Case control study

A case-control study of autism and mumps-measles-rubella vaccination using the general practice research database: design and methodology

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Published: 15 February 2001
BMC Public Health 2001, **1**:2
Received: 22 January 2001
Accepted: 15 February 2001
This article is available from: http://www.biomedcentral.com/1471-2458/1/2

Abstract

Background: An association between mumps-measles-rubella (MMR) vaccination and the onset of symptoms typical of autism has recently been suggested. This has led to considerable concern about the safety of the vaccine.

Methods: A matched case-control study using data derived form the United Kingdom General Practice Research Database. Children with a possible diagnosis of autism will be identified from their electronic health records. All diagnoses will be validated by a detailed review of hospital letters and by using information derived from a parental questionnaire. Ten controls per case will be selected from the database. Conditional logistic regression will be used to assess the association between MMR vaccination and autism. In addition case series analyses will be undertaken to estimate the relative incidence of onset of autism in defined time intervals after vaccination. The study is funded by the United Kingdom Medical Research Council.

Discussion: Electronic health databases offer tremendous opportunities for evaluating the adverse effects of vaccines. However there is much scope for bias and confounding. The rigorous validation of all diagnoses and the collection of additional information by parental questionnaire in this study are essential to minimise the possibility of misleading results.

Background

The epidemiology of autism

Autism is a pervasive developmental disorder characterised by abnormalities in the development of language, communication abilities, and social interactions and by a pattern of restricted play and behaviour which tends to be highly repetitive, unimaginative and rigid [1]. By definition, the abnormalities must be present by the age of three years, although the diagnosis is usually not made until the age of four or five years [2]. In studies of the consistency of diagnosis there has been a high consensus between psychiatrists and coding instruments [3].

The age at which parents first recognise an abnormality is variable, with 40% of autistic children having shown typical features by the age of one year and most by the age of two years[4]. This age is influenced by the degree of associated mental retardation and birth order (the less severe and first born children tending to have later age of parental recognition) [5]. Most population-based studies have found a prevalence of autism between 5 and 10 per 10,000 children [6].

MMR vaccination and autism

In 1998 a link was suggested between mumps-measles-rubella (MMR) vaccination and autism [7]. This was based on an uncontrolled case series of 12 children referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. It was suggested that the gastrointestinal and developmental symptoms were a syndrome that could have been triggered by MMR vaccination. The study was widely criticised [8,9] but generated considerable media interest [10] and led to a small fall in MMR coverage in the United Kingdom [11]. A larger case series of 60 children with the same combination of clinical findings has recently been published [12].

Since the first study by Wakefield et al, a number of published studies have looked specifically at this issue. In a small study from Finland, among 31 children who had reported a gastrointestinal adverse reaction to MMR vaccination, none had subsequently developed signs of autism [13]. A similar larger study looked at all notified serious adverse events following MMR vaccination in Finland over a 14 year period [14]. There were no new cases of autism among 173 notified adverse events. However such routine passive surveillance systems have a number of weaknesses for epidemiological studies [15]. There is no control group, the quality of the data may be suboptimal and detecting an effect depends entirely on clinicians believing a new illness was due to vaccination. In Sweden no increase was apparent in the incidence of autism following the introduction of MMR vaccination [16]. Both these studies included small numbers of children with autism and had limited ability to assess the link between MMR vaccine and autism. The United Kingdom Committee on Safety of Medicines set up a working party to assess parental and medical reports of children who had developed autism, Crohn's disease or similar disorders following MMR vaccination. The Working Party Report was, by its own description, solely a descriptive account of those children whose parents had sought legal advice about possible vaccine damage [17]. The Report highlighted bias in the way affected children were selected for inclusion in the study and the lack of any control group before concluding that they could not prove or refute the suggested associations between MMR vaccine and autism. A single large high quality epidemiological study has been published [18]. This study included 293 children with confirmed autism from North Thames health districts. From time series trends analysis, age of diagnosis in vaccinated and unvaccinated groups and a case series analysis, the authors concluded there was no evidence to support an association. The study did find a positive association between MMR vaccination and first parental concerns in the first six months following vaccination. Although the authors considered that this finding was likely to be either a chance finding or due to inaccuracy in recalling the date of onset of symptoms, this interpretation has been disputed [19]. It was also suggested that because the study only considered relatively short risk periods after vaccination, a causal link may have been missed [20]. The authors of the study have undertaken a re-analysis looking at longer post vaccination risk periods, and again found no evidence to support a link between MMR vaccination and autism (Farrington CP, personal communication).

