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

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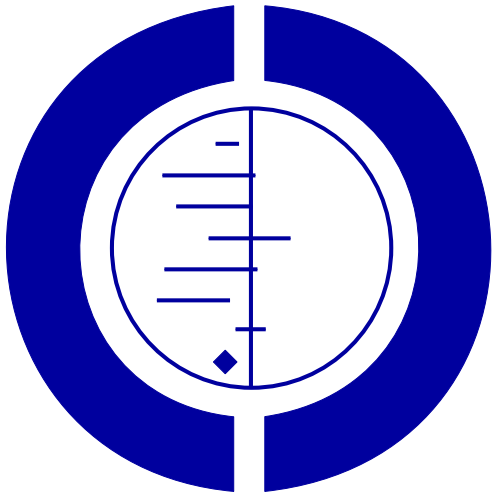

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ABSTRACT

Background
Public debate over the safety of the trivalent measles, mumps and rubella (MMR) vaccine, and the resultant drop in vaccination rates in several countries, persists despite its almost universal use and accepted effectiveness.

Objectives
We carried out a systematic review to assess the evidence of effectiveness and unintended effects associated with MMR.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2004), MEDLINE (1966 to December 2004), EMBASE (1974 to December 2004), Biological Abstracts (from 1985 to December 2004), and Science Citation Index (from 1980 to December 2004). Results from reviews, handsearching and from the consultation of manufacturers and authors were also used.

Selection criteria
Eligible studies were comparative prospective or retrospective trials testing the effects of MMR compared to placebo, do-nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age. These studies were carried out or published by 2004.

Data collection and analysis
We identified 139 articles possibly satisfying our inclusion criteria and included 31 in the review.

Main results
MMR was associated with a lower incidence of upper respiratory tract infections, a higher incidence of irritability, and similar incidence of other adverse effects compared to placebo. The vaccine was likely to be associated with benign thrombocytopenic purpura, parotitis, joint and limb complaints, febrile convulsions within two weeks of vaccination and aseptic meningitis (mumps) (Urabe strain-containing MMR). Exposure to MMR was unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps) (Jeryl-Lynn strain-containing MMR). We could not identify studies assessing the effectiveness of MMR that fulfilled our inclusion criteria even though the impact of mass immunisation on the elimination of the diseases has been largely demonstrated.

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 MMR 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 are three very dangerous infectious diseases which cause a heavy disease, disability and death burden in the developing world. Researchers from the Cochrane Vaccines Field reviewed 139 studies conducted to assess the effects of the live

attenuated combined vaccine to prevent measles, mumps and rubella (MMR) in children. MMR protects children against infections of the upper airways but very rarely may cause a benign form of bleeding under the skin and milder forms of measles, mumps and rubella. No credible evidence of an involvement of MMR with either autism or Crohn's disease was found. No field studies of the vaccine's effectiveness were found but the impact of mass immunisation on the elimination of the diseases has been demonstrated worldwide.

BACKGROUND

Mumps, measles and rubella are serious diseases that can lead to potentially fatal illness, disability and death. Measles, mumps and rubella are particularly prevalent in developing countries where vaccination programmes are inconsistent and the mortality rate from disease is high. In developed countries, however, mumps, measles and rubella are now rare, due to large-scale vaccination programmes.

The single component live attenuated vaccines of measles, mumps, and rubella 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 associated with these childhood illnesses.

Nevertheless, no country recommends that measles, mumps, and rubella be given as three separate vaccines. Combined live attenuated measles, mumps and rubella (MMR) vaccine was introduced in the United States in the 1970s (Redd 1999; Schwarz 1975). MMR is included in the World Health Organisation's 'Expanded Programme on Immunisation' and it is used in over 30 European countries, USA, Canada, Australia and New Zealand. In total, over 90 countries around the world use MMR. 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 4 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, important in reducing costs while increasing immunisation coverage against the three diseases (Makino 1990). The incidence of measles, mumps, and rubella worldwide has been significantly reduced by MMR vaccination (WHO 1999).

The capability of MMR mass immunisation to eliminate the targeted disease has been demonstrated in a number of countries. The United States 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 about 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 and cases of measles notified 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.

The only retrospective observational study, which seemed to show an unexpectedly low clinical efficacy (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 Center for Disease Control (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 history of mumps prior to the outbreak).

The component of monovalent vaccine containing measles, mumps and rubella 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 ten 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, however, 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, all produced using rabbit kidney cells; and Matsuura produced on quail embryo fibroblasts. The RA 27/3 strain is used most often because of consistent immunogenicity, induction of resistance to re-infection, and 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).

At least five MMR vaccines are known of:
(1) Triviraten Berna vaccine is live 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 virus: Schwarz measles strain, 1000 TCID50; Urabe Am 9 mumps strain, 5000 TCID50; and Wistar RA 27/3 rubella strain, 1000TCID50.

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

OBJECTIVES

To review the existing evidence on the absolute effectiveness of MMR vaccine in children (by the effect of the vaccine on the incidence of clinical cases of measles, mumps and rubella).
To assess in children the worldwide occurrence of adverse events, including those that are common, rare, short and long-term, following exposure to MMR.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included all comparative prospective or retrospective studies (see Appendix 1 in the Methods section).

Types of participants

Healthy individuals aged up to 15 years of age.

Types of intervention

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

Types of outcome measures

(1) Clinical cases: measles, mumps or rubella.
(2) Number and type of adverse events observed following MMR vaccination: classified as local or systemic.
(3) Systemic adverse events: including fever, rash, vomiting, diarrhoea and more generalised and severe signs including all the potential adverse events which have been hypothesised so far (thrombocytopenic purpura, parotitis, joint and limb symptoms, Crohn's disease, ulcerative colitis, autism, aseptic meningitis).
(4) Local adverse events: including soreness and redness at the site of inoculation.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Acute Respiratory Infections Group methods used in reviews.

For effectiveness:
we searched the Cochrane Acute Respiratory Infections (ARI) Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (T*he Cochrane Library* Issue 4, 2004), and MEDLINE (1966 to December 2004) to identify randomised and quasi-randomised controlled trials identified

through electronic databases and handsearches. The following search terms were used.

MEDLINE (Webspirs)
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

These subject terms were adapted to search the other databases: EMBASE was searched (from 1980 to the end of 2004) to identify controlled trials in combination with subject terms adapted for EMBASE; Biological Abstracts (1985 to the end of 2004); Science Citation Index (1980 to present). We also searched the Cochrane Database of Systematic Reviews (CDSR) and NHS Database of Abstracts of Reviews of Effects (DARE) for published reviews. 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, first or corresponding authors of studies evaluated and researchers or experts in the field, where appropriate, to identify any unpublished studies. There were no language restrictions.

For safety:
we searched Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2004) to identify reports of randomised and quasi-randomised controlled trials and published reviews in CDSR and DARE. The Cochrane Library was searched to identify reports from the results of handsearching the journal Vaccine (1983 to 2004).

We also searched MEDLINE (1966 to December 2004) using the following search terms.

MEDLINE (OVID)
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) near (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

This filter was adapted for searching EMBASE (1980 to the end of 2004), Biological Abstracts (1985 to the end of 2004), and Science Citation Index (1980 to the end of 2004). We assessed bibliographies of all relevant articles and any published reviews for additional studies. There were no language restrictions.

METHODS OF THE REVIEW

Study selection
Two authors independently applied the inclusion criteria to all identified and retrieved articles.

Quality assessment
Two authors independently assessed the methodological quality of the included studies. The quality of randomised and semi-randomised trials was assessed using the criteria adapted from the Cochrane Reviewers' Handbook (Clarke 2003). Quality assessment of non-randomised studies was made in relation to the presence of potential confounders which could make interpretation of the results difficult. However, because there is 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 trial (HCTs), interrupted time-series and case cross-over studies, and ecological studies. For case-only design studies, we used a classification and methodological quality checklist (unpublished) especially developed by CP Farrington and TO Jefferson and adapted from a paper by CP Farrington (Farrington 2004).

Data extraction

Two authors independently performed data extraction using a data extraction form.

Statistical considerations

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.

Appendix 1 (based on: Farrington 2004; Jefferson 1999; Last 2001)

A **case-control study** is an epidemiological study usually used to investigate the causes of disease. Study participants who have experienced an adverse outcome or disease are compared with participants who have not. Any differences in the presence or absence of hypothesised risk factors are noted.

A **cohort study** is an epidemiological study where groups of individuals are identified who vary in their exposure to an intervention or hazard and are followed to assess outcomes. Association between exposure and outcome are then estimated. Cohort studies are best performed prospectively but can also be undertaken retrospectively if suitable data records are available.

An **historical controlled trial** (HCT) is a study with control participants for whom data were collected at a time preceding that at which the data are gathered on the group being studied.

Indirect comparisons are comparisons of the two or more index groups with a control (usually in randomly allocated groups). The comparisons are usually not contemporaneous and inference is made from the comparisons to the general population.

A **randomised controlled trial** (RCT) is any study on humans in which the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using random allocation.

A **controlled clinical trial** (CCT) is any study on humans in which the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using some quasi-random method of allocation (such as alternation, date of birth or case record number).

A **time-series** is a comparative design with controls in which measurements are made at different times to allow trend detection and before-and-after exposure assessment.

Case-only design studies

An **ecological study** is a study in which the units of analysis are populations or groups of people rather than individuals. Inference is then made by observing the difference in incidence between populations of the event in question.

A **case-crossover study** is a design in which exposures of individuals during one period is compared by matched-pair analyses to their own exposure during a preceding period of similar length.

Case-coverage design is a study comparing prevalence of exposure in individuals with exposure in the reference population. No denominator data are required and the population coverage information is derived from summary statistics. When coverage information is derived from a population sample, the design is that of a case-base study.

A **self-controlled case series** uses individuals as their own controls. The ages at vaccination are regarded as fixed and the age at the time of an adverse event is the random variable of interest within a pre-determined observation period.

DESCRIPTION OF STUDIES

Our searches identified approximately 5,000 articles for screening, a large number of studies because of the deliberately broad search design. Previous research had demonstrated that adverse event data are not indexed consistently and up to 25% of studies reporting adverse event data are not identified through standard searching techniques (Derry 2001). After screening, 139 studies possibly fulfilling our inclusion criteria were retrieved. The data sets of eight studies which were published several times (redundant publications) were only considered once. One hundred and nineteen studies not meeting all criteria were excluded while 31 were included in the review. We could find no comparative studies assessing the effectiveness of MMR that fitted our inclusion criteria as all had serological outcomes.

