No Evidence for A New Variant of Measles-Mumps-Rubella–Induced Autism

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ABSTRACT. *Objective.* **A link has been postulated between measles-mumps-rubella (MMR) vaccine and a form of autism that is a combination of developmental regression and gastrointestinal symptoms that occur shortly after immunization. This hypothesis has involved 3 separate claims: 1) that there is new phenotype of autism involving regression and gastrointestinal symptoms, 2) that this new variant is responsible for the alleged rise of autism rates, and 3) that this phenotype is associated with biological findings suggestive of the persistence of measles infection. We tested the first of these claims. If this new "autistic enterocolitis" syndrome had some validity, then 1 or several of the following 6 predictions should be supported by empirical data: 1) childhood disintegrative disorder has become more frequent, 2) the mean age of first parental concern for autistic children who are exposed to MMR is closer to the mean immunization age than in children who are not exposed to MMR, 3) regression in the development of children with autism has become more common in MMR-vaccinated children, 4) the age of onset for autistic children with regression clusters around the MMR immunization date and is different from that of autistic children without regression, 5) children with regressive autism have distinct symptom and severity profiles, and 6) regressive autism is associated with gastrointestinal symptoms and/or inflammatory bowel disorder.**

Methods. **Three samples were used. Epidemiologic data on 96 children (95 immunized with MMR at a median age of 13.5 months) who were born between 1992 and 1995 and had a pervasive developmental disorder diagnosis as reported in a recent UK survey (post-MMR sample) were compared with data from 2 previous clinical samples (1 pre-MMR [$n = 98$] and 1 post-MMR [$n = 68$]) of autistic patients. All patients were assessed with the standardized Autism Diagnostic Interview (ADI), allowing rigorous comparison of age at first parental concerns and rates of regression across samples. Reliability was excellent on ADI scores, age of parental concern, and developmental regression. Furthermore, data on bowel symptoms and disorders were available in the epidemiologic survey from both pediatric and parental sources, and immunization dates were obtained from computerized records.**

Results. **The prevalence of childhood disintegrative disorder was 0.6/10 000 (95% confidence interval: 0.02–3.6/10 000); this very low rate is consistent with previous estimates and is not suggestive of an increased frequency of this form of pervasive developmental disorder in samples of children who are immunized with MMR. There was no difference in the mean age at first parental concern between the 2 samples exposed to MMR (19.3 and 19.2 months) and the pre-MMR sample (19.5 months). Thus, MMR immunization was not associated with a shift toward an earlier age for first parental concerns. Similarly, the rate of developmental regression reported in the post-MMR sample (15.6%) was not different from that in the pre-MMR sample (18.4%); therefore, there was no suggestion that regression in the developmental course of autism had increased in frequency since MMR was introduced. In the epidemiologic sample, the subset of autistic children with regression had no other developmental or clinical characteristics, which would have argued for a specific, etiologically distinct phenotype. Parents of autistic children with developmental regression detected the first symptoms at a very similar age (19.8 months) to those of autistic children without regression (19.3 months). Moreover, the mean intervals from MMR immunization to parental recognition of autistic symptoms were comparable in autistic children with or without regression (248 vs 272 days; not significant). In the epidemiologic sample, gastrointestinal symptoms were reported in 18.8% of children. Constipation was the most common symptom (9.4%), and no inflammatory bowel disorder was reported. Furthermore, there was no association between developmental regression and gastrointestinal symptoms (odds ratio: 0.63; 95% confidence interval: 0.06–3.2; not significant), and only 2.1% of the sample experienced both problems, a rate that did not exceed chance expectations.**

Conclusions. **No evidence was found to support a distinct syndrome of MMR-induced autism or of "autistic enterocolitis." These results add to the recent accumulation of large-scale epidemiologic studies that all failed to support an association between MMR and autism at population level. When combined, the current findings do not argue for changes in current immunization programs and recommendations.** *Pediatrics* **2001;108(4). URL: http://www.pediatrics.org/cgi/content/full/108/4/e58; *autism, immunization, MMR, regression, epidemiology.***

ABBREVIATIONS. PDD, pervasive developmental disorders; CDD, childhood disintegrative disorder; ADI-R, Autism Diagnostic Interview-Revised; MHC, Maudsley Hospital Clinical; MFS, Maudsley Family Study; SD, standard deviation.

Autism is a severe developmental disorder that involves delay and deviance in the development of language and communication and of social interaction and reciprocity, and restricted patterns of play, interests, and behaviors.[1,2] Autism is a

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disorder that belongs to a larger group of conditions referred to as pervasive developmental disorders (PDD), which also include less severe autistic patterns of development, such as atypical autism and Asperger syndrome. A very rare PDD, childhood disintegrative disorder (CDD), applies to children who develop normally up to age 2 (and more often 3) and present subsequently with a profound behavioral disintegration followed by severe autism and intellectual impairments. Autism is associated with mental retardation in 70% of cases, and males are 4 times more likely than females to be affected.[3] Twin and family studies have accumulated evidence for a strong genetic component in cases of idiopathic autism.[4,5]

In a small proportion not exceeding 10%,[3,6] autism and autistic syndromes occur in conjunction with known medical disorders that are likely to be causally associated with the syndrome. Prime examples of these medical conditions are tuberous sclerosis,[7] fragile X,[8] and congenital rubella.[9,10] When autism occurs as a result of these medical conditions, a distinct behavioral phenotype has been reported. Thus, autistic individuals with tuberous sclerosis have elevated rates of epilepsy and mental retardation and brain and skin lesions, and the male:female ratio in affected individuals is closer to unity.[7] Autistic individuals with fragile X have high levels of social anxiety and avoidance (rather than aloofness) and of overactivity and attention deficits, and males almost always have intellectual impairments and present specific physical features.[11] Autistic children with congenital rubella have specific congenital abnormalities,[9] and autistic symptoms tend to improve in the longer term.[10] Thus, variants of autism associated with specific causal pathways exhibit specific phenotypic and developmental features that help differentiate them from idiopathic autism.

Recent reports claim to have identified another variant of autism (called "autistic enterocolitis") in children referred to a gastroenterology department.[12,13] The hypothesis has involved 3 separate claims: 1) that a new phenotype of autism associated with developmental regression and gastrointestinal symptoms has emerged as a consequence of measles-mumps-rubella (MMR) immunization,[12,13] 2) that this new variant of autism is responsible for the alleged rise of autism rates,[14] and 3) that this phenotype is associated with particular biological findings consistent with a persistence of measles virus infection.[13] There are 2 potentially serious implications of these claims. First, if true, these might have important implications for neurobiological causal models of autism and for the conduct and interpretation of ongoing molecular genetic studies of autism. Second, the public health consequences of these claims cannot be ignored. The MMR immunization program was introduced in 1988 in the United Kingdom (with first MMR given between 12 and 15 months of age) with coverage rates quickly rising above 90%, a level required for efficient herd immunity.[15] However, in the wake of the initial report,[12] MMR coverage rates in 2-year-olds fell from 92% in 1995 to 88% in 2000.[16] This article is concerned with the first set of claims, ie, the emergence of a new autism phenotype. If, as argued by Wakefield et al,[12,13] a new syndrome has appeared, then precise delineation of its clinical and developmental characteristics is required to validate and research it.

Unfortunately, the precise phenotype has not been described clearly yet. In the most recent series of 60 patients[13] (which includes all children of the first report[12]), 57 children had a PDD diagnosis but 3 children with other diagnoses were included (1 dyslexia, 1 schizophrenia, 1 attention-deficit/hyperactivity disorder), raising serious questions about the specificity of the hypothesis under investigation. The male:female ratio otherwise was typical of autism samples, but it is worth noting that no quantitative data were available on intellectual functioning, language level, severity of autistic symptomatology, and associated neurologic signs. Normal electroencephalograms, brain magnetic resonance imaging, and cerebrospinal fluid profiles in the first series[12] were not particularly suggestive of brain pathology.

Three features, however, could act as pointers toward a specific variant of autism. First, 2 children had a diagnosis of CDD; as CDD is extremely rare,[3] (E. Fombonne, submitted) it raised the possibility that CDD might be part of this new phenotype. Second, based on retrospective parental accounts, developmental regression was reported in almost all cases.[13] Regression, however, was defined loosely as loss of acquired skills after a period of normal development as determined by the presence of uneventful general practitioner and health visitor records up to the first birthday. Onset of behavioral symptoms occurred within 2 weeks of MMR immunization in 8 patients from the first case series[12]; unfortunately, the mean age at regression was not provided in the larger series,[13] and there was no indication of how regression was assessed, which levels of skills were attained before the regression occurred, and which particular skills were lost and for how long. Third, almost all cases displayed gastrointestinal symptoms, including constipation, diarrhea, alternating constipation and diarrhea, abdominal pains, and bloating, although the timing of these symptoms relative to the behavioral disturbances was vague.

Regression in the developmental course of autism is not a new phenomenon, and studies that were conducted long before MMR existed documented rates of regression or loss of skills ranging from 20% to 50% in both epidemiologic and clinical samples[17–22] (Table 1). Therefore, rather than to describe regression in case series, it is important to establish whether regression has increased in frequency and occurs at particular times in the developmental course, particularly in relation to vaccine exposure. Similarly, the age at which parents first become concerned with symptoms of autistic dysfunction in their child tends to be in the second year of life rather than before the first birthday.[23,24] Thus, retrospective reports by parents, general practitioners, or health visitors of a normal period of development up to age 1 and recognition of first autistic symptoms in the second year followed by loss of skills are consistent with autism development as known for several decades.[17–22,25] Finally, although inflammatory bowel

TABLE 1. Regression in Autism: Not a New Phenomenon*

Author/Year	Study Description	Description of the Regression	Rate (%)
Lotter, 1966[17]	Epidemiologic (n = 32)	Developmental setback that included speech loss	31.3
Kurita, 1985[18]	Clinical (n = 261)	Speech/gesture loss lasting over 6 months	37.2
Creak, 1963[19]	Clinical (n = 100)	Setback in development	25.0
Wolff and Chess, 1964[20]	Clinical (n = 14)	Setback in development	50.0
Wakabayashi, 1974[21]	Clinical (n = 116)	Retrogressive shift with speech disappearance	22.4
Kobayashi and Murata, 1998[22]†	Clinical (n = 179)	Normal development followed by loss of words/interest for a minimum of 3 months	29.6

* An appendix containing clinical descriptions of loss of skills and regression from this earlier literature can be obtained from the first author upon request.
† Subjects were born before 1975.

disorders seem to be extremely rare in children with autism,[26] gastrointestinal symptoms have been much less studied among individuals with autism, and their type, frequency, and possible association with a regressive pattern of development have not been documented in the literature.

From this background, the following testable predictions could be made to validate the potentially new syndrome. If an autistic enterocolitis syndrome occurs in children who have autism and were immunized with MMR, then

1. Childhood disintegrative disorder might have become more frequent;
2. The mean and distribution of age at which parents become concerned has changed and is closer to the mean immunization age than in children who were not exposed to MMR;
3. Regression in the development of children with autism has become more common;
4. The age of onset of symptoms for autistic children with regression clusters around the immunization date and is different from that of autistic children without regression;
5. Children with regressive autism may have distinct symptom and severity profiles; and
6. Regressive autism is associated with gastrointestinal symptoms, and children with regressive autism may exhibit increased frequency of inflammatory bowel disorders.

This study tested this set of predictions using 1 epidemiologic sample and 2 clinical samples of children who were assessed carefully with state-of-the-art standardized diagnostic measures.

MATERIALS AND METHODS

Stafford Sample

The main sample used for this study, the Stafford sample, was selected as part of an epidemiologic survey of PDD conducted in Staffordshire (Midlands, United Kingdom) in the total population (n = 15 500) of children born between 1992 and 1995 (for full details, see Chakrabarti and Fombonne[27]). Before the survey date (July 1st, 1999), 576 children were referred for developmental problems to the local Child Development Center team, 426 of whom had benefited from a thorough 2-week multidisciplinary assessment. Of these, additional clinical investigations confirmed the presence of a PDD diagnosis in 97 children, leading to a prevalence rate for all PDD of 62.6/10 000 in this survey. Of the 97 children, 1 girl with Rett syndrome was excluded from additional analysis, leaving 96 children with the following diagnostic repartition: autistic disorder (n = 26), atypical autism (n = 56), Asperger syndrome (n = 13), and childhood disintegrative disorder (n = 1).

For 91 of these children, the Autism Diagnostic Interview-Revised (ADI-R)[28] was administered with the parents by 1 of the authors (S.C.), who is trained to the instrument, and videotaped. Interrater reliability on the ADI-R interviews was assessed by selecting at random 38 videotapes, which were rated blindly by the first author and his team. The reliability for the total ADI-R score was excellent (intraclass correlation coefficient: 0.86). Psychological tests such as the Wechsler Preschool Scale of Intelligence[29] and the Merrill-Palmer[30] were used to assess intellectual functioning. Biological investigations included detection of fragile X, karyotype, full blood count, urea and electrolytes, serum creatinine, liver function test, serum calcium, thyroid stimulating hormone, T4, creatine kinase, plasma and urine amino acid chromatogram, urine organic acids, electroencephalogram, and when clinically indicated, computed tomography or magnetic resonance imaging brain scan.

