cases
Interventions	MMR vaccine and monovalent measles
Outcomes	Association between vaccine exposure before diagnosis or symptoms onset
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable

Mrozek-Budzyn 2010 (*Continued)*

Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Ong 2005

Methods	Retrospective cohort study carried out on children aged between about 5 and 12 years in order to state protection conferred from MMR immunisation (containing different mumps strains) against clinical defined mumps during an outbreak in Singapore in 1999
Participants	Children from childcare centres (n = 2533) and primary schools (n = 2539)
Interventions	MMR vaccination status of each child (MMR or nothing) was obtained from health booklet (updated in Singapore when a child receives vaccination in accordance with the immunisation schedule). The specific strain type (Rubini, Jeryl Lynn, Urabe, or unknown mumps strain) has been identified by matching the batch number of vaccine in health booklet with the record of the vaccine in polyclinic or family doctor's clinic. Even if the number of administered doses was not indicated, we can suppose that only older children could have received a 2nd MMR dose, as it was routinely introduced in January 1998
Outcomes	Mumps: clinically defined as fever associated with unilateral or bilateral swelling and tenderness of one or more salivary glands, usually the parotid gland. Diagnosed by physician. Serological confirmation was not carried out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Ong 2007

Methods	Retrospective cohort study carried out in Singapore during a measles outbreak in April to May 2004 in primary 3 and 6 school to evaluate the MMR vaccine effectiveness
Participants	Students (n = 184, age 8 to 14 years) from 5 classes of primary school in Singapore

Ong 2007 (*Continued*)

Interventions	MMR vaccine (no description). Only 1 dose administered. Data about vaccination (date and type vaccine administered) were noted in health booklet of each child and confirmed with the National Immunisation Registry (NIR) Control: do nothing
Outcomes	Measles cases laboratory-confirmed, defined following the World Health Organization criteria (WHO 2001)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Park 2004

Methods	Case cross-over. The design divides the study period (1 year of 365 days) into a hazard period (42 days after MMR - or before meningitis as defined by the authors) and a control period of 323 days
Participants	Children aged 13 to 29 months
Interventions	Immunisation with MMR
Outcomes	Cases of aseptic meningitis before and after immunisation
Notes	There is a likelihood of selection bias which the authors dismiss as they say that moving (probable cause of wrong phone numbers) is not associated with MMR exposure. The missing 27% of hospital records is also worrying

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Peltola 1986

Methods	RCT, double-blind
Participants	6086 pairs of twins aged between 14 months and 6 years
Interventions	MMR vaccine (Virivac, Merck Sharp & Dohme) versus Placebo One 0.5 ml dose subcutaneously administered
Outcomes	- Temperature (< 38.5 °C; 38.6 to 39.5 °C; > 39.5 °C) rectal - Irritability - Drowsiness - Willingness to stay in bed - Rash generalised - Conjunctivitis - Arthropathy - Tremor peripheral - Cough and/or coryza - Nausea or vomiting - Diarrhoea Measured by parental completed questionnaire for 21 days - parents given a thermometer
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	Unclear risk	Unclear
Allocation concealment	Low risk	Adequate
Blinding All outcomes	Low risk	Double-blind
Incomplete outcome data addressed All outcomes	Low risk	Adequate

Ray 2006

Methods	Case-control study investigating possible relationship between MMR and DTP immunisation and hospital admission for encephalopathy within 60 days. Data from 4 health maintenance organisations (Group Health Cooperative, Washington, Northern and Southern California Kaiser Permanente, Northwest Kaiser Permanente, Oregon and Washington), involving children aged 0 to 6 years, who were hospitalised for encephalopathy or related conditions between 1 January 1981 and 31 December 1995 (from 1 August 1998 for Southern California Kaiser Permanente) were reviewed

Ray 2006 (*Continued*)

Participants	Cases (n = 452): children (aged 0 to 6 years) with encephalopathy, Reye syndrome or encephalitis defined accordingly to definition (see Table 8) Controls (n = about 1280): for each case up to 3 controls were selected, matching for health maintenance organisation location, age within 7 days, sex and length of enrolment in health plan
Interventions	Vaccination status concerning MMR and DTP vaccines exposure of both cases and controls was assessed by vaccination records. Only the neurologist who made the final case diagnosis was blind to vaccination status, not so the abstracter. Exposure to both vaccines was stratified in the results on the basis of the time elapsed between vaccination and hospital admission (0 to 90 days, 0 to 60 days, 0 to 30 days, 0 to 14 days, 7 to 14 days, 0 to 7 days)
Outcomes	Observed cases (encephalopathy, Reye syndrome or encephalitis) were further classified considering disease aetiology: known, unknown or suspected but unconfirmed (this latter includes cases in which a diagnosis such a meningitis has not been confirmed by specific laboratory test)
Notes	Authors did not indicate formally how many controls have been included in the analysis. Controls included in each stratification could be calculated from percentages in tables 2, 3, 4. Regarding vaccine exposure, we know only that it has been assessed by means of vaccination record, but any further informations (e.g. vaccine type and composition, number of administered doses) is absent in the report. This is would be an important information, as it would permit to test association with diseases and single vaccine strains: cases were enrolled between 1981 and 1995, during this time different vaccines formulation have been in use

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Robertson 1988

Methods	Prospective cohort
Participants	319 children aged 13 months
Interventions	MMR vaccine (Mérieux, containing measles strain Schwarz, mumps Urabe AM/9 and rubella Wistar RA 27/3) versus Measles vaccine (Schwarz strain) Allocation by parental choice

Outcomes	- Irritability - Rash - Coryza - Temperature (parental touch) - Cough - Lethargy - Diarrhoea - Vomiting - Anorexia - Conjunctivitis - Lymphadenopathy - Parotitis - Local reactions - No symptoms - Paracetamol use - Seen by GP - Convulsion Parental completed diaries of symptoms. 3-week follow-up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Schlegel 1999

Methods	Retrospective cohort study carried out on children aged between 5 and 13 years in order to assess protective effectiveness of MMR vaccine prepared with different mumps strains (Rubini, Jeryl Lynn, Urabe) during a mumps epidemic in comparison with no vaccination
Participants	Participants were children aged 5 to 13 years from a small village in Switzerland (n = 165). Vaccination coverage in this population was high (95%)
Interventions	Immunisation with MMR vaccine prepared with different mumps strain. 79 children were immunised with Rubini-containing MMR vaccine, 36 with Jeryl Lynn containing MMR vaccine, and 40 with Urabe-containing MMR vaccine. 8 participants were not MMR vaccinated. Vaccine strain was not known for 2 children without mumps, who were excluded from study. Vaccination status was ascertained by study investigators from vaccination certificates. All children received immunisation within 2 years of age

Schlegel 1999 (*Continued)*

Outcomes	A mumps case was defined by viral isolation of mumps virus in a culture, doctor's confirm of diagnosis or if the presence of the typical clinical picture was described in a sibling of a patient with confirmed disease. Investigators who ascertained mumps cases were blind to vaccination status
Notes	Many study details are described with insufficient detail present in this brief report (e.g. mumps case definition, onset and duration of the outbreak, methods of cases ascertainment)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Schwarz 1975

Methods	Multicentre RCT, double-blind
Participants	Altogether 1481 healthy children from different countries in North and South America were allocated
Interventions	Three lots of MMR vaccine (Liutrin, Do Chemical containing live attenuated measles strain Schwarz, at least 1000 TCID50; mumps live strain Jeryl Lynn, at least 5000 TCID50; live rubella Cenedehill strain, at least 1000 TCID50) versus Placebo One dose subcutaneously administered
Outcomes	Axillary and rectal temperature, rash, lymphadenopathy, conjunctivitis, otitis media, coryza, rhinitis, pharyngitis, cough, headache, parotitis, orchitis, arthralgia, paraesthesia, site adverse events, hypersensitivity. Children were observed for adverse events approximately 3 times each between 7 to 21 days
Notes	- Age restriction (1 to 4 years) was not enforced - A large number of patients were missing from all observations

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	Unclear risk	Not described
Allocation concealment	High risk	Inadequate

Schwarz 1975 (*Continued)*

Blinding All outcomes	Low risk	Double-blind
Incomplete outcome data addressed All outcomes	High risk	

Seagroatt 2005

Methods	Ecological study
Participants	England population aged between 4 and 18 years between April 1991 and March 2003 (about 11.6 million)
Interventions	Introduction of MMR vaccination (1988)
Outcomes	Emergency hospitalisation for Crohn's disease (CD). Age specific ranges were calculated so as rates in population with at least 84% coverage and that in population with coverage below 7% were compared
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Sharma 2010

Methods	Cohort study carried out in Egypt, assessing reaction observed after immunisation with MMR in occasion of compulsory vaccinations
Participants	Children aged 16 to 24 months (n = 73,745) from 9 Egyptian governorates and aged 5 to 7 years (n = 371,184) from 8 Egyptian governorates
Interventions	Immunisation with MMR vaccine containing Leningrad-Zagreb mumps strain (Tresivac, Serum Institute of India) It contains 1000 $CCID_{50}$ live attenuated measles Edmonston-Zagreb strains, 5000 $CCID_{50}$ of mumps strain Leningrad-Zagreb, 1000 $CCID_{50}$ of rubella strain Wistar RA 27/3 in each 0.5 ml dose. Partially hydrolysed gelatin (2.5%), sorbitol (5%), neomycin ($\leq 15\mu g$) and water as diluent belong also to vaccine composition. 24 different lots (EU 615V, EU 618V - EU 640V) were used in the study. Younger children were immunised in the thigh, older in the deltoid

Sharma 2010 (*Continued)*

Outcomes	Pain, redness, swelling, fever, rash, parotitis, arthralgia, lymphadenopathy. Data collected by means of a structured questionnaires for the time within 42 days after vaccination
Notes	One of the main study purpose was to investigate the association between MMR and aseptic meningitis. No disease cases have been identified

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Smeeth 2004

Methods	Retrospective case-control study
Participants	All person born in 1973 or later registered in the General Practice Research Database (GPRD) Cases: participants with diagnosis of pervasive developmental disorders Controls: individuals matched to cases by year of birth or by practice registration
Interventions	Exposure to MMR vaccination from birth to index date (date of the first diagnosis with PDD)
Outcomes	Number of MMR vaccination among cases and controls prior to PDD diagnosis and prior PDD diagnosis and 3rd birthday
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Stokes 1971

Methods	Prospective cohort
Participants	Altogether 966 children (334 in the US and 632 in Cost Rica)
Interventions	MMR vaccine (Merck Sharp & Dohme containing measles strain Moraten 1000 TCID50, mumps strain Jeryl Lynn 5000 TCID50, rubella strains HPV - 77 1000 TCID50) 1 dose subcutaneous versus No treatment
Outcomes	- Temperature (> 38 °C in US, no range given in Costa Rica) - Conjunctivitis - Upper respiratory tract illness - Lymphadenopathy - Gastroenteritis - Fretfulness - Malaise and anorexia - Measles-like rash - Arthralgia (only in Costa Rica) Follow-up 28 days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Stowe 2009

Methods	Self controlled case series
Participants	Children aged 12 to 23 months with hospitalisation for bacterial or viral infections identified from hospital admission records by reviewing ICD-9 or -10 codes (n = 2025)
Interventions	MMR vaccination
Outcomes	- Bacterial infections: lobar pneumonia or invasive bacterial infection - Viral infections: encephalitis/meningitis, herpes, pneumonia, varicella Zoster, or miscellaneous virus Relative incidence (RI) of each disease was assessed within specified time risk intervals (0 to 30, 31 to 60, 61 to 90 or 0 to 90 days) after MMR immunisation
Notes	

Stowe 2009 (*Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Swartz 1974

Methods	Prospective cohort
Participants	59 children aged 1 to 6 years (mean about 2 years)
Interventions	MMR vaccine (Merck Institute for Therapeutic Research) versus Mumps - rubella vaccine (Merck Institute for Therapeutic Research) versus Rubella vaccine (Merck - Meruvax HPV 77-DE5 No information about doses and schedule
Outcomes	- Temperature (37.2 to 38.2; 38.3 to 39.3; over 39.4 °C) - Lymphadenopathy - Enanthema - Conjunctivitis - Rash Complaints - any (up to 60 days) Follow-up 7 to 15 days
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Taylor 1999

Methods	Case-coverage comparing incidence of autistic disorders in 8 health districts in UK	
Participants	498 children with autism	
Interventions	MMR vaccine and, in some cases, measles or MR vaccines identified through a computerised register	
Outcomes	Typical and atypical autism and Asperger's syndrome. No definition given, but identification of some of the cases was made through ICD 10 codes	
Notes	The absence of unvaccinated controls limits the inductive statements that can be made from this study	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Uchiyama 2007

Methods	Retrospective cohort study conducted in Japan, employing data from patients of a private child psychiatric clinic in Yokohama to evaluate association between MMR vaccination and regression in autism spectrum disorders (ASD) and to evaluate the "change over time" in proportion of children who presented regressive symptoms during the pre-MMR (before MMR vaccine programme), MMR (during MMR vaccine programme) and post MMR era (when the programme ceased)	
Participants	Children born between 1976 and 1999 with clinical diagnosis of ASD assessed at the Yokohama Psycho-Developmental Clinic (YPDC, n = 904)	
Interventions	MMR vaccine containing AIK-C (measles), Urabe AM9 (mumps) and To-336 (rubella) strains	
Outcomes	ASD regression	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable

Uchiyama 2007 *(Continued)*

Blinding All outcomes	High risk	Not applicable

Vestergaard 2004

Methods	Person-time cohort study
Participants	537,171 Danish children
Interventions	Exposure to MMR vaccine (containing measles strain Moraten, Mumps Jeryl Lynn and rubella Wistar)
Outcomes	Febrile seizure (ICD definition) in children aged 3 months to 5 years: cases occurred within 2 weeks after vaccination and cases occurred after this time
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Ward 2007

Methods	Self controlled case series study carried out to assess whether exposure to MMR and other vaccines (DTP/Hib, MenC) was associated with onset of serious neurological diseases
Participants	155 children aged between 2 and 35 months from Republic of Ireland and Britain with serial neurological disease (see outcome definition) and documented vaccination history. Data about cases were collected between October 1998 and September 2001
Interventions	Immunisation with MMR or DTP vaccine. Data were obtained from child's GP by Immunisation Department and Center for Infection. Vaccination history should cover 1 year after disease onset. Authors consider as at risk period the time between 0 and 3 days or 0 and 7 days following DTP, Hib and MenC vaccinations and the time between 6 and 11 days or 15 and 35 days following MMR vaccination
Outcomes	- Severe illness with fever and convulsion - Encephalitis (see Table 8 for detailed definition)

Ward 2007 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

Weibel 1980

Methods	Prospective cohort
Participants	135 children
Interventions	MMR vaccine (Merck, containing measles strain Moraten, mumps Jeryl Lynn, rubella RA 27/3) versus Rubella vaccine (strain RA 27/3) One dose subcutaneous
Outcomes	- Temperature > 38 °C - Rash - Lymphadenopathy - Arthralgia - Myalgia - Anorexia Follow-up 42 days
Notes	No information given on how the children were distributed between the 3 arms. Sparse detail on safety data collection procedures

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	High risk	Not applicable
Allocation concealment	High risk	Not applicable
Blinding All outcomes	High risk	Not applicable

AIT = acute immune thrombocytopaenia

AM = aseptic meningitis
BCG = Bacillus Calmette-Guérin
DIN = Doctors' Independent Network
DPT = diphtheria, pertussis and tetanus
GPRD =General Practice Database
HMO = Health Maintenance Organisation
IM = intra-muscular
MMR = measles, mumps, rubella
MS = multiple sclerosis
n = number
PCR = polymerase chain reaction
sc = subcutaneous
wks = weeks

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akobeng 1999	No original research - review
Andre 1984	No direct data on MMR; only observation that it may interfere with varicella vaccine
Anonymous 1982	Non-comparative
Anonymous 1997	No original data
Anonymous 1999	Not original research - review
Anonymous 2004	Abstract of Hviid 2004 (included study)
Aozasa 1982	Not MMR vaccine
Asaria 2008	Review
Autret 1996	Epidemiological survey comparing onset of ITP following vaccination with MMR compared to M, M and R
Bakker 2001	Authors attribute school mumps outbreak to bad attenuated MMR vaccine lots; uncertain data about relationship between MMR exposure and symptoms onset
Balraj 1995	Review on mumps vaccine
Beck 1991	Assesses safety of MMR vaccination in children allergic to eggs
Bedford 2010	Editorial
Beeler 1996	Case series

(*Continued*)

Benjamin 1991	No new research review
Berger 1988a	Serology outcomes only
Berger 1988b	Serology (seroconversion) outcomes only
Berlin 1983	Surveillance data
Bernsen 2008	No outcomes
Bhargava 1995	Non-comparative
Bonanni 2005	Non-comparative
Borchardt 2007	Not comparative
Borgono 1973	Insufficient data presented
Boxall 2008	Non-comparative
Brockhoff 2010	Non-comparative
Bruno 1997	Compares 2 types of MMR
Buntain 1976	Case report
Buynak 1969	Several studies - non-comparative
Cardenosa 2006	Non-comparative
Castilla 2009b	Same study as Castilla 2009a (included study)
Chang 1982	No adverse effect data
Chen 1991	Individuals over 15 years
Chen 2000	Review
Cherian 2010	No data
Chiodo 1992	Non-comparative
Cinquetti 1994	Compares 2 types of MMR
Contardi 1989	Non-comparative
Contardi 1992	Compares 3 types of MMR

(*Continued*)

Coplan 2000	Does not compare against a single component or do nothing
Coronado 2006	Case-fatality rate study
Cox 2009	Letter
Curtale 2010	Non-comparative
Czajka 2009	No comparison: MMR-v versus MMR+V
D'Argenio 1998	No safety data
D'Souza 2000	Non-comparative
Dales 2001	Non-comparative
Dallaire 2009	Non-comparative
Dankova 1995	No adverse event data
Dashefsky 1990	MMR not given independently
Davis 1997	MMR not given independently
Dayan 2008a	Non-comparative
De Laval 2010	Seroprevalence study
Deforest 1986	MMR given with DTP and OPV in different schedules
Deforest 1988	DTP/OPV plus or minus MMR versus placebo or without MMR
DeStefano 2000	Duplicate data
Diaz-Ortega 2010	No comparison: MMR versus MMR versus MMR
Dobrosavljevic 1999	Case report
Dominguez 2008	Surveillance study
Dos Santos 2002	MMR versus MMR versus MMR
Doshi 2009	Effectiveness of measles-containing vaccines has been assessed, not specifically MMR
Dyer 2010a	Commentary
Dyer 2010b	Commentary

(*Continued*)

Ehrenkranz 1975	Duplicate data Schwarz 1975
Elphinstone 2000	Data free
Englund 1989	MMR not given independently
Farrington 1996	Non-comparative
Farrington 2001	No new data
Fitzpatrick 2007	Commentary
Fletcher 2001	No data
Garrido L 1992	Non-comparative
Geier 2004	Uncertain MMR focus, mixed with thimerosal
Gerber 2009	Review
Goodson 2010	Monovalent measles vaccine
Griffin 1991	Non-comparative
Grilli 1992	Comparison of different types of measles in MMR
Hilton 2009	Content analysis
Hindiyeh 2009	No outcomes of interest
Hornig 2008	Subjects affected by gastrointestinal disturbance
Hu 2007	Non-comparative
Hua 2009	Association with KD tested for vaccines other than MMR
Huang 1990	No safety data
Ipp 2003	Head-to-head of 2 types of MMR
Jiang 2009	Non-comparative
Jones 1991	Non-comparative
Just 1985	Comparison of different types of MMR; CCT with serological outcomes
Just 1986	MMR not given independently - comparison of MMR plus or minus varicella vaccine

(*Continued*)

Just 1987a	Not given independently - comparison of MMR plus or minus OPV
Just 1987b	Comparison of MMR plus or minus DTP
Kaaber 1990	Comparison of MMR with or without other vaccine versus other vaccines (DTP and OPV)
Karim 2002	Case report
Kaye 2001	Non-comparative
Kazarian 1978	Case report
Khalil 2005	Cross-sectional study
Kiepiela 1991	RCT of 2 types of measles vaccine
Kulkarni 2005	Review
Kurtzke 1997	Case-control of exposure to anything/measles vaccine and MS
Lee 1998	Data free
Lee 2007	Retrospective analysis of medical records
Lucena 2002	No comparator
Maekawa 1991	Non-comparative - non-inferential
Maguire 1991	Non-comparative
Mantadakis 2010	Review
Matter 1995	Non-comparative
Matter 1997	Seroprevalence study
Meissner 2004	Review
Menniti-Ippolito 2007	Previous report of Bertuola 2010 (included study)
Miller 1983	Non-comparative; egg allergy
Miller 1993	Non-comparative
Miller 2001	Non-comparative
Miller 2002	No new data

(*Continued*)

Min 1991	Compares 2 types of MMR
Minekawa 1974	Non-comparative
Mommers 2004	MMR and all other childhood vaccines, indistinguishable comparison
Mupere 2006	No MMR vaccine
Nalin 1999	No data
Nicoll 1998	No data
Noble 2003	Follow-up of the Madsen et al study with some data about resurgence of measles in Japan after vaccination became optional
O'Brien 1998	No data presented
Ong 2006	Review
Patja 2000	Non-comparative
Patja 2001	Non-comparative
Pekmezovic 2004	Not about MMR
Peltola 1998	Non-comparative case series
Peltola 2007	Review
Puvvada 1993	Non-comparative case series
Rajantie 2007	Non-comparative (unclear study design)
Ramos-Alvarez 1976	Duplicate publication of Schwarz 1975
Roost 2004	Cross-sectional study
Sabra 1998	Data free
Saraswathy 2009	Seroprevalence study
Scarpa 1990	Non-comparative
Schaffzin 2007	Differences between the 2 subpopulations in the study were not taken into account. Partially outside age. Effectiveness was calculated cumulatively for campers (n = 368, age 7 to 15 years, mean 12 years, 366/368 previously immunised with 2 doses of mumps containing vaccine, only 2/368 with one dose) and staff members (n = 139, age 14 to 65 years, mean 21 years, of whom 74, 44, and 21 received respectively 2, 1 or no doses of a mumps-containing vaccine)

(*Continued*)

Schettini 1989	No safety data
Schettini 1990	Non-comparative
Schmid 2008	Non-comparative
Schwarz 2010	No treatment: measles + MMR vaccine
Schwarzer 1998	Compares 2 types of MMR
Seagroatt 2003	Assesses measles vaccine
Sharma 2004	Non-comparative
Shinefield 2002	MMR not given independently
Spitzer 2001	No data
Stetler 1985	DTP vaccine
Stokes 1967	No safety data
Stratton 1994	Review
Sugiura 1982	Data not reported by arm
Ueda 1995	Compares 2 types of MMR
Vesikari 1979	No new data to review
Vesikari 1984	Compares 2 types of MMR
Wakefield 1998	Case series
Wakefield 1999a	No comparative data
Wakefield 1999b	No data
Wakefield 2000	No comparative data
Walters 1975	Redundant publication: Schwarz 1975
Wilson 2003	Systematic review
Woyciechowska 1985	Not MMR

(*Continued)*

Yamashiro 1998	Children past age limit
Yu 2007	Non-comparative

CCT = controlled clinical trial
DTP = diphtheria, pertussis and tetanus
ITP = idiopathic thrombocytopaenic purpura
KD = Kawasaki disease
MMR = measles, mumps, rubella
MS = multiple sclerosis
OPV = trivalent oral poliovirus

Characteristics of studies awaiting assessment *[ordered by study ID]*

Arenz 2005

Methods	Cohort study
Participants	Child household contacts in families with at least 1 mumps case
Interventions	Vaccination with measles-containing vaccine
Outcomes	Measles secondary cases
Notes	Insufficient information about vaccine composition (if MMR or bivalent) for household contact study. Screening method was used for vaccine effectiveness assessment in Coburg school population aged above 5 years. Many important details are missing

Barlow 2001

Methods	Cohort study
Participants	Children (n = 137,457) from 4 Health Maintenance Organisations in USA
Interventions	Immunisation with MMR vaccine
Outcomes	Risk of febrile seizure within 0 to 7, 8 to 14, 15 to 30 days after immunisation
Notes	

Barrabeig 2011

Methods	Cohort study
Participants	School children (n = 166)
Interventions	Post-exposure prophylaxis with MMR vaccine
Outcomes	Measles
Notes	

Benke 2004

Methods	Retrospective cohort
Participants	Young adults aged between 22 and 44 years
Interventions	Immunisation with MMR and other vaccines
Outcomes	Possible association between vaccination and asthma was tested
Notes	Outside of age range

Cohen 2007

Methods	Screening method
Participants	Children (n = 312) with confirmed mumps in England
Interventions	Immunisation with MMR vaccine
Outcomes	Effectiveness against mumps diseases
Notes	Screening method design (effectiveness is estimated considering the proportion of vaccinated among cases and in the general population)

da Silveira 2002

Methods	Surveillance study carried out in Rio Grande do Sul (Brazil) following an immunisation campaign with MMR vaccine containing Leningrad-Zagreb mumps strain
Participants	Children between 1 and 11 with aseptic meningitis
Interventions	Immunisation with Leningrad-Zagreb MMR vaccine
Outcomes	Risk association with aseptic meningitis

da Silveira 2002 (*Continued)*

Notes	

Dominguez 2010

Methods	Screening method
Participants	Children and adults (n = 381) measles cases
Interventions	Immunisation with MMR vaccine
Outcomes	Effectiveness against measles diseases
Notes	Screening method (effectiveness is estimated considering the proportion of vaccinated among cases and in the general population)

Huang 2009

Methods	Case-control study
Participants	Cases = 126 undergraduate students with mumps Controls = 147 controls matched for age, sex, dormitory
Interventions	Case and controls with adequate MMR immunisation (at least 2 doses) were compared in univariate and multivariate analysis
Outcomes	Risk factor for developing mumps
Notes	Outside of age range

Jick 2010

Methods	Case-control study carried out in England
Participants	Cases = measles cases diagnosed in 1994, age 1 to 19 years, born from 1982 onwards (n = 1261) Controls = no prior measles, matched to each case on year of birth, gender, general practice attended, index date (n = 4996)
Interventions	
Outcomes	
Notes	Unclear MMR or MR exposure. Author was asked about. Further review of the study is needed