The studies included in the review were as follows:
five randomised controlled trials (RCTs) (Bloom 1975; Edees 1991; Lerman 1981; Peltola 1986; Schwarz 1975);
one controlled clinical trial (CCT) (Ceyhan 2001);
fourteen cohort studies (Beck 1989; Benjamin 1992; DeStefano 2002; Dunlop 1989; Fombonne 2001; Madsen 2002; Makela 2002; Makino 1990; Miller 1989; Robertson 1988; Stokes 1971; Swartz 1974; Vestergaard 2004; Weibel 1980);

five case-control studies (Black 1997; Black 2003; Davis 2001; DeStefano 2004; Smeeth 2004);
three time-series trials (da Cunha 2002; Dourado 2000; Freeman 1993);
one case-crossover trial (Park 2004);
one ecological trial (Jonville-Bera 1996);
one self-controlled case series trial (Taylor 1999).

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

Ten studies included data on effectiveness and safety outcomes (Ceyhan 2001; Dunlop 1989; Edees 1991; Lerman 1981; Makino 1990; Robertson 1988; Schwarz 1975; Stokes 1971; Swartz 1974; Weibel 1980), one was unclear (Beck 1989) and the remaining 20 reported safety outcomes.

METHODOLOGICAL QUALITY

The reporting of information on vaccine content and the schedule used varied considerably between studies. No study, across all designs, reported complete vaccine identification information, including: lot numbers, adjuvants, preservatives, strains, product and manufacturer. Twelve studies failed to report any vaccine strains (Benjamin 1992; Black 2003; Bloom 1975; DeStefano 2002; DeStefano 2004; Fombonne 2001; Freeman 1993; Park 2004; Peltola 1986; Smeeth 2004; Stokes 1971; Taylor 1999). Fourteen studies reported all strains contained in the tested MMR (Beck 1989; Ceyhan 2001; Dunlop 1989; Edees 1991; Jonville-Bera 1996; Lerman 1981; Madsen 2002; Makela 2002; Makino 1990; Peltola 1986; Robertson 1988; Schwarz 1975; Swartz 1974; Vestergaard 2004) while three reported the strain for a single component of MMR only (da Cunha 2002; Dourado 2000; Weibel 1980). Complete information on the schedule, doses and route of administration was available for five studies (Bloom 1975; Lerman 1981; Makino 1990; Robertson 1988; Swartz 1974).

Thirteen recent studies reported definitions for all possible adverse events monitored for (Black 1997; Black 2003; da Cunha 2002; Davis 2001; DeStefano 2002; DeStefano 2004; Dourado 2000; Fombonne 2001; Jonville-Bera 1996; Makela 2002; Park 2004; Smeeth 2004; Vestergaard 2004), three of these were single event-specific studies (Black 2003; DeStefano 2002; Jonville-Bera 1996). Six studies had no definitions of any safety outcomes measured beyond a description of temperature measurement ranges (Ceyhan 2001; Beck 1989; Bloom 1975; Lerman 1981; Stokes 1971; Swartz 1974). Four studies had one outcome with a description (Dunlop 1989; Makino 1990; Robertson 1988; Weibel 1980) and five studies had more than one outcome with a description (Edees 1991; Freeman 1993; Miller 2002; Peltola 1986; Schwarz 1975). Of the 15 studies that monitored temperature, five gave no further description either of a numerical range or a base reading (Dunlop 1989; Freeman 1993; Miller 1989; Peltola 1986; Swartz 1974).

Six studies reported no participants missing for adverse event monitoring (Ceyhan 2001; DeStefano 2002; Edees 1991; Robertson 1988; Stokes 1971; Swartz 1974). In one case it was not possible to determine if participants were missing (Weibel 1980). Of the seventeen studies with clearly missing unintended-event data, three had less than 10% missing from all arms (Benjamin 1992; Dunlop 1989; Lerman 1981), four had between 11% to 20% missing (Bloom 1975; Madsen 2002; Makela 2002; Smeeth 2004), eight had between 20% to 60% missing (Beck 1989; Black 2003; Freeman 1993; Makino 1990; Miller 1989; Park 2004; Peltola 1986; Schwarz 1975) and in two studies the number of children missing from both arms could not be determined (Dourado 2000; Jonville-Bera 1996). Eight studies (Beck 1989; DeStefano 2004; Freeman 1993; Lerman 1981; Makela 2002; Park 2004; Peltola 1986; Schwarz 1975) provided inadequate explanations for missing data, including one in which no explanations were offered (Beck 1989). Two recent studies had discrepancies in reporting of denominators (Makela 2002; Vestergaard 2004) while one (DeStefano 2004) excluded more than third of cases.

Information on study population and enrolment process was insufficient in ten studies (Beck 1989; Ceyhan 2001; Freeman 1993; Lerman 1981; Makino 1990; Peltola 1986; Robertson 1988; Schwarz 1975; Weibel 1980); in a further seven studies the population description raised doubts about the generalisability of the conclusions to other settings (Dourado 2000; Dunlop 1989; Edees 1991; Fombonne 2001; Jonville-Bera 1996; Miller 1989; Swartz 1974). We were uncertain as to the power and generalisability of the findings from the single case-only design study (Taylor 1999).

In the GPRD - based studies (Black 2003; Smeeth 2004) the precise nature of controlled unexposed to MMR and their generalisability was impossible to determine.

RESULTS

RCTs and CCTs

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 MMR with lower incidence of respiratory symptoms; nausea and vomiting, or either alone; and no difference in incidence of other unintended effects compared with placebo, with the exception of irritability. Another trial concluded that there was no increased clinical reactivity with an MMR 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).

We classified two trials as being at low risk of bias (Lerman 1981; Peltola 1986), two trials at moderate risk (Ceyhan 2001; Edees 1991) and two trials at high risk of bias (Bloom 1975; Schwarz 1975) (Table 01). The Peltola trial was unique in reporting the vaccine excipients (adjuvant and preservatives) and being the sole RCT designed to assess safety only (Peltola 1986). The extent to which the study results from three of the trials provide a correct basis for applicability to other settings is debatable (Ceyhan 2001; Edees 1991; Lerman 1981). In the Ceyhan (Ceyhan 2001) and Lerman (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 (Lerman 1981). Similarly in the Edees trial (Edees 1991) 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.

The trials by Edees and Ceyhan were single blind (parents only) and unblended, respectively. We considered to have a moderate risk of detection bias affecting the outcomes (Ceyhan 2001; Edees 1991). The reasons for not blinding the researchers during the collection and collation of the parent-completed questionnaires were unclear. In the two trials assessed as being at high risk of reporting bias, adverse effects were reported for only 60% (Bloom 1975) and 39% (Schwarz 1975) of participants.

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 degrees Centigrade 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 02).

Cohort Studies

We included fourteen cohort studies altogether. They compared MMR 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; DeStefano 2002; Fombonne 2001; Madsen 2002; Makela 2002; Stokes 1971; Vestergaard 2004).

The study by Benjamin found that MMR 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 MMR 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 (Miller 1989). Makino reported a higher incidence of diarrhoea in the MMR 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 and placebo (Beck 1989) or do-nothing (Stokes 1971). Stokes (Stokes 1971), however, reported an increase in the incidence of fever in the period day 5 to day 12 postvaccination but Beck reported no difference (Beck 1989).

The study by Madsen reported no increased risk of autism or other autistic spectrum disorders between vaccinated and unvaccinated children (Madsen 2002). The interpretation of the study by Madsen was made difficult by the unequal length of follow up for younger cohort members as well as the use of date of diagnosis rather than onset of symptoms for autism (Madsen 2002).

The study by Vestergaard (Vestergaard 2004) was a large (537,171 Danish children) retrospective cohort study assessing a possible association between MMR (containing the Moraten, Jeryl Lyn and Wistar strains of the three viral antigens, respectively) and febrile seizures or epilepsy in children aged three months to five years. The authors reported that the rate of febrile seizures was significantly higher during the first (risk ratio (RR) 2.46, 95% confidence interval (CI) and second (RR 3.17, 95% CI) weeks after vaccination but not thereafter. Overall, MMR was associated with a higher risk of febrile seizures (RR 1.1, 95% CI 1.05 to 1.15). These are plausible conclusions given that MMR is a viral live attenuated vaccine. There appeared to be no association with a family history of febrile seizures but there was a four-fold increase in risk of seizures within the first two weeks after MMR in siblings of children with epilepsy and a 19% increase in the risk of a second febrile seizure. Overall, this was a well-reported, powerful study with credible conclusions as all possible efforts to account for confounders were made.

The retrospective cohort study by Fombonne et al tested several causal hypotheses and mechanisms of association between exposure to MMR and pervasive development disorders (PDD). The population was made up of three cohorts of participants; one was of older children acting as the control (pre-MMR introduction). The authors concluded that there was no evidence that PDD had become more frequent, the mean age at parental concern had not moved closer to the date of exposure to MMR, 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 (Fombonne 2001).
The number and possible impact of biases in this study was so high that interpretation of the results was difficult (Fombonne 2001).

The retrospective person-time cohort study by Makela assessed the association between exposure to MMR and encephalitis (EN), aseptic meningitis (AM) and autism (AU) in a cohort of 535,544 Finnish children (95% of the surveillance cohort); the children were aged one to seven years at the time of vaccination. The authors compared the incidence of outcomes in the first three months after vaccination with the incidence in the following months and years. They concluded that there was no evidence of association. The study was weakened by the loss of 14% of the original birth cohort and the effects of the rather long time frame of follow up. What the impact of either of these factors was in terms of confounders is open to debate, however the long follow up for autism was due to the lack of a properly constructed causal hypothesis (Makela 2002).

DeStefano reported a large retrospective data-linked cohort study carried out on 167,240 children who were enrolled in four large health maintenance organisations in the US, from 1991 to 1997 (DeStefano 2002). The study tested the evidence for an association between childhood vaccinations (including MMR) and asthma. The authors concluded that there was evidence of a weak increased risk of childhood asthma following exposure to other vaccines but not MMR, regardless of age at first vaccination. Vaccine coverage and the structure of comparisons was unclear, raising the possibility of bias (DeStefano 2002).

Only the study by Vestergaard was judged to have a low probability of bias (Vestergaard 2004). Four studies were classified to be at moderate risk of bias (Benjamin 1992; DeStefano 2002; Makela 2002; Robertson 1988). The conclusions of Benjamin (Benjamin 1992) were undermined by textual errors and the open clinical assessment of cases and those of Robertson (Robertson 1988) by vaccine assignment by parental choice (with no reported controls).

