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Is there really an epidemic of autism?

Czy rzeczywiście istnieje epidemia autyzmu?

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S u m m a r y

Autistic disorder, pervasive developmental disorder-not otherwise specified and Asperger syndrome belong to a group of disorders called autism spectrum disorders (ASDs). In the past 25 years, an increase in the prevalence of ASDs has been observed in the USA, Europe, Japan, and Canada. According to data from more than a dozen epidemiological studies conducted in the last two decades, ASD is diagnosed in 60-70 children/10 000. In popular press and the media, this phenomenon is often described as an "autism epidemic", which may suggest that there has been a real increase in the incidence of autism, not just in the prevalence of the disorder. However, the latest publications clearly indicate that there are other variables (e.g., change in the diagnostic criteria, availability of services, awareness of the disorder) responsible for the rise of ASDs. In this article the following issues will be examined: 1) range of prevalence estimates for autism and related disorders, 2) hypothesis of a secular increase in rates of autism, and 3) major sources of misunderstanding related to the increased number of diagnosed cases of autism.

Keywords: autism, autism spectrum disorders, epidemiology, incidence, prevalence, diagnosis

S t r e s z c z e n i e

Zaburzenie autystyczne, zaburzenie Aspergera i całościowe zaburzenie rozwoju – nieokreślone inaczej należą do grupy spektrum zaburzeń autystycznych (*autism spectrum disorders*, ASD). W ciągu ostatnich 25 lat zaobserwowano znaczny wzrost liczby osób diagnozowanych z ASD, zarówno w USA jaki i w krajach europejskich, w Japonii i w Kanadzie. Wg danych pochodzących z kilkunastu badań epidemiologicznych wykonanych w dwóch minionych dekadach, ASD jest diagnozowane u 60-70 dzieci na każde 10 000. W prasie popularnej i mediach temat większej liczby przypadków ASD jest często określany jako „epidemia autyzmu", co mogłoby sugerować, że nastąpił wzrost zachorowalności (*ncidence*) na autyzm a nie wzrost rozpowszechnienia autyzmu (*prevalence*). Jednakże, publikacje naukowe donoszą, iż za częstsze diagnozowanie ASD w minionych latach są odpowiedzialne inne czynniki niż rzeczywisty wzrost liczby dzieci, które rodzą się z ASD. W artykule omówione zostaną: 1) dane dotyczące rozpowszechnienia autyzmu, całościowego zaburzenia rozwoju – nieokreślonego inaczej i zaburzenia Aspergera, 2) hipoteza o rzeczywistym wzroście zachorowalności, 3) główne nieporozumienia związane z większym rozpowszechnieniem autyzmu.

Słowa kluczowe: autyzm, spektrum zaburzeń autystycznych, epidemiologia, zachorowalność, diagnoza

INTRODUCTION

The answer is straightforward. No. One may not come to this conclusion, however, when he reads popular media, especially articles written in the US press. The possibility that the rate of autism is increasing has sparked and then fueled a debate on the purported epidemic of this disorder and its causes (1). According to Russell, Kelly, and Golding (2) many lay people believe that increased incidence of autism is due to exposure to new environmental, medical and technological hazards, including vaccinations, folate supplements, pluripotent mast cells, and growth of cable television. However, no sound scientific evidence indicates that the increase in the number of diagnosed cases of autism arises from environmental causes that were not present in the world 70 years ago, but came to being during the last decade of the previous century (3). In this article I will: 1) review the range of prevalence estimates for autism and related disorders, 2) examine the hypothesis of a secular increase in rates of autism, and 3) discuss several major sources of misunderstanding related to the increased number of diagnosed cases of autism.

RANGE OF PREVALENCE ESTIMATES FOR AUTISM AND RELATED DISORDERS

Information on the rates of autism comes from epidemiological studies, which started in the mid-1960s in

