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No effect of MMR withdrawal on the incidence of autism: a total population study

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Background: A causal relationship between the measles, mumps, and rubella (MMR) vaccine and occurrence of autism spectrum disorders (ASD) has been claimed, based on an increase in ASD in the USA and the UK after introduction of the MMR vaccine. However, the possibility that this increase is coincidental has not been eliminated. The unique circumstances of a Japanese MMR vaccination program provide an opportunity for comparison of ASD incidence before and after termination of the program. **Methods:** This study examined cumulative incidence of ASD up to age seven for children born from 1988 to 1996 in Kohoku Ward (population approximately 300,000), Yokohama, Japan. ASD cases included all cases of pervasive developmental disorders according to ICD-10 guidelines. **Results:** The MMR vaccination rate in the city of Yokohama declined significantly in the birth cohorts of years 1988 through 1992, and not a single vaccination was administered in 1993 or thereafter. In contrast, cumulative incidence of ASD up to age seven increased significantly in the birth cohorts of years 1988 through 1996 and most notably rose dramatically beginning with the birth cohort of 1993. **Conclusions:** The significance of this finding is that MMR vaccination is most unlikely to be a main cause of ASD, that it cannot explain the rise over time in the incidence of ASD, and that withdrawal of MMR in countries where it is still being used cannot be expected to lead to a reduction in the incidence of ASD. **Keywords:** MMR vaccine, autism, incidence, etiology, regression, total population study. **Abbreviations:** ISCO-68: International Standard Classification of Occupations, 1968; DISCOVERY: Detection and Invention System in the COmmunity for VERy Young children with developmental disorders; YACHT: Young Autism and other developmental disorders Checkup Tool.

Publication of a study claiming a causal relationship between the measles, mumps, and rubella (MMR) vaccine and autism spectrum disorders (ASD) (Wakefield, 1999; Wakefield et al., 1998) sparked a heated debate, primarily in the USA and UK, which relates not only to the etiology of ASD, but also impacts immunization policy. Among data used to argue the case are ASD frequency studies. Recent US and British research examining the relationship of trends in MMR vaccination rates and ASD frequency have noted a dramatic increase in ASD frequency most strikingly in the late 1980s (Croen, Grether, Hoogstrate, & Selvin, 2002; Dales, Hammer, & Smith, 2001; Department of Developmental Services, 1999; Hillman, Kanafani, Takahashi, & Miles, 2000; Kaye, der Mar Melero-Montes, & Jick, 2001; Lingam, Simmons, Andrews, Miller, & Stowe, 2003; Powell et al., 2000; Taylor et al., 1999), although evidence of a rise appeared before then (Gillberg, Steffenburg, & Schaumann, 1991; Taylor et al., 1999; Webb, Lobo, Hervas, Scourfield, & Fraser, 1997). However, because there was no stepwise increase in the frequency of ASD after MMR was introduced, and because the frequency of ASD continued to rise while the rate of MMR vaccination remained stably high, there have been major doubts about the claimed causal relationship between the MMR vaccine and ASD occurrence.

Nevertheless, these epidemiological studies, although not providing any support for the causal hypothesis, are inconclusive because they do not test what happens when the postulated risk factor, namely MMR, ceases to be operative. When examining causal hypotheses regarding effects of a risk factor on time trends in the frequency of a disorder, it is highly desirable to study the effects of *withdrawal* of the risk factor on frequency of disorder as well as the effects on frequency following *introduction* of the risk factor (Rutter & Smith, 1995). With respect to MMR, the Japanese situation provides just such a test.

In Japan, the Immunization Law had provided measles vaccination of children aged 12 months to 72 months since 1978 and rubella vaccination of junior high school female students since 1977; then an MMR vaccination program was launched in April 1989. In contrast to the practice in many countries where an MMR booster is administered a few years following the initial vaccination, in Japan only one vaccination was administered to children between 12 and 72 months of age, with the majority vaccinated between 12 and 18 months of age. However, due to a high frequency of reports of aseptic meningitis, a suspected side effect of the mumps vaccine (Urabe strain), the program was terminated in April 1993. Subsequently, only monovalent vaccines were administered. Following a reform of the Immunization Law in 1994, measles and rubella vaccinations were each specified for children between the ages of 12 and 90 months (the measles vaccine was recommended between 12 and 24 months of age and the rubella vaccine between 12 and 36 months). The

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mumps vaccination was voluntary and aimed at children one year of age or older who had not contracted mumps. It was also stipulated that an interval of at least four weeks separate administration of vaccinations.

