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Incidence of autism spectrum disorders: changes over time and their meaning.

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AIM: Several reviews have noted a huge increase in the rate of diagnosed autism spectrum disorders. The main aims of this paper are: 1) to use published empirical findings to consider whether the rise reflects a true increase in incidence, as distinct from the consequences of better ascertainment and a broadening of the diagnostic concept; and 2) to consider how epidemiological data may be used to test hypotheses about possible causal influences, using MMR and thimerosal as examples. METHODS: Search of the literature for studies with a large epidemiological base population, systematic standardized screening, a focus on an age group for which diagnostic assessments are reliable and valid, and diagnosis by trained professionals using high-quality research assessments. Also, search of a broader literature to consider the evidence from all epidemiological studies with respect to the hypothesized causal effect of MMR and thimerosal on autism spectrum disorders. RESULTS: The true incidence of autism spectrum disorders is likely to be within the range of 30-60 cases per 10 000, a huge increase over the original estimate 40 years ago of 4 per 10000. The increase is largely a consequence of improved ascertainment and a considerable broadening of the diagnostic concept. However, a true risk due to some, as yet to be identified, environmental risk factor cannot be ruled out. There is no support for the hypothesis for a role of either MMR or thimerosal in causation, but the evidence on the latter is more limited. CONCLUSION: Progress in testing environmental risk hypotheses will require the integration of epidemiological and biological studies.

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REVIEW ARTICLE

Incidence of autism spectrum disorders: Changes over time and their meaning*

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Abstract

Aim: Several reviews have noted a huge increase in the rate of diagnosed autism spectrum disorders. The main aims of this paper are: 1) to use published empirical findings to consider whether the rise reflects a true increase in incidence, as distinct from the consequences of better ascertainment and a broadening of the diagnostic concept; and 2) to consider how epidemiological data may be used to test hypotheses about possible causal influences, using MMR and thimerosal as examples. *Methods:* Search of the literature for studies with a large epidemiological base population, systematic standardized screening, a focus on an age group for which diagnostic assessments are reliable and valid, and diagnosis by trained professionals using high-quality research assessments. Also, search of a broader literature to consider the evidence from all epidemiological studies with respect to the hypothesized causal effect of MMR and thimerosal on autism spectrum disorders. *Results:* The true incidence of autism spectrum disorders is likely to be within the range of 30–60 cases per 10 000, a huge increase over the original estimate 40 years ago of 4 per 10 000. The increase is largely a consequence of improved ascertainment and a considerable broadening of the diagnostic concept. However, a true risk due to some, as yet to be identified, environmental risk factor cannot be ruled out. There is no support for the hypothesis for a role of either MMR or thimerosal in causation, but the evidence on the latter is more limited.

Conclusion: Progress in testing environmental risk hypotheses will require the integration of epidemiological and biological studies.

Key Words: *Autism spectrum disorders, diagnostic concept, incidence, measles-mumps-rubella vaccine, thimerosal*

Several authoritative reviews of the prevalence of autism spectrum disorders [1–3] have suggested that, in contrast to the 4 per 10 000 rate in the first survey in 1966 [4], the current rate is 30 to 60 cases per 10 000. The difference between these two figures clearly demands an explanation—the main focus of this paper. Empirical research findings are used to consider whether there has been a true rise over time in the incidence of autism spectrum disorders—ASD—(as distinct from the frequency with which this diagnosis is made) and to go on to consider what the changes over time might mean, together with the consideration of how epidemiological data may be used to test hypotheses about possible causal influences, using MMR and thimerosal as examples.

Large-scale modern epidemiological studies

Valid estimates of the incidence or prevalence of ASD require studies that meet five criteria: 1) a base population of sufficient size to provide a substantial number of individuals with an ASD (so that the confidence interval will be narrow); 2) a defined epidemiological population that covers all the individuals likely to be at risk for an ASD; 3) systematic standardized screening of the total population; 4) a focus on an age group for

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which it is known that diagnostic assessments are reliable and valid; 5) diagnosis by trained professionals using high-quality standardized research assessments.

Three studies using different research strategies are used as exemplars. The first employed multiple cross-sectional screenings followed by the use of a standardized diagnostic interview; the second prospectively studied a birth cohort using multiple screenings followed by a thorough clinical diagnostic assessment; and the third also followed a birth cohort with systematic health check-ups followed by a thorough diagnostic assessment.

Chakrabarti and Fombonne study

The Chakrabarti and Fombonne study [5] in the UK is the survey that comes closest to meeting the requisite criteria. The first stage comprised a standard health professional screening of 15 500 children aged 2½ to 6½ y. On the basis of that screening, 576 children were assessed at a second stage by a developmental paediatrician. That led to a 2-wk multidisciplinary assessment of 426 of those children, which included a thorough medical study. These first three stages served to eliminate children whose problems of various kinds did not seem likely to meet the criteria for an ASD. From the 426 children, 103 were chosen for a systematic standardized assessment using the revised version of the Autism Diagnostic Interview (ADI-R) [6]. On the basis of the ADI-R, six children were considered not to have an ASD. Twenty-six had autism meeting the standard diagnostic criteria and nearly three times that number [71] had some other form of ASD. The autism prevalence was calculated to be 16.8 per 10 000 (confidence interval 11.0 to 24.6). The prevalence of ASD other than autism was 45.8 (confidence interval 35.8 to 57.7). The total rate of ASD provided by the sum of these two figures is 62.6 per 10 000.

The systematic multistage approach makes it rather unlikely that any substantial number of children with ASD were missed by the study. The main concern is that the assessment did not include any direct standardized assessment of the children themselves—such as by using the Autism Diagnostic Observation Schedule (ADOS) [7]. However, there are continuing uncertainties about how to combine the ADI-R and ADOS assessments and what to do with the diagnosis when the two measures give different answers. The findings are particularly noteworthy in terms of the difference in the level of intellectual functioning between the subgroup with autism and the subgroup with other ASD. Nearly all (94%) of those with other ASD showed normal intellectual functioning and none had severe or profound retardation. Of those with autism, 31% had normal intellectual functioning, 19% had severe or profound retardation, and 50% had mild/moderate retardation. The sex ratio was 3.9 to 1. Of the children with an ASD, 9.3% had an associated medical condition that was likely to have played a part in causation. There were three cases of cerebral palsy, two of hydrocephalus, one of tuberous sclerosis and two with sex chromosome anomalies. There were no cases of Fragile X (despite systematic testing for it).

