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Unintended events following immunization with MMR: a systematic review

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Abstract

Public debate over the safety of the trivalent measles, mumps and rubella (MMR) vaccine and the drop in vaccination rates in several countries persists despite its almost universal use and accepted effectiveness. We carried out a systematic review to assess the evidence of unintended effects (beneficial or harmful) associated with MMR and the applicability of systematic reviewing methods to the field of safety evaluation. Eligible studies were comparative prospective or retrospective on healthy individuals up to 15 years of age, carried out or published by 2003.

We identified 120 articles satisfying our inclusion criteria and included 22. MMR is associated with a lower incidence of upper respiratory tract infections, a higher incidence of irritability, similar incidence of other adverse effects compared to placebo and is likely to be associated with benign thrombocytopenic purpura (TP), parotitis, joint and limb complaints and aseptic meningitis (mumps Urabe strain-containing MMR). Exposure to MMR is unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps Jeryl–Lynn strain-containing MMR). 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 immunization with MMR cannot be separated from its role in preventing the target diseases.

Keywords: Measles, mumps and rubella (MMR); Randomized controlled trials (RCTs); CCTs

1. Background

Combined live attenuated mumps, measles and rubella (MMR) vaccine was introduced in the United States in the 1970s [1,2], in Britain in October 1988 and is included in WHO's Expanded Program on Immunization. The single-component live attenuated vaccines of MMR had been licensed in the USA in the 1960s [2–4]. Vaccination with MMR provides significant improvement in the efficiency of pediatric immunization through the administration of three vaccines in a single injection, reducing costs while increasing immunization coverage against the three diseases [5]. MMR is usually administered at 12–15 months and 4–5 years of age. One of the major concerns in any large-scale vaccination program is the occurrence of unintended events.

In recent years, there has been growing controversy over the safety of the MMR vaccine, which has been allegedly associated with a variety of rare conditions including thrombocytopenic purpura, aseptic meningitis, joint pain, sensorineural deafness, convulsion, encephalopathy, chronic enterocolitis with regressive developmental disorder and Crohn's disease [6]. From the public health perspective, it is important to identify whether the combined vaccine is associated with adverse events compared with its component vaccines.

Despite much attention on MMR, the methodological quality and applicability of the evidence of possible unintended events following MMR compared with its single or double antigen component vaccines have not been assessed. Recent reviews are descriptive and mainly focus on the alleged association with Crohn's disease and autism [6,7]. Known adverse events of component vaccines are fever in

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up to 15% and rash in up to 5% of measles vaccine recipients [2], low grade fever and parotitis in up to 0.7% of mumps vaccine recipients [4]. Rubella vaccine is associated with lymphadenopathy (up to 9% of recipients), transient arthralgia or arthritis (up to 10%) and possibly the rare chronic arthropathy [3]. Single-component vaccines could provide alternatives, if the combined vaccine had an unacceptable safety profile. We performed a systematic review aimed at assessing and assembling evidence on the type and frequency of unintended events associated with MMR vaccines compared with no vaccination or placebo or combinations of attenuated measles, mumps and rubella (MMR) vaccines.

The secondary aim was to assess the applicability of systematic reviewing methods to the field of the evaluation of unintended effects.

2. Methods

We considered for inclusion comparative prospective or retrospective studies on healthy individuals aged up to 15 years, carried out or published during the period 1969–2003. Studies had to assess frequency and type of possible adverse or unintended events occurring with any combined MMR vaccine given independently, in any dose, preparation or time schedule, compared with do-nothing, a placebo, or with any single or two components of the vaccine in any combination.

Comparative studies were defined as those in which a group exposed to MMR (index group) is compared with one or more other groups not exposed to MMR or exposed at different times (during control periods) or in which temporal association between exposure and outcome were tested for pre-defined periods. As well as randomized controlled trials (RCTs) and controlled clinical trials (CCTs), we considered for inclusion studies of case-control, case-crossover, cohort, ecological, time-series and case-only designs, provided both index and comparator groups and their exposure were clearly identifiable. To identify each study design pre-specified definitions were used [8–10].