Termination of the vaccination program provided ideal conditions for implementing a more rigorous research design that would compare ASD frequency before and after termination of the MMR vaccination program. If results showed a decline in ASD frequency in Japan (in contrast to the rise elsewhere) after termination of the program, this would strongly suggest that MMR vaccination is causally related to the increase in ASD frequency. However, if cessation of MMR usage did not lead to a decline in the frequency of ASD, this would suggest that the increase in ASD after introduction of the MMR vaccine in the USA and UK is likely to have been purely coincidental.

This research examines annual trends in ASD incidence in Kohoku Ward in Yokohama, Japan. Most earlier ASD frequency research used prevalence (proportion of individuals in a population who have a specified clinical characteristic, such as a disease, at a specific point in time) as an index of frequency, but this type of measure is suboptimal because it is easily influenced by referral and age of diagnosis (Honda, Shimizu, Imai, & Nitto, 2005). An alternative is to calculate cumulative incidence, i.e., the number of new cases of disease that accumulate during a specified time period, divided by the number of persons in the population at risk (Essex-Sorlie, 1995). Cumulative incidence figures up to a standard age at which a definitive diagnosis is possible for all cases, based on a complete birth cohort, constitutes a much more satisfactory index. For childhood autism as defined in *ICD-10 Diagnostic Criteria for Research* (ICD-10 DCR; WHO, 1993), a disorder that is first manifest in early childhood, and in an area with good preschool services available to all, age five has been found to be satisfactory as the standard age (Honda, Shimizu, Misumi, Niimi, & Ohashi, 1996). In this study, cumulative incidence up to age seven was investigated to allow for the possibility of other ASD which would be referred at age five or later due to milder symptoms or symptoms manifesting at age three or later.

Methods

The catchment area clinical system

Yokohama is a city of 3,500,000 in central Japan. Kohoku Ward, in northern Yokohama, is an urban area of 31.37 km^2 with a population of 298,639 as of January 1, 2002. Originally a ward of 43.79 km^2, the boundaries of Kohoku Ward were redrawn in November 1994, thereby reducing its size. The catchment area for this study was the former Kohoku Ward, for birth cohorts from 1988 to 1994, and the redistricted Kohoku Ward, for birth cohorts from 1995 to 1996. The population of the excluded area was 16% of the total ward population and socio-demographically indistinguishable from other areas in the ward. Accordingly, for purposes of investigating annual trends in the cumulative incidence of ASD in Kohoku Ward, treating the catchment areas, before and after redistricting, as identical is fully justified. The percentages of the age strata 14 years of age and younger and the older population 65 and older on January 1, 1988 were 17.8% and 7.5%, respectively, compared to 13.6% and 10.5% on January 1, 1996. This declining proportion of the younger strata and expanding older population is consistent with the aging trend of the Japanese population as a whole.

Recent studies (Baron-Cohen et al., 1998) suggest a link between autism spectrum conditions and parental occupations in physics, engineering, or mathematics. These fall under the major occupational groupings of 'professional, technical and related workers' (hereafter professional), and 'production and related workers, transport equipment operators and laborers' (hereafter production), according to the International Standard Classification of Occupations, 1968 (ISCO-68). The percentage breakdown of occupations represented in the catchment area according to the ISCO-68 was 17.9% professional workers and 27.3% production workers in 1990, making up 45.2% of total workers, and 18.7% professional workers and 24.0% production workers in 1995, comprising 42.8% of total workers. Compared to 1990, the 1995 figures show a slight increase in the percentage of professional workers and a slight decrease in the percentage of production workers, reflecting the national trend. However, both the 1990 and 1995 figures fall roughly within the median range in comparison with major countries where research on the frequency of autism has been conducted.

Since its inception in 1987, the Yokohama Rehabilitation Center (YRC), and more specifically, the YRC Developmental Psychiatry Unit has provided Kohoku Ward with early intervention services for developmental disorders. As part of this effort, we (HH & YS) designed a conceptual model for an early detection and early intervention community-oriented clinical system for developmental disorders, including ASD, called DISCOVERY (Detection and Intervention System in the COmmunity for VERy Young children with developmental disorders; Honda & Shimizu, 2002) and implemented this model in Kohoku Ward. As a result, community services for early detection and intervention to address developmental disorders have rapidly developed and become widely accessible in Kohoku Ward.

The Kohoku Ward public health and welfare center implements routine health checkups for 4-month-old infants (HC-4m), 18-month-old children (HC-18m), and 3-year-old children (HC-3y), and the YRC is responsible for providing diagnostic and intervention services. Health checkups for infants and children are designed to support parenting activities, promote children's health, and detect diseases and developmental disorders, including ASD, as early as possible. The set of items used to screen for autism in health checkups was drawn up by the Public Health Bureau of Yokohama and is called YACHT (Young Autism and other developmental disorders CHeckup Tool). It includes YACHT-18 which is used at the HC-18m and YACHT-36 which

is used at the HC-3y. The YACHT consists of a questionnaire covering the development of motor function, communication and social interaction, interviews with caregivers on the topics of the questionnaire, and a specific examination of children by public health nurses. This is only a part of the whole checkup procedure to detect various diseases and disorders. Public health nurses in Yokohama are specially trained in mass-screening methods and are experienced in screening for autism. YACHT-18 is designed with a sensitivity as high as possible at the first screening to identify children who are likely to have developmental problems and therefore reduce false negatives to a minimum (Honda & Shimizu, 2002). The positive cases identified by the first implementation of YACHT-18, whether or not they are true-positive or false-positive for developmental disorders, are flagged as high-risk children who present a variety of difficulties. These children are therefore followed up actively by public health nurses, their health status is monitored, and their parents receive a variety of information on child-raising.

Each year, the participation rate in the HC-18m reaches approximately 90%. Those who did not participate in or were false-negative in the HC-18m can be screened in another mass screening, i.e., HC-3y. Or, they can be referred to the YRC by kindergartens, nursery schools, child guidance clinics, or general pediatric clinics, all of which function as a 'fail-safe' mechanism to back up the HC-18m. Thus, more accurate recognition of cases was achieved in the first screening of the epidemiological study through the HC-18m in combination with the fail-safe net. For childhood autism, the sensitivity of YACHT-18 is as high as 81%, and the mean age of referral to the YRC is under three years in the true-positive group (Honda et al., 2005). It must be further emphasized here that even children in the false-negative group referred to the YRC are five years of age at the oldest, and on average are three years of age. The fail-safe feature's major contribution to the system is this high degree of case recognition (Honda & Shimizu, 2002).

The YRC Developmental Psychiatry Unit, an interdisciplinary team including developmental psychiatrists, clinical psychologists, speech therapists, social workers, and teaching staff, offers diagnostic and intervention services for all children with ASD, from severely intellectually disabled to high-functioning cases. Mediating between diagnosis and intervention subsystems, a three-month introductory intervention program, called 'EGG' (Early individual assessment, Guidance, Group activity), consisting of weekly group activities both for children and parents, provides detailed assessment, intervention planning, parenting support, and motivation to encourage parents to proceed to the main intervention program. Individual assessment of the child and counseling for parents are also offered during this period. After the introductory program, the developmental psychiatrist re-evaluates the child using his or her own observational data and staff evaluations, makes a definitive diagnosis, and formulates an intervention plan.

After obtaining the parents' informed consent on the diagnosis, assessment, and intervention plan, child and parents are introduced into the main intervention program (group or individual training, or both) which continues until the child enters primary school. Thereafter, periodic follow-ups are conducted on most of the children throughout their school years. In these follow-ups, a developmental psychiatrist reassesses (and re-diagnoses) each child, and a clinical psychologist conducts psychological evaluations. As the principal developmental psychiatrists of the YRC, we (HH & YS) conducted regular and repeated direct observations on most of the children and were able to make precise diagnoses of ASD even in children with mild symptoms.

This type of clinical system is ideal for conducting frequency studies, because all children with developmental disorders born in the catchment area, including those with ASD, are registered with the YRC, and real-time observational data are obtained for the majority of them in follow-up contacts beginning after the HC-18m and extending through their school years. Thanks to this clinical system, in the research catchment area, referral to the YRC and definitive diagnoses are made for children with childhood autism by the age of five and by the age of seven for children with other ASDs which are mild and tend to be referred later.

Because in this research the first screening occurs at the HC-18m, if there are changes in the proportion of infants younger than one year of age who cease to be followed up, then there may be fluctuation in cumulative incidence figures. Therefore, we examined whether or not there were changes in the proportion of infants who had moved out of the area or died by one year of age (proportion derived from the number of children 0 years of age who had moved out or died over the number of births). The proportion of infants 0 years of age who had moved or died during the years 1988 to 1996 ranged from 6.7% to 8.0% of births, but a logistic regression analysis did not reveal significance ($\chi^2 = 8.45$, df = 6, $P = .21$).

Annual trends in ASD incidence

Cumulative incidences of ASD in children up to age seven were calculated for each year from 1988 to 1996. From patient lists of the YRC, the authors selected all children born in the catchment area between 1988 and 1996 who were diagnosed by age seven with pervasive developmental disorder (PDD) using ICD-10 guidelines (WHO, 1992). The number of diagnosed children born in the catchment area, regardless of where they now live, was divided by the area's birth cohort in the corresponding year, based on Yokohama population statistics. In the numerator, we included the total of children born and still living continuously in the catchment area at the age of seven as well as those who had been born in the catchment area but had moved out before age seven. We examined annual trends in cumulative incidence in children up to age seven for all ASD categories (all children who met the diagnostic criteria for all PDD according to ICD-10 guidelines (WHO, 1992)). Further, we divided this group into two and investigated annual trends in cumulative incidence for both childhood autism, the subtype which makes up the core of ASD, as defined by ICD-10 DCR (WHO, 1993), and other ASD (all children with PDD such as Asperger syndrome, atypical autism, etc. according to ICD-10 guidelines, excluding those diagnosed with childhood autism as defined in ICD-10 DCR). Further-

more, we categorized children with ASD into five groups based on Binet IQ scores (–49, 50–69, 70–84, 85–99, 100–) and investigated the association of ASD incidence to each birth year and IQ level.

Wakefield and his colleagues have postulated that the autism associated with MMR almost always involves developmental regression (Furlano et al., 2001; Torrente et al., 2002; Wakefield et al., 2000). Thus, cumulative incidences of ASD with regression were also calculated. To check for developmental regression, real-time interviews were conducted at the HC-18m to determine if a child could produce at least four meaningful words, other than repetitive babbling. If these meaningful words disappeared after the HC-18m, this was considered 'definite regression.' Definite regression also refers to episodes in which caregiver records confirm loss of skills such as aspects of communication skills, including utterances, social behaviors, play activities, adaptive skills, or motor skills that had appeared and become established in the child's daily life. If there is insufficient evidence to confirm that these skills had become firmly acquired, or that they had not fully disappeared, then this is called 'probable regression.'

Results

The Japanese MMR vaccination program targeted one-year-olds between April 1989 and April 1993, then was discontinued. Therefore, children born during the years 1988 to 1992 received the MMR vaccine in years 1989 to 1993 at one year of age. According to Yokohama statistics, MMR vaccination rates declined from 69.8% in the 1988 birth cohort, to 42.9%, 33.6%, 24.0%, and a mere 1.8% in birth cohorts 1989 to 1992. Risk factor analysis using logistic regression revealed a significant decrease ($\chi^2 = 22938.21$, df = 4, $P < .0001$).