Mallol-Mesnard 2007

Methods	Case-control study
Participants	Cases of acute leukaemia in subjects aged < 15 years residing in France (ESCALE study)
Interventions	Vaccination with MMR and other vaccines (diphtheria, tetanus, poliomyelitis, pertussis and others)
Outcomes	Association of vaccine exposure with acute leukaemia
Notes	Effect of exposure to several vaccination (i.e. not MMR only) was evaluated in this study. As data about MMR vaccine were not available from study report, we made an attempt to contact trial authors in order to obtain this information, but no answer was received

Marin 2008

Methods	Cohort study
Participants	Student population from 2 colleges in Iowa, USA (n = 2363)
Interventions	Immunisation with MMR vaccine
Outcomes	Mumps cases following an outbreak
Notes	Study population outside of review's age range

Schultz 2008

Methods	Case-control study
Participants	Cases = 83 children with autistic disorders Controls = 80 children
Interventions	MMR vaccine administration with or without acetaminophen
Outcomes	Association of intervention exposure with autistic disorders
Notes	The study evaluated association between acetaminophen and MMR or MMR alone with autistic disorders

Sheppeard 2009

Methods	Screening method
Participants	Notified measles cases in children from New South Wales, Australia during 2006 (n = 56)
Interventions	MMR immunisation
Outcomes	Effectiveness against measles diseases

Sheppeard 2009 (*Continued)*

Notes	Screening method design (effectiveness is estimated considering the proportion of vaccinated among cases and in the general population)

So 2008

Methods	Retrospective cohort study performed following a measles outbreak
Participants	Preschool students (n = 152) in Incheon, Korea
Interventions	Immunisation with measles-containing vaccine
Outcomes	Measles cases
Notes	Article in Korean. No translation available

Svanstrom 2010

Methods	Person-time cohort
Participants	Children born in Denmark from 1995 to 2007 (n = 918,831)
Interventions	MMR vaccination Enders-Edmonston (measles), Jeryl Lynn (mumps) and Wistar RA 27/3 (rubella)
Outcomes	Possible association between vaccine exposure and febrile convulsion, idiopathic thrombocytopenic purpura, lymphadenopathy and rash was tested
Notes	Unclear design

Wichmann 2007

Methods	Retrospective cohort study
Participants	Students between 10 and 21 years of age (Duisburg, Germany)
Interventions	Immunisation with measles-containing vaccine
Outcomes	Effectiveness of vaccination in preventing measles during an outbreak
Notes	Unclear if all study population was immunised with MMR or single component vaccines

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Effectiveness against measles: summary findings from cohort studies

Study	Population characteristics	Case definition/finding	MMR strain/ exposure	Control	Number of events/ number of exposed Effectiveness estimate VE% (95% CI)	Evaluation of bias risk	Generalisability
Marolla 1998	Children (19 to 67 months) whose parent required a paediatrician visit during a measles outbreak peak	Clinical diagnosis Patients record and parents interview	Schwarz n = 329 (Pluserix) n = 747 (Morupar) 1 dose Vaccination records	n = 646 not vaccinated	- No measles cases observed among 'Pluserix' recipients (0/19, 836 person-months) - Morupar = 2 cases /12,906 person-months - Control 114 cases/22,188 person-months VE = 97% (88% to 99%) for 1 Morupar dose	High	Low
Marolla 1998	See above	Clinical diagnosis Patients record and parents interview	Edmonston-Zagreb (Triviraten) n = 1023 Vaccination records	n = 646 not vaccinated	- Triviraten = 8 cases/31,329 person-months - Control 114/ 22,188 person-months VE = 95% (90-98) for 1 Triviraten dose	High	Low

Table 1. Effectiveness against measles: summary findings from cohort studies *(Continued)*

Ong 2007	Children from primary school in Singapore (aged 8 to 14 years) during a measles outbreak	Clinical with laboratory-confirmation. Active survey and serological confirmation	Not reported n = 171 1 dose Health booklets	n = 13 not vaccinated	- 2 cases/171 vaccinated - 7 cases/13 unvaccinated controls VE = 97.8% for 1 dose	High	Low
Marin 2006	Household contacts (6 months to 14 years) of primary measle cases	Clinical (WHO definition) or IgM positive antibody of secondary cases Standardised questionnaires	Not reported n = 48 (1 MMR dose) n = 106 (2 MMR doses) Vaccination records	n = 21 not vaccinated	- 2 secondary cases/48 contacts vaccinated with 1 MMR dose - 3 secondary cases/106 contacts vaccinated with 2 MMR doses - 11 secondary cases/21 unvaccinated contacts VE = 92% (67 to 98) from 1 MMR dose VE = 95% (82 to 98) for 2 MMR doses	High	Low

IgM: immunoglobulin M
MMR: measles, mumps, rubella vaccine
n: number of participants in intervention and control arm
VE: vaccine effectiveness
WHO: World Health Organization

Table 2. Effectiveness against mumps: summary findings from cohort studies

Study	Population characteristics	Case definition/finding	MMR-strain/exposure	Control	Number of events/number of exposed Effectiveness estimate VE% (95% CI)	Evaluation of bias risk	Generalisability

Table 2. Effectiveness against mumps: summary findings from cohort studies (*Continued*)

Ong 2005	Children from childcare centres and primary schools in Singapore, aged 5 to 12 years	Clinical diagnosis. Standard questionnaire filled by trained public health officer or physician diagnoses	Jeryl Lynn n = 711 1 or 2 MMR doses (health booklet)	n = 614 no vaccination	- Jeryl Lynn = 8 cases/711 vaccinated - Control = 35 cases/614 unvaccinated VE = 80.7% (57.8 to 90.8) for at least 1 dose	High	Low
Ong 2005	See above	See above	Urabe n = 190 1 or 2 MMR doses (health booklet)	n = 614 no vaccination	- Urabe = 5 cases/190 vaccinated - Control = 35 cases 614 unvaccinated VE = 54.4% (from -16.2 to 81.7) for at least 1 dose	High	Low
Ong 2005	See above	See above	Rubini n = 1694 1 or 2 MMR doses (health booklet)	n = 614 no vaccination	- Rubini = 150 cases 1694 vaccinated - Control = 35 cases/614 unvaccinated VE = -55.3% (from -121. 8% to -8.8%) for at least 1 dose	High	Low
Schlegel 1999	Children aged 5 to 13 years from a small village in Switzerland	Clinical confirmation after virus isolation or clinical picture observed in sibling of confirmed cases Parents interview and evaluation by study investigators	Urabe n = 40 vaccination records	n = 8 not vaccinated	- Urabe = 3 cases/40 vaccinated - Control = 5 cases/8 unvaccinated VE = 87% (76 to 94) for at least 1 dose	High	Low

Table 2. Effectiveness against mumps: summary findings from cohort studies *(Continued)*

Schlegel 1999	See above	See above	Jeryl Lynn n = 36 Vaccination records	n = 8 not vaccinated	- Jeryl Lynn = 5 cases/36 vaccinated - Control = 5 cases/8 unvaccinated VE = 78% (64 to 82) for at least 1 dose	High	Low
Schlegel 1999	See above	See above	Rubini n = 79 vaccination records	n = 8 not vaccinated	- Rubini = 53 cases/79 vaccinated - Control = 5 cases/8 unvaccinated VE = -4% (-218 to 15) for at least 1 dose	High	Low
Marolla 1998	Children (19 to 67 months) whose parent required a paediatrician visit during a measles outbreak peak	Clinical diagnosis Patients record and parents interview	Urabe n = 329 (Pluserix) n = 747 (Morupar) 1 dose vaccination records	n = 646 not vaccinated	- Pluserix = 38 cases/19,433 person-months - Morupar = 28 cases/12, 785 person-months - Control = 206 cases/25, 816 person-months VE = 75% (65% to 83%) for 1 dose Pluserix VE = 73% (59 to 82) for 1 dose Morupar	High	Low
Marolla 1998	See above	See above	Rubini (Triviraten) n = 1023 One dose Vaccination records	n = 646 Not vaccinated	- Triviraten = 185 cases/29, 974 person-months VE = 23% (6 to 37) for 1 dose Triviraten	High	Low

Table 2. Effectiveness against mumps: summary findings from cohort studies *(Continued)*

Lopez Hernandez 2000	Male children aged between 3 and 15 years attending a scholastic institute during a mumps outbreak (March to November 1997)	Clinical diagnosis. Cases notified by the Andalusian survey system	Not known n = 685 vaccination record	n = 38 not vaccinated	- 73 cases/685 vaccinated - 8 cases/38 unvaccinated controls VE = 49% (Chi^2 test = 3.91, P = 0.047) for at least 1 dose	High	Low
Chamot 1998	Children aged up to 16 years from Ginevra were household contacts of primary confirmed mumps cases (clinical or with laboratory confirmation notified by a paediatrician)	Clinical diagnosis of secondary cases Phone interview	Urabe n = 75 vaccination records	n = 72 no vaccination	- Urabe = 7 cases/75 vaccinated contacts - Control = 25 cases/72 unvaccinated contacts VE = 73.1% (41.8 to 87.6) Number of doses not specified	Moderate	Low
Chamot 1998	See above	See above	Jeryl Lynn N = 30 vaccination records	n = 72 no vaccination	- Jeryl Lynn = 4 cases/30 vaccinated contacts - Control = 25 cases/72 unvaccinated contacts VE = 61.6 % (-0.9 to 85.4) Number of doses not specified	Moderate	Low
Chamot 1998	See above	See above	Rubini n = 83 vaccination records	n = 72 no vaccination	- Rubini = 27 cases/83 vaccinated contacts - Control = 25 cases/72 unvaccinated contacts VE = 6. 3% (-	Moderate	Low

Table 2. Effectiveness against mumps: summary findings from cohort studies *(Continued)*

					45.9 to 39.8) Number of doses not specified		

MMR: measles, mumps, rubella vaccine
n: number of participants in intervention and control arm
VE: vaccine effectiveness

Table 3. Effectiveness against mumps: summary findings from case-control studies

Study	Population characteristics	Case definition/finding	Controls/selection	MMR strain/exposure	Number of vaccinated in cases/controls Effectiveness estimate VE % (95% CI)	Evaluation of bias risk	Generalisability
Harling 2005	Children and adolescents aged between 1 and 18 years from religious community in NE London. Mumps outbreak	Clinical diagnosis n = 156 (GP notification to the local CCDC, mumps diagnoses from electronic practice list, verbal reports by community members)	n = 175 randomly selected and stratified for age and sex from practice list	Jeryl Lynn 1 or 2 MMR doses received at least 1 month before index date	79/156 cases and 134/175 controls received at least 1 MMR dose VE = 69% (41 to 84) for at least 1 dose, adjusted for age, sex, practice	Moderate	Medium
Harling 2005	See above	Laboratory-confirmation of clinical diagnosis n = 43 - GP notification to the local CCDC To notified cases, IgM and mumps RNA testing was offered	See above	See above	- VE for at least 1 dose = 65% (25 to 84) - VE for 1 dose = 64% (40 to 78) - VE for 2 doses = 88% (62 to 96) All adjusted for age,	Moderate	Medium

Table 3. Effectiveness against mumps: summary findings from case-control studies (*Continued)*

					sex, practice Proportion of vaccinated in cases and controls not provided		
Goncalves 1998	Children and adolescents (15 months to 16 years) from Oporto (Portugal)	Clinical diagnosis n = 73 Cases reported by GPs or hospital doctors, occurred during the 1995 to 1996 mumps outbreak	n = 169, 2 consecutive vaccination records of the same sex, month and birth year as the case, were selected	Urabe vaccination records (assuming that before 1 November 1992 MMR mumps Urabe strain was administered)	56/ 73 cases and 142/169 controls received at least 1 MMR dose VE = 70% (25 to 88) for at least 1 dose	High	Low
Goncalves 1998	See above	Clinical diagnosis n = 133 Cases reported by GPs or hospital doctors, occurred during the 1995 to 1996 mumps outbreak	n = 236 see above	Rubini vaccination records (assuming that after 1 November 1992 MMR mumps Rubini strain was administered)	116/133 cases and 209/236 controls received at least 1 MMR dose VE = 1% (from -108 to 53) for at least 1 dose	High	Low
Giovanetti 2002	Children and adolescent aged from 14 months to 15 years from urban area of Alba and Bra and 10 rural towns (12,880 residents from 0 to 15 years) . During 2000 to 2001 epidemic	Clinical diagnosis (cases notified by national infectious diseases surveillance system) n = 139 - Notified mumps cases	n = 139 randomly selected from immunisation registry, matched for birth year and address	Not specified Vaccination registry and phone interviews, immunisation should have been received at least 30 days before disease onset	90/139 cases and 111/139 controls received at least 1 MMR dose VE = 53.7% (20.4 to 73.0) for at least 1 dose	High	Low
Castilla 2009a	Children aged between 15 months and 10 years from Navarre region (North-	Laboratory or epidemiological confirmation of clinical cases: swelling of 1 of more	n = 1205 matched for sex, municipality, district of residence and	Jeryl Lynn 1 or 2 MMR doses received at least 30 days before symp-	- 169/241 cases and 852/1205 matched controls were im-	Moderate	Medium

	ern Spain) at the time when a mumps outbreak occurred (between August 2006 and June 2008)	salivary glands for at least 2 days with either laboratory (PCR or IgM positive) or epidemiological confirmation (i.e. epidemiological relation with other laboratory-confirmed or clinical mumps cases) Obtained from cases notified to the regional health authority n = 241	paediatrician	tom disease onset. Blinded review of primary care vaccination registry	munised with 1 MMR dose - 59/241 cases and matched 330/1205 controls were immunised with 2 MMR doses VE for any doses = 72% (95% CI from 39% to 87% , P = 0.0013) VE for 1 dose = 66% (95% CI 25% to 85%, P = 0.0075) VE for 2 doses = 83% (95% CI 54% to 94%, P = 0.0005)		
Mackenzie 2006	About 600 pupils attending a boarding schools in Scotland during a mumps outbreak that peaked between October and November 2004	Virological confirmation of clinical diagnosis n = 20 (age 13 to 17 years) Cases notified to consultant in public health medicine. Acute cases with virological positive test	n = 40 matched for age, sex, residential status, UK or international students	Not specified Pre-outbreak vaccination status obtained by medical notes held in the school, communication with parents and from Scottish Immunisation Recall System	- 9/20 cases and 20/40 controls received 1 MMR dose - 2/20 cases and 6/40 controls received 2 MMR doses - VE (at least 1 versus unvaccinated) = 34% (from -100 to 88) - VE (For 2 doses versus unvaccinated) = 48% (from -216 to 91) VE (1 versus 2 doses) = 26% (from -340 to 88)	High	Low