In 1999 to 2000, all medical data were abstracted on an ad hoc questionnaire by the community pediatrician who had assessed all of the children. Immunization dates were obtained and subsequently verified against the computerized records of the Child Health System. In this sample, 99% of the sample had had their first MMR immunization (median age: 13.5 months; interquartile range: 13.1–14.4 months), and 65.6% had had their second immunization with MMR (median age: 43.6 months). Details about co-occurring medical conditions and symptoms, including specific gastrointestinal symptoms such as abdominal pain, diarrhea, constipation, bloody stool, and other symptoms, were abstracted from medical records. A survey of parents also was performed in 1999 to 2000 to collect additional information about the lifetime history of medical, psychiatric, and developmental disorders in the first- and second-degree relatives of the proband child; questions also were asked about the occurrence of gastrointestinal symptoms in the index child during previous years, including any occurrence of abdominal pain, bloody stool, diarrhea, and other problems such as constipation. Seventy-seven questionnaires were completed and returned by the parents.

Comparison Samples

Two clinical samples were used for comparison purposes, the Maudsley Hospital Clinical (MHC) sample and the Maudsley Family Study (MFS) sample.

MHC Sample

The MHC sample consisted of a series of consecutive referrals to the first author's specialist autism team at the Maudsley Hospital and was included in an earlier study of age of "onset," or age of parental recognition, of first autistic symptoms in the development of their child. Details of this sample and its results have been provided elsewhere.[24] For this study, we excluded from the original sample all children who were born before 1987, leaving a total sample of 68 children who were born between 1987 and 1996 and had a confirmed diagnosis of PDD. Because of their birth dates, these children were likely to have been exposed to MMR immu-

nizations. As part of the assessment procedure used in the clinic, all parents participated in the ADI-R interview conducted by trained registrars. For this sample, only the question that assessed age of first parental concerns (see below) was available for additional analysis.

MFS Sample

The MFS sample included 99 probands who had an ICD-10 diagnosis of autism and were born between 1954 and 1979[5]; therefore, none of them had been exposed to MMR immunizations. ADI data were available on 98 probands. Interviews were conducted by trained research assistants with the first version of the ADI,[31] an earlier version of the ADI-R. The mean age of probands with autism was 17.8 years (standard deviation [SD]: 5.8), and the sample was 63% male; 59.1% of the sample scored in the mental retardation range on performance IQ measures.

Age at First Parental Concern

In the 3 samples, item 2 of the ADI was used to assess the first onset of autistic symptoms, or the age of the child at which parents first became concerned with their child's development. The precise wording of the question is, "How old was your child when you first wondered if there might be something not quite right with his/her development?" All interviewers who are trained to the ADI-R facilitate recall by informants using an approach to timing of events that avoids calendar dating but relies on reliving actual experiences and past memories. Parents' answers to this question were provided in months. To assess the interval between MMR immunization and age at first parental concern, the latter variable also was recoded in days (eg, an age of 24 months was treated as 730 days). When parents could not remember or could remember only whether the first autistic symptoms were evident before or after the third birthday, specific codes were used to allow these cases to be deleted from the analysis. For 6 individuals in the Stafford sample for whom ADI-R data were not available, age at first parental concern was estimated from the medical notes. Interrater reliability on 38 videotaped ADI-R interviews in the epidemiologic sample was excellent for this variable (intraclass correlation coefficient: 0.84).

Definition and Assessment of Regression

The assessment of regression in the ADI-R is covered with items 37 to 41 (for language) and items 95 to 103 (for other domains). The regression is assessed for language skills as follows: "Were you ever concerned that your child might have lost language skills during the first years of his/her life? Was there ever a time when he/she stopped speaking for some months after having learned to talk?"