Table 1 and Figure 1 show annual trends in cumulative incidence of all ASD categories up to seven years (children who met any of the diagnostic criteria for PDD according to ICD-10 guidelines), as well as annual trends in cumulative incidence of both childhood autism as defined in the ICD-10 DCR (WHO, 1993) and other ASD. These figures include immunized children born in years 1988 to 1992. The 1988 to 1996 birth cohort of children in the catchment area totaled 31,426, of which 278 were diagnosed with ASD by age seven. Of these, 276 children were referred to the YRC by the age of five and only two children (one girl and one boy), born in 1991 and diagnosed with ASD other than childhood autism, were referred to the YRC at age six. The cumulative incidence of ASD up to age seven was 88.5 per 10,000 (95% CI, 78.1–98.8). The cumulative incidence of ASD up to seven years of age ranged from 47.6 to 85.9 per 10,000 in birth cohorts 1988 to 1992. In birth cohorts 1993 to 1996, when not a single child was immunized, cumulative incidence up to seven years ranged from 96.7 to 161.3 per 10,000.

When all birth years were examined with risk factor analysis using logistic regression, a significant increase in cumulative incidence of ASD was confirmed ($\chi^2 = 45.17$, df = 8, $P < .0001$). However, this trend differed after 1993 and before 1992. When 1996 is used as the standard, ASD incidence is significantly low in each birth year until 1992, and cumulative incidence of ASD after 1993 was no different from 1996 in significance. When categorized into the two groups of childhood autism and other ASD and analyzed with risk factor analysis using logistic regression, cumulative incidence of both groups showed a significant increase ($\chi^2 = 31.86$, df = 8, $P < .0001$ for childhood autism and $\chi^2 = 19.25$, df = 8, $P = .01$ for other ASD).

Next, the cases of ASD were divided into five groups according to Binet IQ scores (–49, 50–69, 70–84, 85–99, 100–), and the association of ASD incidence to birth year and IQ were examined using the Cochran–Mantel–Haenszel χ^2 test. The results showed Mantel–Haenszel $\chi^2 = 5.24$, df = 1, $P = .02$, and an examination of all birth years confirmed a significant increase in ASD cases with high IQ (Figure 2).

Table 2 shows numbers and cumulative incidences of all ASD, ASD with developmental regression of any kind (i.e., definite + probable), and ASD with episodes of definite regression in children up to

Table 1 Number and cumulative incidence up to age seven of childhood autism, other ASD, and total ASD for each year from 1988 to 1996

Year of birth	Birth cohort	Childhood autism		Other ASD		All ASD	
		N	Incidence per 10,000 (95% CI)	*N*	Incidence per 10,000 (95% CI)	*N*	Incidence per 10,000 (95% CI)
1988	3571	7	19.6 (5.1–34.1)	10	28.0 (10.7–45.3)	17	47.6 (25.0–70.2)
1989	3246	12	37.0 (16.1–57.8)	5	15.4 (1.9–28.9)	17	52.4 (27.5–77.2)
1990	3492	18	51.5 (27.8–75.3)	12	34.4 (15.0–53.8)	30	85.9 (55.3–116.5)
1991	3763	10	26.6 (10.1–43.0)	11	29.2 (12.0–46.5)	21	55.8 (32.0–79.6)
1992	3632	11	30.3 (12.4–48.2)	12	33.0 (14.4–51.7)	23	63.3 (37.5–89.1)
1993	3618	18	49.8 (26.8–72.7)	17	47.0 (24.7–69.3)	35	96.7 (64.8–128.6)
1994	3905	34	87.1 (57.9–116.2)	29	74.3 (47.3–101.2)	63	161.3 (121.8–200.8)
1995	3128	23	73.5 (43.6–103.5)	13	41.6 (19.0–64.1)	36	115.1 (77.7–152.5)
1996	3071	25	81.4 (49.6–113.2)	11	35.8 (14.7–56.9)	36	117.2 (79.2–155.3)
Total	31426	158	50.3 (42.5–58.1)	120	38.2 (31.4–45.0)	278	88.5 (78.1–98.8)