CCDC: Consultant in Communicable Disease Control

IgM: immunoglobulin M
MMR: measles, mumps, rubella vaccine
n: number of cases or control participants
PCR: polymerase chain reaction
VE: vaccine effectiveness

Table 4. Salient characteristics of studies evaluating short-term side effects

Study	Study design	Population enrolled	Risk of bias	Likely bias	Generalisability
Bloom 1975	RCT	282	High	Reporting	Low
Ceyhan 2001	CCT	1000	Moderate	Detection	Medium
Edees 1991	RCT	420	Moderate	Detection	Medium
Lerman 1981	RCT	502	Low	Detection	Medium
Peltola 1986	RCT	686	Low	Detection	High
Schwarz 1975	RCT	1481	High	Reporting	Low
Beck 1989	Cohort	196 *	High	Selection	Low
Benjamin 1992	Cohort	5017	Moderate	Detection	Medium
Dunlop 1989	Cohort	335	High	Selection	Low
Makino 1990	Cohort	1638	High	Selection	Low
Miller 1989	Cohort	12185	High	Reporting	Low
Robertson 1988	Cohort	319	Moderate	Selection	Medium
Sharma 2010	Cohort	453,119	High	Reporting	Low
Stokes 1971	Cohort	966	High	Selection	Low
Swartz 1974	Cohort	59	High	Selection	Low
Weibel 1980	Cohort	135	High	Selection	Low
Freeman 1993	Time-series	375	High	Attrition	Low
		* The number enrolled is unclear			

Table 5. Reporting of temperature in RCTs (MMR versus single components/placebo/do nothing)

Temperature increment (°C)	Measurement site	Reporting frequency	Observation period	Reference
38.0 to 38.4	Axilla	All episodes	21	Schwarz 1975
38.0 to 38.4	Rectal	All episodes	21	Schwarz 1975
38.5 to 38.9	Axilla	All episodes	21	Schwarz 1975
38.5 to 38.9	Rectal	All episodes	21	Schwarz 1975
38.6 to 39.5	Not reported	Mean number of episodes	21	Peltola 1986
39.0 to 39.4	Axilla	All episodes	21	Schwarz 1975
39.0 to 39.4	Rectal	All episodes	21	Schwarz 1975
39.5 to 39.9	Axilla	All episodes	21	Schwarz 1975
39.5 to 39.9	Rectal	All episodes	21	Schwarz 1975
40.0 to 40.4	Rectal	All episodes	21	Schwarz 1975
Up to 38.5	Not reported	Mean number of episodes	21	Peltola 1986
> 1 C above normal	Not reported	First episode	21	Bloom 1975
> 38	Not reported	All episodes	42	Lerman 1981
Not reported	Not reported	First episode	21	Edees 1991
Up to 39.5	Not reported	Mean number of episodes	21	Peltola 1986

Table 6. MMR and encephalitis/encephalopathy

Study and design	Outcome	Population	Outcome definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Ray 2006 *Case-control*	Encephalopathy, Reyes syndrome or encephalitis	Cases (n = 452): children aged 0 to 6 years with outcome of interest Controls (n = 1280)	1. Encephalopathy: acute generalised disturbance of brain function requiring	Hospitalisation cases for encephalopathy, Reyes syndrome or en-	Not reported. Vaccination status of both cases and controls was ascer-	7 to 14, 0 to 14, 0 to 30, 0 to 60 and 0 to 90 days	Not significant - OR 7 to 14 days 0.40 (95% CI from 0. 05 to 3.46) - OR 0	Moderate	Medium

Table 6. MMR and encephalitis/encephalopathy *(Continued)*

		: matching for health maintenance Organisation location, age within 7 days, sex and length of enrolment in health plan	hospitalisation and consisting of coma or stupor that cannot be attributed to medication or postictal state. Such cases must have altered consciousness, delirium, obtundation and/or confusion 2. Reyes syndrome: clinical symptoms of acute encephalopathy with altered level of consciousness as well as: a. Absence of inflammatory changes in cerebrospinal fluid as indicated by 5 white blood cells/mm ^{3} or brain histology showing cerebral	cephalitis (primary or secondary diagnosis) in children aged 0 to 6 years, members of the health plan of 4 Health Maintenance Organisations in the USA and occurred between 1 January 1981 and 31 December 1995, were considered as possible cases. Hospital charts were reviewed by abstracter (not blind to vaccination status of the cases) who included in first instance encephalitis diagnoses by a neurologist with clear	tained from medical records		to 14 days 0.35 (95% CI from 0.04 to 2.95) - OR 0 to 30 days 0.85 (95% CI from 0.27 to 2.68) - OR 0 to 60 days 0.64 (95% CI from 0.27 to 1.50) - OR 0 to 90 days 0.98 (95% CI from 0.47 to 2.01)		

Table 6. MMR and encephalitis/encephalopathy (*Continued*)

			oedema without perivascular or meningeal inflammation, plus b. Evidence of hepatitis or liver failure documented by a 3-fold or greater elevation in serum glutamic oxaloacetic transaminase, serum glutamate pyruvate transaminase or serum ammonia or fatty changes of hepatocytes on liver biopsy or autopsy, plus c. Absence of other aetiologies for cerebral or hepatic abnormalities 3. Encephalitis/en-	aetiology and excluded all cases with a condition other than encephalopathy. All other neurologic cases were reviewed by a neurologist (blind to vaccination status of the cases) an included as cases if they met case definition (see column on the right)					

Table 6. MMR and encephalitis/encephalopathy (*Continued*)

			cephalomyelitis: evidence of acute neurologic disease presenting with non-specific signs such as fever, seizures, altered consciousness, headache, vomiting, meningismus or anorexia. We required multifocal involvement of the central nervous system and evidence of cerebrospinal fluid inflammation (7 white blood cells/mm^3) Disease with other known etiologies were excluded. For data analysis all cases were strati-						

Table 6. MMR and encephalitis/encephalopathy *(Continued)*

			fied on the basis of their aetiology: known, unknown, suspected but unconfirmed (this last when a diagnosis was not confirmed by a diagnostic test)						
Makela 2002 *Self controlled case series*	Encephalitis/encephalopathy	Children immunised between 1 and 7 years of age between November 1982 and June 1986 (535,544) with outcome of interest (n = 199)	Encephalitis: acute or subacute onset of neurologic symptoms. Presence of neurologic symptoms or findings (clinical or laboratory, for example microbiological, electroencephalographic, computed tomographic) indicative of involvement of the brain parenchyma, such as coma, seizures, focal	The National Hospital Discharge Register was consulted by using the following ICD-8 codes: 065.99, 066.01, 066.02, 072.01, 292.20, 292.38, 292.39, 323.00, 323.01, 323.08, 323.09, 781.70, 999, 999.10 Medical records of hospitalised subjects were reviewed	MMR II Enders-Edmonston (measles) Jeryl Lynn (mumps) Wistar RA 27/3 (rubella) Vaccination data were assessed through vaccination register	3 months after immunisation	Not significant excess of hospitalisation within 3 months of vaccination (P = 0.28)	Moderate	Medium

Table 6. MMR and encephalitis/encephalopathy *(Continued)*

			neurologic findings, or mental function impairment. Absence of evidence of other diagnoses, including non-inflammatory conditions and no microbiological or other laboratory findings suggestive of a nonviral infection. When pleocytosis in CSF is present, the term encephalitis is used, implying an inflammatory response within the brain. The presence of normal CSF findings does not preclude the diagnosis if the other criteria are	(in order to evaluate possible other causes of the event) and their correspondence to diagnostic criteria (see column on the right) examined					

Table 6. MMR and encephalitis/encephalopathy *(Continued)*

			satisfied Encephalopathy: clinically resembles encephalitis but no inflammatory response is evident. Chronic encephalopathy: persistence of acute findings usually over several months						
Ward 2007 *Self controlled case series*	Encephalitis	Children aged 12 to 35 months, (immunised with MMR; NK) with outcome of interest diagnosed between October 98 and September 2001 (n = 106)	Encephalitis: (i) Encephalopathy for at least 24 hours and at least 2 of the following: fever, convulsions, focal neurologic findings ($\geq$ 24 hrs), pleocytosis (> 5 leukocytes per μL CSF) , characteristic abnormal results	Cases of suspected encephalitis and/ or severe illness with fever and convulsion occurring in children aged between 2 and 35 months through Britain and Ireland, were identified by consultant paediatricians taking part in a survey	Not reported. Immunisation history of cases was obtained by the Immunisation Department of the Health Protection Agency (other than MMR vaccine the study considers also DTP, Hib and MenC vaccines)	15 to 35 days after immunisation	The incidence of encephalitis was not statistically different between "at risk" and control period: relative incidence 1.34 (95% CI from 0. 52 to 3.47)	Low	High

Table 6. MMR and encephalitis/encephalopathy *(Continued)*

			of neuroimaging (computerised tomography or MRI), herpes simplex virus nucleic acid (or nucleic acid of any other virus proven to cause encephalitis) in CSF; or (ii) postmortem histologic evidence of encephalitis Exclude: (i) viral (aseptic) meningitis without encephalopathy (ii) the following confirmed causes were excluded: hypoxic/ ischaemic; vascular; toxic; metabolic, neoplastic, traumatic and pyogenic infections (iii)	(October 1998 to September 2001) and notified to the British Paediatric Surveillance Unit. Details about neurologic illnesses were collected by reporting paediatricians by means of a detailed questionnaires. For diagnostic purposes saliva, blood and cerebrospinal samples were also collected. Questionnaires were reviewed by study investigators in order to assess whether reported cases corresponded to an analytical case definition	. Only cases with known vaccination history were included in the analysis				

Table 6. MMR and encephalitis/encephalopathy (*Continued*)

			uncomplicated convulsions or a series of convulsions lasting < 30 minutes (iv) immunocompromised children	taking in account severe illness with fever and convulsion and encephalitis (see column on the right)					

CI: confidence interval
CSF: cerebro-spinal fluid
DTP: diphtheria, tetanus, pertussis vaccine
Hib: *Haemophilus influenzae* b vaccine
MenC: meningococcus C vaccine
MMR: measles, mumps, rubella vaccine
n: number of participants
OR: odds ratio

Table 7. MMR and aseptic meningitis

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Black 1997 *Case-control*	Aseptic meningitis	59 cases and 118 matched controls (age 12 to 23 months at the time of discharge diagnosis, between 1984 and 1993). For each ascertained case (n = 59), 2 controls matched for age,	No evidence of prior underlying meningitis or underlying disease caused by toxoplasmosis, syphilis, cytomegaloviru neonatal herpes simplex or human immunod-	Potential cases of aseptic meningitis were identified by computerised hospitalisation at 4 Health Maintenance Organisations (HMO) that participated in the Vaccine	Jeryl Lynn mumps strain Vaccination status of both cases and controls was derived from medical record review	0 to 14, 0 to 30, 8 to 14 days after immunisation	No statistically relevant difference in exposure to MMR for any of the considered at risk time intervals - OR (0 to 14 days) 0.50 (95% CI from 0. 1 to 4.5) - OR (0 to 30 days)	Low	High

		sex, HMO and HMO membership status were selected	eficiency virus. (The same exclusion criteria were also used for controls.) In addition bacterial, mycobacterial and fungal cultures of the cerebrospinal fluid must have been negative, and the patient must have had a cerebrospinal fluid white blood cell count of >= 10 cells/mm^3	Safety Datalink project. They were children aged 12 to 23 months with ICD-9 discharge diagnoses 045.2, 047.*, 048, 072.1, 321.2 or 322.* between 1984 and 1993. Medical records of potential cases were reviewed and included as cases when correspond to a validation criteria (see column on the right)			0.84 (95% CI from 0.2 to 3.5) - OR (8 to 14 days) 1.00 (95% CI from 0.1 to 9.2)		
Park 2004 *Case cross-over*	Aseptic meningitis	39 subjects with AS aged 13 to 29 months of both sexes identified from insurance claims and hospitalisation data during 1998 in Korea who had	Generically defined as syndrome characterised by acute onset of meningeal symptoms, fever and cerebrospinal fluid pleocytosis,	Cases of aseptic meningitis were identified from insurance claims and hospitalisation data during 1998 in Korea. Authors considered cases cor-	Not reported	42 days	Strong association with exposure to MMR within 42 days. OR 3.0; 95% CI from 1.5 to 6.1	Moderate	Medium