We developed a specialized search strategy with the guidance of an information specialist, aimed at identifying all relevant studies carried out or published between 1969 and January 2003. The detailed search strategy is available from the corresponding author. We searched the Cochrane Control Register of Controlled Trials, Cochrane Database of Systematic Review, the NHS Database of Abstracts of Reviews of Effects, MEDLINE and Biological Abstracts from 1985, and EMBASE and the Science Citation Index from 1974. Additional unpublished and published references were sought from researchers, vaccine manufacturers and public health officials. Bibliographies of relevant articles and published reviews were assessed and related articles were tracked for additional studies.

All references were screened and hard copies of possible articles for inclusion were retrieved. Two researchers (DP and TJ or DP and EB) then applied inclusion criteria to all possible studies. A third reviewer (VD) acted as arbitrator in the result of a disagreement over the inclusion of a study in the review. Data extraction was performed independently by two reviewers using standardized data extraction forms. The completed forms are available on request from the corresponding author. Two reviewers separately assessed the methodological quality of the included studies.

Study design-specific quality assessment tools were used, empirically validated where possible, to assess the methodology of the studies. Assessment of randomized and quasi-randomized trials was based on *Cochrane Reviewers' Handbook* 4.1.6 quality criteria [11]; cohort and case-control studies assessments were adapted from the Newcastle–Ottawa Scales (NOS) [12]; the methodological assessment of time-series (before and after) was based on a checklist developed by the University of York, NHS Center for Reviews and Dissemination [13] and by Jefferson and Demicheli [9], and Farrington [10] for case-only designs and unpublished information. We assigned risk of bias categories (low, moderate, high) on the basis of how many of the criteria in the design-specific assessment tools were met by each study. The threshold necessary to achieve each level of risk varied depending on the tool used.

3. Results

Our searches identified approximately 4500 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 [14]. After screening, 120 studies possibly fulfilling our inclusion criteria were retrieved. Ninety-eight studies not meeting all criteria were excluded, the data sets of eight studies had been published several times (redundant publications) and 22 were included in the review. A list of excluded studies is available from the corresponding author on request.

Five RCTs, one CCT, nine cohort studies, two case-control studies, three time-series, one ecological and one self-controlled case series were included in the review. One study [15], had a mixed RCT—time-series design and was classified as the latter because adverse event data comparison was carried out on outcomes in subjects before and after vaccination. Studies reported as 'field trials' or 'controlled trials', were classified as cohort studies when randomization was not mentioned.

Ten studies included data on effectiveness and safety outcomes [1,5,16–23], one was unclear [24] and the remaining 11 reported only safety outcomes.

The total number of unintended events for which data could be extracted was 165, ranging from 1 to 18 outcomes measured in a single study. The mean was 7.5 (S.D. 5.17) and the median 7 (IQR 3.75–11).

Table 1
Summary of salient characteristics of RCTs and CCTs included in the review

Study	Population enrolled	Risk of bias	Type of bias most likely to weaken confidence in results	Generalisability of results beyond study population
Bloom et al. [25]	282	High	Reporting	Low
Ceyhan et al. [16]	1000	Moderate	Detection	Medium
Edees et al. [18]	420	Moderate	Detection	Medium
Lerman et al. [19]	502	Low	–	Medium
Peltola and Heinonen [26]	686	Low	–	High
Schwarz et al. [1]	1481	High	Reporting	Low

3.1. RCTs and CCTs

MMR vaccines were compared with monovalent measles vaccine [16,18,19], two types of monovalent mumps and rubella vaccines [19], or placebo [1,19,25,26].

