Psychological Medicine, 2004, **34**, 543–553. © 2004 Cambridge University Press
DOI: 10.1017/S0033291703001259 Printed in the United Kingdom

No evidence for links between autism, MMR and measles virus

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ABSTRACT

Background. We examined whether, in the UK, there is an increased risk of autism (AD) following exposures, in early life, to: (1) wild measles; (2) live attenuated measles, alone or in combination as MMR; and (3) the alteration of the mumps strain within MMR.

Method. We conducted time trend analyses of 2407 AD subjects born between 1959–93; and for comparison, 4640 Down's syndrome (DS) subjects born between 1966–93. Between 1968–86, we correlated variations in AD and DS births with wild measles incidence. Between 1959–93, we tested for abrupt changes in the long-term AD birth trend for the effects of introducing: (1) monovalent measles vaccines in 1968; (2) MMR immunization in 1988; and (3) the 'overnight switch' from mixed use of Urabe MMR to exclusive use of Jeryl–Lynn MMR in 1992. Incidence rate ratios (IRRs) were used as measures of association.

Results. We found no significant association between AD births and exposure (prenatal and postnatal up to 18 months age) to population rates of measles infections, and no 'step-up' increase in AD births associated with the introduction of monovalent measles and MMR vaccines, and changing mumps strain. An unexpected reduction in AD births of 21% (95% CI 6·9–33·3%; $P = 0{\cdot}005$) among the post-1987 birth cohorts was detected.

Conclusion. No increased risk of AD following exposures to wild measles and vaccinations with monovalent measles, and Urabe or Jeryl–Lynn variants of MMR was detected. The precise meaning of the detected AD births reduction is unclear. Our study cannot exclude rare complications of MMR, given its correlational design.

INTRODUCTION

A case-series study reporting a temporal association between the onset of autistic symptoms, gastro-intestinal symptoms and MMR immunization raised the concerns of measles and MMR as risk factors for autism (Wakefield *et al.* 1998). In subsequent tissue studies of autistic subjects, the investigators identified measles virus in the bowel walls (Kawashima *et al.* 2000); and reported the RNA sequences of measles viruses present in blood as consistent with vaccine strain (Uhlmann *et al.* 2002). A similar clustering of gastro-intestinal symptoms, developmental regression and autism has been reported in a US case-series in a testimony during congressional hearings (Krigsman, 2002). However, large epidemiological studies on autism and MMR have not hitherto detected any significant link (Taylor *et al.* 1999; Dales *et al.* 2001; Fombonne & Chakrabarti, 2001; Kaye *et al.* 2001; Madsen *et al.* 2002). Though Urabe strain of mumps virus in MMR might increase the risk of aseptic meningitis (Miller *et al.* 1993; Dourado *et al.* 2000), it was replaced by the Jeryl–Lynn strain in the MMR vaccine in the UK in 1992

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(Balraj & Miller, 1995). While the debates on the validity of published evidence (Edwardes & Baltzan, 2001; Heller, D. 2001; Heller, T. 2001; Yazbak, 2001; Fombonne & Cook, 2003) and MMR safety (Edwardes & Baltzan, 2001; Heller, T. 2001; Yazbak, 2001) continue, uncertainty still exists among health professionals and parents (Evans *et al*. 2001; Petrovic *et al*. 2001), adversely affecting vaccine uptake. Nonetheless, both vaccine coverage and vaccine safety are serious public health concerns. In 3 consecutive years, US congressional hearings have been held to examine these issues.

Our large sample of 2407 autistic subjects presented an opportunity to examine the effect of MMR and wild measles infection. With increased statistical power, a smaller effect of the hypothesized association with autism should be detected, when compared with previous studies based on smaller sample sizes of 498 subjects born between 1979–92 (Taylor *et al*. 1999) and of 114 subjects born between 1988–93 (Kaye *et al*. 2001). Moreover, three important strands of the debate have not been covered by previous publications: the specific differential risks (1) of Urabe and Jeryl–Lynn mumps viral strains within the MMR; (2) of monovalent measles vaccines; and (3) of wild measles infections. That is, examining the risks of measles in isolation and in combination of other agents, as well as in the contexts of air-borne infection and vaccination.

In this study, we examined whether there is an increased risk of later developing autism associated with an exposure, early in life: (1) to wild measles epidemics; (2) to live attenuated measles virus, either alone or in combination; and (3) whether the alteration of the mumps component (Urabe or Jeryl–Lynn) within the MMR vaccine in UK in 1992 itself posed an additional risk.