Table 7. MMR and aseptic meningitis *(Continued)*

		received MMR vaccine within 1 year before disease onset and for whom vaccination record were available	with bacteriologically sterile cultures	responding to diagnosis criteria occurred in children aged 8 to 36 months who had received MMR vaccine within 1 year before disease onset and for whom vaccination record were available					
Makela 2002 *Self controlled case series*	Aseptic meningitis	Children immunised between 1 and 7 years of age between November 82 and June 86 (535,544) with outcome of interest (n = 161)	Inflammation of the meninges. Usually a self limiting disease of known or suspected viral cause consisting of fever, headache, signs of meningeal irritation, without evidence of brain parenchymal involvement and a lymphocytic and mononu-	Hospitalisation records (ICD-8 codes: 045.99, 320.88, 320.99) and review of patients' medical record for assess correspondence to case definition	MMR II Enders-Edmonston (measles) Jeryl Lynn (mumps) Wistar RA 27/3 (rubella)	3 months after immunisation	Not significant excess of hospitalisation within 3 months of vaccination (P = 0.57)	Moderate	Medium

Table 7. MMR and aseptic meningitis *(Continued)*

			clear pleocytosis of CSF. The term meningoencephalitis does not differentiate cases with prominent involvement of the brain parenchyma from those with meningeal involvement only						
Dourado 2000 *Time-series*	Aseptic meningitis	About 452,334 children aged 1 to 11 years in Salvador city (Bahia, NE Brazil). 29 hospitalisations for AM has been recorded during the reference period before the campaign began (surveillance weeks 10 to 33), 58 thereafter weeks	1) Residence in the city of Salvador 2) Age 1 to 11 years 3) Cerebrospinal fluid with a cell count of > 10 and < 1200 cells per ml (higher counts could be attributed to unconfirmed bacterial meningitis) 4) Predominance	Data about meningitis were obtained from the state Epidemiology Surveillance System and from the neurologic service of the state referral hospital for infectious disease (Hospital Couto Maia), by reviewing hospital records of children	Pluserix vaccine (Smith-Kline Beecham, UK) containing mumps **Urabe** Strain. Vaccination began on 16 August 1997 (National Immunisation Day, surveillance week 33), 45% coverage of the target population was	1 to 10 weeks after immunisation (as time-series) 3 to 5 weeks (i.e.15 to 35 days) after immunisation (as case series)	Strong association The incidence of aseptic meningitis hospitalisation was significantly higher during the third (18 cases risk ratio (RR) 14.28; 95% CI 7.93 to 25.71), fourth (15 cases RR 11.90; 95% CI 6.38 to 22.19), fifth (9	Moderate	Medium

Table 7. MMR and aseptic meningitis *(Continued)*

		(surveillance weeks 34 to 43)	of lymphocytes in the cerebrospinal fluid of > 50 percent of the total number of cells 5) Exclusion of any bacteriologic or fungal confirmation through the use of Gram stain, latex, immunoelectrophoresis, stain for *Cryptococcus neoformans,* Ziehl-Neelsen stain, or culture for bacteria and *Mycobacterium tuberculosis;* and 6) Exclusion of all cases with a history of prior meningitis or any neurologic disorder and any cases	admitted between the 10th and the 43rd epidemiological surveillance weeks. Demographic, clinical, and laboratory data were collected on a standardised form	achieved on that day, high coverage (exact data not reported, but very close to 100%) during the 2 following weeks Vaccination history was obtained by vaccination cards or visits/ phone call		cases, RR 7.14; 95% CI 3.38 to 15.08) and sixth (4 cases, RR 3.17; 95% CI 1.12 to 9. 02) weeks following the start of the immunisation campaign when compared with that observed during the reference period		

Table 7. MMR and aseptic meningitis (*Continued*)

			with sepsis, pneumonia, otitis, or any other disease that might be associated with an increased cell count in the cerebrospinal fluid						
da Cunha 2002 *Time-series*	Aseptic meningitis	About 580,587 in MS (Mato Grosso do Sul) and 473,718 in MT (Mato Grosso) children aged 1 to 11 years. Accordingly to the first case definition 22 cases of AM (with viral or unknown aetiology) were notified before the start of the immunisation campaign (weeks 1 to 31, 1998) and 48 during weeks 32 to 42 in	First definition: If the diagnosis in the form was of viral aetiology or unknown aetiology, cases were classified as AM. They were classified as not having AM if they had a suspected or confirmed diagnosis of meningitis by a known (non-viral) agent through any laboratory or clinical finding Second	Cases of aseptic meningitis notified from routine surveillance system were reviewed considering 2 different definitions, one based on the diagnosis reported in the notification form (first definition) and one based on the laboratory findings of the same form (when these are	Serum Institute of India, Ltd, Pune. containing Leningrad-Zagreb mumps strain. Three different lots were used in each state (MS and MT) Mass immunisation campaign started in mid August 1998 (32nd epidemiological week) in MS and late September in MS (week 38),	1 to 10 weeks after immunisation	Strong association AM incidence in MS became significantly higher than in the pre-immunisation time from 2 weeks after the start of the campaign (4 cases, RR 5.6; 95% CI 1. 3 to 14.1), peaked at 3 weeks (16 cases, RR 22.5; 95% CI 11.8 to 42.9) and 4 weeks after the start of the campaign (15	Moderate	High

Table 7. MMR and aseptic meningitis *(Continued)*

		MS. In MT they were 71 before the campaign started (weeks 1 to 37 of 1998) and 103 thereafter (weeks 38 to 48). Data analysis by using the second case definition reflected an analogous trend	definition: cases were considered AM if they had a CSF with the following findings: cell count greater than 10 and lesser than 1500 and presence of lymphocytes greater that 49%. (Applied for the cases in which laboratory data were present in the notification forms. In their absence, cases were excluded)	available on it). These definitions are independent but not exclusive	and lasted for about 1 month, even if the most part of the doses has been administered during the first 2 campaign weeks. Vaccination was reported for 69.4% and 93.5% of the target population in MT and in MS respectively		cases, RR 21.1; 95% CI 11.0 to 40.7) and returned to the average after week 39 In MT, incidence of AM cases became significantly higher during the third week (40) after the start of the campaign (5 cases, RR 2.6; 95% CI 1.1 to 6.5), peaked in week 42 (30 cases, RR 15.6; 95% CI 10.3 to 24.2) and week 43 (23 cases, RR 12.0; 95% CI 7.6 to 19.4) and returned to the average from week 46 onwards		

AM: aseptic meningitis
CI: confidence interval
HMO: Health Maintenance Organisation
ICD: international classification of diseases
MS: multiple sclerosis
MT: Mato Grosso do Sul

n: number of participants
RR: risk ratio

Table 8. MMR and febrile seizure

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Vestergaard 2004 *Person-time cohort*	Febrile seizure (first episode)	Children born in Denmark between 1 January 1991 and 31 December 1998 aged between 3 months and 5 years (n = 537,171)	Discharge diagnoses corresponding to the indicated ICD-8 and ICD-10 codes. Only cases without recorded history of non-febrile seizure, cerebral palsy, severe head traumas, intracranial tumours, meningitis, or encephalitis were included	ICD-8 code 780.21 or ICD-10 code R56.0 from National Register of Hospitalisations	Moraten measles, Jeryl Lynn mumps, and Wistar RA 27/3. Vaccination status of the children was ascertained by using data of the National Board of Health to which vaccination data were transmitted by general practitioners	1 to 260 weeks after immunisation	Association within 2 weeks following vaccination RR 1.10; 95% CI from 1.05 to 1.15	Low	High
	Recurrent febrile seizure					Not specified	Association when MMR was administered within 14 days before first episode RR 1.19; 95% CI from 1.10 to 1.41		
	Epilepsy subsequent to a first febrile seizure episode					Not specified	Not significant RR 0.70; 95% CI from 0.33 to 1.50		
Ward 2007 *Self controlled case series*	Severe illness with fever and convulsions	Children aged 12 to 35 months, (immunised with MMR; NK) with outcome of in-	Severe illness with fever and convulsions (i) with a total duration of 30 min; or (ii)	Paediatrician survey (questionnaires) and review of the collected data	Not reported	6 to 11 days after immunisation	Strong association. RI 5.68; 95% CI from 2.31 to 13.97	Low	High

Table 8. MMR and febrile seizure (*Continued*)

		terest diagnosed between October 98 and September 2001 (n = 107)	followed by encephalopathy for 2 to 23 hours; or (iii) followed by paralysis or other neurologic signs not previously present for 24 hours Exclude : (i) viral (aseptic) meningitis without encephalopathy (ii) the following confirmed causes were excluded: hypoxic/ ischaemic; vascular; toxic; metabolic, neoplastic, traumatic, and pyogenic infections (iii) uncomplicated convulsions or a series of convulsions lasting < 30						

Table 8. MMR and febrile seizure *(Continued)*

			minutes (iv) immunocompromised children						
Miller 2007 *Self controlled case series*	Febrile convulsion	Children aged 12 to 23 months with discharge diagnosis corresponding to the outcome of interest and hospitalised between January 1998 and June 2002 who received MMR (n = 894)	Hospital discharge diagnoses with ICD-10 codes R560 or R568. Case review not performed	Cases with discharge diagnoses corresponding to the given ICD-10 codes (febrile convulsion or fit, not otherwise specified). Episodes within a same individual were considered as separate when occurred at least 10 days apart	- MMRII (Sanofi Pasteur Lyon, France) containing Jeryl Lynn mumps - Priorix, mumps vaccine component RIT 4385 - Unknown vaccine type - Priorix, MMRII or unknown	6 to 11 days after immunisation 15 to 35 days after immunisation	Strong association within 6 to 11 days for all vaccine types RI 4.09; 95% CI from 3.1 to 5.33 Not statistically relevant within 15 to 35 days after immunisation RI 1.13; 95% CI from 0.87 to 1.48	Moderate	Medium
	Febrile convulsion	See above			Priorix, MMRII or unknown	6 to 11 days af-	Strong association within 6 to 11 days RI 4.27; 95% CI from 3.17 to 5.76 Not statistically relevant within 15 to 35 days after immu-		

Table 8. MMR and febrile seizure *(Continued)*

							nisation RI 1.33; 95% CI from 1. 00 to 1.77		

CI: confidence interval
ICD: international classification of diseases
n: number of participants
RR: risk ratio

Table 9. MMR and autism

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Madsen 2002 *Retrospective cohort*	Autistic disorders or other autistic spectrum disorders	Danish children born between January 1991 and December 1998 (n = 537,303)	Diagnosis of autism using ICD-10 codes F84.0 or similar DSM-IV code 299; for autistic spectrum disorders ICD-10 codes F84. 1 through F84.9 and DSM-IV codes 299. 1- through 299.80. (DSM= Diagnostic and Statistical manual of Mental Disorders)	From medical records in Danish Psychiatric Central Register	MMR: Moraten (measles), Jeryl Lynn (mumps), Wistar RA 27/3. Vaccination data reported in the National Board of Health	Not to assess	Not significant association either for autism (RR 0.92; 95% CI from 0.68 to 1.24) or for autistic-spectrum disorders (RR 0.83; 95% CI from 0. 65 to 1.07)	Moderate	High
Fombonne 2001 *Retrospective cohort*	Regressive autism	Stafford sample (96 with PDD chil-	Regression defined with Autism	Autism Diagnostic Interview (ADI) ad-	Stafford sample (no description vac-	Not to assess	No statistically relevant differences	High	Low

Table 9. MMR and autism (Continued)

		dren born between 1992 and 1995) and MFS sample (99 cases of autism born between 1954 and 1979 (mean age 17.8 years)	Diagnostic Interview-Revised (ADI-R). E.G ("Regression is assessed for language skills as follows: Were you ever concerned that your child might have lost language skills during the first years of his/ her life? Was there never a time when he/she stopped speaking for some months after having learned to talk" in Stafford sample. For MFS sample: "slightly different version of ADI...and regression was defined using three items of the	ministered to parents	cine, but there were immunization data) MFS sample (none vaccinated with MMR vaccine)		across the 2 samples for the rate of probable or definite regression, P = 0.70		

			original ADI version that assessed probable and definite level of regression and loss of skills, in the first 5 years of life and in 3 domains: language, social interactions, and play and imagination"						
Uchiyama 2007 *Retrospective cohort*	Regression in autism spectrum disorders	Children born between 1976 and 1999 with clinical diagnosis of ASD (n = 904)	ASD regression defined as "a documented deterioration in any aspect of development or reported loss of skills, however transient" Note: in process of time 2 different diagnostic processes has been adopted at YPCD: until February	Consulting of questionnaires about patient's developmental, behavioural and medical history filled out by parents, and archived in a database	Measles, mumps and rubella (MMR) vaccine containing AIK-C (measles) , Urabe AM9 (mumps) and To-336 (rubella) strains Participants were classified according to the chance of having received MMR vaccine (MMR	Not to assess	Within MMR generation group, the estimate of association between regression and MMR vaccine exposure was not significant (OR 0. 744; 95% CI from 0. 349 to 1. 517, P = 0.490), so as when both pre- and post-MMR vaccine generation	High	Low