One trial [26], carried out in twins, reported a possible protective effect of MMR with lower incidence of respiratory symptoms, nausea and/or vomiting and no difference in incidence of other unintended effects from placebo, with the exception of irritability. Another trial concluded that there was no increased clinical reactivity with MMR containing different strains of rubella [19].

The trial by Edees et al. concludes that there is no significant difference between the numbers of children developing symptoms after MMR or measles vaccination [18]. The trials by Bloom et al. [25] and Schwarz et al. [1] conclude that the incidence of raised temperature, rash, lymphadenopathy, coryza, rhinitis, cough, local reactions or limb and joint symptoms are not significantly different from placebo.

We classified two trials as at low risk of bias [19,26], two [16,18] at moderate risk and two [1,25] at high risk of bias (Table 1). The Peltola and Heinonen trial was unique in reporting vaccine excipients (adjuvant and preservatives) and being the sole RCT designed to assess safety only [26]. The extent to which the study results from three trials provide a correct basis for applicability to other settings is debatable [16,18,19]. In the Ceyhan et al. [16] and Lerman et al. [19] trials, the selection of pediatric practices involved in the recruitment of subjects is not explained and the number and assessment of non-responders are not reported [19]. Similarly in the Edees et al. [18] 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.

The trials by Edees et al. [18] and Ceyhan et al. [16] were single blind (parents only) and unblinded, respectively, and were considered at moderate risk of detection bias affecting the outcomes. The reasons for not blinding the researchers during the collection and collation of the parental-completed questionnaires are unclear. In the two trials assessed as being at high risk of reporting bias, adverse effects are reported for only 60% [25] and 39% [1] of participants.

All RCTs and CCTs reported a wide range of outcomes, using different terms often with no definition. For example, in RCTs body temperature higher than 38 °C was measured or reported in 16 ways. Different temperature increments, recording methods, observation periods and incidence, when reported, made comparisons between trials and pooling impossible (Table 2).

Table 2
Reporting of temperature in randomised controlled trials of immunisation with MMR compared with its component vaccines or placebo or do-nothing

Temperature increment (°C)	Measurement site	Frequency of reporting	Observation period from immunisation (in days)	Reference
38.0–38.4	Axilla	All episodes	21	Schwarz et al. [1]
38.0–38.4	Rectal	All episodes	21	Schwarz et al. [1]
38.5–38.9	Axilla	All episodes	21	Schwarz et al. [1]
38.5–38.9	Rectal	All episodes	21	Schwarz et al. [1]
38.6–39.5	Not reported	Mean number of episodes	21	Peltola and Heinonen [26]
39.0–39.4	Axilla	All episodes	21	Schwarz et al. [1]
39.0–39.4	Rectal	All episodes	21	Schwarz et al. [1]
39.5–39.9	Axilla	All episodes	21	Schwarz et al. [1]
39.5–39.9	Rectal	All episodes	21	Schwarz et al. [1]
40.0–40.4	Rectal	All episodes	21	Schwarz et al. [1]
≤38.5	Not reported	Mean number of episodes	21	Peltola and Heininen [26]
>1 above normal	Not reported	First episode	21	Bloom et al. [25]
>38.0	Not reported	All episodes	42	Lerman et al. [19]
	Not reported	First episode	21	Edees et al. [18]
≥39.5	Not reported	Mean number of episodes	21	Peltola and Heinonen [26]

The instrument used was not reported in any of the studies.

Table 3
Summary of salient characteristics of Cohort studies included in the review

Study	Population enrolled	Risk of bias	Type of bias most likely to weaken confidence in results	Generalisability of results beyond study population
Beck et al. [24]	196[a]	High	Selection	Low
Benjamin et al. [28]	5017	Moderate	Detection	Medium
Dunlop et al. [17]	335	High	Selection	Low
Makino et al. [5]	1638	High	Selection	Low
Miller et al. [27]	12185	High	Reporting	Low
Robertson et al. [22]	319	Moderate	Selection	Medium
Stokes et al. [20]	966	High	Selection	Low
Swartz et al. [21]	59	High	Selection	Low
Weibel et al. [23]	135	High	Selection	Low

[a] The number enrolled is unclear.