In the light of continuing concern about the proposed link between MMR vaccination and autism [21,22,23,24,25,26] we plan to undertake a case-control study using data derived form the General Practice Research Database.

Objectives

The study has two linked objectives with respect to MMR vaccination. Firstly to determine if autistic children are more likely to have received MMR vaccine prior to disease onset. Secondly to examine whether there is any association between clinical onset of disease and the timing of MMR vaccination.

Materials and methods

The General Practice Research Database (GPRD)

The GPRD (previously known as the VAMP Research Bank) was set up in 1987 and is now held by the Medicines Control Agency [27,28]. It contains complete prescribing and diagnostic information from a large number of general practices and is the largest source of continuous data on illness and prescribing habits in the United Kingdom. Over 200 published studies have been completed using the database. Participating general practitioners were given instruction over a 12-month period regarding standardised recording of clinical information into their computing systems. The general practices are broadly representative of all practices in the United Kingdom in terms of geographical distribution and size and the age and sex distributions of the population included in the GPRD are similar to the whole United Kingdom population [29]. The data available directly from the database include all drug prescrip-

tions and their indication, a record of every consultation and of every diagnosis. The data collected is audited regularly and the participating general practices are subjected to a number of quality checks. Of the practices contributing to the database, about 280 practices, with a combined population of around 2.1 million patients currently pass these rigorous quality checks. The quality of the information in the database has been validated in a number of independent studies and has been found to be high [30,31,32,33,34,35].

The general practitioners keep all referral letters, hospital discharge summaries and other clinically relevant letters in a manual file. In addition to the electronic health record, questionnaires can be sent to patients (or their parents) via general practitioners, and copies of letters relating to referrals and hospital care can be obtained. The data are held anonymously in the central GPRD database, with patient identifiers removed.

Identification of affected children

Children with putative autism will be identified by searching the whole electronic record of all people included in the GPRD for diagnostic codes which possibly relate to a diagnosis of autism. MMR vaccine was introduced in the United Kingdom for all children aged 12 to 15 months in October 1988. An MMR catch-up campaign was also launched for older children in 1988. We will separately identify those children with putative autism born after and before mid-1987, which separates out those children likely to have received the MMR vaccine around the age of 1 year and those likely to have received it at a later date. Separate analyses will be conducted on these two groups. Although all major past diagnoses are recorded in practice computers when new patients register with practices, such recording may be incomplete. To overcome this potential problem, we will identify children first diagnosed when they were registered with practices participating in the GPRD. Children diagnosed prior to registration with the GPRD will be analysed separately with their matched controls. The results from these two groups will be pooled if they are similar.

Identification and selection of controls

For each affected child we will sample two groups of matched controls from the GPRD. The first group will consist of five people with no record of autism matched on age (± one year), sex and practice. Matching is this group aims to control for possible confounding by the general practice with which participants are registered. The second group will be of similar size and will be matched on age and sex but not on practice, to avoid the possibility of overmatching. For children diagnosed while registered with a GPRD practice, the date of diagnosis will be called the index date. The controls will be selected from those patients registered with the GPRD on the index date of the affected child to whom they are matched. We will not be able to apply the same method for selecting controls for children with autism diagnosed prior to registering with a practice participating in the GPRD because they will not have an index date. Therefore the matched controls for children diagnosed prior to registering with a practice participating in the GPRD will be selected from all patients registered with the GPRD on the date the affected child registered with the GPRD.

Questionnaire to parents of affected children and controls

Subject to ethical approval, a questionnaire will be sent to the parents of all affected children and to two controls per affected child, one matched on practice and one not matched on practice and closest in age to the affected child. The questionnaire to parents of children with autism will include an autism screening questionnaire[36] and will solicit information on: the date of first symptoms of autism and earliest date of parental concern about symptoms possibly related to autism; the educational status of the child; the knowledge and beliefs of parents regarding the causes of autism; and family history of pervasive developmental problems. In addition the questionnaire will specifically ask about family history of pervasive developmental problems, genetic disorders and about regression (loss of skills) allowing us to classify affected children into those with reported regression and those with no regression.

For both affected children and controls the questionnaire will include questions about: the socioeconomic status of the parents; birth order and family size; history of bowel disturbance in the child; and vaccination history.

Diagnosis: definition and validation

As a first step to validate the diagnoses, copies of all hospital summaries will be requested from the GPs concerned. Previous studies using the GPRD have obtained full copies of hospital summaries on over 90% of patients still registered with a collaborating practices [35,37]. We will obtain copies of letters relating to both autism and to all other reasons for hospital investigation or attendance, including bowel investigations and inflammatory bowel disease (see below). The basis for the diagnosis of autism, evidence of associated genetic disorders and the date of first attendance for possible autism will be extracted from the records.