Table 9. MMR and autism (*Continued*)

			2000 diagnosis process consisted in the assessment of ASD initially conducted by a child psychiatrist using The Diagnostic and Statistical Manual (DSM-IV, American Psychiatric Association, 1994), afterward a clinical psychologist conducted an intelligence test. After admission a psychiatrist followed the patients once or twice a month. All doctors had received a training using a common concept of diagnosis. From		was administered in Japan in the time April 1989 to April 1993 to children between 12 and 36 months of age): 1) Pre-MMR generation: born between January 1976 and December 1984, n = 113 2) MMR generation: born between January 1985 and December 1991, n = 292 3) Post-MMR generation with an age of 1 to 3 years old after 1993 when MMR programme was terminated, n = 499		groups were used as control (OR 0.626; 95% CI from 0.323 to 1.200)		

Table 9. MMR and autism *(Continued)*

			February 2000 onwards a child psychiatrist with clinical psychologist conducted the full assessment in one day. Diagnoses of ASD was made by 3 experienced child psychiatrists basing on clinical observations, intellectual and developmental tests, interviews with parents and patients		Data concerning MMR vaccination were moreover obtained from records of the Maternal and Child Health (MCH) handbook and were referred to the MMR generation group only				
[Smeeth 2004](#) *Case-control*	Pervasive developmental disorder (PDD)	Cases: 1294 children with a first diagnosis of a PDD (either by OXMIS or READ codes) during the study period registered with a GPRD practice. Controls:n = 4469	"Those with autistic disorders and similar presentations were classified as having "autism" and those with other description (such as Asperger's syndrome) were	From diagnosis contained in UK General Practice Research Database (GPRD electronic records). Codes were available from request	No single clinical code was immediately implemented for MMR, then MMR was identified by codes of measle, mumps and rubella administered at the same day	Data on exposure to MMR for cases: from their date of birth up to the index date for cases. For controls: from their date of birth up to index date to the near-	No significant for PDD and autism only and other PDD OR 0. 86; 95%CI from 0.68 to 1.09	Moderate	Medium

Table 9. MMR and autism *(Continued)*

			classified as having "other PDD"". Patients who had more than one PDD diagnostic code recorded at different times (for example, autism and then Asperger's syndrome) were classified as having the most specific diagnosis (in this example Asperger's syndrome) "			est month of age			
DeStefano 2004 *Case-control*	Autism	Cases: 624 children with autism aged 3-10 years in 1996. Controls: 1824	Defined as behavioural characteristics consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4 th edition (DSM-IV) criteria for autism spectrum	Records about children with autism were abstracted from source files at schools, hospitals, clinics and specialty providers. Furthermore clinical psychologists reviewed	MMR vaccination was abstracted from "standardized state immunization forms"	Not to assess	No significant difference in the age at first vaccination. - Up 18 months OR 0.94 ; 95%CI from 0.65 to 1.38 - Up to 24 months OR 1.01 ; 95% CI from 0.61 to 1.67	Moderate	Medium

Table 9. MMR and autism *(Continued)*

			disorders (ASDs)	records according to DMS-IV			- Up to 36 months OR 1.23 ; 95% CI from 0. 64 to 2.36		
Mrozek-Budzyn 2010 *Case-control*	Childhood or atypical autism	Cases: 96 children aged between 2 and 15 years with diagnoses of childhood or atypical autism (ICD-10 codes F84. 0 and F84. 1) identified from practitioner registers in the Lesser Poland region Controls: 192 children matched for birth year, gender and practice	Cases with ICD-10 diagnoses codes F84. 0 and F84. 1 determined by child psychiatrist	Data from general practitioner records from Lesser Poland region	MMR (not described) and/ or monovalent measles vaccine Informations about vaccination history were extracted from physician's records	At any time before autism diagnosis At any time before symptoms onset	No association. Lower risk of autism in children immunised with MMR before diagnosis (OR 0.17; 95% CI from 0. 06 to 0.52) Estimate not statistically relevant when exposure to MMR was considered before symptom onset (OR 0.42; 95% CI from 0. 15 to 1.16)	Moderate	Medium
Fombonne 2006 *Time-series*	Pervasive developmental disorders (PDD)	Children aged 5 to 11 years (birth cohorts 1987 to 1998 attending a school board in Montreal (n = 27,	Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)	Administratively identified by code 51 (autism), code 50 (autism spectrum disorder) of Ministry of Ed-	MMR (no description) Identified by vaccination records	Not to assess	No association. Significant increase in rates of PDDs from 1987 to 1998 (OR 1.10; 95% CI1.	High	Medium

Table 9. MMR and autism *(Continued)*

		749 out of whom 180 with PDD)		ucation of Quebec (MEQ). In this study a special list was available filled by a team that monitored children with PDD diagnosis			05 to 1.16; P < 0.001) despite decrease in MMR uptake through birth cohorts from 1988 to 1998 (X^2 for trend = 80.7; *df* = 1; P < 0. 001)		
Honda 2005 *Time-series*	Autism spectrum disorders (ADS)	Children born from 1988 to 1996	ASD cases defined as all cases of pervasive developmental disorders according to ICD-guidelines, but in Kohoku Ward was active an early detection clinical system called DISCOVERY that included items drawn up by the Public Health Bureau of Yokohama called YACHT (Young	Community-based early detection	MMR (no description)	6 years after MMR	No association Significant increased incidence for ASD (χ^2 = 19.25, df = 8, P = 0. 01) was assessed after vaccination programme was stopped	Moderate	Medium

Table 9. MMR and autism *(Continued)*

			autism and other developmental disorders Checkup tool)						
Makela 2002 *Self controlled case series*	Autism	Children 1 to 7 years old (535,544)	Autistic disorder: "Severe qualitative impairment in reciprocal social interaction, in verbal and non verbal communication and in imaginative activity and markedly restricted repertoire of activities and interests" (Steffenburg 1989)	Data about first hospital visits during the study period identified by ICD-8/ 9 codes respectively effective from 1969 to 1986 and from1987 through 1995 (299- Psychoses ex origine infantia; 2990 - Autismus infantilis; 2998- Developmental disorder; 2999- Developmental disorder)	MMRII (Merck & Co, West Point, PA) containing Enders-Edmonston strain, Jeryl Lynn, Wistar RA 27/3 strain	For autism the risk period is open ended	Unclear without data reported in article	Moderate	Medium
Taylor 1999 *Self controlled case series*	Autistic disorder	Children born since 1979 from 8 health districts (North Thames,	"By use of criteria of the International Classification of Diseases,	ICD10-confirmed and non-confirmed cases from computerised	MMR vaccination identified by Regional Interactive Child	Periods within 1 or 2 years, so as 2, 4, 6 months after vaccination	No temporal association between onset of autism within	Moderate	Medium

Table 9. MMR and autism *(Continued)*

		UK)	tenth revision (ICD10), the diagnosis of autism was checked against information in the available records on the child's present condition and his or her condition between the ages of 18 months and 3 years."	special needs/disability registers at child development centres and from records in special schools. Information on children with such disorders who were younger than 16 years of age was extracted from clinical records by 1 of 3 experienced paediatric registrars	Health Computing System (RICHS)	were considered	12 months (RI 0.94; 95% CI from 0.60 to 1.47) or 24 months from MMR vaccination (RI 1.09; 95% CI from 0.79 to 1.52)		

ADS: autism spectrum disorders
CI: confidence interval
ICD: international classification of diseases
MMR: measles, mumps, rubella vaccine
n: number of participants
OR: odds ratio
PDD: pervasive developmental disorders
RI: relative incidence

Table 10. MMR and thrombocytopaenic purpura

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Black 2003 *Case-control study*	Idiopathic thrombocytopaenic purpura	Cases: 23 children with outcome	From cases with first time diagnosis of	General Practice Research Database	Not reported Data about MMR vac-	0 to 6 weeks following MMR im-	Association within 6 weeks from	Moderate	Medium

Table 10. MMR and thrombocytopaenic purpura *(Continued)*

		of interest at 12 to 23 months, between 1988 and 1999, GPRD members Controls: 116 subjects matching for index date (age), sex, practice	thrombocytopaenia (ICD-9 code 287.1) were excluded those with bone marrow failure, congenital thrombocytopaenia, severe malabsorption, severe sepsis and neonatal thrombocytopaenia	(GPRD) electronic records with first time diagnosis of thrombocytopaenia (ICD-9 code 287.1)	cination were presumably obtained from GPRD records (type and composition not reported)	munisation 7 to 26 weeks following MMR immunisation	immunisation. RR 6.3; 95% CI from 1.3 to 30.1 No significant association within 7 to 26 weeks following MMR immunisation RR 1.5 ; 95% CI from 0.4 to 4.8		
Bertuola 2010 *Case-control study*	Acute immune thrombocytopaenia	Cases: 387 children aged 1 month to 18 years, hospitalised at emergency department with outcome of interest between November 1999 and September 2007, with outcome of interest Controls: 1924 children of same age interval hos-	Platelets count < 100, 000/μl at admission. Subjects with following conditions were excluded: cancer, immunodeficiency, chronic renal and hepatic failure, so as acute events related to a reactivation of an underlying chronic disease or a	Hospitalisation (emergency department) records review	Not reported. Exposure to the vaccine (and other drugs) was assessed during hospital admission by means of parents interview	0 to 6 weeks following MMR immunisation	Association within 6 weeks following immunisation OR 2.4; 95% CI from 1.2 to 4.7	High	Low

Table 10. MMR and thrombocytopaenic purpura *(Continued)*

		pitalised at emergency department for acute neurological disorders or endoscopically confirmed gastroduodenal lesions	congenital anomaly						
France 2008 *Self controlled case series*	Immune thrombocytopaenic purpura	63 children aged 12 to 23 months with outcome of interest	Subjects with 2 platelet counts ≤ 50,000/ μL within 6 weeks period or with 1 platelets count ≤ 50, 000/μL associated with ICD-9 diagnosis codes 287.0-287.9 within 6 weeks, with exclusion of: cases of thrombocytopaenia from a known condition (neonatal thrombocytopenia, aplastic anaemia, defibri-	Vaccine Safety Datalink database (1991 to 2000) and patient charts review	Not reported. MMR vaccination date assessed by means of separate audit of patient charts	0 to 42 days following MMR immunisation	Strong association IRR 5.38; 95% CI from 2.72 to 10.62	Low	High

Table 10. MMR and thrombocytopaenic purpura *(Continued)*

			nation syndrome, acquired haemolytic anaemia, chronic liver disease, malignant neoplasm), thrombocytopaenia diagnosed within the 30th day of life. By subsequent patient charts reviews subjects who did not have not have ITP, who had drug exposure, with acute illness, or with serendipitous finding during routine care were further excluded						
France 2008 *Risk interval*	Immune thrombocytopaenic purpura	See above	See above	See above	See above	0 to 42 days following MMR immunisation	Strong association IRR 3.94; 95% CI from 2.01 to 25.03	Low	High
Jonville-Bera 1996 *Ecological*	Thrombocytopaenic purpura	Case observed after vaccine ad-	Acute haemor-	Pharmacovigilance	Intervention:	2 to 45 days	Strict temporal oc-	Moderate	Medium

Table 10. MMR and thrombocytopaenic purpura (Continued)

study	(TP)	minis-tration between 1984 and June 30th, 1992 (n = 60). Estimate number of administered vaccine doses was 9,205, 483	rhagic syndrome associated with platelet count of < 100,000/ mm³, all cases within 45 days of vaccination, over 8-year period	reports	ROR, Trimovax (MMR), comparators: Rouvax (measles), DTbis Rudivax (rubella, diptheria, tetanus) Imovax Oreillons (mumps), Rudi-Rouvax (measles/ rubella), Rudivax (rubella)	following immunisation	currence of TP after MMR makes association possible, even if not proven Incidence of TP was estimated between 0. 5 and 3 cases/100, 000 MMR doses		

CI: confidence interval
GPRD: general practice research database
ICD: international classification of diseases
IRR: incident rate ratio
ITP: immune thrombocytopaenic purpura
MMR: measles, mumps, rubella vaccine
TP: thrombocytopaenic purpura
yr: years

Table 11. MMR and asthma

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
DeStefano 2002 *Cohort Study*	Asthma	Children (0 to 6 years) enrolled in VSD project (4 HMO) between 1991 and 1997 (n = 167,240)	To be classified as having asthma a child had to meet one of the following criteria: - At least 1 diagnosis of asthma	Reviewing of computerised data bases maintained at each HMO. In these databases hospital	Not reported	Not specified. Any time after MMR immunisation	No significant association. RR 0.97; 95% CI from 0. 91 to 1.04	Moderate	Medium

Table 11. MMR and asthma *(Continued)*

			(ICD9 = 493) and at least 1 prescription for an asthma medication; the first diagnosis and the first prescription had to be within a 2-year period. Asthma medications included oral or inhaled beta-antagonist, theophylline, oral or inhaled corticosteroids, cromolyn sodium, adrenergic drugs not elsewhere specified and unclassified asthma medications; - At least 1 prescription for an in- haled beta-antagonist	discharge, emergency room visits, and medication prescriptions were registered					

Table 11. MMR and asthma *(Continued)*

			and at least 1 prescription for cromolyn within a 2 year period; - At least 5 prescriptions or asthma medications during a 2-year period. In addition to these criteria it was also required that the child had at least one asthma diagnosis or prescription at 1 year of age or older. Authors defined the asthma incidence date as the earliest of the first asthma diagnosis date or the first date of an asthma medication prescription. A child						