Baird study

A second study that meets many, but not all, of the relevant criteria is that undertaken by Baird et al. [8]. It differs in that it started with a systematic screening of 16 235 children aged 18 mo using the Checklist for Autism in Toddlers (CHAT) [8]. This population was re-screened with the CHAT at 3½ y. There was some attrition over this period, so that the number assessed at 3½ was 12 770. There was a further re-screening of 7776 children at 5½ y (using a parental questionnaire), some children were referred to a regional assessment for diagnostic assessment during the course of the project, and a records check was undertaken at 7 to 8 y. All children picked up on any of the screening measures or who were referred to the regional centre were directly assessed by the research team. The estimated rate of ASD was 30.8 per 10 000 (confidence interval 22.9 to 40.6). The estimated IQs suggested that 60% were in the normal range. The study finding is unusual, however, in that the male–female ratio of 15.7 : 1 was much greater than usually found. The study has all the advantages of multiple screening and the use of a prospective longitudinal design. On the other hand, it has the limitation of a substantial attrition rate and the fact that the diagnoses were based on non-standardized clinical assessments rather than the use of high-quality research measures. The population is currently being re-examined using such standardized measures.

Honda study

Honda et al. [9] adopted a different strategy in their epidemiological study of autism in the northern part of Yokohama, Japan. They surveyed children born in 1988. A systematic health check-up was undertaken at 18 mo and at 3 y for 90% of the children. Children suspected of having disorders were referred to the Yokohama Rehabilitation Centre, where a detailed diagnostic assessment for autism was undertaken. Eighteen children were diagnosed as having autism (ASD other than autism were excluded), giving a cumulative incidence by age 5 y of 16.2 per 10 000 (and a prevalence of 21.1 per 10 000). Half the children with autism had an IQ above 70, with all but one of these scoring 85 or above. The study has the advantages of measuring incidence and not just prevalence and of systematic total population screening leading to a thorough clinical assessment. However, it is limited

by the fact that standardized research diagnostic measures were not employed.

Other surveys

Many of the other surveys undertaken in the last decade have lacked systematic total population screening, but this was carried out in the studies undertaken by Kadsejö et al. [10], Fombonne et al. [11], and by Arvidsson et al. [12], with prevalence rates of 72.6, 26.1 and 46.4 per 10 000, respectively, for ASD (including, but not confined to, autism). However, these were based on very small numbers, apart from the Fombonne et al. study [11].

Conclusions about the true current rate of ASD

It is not possible to derive a precise figure for the current true incidence of ASD, because of uncertainty over the boundaries of the syndrome. Nevertheless, the rate is likely to be in the region of 30 to 60 cases per 10 000, with about a quarter of those meeting the full criteria for autism. It is unlikely that the true figure will turn out to be greatly below that, and it is obvious that it is far higher than the estimates from the earlier studies. Reasonable confidence can be placed in these large-scale modern studies because they have not been reliant on children being referred to specialized clinics, because the findings are broadly comparable across studies, and because several have used well-standardized and well-tested diagnostic instruments.

Early studies

The same confidence cannot be expressed with respect to the much lower rates found in the earlier studies. Most relied to a considerable extent on some form of screening based on the children attending some clinical facility or special school or residential unit. There was much less satisfactory coverage of children attending ordinary schools, and both hospital and educational services for children with ASD were very much less well developed and much less freely available than is the case today. During the 1960s and 1970s, few child psychiatrists and few paediatricians, and even fewer general practitioners, were experienced in the recognition and diagnosis of ASD. This is reflected in the finding [13] that children are now receiving diagnoses of ASD at a substantially earlier age than was the case some years ago. Much less satisfactory ascertainment of cases will certainly have led to cases of ASD being missed in the epidemiological studies undertaken at that time. To what extent the lower rate of autism in the past was also the function of a narrower diagnostic concept is difficult to determine because the data are not available to apply current concepts to the measures obtained years ago. Nevertheless, one preliminary study sought to consider whether the application of modern concepts to old data would increase the rates of ASD in those early studies and concluded that it did [14].

Changing concepts of autism

Even in the 1960s there was an awareness of the frequency with which children showed disorders that were closely comparable to autism but which did not quite meet the prevailing diagnostic criteria. Thus, Lotter [4] differentiated between the 2.0 per 10 000 with the core syndrome and the 2.5 per 10 000 with a somewhat less consistent pattern (these two groups being pooled to cover "autistic conditions"). In addition, he had a third group called "non-autistic" but who showed many autistic features—the prevalence being 2.8 per 10 000. If these are included in what might be regarded now as ASD, the overall rate would be 7.3 per 10 000. Two-thirds of the children with "autistic conditions" had an IQ in the severely retarded range. At first there was a tendency to concentrate mainly on the supposed core syndrome of autism that was thought to meet Kanner's [15] criteria. Over the years there has been a marked move to the acceptance that it was probably preferable, from both a service perspective and a biological point of view, to include the broader range of autism-like disorders. The broadening of the diagnostic concept came about in four somewhat different ways.

First, epidemiological evidence highlighted the high frequency with which autistic-like problems occurred in children with severe or profound mental retardation [16]. At one time, clinicians had tended to differentiate between primary autism and autism that was secondary to mental retardation. This primary–secondary distinction was never very satisfactory because, if it was accepted that the disorder of autism could give rise to impaired cognitive functioning, there had to be a way of determining whether the autism caused the mental retardation or whether the causal arrow ran in the opposite direction. It was never at all clear how that decision could be made on either empirical or logical grounds.