We assessed nine studies as having a high likelihood of bias (Table 03) (Beck 1989; Dunlop 1989; Fombonne 2001; Makino 1990; Miller 1989; Robertson 1988; Stokes 1971; Swartz 1974; Weibel 1980). The most common reason was the selection of the cohorts, with missing descriptions of the reference population. The studies' conclusions that MMR is 'safe', 'equally safe', 'well-tolerated', has 'low-reactogenicity' need to be interpreted with caution given the potential for confounding. The validity of the conclusions was affected by selective reporting in the comparative analysis (with just over half the responses from participants in some cases).

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.

Case-control studies

Two case-control studies reported that exposure to MMR was not associated with an increased risk of Crohn's disease and ulcerative colitis (Davis 2001) or with aseptic meningitis (MMR containing Jeryl-Lynn mumps strain) (Black 1997). Both studies had low chance of bias but lacked details of exposure (type of vaccines used) (Table 04) and a discussion of the reference population.

The study by Smeeth (Smeeth 2004) assessed the association between exposure to MMR and the onset of autism and other PDD. The study was based on data from the UK's General Practice Research Database (GPRD) which was set up on the first of June 1987. The authors concluded that their study added to the evidence that MMR vaccination was not associated with an increased risk of PDD. The odds ratio (OR) for the association between MMR vaccination and PDD 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 the third birthday, or to the period prior to media coverage of the hypothesis linking MMR vaccination with autism.

The study appeared carefully conducted and well reported, however, GPRD-based MMR studies had no unexposed (to MMR) representative controls. In this study the approximately 4% to 13% seemed to be unexposed controls regarded by the authors as representative. Such a small number may indicate some bias in the selection of controls.

This problem appeared to provide the rationale for the design of DeStefano 2004, a study assessing the association between MMR vaccine and the onset of autism. The authors compared the distribution of ages at first MMR vaccination in children with autism (cases) 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 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. This was a well-reported and designed study. The conclusion, however, implied bias in the enrollment of cases which may not be representative of the rest of the autistic population of the city of Atlanta, USA where the study was set.

Black 2003 was a GPRD-based case-control study designed to assess the relationship between MMR vaccine and idiopathic thrombocytopaenic purpura (ITP). The authors concluded that the study confirmed the increased risk of ITP within six weeks after

MMR vaccination. Lack of clarity over the vaccine exposure status of controls makes the results of this study difficult to interpret.

Time series

There were three studies with a before-and-after design (da Cunha 2002; Dourado 2000; Freeman 1993). The study by Dourado assessed a possible association between mumps Urabe-containing MMR and aseptic meningitis; it reported a positive association (Dourado 2000). In the study by Freeman, the incidence of rash, lymphadenopathy and nasal discharge was found to be higher after exposure to MMR in two age groups (13 and 15 months olds) (Freeman 1993).

The study by Da Cuhna et al (da Cunha 2002) assessed the risk of acute aseptic meningitis and mumps in two regions of Brazil. In this study, over 800,000 children aged 1 to 11 years were observed before and after vaccination with Leningrad-Zagreb mumps strain-containing MMR (LZ-MMR).The authors concluded that there was a marked increase in the number of notified cases of aseptic meningitis (AM) in the two states studied. This was three to four weeks after the mass immunisation campaign using LZ mumps strain MMR vaccine.

In the study by Dourado, limited error was introduced by using an estimation of the denominator from a prior census and the number of doses administered (as opposed to supplied) in the mass vaccination programme (Dourado 2000). In the study by Freeman, the number of completed weekly diaries varied over the eight-week study period, with no indication of whether the losses occurred pre or postvaccination (Freeman 1993). In addition, there was an overall attrition rate of 33%. The risk estimates varied depending on the diagnostic criteria used and the geographical area. There was also an increase in the incidence of notified mumps after the campaign in the area where data were available.

In the study by Da Cuhna (da Cunha 2002), despite uncertainties about the correlation between denominators before and after immunisation, both sets of comparisons appeared to show a notable rise in aseptic meningitis and mumps following immunisation with LZ-MMR. Some confounding may have taken place especially around the date of immunisation and the exact before immunisation denominators (coverage was unequal in the two states). These were, however, unlikely to have affected conclusions given the sheer size of the study.

Ecological study

The single ecological study that was included assessed the evidence of association between MMR, or any of its component vaccines, and the onset of thrombocytopenic purpura (TP) (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.

Case-only designs

The single included self-controlled case series study assessed clustering of cases of autism by postexposure periods in a cohort of 498 (with 293 confirmed cases) children (Taylor 1999). The authors reported a significant increase in onset of parental concern at six months postvaccination. The authors plausibly argued that this may have been due to multiple testing, caused by an unclear causal hypothesis, and concluded that the evidence did not support an association with autism. The study demonstrates the difficulties of drawing inferences in the absence of a non-exposed population or a clearly defined causal hypothesis.

The single case-crossover study (Park 2004) suggested that MMR and aseptic meningitis are associated (OR 3.02). 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.

DISCUSSION

We found only limited evidence of the safety of MMR compared to its single component vaccines from studies that had a low risk of bias. The few studies least likely to be affected by systematic error pointed to a likely association with fewer upper respiratory tract infections, increased febrile convulsions in the first two weeks postvaccination and no increased incidence of aseptic meningitis (for Jeryl-Lynn strain-containing mumps vaccine). Low risk of bias evidence did not support a causal association with Crohn's disease, ulcerative colitis or autism. 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.