Table 11. MMR and asthma *(Continued)*

			could have had an asthma onset date when younger than 1 years of age, but to be classified as a case the child had to have an indication that asthma was still present when he or she was older than 1 year of age						
McKeever 2004 *Cohort Study*	Asthma	Children (n = 16,470) aged from 20 months to 11 years, accounting for 69, 602 person-years	Not provided	West Midlands General Practice Research Database	Not reported	Not specified. Any time after MMR immunisation	Significant association only for the group with lower GP consultation during the first 6 live months (hazard ratio 7.18; 95% CI from 2. 95 to 17. 49)	High	Medium
McKeever 2004 *Cohort Study*	Eczema	Children (n = 14,353) aged from 20 months to 11 years,	Not provided	West Midlands General Practice Research Database	Not reported	Not specified. Any time after MMR immunisation	Significant association only for the group with lower GP consul-	High	Medium

Table 11. MMR and asthma (*Continued*)

		accounting for 59, 520 person-years					tation during the first 6 live months (hazard ratio 10.4; 95% CI from 4. 61 to 23. 29)		
Hviid 2008 *Person-time cohort*	Asthma hospitalisation	Danish birth cohorts 1991 to 2003 followed up between 1 January 1991 and 31 December 2003, or between 1 and 5 years of age (n = 871,234; 2,926,406 person-years)	Inpatient hospitalisation with asthma diagnosis (occurred between 1 January 1992 and 31 December 2004) - Asthma diagnosis: 493. xx (ICD-8) and J45. x, J46.x (ICD-10) - Severe asthma (status asthmaticus) 493. 01 (ICD-8) and J49. 9 for severe asthma	Data from the Danish National Hospital Register	MMR: Moraten (measles), Jeryl Lynn (mumps), Wistar RA 27/3 Dates of MMR vaccination were obtained from the National Board of Health, NBH	Not specified. Any time after MMR immunisation	Significant protective effect of MMR vaccination was observed against Asthma (RR 0.75; 95% CI from 0. 73 to 0.78) and severe asthma (RR 0.63 ; 95% CI from 0.49 to 0.82) was globally assessed	Moderate	High
Hviid 2008 *Person-time cohort*	Anti-asthma medication	Danish birth cohorts 1991 to 2003 followed up between 1 January 1996 and	Prescription of the following cases of anti-asthma medications have been con-	Data from the Danish Prescription Drug Database	MMR: Moraten (measles), Jeryl Lynn (mumps), Wistar RA 27/3 Dates of MMR vac-	Not specified. Any time after MMR immunisation	Use of anti-asthma medications (all types) was significantly less frequent	Moderate	High

Table 11. MMR and asthma *(Continued)*

		31 December 2003, or between 1 and 5 years of age (n = 600,938; 1,858,199 person-years)	sidered: - glucocorticoid inhalants (ATC code R03BA) - short-acting b2-agonist inhalants (ATC codes R03AC02, R03AC03, and R03AC04) - long-acting b2-agonist inhalants (ACT codes R03AC12 and R03AC13) - systemic b2-agonists (ACT code R03CC) - other types of anti-asthma medication (all other ATC codes under R03)		cination were obtained from the National Board of Health, NBH		among subjects immunised with MMR (RR 0.92; 95% CI from 0.91 to 0.92) Considering single classes of medication, reduction in use of b2-agonists was not observed (RR 1.02; 95% CI from 1.01 to 1.02)		

CI: confidence interval
HMO: Health Maintenance Organisation
ICD: international classification of diseases
n: number of participants
RR: risk ratio
VSD: Vaccine Safety Datalink

Table 12. MMR and leukaemia

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Ma 2005 *Case-control*	Leukaemia	Leukaemia cases (n = 323) aged 0 to 14 years identified within the Northern California Childhood Leukaemia Study (NCCLS) between 1995 and 2002 Controls (n = 409) : matched to cases for date of birth, gender, Hispanic status (either parent Hispanic) , maternal race (white, African American, or other) and maternal county of residence, by means of birth certificates To be eligible,	Not provided	Within the NCCLS study, incident leukaemia cases were ascertained from major paediatric clinical centres within 72 hours after diagnosis. This study was carried out in order to assess if there is a link between exposure to vaccines and leukaemia in children aged below 14 years. Population coverage includes initially 17 countries in the Greater San Francisco Bay Area and since 1999 was expanded to	Not reported A copy of child's complete vaccination record was requested to primary care takers of case or control subjects (usually the biological mother) were interviewed after informed consent was obtained and asked to provide a copy of child's complete vaccination record or to the primary care physician. Other than MMR, vaccinations against diphtheria,	Any time after MMR immunisation	No significant association OR 1.06; 95% CI from 0. 69 to 1.63	Medium	Medium

Table 12. MMR and leukaemia *(Continued)*

		each case or control had to reside in the study area, be less than 15 years of age at the reference date (time of diagnosis for cases and the corresponding date for matched controls), have at least one parent or guardian who speaks English or Spanish, and have no previous history of any malignancy		further 18 countries in Northern and Southern California. The present studies relies on cases of leukaemia ascertained between 1995 and 2002	pertussis and tetanus (DPT), DT, Td, poliomyelitis, MMR, hepatitis B or Hib has been considered in the study				
Ma 2005 *Case-control*	Acute Lymphoblastic Leukaemia (ALL)	All cases (n = 282) aged 0 to 14 years identified within the Northern California Childhood Leukaemia Study (NCCLS) between 1995 and 2002 Controls	Not provided	Within the NCCLS study, incident leukaemia cases were ascertained from major paediatric clinical centres within 72 hours after diagnosis. This study	Not reported A copy of child's complete vaccination record was requested to primary care takers of case or control subjects (usually the bi-	Any time after MMR immunisation	No significant association OR 0.87; 95% CI from 0.55 to 1.37	Medium	Medium

Table 12. MMR and leukaemia *(Continued)*

		(n = 360) matched to cases for date of birth, gender, Hispanic status (either parent Hispanic) , maternal race (white, African American, or other) and maternal county of residence, by means of birth certificates To be eligible, each case or control had to reside in the study area, be less than 15 years of age at the reference date (time of diagnosis for cases and the corresponding date for matched controls) , have at least one parent or		was carried out in order to assess if there is a link between exposure to vaccines and leukaemia in children aged below 14 years. Population coverage includes initially 17 countries in the Greater San Francisco Bay Area and since 1999 was expanded to further 18 countries in Northern and Southern California. The present studies relies on cases of leukaemia ascertained between 1995 and 2002	ological mother) were interviewed after informed consent was obtained and asked to provide a copy of child's complete vaccination record or to the primary care physician. Other than MMR, vaccinations against diphtheria, pertussis and tetanus (DPT) , DT, Td, poliomyelitis, MMR, hepatitis B or Hib has been considered in the study				

Table 12. MMR and leukaemia (*Continued*)

		guardian who speaks English or Spanish, and have no previous history of any malignancy							

CI: confidence interval
DTP: diphtheria, tetanus, pertussis vaccine
DT: diphtheria, tetanus vaccine
Hib: *Haemophilus influenzae* b vaccine
MMR: measles, mumps, rubella vaccine
n: number of participants
NCCLS: northern California childhood leukaemia study
OR: odds ratio
Td: tetanus, diphtheria vaccine

Table 13. MMR and hay fever

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Bremner 2005 *Case-control*	Hay fever risk	The cases and controls were children with at least 5 years of follow-up from birth and registered "within the practice within 3 months of birth"	"Only codes synonymous with "allergic rhinitis" and with seasonal variation in recording were permitted	From GPRD and DIN database	MMR II	MMR (first entries) The time categories for MMR immunisation were: 1st to 13th month, 14th, 15th, 16th, 17th, 18th-24th, 25th month or later	Not significant (comparing vaccinated at 14th month versus unvaccinated children), but with result significant (OR 0.62; 95% CI from 0.48 to 0.80) of reduced hay risk fever after com-	Moderate	Medium

Table 13. MMR and hay fever (*Continued)*

							pletion of MMR after 2 years		
[Bremner 2007](#) *Case-control*	Hay fever risk in the first grass pollen season	Case of hay fever were children with diagnostic codes and/ or treatment for hay fever, after 2 years of age Control was child that matched for general practice, sex, birth month and follow-up of control to at least date of diagnosis case	"Cases of hayfever were those who had diagnostic codes and/ or treatment for hayfever, after 2 years of age"	From GPRD and DIN database	MMR II	MMR exposure by 24 months in a grass pollen season (May, June, July) versus outside 1	Not significant OR 1.05; 95% CI from 0.94 to 1.18	Moderate	Medium

CI: confidence interval
DIN: doctors' independent network
GPRD: general practice research database
MMR: measles, mumps, rubella vaccine
OR: odds ratio

Table 14. MMR and type 1 diabetes

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
[Hviid 2004](#) *Person time*	Type 1 diabetes coded as 249 and E10	A cohort of children born from 1 January 1990 to 31 De-	From 1990 to 1993 the codes used (E10) were obtained	The diagnosis of type 1 diabetes, within 1 January	Measles, mumps, and rubella (1990 to 2001) ; sched-	Not specified. Any time after MMR immunisation	No significant association. RR 1.14; 95% CI from 0.	Low	High

Table 14. MMR and type 1 diabetes *(Continued)*

		cember 2000 from the Danish Civil Registration System (739,694)	from a modified version of the International Classification of Diseases, 8th version (ICD-8) From 1994 to 2001 the codes used (249 and E10) were obtained by the International Classification of Disease, 10th version	1990 to 31 December 2001, was obtained from the Danish National Hospital Register that in 1995 began to register outpatients visits and visits to the emergency room Type 1 diabetes among siblings of cases (aged 0 to 14 years between 1 January 1997 to 31 December 2001) were obtained from the Danish National Hospital Register. Before 1 January 1987 ICD-8 code 250 was used for type 1 diabetes diagnosis,	ule (15 months and 12 years of age); composition (Live , attenuated measles (Moraten) , mumps (Jeryl Lynn), and rubella (Wistar RA 27/3)) virus The authors did not obtain information about the second dose of MMR vaccine because the administration of this dose was recommended at 12 years of years (out of inclusion range)		90 to 1.45		

Table 14. MMR and type 1 diabetes *(Continued)*

				whereas codes 249 or E10 were used thereafter					

CI: confidence interval
ICD: international classification of diseases
MMR: measles, mumps, rubella vaccine
RR: risk ratio

Table 15. MMR and gait disturbances

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Miller 2005 *Self controlled case series*	Hospitalisation for gait disturbance	127 children aged 12 to 24 months with admission between April 1995 and June 2001	(1) presumptive viral/post-viral ataxia (clinical history of ataxia and evidence of encephalomyeltis or cerebellitis with lymphocytosis in the cerebrospinal fluid (CSF) or encephalographic changes); (2) probable post-viral ataxia (history consistent with ataxia but CSF/ other investigations in-	Review of hospital computerised records (April 1995 to June 2001, children aged 12 to 24 months) with ICD-10 diagnoses related to acute gait disorder (G111, G112, G25, R26, R27, R29, H55, and F984)	Not reported	0 to 30 and 0 to 60 days	No significant association. Relative incidence not statistically relevant neither for the to 30 days risk time (RI 0.83; 95% CI 0.24 to 2.84) nor for the 31 to 60 days risk time (RI 0.20; 95% CI 0.03 to 1.47)	Medium	Low

Table 15. MMR and gait disturbances (*Continued*)

			conclusive or not done and no other cause identified); (3) probably not post-viral gait disturbance (vague symptoms not suggestive of cerebellar ataxia, e.g. unsteady gait associated with constipation or gastroenteritis); (4) non-ataxic, non-viral gait disturbance (including limp after trauma, septic bone or joint disease, unsteadiness following drug ingestion); (5) transient synovitis/"irritable hip" (a transient con-						

Table 15. MMR and gait disturbances *(Continued)*

			dition described following viral illnesses and with no long term sequelae)						
Miller 2005 *Self controlled case series*	GP visits for gait disturbance	1398 children aged 12 to 24 months born between 1988 and 1997	(A) ataxia (including cerebellar ataxia and ataxic gait) (B) unsteady/ veering/ shuffling gait (C) gait abnormality - unspecified (D) limp/ limping gait (E) poor mobility (F) abnormal /involuntary movements	Analysis of General Practice Research Database (GPRD) records (children aged 12 to 24 months, born between 1988 and 1997)	Not reported	0 to 5, 6 to 30, 31 to 60, 6 to 60 days	No significant association. Relative incidence of all cases (A to F): - within 6 to 30 days: 0.90; 95% CI from 0.70 to 1.17 - within 31 to 60 days: 0.95; 95% CI from 0.77 to 1.19 - within 6 to 60 days: 0.93; 95% CI from 0.78 to 1.12	Medium	Medium

CI: confidence interval
CSF: cerebro-spinal fluid
GP: general practitioner
RI: relative incidence

Table 16. MMR and inflammatory bowel disease

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Davis 2001 *Case-control*	Inflammatory bowel diseases (IBD) hos-	142 IBD cases (75 with Crohn's	After abstraction of medical records,	Review of medical records contained	Not reported	Not specified. MMR administered	No statistically relevant association be-	Low	High