METHOD

Subjects

Dates of birth of subjects with autistic disorder (AD) were obtained from the 1999 membership list of the National Autism Society (NAS) in the UK. The NAS is a nationwide family association for individuals with autism or autistic spectrum disorders, in operation since 1967 (Bolton *et al*. 1992). It is a charity organization partly funded by membership subscription, which requires annual renewal. As AD is associated with learning difficulties and many AD subjects are children, the annual subscription is usually made by parents or carers who supply the information on the dates of birth of AD subjects. The 1999 annual membership list contains the birth data of AD subjects whose membership subscription had been made that year. The NAS membership lists have been used for previous epidemiological studies (Bolton *et al*. 1992; Dassa *et al*. 1995). In the 1999 membership list, constraints in data protection of membership lists did not permit individual confirmation of diagnoses; thus subjects with 'autism' and 'autistic spectrum disorders' were grouped together as 'autistic disorder' (AD). No information on severity, diagnostic categories or history of regression was available from the NAS, which as a policy did not disclose personal information that would have permitted identification of or contacts with the families or AD subjects. We excluded births before July 1959, because of low rate of registration for individuals with autism over age 40. Post-1993 births were also excluded due to low rate of diagnosis and membership registration under age 5, leaving a total sample of 2407 subjects (1936 males, 468 females, three unrecorded).

We identified 4 week intervals as the most suitable time frame for our analyses. This was used as the denominator of the AD birth rates, yielding '4-weekly birth rates' instead of weekly or monthly birth rates. From July 1959 to December 1993, there were 450 4-weekly intervals.

To adjust AD births for population variations in birth rate, we obtained monthly live births statistics for England and Wales (Birth Statistics Series 1938–1994) from the Office of National Statistics (ONS) London. These monthly birth rates were mapped onto the four-weekly intervals so that monthly birth rates would contribute to each interval rate proportionally.

Comparison group

Down's syndrome (DS) has been used as a comparison group in autism research (Wing, 1969; August *et al*. 1981; Bolton *et al*. 1994; Piven & Palmer, 1999; Murphy *et al*. 2000). In keeping with previous autism research, we obtained the birth data for subjects with DS from the Down's

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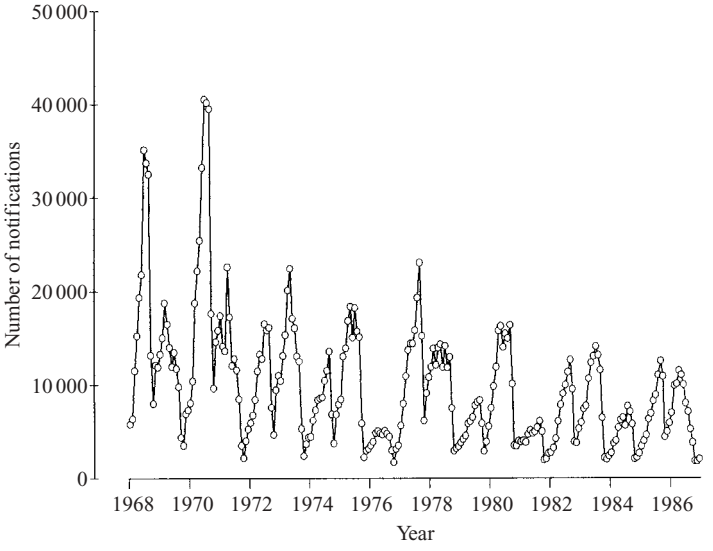

FIG. 1. Numbers of measles notifications (per 4-weekly period) in England and Wales reported to the OPCS between 1968–86. A change of measles incidence of 10 000 measles notifications appeared to represent the magnitude of the smaller measles infection cycles within the studied period, as the gradual introduction of monovalent measles vaccine from 1968 onwards, leading to declining peaks while the vaccine gained increasing public acceptance.

Syndrome Society membership list of 1999 as a comparison group. DS birth series was used as a comparison group in the analyses of the effect of wild measles infections. It was hypothesized that any valid association between wild measles infections and autism would not be replicated in the DS sample given the genetic aetiology of DS. Because of two historical changes in public vaccination programmes in the UK occurring in 1967 and 1987 (see Table 1), we restricted the analysis of wild measles infections to the period between 1968–86, in order to limit the potential confounding effects of changing vaccine programmes in our analyses.