For the parents' descriptions of the development of the child to match the concept of regression, it is mandatory for the interviewer to verify 3 features: the level of the skill before the loss occurred, the intensity of the loss of the skill, and the duration of the loss of the skill. Thus, for language skills, it is required that the child have used words (at least 5 different words other than "mamma" and "dadda") regularly, on a daily basis, for at least 3 months, either to communicate or as spontaneous vocalizations or as elicited imitations of words. If this criterion is met, then the loss is subsequently defined as the absence of use of words to communicate or verbalize or imitate, for a duration of at least 3 months, to be scored as evidence of definite regression. The loss of a specified skill that does not meet these stringent criteria, nevertheless, can be coded as probable if there is sufficient evidence of regression. Following similar rules, loss of skills is assessed further in other developmental domains, including broader aspects of communication, social interests and responsiveness, play and imagination, adaptive skills, preacademic/academic or vocational skills, and motor skills. Two time periods for loss of skills (before and after age 5) are assessed separately. For analysis purposes, regression was assessed in the Stafford sample by identifying any probable or definite loss of skills in 1 of the 7 domains in which loss could have occurred. A record of a definite loss of skills in 1 domain was sufficient to score a definite level of regression in any child. Only data scored below age 5 were used to make the measurement of regression more consistent across samples (see below). Interrater reliability on the assessment of regression was very good on 38 double-rated interview tapes ($\kappa = 0.60$).

For the MFS sample, a slightly different version of the ADI was used and regression was defined using 3 items of the original ADI version that assessed probable and definite levels of regression and loss of skills, in the first 5 years of life, and in 3 domains: language, social interactions, and play and imagination. A fourth item, loss of skills over the lifetime, was not included in our definition of regression to avoid confounding the comparisons by age.

Assessment of Bowel Disorders and Symptoms

These data were available only from the epidemiologic sample (Stafford sample). All children were reviewed regularly and are still followed up by the pediatrician (S.C.), who has records of any additional hospital admissions/medical investigations for bowel disorders in these children.

The occurrence of gastrointestinal symptoms was assessed by 2 sources: the parents and the pediatrician. On 76 children for whom data were available from both sources, there was good agreement between the presence/absence of any gastrointestinal symptom in the children ($\kappa = 0.86$). For the remaining 20 children for whom parental questionnaires were missing, the pediatric assessments of gastrointestinal symptoms were used.

Statistical Analysis

Fisher's exact test and χ^2 tests were used for categorical variables, and Student's t test and Fisher's analysis of variance were used for continuous measures. Reliability of the measures was assessed with the intraclass correlation and κ coefficients. Throughout, a conventional P value of .05 was retained as the level of statistical significance.

RESULTS

The results are laid out in the order of the specific set of predictions that were tested in this study.

CDD Might Have Increased

One boy only met criteria for CDD in the epidemiologic sample (Stafford sample), which yielded a prevalence of 0.6/10 000[27] (95% confidence interval: 0.02–3.6/10 000). This child had profound behavioral deterioration at age 4, although he had had earlier signs of brain pathology, and cerebral palsy was diagnosed at 9 months with small right parietal infarct on computed tomographic brain scan. Additional medical investigations after the disintegration showed continuous seizure activity from the right hemisphere. There were no other cases of CDD in this sample. Therefore, there was no evidence that CDD rate was increased among children who were exposed to MMR immunization.

Age at First Parental Concern Has Changed in Samples Who Were Exposed to MMR

There was no difference in the mean age of first parental concerns among the 3 study samples ($F_{2,250} = 0.02$; not significant; Table 2, Fig 1). The lack of a difference between the mean age at first parental concerns of the Stafford and the MHC samples indicates that the mode of sample ascertainment did not influence parental reports. The slightly larger standard deviation for the MFS sample reflects the older age of this sample; thus, 1 individual had an age of first parental concern of 96 months. Excluding this individual, the mean age at first parental concern in the MFS sample was 18.6 months (SD: 10.9) and a repeat comparison of the 3 samples yielded the same nonsignificant results ($F_{2,249} = 0.13$; $P = .88$). Therefore, there was no evidence that the shape and loca-

TABLE 2. Age at First Parental Concern and Regression in Pre- and Post-MMR Samples

	MFS Sample	MHC Sample	Epidemiological Stafford Sample	*P* Value
n	98	68	96	
Birth period	1954–1979	1987–1996	1992–1995	
MMR status	Pre-MMR	Post-MMR	Post-MMR	
Age at first parental concern in months ($\bar{X}$ [SD])	19.5 (13.6)	19.2 (8.8)	19.3 (8.7)	NS
Regression				
Probable	14 (14.3)	—	7 (7.3)	NS
Definite	4 (4.1)	—	8 (8.3)	
Any	18 (18.4)	—	15 (15.6)	NS

NS indicates not significant.