Table 16. MMR and inflammatory bowel disease (*Continued*)

	pitalisation	disease and 67 with ulcerative colitis) 432 controls matched for sex, Health Maintenance Organisation and birth year	IBD cases were classified as: Definite IBD: as persons diagnosed with IBD by a gastroenterologist at one of the HMOs who had at least 1 sign or symptom compatible with IBD (such as bloody stool and/or bloody diarrhoea or severe and/or recurrent abdominal pain) recorded and a diagnostic test result (such as biopsy with pathology specimen, colonoscopy or sigmoidoscopy) consistent with IBD Probable IBD: the diagnosis of IBD	in the Vaccine Safety Datalink database of 4 Health Maintenance Organisations (HMOs) and identified by using ICD-9 codes specific for Crohn's disease, ulcerative colitis and idiopathic proctocolitis (555 and 556). Outpatient, emergency department, urgent care clinic visits were available for 3 out of the 4 HMOs and were also taken in account		at any time before index date	tween MMR vaccine exposure and increased risk of: - all IBD (OR 0.59; 95% CI 0.21 to 1.69); - CD (OR 0.4; 95% CI 0.08 to 2.0) - ulcerative colitis (OR 0.80; 95% CI 0.18 to 3.56)		

Table 16. MMR and inflammatory bowel disease (*Continued*)

			was made by either an HMO non-gastroenterologist physician or a gastroenterologist outside the HMO, there was at least 1 sign or symptom compatible with IBD, and there was a diagnostic test result consistent with IBD IBD cases (suspected or questionable) , that did not correspond to these criteria were excluded from analysis. IBD (definite and probable) were further classified as Crohn's disease and ulcerative colitis cases						
Seagroatt 2005 *Ecological*	Crohn's disease (CD)	CD emergency admission		Emergency ad-	Not reported	Not specified	No significant asso-	High	Medium

Table 16. MMR and inflammatory bowel disease *(Continued)*

	emergency admissions	cases (n = 4463) observed between April 1991 and March 2003 in England population aged below 19 years (about 11.6 million)		missions for CD between April 1991 and March 2003 among subjects aged 4 to 18 years in England			ciation RR 0.95; 95% CI from 0.84 to 1.08		

CD: Crohn's disease
CI: confidence interval
IBD: inflammatory bowel diseases
HMO: Health Maintenance Organisation
OR: odds ratio
RR: risk ratio

Table 17. MMR and demyelinating diseases

Study and design	**Outcome**	**Population**	**Definition**	**Findings**	**MMR-type**	**Risk time**	**Results**	**Risk of bias**	**Generalisability**
Ahlgren 2009a *Cohort study*	Multiple sclerosis (MS, probable or definite) and Clinically Isolated Syndromes (CIS)	Birth cohorts 1959 to 1990 from residents in the greater Gothenburg area (Sweden), corresponding to 5.9 million person-years. 534 MS and CIS cases with onset between 10 and	MS defined accordingly to the 4 Poser's criteria with addition of CIS cases	Analysis, review, and reclassification of medical records contained in the Gothenburg MS register	Not specified. Impact of mass vaccination with different vaccine type (monovalent measles, mumps or rubella, so as MMR) in different birth cohorts in different times on	Not specified	No vaccine related changes in MS incidence changes were detected	High	Medium

Table 17. MMR and demyelinating diseases (Continued)

		39 years before July 2004 has been ascertained			MS incidence was assessed				
[Ahlgren 2009b](#) *Case-control study*	Multiple sclerosis (MS, probable or definite) and Clinically Isolated Syndromes (CIS)	Cases (n = 206) : Birth years 1959 to 1986, to be resident in the greater Gothenburg area (Sweden), MS onset from age of 10 years onwards, did attend the 6th school grade within study area, availability of CHSH records Controls (n = 888) : matched to cases for year of birth by random selection from the population register. Controls should have attended the 6th school grade within study area,	See above	See above	Not specified. Exposure to MMR vaccine was classified in 4 categories, accordingly to age of subjects at MMR immunisation: - no MMR vaccination; - early MMR vaccination only (MMR immunisation within 10 years of age); - late MMR vaccination only (MMR immunisation after 10 years of age); - both an early and late MMR vac-	Not specified	No significant association for vaccinated versus unvaccinated OR 1.13; 95% CI from 0. 62 to 2.05	High	Medium

Table 17. MMR and demyelinating diseases (Continued)

		and have available CHSH record			cination				

CHSH: child health and school health records
CI: confidence interval
CIS: clinically isolated syndromes
MMR: measles, mumps, rubella vaccine
MS: multiple sclerosis
OR: odds ratio

Table 18. MMR and bacterial or viral infections

Study and design	Outcome	Population	Definition	Findings	MMR type	Risk time	Results	Risk of bias	Generalisability
Stowe 2009 *Self controlled case series*	Lobar pneumonia	Infants aged 12 to 23 months hospitalised for viral or bacterial infection between April 1995 and May 2005 identified from hospital admission records (n = 2025 accounting for 2077 admissions)	ICD-9 codes: 481 ICD-10 codes: J18.1	Review of computerised hospital admission records from North, East, and South London, Essex, East Anglia, Sussex and Kent using ICD-9 or ICD-10 codes	Not specified	0 to 30; 31 to 60; 61 to 90; 0 to 90 days after immunisation	Lower risk association within 0 to 30 (OR 0.65; 95% CI from 0.48 to 0.86) or 0 to 90 days after immunisation (OR 0.77; 95% CI from 0.64 to 0.93)	High	Low
Stowe 2009 *Self controlled case series*	Invasive bacterial infections	See above	ICD-9 codes: 036, 038, 320, 711.0, 730.0 ICD-10 codes: A39, A40, A41, G00,	See above	Not specified	0 to 30; 31 to 60; 61 to 90 ; 0 to 90 days after immunisation	No significant association within any of the considered times intervals af-	High	Low

Table 18. MMR and bacterial or viral infections (*Continued*)

			M00, M86, J13 X				ter immunisation		
Stowe 2009 *Self controlled case series*	Encephalitis/ meningitis	See above	ICD-9 codes: not specified ICD-10 codes: A85, A86, A87, A88, A89	See above	Not specified	0 to 30; 31 to 60; 61 to 90; 0 to 90 days after immunisation	No significant association within any of the considered times intervals after immunisation	High	Low
Stowe 2009 *Self controlled case series*	Herpes	See above	ICD-9 codes: not specified ICD-10 codes: B00	See above	Not specified	0 to 30; 31 to 60; 61 to 90; 0 to 90 days after immunisation	Increased risk between 31 and 60 days after immunisation (OR 1.69; 95% CI from 1. 06 to 2.70) . No significant association for the other time intervals	High	Low
Stowe 2009 *Self controlled case series*	Pneumonia	See above	ICD-9 codes: not specified ICD-10 codes: J12	See above	Not specified	0-30; 31-60; 61-90; 0-90 days after immunisation	No significant association within any of the considered times intervals after immunisation	High	Low
Stowe 2009 *Self-controlled case series*	Varicella zoster	See above	ICD-9 codes: not specified ICD-10 codes: B01, B02	See above	Not specified	0 to 30; 31 to 60; 61 to 90; 0 to 90 days after immunisation	Lower risk within 30 days after immunisation. No signif-	High	Low

Table 18. MMR and bacterial or viral infections *(Continued)*

							icant association for the other time intervals		
Stowe 2009 *Self controlled case series*	Miscellaneous viral infections	See above	ICD-9 codes: not specified ICD-10 codes: B08, B09, B15, B17, B25, B27, B34	See above	Not specified	0 to 30; 31 to 60; 61 to 90; 0 to 90 days after immunisation	No significant association within any of the considered times intervals after immunisation	High	Low

CI: confidence interval
ICD: international classification of diseases
n: number of participants
OR: odds ratio

FEEDBACK

Vaccines for MMR in children

Summary

Based on the title and the introduction, this is a review of the effectiveness and safety of MMR vaccine. However, the authors concluded that they "could find no comparative studies assessing the effectiveness of MMR that fitted [their] inclusion criteria as all had serological outcomes" and then continued to discuss only studies of MMR vaccine safety. The review and discussion of the safety of these vaccines accurately reflects the literature; rather this letter is about the conclusions regarding vaccine effectiveness.
The authors' conclusion that no comparative studies exist about the effectiveness of MMR vaccines do not seem to be borne out by other reviews of the literature. Using the stated inclusion criteria, one can find several studies of the effectiveness of MMR vaccine against individual diseases (measles, mumps or rubella) using cohort and case-control methods. Numerous retrospective studies have also documented the effectiveness of measles-containing vaccines (vs. MMR vaccine) for preventing measles. A partial list of articles found in PubMed using the criteria (measles OR mumps OR rubella) AND "vaccine efficacy", screened for articles including calculation of clinical vaccine efficacy, follows this feedback.
The authors also restricted their search to articles appearing in 1966 and later; given that measles vaccines were developed and used in clinical trials in the late 1950s and 1960s, the authors should strongly consider repeating their search for all years ? or, at a minimum, from 1954 to the present, given that measles virus was first isolated in 1954.
The authors fail to note that the effectiveness of measles, mumps and rubella vaccines were documented individually before their combination into MMR vaccine, and that the serological correlates of protection are well defined for protection against measles and rubella virus infections. These serological correlates of protection are now used to compare various vaccine virus strains and combinations.
I would strongly suggest that this review be revised so that it includes a discussion of articles that assess the efficacy of MMR vaccines or the individual vaccines included in MMR vaccines against their target diseases using any appropriate methodology. The authors could then compare the efficacy of the individual vaccines with that of the combined vaccine. If they choose not to include any of the articles

found that demonstrate clinical vaccine efficacy, it would be helpful if the authors could provide a clear justification for doing so. At the very least, the title and introduction should be changed so that it is clear that the review is of studies of the safety of the vaccines, not their efficacy.
Thank you for your consideration of these comments

Reply

Dear Dr. Perry,
Many thanks for the attention paid to our MMR vaccines review. We have read with interest you observation, we must though call your attention to the fact that for Cochrane Reviews inclusion criteria are established rigorously from an experienced team of specialists with the aim to made comparisons so homogeneous as possible and to consider preferably those outcomes that have direct implications for decision making in Public Health. For this reason the evaluation of evidences based only on serological parameters is debatable or at least not overall accepted at the rate of their indirect nature.
It shouldn't be forgotten that our review was also performed in order to provide some responses to an important specific question in Public Health regarding the suspected association of MMR vaccine with serious diseases. As reported in the conclusions, vaccine efficacy is in any case out of the question, since we consider as important point of evidence the fact that in many countries eradication of the targeted diseases could be achieved by means of mass immunisation programs.
We agree that studies in which single MMR antigens are tested could contribute some evidence, but in this review the only MMR in comparison with placebo or not intervention was considered. Effectiveness or efficacy of measles vaccine has been already reviewed by other authors (e.g. 1, 2, 3 ; all present in DARE).
Many studies out of those indicated by you in the list, report results of a single component vaccines and are for this reason not includible. In some of them MMR is tested, but all appear results of surveys and consequently their design is markedly affected from different types of biases which would preclude in any case their inclusion in the analysis. To complete background information about efficacy of MMR vaccines (or of different strain combinations), we may comment briefly on the evidence from these and other similar reports in occasion of the next update of the review.
All Authors

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Contributors

Robert Perry, MD, MPH
Feedback added 09/08/06

WHAT'S NEW

Last assessed as up-to-date: 12 May 2011.

Date	Event	Description
12 May 2011	New search has been performed	The searches have been updated and 33 new trials have been included in the review, including one previously excluded trial (Marolla 1998). Fifty new trials were excluded and 13 new trials are awaiting classification. The conclusions remain unchanged

(*Continued*)

1 February 2011	New citation required but conclusions have not changed	A new author joined the team to update this review.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 4, 2005

Date	Event	Description
6 May 2008	Amended	Converted to new review format.
8 August 2006	Feedback has been incorporated	Feedback comment and reply added to review.
18 December 2004	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

For this update Alessandro Rivetti (AR) performed the searches, and together with Maria Grazia Debalni (MGD) and Carlo Di Pietrantonj (CDP) applied inclusion criteria and extracted data. Vittorio Demicheli (VD) arbitrated on both study inclusion and extraction. All authors contributed to the final draft.

In the previous version, Vittorio Demicheli (VD), Tom Jefferson (TOJ) and Deirdre Price (DP) designed the protocol and carried out data extraction. VD arbitrated on study inclusion. Alessandro Rivetti (AR) carried out the effectiveness assessment and updated safety searches. All authors contributed to the final draft.

DECLARATIONS OF INTEREST

Dr Jefferson in 1999 acted as an ad hoc consultant for a legal team advising MMR manufacturers.

SOURCES OF SUPPORT

Internal sources

- Istituto Superiore di Sanita, Italy.

External sources

- European Union Programme for Improved Vaccine Safety Surveillance. EU Contract Number 1999/C64/14, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

Age Factors; Autistic Disorder [etiology]; Clinical Trials as Topic; Crohn Disease [etiology]; Epidemiologic Studies; Measles [*prevention & control]; Measles-Mumps-Rubella Vaccine [*administration & dosage; *adverse effects]; Mumps [*prevention & control]; Purpura, Thrombocytopenic [etiology]; Rubella [*prevention & control]; Seizures, Febrile [etiology]; Vaccines, Attenuated [administration & dosage; adverse effects]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant