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MMR and autism: further evidence against a causal association

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Abstract

The hypothesis that MMR vaccines cause autism was first raised by reports of cases in which developmental regression occurred soon after MMR vaccination. A previous study found no evidence to support this hypothesis. It has recently been suggested that MMR vaccine might cause autism, but that the induction interval need not be short. The data from the earlier study were reanalysed to test this second hypothesis. Our results do not support this hypothesis, and provide further evidence against a causal association between MMR vaccination and autism. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The hypothesis that autism might be caused by MMR vaccine was first proposed in a 1998 study by Wakefield et al. that reported a close temporal association between MMR vaccination and first appearance of autistic spectrum developmental disorders, typically developmental regression [1]. So far, no firm epidemiological evidence has been published in support of such a link. In particular, a large population-based study did not support a causal association [2]. Nevertheless, the controversy surrounding a possible link between MMR vaccine and autism has continued, with detrimental repercussions on MMR vaccine coverage [3].

A striking feature of the original Wakefield study, based on only 12 children, was the very close temporal association between vaccination and autism: the interval between receipt of MMR and first behavioural symptoms varied from 24 hours to 2 months. The parents or physician of eight of the 12 children linked the onset of their child's behavioural problems to receipt of MMR vaccine. In these eight the mean interval from MMR to onset was 6.3 days, range 1–14. Two children also received a measles vaccine. All children had a history of normal development followed by loss of acquired skills; in some cases the onset and course of regression was precipitous.

Taylor et al. set out to test the hypothesis suggested by Wakefield et al.'s data: namely, that onset of autistic developmental disorder, particularly developmental regression, is caused by MMR vaccination, and that the onset of symptoms occurs in close temporal association with vaccination. Evidence for an increased incidence following vaccination was sought using the case–series method, a powerful technique developed in order to evaluate short-term risks following transient exposures. Three outcome measures were used: regression, first parental concern, and autism diagnosis. In accordance with the Wakefield data, short risk periods of up to 6 months after vaccination were investigated for evidence of clustering of regression. In order to accommodate diagnostic delays, longer risk periods were used for parental concern and autism diagnosis. We found no evidence to support a causal association. We concluded that the most likely explanation of the close temporal association observed in the 12 cases of the Wakefield study is a combination of selection bias and chance

Abbreviations: MMR, measles, mumps and rubella.

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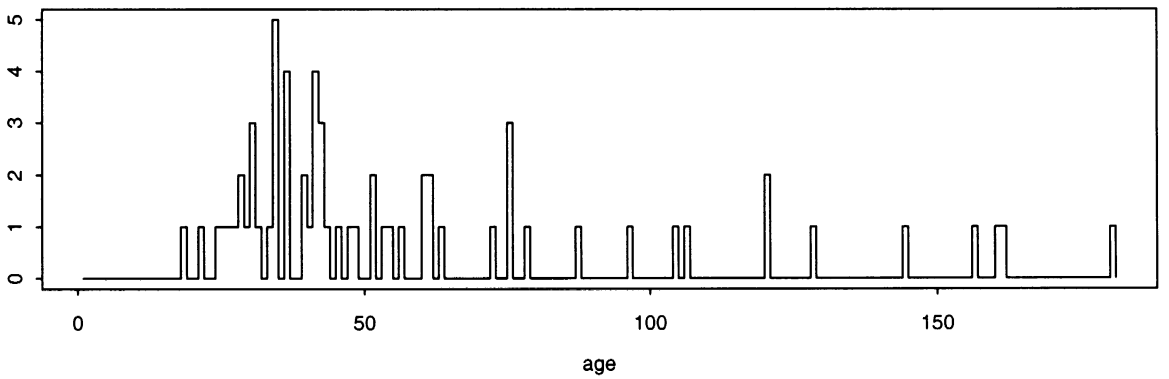

Fig. 1. Distribution of age at autism diagnosis (in months) of 64 unvaccinated children with autism.

association, the age at regression typically coinciding with the age at which MMR vaccine is administered.

It has recently been suggested that owing to autism being a chronic condition with progressive onset, delays in diagnosis, and inaccurate parental recall, we may have failed to identify a true causal link with MMR vaccination by confining ourselves to short risk periods [4]. As noted above, this choice was made in response to the time intervals reported by Wakefield et al. [5]. In the present paper, we reanalyse the data of Taylor et al. to test the hypothesis that MMR vaccination causes autism, without pre-specifying any fixed time interval after vaccination in which the risk of autism might be increased.

2. Methods

The data have been described in [2]. As in our earlier paper, we used the self-matched case series method [6,7]. The method is appropriate for this particular data set because vaccination ages span the observation pe-

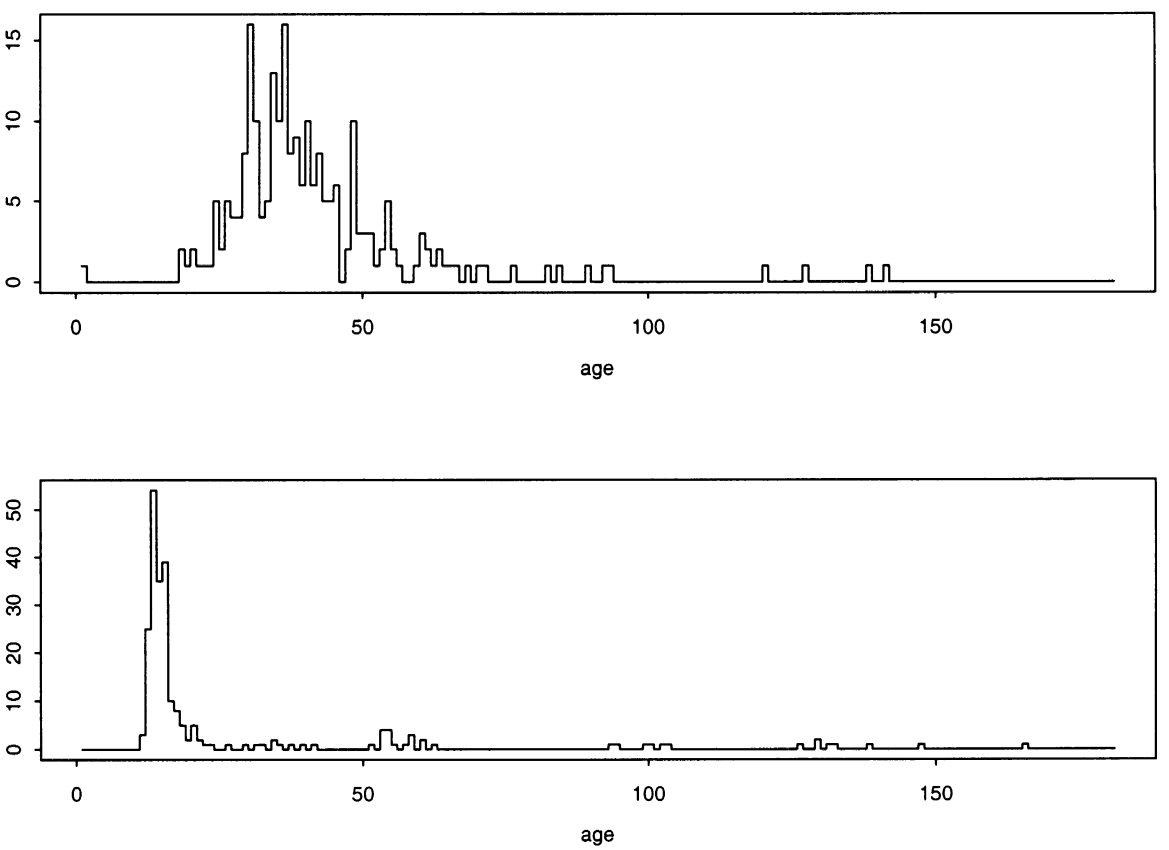

Fig. 2. Distribution of (top) age at autism diagnosis and (bottom) age at vaccination (in months) of 231 children with autism who received a single dose of MMR vaccine.

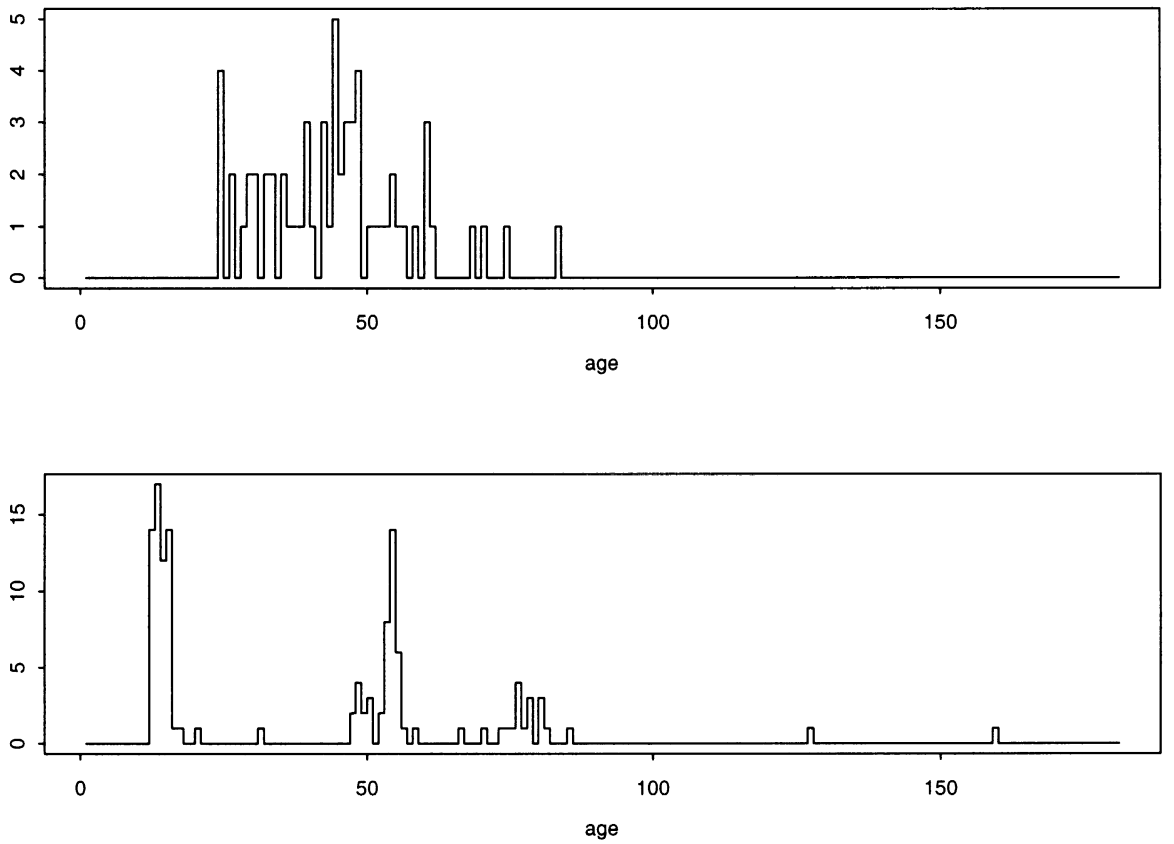

Fig. 3. Distribution of (top) age at autism diagnosis and (bottom) ages at vaccination (in months) of 62 children with autism who received two doses of MMR vaccine.

riod and an appreciable number of cases are unvaccinated. In consequence the risk period can be extended without substantial loss of power, while controlling for age. We used the same age groups as in [2]. In addition, we included a 16-level factor for calendar time, taking distinct values in the period 1979–1983 and in each subsequent calendar year. The observation period for each case was defined as the time from birth to age 191 months or August 1998 inclusive, whichever was earlier. The main hypothesis we investigated was whether MMR vaccination increased the risk of autism at any time after vaccination. For this hypothesis we used any time after any MMR vaccine as the risk period. We also undertook analyses for arbitrarily selected post-vaccination risk periods of 0–59 months for autism diagnosis, 0–35 months for parental concern and 0–23

Table 1
Relative incidence and number of events in risk periods after vaccination with one or more MMR vaccines or one or more MMR, single-antigen measles, and combined measles plus rubella vaccines, by event type in children with autism.