DS birth series was not used as a comparison group in the subsequent analyses of the effects of MMR vaccines. This is because the DS series demonstrated a reduction in DS births after the introduction of 'triple-marker screening' (serum alpha-foetoprotein, human chorionic gonadotrophin and unconjugated oestriol) in the UK in the mid-1980s (Harris & Andrews, 1988), reflecting the effectiveness of this programme in antenatal DS diagnosis. As a result, a potential effect of MMR, which was introduced around the same time, could not be distinguished from the effect of triple-marker screening. Therefore, we did not employ the DS series as a comparison group for assessing the effect of MMR. Furthermore, the DS series could also not be used for assessing the effect of monovalent measles vaccines, because all our DS subjects from the membership list were born after 1966. The DS list contained 4640 subjects (2534 males, 2106 females), born between January 1966 to December 1993. Of 4640 individuals, only 2372 subjects (born between 1968–86) were used in the wild measles analysis.

Infection data

For measles incidence, we obtained the weekly measles notifications in England and Wales between April 1967 and May 1988, reported to the Office of Population Census and Surveys (OPCS) available from the Office of National Statistics (ONS) (Notification of infectious diseases, 1968–1993). OPCS measles statistics in England and Wales had been validated as of high quality (Fine & Clarkson, 1982; Clarkson & Fine, 1985) and short delay between onset and notification (median delay = 5 days) (Clarkson & Fine, 1987). Measles notifications were collapsed into the same 4-weekly intervals as in the AD and DS birth data, thus yielding 'four weekly measles incidence rates', instead of conventional weekly or monthly incidence rates (as shown in Fig. 1).

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Table 1. *Measles vaccination periods investigated in the study*

Vaccination period	1	2	3	4
Measles vaccine available during the period	No vaccine	Monovalent measles vaccine	Trivalent MMR vaccine (mixed Urabe and Jeryl–Lynn)	Jeryl–Lynn MMR (no Urabe strain)
Event defining the start of the period		Introduction of measles vaccine in 1968	Introduction of MMR in 10/1988	Stopped Urabe strain MMR at 9/1992
Birth period during which children were eligible to the vaccine	7/59–12/67	1/68–12/86	1/87–8/91	9/91–12/93
Four-weekly intervals during the period, *N*	111	248	61	30
AD births during the birth period recorded by the NAS, *N*	194	995	673	545
DS births during the birth period recorded by the DSA, *N*	42	2372	1469	757

AD, Autism; NAS, National Autism Society; DS, Down's syndrome; DSA, Down's Syndrome Association.

Vaccination periods

The 1959–1993 period was divided in four separate periods, characterized by different vaccination programmes (Table 1). Monovalent measles vaccine was introduced in the UK in 1968, recommended for immunization between ages 1 to 2 years (Department of Health, 1972). MMR was introduced in October 1988 for children 12–15 months of age, with a catch up programme for those up to age 5 (Balraj & Miller, 1995). The uptake was high, increasing from 80% in 1988–89 to 91% in 1992–93 (Statistical Bulletin, 1998). During 'period 3', MMR containing the Urabe strain of mumps virus was used in 80% of vaccinated children whereas the Jeryl–Lynn strain was used in the remaining 20%. This period was characterized by the mixed use of MMR vaccines, though predominantly of Urabe variant. The beginning of 'period 4' marked the 'overnight' transition to the exclusive use of MMR containing the Jeryl–Lynn strain in the mid-September of 1992 (Balraj & Miller, 1995). The Department of Health in the UK replaced the entire stock of Urabe MMR as a precautionary measure following reported association of the Urabe strain MMR with aseptic meningitis (Balraj & Miller, 1995), which has subsequently been confirmed (Dourado *et al.* 2000).

Statistical analysis

For both AD and DS birth series, statistical analyses were carried out using Poisson regression modelling (McCullagh & Nelder, 1989). We adopted a two-stage procedure.