3.2. Cohort studies

We included nine cohort studies, comparing MMR with single measles vaccine [5,17,22,27], mumps–rubella vaccine [21], single mumps [5], single rubella [21,23], placebo [24] or no intervention [20,28].

The study by Benjamin et al. found that MMR was associated with an increased risk of episodes of joint and limb symptoms in girls under 5 years of age [28].

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 [5,21,23], mumps–rubella vaccine [21] single mumps [5] or measles vaccine [5,17]. Two studies [22,27] found that symptoms were similar following MMR and measles vaccination except for a higher incidence of parotitis following MMR [27]. Makino reported a higher incidence of diarrhea in the MMR arm compared to the single measles or rubella vaccines arms [5]. The studies by Beck and Stokes reported no difference in the incidence of rash and lymphadenopathy between MMR and placebo [24] or do-nothing [20]. Stokes et al. [20] however reported an increase in the incidence of fever in the period 5–12 days post-vaccination but Beck reported no difference [24].

No cohort studies were judged to have a low probability of bias. Two studies were classified at moderate risk of bias [22,28]. The conclusions of Benjamin et al. [28] are undermined by textual errors and the open clinical assessment of cases and, those of Robertson et al. [22] by vaccine assignment by parental choice (with no reported controls).

We assessed seven studies as having a high likelihood of bias (Table 3) [5,17,20,21,23,24,27]. 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 is effected 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.

3.3. Case-control studies

The two case-control studies reported that exposure to MMR was not associated with an increased risk of Crohn's disease and ulcerative colitis [29] or with aseptic meningitis (MMR containing Jeryl–Lynn mumps strain) [30]. Both studies had low chance of bias, but lacked details of exposure (type of vaccines used) (Table 4) and a discussion of the reference population.

Table 4
Summary of salient characteristics of other study designs included in the review

Study	Design	Population	Risk of bias	Type of bias most likely to weaken confidence in results	Generalisablity of results beyond study population
Davis et al. [29]	Case-control	211	Low	–	High
Black et al. [30]	Case-control	587	Low	–	High
Dourado et al. [31]	Before and after	452344	Moderate	Detection	Medium
Madsen et al. [32]	Before and after	537303	Moderate	Detection	High
Freeman et al. [15]	Before and after	375	High	Attrition	Low
Jonville-Bera et al. [33]	Ecological	9205483[a]	Moderate	Selection	Medium
Taylor et al. [34]	Case-only	498	Moderate	Confounding	Medium

[a] Estimated number of vaccine doses.

3.4. Time-series (before and after)

There were three studies with a before and after design. The study by Dourado et al. assessed a possible association between mumps Urabe-containing MMR and aseptic meningitis and reported a positive association [31]. In the study by Freeman et al. [15], 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 old).

The study by Madsen et al. reports no increased risk of autism or other autistic spectrum disorders between vaccinated and unvaccinated children [32].

In the study by Dourado et al. [31], limited error was introduced by estimation of the denominator from a prior census and the number of doses administered (as opposed to supplied), in the mass vaccination program. In the study by Freeman et al. [15], the number of completed weekly diaries varied over the 8-week study period with no indication of whether the losses occurred pre or post-vaccination. In addition, there is an overall attrition rate of 33%.

The interpretation of the study by Madsen is 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 [32].

3.5. Ecological study

The single ecological study included assessed the evidence of association between MMR or any of its component vaccines, and the onset of thrombocytopenic purpura (TP) [33]. The study concludes that the evidence favors an association, but in all cases TP appeared 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 discusses the weakness of relying on the passive reporting system for the identification of cases and acknowledges a possible underreporting of cases.