Reasons presented by the papers to justify missing data were analysed. Despite accepting as 'adequate' explanations such as 'non-response to questionnaire' and 'medical records unavailable', not all reports offered adequate explanations for missing data.

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)), limited observation periods (maximum 42 days) and selective reporting of results contributed to our decision not to attempt pooling data by study design.

There are some weaknesses in our review. 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 are 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.

We were disappointed by our inability to identify effectiveness studies with population or clinical outcomes. Given the existence of documented elimination of targeted diseases in large population by means of mass immunisation campaigns however, we have no reason to doubt the effectiveness of MMR.

The safety record of MMR is possibly best attested by its almost universal use; its evaluation cannot be divorced from its effectiveness and the importance of the target diseases. As such, MMR remains an important preventive global intervention.

More attention needs to be paid to the design and reporting of safety outcomes in vaccine studies, both pre and postmarketing.

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 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 postmarketing, need to be improved and standardised definitions of adverse events should be adopted.

POTENTIAL CONFLICT OF INTEREST

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

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TABLES

Characteristics of included studies

Study	**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)
Allocation concealment	D

Study	**Benjamin 1992**
Methods	Retrospective cohort comparing incidence of joint and limb symptoms in MMR vaccinated children versus non-vaccinated

Characteristics of included studies (*Continued*)

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 subjects 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 six-week parental recall questionnaire and clinician home visit
Notes	Low response rate in non-immunized group
Allocation concealment	D

Study	**Black 1997**
Methods	Case-control
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	
Allocation concealment	D

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

Study	**Bloom 1975**
Methods	RCT, double blind
Participants	Two hundred and eighty two children
Interventions	Three lots of MMR vaccine (lot 1, 2, 3 prepared from Schwarz live attenuated measles virus, Jerryl 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

Characteristics of included studies (*Continued*)

Outcomes	Observations for intercurrent illness and vaccine reactions made approx. 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
Allocation concealment	B

Study	**Ceyhan 2001**
Methods	CCT
Participants	One thousand infants aged 38 to 40 months from 5 maternity and child health centers in Ankara, Turkey
Interventions	Measles vaccine (Rouvax, Schwarz measles strain, 1000 TCID50) administered at 9 month 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 - Diarrhea - Redness - Swelling Even if visits by midwife 7,14,28 days after vaccination to collect adverse reactions records from parents and every 3 month for 60 month phone call/visit for standard questionnaire were carried out, the time of observation for adverse events is not specified
Notes	
Allocation concealment	D

Study	**Davis 2001**
Methods	Case-control
Participants	Vaccine Safety Datalink Projekt (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
Allocation concealment	D

Study	**DeStefano 2002**
Methods	Retrospective cohort (from the Vaccine Safety Datalink Project)

Characteristics of included studies (*Continued*)

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	
Allocation concealment	D

Study	**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 enrollment in MADDSP and cases may not be representative of the rest of the autistic population of the city
Allocation concealment	D

Study	**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, cont. mumps strain Urabe)
Outcomes	Aseptic meningitis Periods of 23 weeks pre-vacc and 10 weeks post were compared
Notes	
Allocation concealment	D

Study	**Dunlop 1989**
Methods	Prospective cohort
Participants	335 healthy children aged about 15 months
Interventions	MMR vaccine Timovax (Merieux, cont. measles strain Schwarz 1000 TCID50, rubella RA 27/3 1000 TCID50, mumps Urabe Am/9 5000 TCID50) versus Measles vaccine Rouvax (Merieux, cont. 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 wks and wkly for 3 more weeks

Characteristics of included studies (*Continued*)

Notes	
Allocation concealment	D

Study	**Edees 1991**
Methods	RCT, single blind
Participants	Four hundred twenty 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) Both In upper arm or leg administered
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	
Allocation concealment	D

Study	**Fombonne 2001**
Methods	Retrospective cohort
Participants	283 children from three 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
Allocation concealment	D

Study	**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 wks before to 4 wks 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
Allocation concealment	D

Characteristics of included studies (*Continued*)

Study	**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 centers after. All case within 45 days from vaccination. Over 8 years period immunisation
Notes	The denominator is determined by the number of doses distributed
Allocation concealment	D

Study	**Lerman 1981**
Methods	RCT, double blind
Participants	Five hundred two 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 wks) - Rash (6 wks) - Lymphadenopathy (6 wks) - Sore eyes (6 wks) - Joint symptoms (6 wks)
Notes	
Allocation concealment	A

Study	**Madsen 2002**
Methods	Retrospective cohort
Participants	All Danish children born between Jan 1991 and Dec 1998: 537,303
Interventions	MMR vaccine (cont. 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)

Characteristics of included studies (*Continued*)

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
Allocation concealment	D

Study	**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, cont. 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)
Allocation concealment	D

Study	**Makino 1990**
Methods	Prospective cohort
Participants	1638 healthy children
Interventions	MMR vaccine MPR (Kitasato Institute, Japan cont. measles AIK-C 5000 TCID50 , mumps Hoshino 15000 TCID50 and rubella Takahashi 32000 TCID50) versus Measles vaccine (Kitasato Institute, cont. measles AIK-C 25000 TCID50) versus Mumps vaccine (Kitasato Institute, cont. 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 - Diarrhea Within twenty-eight days after vaccination
Notes	Inadequate description of the cohorts
Allocation concealment	D