First, for each disorder time series, we identified a model ('base model'), which accounted for variations in population birth rate, seasonality and (smooth) long-term trend. This smooth long-term trend is intended to represent gradual changes in disorder incidence unrelated to the variables under investigation – i.e. long-term factors such as gradual change over time in diagnostic practice, referral pattern and case detection. To account for the fluctuating population birth rates (to which we assumed the AD and DS births counts to be increasing proportionally), we included the (log-) 4-weekly population birth rate in the model as an offset. For seasonal effects, we included a 12-level factor (one for each month). Furthermore, we modelled long-term trend (i.e. gradual temporal changes in registered birth counts unrelated to wild measles exposure and MMR, e.g. due to increasing diagnosis and registration) by using the Stata command 'fracpoly'. For a chosen degree of smoothness of the time trend function, this command provides a procedure which determines the best-fitting fractional polynomial of time (for details on fractional polynomials and the default functions considered: see Stata Corporation, 2001). The degree of the function was determined by adding further terms until there was no improvement in the model according to the likelihood ratio test at level 10%. Fractional polynomials are more flexible in their range of curve shapes than

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conventional polynomials, thus avoiding some 'edge effects' and 'waves' often found with higher order polynomials. By using this stepwise fractional polynomial procedure, we intended to minimize the chance of misidentifying gradual temporal changes (due to unrelated factors) as an abrupt 'jump', wrongly attributable as an effect of a new vaccine in our final analyses.

Secondly, the observed data were analysed against the respective identified 'base models' in order to investigate: (1) abrupt changes related to the introduction of different vaccine programmes; and (2) the effect of measles occurrences. This approach ensured adjustment for the confounding effects of seasonality, variations in baseline population birth rates and long-term trend in all final analyses.

We restricted the analysis of the effect of measles occurrences to births from period 2 only, in order to avoid confounding the effects of wild measles infections with that of changing vaccine programmes (see above). Because monovalent measles vaccines were introduced in 1967, we excluded from the analysis measles data for the period from 1959 to 1967; and because MMR was introduced for subjects born in 1986, we also did not analyse wild measles data after 1986. Hence, we developed two 'base models' for each disorder (AD and DS): (1) a model for the whole birth series (e.g. from 1959 to 1993 for AD), against which the effects of different vaccines were tested; and (2) a model for the middle section of the series from 1968–86 (i.e. period 2), against which the effects of wild measles infections were tested. Altogether, there were thus four different 'base models': for convenience, we referred them as 'AD base model 1' or 'DS base model 1' for the long birth series models, 'AD base model 2' or 'DS base model 2' for the short series models. The fit of these 'base models' was assessed by F test for the null hypothesis of zero fit and a dispersion estimate (for which a value of 1 indicates adequate fit of the Poisson model). All statistical analyses were carried out in Stata 7 (Stata Corporation, 2001).

(*a*) *Testing the effect of wild measles occurrences*

We hypothesized that if measles occurrences were associated with the risk of later developing AD, a new model containing an additional term representing the effect of measles notifications would explain variations in observed AD incidences better than the 'base model' without this term (i.e. 'AD base model 2'). Thus, we compared the model fit of these two models to test and estimate the effect of measles notifications. The same analyses were applied to the DS series.

The effects of measles notifications were assessed over 28 exposure windows, between conception and the approximate post-natal age of 17 months (i.e. 18 post-natal 4-weekly periods). It was not known during which developmental stage (pre-, peri- or post-natal) the measles virus could affect a child's risk of later developing autism. We thus tested for the effect of wild measles infection in specific 'exposure windows' (of a 4-weekly period per 'frame') from the time of conception to post-natal age 17 months. There were 28 such 'exposure windows', leading to 28 separate statistical tests (i.e. nine of 4-weekly periods before birth and 18 after birth, assuming full-term births). In order to adjust for multiple testing, we used the Bonferroni correction to maintain the experiment-wise significance level of 5% (i.e. we adopted a nominal significance level of $0{\cdot}05/28 \approx 0{\cdot}0018$).

The effects of wild measles infections were quantified by an incidence rate ratio (IRR), a measure of relative risk. This was defined as:

$$\mathrm{IRR} = \frac{\text{incidence of AD (4-weekly period) per reference measles plus 10 000 notifications (4-weekly)}}{\text{incidence of AD (4-weekly period) per reference measles notifications (4-weekly)}}.$$

In this instance, IRR measures the relative change in AD incidence per 10 000 extra measles notifications. We choose to measure the IRR per 10 000 extra notifications, since such an increase in measles incidence appeared to represent the magnitude of the smaller measles infection cycles in our data (see Fig. 1).

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(*b*) *Testing the effect of different vaccine periods*

We hypothesized that if vaccination period were associated with the risk of later developing AD, a new model containing an additional parameter (i.e. relating to an abrupt 'jump' in AD incidence at the start of the period) would explain variations in observed AD incidences better than the 'base model' without this term (i.e. 'AD base model 1'). Thus, we compared the model fit of these two models to test and estimate the effect of introducing a new vaccination regime.

Specifically, for AD incidence, to assess the effect of the monovalent measles vaccine, we tested for an abrupt change between period 1 and period 2. To assess the effect of the introduction of MMR, we tested for an abrupt change between period 2 and period 3. To assess the effect of the transition to the exclusive use of the Jeryl–Lynn strain, we tested for an abrupt change between period 3 and period 4 (for period definitions see Table 1).

The effects of different vaccination programmes were expressed as incidence rate ratios (IRRs). This is a measure of relative changes in disorder incidence rates, by comparing the incidence rate of a specific period with that of a reference period – for example, the effect of MMR was estimated as the incidence rate of period 3 relative to that of period 2. IRRs were estimated together with 95% confidence intervals.

RESULTS

Effect of wild measles incidence

There appeared no significant effect of wild measles infections on either AD or DS birth counts after Bonferroni correction.

Figs. 2(*a*) and (*b*) illustrate the IRRs, which represented the estimated effect of an extra 10 000 wild measles occurrences on the risks of later developing AD and DS respectively, after adjusting for population birth rate, seasonality and long-term trend. The figure shows the estimated IRRs together with 95% and 99·82% confidence intervals. The 95% confidence level corresponds to a test at the 5% significance level; while the 99·82% confidence level corresponds to the 0·18% significance test level after Bonferroni correction for 28 multiple tests. Confidence intervals overlapping IRR of 1 indicated no statistical significant association at their corresponding significance test levels.

Before Bonferroni correction, the effects for AD were detected at the 9th (estimated IRR = 1·18; Wald test, $Z = 2{\cdot}1$, $P = 0{\cdot}036$), 10th (estimated IRR = 1·21; Wald test, $Z = 2{\cdot}53$, $P = 0{\cdot}011$), 11th (estimated IRR = 1·19; Wald test, $Z = 2{\cdot}18$, $P = 0{\cdot}029$) and 18th (estimated IRR = 0·84; Wald test, $Z = 2{\cdot}84$, $P = 0{\cdot}005$) post-natal exposure window. But these effects were of small magnitude, had inconsistent directions, and failed to reach statistical significance after Bonferroni correction.

Likewise, for the DS series, effects were also detected for the 6th (estimated IRR = 1·13; Wald test, $Z = 2{\cdot}18$, $P = 0{\cdot}029$) and 7th (estimated IRR = 1·14; Wald test, $Z = 2{\cdot}38$, $P = 0{\cdot}017$) post-natal exposure window at the unadjusted level. Again, these effects failed to reach statistical significance after Bonferroni correction.

Effect of introduction of monovalent measles vaccines

There was no significant 'step-up' increase in AD birth rates related to the introduction of monovalent measles vaccines.

The effects of different vaccination programmes were expressed as incidence rate ratios (IRRs), with 1 or 100% indicating no difference in incidence rate of the disorder, while a value above represented an increase and one below a reduction in incidence rate.

After adjusting for birth rate, seasonality and long-term trend, we found no evidence of an abrupt change in AD counts between the vaccination periods 1 and 2 (IRR of period 2 relative to period 1 = 96·1%; 95% CI, 67·2–137·3%; Wald test, $Z = 0{\cdot}22$, $P = 0{\cdot}83$) in relation to the introduction of monovalent measles vaccines.

Effect of introduction of MMR vaccines

There was a significant decrease in AD counts associated with the introduction of MMR in 1988 (IRR of period 3 relative to period 2 = 78·8%, 95% CI, 66·7–93·1%; Wald test, $Z = 2{\cdot}81$, $P = 0{\cdot}005$) (see Fig. 3).

To examine further this apparent 'risk reduction' finding, we explored the sensitivity of the result to the changing definitions of period 3. We varied the commencement of this 'post-MMR period' as starting at 1/84, 1/85, 1/86,

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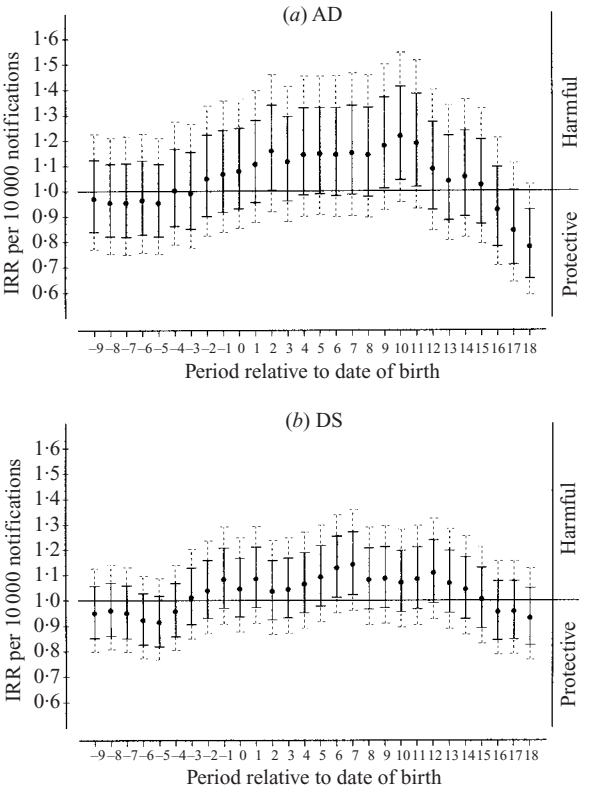

FIG. 2. Incidence rate ratio (IRR) with 95% and 99·82% confidence intervals (CI) of AD (*a*) and DS (*b*), showing the effect on birth rate per 10 000 measles notifications. The effect of wild measles on AD and DS birth rates are shown in the figures. The *x*-axis indicates the 4-weekly period relative to the time of birth. The measles incidence was measured as '4-weekly incidence rate'. The effects of measles occurrences on AD or DS births were represented by the IRRs. The solid-line error bars represented uncorrected 95% CIs for the effect of measles notifications on disorder incidence. The broken lines extended the intervals to the 99·82% confidence level, subjected to Bonferroni correction for multiple testing (Bonferroni corrected 0·05/28 = 0·18% significance level, thus 99·82% confidence intervals). IRR of the value 1 indicates no effect of association.

1/87, 1/88, 1/89, 1/90 respectively. The *P* values of such a 'step-down' effect for each year were 0·54, 0·43, 0·0001, 0·0029, 0·062, 0·13 and 0·45, respectively. *P* values mostly increased departing from the 1/87 date: the lowest lied between 1/1986 to 1/1988. Thus, the 'step-down' effect (i.e. a reduction of 21·2% in AD birth, 95% CI, 6·9–33·3%) appears to be confined to those born between 1986 to the end of 1987.

Change in MMR vaccine composition

The change in mumps virus strain in 1992 was not significantly associated with an abrupt change in AD incidence (Fig. 3(*c*), IRR of period 4 relative to period 3 = 109%; 95% CI, 95·4–124·7%; Wald test, $Z = 1{\cdot}26$, $P = 0{\cdot}21$).

DISCUSSION

The findings of this study did not support the three hypotheses tested.

First, during the 1968–1986 period, there appeared no significant association between AD birth rates and the population incidence of wild measles infections in the UK, after Bonferroni correction. This analysis examined the effects of wild measles in relation to 28 narrow windows of exposure, from conception to age of 18 months. Given the large sample size, statistical power is available to detect a small effect of wild measles. A clinically significant association existing between autism and wild measles infections (prenatal and post-natal) is unlikely.

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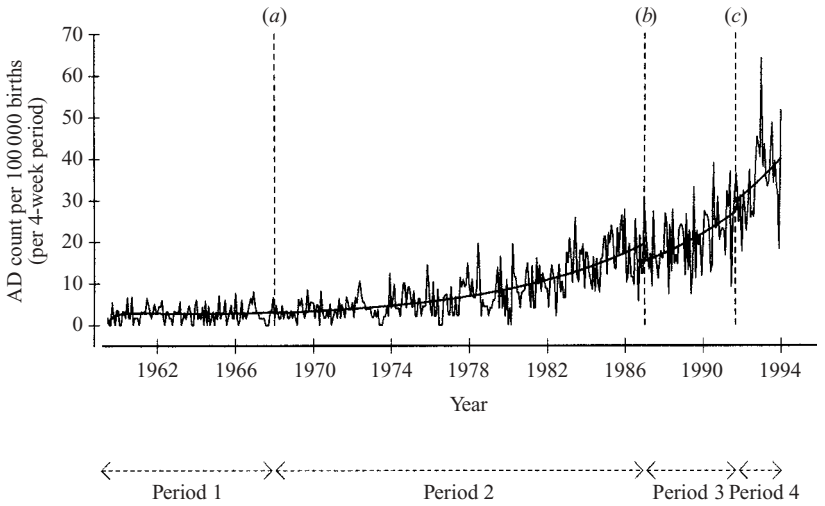