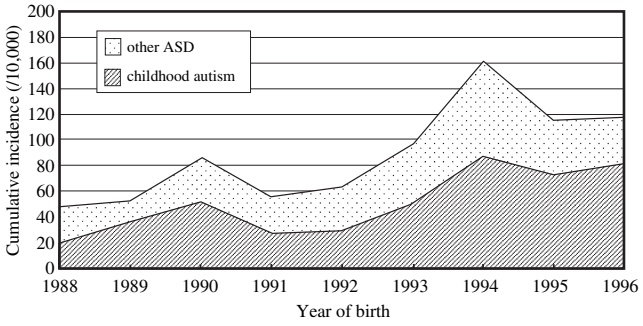

Figure 1 Annual trends in cumulative incidences up to seven years of childhood autism and other ASD

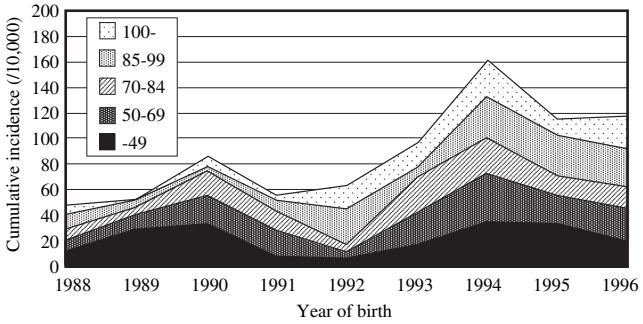

Figure 2 Annual trends in cumulative incidences of ASD by Binet IQ

age seven born in years 1988 to 1996. Figure 3 shows the relation of these figures on cumulative incidences to MMR vaccination rates in Yokohama. Seventy-two children, 25.9% of the 278 with ASD, had regressive episodes of any kind, resulting in an incidence of 22.9 per 10,000. Of these, 60 children had episodes of definite regression, resulting in an incidence of 19.1 per 10,000. When performing a risk factor analysis using logistic regression on both cumulative incidence of regression of any kind and cumulative incidence of definite regression, the cumulative incidences of both showed no significant change over the period of this study (for regression of any kind: $\chi^2 = 9.30$, df = 8, $P = .32$; for definite regression: $\chi^2 = 12.65$, df = 8, $P = .12$).

Discussion

This research examined the relationship between MMR vaccination and annual trends in ASD incidence in Kohoku Ward in Yokohama, Japan. For childhood autism as defined in ICD-10 DCR (WHO, 1993), cumulative incidence up to age five based on a complete birth cohort has been found to be a satisfactory index (Honda et al., 1996). However, in this research we sought cumulative incidence up to age seven with the intention of examining cases of other ASD in which the age of referral might be five years of age and above, because symptoms tend to be milder or manifest themselves at age three or later. According to our findings, all of the 158 children with childhood autism were registered by the age of five, and of the 120 children with other ASD, 118 were registered at age five and 2 children at age six. Our findings indicate that five years of age is appropriate for determining cumulative incidence of childhood autism, and this was made possible by a community-based early detection and treatment system in which public health nurses trained in mass screening for developmental disorders implement the YACHT-18 screening tool in the initial screening, accompanied by a fail-safe mechanism which serves as a backup. When including other ASD, it was appropriate that the age for cumulative incidence calculations was raised to age seven since some cases with other ASD, though few in number, were registered after age five.