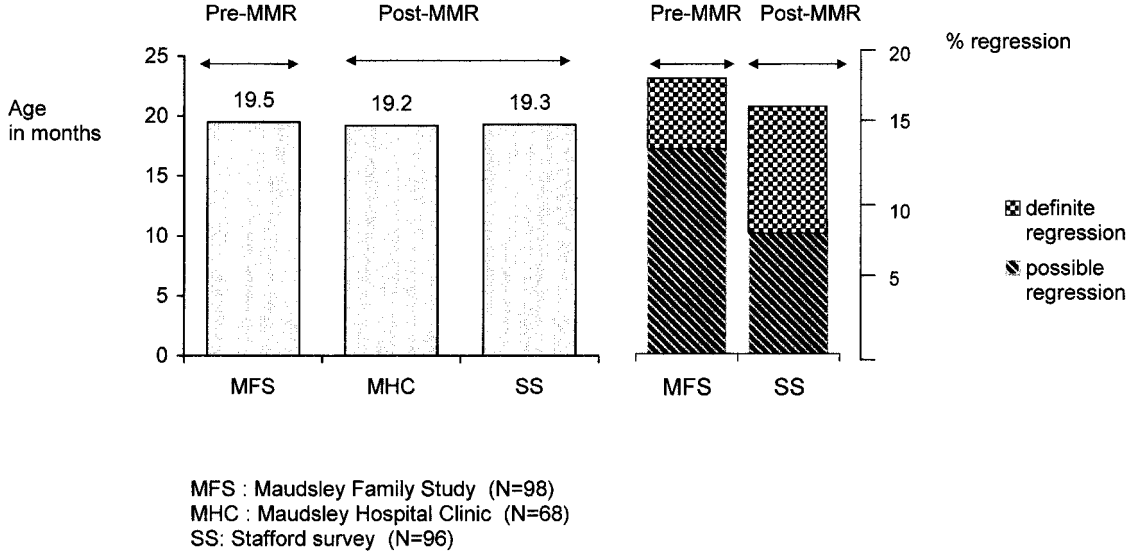

Fig 1. Age at first parental concern and autistic regression in pre- and post-MMR samples.

tion of the distribution of ages at first parental concerns in the 2 post-MMR samples were different from that in the pre-MMR sample.

The Rate of Regressive Autism Has Increased

In the 2 samples for which regression data were available (Table 2, Fig 1), no difference was found in the rates of probable and definite regression ($\chi^2 = 3.65$; $df = 2$; $P > .15$). Comparisons of definite levels of regression only across the 2 samples also was not significant (Fisher's exact test; $P = .25$). Similarly, there was no difference across the 2 samples for the rates of any (probable or definite) regression (Fisher's exact test; $P = .70$). Therefore, there was no evidence that regressive autism has increased in frequency.

Parents of Children With Regression Were Concerned at a Different Age and at an Age Closer to Immunization Than Those of Children Without Regression

In the Stafford sample, the mean age at which parents first were concerned was 19.8 months (SD: 7.4) for the 15 children with regression as compared with 19.3 months (SD: 9.0) for the 81 children without regression ($t = 0.22$; $df = 94$; not significant). Furthermore, for the 67 children whose parents' concerns postdated MMR immunization, no difference was found for the mean interval between immunization date and age of first parental concern between children with or without regression (248 vs 272 days; $t = 0.32$; not significant). Therefore, when compared with parents of autistic children without regression, parents of children with regressive autism did not become concerned at an earlier age or at an age closer to the MMR immunization date.

Children With Regression Have a Different Symptom Profile Than Those Without Regression

Scores obtained with the ADI-R in the 3 domains that define PDDs were compared for children with and without regression in the Stafford sample (Table 3). For all scores, no statistically significant difference was found between the 2 groups, suggesting a great similarity for patterns and levels of autistic symptomatology. We further compared these 2 groups for the 92 children for whom psychometric data were available. Consistent with previous reports in the literature, there was a trend for lower cognitive functioning in the regressive group as indexed by higher rates of mental retardation (IQ < 70) in the children with regression than in those without regression (46.1% vs 21.5%; Fisher's exact test: $P = .08$).