FIG. 3. Observed AD counts (per 100 000 life births per 4-weekly period) from July 1959 to December 1993. The smooth line shows the long-term temporal trend fitted by the Poisson model used for the whole series (smoothed for seasonality), plus the estimated effects of changes in vaccination regimes. The broken vertical lines indicate the four different vaccination periods (Table 1). For time: (*a*) IRR of period 2 relative to period 1 = 96·1%, 95% CI from 67·2 to 137·3%, $P = 0{\cdot}83$; (*b*) IRR of period 3 relative to period 2 = 78·8%, 95% CI from 66·7 to 93·1%, $P = 0{\cdot}005$; (*c*) IRR of period 4 relative to period 3 = 109%, 95% CI from 95·4 to 124·7%, $P = 0{\cdot}21$.

Nevertheless, Bonferroni correction can be considered conservative; four exposure windows in the AD series instead of two in the DS series reached the 5% significance level; and the sample size of the DS series was larger ($N = 2372$) than the AD sample ($N = 995$) of the corresponding period, thereby conferring narrower confidence intervals for the DS series. Yet, before Bonferroni correction, the detected effect size of 'harmful' association in AD subjects were small (IRRs ranged between 1·18 to 1·21), and were similar to that detected in the DS series (IRRs ranged between 1·13–1·14). In addition, the most significant effect in the AD series was 'protective' (IRR = 0·84; $P = 0{\cdot}005$). The cause of DS is genetic and the birth-rate of DS cannot be affected by the incidence of wild measles infection. Therefore, the significant findings at the 5% test significance level identified in the DS series were most likely attributable to Type 1 error (i.e. false positive findings due to multiple testing). Since both the sinusoidal patterns of periodicity and the effect sizes detected were similar (Fig. 2), Type 1 errors were the most likely explanation for both series.

Our results are consistent with the lack of demonstrated association of autism with measles-related diseases. Only one case–control study reported a significant association with exposure or clinical illness of measles infections (Deykin & MacMahon, 1979). However, several other viral associations were also reported in the same investigation, such as mumps and influenza infections. This pattern of findings might have reflected unmeasured confounders or biases. In general, the proportion of autistic cases attributable to known infections or medical disorders is very low (6%) as demonstrated in recent reviews of epidemiological studies (Fombonne, 2002, 2003), with no indication in these surveys that measles might play any causative role in autism.

Secondly, regarding the risks of attenuated measles virus, no 'step-up' increase in AD births has been detected in our study following the introduction of monovalent measles vaccines in 1968 and MMR in 1988. Our finding on MMR is consistent with other studies: five recent epidemiological investigations (Taylor *et al.* 1999; Dales *et al.* 2001; Fombonne & Chakrabarti, 2001; Kaye *et al.* 2001; Madsen *et al.* 2002); three reviews of vaccine safety (Stratton *et al.* 1994, 2001; Halsey & Hyman, 2000); and three studies on data derived from passive surveillance systems (Peltola *et al.* 1998; Patja *et al.* 2000; Plesner *et al.* 2000) all failed

to detect any significant association. Results from passive surveillance, vaccine safety review bodies and autistic case analyses are consistent. In view of the large sample studied, it is thus unlikely that MMR represents a major risk factor for autism at the population level. It could still be argued that MMR is a risk factor for a small subset of children with autism, for instance those children exhibiting a regression in the second year of life after a seemingly normal development, a hypothesis that was put forward by Wakefield and colleagues (1998; Uhlmann *et al*. 2002; Spitzer, 2003). However, three major caveats must be considered with this hypothesis. First, there were serious methodological weaknesses in Wakefield's samples, such as imprecise clinical descriptions and inclusion of children with non-autism diagnoses, and more importantly a lack of evidence for the validity of regression data presented in the course of the development of autistic children (Fombonne & Cook, 2003). Secondly, a recent study examined a group of children with autistic-spectrum disorders who had been exposed to MMR, ascertained from a larger community sample and diagnosed with a validated instrument. In this epidemiological sample, the subset of autistic children with regression had no developmental or clinical characteristics that would distinguish them from those without regression. Thus, there was no evidence to support a specific aetiologically distinct regressive phenotype (Fombonne & Chakrabarti, 2001). Thirdly, there is no evidence in independent studies that the incidence of 'regressive' autism has increased after the introduction of MMR (Fombonne & Chakrabarti, 2001; Taylor *et al*. 2002).