The key findings are that the seven-year cumulative incidence of ASD rose progressively from 47.6 per 10,000 for children born in 1988 to 117.2 for those born in 1996, that this rise continued in cohorts of children born after MMR was withdrawn, and that no decline in ASD incidence occurred in the five-year period from 1988 to 1992 during

Table 2 Number and cumulative incidence up to age seven of ASD with developmental regression and total ASD for each year from 1988 to 1996

Year of birth	Birth cohort	ASD with regression				All ASD	
		Definite only		Definite + probable			
		N	Incidence per 10,000 (95% CI)	*N*	Incidence per 10,000 (95% CI)	*N*	Incidence per 10000 (95% CI)
1988	3571	4	11.2 (.2–22.2)	4	11.2 (.2–22.2)	17	47.6 (25.0–70.2)
1989	3246	5	15.4 (1.9–28.9)	5	15.4 (1.9–28.9)	17	52.4 (27.5–77.2)
1990	3492	9	25.8 (9.0–42.6)	10	28.6 (10.9–46.4)	30	85.9 (55.3–116.5)
1991	3763	5	13.3 (1.6–24.9)	8	21.3 (6.5–36.0)	21	55.8 (32.0–79.6)
1992	3632	6	16.5 (3.3–29.7)	8	22.0 (6.8–37.3)	23	63.3 (37.5–89.1)
1993	3618	6	16.6 (3.3–29.8)	8	22.1 (6.8–37.4)	35	96.7 (64.8–128.6)
1994	3905	16	41.0 (20.9–61.0)	16	41.0 (20.9–61.0)	63	161.3 (121.8–200.8)
1995	3128	4	12.8 (.3–25.3)	5	16.0 (2.0–30.0)	36	115.1 (77.7–152.5)
1996	3071	5	16.3 (2.0–30.5)	8	26.1 (8.0–44.1)	36	117.2 (79.2–155.3)
Total	31426	60	19.1 (14.3–23.9)	72	22.9 (17.6–28.2)	278	88.5 (78.1–98.8)

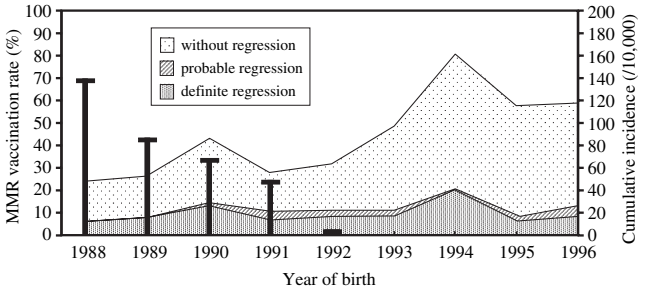

Figure 3 Yokohama City MMR vaccination rates by birth year (1988–1992), and annual trends in cumulative incidences of ASD with and without developmental regression up to seven years in the birth cohort in the catchment area

which MMR vaccine usage fell from 69.8% to zero population coverage. If the vaccine had been responsible for a rise in the incidence of ASD, there ought to have been a fall in incidence following withdrawal of the MMR vaccine, but this did not occur. Necessarily, that finding runs counter to expectations deriving from the causal hypothesis. The continuing rise in the incidence of ASD after withdrawal of the MMR vaccine seems to be incompatible with the causal hypothesis. Although uncertainties remain on where the boundaries of ASD should be drawn, in our study we examined time trends as evident in relation to both a broader concept of ASD and a narrower concept of childhood autism (ICD-10 DCR). The findings are basically the same either way, i.e., the incidence of both childhood autism and other ASD increased. But based on a closer look at IQ levels showing an increase in ASD cases with high IQ, either the rise was a consequence of better ascertainment of cases with high IQ together with a broadening of the diagnostic concept, or it is real but due to some risk factor other than MMR. Either way it cannot be attributed to MMR because MMR was not being used then.

Before rejecting the causal hypothesis, it is essential to consider possible objections to our study. There are five that need attention. First, Wakefield and his colleagues have postulated that the autism associated with MMR almost always involves developmental regression (Furlano et al., 2001; Torrente et al., 2002; Wakefield et al., 2000). Accordingly, it could be suggested that we needed to focus on autism with regression. We found no change in the incidence of ASD with regression between the periods before and after withdrawal of MMR. Three British studies (Fombonne & Chakrabarti, 2001; Taylor et al., 2002; Fombonne et al., 2004) have also shown no change in the rate of regression across time periods beginning before introduction of MMR and continuing during a time of high take-up of the vaccine. In any case, the Spitzer, Aitken, Dell'Aniello, and Davis (2001) finding on a large sample of cases of ASD supposed to be attributable to the MMR vaccine found only 39% with regression, a proportion broadly in line with that reported during the pre-MMR era.