3.6. Case-only designs

The single included self-controlled case series study assessed clustering of cases of autism by post-exposure periods in a cohort of 498 (293 confirmed cases) children [34]. The authors report a significant increase of onset of parental concern at 6 months post-vaccination. The authors plausibly argue that this may be due to multiple testing caused by an unclear causal hypothesis and conclude that the evidence does not support an association with autism. The study demonstrates the difficulties of drawing inferences in the absence of a non-exposed population and a clearly defined causal hypothesis.

3.7. Overall methodological quality of included studies

The reporting of information on vaccine content and schedule varied considerably between studies. No study, across all designs, reported complete vaccine identification information including lot numbers, adjuvants, preservatives, strains, product and manufacturer. Six studies failed to report any vaccine strains [15,21,26,28,29,34], 13 reported all strains contained in the tested MMR [1,5,16–20,22,23,25,27,32,33], while 3 reported the strain for a single component of MMR only [24,30,31]. Complete information on the schedule, doses and route of administration was available for five studies [5,20,22,23,26].

Five recent studies reported definitions for all adverse events monitored [29–33], three of these were single event-specific studies [30,31,33]. Five studies had no definitions of any safety outcomes measured beyond a description of temperature measurement ranges [17,20,21,25,26]. Five studies had one outcome with a description [5,18,22–24], and seven studies had more than one outcome with a description [1,15,16,19,27,28,34]. Of the 16 studies that monitored temperature, 6 gave no further description either of a numerical range or a base reading [15,17,18,22,27,28].

Five studies reported no participants missing for adverse event monitoring [17,19,21–23]. In one case, it was not possible to determine if participants were missing [24]. Of the 16 studies with clearly missing unintended event data, 6 had less than 10% missing from all arms [16,18,20,29,32,34], 2 had between 11 and 20% missing [26,30], 6 had between 20 and 60% [1,5,15,25,27,28], and in 2 cases the number of subjects missing from both arms could not be determined [31,32]. Eight studies [1,15,16,20,25,27,34] provided inadequate explanations for missing data, including one in which no explanations were offered [25].

Information on study population, enrolment process was insufficient in 11 studies [1,5,15–17,20,21,23–25,27] and in a further 6 studies the population description raised doubts about the generalisability of the conclusions to other settings [18,19,22,28,31,33]. We are uncertain as to the power and generalisability of the findings from the single case-only design study [34].

4. Discussion

We found limited evidence of safety of MMR compared to its single-component vaccines from low risk of bias studies. The few studies least likely to be effected by systematic error point to a likely association with fewer upper respiratory tract infections, and no increased incidence of aseptic meningitis (for Jeryl–Lynn strain-containing mumps vaccine). Low risk of bias evidence does not support a causal association with Crohn's disease or ulcerative colitis, although this observation is based on a relatively small case-control study [29]. 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 is selection.

We used 'adequate explanation' to categorize reasons presented for missing data. Despite accepting explanations such as 'non-response to questionnaire' and 'medical records unavailable' as adequate, 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-randomized 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) [35], 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 subjects, although substantially justified by public health concerns about the effects of vaccination on the developing child, did lead us to exclude two potentially good-quality studies. Additionally the methodological quality tools used to assess the ecological, time-series and case-only designs to our knowledge have not 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.

As MMR vaccine is universally recommended, recent studies are constrained by the lack of a non-exposed control group. 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 universally used in public health programs. Whichever view is chosen, we believe that meaningful inferences from individual studies lacking a non-exposed control group are difficult to make. In our view, the methodology of systematic reviewing can be adapted to the topic of vaccines safety and provides an additional powerful tool for synthesizing evidence. The main advantages of such a method are the search for all relevant evidence its interpretation weighted by its quality and the pre-defined contribution of each study design to causality assessment. Although efforts to identify all relevant studies have been made, the authors would like to hear from anyone who has knowledge of studies not included in the review meeting our inclusion criteria.

The safety record of MMR is possibly best attested by its almost universal use and 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 post-marketing.

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