Over the years, during the course of the development of standardized diagnostic measures, both clinicians and researchers became aware of the need to differentiate between impairments in social and communicative functioning that were directly related to mental level (i.e. the impairment was no more than would be expected in relation to the child's mental age) and qualitative abnormalities in social and communicative functioning that would be abnormal at any mental age level [17]. It came to be accepted that if the social and communicative functioning was qualitatively abnormal, the mere presence of associated

mental retardation should not be taken as an exclusion criterion and that the old-style primary/secondary distinction was not a useful one. This led to a greater acceptance that ASD could be diagnosed even in quite severely retarded individuals. Hence, for example, there were occasional reports of the occurrence of autism in individuals with Down syndrome [18,19].

Second, a proportion of children with autism were shown to have diagnosable somatic diseases or disorders of various kinds [20]. Half a century ago these would usually have been excluded—again, on the grounds that the autism was simply an incidental secondary condition. Such exclusion might have been appropriate at a time when the prevailing concept was that of autism being a psychogenic condition, but it was inappropriate if autism was, in fact, a biologically determined neurodevelopmental disorder. Accordingly, cases of autism that were associated with a medical disease came to be included. There have been some controversies over the frequency with which these medical associations arise, but probably the figure is something of the order of 10% [21], although some investigators have put the proportion higher [22].

Third, twin and family studies were consistent in showing the high frequency with which milder, autistic-like features were found in the relatives of individuals with autism [23]. These features came to be termed the "broader phenotype" of autism. The twin data were also important in showing both that the genetic liability to autism extended much more broadly than the traditional diagnostic concept of a serious handicapping disorder, and that within monozygotic twin pairs, both of whom showed autism, the pattern of clinical expression, and also the degree of cognitive impairment, differed markedly in many instances [24,25]. This broader phenotype of autism, interestingly, was not usually associated with either mental retardation or epilepsy, both of which were common in traditionally diagnosed autism. The consequence was that clinicians and researchers came to accept that ASD occurred quite often in individuals of normal intelligence, although often with specific deficits in social cognition.

The fourth influence derived from the much greater recognition of features of Asperger syndrome [26,27]. Asperger's original paper made a much smaller impact than did Kanner's paper, published the previous year. There was some take up in parts of Europe of the concept of what van Krevelen [28] called "autistic psychopathy", but the term received only very limited use. Probably, the key stimulus came from Wing's [29] paper on the syndrome, which led to a variety of empirical studies. There is still no agreement on the diagnostic criteria for Asperger syndrome, but the importance of the concept lies in the recognition that autistic-like syndromes not infrequently arise in individuals of normal intelligence who have not shown a major delay in the acquisition of language, although they have often shown more subtle abnormalities in communication patterns [30]. Like the genetic findings, the result was the broadening of the diagnosis of ASD to individuals without mental retardation and without major language delay. Probably because of the absence of early language delay, all the findings indicate that Asperger syndrome tends to be diagnosed rather later than does autism as such [31].

These different influences may be expected to have had different consequences on the patterns of ASD in epidemiological studies. Thus, the acceptance that the autism diagnosis should not be excluded by severe mental retardation ought to have led to an increase in the proportion of children whose autism is accompanied by severe or profound mental retardation. This is not what has been found. The second consideration means an expectation of an increase in the proportion of cases associated with diagnosable medical conditions. Again, this is not what has been found. Conversely, the third and fourth influences should have operated in the reverse direction by being likely to lead to a marked increase in the proportion of cases of autism occurring in individuals of normal non-verbal intelligence; this has been the case. The inclusion of Asperger syndrome might also be expected to lead to an increase in the average age of diagnosis; the evidence shows the reverse.

In one important respect there has also been a narrowing of the concept of ASD. This followed the identification of Rett syndrome [32], which became widely recognized following a key paper by Hagberg et al. [33]. Although many individuals with Rett syndrome go through a phase in early childhood when they show somewhat atypical autistic features [34], the overall pattern is rather different, the course is progressively associated with neurological deterioration, and it is now known that the great majority of cases are due to a mutation in the MECP2 gene [35]. Because Rett syndrome is so much rarer than autism, the exclusion of such cases from epidemiological studies is not likely to have made much appreciable difference.

A further syndrome that complicates the picture is that of so-called disintegrative disorder [36]. The mode of onset is different from autism in there being a substantial period of normal development before the occurrence of a profound developmental regression. The condition is much less frequent than autism and it has been much less investigated. It remains quite unknown whether it constitutes an unusual variant of autism or something quite different. On the whole, it would nowadays ordinarily be included in the broader concept of ASD, but its relative infrequency means that its inclusion or exclusion is not likely to make a major difference to the findings on the population base rate of ASD.

Attention also needs to be paid to the changes over time in the diagnostic criteria for autism and for ASD in the major classification systems. These have been considered with respect to the changes between DSM-III, DSM-IIIR and DSM-IV, as well as associations with ICD-9 and ICD-10 [37]. However, it would be a mistake to pay too much attention to these changes because the shifts over time in the concepts of ASD have not been primarily driven by the minor changes in specifications of individual criteria or the number of criteria that must be met. Nevertheless, it is true that the current criteria tend to pick up a larger number of cases than the older criteria.

Ascertainment

Since the first survey in the 1960s, there has been a major expansion in educational or therapeutic facilities for children with ASD, and professional and public awareness of the syndrome has greatly increased. The quality and quantity of services for young people with ASD fall well short of the ideal, but they are incomparably better and a great deal more widespread than they used to be. As a consequence, not only are paediatricians, psychiatrists, psychologists and social workers much more aware of ASD than they used to be, but so too are teachers and the general public. Although adequate quantification of the changes over time is lacking, there is no doubt that children with an ASD are much more likely to come to clinical notice now than used to be the case and, moreover, that it is much more likely that their problems will be recognized as belonging to the syndrome of an ASD. It is clear that this markedly improved ascertainment will have meant that far fewer cases are likely to have been missed in modern epidemiological studies, as compared with their predecessors several decades ago.

Has there been a true rise in the incidence of ASD?

It is clear that, to a very considerable extent, the rise over time in the rate of diagnosed ASD is a consequence of better ascertainment and a broadening of the concept of ASD. However, this conclusion does not necessarily rule out the possibility of a true rise in incidence.

Three studies of autism in California have attempted to determine whether the rise in rate reflects a true increase over time in incidence, but the findings are not entirely consistent. The Department of Developmental Services [38] used standard records data from 21 regional centres over the time period from January 1987 through December 1998. They found that the percentage increase was substantially greater for autism (210%) than for mental retardation (49%) and other neurodevelopmental disorders. The increase in autism as such was, however, less than that for other ASD categories. It was noteworthy that there was a significant increase over time in the proportion of individuals with autism whose intellectual functioning was in the normal range. An update using data covering 1999 through 2002 [39] showed that earlier trends were generally continuing, with the rate of ASD still rising, and the proportion of cases of ASD without mental retardation also increasing. The findings are limited by the fact that they reflect administrative prevalence, rather than true incidence.

Croen et al. [40] conducted a population-based study of birth cohorts across the time period 1987 to 1994, using the same data records and the 1999 study outlined above. The study had the advantage of linkage with birth certificates and hence the ability to generate incidence figures, albeit based on records diagnoses. The findings showed an increase in the rate of autism from 5.8 per 10 000 for children born in 1987 to 14.9 per 10 000 for those born in 1994 (despite the fact that the latter group had a shorter period of time during which there was the opportunity of making a diagnosis). The increase in the rate of autism was somewhat greater for those without mental retardation. Over the same time period, the rate of diagnosed mental retardation fell from 28.8 per 10 000 to 19.5 per 10 000. The authors concluded that the findings suggested that at least part of the rise in rate was likely to be due to changes in diagnostic practice and better ascertainment.

Blaxill et al. [41] pointed out that ascertainment bias was likely to have led to an underestimation of the rate of autism in the younger cohorts and that the usually later age of recognition of mental retardation as compared with autism means that the mental retardation figures would be underestimates that provide a misleading picture of a fall of rate over time. In response, Croen and Grether [42] undertook a reanalysis of this, which focused only on the diagnosis by age 4 y. The result showed a marked rise over time for the diagnosis of autism but no change over time in the rate of mental retardation. They concluded that their original suggestion, that the diagnosis of autism might, in part, represent a diagnostic substitution for mental retardation, could not be upheld.

The third study, by the MIND Institute [43], used the same records data but differed in that subsamples were assessed using standardized diagnostic measures. They, too, found an increase over time in the proportion of children with autism who were said not to be mentally retarded (50% in the 1983–1985 group versus 78% in the 1993–1995 group), but the IQs were estimated rather than measured. There was no change over time in the proportion showing developmental regression (28% vs 34%). Because there was no change over time in the level of agreement between

the administrative diagnosis and the standardized research diagnosis, it was concluded that the rise over time was not due to changes in diagnostic practice. Unfortunately, the findings are severely constrained by the fact that the response rate was so extremely low (10 to 24% according to subgroups). Also, because the ADI-R diagnostic algorithm [6] reflects modern concepts of ASD, it would be expected to confirm contemporary diagnoses. Necessarily, it would also confirm the earlier diagnosis based on a narrower concept, but one that used the same qualitative features.

Jick et al. [44,45] used the UK General Practice Research Database (GPRD) to examine the annual rate of diagnosed autism in 2–4-y-olds for birth cohorts extending from 1990 to 1997. The rate rose from 1.6 per 10 000 to 9.5 per 10 000, with a parallel decrease in the annual rate of diagnosis of some form of developmental disorder from 17.6 per 10 000 to 3.3 per 10 000. It was suggested that the rise in the rate of diagnosed autism was primarily a reflection of a change in diagnostic practice (but this is uncertain for the reasons that applied to the Croen study).

Other epidemiological studies have also shown that the proportion of cases associated with normal non-verbal intelligence is probably substantially higher than that found in the earlier studies. In Lotter's 1966 survey, two-thirds of the children with an ASD had an IQ below 55. Similarly, in Gillberg's Swedish population studies in the late 1970s/early 1980s, the majority had an IQ under 50 [46,47]. His further study in 1988 [48] showed an increased rate of autism (11.6 per 10 000) compared with the first two surveys (4.0 per 10 000 in 1980 and 7.5 per 10 000 in 1984). He commented that there had been a parallel rise in the proportion of children with ASD who had a normal, or near normal, IQ. Precise figures were not given, but in the 1988 survey only 18% had an IQ above 70. By contrast, as already noted, the modern studies have all shown a much higher proportion of children with a normal IQ and a lower proportion with severe retardation. In summary, although there appears to have been a substantial rise in all varieties of ASD, the rise appears to have been greatest in those with a non-verbal IQ in the normal range. This implies a broadening of the diagnostic criteria.

The evidence is far too fragmentary for there to be any quantitative estimate of the size of this effect, but there can be no doubt from the evidence considered as a whole that a substantial part of the rise in the rate of ASD as diagnosed reflects a combination of better ascertainment and the broadening of the diagnostic concept. What is impossible to determine, however, is whether these account for the whole of the interest over time in the rate of diagnosed autism. When this issue was discussed at a meeting of international experts [49], there was a consensus that no firm conclusions were possible. Although much of the apparent rise has undoubtedly been a function of better ascertainment and a broadening of the diagnostic concept, it remains possible that there has, in addition, been a true rise that is not simply a consequence of changes in methodology.

Timing of the increase in the rate of diagnosed ASD

One possible, albeit rather indirect, approach to the question of the validity or invalidity of the supposed rise in true incidence of ASD is to consider whether the rise has occurred in all parts of the world and, if it has, whether it has occurred at much the same time. The rise in rate of diagnosed autism is evident in studies in the United Kingdom, in the USA, in Scandinavia, and in Japan. For example, the rate of autism in children born during 1977 to 1979 in a particular geographic area in Wales was 3.3 per 10 000, whereas that for children born during the period 1987 to 1989 was 9.2 per 10 000 [50]. The detailed findings show that the main rise occurred in the early 1980s, with little change thereafter. Magnusson and Saemundsen [51], using a clinical case register data in Iceland, estimated a prevalence rate of autism plus atypical autism of 4.2 per 10 000 for children born in 1974 to 1983 and 13.2 for those born in 1984 to 1993.

As already noted, Gillberg et al. [48], using epidemiological data on rather small samples, showed a rise in the rate of diagnosed ASD between 1980 and 1988 in the city of Göteborg. Powell et al. [52], studying ASD in preschool children from two areas of the West Midlands in the United Kingdom, found a substantial increase in rate between 1991/2 and 1995/6. The increase was more marked for the broader range of ASD than for "classical" autism *per se*. Hillman et al. [53], using the computerized client registries from regional diagnostic centres in Missouri, showed a huge increase in the rate of age-specific prevalence of autism between 1988 and 1995. Dales et al. [54] used data from the California Department of Developmental Services and found that the rise in the rate of diagnosed autism was continuous over the period between 1980 and 1994. Kaye et al. [44,45,55], using the General Practice Research Database in the UK, showed a steady rise in the rate of autism over the period between 1988 and 1996. Honda et al. [56] used incidence data on ASD (including both autism and other ASD) diagnosed by the age of 5 y for children born between 1988 and 1996 in an area of Yokohama in Japan with a population of just less than 300 000. Systematic screening for ASD followed by a detailed clinical assessment meant that the incidence figures are likely to be valid. For birth cohorts born between 1988 and 1996, the incidence of ASD rose from 54 per 10 000 to 88 per 10 000, with the main rise in the mid-1990s. Lingam et al. [57] used general practice research database records up to the year 2000 to determine

whether the rise in rate of diagnosed ASD was continuing during the 1990s. Their findings suggested a plateau for birth cohorts from 1992 onwards but unfortunately conclusions are based on statistical adjustments to take account of differing periods of opportunity for diagnosis, rather than confining analyses to cases of autism diagnosed by a standard age, such as 5 y. Gurney et al. [58] analysed data on children in Minnesota diagnosed with ASD over the time period from 1981 to 2002, using routinely collected special educational services disability designations. The data showed that the main rise began in the mid-1990s, with the increase most marked during the late 1990s and the first two years of this century.

Because the various studies have used different measures and different time periods, it is difficult to come to definitive conclusions. However, what is apparent is that all studies have shown a rise in the rate of diagnosed ASD. What is more variable is the time period when the main rise in rate took place. In some places, it seems to have begun during the 1970s and 1980s, whereas in other places the main rise has been in the 1990s. This variation in the timing of the rise might well be expected if the rise was a function of changes in concepts and changes in ascertainment, which is quite likely to have varied according to the development of services. If there had been a true rise due to some new environmental hazard, it would seem that the hazard must have been operating in Europe, the United States and Japan, but that it had its effect at somewhat different times in these different parts of the world. There is no very obvious candidate for what this universal hazard, which varied geographically in the timing of its effects, might be.

The alleged links between ASD and use of the MMR vaccine

Temporal clustering of MMR vaccinations and onset of ASD

In 1998, Wakefield et al. [59] postulated a causal connection between the use of the MMR vaccine and the onset of ASD associated with chronic enterocolitis. The emphasis was placed on the supposed close temporal association between the administration of the vaccine and the onset of autism. Among the 12 cases reported, in 9 the interval from exposure to the MMR vaccine and the first behavioural symptom was 2 wk or less. It was unwarranted to infer causation on the basis of this temporal association because the vaccine was given at about the same time period that the first manifestations of autism ordinarily become evident. Accordingly, chance alone was bound to provide an association. Nevertheless, the timing appeared close and it was important to examine the claim. Taylor et al. [60] used a systematic case series methodology to test the hypothesis of a temporal relationship between MMR immunization and the development of autism. Given the hypothesis of an acute effect, this was an appropriate research design even though, in the absence of an MMR effect, the onset of symptoms is frequently gradual. Children with autism born since 1979 were identified from registers in eight North Thames health districts in London. The results showed no significant clustering of interval to diagnosis within the monthly time periods from under 1 mo to 11–12 mo after vaccination. Also, developmental regression, which had been emphasized in the report by Wakefield et al., similarly showed no clustering in the months after vaccination. The data were constrained by the need for reliance on standard clinical records, rather than standardized research assessments, but it is not apparent why this should bias the findings in favour of a lack of association.

At a later date, the claims were modified to include the possibility of a delayed or chronic onset following administration of the MMR vaccine [61,62]. Spitzer et al. [63] undertook a study of the medical records of 493 children who were seeking redress for an alleged role of MMR in the development of their ASD. The mean length of time between MMR and the emergence of autistic symptoms was 1.2 y (range 0.1 to 7.2 y), and the mean time to diagnosis was 3.2 y (range 0.5 to 11.8 y). Only 39% of the children showed developmental regression; a figure within the range reported prior to the introduction of MMR, albeit on the high side. The sample was unrepresentative and self-selected but it indicates that, if MMR plays any role in causation, the effect might be considerably delayed. In an attempt to deal with that possibility, Farrington et al. [64] re-analysed the data from the Taylor et al. (1999) [60] study to examine the possibility of delayed effects. In the second study, they used data on all MMR vaccinations, including those given as part of a catch-up programme or as booster doses. Again, no temporal clustering was found. However, there are inevitable difficulties in using the self-controlled case series method for chronic diseases in which there is no clearly identified time of onset and possible variations in the time period between exposure to the risk factor and the onset of disorder [61].

Subsequently, there was a further change in the arguments put forward in support of the postulated association between MMR and autism. Wakefield [62,65] (and also Thrower [66]) suggested that the rate of autism had increased greatly since the MMR vaccine had been introduced and that this was a causal effect. The hypothesis requires the assumption that a high proportion of cases of current ASD have been caused, at least in part, by the vaccine. This possibility has been examined in several different studies using a range of methodologies, each of which has its own particular strengths and limitations.

Time trends in rate of ASD and the use of the MMR vaccine

In their 1999 report, Taylor et al. [60] used a time series approach to test the hypothesis that, at a group level, there was a temporal association between the introduction of the MMR vaccine and the rise in the rate of autism. The results showed that there had indeed been a rise in the rate of diagnosed autism but that there was no evidence of a sudden change in the trajectory of increase that was linked in time with the introduction of the MMR vaccine. The findings are inevitably constrained by the lack of data at an individual level on which children had actually received the MMR vaccine. In most circumstances, that would be quite a severe limitation, but in the case of MMR it was actually less of a problem because, in the UK, the take-up and use of the MMR vaccine was rapid and extremely high at that time.

Since then, there have been several further papers reporting time trend analyses using various available databases. Kaye et al. [55] used the General Practice Research Database for cohorts extending from 1988 to 1993. They showed a steady rise in the rate of autism over this 5-y period during which the prevalence of MMR vaccination remained unchanged at over 95%. The study has the limitation that the diagnoses were necessarily dependent on general practitioner records and there was, therefore, no independent check through more detailed hospital or clinic records or the use of standardized research criteria. On the other hand, it is not at all likely that the differential misclassification of diagnosis in vaccinated and unvaccinated children would have varied over the period of the study. The study has the comparable, very considerable strength of being based on the standard research database provided by general practitioners committed to participation in research.

The paper by Dales et al. [54] used data from the California Department of Developmental Services in much the same way. The study differed from the UK study by Kaye et al. in several key respects. First, it extended over a much wider time period, reflecting the fact that MMR was introduced in the United States well before its introduction in the UK. It also covered a time period when there was little change in the take-up of MMR as well as a time period in which it increased. What the findings showed was that the rise in the rate of diagnosed autism was continuous over the period between 1980 and 1994, and was not substantially affected by the shift from the stable but relatively low take-up of MMR in the 1980s to the somewhat higher rate in the 1990s. The findings are limited, however, by the uncertainty on the proportion of children who received MMR as distinct from single vaccines (although the available evidence suggests that the great majority received the combined vaccine). There is also the important constraint of lack of information on the individual vaccination experience of the children with and without autism.

Chen et al. [67] studied time trends for 2407 individuals with ASD born between 1959 and 1993, using National Autistic Society records. The findings showed no association between ASD rates and population usage of MMR vaccines. The study has the strength of a large sample size but also the limitations of lack of data at the individual level and reliance on membership of a parent group.

There is always a major problem in inferring causation between two time trends that rise in parallel, without reversal for either. Accordingly, the findings from Japan are particularly crucial because, unlike the situation in most other countries, the MMR vaccine ceased to be used from the early 1990s because of concern over the mumps component. If the rise in the rate of autism had been caused by use of the MMR vaccine, it should follow that the withdrawal of the vaccine would be followed by a consequent fall in the rate of autism. The findings are clear-cut in showing that this did not happen [56]. Incidence data on ASD diagnosed by the age of 7 y were obtained for children born from 1988 to 1996 in an area of Yokohama with a population of just less than 300 000. For children born in 1988, the trivalent MMR vaccination rate was about 70%; it declined to 43% in the following year and by 1993 (applying to children born in 1992) it was only 1.8%, with MMR vaccination ceasing completely after that. Over the same period of time, the incidence of ASD rose from 48 per 10 000 to 97 per 10 000, and continued to rise over the following years during which there was no use of MMR. Systematic clinical assessments were used to diagnose ASD associated with regression; the incidence pattern over time was broadly comparable to that for ASD as a whole. That is, the incidence rose over the period during which MMR was being phased out and remained increased compared with 1988. The findings show that MMR cannot have been responsible for the rising incidence of ASD in Yokohama and they also run counter to what would be expected if MMR was a causal factor for autism in a substantial minority of cases.

Case-control comparisons between vaccinated and non-vaccinated children

A different powerful test is possible when there are data on a general population sample that provides information both on individual experience of the MMR vaccine and on individual diagnosis of an ASD. Such data are available from Danish national register records [68]. The study focused on all children born in Denmark from 1991 to 1998 inclusive. Comparison was made between the 440 655 vaccinated children and the 96 648 unvaccinated children. The results

showed no difference in the risk of an ASD among vaccinated children as compared with unvaccinated children. Also, no associations were found between the development of an ASD and the age at vaccination, the interval since vaccination, and the calendar period at the time of vaccination. Adjustment for potential confounding variables did not affect this negative finding. The study has the very considerable strength of being based on individual reports of vaccination and of diagnoses of autism in a well-defined geographic area. Also, as the authors emphasized, the data on vaccination were collected prospectively, independently of parental recall and before the diagnosis of autism. In addition, the sample size was sufficiently great for the comparison on the incidence of autism in the vaccinated and unvaccinated children to be meaningful, as well as statistically reliable. Thus, there were 47 cases of autism and 70 cases of another ASD in the unvaccinated group. Also, the rates of autism (7.7 per 10 000 for autism and 22.2 per 10 000 for other ASD) are consistent with the rates from other studies.

The findings are, however, constrained by the need to rely on standard medical records. Nevertheless, a detailed review of the records of a subgroup of 40 children confirmed the diagnosis of autism in 92% of cases. A further limitation is that it is not known why the children who were not vaccinated did not receive vaccination. If that decision meant that they were a group at unusually high risk for autism (there is no evidence that this was the case), this could have biased the comparison. Even so, the findings are incompatible with the hypothesis that MMR vaccination had a major effect on the liability to autism. The records did not include any systematic data on either developmental regression or bowel symptoms and, hence, could not deal with the possibility that the MMR vaccine is associated with a form of ASD that is distinctive in being accompanied by developmental regression and/or bowel symptoms. This possibility has been examined in a further set of studies.

Time trends in ASD associated with regression after bowel symptoms

Taylor et al. [60] used the computerized health registers of children with disabilities in five health districts in northeast London to examine time trends for ASD associated with regression and/or bowel disturbance. The rates of developmental regression and of bowel symptoms were analysed according to the year of birth of the children diagnosed with either autism or atypical autism. The findings showed no change in the rate of associated bowel symptoms in the children born before the introduction of MMR in 1988 and those born afterwards. Similarly, there were no significant time trends for autism associated with regression. On the other hand, there was an association between regression and bowel symptoms at an individual level. The lack of a significant association over time was argued to conclude that the introduction of MMR had not been associated with any increase in autism that was associated with either development regression or bowel symptoms. The study was inevitably limited by the need to rely on the recording of both regression and bowel symptoms in the records in the computer database, but there is no particular reason to suppose that misdiagnoses will have varied over time in relation to the introduction of MMR.

Fombonne and Chakrabarti [69] used a somewhat different research approach in making comparisons across samples. Their first sample comprised cases seen at the Maudsley Hospital during the pre-MMR era who were participants in a family study. Their second sample also used the Maudsley Hospital database but focused on those in the post-MMR era. Their third sample was their own epidemiological sample in Stafford, also dealing with children in the post-MMR era. The findings showed no increase in the proportion of cases of autism accompanied by regression, and no decrease (or increase) in the age of first parental concern between the pre-MMR and post-MMR era. Unlike the Taylor et al. study, gastrointestinal symptoms were not significantly associated with regression in this study.

As with the findings on time trends in the rate of autism, the test of reversal is again a most important one. A Japanese study based on the findings from a clinic in Yokohama, using routine clinical records that included a specific question on regression, addressed the issue [70]. They examined the rate of regression in children with ASD during the time periods before MMR was used, the period during which it was used, and the time period after its use was stopped. Within the period during which MMR was available, the rate of regression was compared according to whether individual children actually received MMR. No differences in the rate of regression were found between time periods, the sample sizes being substantial. Similarly, within the MMR period, the rate of regression did not differ between those who did and those who did not receive MMR. The findings argue strongly against the hypothesis that MMR specifically causes regressive autism, because the rate of regression was found to have no association with MMR. As already noted, Honda et al. [56] similarly found no change in the rate of ASD with regression following withdrawal of MMR.

Conclusions on epidemiological associations between MMR vaccination and ASD

It is apparent that none of the studies reviewed provide any evidence linking the MMR vaccine with ASD. As noted, all of the studies have limitations, but

they differ in their pattern of strengths and weaknesses. In considering the totality of the epidemiological evidence, it is useful to focus on the key expectations that would follow the true causal connection. Three expectations stand out. First, in the countries (such as the UK) where the introduction of the vaccine occurred at a particular point in time that was rapidly followed by a high level of take-up of the vaccine, it would be expected that there should be a stepwise increase in the rate of ASD that markedly differed from any time trends before or afterwards. None of the studies have shown such a stepwise increase. Second, once a high stable rate of use of the MMR vaccine had been achieved, there should be a plateau during which time the rate of ASD remained stable. Again, that was not found in any of the studies (with the possible exception of the Lingam et al. [57] study that had substantial methodological limitations).

Third, when the MMR vaccine ceased to be used, as was the case in Japan, it was to be expected that there should be a fall in the rate of ASD. In fact, the results showed the contrary. That is, the rate of ASD continued to rise even more sharply. If there were marked variations in the time over which autism developed following MMR, as claimed by Spitzer et al. [63], this would inevitably introduce a certain amount of "noise" into the time trends data. Nevertheless, the general expectations would remain much the same, and it is clear that none of the expectations are borne out. The comparison of vaccinated and unvaccinated children provides additional negative evidence. The chief uncertainty with respect to this comparison, however, concerns the query regarding the reasons why some children were vaccinated and others were not. The data used in this comparison also did not include data on either developmental regression or bowel symptoms. However, given that the other epidemiological studies have provided no indication that these have changed in relation to the use of MMR, this limitation is more theoretical than practical.

It is clear that none of the epidemiological findings provide support for an association between the MMR vaccine and ASD. By the nature of epidemiological evidence, it is very difficult to prove a negative. In particular, population data of the kind discussed here cannot rule in, or rule out, the possibility of an occasional causal connection associated with an idiosyncratic response to the vaccine. However, the findings make it very unlikely that MMR plays a role in the causation of any significant number of cases of ASD, and there is no supporting evidence for the hypothesis that it may be causal in an unusually vulnerable minority group. The problem with this latter hypothesis is that there is no independent evidence that indicates how such a vulnerability might be shown or diagnosed.

Regressive autism with bowel disturbance

One of the key planks in the argument that MMR causes ASD concerns the claim that it gives rise to a characteristic pattern of ASD involving developmental regression and bowel disturbance. If, indeed, the type of ASD supposedly brought about by MMR followed a readily recognizable distinctive pattern, that would undoubtedly help in determining whether or not there was a causal connection in children with an unusual vulnerability. However, the epidemiological findings provide no support for the suggestion that there has been an increase in so-called regressive ASD in the period since MMR was introduced and no evidence of an increase in bowel disturbance associated with ASD.

The problem, however, is that neither developmental regression nor bowel disturbance constitute an easily recognizable distinctive feature. Numerous studies over the years [70,71] have shown that developmental regression occurs in between one-fifth and two-fifths of children with autism. These figures do not mean very much, however, without further specification. At one extreme, there are children who acquire the use of just a few words, which are then lost for a period, before language is re-acquired. The trouble here is that, even with normally developed children, it is common for development to proceed with a variety of minor ups and downs. Accordingly, such minor transient losses may have no particular meaning and are little more than measurement error. The issues have been well discussed in relation to the study of cognitive gains and losses found in longitudinal studies [72,73].

At the other extreme, there are cases of disintegrative disorder in which there has been a substantial period of apparently normal development followed by a widespread loss of skills not only in language and play but in other functions as well. The syndrome has been known for a long while [36,74–76], and there is every reason to accept the reality of the loss that occurs in these cases. It might well be meaningful if the evidence showed a substantial increase in the frequency of what had hitherto been a rather uncommon variety of ASD. However, there is no evidence that that has been the situation. However, in the middle there are instances in which the children have clearly made a start on language development and have used language skills in a regular and spontaneous fashion but have then, subsequently, lost these skills over varying time periods (but usually a matter of some months). Detailed accounts from parents together with the use of home videos [77] are convincing that both the initial acquisition of language was real (albeit limited) and that the period of loss was equally real. Unfortunately, most of the assessments of developmental regression are not sufficiently detailed to differentiate adequately among

these different varieties. The new version of the ADI-R [6] provides a much more satisfactory assessment, but the instrument has been used for too short a time for data to have accumulated.