There is strong agreement among child psychiatrists about concepts of and operational definitions for autism [3]. We believe that no child will be labelled as autistic in the GP record without referral to child psychiatry servic-

es. Two studies have specifically documented the completeness of the information in the GPRD about referrals occurring and their outcome [30,31].

All information about children possibly affected by an autistic spectrum disorder, including information about the current educational status of the child from the questionnaire, will be reviewed independently by two child psychiatrists. They will use DSM-IV / ICD 10 research diagnostic criteria to define autistic spectrum disorders, and will attempt to subtype the disorders according to their phenomenology. In particular they will separate and sub-classify autistic disorder in DSM-IV or childhood autism in ICD-10, Asperger's disorder, atypical autism / pervasive developmental disorder not otherwise specified, and other forms of pervasive developmental disorders (i.e. Rett's syndrome and childhood disintegrative disorder). This will be achieved by rating the developmental abnormalities on a symptom basis and then applying diagnostic algorithms. They will also make an overall global judgement about the clinical pattern and rate their confidence in this final diagnostic judgement in order to allow for difficult or improbable diagnoses to be treated separately. Inter-rater reliability estimates will result from this exercise. Separate analyses will be carried out for children with a definite diagnosis and for children with a definite or probable diagnosis in order to assess the potential impact of misclassification.

Exclusion of affected children with an alternative aetiology

Inclusion of affected children who have an established alternative aetiology may bias the estimated odds ratio for the association between vaccination and adverse outcome towards unity [38]. Some children will have medical disorders thought to have a causal association with autism (fragile X disorder, tuberous sclerosis, phenylketonuria, congenital rubella) and will be excluded. A recent review estimated that this will lead to the exclusion of at most 6% of affected children [6].

Determination of date of onset

From the GP record, hospital letters and parental questionnaire for each affected child we will extract the date of:

• first attendance to the GP with symptoms or problems potentially relating to a future diagnosis of autism, such as behavioural difficulties (e.g. sleeping or eating difficulties), delay in motor development and milestones, delay in language development, abnormalities in social development (for example delayed smiling, lack of reciprocity, lack of anticipation, odd behaviours);

• first concerns or symptoms as recorded in the hospital letters;

• definitive diagnosis from the hospital letters;

• first parental concern of symptoms of autism collected retrospectively.

The first three dates will be based on existing records and both the date and the relationship of the date to the timing of MMR vaccination will not be affected by errors of memory. First parental concerns about autism may have occurred many years ago and some error in accurately remembering the exact date is to be expected. In addition, it is possible that parental recall of the date of onset of symptoms relative to the timing of MMR vaccination may be affected by the recent publicity about a possible link between MMR and autism. The proposed link between MMR vaccine and autism was first publicised in February 1998. After this date public and media concern about the possible link may have affected the likelihood of a child attending the GP with problems and in particular the timing of the presentation relative to MMR vaccination. Children with a date of first symptoms after February 1998 will be analysed separately to assess the effect of possible bias.

For the main analyses the date of onset will be the earliest of either the date of first attendance to the GP with symptoms potentially relating to a future diagnosis of autism or the date of first concerns or symptoms as recorded in the hospital letters.

Assessment of exposure

Exposure to MMR vaccine will be extracted from the GP electronic record. This method has two advantages. Firstly it will avoid recall bias either about vaccine status or about the timing of vaccination relative to the onset of symptoms. Secondly there are good reasons to expect the vaccine data to be complete. All general practitioners participating in the GPRD undertake to include all medications prescribed or administered in the computerised record. In addition, United Kingdom general practitioners have a financial incentive to accurately record childhood vaccination status. Finally there is excellent agreement between prescribing data from the GPRD and national data from the Prescription Pricing Authority[34].

Confounding

Potential confounding factors include those factors known to affect uptake of vaccination in the United Kingdom: the knowledge and attitude of the health care provider; presence in the family of a child with a major illness; social class; birth order; family size; education of

parents; and religion[39]. Matching on general practice for one of the control groups will control for confounding by health care provider. Data on the other potential confounding factors will be derived from the questionnaire to parents of affected children and controls. Very little is known about factors associated with autism and its diagnosis, although a family history of autism is a clear risk factor. Age of parental recognition is known to be associated with sibship order. We will be collecting information on these variables in the questionnaire. These potential confounders will be controlled for in the case-control analysis and in the case series analysis.