Study	**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 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%
Allocation concealment	D

Study	**Park 2004**
Methods	Case-crossover. 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
Allocation concealment	D

Study	**Peltola 1986**
Methods	RCT, double blind
Participants	Six thousand eighty six pairs of twins aged between 14 months and 6 years
Interventions	MMR vaccine (Vivirac, 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	
Allocation concealment	A

Study	**Robertson 1988**
Methods	Prospective cohort
Participants	319 children aged 13 months
Interventions	MMR vaccine (Merieux, cont. measles strain Schwarz, mumps Urabe AM/9 and rubella Wistar RA 27/3) versus Measles vaccine (Schwarz strain)

Characteristics of included studies (*Continued*)

	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. Three week follow up
Notes	
Allocation concealment	D

Study	**Schwarz 1975**
Methods	Multicentre-RCT, double blind.
Participants	Altogether 1481 healthy children from different countries in N and S 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 Jeryly 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, Arthalgia, Paresthesia, 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
Allocation concealment	D

Study	**Smeeth 2004**
Methods	Retrospective case-control study
Participants	All person born in 1973 or later registered in the General Practice Research Database (GPRD) Cases: Subjects 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	
Allocation concealment	D

Characteristics of included studies (*Continued*)

Study	**Stokes 1971**
Methods	Prospective cohort
Participants	Altogether 966 children (334 in the US and 632 in Cost Rica)
Interventions	MMR vaccine (Merck Sharp & Dohme cont. measles strain Moraten 1000 TCID50, mumps strain Jeryl Lynn 5000 TCID50, rubella strains HPV - 77 1000 TCID50) one dose subcutaneous versus No treatment
Outcomes	- Temperature (> 38 ºC 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	
Allocation concealment	D

Study	**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) - Lymphadenopathy - Enanthema - Conjunctivitis - Rash Complaints any (up to 60 days) Follow up 7 to 15 days
Notes	
Allocation concealment	D

Study	**Taylor 1999**
Methods	Case-coverage comparing incidence of autistic disorders in eight health districts in UK
Participants	Four hundred and ninety eight 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
Allocation concealment	D

Characteristics of included studies (*Continued*)

Study	**Vestergaard 2004**
Methods	Person-time cohort study
Participants	537,171 Danish children
Interventions	Exposure to MMR vaccine (cont 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	
Allocation concealment	D

Study	**Weibel 1980**
Methods	Prospective cohort
Participants	135 children
Interventions	MMR vaccine (Merck, cont. 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 three arms. Sparse detail on safety data collection procedures
Allocation concealment	D

Study	**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 two 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 (SerumInstitute of India Ltd)
Outcomes	Aseptic meningitis (clinical diagnosis or notification form). Thirty one (in MT) or thirty seven (in MS) weeks before and ten weeks after vaccination campaign
Notes	
Allocation concealment	D

n = number
im = Intra-muscular
sc = subcutaneous
wks = weeks

Characteristics of excluded studies

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

Characteristics of excluded studies (*Continued*)

Anonymous 1997	No original data
Anonymous 1999	Not original research - review
Aozasa 1982	Not MMR vaccine
Autret 1996	Epidemiological survey comparing onset of ITP following vaccination with MMR compared to M, M and R
Balraj 1995	Review on mumps vaccine
Beck 1991	Assesses safety of MMR vaccination in children allergic to eggs
Beeler 1996	Case series
Benjamin 1991	No new research review
Berger 1988a	Serology outcomes only
Berger 1988b	Serology (seroconversion) outcomes only
Berlin 1983	Surveillance data
Bhargava 1995	Non-comparative
Borgono 1973	Insufficient data presented
Bruno 1997	Compares two types of MMR
Buntain 1976	Case report
Buynak 1969	Several study - non-comparative
Chang 1982	No adverse effect data
Chen 1991	Individuals over 15 years
Chen 2000	Review
Chiodo 1992	Non-comparative
Cinquetti 1994	Compares two types of MMR
Contardi 1989	Non-comparative
Contardi 1992	Compares three types of MMR
Coplan 2000	Does not compare against a single component or do-nothing
D'Argenio 1998	No safety data
D'Souza 2000	Non-comparative
Dales 2001	Non-comparative
Dankova 1995	No adverse event data
Dashefsky 1990	MMR not given independently
Davis 1997	MMR not given independently
DeStefano 2000	Duplicate data
Deforest 1986	MMR given with DTP and OPV in different schedules
Deforest 1988	DTP/OPV plus or minus MMR versus placebo or without MMR
Dobrosavljevic 1999	Case report
Dos Santos 2002	MMR versus MMR versus MMR
Ehrenkranz 1975	Duplicate data Schwarz, Jackson, Ehrenkran, 1975
Elphinstone 2000	Data free
Englund 1989	MMR not given independently
Farrington 1996	Non-comparative
Farrington 2001	No new data
Fletcher 2001	No data

Characteristics of excluded studies (*Continued*)