TABLE 3. Regression and Severity of Autistic Symptoms

ADI-R Mean Scores	Without Regression* (n = 75) ($\bar{x}$ [SD])	With Regression (n = 14) ($\bar{x}$ [SD])	P Value
Social interactions	15.8 (6.0)	17.4 (7.5)	NS
Communication			
Nonverbal	7.9 (3.7)	9.1 (3.8)	NS
Verbal	12.6 (4.6)	14.1 (4.2)	NS
Repetitive/restricted behaviors	5.5 (2.3)	5.1 (2.4)	NS
Total ADI-R	33.5 (9.1)	35.9 (9.4)	NS

NS indicates not significant.
* One case with incomplete scores was excluded.

Children Who Regress Have High Rates of Gastrointestinal Symptoms

There was no report of inflammatory bowel disorder in this sample or of children having been admitted to the hospital or having had medical investigations for bowel syndromes.

Gastrointestinal symptoms were reported in 18 children (18.8%), with constipation being the most common of the symptoms (n = 9 [9.4%]), followed by abdominal pain (n = 5 [5.2%]), bloody stools (n = 5 [5.2%]), and diarrhea (n = 3 [3.1%]). Bloody stools were transient and mostly associated with constipation. No association was found between gastrointestinal symptoms and regression (odds ratio: 0.63; 95% confidence interval: 0.06–3.2; Fisher's exact test: P = .86; not significant). Thus, only 2 children in the whole sample (2.1%) had both gastrointestinal symptoms and regression in their development, a rate that did not exceed that predicted by chance alone; this represented 11.1% and 13.3%, respectively, of children with any occurrence of bowel symptoms or any regression in their development. The analysis was repeated on the 76 children for whom only parental reports were available, and identical results were obtained; only 1 child (1.3%) had experienced both problems.

DISCUSSION

None of the 6 predictions tested in this study to validate an autistic enterocolitis phenotype was supported by the data. Only 1 child had CDD, which most likely originated from associated comorbid brain pathology predating MMR immunization. The prevalence rate of CDD derived from this epidemiologic survey is consistent with the very low estimates available in 3 other epidemiologic surveys,[32–34] all suggesting that the rate of CDD is 50 to 100 times less than that for autistic disorder (E. Fombonne, submitted). In this epidemiologically ascertained sample with almost all children exposed to MMR vaccination, it can be concluded safely that CDD is not increased as a function of vaccine exposure.

Second, no changes in the mean age of parental recognition of first autistic symptoms were found when 2 samples of children, 1 clinical and 1 epidemiologic, all exposed to MMR immunization, were compared with a pre-MMR sample. Ages of first parental concerns were assessed using the same standardized diagnostic interview that is widely regarded as the best developmental diagnostic measure available for professionals who work with children with PDDs. Although the account of the age of onset is based on retrospective parental estimates (and, as such, the accuracy of this retrospective dating remains questionable), that the mean ages reported by parents were similar across the 3 samples investigated with identical methods was striking. In the post-MMR samples, parents did not report a shift toward an earlier age of onset, which was expected under the hypothesis of an impact of MMR immunization on the onset of autistic symptoms. Furthermore, there was no difference between the epidemiologic sample, for which all interviews were conducted by 1 interviewer, and the clinical sample, for which many different clinically trained interviewers, blind to the hypothesis tested in this study, were used.

Third, rates of regression in the development of children with autism were found to be similar in a pre- and post-MMR sample, suggesting that there has been no increase in the rate of regressive autism in recent years. Slight differences in the operationalization of regression in the versions of the ADI used across the 2 studies might account for some of the differences observed between the 2 samples in the rates of probable and definite regression. The ADI-R used in the Stafford sample investigated regression in more developmental domains than the ADI used in the MFS sample, which might explain the slightly raised proportion of cases with definite regression in the epidemiologic sample, albeit this difference was far from being significant. Moreover, the differences in the definition of regression across the 2 samples should have produced, if anything, an increase in the overall frequency of regression phenomena in the more recent sample, which was not observed. This pattern of findings allows us to rule out confidently any increase over time in the rate of regression in PDDs.