Analyses

Case-control

Conditional logistic regression will be used to undertake matched case-control analyses. We will initially undertake a series of univariate analyses. Factors that appear to be associated with autism ($P < 0.2$) will be carried forward to a multivariate model. Likelihood ratio tests will be used for all tests of significance. Two analyses will be carried out. The first will estimate the odds ratio for the development of symptoms in specific time periods after vaccination with MMR. This method provides an alternative approach to the case series approach outlined below. The second will assess exposure to MMR vaccine at any time prior to symptom development. This analysis differs from the case series approach in that no assumption is required about the likely interval from vaccination to disease onset if there is a causal association.

We will examine the effects of the age matching: comparing the results for those children very closely matched on age (for example within 6 months) with the results for any children less well matched on age.

The two control groups will be analysed separately. If the odds ratios differ substantially, this will indicate that practice was an important confounding factor (i.e., that some practices were better at diagnosing autism and also had a higher vaccine coverage). The results for the two groups will then be reported separately, but we will consider the correct result to be that from the practice matched group. If the results for the two groups are similar, they will be pooled. In this situation it is possible we may have "over-matched" in the practice matched group, but this will only lead to a loss of power, not to a bias in the estimate.

Case series

The case series uses data on affected children only to estimate the relative incidence of clinical events either in a defined interval after vaccination compared to time periods outside this defined interval, or at any time after vaccination compared with the time period before vaccination [40,41]. The method has been used to estimate the relative incidence of febrile convulsions following DTP and MMR vaccines [42] and was also used in a recent study of the onset of autism following MMR vaccine [18]. We will examine periods of 1 month, 2 months, 4 months, 6 months and 1 and 2 years after vaccination. The reference period for each individual will consist of every month from birth up until February 1998, which was when the possible link between MMR vaccine and autism became widely known, excluding the post-vaccination period being studied. All analyses will be finely stratified for age, the exact stratification will depend on the age distribution of the affected children.

The two approaches estimate different parameters. The case-control approach will estimate the odds ratio for whether children who are vaccinated have an increased chance overall of developing autism than children who are not vaccinated. The case series will estimate the relative incidence of autism in the period following MMR vaccination.

Power

We estimate we will be able to include a minimum of 400 children with a diagnosis of autism in the analyses. Over the entire study period we estimate the proportion of children in the control group who will have received MMR vaccination to be around 85% [11]. With 5 controls per affected child in the case-control analysis we will be able to detect the following minimum odds ratios for the association between autism and MMR vaccination with 90% power at the 5% significance level: 1.8 if average MMR coverage among controls is 85%, or 2.0 if average MMR coverage among controls is 90%. For the case series analysis assuming an 85% vaccine coverage rate (a conservative estimate), we will have 90% power at the 5% significance level to detect a minimum relative incidence for autism of 1.6 in the 1 month following MMR vaccine.

Ethical approval

The Scientific and Ethical Advisory Group is a central ethical committee specially set up by the Department of Health to oversee use of the GPRD. They have approved the study, subject to approval of the questionnaire, as have the ethics committee of the London School of Hygiene and Tropical Medicine. The use of confidential patient data in this study is fully within the recent guidelines from both the United Kingdom Medical Research Council [43] and the General Medical Council [44] about the use of personal information in medical research.

Discussion

Electronic databases offer several important advantages for epidemiological studies of adverse events from vaccination. All people affected by the adverse event (or a random sample) can be drawn from existing records, usually avoiding the problem of ascertainment being linked to exposure, although bias may not entirely be removed if people affected were diagnosed after the hypothesis was known. As controls can be sampled from all other participants in the database, biased selection of controls is less likely to occur. Records of date of vaccination and onset of symptoms, are also less likely to be biased, in particular if they precede the hypothesis coming into public domain. The major disadvantage of such databases is that data quality and completeness may not always be optimal. In particular, all diagnoses of autism will not have been made using the same criteria applied in a consistent manner.

Vaccines are without doubt among the most effective public health interventions, but thorough investigation of suspected adverse effects is necessary. Case-control studies using electronic health databases offer a uniquely efficient method for evaluating adverse effects of vaccines. However they also offer scope for bias and confounding to produce misleading results. The rigorous validation of all possible diagnoses and the collection of additional information by parental questionnaire in this study will be both time consuming and expensive, but we view this as essential to minimise the possibility of biased results.

Acknowledgements

The study is funded by the United Kingdom Medical Research Council. Liam Smeeth is funded by a Research Fellowship from London NHS Research and Development Directorate.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/content/backmatter/1471-2458-1-2-b1.pdf