Second, it could be claimed that the proportion of cases of autism due to the vaccine is too low to be detectable in a total population study of time trends in incidence. However, this runs counter to the argument that the effect was big enough to result in an overall rise in the frequency of autism (Wakefield, 1999). If it was sufficient to cause an overall rise, the cessation of MMR usage should be sufficient to result in a measurable fall. Also, the Spitzer et al. study in the UK concerned 325 cases of ASD thought to be due to MMR; this is a sizeable number.

Third, it has been argued that previous studies have been misleading because their follow-up has not extended over at least three years (Spitzer et al., 2001). That objection cannot be applied to our study because we have deliberately focused on incidence in birth cohorts followed to age seven, meaning an age roughly six years after MMR (if used).

Fourth, it might be suggested that our surveillance system missed many cases of autism. That is extremely unlikely because our system is unusually thorough and because our overall incidence figure of 88.5 per 10,000 for ASD is in line with some other recent estimates (Kadesjö, Gillberg, & Hagberg, 1999; Wing, 1996) and higher than the 60 per 10,000 that has been put forward as the best estimate (Medical Research Council, 2001) based on high quality total population epidemiological data (Baird et al., 2000; Chakrabarti & Fombonne, 2001).

One possibility might be an increase, after the termination of the MMR vaccination program, of children without ASD who moved out of the catchment area. The findings given in the Methods section indicate that the proportion leaving the area was actually quite small and did not change over the period studied. Only a very large change could account for our findings. It is implausible, therefore, that time trends in movement patterns could account for the incidence findings.

In summary, none of these concerns invalidate our study. Our findings are novel and important in three different ways. First, unlike the previously published data dealing with time trends in frequency of ASD following *introduction* of MMR, we have findings on the effects on incidence following *withdrawal* of MMR. The use of epidemiological data to test a causal hypothesis is immensely strengthened by the availability of time trends that relate to the loss of a postulated risk factor as well as those related to its appearance (Rutter & Smith, 1995). Second, we have data on the likely true incidence of ASD in a general population with systematic screening and an effective system for early diagnosis. This has major advantages over reliance on administrative rates that are well below the true rates. Third, we have used incidence based on systematic follow-up of birth cohorts, rather than prevalence figures, which are much more open to biases.

Time trends data constitute a good test of a causal hypothesis provided that they cover a time period that spans both onset and offset of the risk factor. These are available across studies and they give no support for the causal hypothesis. An alternative, complementary approach involves the comparison of incidences of ASD in vaccinated and unvaccinated children during a period when MMR is potentially available to all. A large-scale Danish cohort study (Madsen et al., 2002) and a British case–control study (Smeeth et al., 2004) showed no effect of vaccination on ASD. The strategy is constrained by uncertainties over the factors that led parents not to have their children vaccinated. However, taken in conjunction with the time trends data, the findings on the causal hypothesis are resoundingly negative. Accordingly, it is possible to conclude that it is extremely unlikely that MMR has been responsible for the rise over time in the incidence of diagnosed autism. It follows that it is similarly unlikely that it causes autism frequently or at all. It cannot have caused autism in the many children with ASD in Japan who were born and grew up in the era when MMR was not available. Because this frequency is at least as high as in populations in other countries in which most children were vaccinated, it implies that MMR could not cause a substantial proportion of cases of autism.

Epidemiological data, however, cannot test the very different hypothesis that MMR might involve an increased risk of ASD in a very small number of children who, for some reason, are unusually susceptible to damage from the vaccine. There is no evidence in support of such a hypothesis and no indication of how such a postulated susceptibility might be manifest. Hence, the burden of proof must be on those who favor such a hypothesis.

Finally, in terms of immunization policy, in countries such as the USA and UK where the MMR vaccine is still being administered, our findings indicate that simply terminating MMR vaccination programs will not lead to a reduction in the incidence of ASD.

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