The rates of regression reported in both samples were lower than those reported in the earlier literature (Table 1) and in other large clinical series.[35] This difference most certainly is explained by the higher degree of operationalization of the definition of regression in the ADI interviews, as compared with the more lax clinical definition used in other studies. Thus, the ADI required that a skill have been exerted at a certain level for a period of time before being lost for a nontrivial duration. These definitional constraints clearly would lead to fewer children matching precisely this regression pattern. Moreover, it is noteworthy that the rate of definite regression in the Stafford epidemiologic sample was only 8.3%, which is consistent with other recent studies in which regression and first autistic symptoms were assessed with carefully designed methods.[36] In the current debate about the hypothesized links between the increased rates of autism and the introduction of MMR immunization, that rates of regressive autism as reported in recent studies remain at low levels (and therefore could not have increased massively) rules out MMR-induced regressive autism as a cause of the observed increase in autism rates. Our results add to the accumulation of recent large-scale epide-

miologic studies[37–39] (W. Chen, S. Landau, P. Sham, E. Fombonne, submitted) that all failed to support an association between MMR and autism at population level, as claimed previously.[14]

Fourth, additional analysis of the subset of children with a regressive pattern of development failed to detect phenomenological differences from the other nonregressive children, a lack of difference that does not argue for separate causal mechanisms operating in these 2 groups, although, admittedly, it does not rule out this possibility. Equally, that parents of children with regressive autism were not concerned at an earlier age, closer to the mean age of MMR immunization, clearly does not support that MMR triggers autism in the regressive subgroup. Moreover, the average intervals between immunization date and first parental concerns in our data certainly ruled out a precipitous onset within days after immunization as reported previously.[12]

Fifth, one of the tenets of the autistic enterocolitis syndrome relies on the clinical association between gastrointestinal symptoms and regression. The rates of gastrointestinal symptoms reported in our epidemiologic sample was not different from that reported by parents in other recent epidemiologic surveys conducted in the United Kingdom. Thus, stomach problems/abdominal pains were endorsed by 5.6% of parents of children without a diagnosis and 6.9% of parents of children with a diagnosis of attention-deficit/hyperactivity disorder in a recent epidemiologic nationwide survey[40]; these figures were comparable to our rate of 5.2% for abdominal pain. It is noteworthy that the severity of these symptoms was mild and did not require additional medical investigations. Arguing strongly against the validity of an autistic enterocolitis phenotype, we found no association between the occurrence of gastrointestinal symptoms and regression in this representative series of children with PDDs. Because gastrointestinal symptoms were reported by parents, as in the 2 previous reports,[12,13] the lack of association between gastrointestinal symptoms and regression must be regarded as a valid result because had parents observed the co-occurrence of these problems in their children, they most certainly would have reported them. In addition, children in this sample all were young, which should have reduced any recall problem. Furthermore, as shown by the point estimate (odds ratio < 1) of the association between gastrointestinal symptoms and regression, there was not even a trend for a positive association and reduced statistical power therefore is unlikely to account for our negative results.

There are particular strengths in this study that need to be emphasized. The sample of 97 children with a PDD diagnosis was ascertained in an epidemiologic survey in a geographically defined area, and all children were seen and assessed with a multidisciplinary team during a 2-week period.[27] Moreover, children and their families were followed up over the years by one of the authors, who has an intimate clinical knowledge of their predicament. We relied in the assessments of these children on standardized diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[2]) and standardized diagnostic interview measures,[28] which are considered the current standard of the diagnostic measures available in that field. Furthermore, we demonstrated that the key variables used in this investigation (age of first parental concern and regression) were measured with high levels of reliability. Similarly, the comparison samples were investigated with the same comprehensive diagnostic measures and with interviewers who were both trained and blind to the hypothesis under investigation in this study.

Some limitations of this study also need to be mentioned. First, the sample size was limited, although, compared with most other epidemiologic studies, the number of available individuals with a PDD was satisfactory.[3,41] Second, the investigation of gastrointestinal symptoms was performed mostly via a questionnaire survey of parents and clinical examinations by a pediatrician; no specific biological investigations were performed on the guts of these children, whether with or without reports of regression. As a consequence, this study cannot test further the validity of the biological findings that have been reported.[13] Nevertheless, as mentioned before, that parents were informants on the gastrointestinal symptoms in their children provides a robust test of the validity of a new autistic enterocolitis syndrome for which no corroborative evidence has been found in this study.

Two important messages derive from this study. First, combined with the mounting negative epidemiologic evidence, the lack of evidence for a new phenotype of MMR-induced autism strongly argues against any change in existing MMR immunization programs, a conclusion also reached in recent reviews by ad hoc committees.[42,43] Second, it no longer should be acceptable that investigators who still argue for a MMR-autism link fail to provide precise and replicable clinical and developmental data on their autism samples, thereby maintaining a degree of ambiguity and confusion that is damaging to both the public health and the science.

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