The post-MMR 'step-down' reduction in AD incidence detected in our study was unexpected. A similar non-significant downward trend in prevalence has been previously reported in a small Swedish sample (Gillberg & Heijbel, 1998). Furthermore, a recent retrospective cohort study has also detected a non-significant trend in reduction of relative risks in the MMR exposed groups. For subgroup analysis of autistic-spectrum disorders, three out of 17 tests reached significance for risk reduction in the MMR exposed subjects (Madsen *et al*. 2002). Our detected post-MMR 'step-down' reduction may be a chance finding or the reflection of an unmeasured confounder. However, if it represents a valid 'protective' effect (which is unlikely), the underlying mechanism remains intriguing.

MMR was introduced in October 1988 for children age 12–15 month of age, with a catch up programme to those up to age 5 (Balraj & Miller, 1995). Our analyses also explored the effect of the catch up programme as many children vaccinated would be born before January 1987 (children older than 19 months). We thus varied the commencement of this 'post-MMR period' as starting at 1/84, 1/85, 1/86, 1/87, 1/88, 1/89, 1/90 respectively. Those born in January 1984 would be around age $4\frac{1}{2}$ years in October 1988. In the catch-up period, they would be close to age five. The *P* values mostly increased departing from the 1/87 date, and the lowest lay between 1/1986 to 1/1988. Thus, the 'step-down' effect (i.e. a reduction of 21·2% in AD birth, 95% CI, 6·9–33·3%) appears to be confined to those born between 1986 to the end of 1987. It is unclear whether this is due to the effect of a specific age exposure window. However, this analysis confirms the validity of our cut-point of January 1987.

Finally, no abrupt change in AD births was detected following the alteration of mumps vaccine strains in 1992. The absence of 'step-down' reduction following this change is consistent with the view that the prior Urabe strain, which is known to lead to neurological complications (aseptic meningitis), does not play a major aetiological role in the development of autism.

Some limitations of this study must be borne in mind. First, the diagnostic status of our cases could not be confirmed. A survey on the members of West Midland Autistic Society, nevertheless, indicated that AD children on their membership list were diagnosed by either paediatricians or psychiatrists, and many sought further specialist opinions including 'university experts' before accepting the formal diagnosis (Smith *et al*. 1994). As AD and DS are such impairing, characteristic and largely stigmatizing disorders, misclassification is unlikely to be substantial; and the size of the studied samples is large. However, incomplete case ascertainment and changing diagnostic criteria over time remain important limitations, similar to other studies using retrospective data on this topic

and including clinical series (Taylor *et al*. 1999; Dales *et al*. 2001; Kaye *et al*. 2001) or surveillance data (Peltola *et al*. 1998; Patja *et al*. 2000; Plesner *et al*. 2000). Secondly, our AD cases were derived from a current membership list of 1999, and thus represent a cross-sectional sample of consecutive birth cohorts between 1959–93. Apart from the changing trend in detection of autism, the apparent steady rise of autistic disorder births (Fig. 3) can be explained by the self-selection nature of our sample rather than an actual rise in the incidence AD. The condition is associated with learning difficulties, thus membership subscription and renewal are likely to be made by parents or carers. The support and advice offered are likely to be most useful to those close to the time of diagnosis, entering schools or choosing specialist education. This gradual 'dropout' over increasing age would thus bias towards a higher rate of case ascertainment for younger subjects. However, the extent and the pattern of incomplete case ascertainment confounded by other cohort, survivor, or period effect cannot be independently measured or adjusted, which constitutes another potential limitation. On testing for the MMR related abrupt change, we would expect the self-selection bias in the voluntary membership list to produce a post-MMR 'step-up' increase, because more, rather than less, parents of post-MMR AD children may join the National Autistic Society, given the media publicity. Despite this potential artefact, no 'step-up' increase was detected. Finally, this correlational study has well-known limitations in testing causal relations, especially as individual exposure data were not available. Our findings cannot totally exclude rare or idiosyncratic adverse outcomes.

Conclusion

We were unable to detect any association between autism and exposure to wild measles infections early in life. No association was detected between increased risks of developing autism and exposure to monovalent measles vaccines, to Urabe or to Jeryl–Lynn MMR vaccines. The precise meaning of the possible reduction in AD births around the time of MMR introduction is unclear.

The authors wish to thank the staff of the National Autistic Society and Down's Syndrome Association for their assistance; and Dr Z. Doherty for advice on Down's Syndrome pre-natal screening; and Professor E. Simonoff, Dr G. Baird and Dr T. Crawford for their comments on the manuscript.

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