England (4) and have since been conducted in many countries (5). These surveys have focused on a categorical-diagnostic approach to autism that has relied over the years on different sets of criteria. In general, they were concerned with the autistic disorder/childhood autism as characterized by severe impairments in communication and language, social interactions, as well as play (6). In other words, the majority of those studies did not investigate other pervasive developmental disorders (PDD). Some recent epidemiological surveys also included PDDs that fell short of strict diagnostic criteria for autistic disorder (i.e., PDD not otherwise specified – PDD-NOS and Asperger syndrome). Another aspect of the epidemiological research is whether it reports the prevalence or the incidence of a phenomenon. Prevalence refers to the number of individuals in a specified population who have the condition being studied at a specified time. It is the number of cases affected with a given condition divided by the population. It usually is expressed as percentage or the number of cases per 1.000 or 10.000 (7). Incidence refers to the number of individuals in a specified population in whom the condition being studied *begins* within a specified time period, such as one year. Both indexes are important but the usefulness of each depends on the condition being studied. In the case of autism, knowing the incidence would be vital because incidence rates are a more sensitive indicator than prevalence rates of potential new etiological factors (1). Unfortunately, calculating incidence rates for autism is problematic and thus most epidemiological research reports prevalence. Review of the range of prevalence estimates for autism and other PDDs comes from a series of publications by Fombonne (8-12). In the last article, Fombonne reported the most up-to-date review of published epidemiological surveys of PDDs. He included 53 studies published between 1966 and 2008, 43 of which provided information on the autistic disorder and 19 on all PDDs combined. Surveys were conducted in 17 countries and more than 50% of results were published after the year 2000. Most studies were conducted in urban areas, with school-age samples (median age of 8.0) of a mostly non-immigrant status and median population surveyed of over 63 000 subjects, however the variation in the size of the population surveyed was significant. Most investigations relied on a two-stage approach to identify cases in underlying populations and used batteries of standardized measures, specifically the gold standard diagnostic tools such as the Autism Diagnostic Interview – Revised (ADI-R) or the Autism Diagnostic Observational Schedule (ADOS). The diagnostic criteria used to define caseness varied and reflected historical changes in classification systems. The following criteria were used: Kanner's, Lotter's, and Rutter's for studies done before 1980 and DSM- or ICD-based criteria for studies conducted thereafter.

Prevalence estimations

Autistic disorder (*AD*). Data on children with autism were available in 43 studies. The earliest one was done by Lotter in 1966 in the UK, Middlesex area. The target population was 78 000 children between ages 8 and 10, 32 subjects with autism were identified with the use of a rating scale, about 15% of them had IQ above 70, gender ratio of males to females was 2.6:1. The estimated prevalence was 4.1/10 000. The latest one was done by Latif and Williams in 2007 also in the UK, Wales region. The target population was slightly over 39 000 children between ages 0 and 17, 50 subjects with autism were identified with the use of Kanner's criteria, no information was reported on the IQ score, neither on the gender ratio of males to females. The estimated prevalence was 12.7/10 000. For all 43 surveys, prevalence estimates ranged from 0.7/10 000 to 72.6/10 000. Prevalence was negatively correlated with sample size, that is the smaller sample the higher prevalence. The correlation between prevalence and year of publication was significant. All studies published after 1987 reported prevalence higher than 7/10 000. In 18 studies published since 2000, the prevalence varied from 7.2 to 40.5/10 000. The average prevalence for the autistic disorder was 20.6/10 000. The author writes that this value can be used as "the best current estimate" for the prevalence of AD (12), str. 592.

PDD-NOS/Unspecified PDD. Seventeen of the 43 provided separate estimates for the prevalence of the atypical autistic syndromes, which were labeled differently but corresponded to the current diagnostic criteria for PDD-NOS. Fourteen of those 17 studies showed higher prevalence for those disorders than for autism. The ratio of the prevalence for PDD-NOS to the prevalence of autism had a mean value of 1.8, which translates into an average prevalence estimate of 37.1/10 000 for PDD-NOS if we take the value of 20.6/10 000 as the prevalence for autism.

Asperger Syndrome. There are very few epidemiological studies of Asperger Syndrome (AS), most likely due to the fact that this disorder was acknowledged as a separate diagnostic category only in the early 1990s with the revisions of ICD and DSM (ICD-10 and DSM-IV). Only two epidemiological surveys focused exclusively on the prevalence of AS. Unfortunately, due to extremely small number of cases identified (fewer than 5), the resulting prevalence estimates are imprecise. However, from the recent autism surveys we can gather information on the AS prevalence. It is consistently lower than that for autism. It is difficult to establish how much lower, but the ratio of 3 or 4 to 1 appears appropriate. This translates into a prevalence rate for AS of 6/10 000. Fombonne, however, cautions that there are strong limitations of data on AS.

Prevalence for combined PDDs. Based on the calculated estimates for each of the PDDs, the prevalence for all PDDs is approximately 63.7/10 000 (i.e., the sum of estimates for AD, PDD-NOS, and AS). Although these results should be treated as estimations, 19 recent epidemiological studies that have focused on PDD as the case definition obtained similar values (specifically 63.5/10 000). Also, surveys done by the Centers for Disease Control in 2002 and 2006 showed the pre-

valence for combined PDDs to be at least 60/10 000 (13, 14). Fombonne writes that the estimates of around 60 to 70 per 10 000 for all PDDs represent "the best estimate for the prevalence of PDDs currently available" (12, p. 593).

HYPOTHESIS OF A SECULAR INCREASE IN RATES OF AUTISM

In order to answer the question regarding presence of the epidemic of autism, we must prove that there is a secular increase in rates of autism. Time trends in prevalence and incidence data should be evaluated. Data available from epidemiological research should also be analyzed in the light of such methodological requirements as: constant case definition and constant case ascertainment. Various researchers investigated several factors related to shown increases in the rates of autism (5, 15, 16). First – referral statistics. If we take the number of children referred to special services as a proof for increased incidence of PDDs, we may be mistaken. Increased number of referrals can be confounded by referral patterns, availability of services, public awareness, decreasing age of diagnosis, and changes over time in diagnostic concepts and practices (12). Such confounds can be found in the report from the Department of Developmental Services in California, which is often quoted as evidence for the epidemic of autism (11). Thus, the information provided in the report and showing an increase of several hundred percent in the rates of autism referrals, has to be evaluated critically because the numbers fail to account for changes in the size and composition of the underlying population, no attempt was made to control for changes in diagnostic concepts and definitions, the fact that autistic children are diagnosed nowadays at a much earlier age did not motivate the researchers to get age-specific rates among older children, and finally, changes in the rates of other disorders were not taken into account. Fombonne (12) summarizes that evidence from referral statistics are meager and weak to support the idea of secular increase in rates of autism.

Second – comparisons of cross-sectional epidemiological studies. Many of the epidemiological surveys of autism are characterized by unique design features which makes it difficult to compare their results on the rates of the disorder. Time trends in prevalence and incidence of autism are, thus, very difficult to gauge. If we compare eight surveys conducted at roughly the same time and with similar age groups in the UK and in the USA, four in each country, we will find out large differences in prevalence estimations. As no passage of time was involved, most likely the differences can be attributed to variations in case identification methods (intensive population-based screening techniques vs. administrative methods for case finding). Fombonne writes: "no inference of trends in the incidence of PDDs can be derived from a simple comparison of prevalence estimates over time, since studies conducted at different periods are likely to differ even more with respect to their methodology" (12, p. 595) than studies done at the same time.

Third – repeat surveys in defined geographical areas. Repeated surveys, which use similar methodology and are conducted in the same geographical area at different points in time, can provide useful information on time trends. There were several studies done that strived to achieve this goal, but they also were flawed methodologically. Namely, different age groups were included in the surveys, improved detection among mentally retarded was not controlled for, neither were the changes in the diagnostic concepts and criteria. Thus, prevalence estimates which indeed were increasing should not be taken as proof for an increased incidence in the rate of autism. On the other hand, two surveys (17, 18) which were performed very rigorously did not result in the prevalence rates that were statistically different.

Fourth – successive birth cohorts. If one examined data from well-designed large surveys encompassing a wide age range and found increased prevalence among most recent birth cohorts, this could be interpreted as indicating secular increase in the incidence of a disorder. However, the increased prevalence should be specific only to the disorder of interest. For example, an analysis of special education disability data in Minessota showed a 16-fold increase in the number of children diagnosed with a PDD from 1991-1992 to 2001-2002 (19), but the increase was not specific to autism and also was observed for other disability categories, which may be indicative of better services and methods for diagnosis. Moreover, in the early 1990s PDDs were included in the federal Individual with Disabilities Educational Act (IDEA) funding and reporting mechanisms in the USA.

Fifth – incidence studies. Three studies provided incidence estimates for PDDs. All showed an upward trend in incidence over short periods of time, none of them, however, could determine the impact of other factors (e.g., changes in the diagnostic criteria, improved awareness and service availability) on the upward trend.

To summarize, the available epidemiological studies indeed show an increase in the prevalence of autism, but those estimates cannot be directly attributed to the increase in incidence of the disorder. Rather, other variables may be responsible for such state of affairs. They will be discussed in the next section.

SOURCES OF MISUNDERSTANDING RELATED TO THE INCREASED PREVALENCE OF PDDS

Changes in diagnostic criteria

Autism is a pervasive developmental disorder defined behaviorally and characterized by impairments in three areas: social interactions, reciprocal verbal and nonverbal communication and the range of interests and activities (6). Although recognition of this disorder may have its origins in Jean-Marc Gaspard Itard's de-

scription of the "wild boy of Aveyron" from 1801 (20), the first formal account of autistic individuals was published by Leo Kanner in 1943 (21). It was Kanner and Eisenberg (22) who published a list of diagnostic criteria for "early infantile autism". They included aloofness and indifference to others as well as resistance to change. These features had to be present in the repertoire of a child by the end of his second year of life. Later, Rutter (23) described a condition that he called "childhood autism" as one characterized by impaired social development, delayed and deviant language development, and insistence on sameness. These symptoms had to be present by 30 months. It was not until when the third edition of the Diagnostic and Statistical Manual of Mental Disorders (24) was published, that there was a major change in the concept of childhood autism. The shift was related to moving autism from a category of psychiatric disorders to a new category of pervasive developmental disorders (PDDs). Within this category, two subcategories were identified: "infantile autism" and "childhood onset pervasive developmental disorder". There were brief diagnostic criteria provided for each subgroup. In 1987 in the DSM-III-R, broader criteria were provided for what was named "autistic disorder" and "pervasive developmental disorder not otherwise specified (25). The current definition of autism, although consistent with the deficits observed in Kanner's original group of children, has been refined and broadened. Nowadays, persons with autism are considered to have one of the neurodevelopmental disorders that have such wide range of behavioral consequences and severity that they are collectively referred to as pervasive developmental disorders (PDDs) in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, Text Revised (6). Within the group of five pervasive developmental disorders, a narrower term of autism spectrum disorders (ASDs) is used to refer to: autistic disorder, Asperger's syndrome and pervasive developmental disorder – not otherwise specified. Thus, until 1980 estimates of prevalence were based on individual clinicians' or specific researchers' conceptions, whereas since then they have been based on the diagnostic criteria of ICD and DSM, also reflecting modifications in the subsequent editions of the manuals. Given the nature of the diagnostic criteria for different disorders within ASDs, it is highly probable that the differences in prevalence rates among various studies stem from: 1) using different criteria for autism diagnosis across the years and 2) applying the same criteria differently by different investigators (1).

Increased awareness of autism and development of specialized services

Despite the fact that autism was described by Kanner in 1943, still in the early 1960s there was little general interest in or awareness of the autism. One reason may be that the disorder was thought to be very rare and not malleable to change (20). In the course of the 1960s voluntary associations of parents of autistic children as well as professional-oriented organizations began to operate in the USA and the UK. The goal was to push for educational and treatment services for autistic children and to encourage research on this disorder. Indeed, publicity concerning the children and their needs was ensured and scientific investigations into the nature of autism were undertaken (1). Awareness of the wide spectrum of autistic characteristics, and specifically of the Aspreger syndrome has also grown with the changes in the diagnostic criteria. Despite the fact that the impact of public and professional awareness of autism on prevalence rates is hard to quantify (5), it is also difficult to deny that greater interest in the emotional, social and psychological issues relating to autism did not influence identification of affected children. Moreover, changes in the types of services, the availability of services and the fashion these services are provided for children with autism, may have changed the way the children are labeled and counted. Such "diagnostic switch" was observed in California and in all US states (26), indicating that a relatively high proportion of children previously diagnosed as having mental retardation were now identified as having a PDD diagnosis. Adding autism to the IDEA in early 1990s meant that there were concrete benefits to getting a diagnosis of autism. Thus, although the impact of increased awareness and service changes on prevalence estimates in unknown, it should not be underestimated.

Possible true increase in incidence of autism

Wing and Potter (1) list several potential reasons for a marked rise in prevalence, among them a genuine rise in incidence of ASDs. If there were a true increase in incidence of ASDs it could be attributable to some environmental hazard (27). Many suggestions have been made considering the influence of environmental factors on autism: prenatal exposure to chemical agents such as thalidomide and valproic acid, as well as to infectious agents such as the rubella and influenza viruses, postnatal influences of diets, environmental pollutants, antibiotics, vaccinations, and neurotoxins such as mercury present in preservatives used for some vaccines. None of those, however, has been yet scientifically validated. The purported link between measles-mumps-rubella (MMR) vaccine and ASDs has received much public and political attention (28-30) and will be the focus of the remainder of this section. Information presented below is a summary of an article by Suchowierska and Novak (31).