Similar, but probably even greater problems surround the assessment of bowel disturbances. It has long been known that bowel disturbances are relatively frequent in children with ASD and that they arise through a variety of different routes including pica (the ingestion of inedible substances), problems in acquiring adequate bowel control, fears associated with the use of the lavatory, and various forms of oppositional behaviour. The question, therefore, is whether or not the introduction of MMR has been associated with forms of bowel disturbance that are different from these or which have a distinctive pattern of laboratory findings. The evidence on all of these points is inadequate and inconclusive.

Thimerosal and ASD

Concerns somewhat similar to those expressed in relation to MMR have been put forward with respect to the use of thimerosal, a vaccine preservative that contains ethyl mercury [78]. The situation differs from MMR with respect to the greater strength of the biological plausibility argument. That is, it is known that mercury, in high dosage, can cause neurodevelopmental sequelae [79,80]. It also differs in that it would seem that the expectation is of a relatively direct toxic effect on the brain, rather than the much more indirect and prolonged causal chain that was postulated for MMR (i.e. with the bowel disturbance being supposedly instrumental in allowing the passage of toxic products into the bloodstream that then, in turn, had adverse effects on brain function). Accordingly, in theory, it ought to be much easier to determine whether or not any particular child suffered immediate side effects that suggested sequelae involving damage to brain function. Unfortunately, the situation is greatly complicated by the fact that thimerosal is present in several different vaccines and, moreover, these are given many times over the course of the first year or so of life, beginning in early infancy. There is the further complication with respect to the uncertainty as to whether the risks primarily derive from acute effects of a relatively high dose at one specific point in time (as would be the case with a single administration of a thimerosal-containing vaccine) or, rather, with cumulative effects of mercury over time (which would ordinarily be quite low).

Geier and Geier [81,82] used the Vaccine Adverse Events Reporting System (VAERS) to compare the rates of autism and of neurodevelopmental disorders in groups with inferred higher and lower doses of thimerosal according to the vaccines they had received. Higher rates of both groups of disorders were found in those receiving higher doses of mercury. It was suggested that the disorders had been caused in part by the neural damage resulting from the mercury in the vaccine. The causal inference, however, is most uncertain because of the vagaries involved in adverse reaction reporting. The data from computerized health maintenance records in the USA are rather better, and these showed no associations between thimerosal vaccines and ASD [83].

Epidemiological evidence can be helpful, as it was with MMR, in terms of looking at the effects on the rate of ASD of either the introduction or phasing out of thimerosal-containing vaccines. A natural experiment arose in Denmark, where, from 1970 onwards, the only thimerosal-containing vaccine was the whole cell pertussis vaccine. Between April 1992 and January 1997 the same vaccine was used but without thimerosal, and the vaccine was then replaced by an acellular pertussis vaccine. Data from the Danish Psychiatric Central Register could be used to compare the rate of ASD in the individuals who received only thimerosal-free vaccinations and those who received vaccinations containing thimerosal. The Danish Civil Registration system allowed there to be identification of the vaccine used in each child, and the number of doses given, thereby allowing calculation of the total thimerosal received. No difference in the rate of ASD was found between the groups that differed with respect to the receipt of thimerosal [84]. However, some caution is needed because the method of case registration changed in 1995 to include outpatient as well as inpatient cases, and because of some uncertainties over the completeness of the register.

The causal hypothesis could also be tested by looking at time trends in the incidence of ASD among children aged between 2 and 10 y before and after the removal of thimerosal from vaccines [85]. The findings showed that the discontinuation of the thimerosal-containing vaccines in 1992 was followed by an increase in the incidence of ASD and not the predicted decrease. Again, there is the concern that the method of case registration changed in 1995. Accordingly, most attention needs to be paid to the time trends between 1992 and 1995 versus those in the preceding years, using comparable age groups. The findings show a flat trajectory up to 1990, with a rise beginning about 1991 and continuing without change in slope up to 1995. In short, the withdrawal of mercury as a preservative in the vaccine was associated with a rising, rather than falling, rate of autism.

The natural experiment provided by the removal of the postulated risk factor (namely thimerosal) provided a good opportunity to test the causal hypothesis, with findings that were completely negative. There is the usual limitation of reliance on register diagnoses, rather than diagnoses based on the use of standardized research measures, but the findings provide no indication

that thimerosal is likely to be a general risk factor for ASD, and certainly it cannot account for the rise of diagnosed ASD. Further evidence is provided by cross-national comparisons between the USA, where the average thimerosal dose increased during the 1990s, and Denmark/Sweden, where it decreased and was then eliminated [86]. Despite the sharp contrast in thimerosal exposure, the rate of ASD rose in all three countries without any association with the variations in thimerosal usage. As with MMR, the data do not allow testing of the different hypothesis of a rare, unusual, idiosyncratic response to thimerosal in individual children, although there is no available evidence to indicate that such a response actually occurs.

Conclusions

In summary, there are good epidemiological data indicating that the true incidence of ASD now is likely to be of the order of 30 to 60 cases per 10 000, as compared with the original estimate of 4 per 10 000 made some four decades ago. Although the precise figure must be somewhat uncertain, there are good grounds for assuming that current estimates are approximately correct. Administrative data show massive increases over time in the rate of diagnosed ASD, and it is clear that, in large part, this is due to the combination of better ascertainment and a broadening of the diagnostic concept, but a true rise over time in the incidence of ASD cannot be entirely ruled out. The marked increase in the rate of ASD primarily concerns individuals of normal intelligence and there is some suggestion that there may also be an increase in the male preponderance that is evident. Despite strong claims made about the possible role of MMR in relation to the causation of autism, there is no convincing evidence in support of this hypothesis. In particular, the rate of ASD shows no particular association with either the stopping or starting of MMR and there has been no change over time in the pattern of association between ASD and either bowel disturbance or developmental regression. The evidence with respect to a possible association with thimerosal, a preservative in some vaccines, is much more limited but, again, there is no supporting epidemiological evidence of a causal association. It remains possible that there has been a true rise in incidence due to some environmental risk factor but, if so, it remains quite obscure as to what that factor might be.

Epidemiological findings have been helpful in both ruling in and ruling out various postulated causal influences, and they will continue to be formative in that connection [87]. Nevertheless, it is evident that progress is going to be crucially dependent on the integration of epidemiology with more basic science laboratory studies.

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