Event and post-vaccination risk period (months)	MMR vaccine(s)		Any measles-containing vaccine(s)	
	Relative incidence 95% CI	Number of events	Relative incidence 95% CI	Number of events
Autism diagnosis (n = 357)				
<60	1.24 (0.67, 2.27)	254	0.96 (0.52, 1.77)	296
Any time after vaccine	1.06 (0.49, 2.30)	263	2.03 (0.80, 5.18)	308
Parental concern (n = 326)				
<36	0.83 (0.50, 1.36)	175	0.92 (0.56, 1.49)	209
Any time after vaccine	0.76 (0.45, 1.27)	175	0.89 (0.54, 1.48)	210
Regression (n = 105)				
<24	0.76 (0.33, 1.71)	56	0.98 (0.46, 2.11)	67
Any time after vaccine	0.66 (0.26, 1.66)	59	0.81 (0.35, 1.91)	71

months for regression. These are considerably longer than those previously investigated. As previously, we repeated the analyses for any measles-containing vaccines.

3. Results

For the 357 cases with autism diagnosis (core and atypical), the observation periods had median 89 months, maximum 191; the oldest age at diagnosis was 180 months; 64 cases did not receive any MMR; 43 cases with a single dose of MMR received it after age 2 years, at median age 57 months, maximum 165 months; 62 cases received a second dose of MMR, at median age 54 months, maximum 159.

Figs. 1–3 show the distribution of age at autism diagnosis and age at vaccination for children who received zero, one, or two doses of MMR vaccine. In interpreting the distributions of age at autism diagnosis, allowance should be made for the different lengths of follow-up: for example, the unvaccinated cases tend to have been born earlier, prior to the introduction of MMR vaccine, and hence have longer follow-up times. This affects the tails of the distributions and hence their mean (see [2] for more detailed analysis). In all three groups, however, most diagnoses are made between ages 24 and 48 months of age.

The relative incidences are shown in Table 1. The estimates reported are all adjusted for temporal effects, but are similar whether or not the time factor is included in the model. In all instances the relative incidence is not significantly different from 1, indicating no association between vaccination and autism in the subsequent risk periods.

4. Discussion

Our results do not support the hypothesis that MMR or measles-containing vaccines cause autism at any time after vaccination. The point estimates are generally close to unity, with narrow confidence intervals, indicating that the analyses have good power. In addition to its simplicity, the self-matched case series method has the advantage of avoiding any bias due to individual-level confounding, as might occur in cohort or case-control studies, for example due to confounding of vaccination and unmeasured risk factors for autism [6,7].

Our study used data on all MMR vaccines, including those given later than the recommended schedule, as part of the catch-up programme, or as booster doses. It has been suggested [8] that second exposures to MMR vaccine might further increase the risk of autism. Our results do not support this contention.

The results also demonstrate that, in the right conditions, the case series method can be a powerful tool in the analysis of delayed reactions to vaccines. The case series method was originally developed specifically for investigating acute reactions. Generally, as the risk interval is extended, the method loses power. However, when the spread of ages at vaccination is substantial, or when a proportion of cases are unvaccinated, or a combination of both as is the case here, high power may be achieved with long risk intervals.

In conclusion, the results presented here, combined with those we obtained earlier [2], provide powerful evidence against the hypothesis that MMR vaccine, or indeed any measles-containing vaccine, causes autism at any time after vaccination.

References

[1] Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998;351:637–41.

[2] Taylor B, Miller E, Farrington CP, Petropoulos M-C, Favot-Mayaud I, Li J, Waight PA. Autism and measles, mumps and rubella vaccine: no epidemiological evidence for a causal association. Lancet 1999;353:2026–9.

[3] Begg N, Ramsay M, White J, Bozoky Z. Media dents confidence in MMR vaccine. Br Med J 1998;316:561.

[4] Roger JH. The MMR question. Lancet 2000;356:160–1 corresp.

[5] Taylor B, Miller E, Farrington CP. Response to the MMR question. Lancet 2000;356:1273 corresp.

[6] Farrington CP. Relative incidence estimation for vaccine safety evaluation. Biometrics 1995;51:228–35.

[7] Farrington CP. Case series analysis of adverse reactions to vaccines: a comparative evaluation. Am J Epidemiol 1996;143:1165–73.

[8] Wakefield A.J. Testimony before Congressional Oversight Committee on Autism and Immunisation. 106th Congress of the United States of America, House of Representatives Committee on Government Reform, 6th April 2000.