Garrido L 1992	Non-comparative
Geier 2004	Uncertain MMR focus, mixed with thimerosal
Griffin 1991	Non-comparative
Grilli 1992	Comparison of different types of measles in MMR
Huang 1990	No safety data
Ipp 2003	Head-to-head of two types of MMR
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
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
Kiepiela 1991	RCT of two types of measles vaccine
Kurtzke 1997	Case-control of exposure to anything/measles vaccine and MS
Lee 1998	Data free
Lucena 2002	No comparator
Maekawa 1991	Non-comparative - non-inferential
Maguire 1991	Non-comparative
Marolla 1998	No safety data
Matter 1995	Non-comparative
Matter 1997	Seroprevalence study
Miller 1983	Non-comparative; egg allergy
Miller 1993	Non-comparative
Miller 2001	Non-comparative
Miller 2002	No new data
Min 1991	Compares two types of MMR
Minekawa 1974	Non-comparative
Mommers 2004	MMR and all other childhood vaccines, indistinguishable comparison
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
Patja 2000	Non-comparative
Patja 2001	Non-comparative
Pekmezovic 2004	Not about MMR
Peltola 1998	Non-comparative case series
Puvvada 1993	Non-comparative case series
Ramos-Alvarez 1976	Duplicate publication of Schwarz, Jackson, Ehrenkranz 1975

Characteristics of excluded studies (*Continued*)

Sabra 1998	Data free
Scarpa 1990	Non-comparative
Schettini 1989	No safety data
Schettini 1990	Non-comparative
Schwarzer 1998	Compares two types of MMR
Seagroatt 2003	Assesses measles vaccine
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 two types of MMR
Vesikari 1979	No new data review
Vesikari 1984	Compares two 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, Jackson, Ehrenkranz 1975
Wilson 2003	Systematic review
Woyciechowska 1985	Not MMR
Yamashiro 1998	Children past age limit

ADDITIONAL TABLES

Table 01. Summary of salient characteristic of RCTs and CCTs included in the review

Study	Population enrolled	Risk of bias	Likely bias	Generalisability
Bloom 1975	282	High	Reporting	Low
Ceyan 2001	1000	Moderate	Detection	Medium
Edees 1991	420	Moderate	Detection	Medium
Lerman 1981	502	Low	Detection	Medium
Peltola 1986	686	Low	Detection	High
Schwarz 1975	1481	High	Reporting	Low

Table 02. Reporting of temp. in RCTs (MMR versus single components/placebo/do-nothing)

Temp. increment (C)	Measurement site	Reporting frequency	Observation period	Reference
38.0 - 38.4	Axilla	All episodes	21	Schwarz 1975
38.0 - 38.4	Rectal	All episodes	21	Schwarz 1975
38.5 - 38.9	Axilla	All episodes	21	Schwarz 1975
38.5 - 38.9	Rectal	All episodes	21	Schwarz 1975
38.6 - 39.5	Not reported	Mean number of episodes	21	Peltola 1986
39.0 - 39.4	Axilla	All episodes	21	Schwarz 1975
39.0 - 39.4	Rectal	All episodes	21	Schwarz 1975
39.5 - 39.9	Axilla	All episodes	21	Schwarz 1975
39.5 - 39.9	Rectal	All episodes	21	Schwarz 1975
40.0 - 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 03. Summary of salient characteristics of Cohort studies included in the review

Study	Population enrolled	Risk of bias	Likely bias	Generalisability
Beck 1989	196 *	High	Selection	Low
Benjamin 1992	5017	Moderate	Detection	Medium
Dunlop 1989	335	High	Selection	Low
Makino 1990	1638	High	Selection	Low
Miller 1989	12185	High	Reporting	Low
Robertson 1988	319	Moderate	Selection	Medium
Stokes 1971	966	High	Selection	Low
Swartz 1974	59	High	Selection	Low
Weibel 1980	135	High	Selection	Low
Madsen 2002	537303	Moderate	Detection	High
Fombonne 2001	263	High	Selection	Low
Makela 2002	561089	Moderate	Selection	Medium
Vestergaard 2004	537171	Low	Selection	High

Table 03. Summary of salient characteristics of Cohort studies included in the review (*Continued*)

Study	Population enrolled	Risk of bias	Likely bias	Generalisability
DeStefano 2002	167240	Moderate	Selection	Medium
	* The number enrolled is unclear			

Table 04. Summary of salient characteristics of other study designs included in the review

Study	Design	Population	Risk of bias	Likely bias	Generalisability
Davis 2001	Case - control	211	Low	-	High
Black 1997	Case - control	587	Low	-	High
DeStefano 2004	Case - control	2448	Moderate	Selection	Medium
Black 2003	Case - control	139	Moderate	Selection	Medium
Smeeth 2004	Case - control	10697	Moderate	Selection	Medium
Dourado 2000	Before and after	452,344	Moderate	Detection	Medium
Freeman 1993	Before and after	375	High	Attrition	Low
Jonville-Bera 1996	Ecological	9,205,483*	Moderate	Selection	Medium
Taylor 1999	Case-coverage	498	Moderate	Confounding	Medium
Park 2004	Case-crossover	39	Moderate	Selection	Medium
Da Cuhna 2002	Before and after	845,889	Moderate	Selection	High
		*Estimated number of vaccine doses			

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Autistic Disorder [etiology]; Clinical Trials; Crohn Disease [etiology]; Measles [*prevention & control]; Measles-Mumps-Rubella Vaccine [administration & dosage; *adverse effects]; Mumps [*prevention & control]; Rubella [*prevention & control]; Vaccines, Attenuated [administration & dosage; adverse effects]

MeSH check words

Child; Humans

COVER SHEET

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