The hypothesis relating MMR immunization and the onset of symptoms of ASD was advanced by Andrew Wakefield and his colleagues in an 1998 article describing 12 children with inflammatory bowel conditions and developmental disorders, primarily autism (32). For 8 out of the 12 children either the parent or the physician associated the MMR vaccination with the onset of behavioral problems and regression in the child's functioning. The average latency between the receipt of the injection and the occurrence of the symptoms was

6 days. Additionally, 9 children were diagnosed with lymphoid nodular hyperplasia in the terminal ileum as determined by endoscopy. A hypothesis was put forth that there is a new variant of ASD (regressive autism characterized by gastrointestinal symptoms) that originates from the MMR vaccine. The authors proposed the following sequence of events: 1) MMR produces inflammation in the intestines, 2) inflammation in the gut results in the change in intestinal barrier function that allows for the passage of toxic neuropeptides, 3) peptides disregulate the endogenous opioid system and subsequently cause central nervous system damage, which in turn results in developmental regression. Despite the fact that Wakefield's study was heavily criticized on methodological grounds (i.e., small number of cases, no unaffected comparison group, possibility of a coincidental, not causal, temporal relation between the MMR vaccine and autism), the fact that subsequent studies by the same group of researchers did not support the original hypothesis (33) and the fact that in 2004 10 of the 13 authors of the 1998 paper asked to "formally retract the interpretation placed upon these findings" (34), the original publication raised great interest and public attention with regards to safety of the MMR vaccine.

There are at least 20 epidemiological studies related to MMR and ASDs that have been published since the 1998 Wakefield's article. Sixteen of them were closely scrutinized and evaluated in the Immunization Safety Review. The 20 studies were conducted in six different countries (the United States, the United Kingdom, Finland, Denmark, Sweden, and Japan), used at least 12 distinct data sources, and employed a variety of study designs, including time-series analysis, cross-sectional analysis, ecologic analysis, case control, and retrospective cohort. The majority of studies were designed to address specific hypotheses that stemmed from Wakefield's study. These hypotheses are: 1) ASD rates are higher among children who have received the MMR vaccine as opposed to those who have not, 2) increased rates of ASD occur as a consequence of the MMR vaccine, 3) the onset of ASD is temporally associated with receipt of the MMR vaccine, and 4) there is a new variant of ASD related to the MMR vaccine (35).

Only one study examined Hypothesis 1 (36). Danish researchers conducted a retrospective cohort study of all children born in Denmark between January 1991 and December 1998. A total of 537.303 children were included in the cohort, 440.655 (82%) of whom were vaccinated with the MMR vaccination. The researchers analyzed the relative risk of autistic disorder and other ASDs in vaccinated and unvaccinated children. Analysis was adjusted for age, calendar period, sex, birth weight, gestational age, mother's education, and socioeconomic status of the family. The results showed no statistically significant differences in rates of autism and ASDs in those two populations. Additionally, there was no relation between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of ASD. The authors concluded that their "study provides three strong arguments against a causal relation between MMR vaccination and autism" (p. 1480): 1) the risk of autism was similar in vaccinated and unvaccinated children, 2) there was no temporal clustering of cases of autism at any time after immunization, 3) neither autism nor other ASDs were associated with the MMR vaccination.

Six studies examined Hypothesis 2 (37-42).

Dales et al. (37) investigated whether there is correspondence between the trends in MMR coverage and numbers of ASD cases. The authors conducted a retrospective analysis of MMR immunization rates among children born between 1980 and 1994 who were enrolled in California kindergartens and cases of children born in these years who were diagnosed with autism and were enrolled in the California Developmental Services system. The results show essentially no correlation between those two variables. Between the years 1980 and 1994, the increase in the coverage of the MMR vaccination was 14% and the increase was observed for the cohort born in 1988 – before that year and after that year the data were stable. As for the autism caseloads, there was a steeply increasing trend (a relative increase of 572%) beginning in 1985 and continuing to 1994. The authors concluded that their results "do not support the hypothesis that increasingly widespread MMR immunization of young children is associated with the marked secular trend of increasing number of autism cases" (p. 1185).

Fombonne and Chakrabarti (38) conducted a cross-sectional study to examine whether a new variant of autism, characterized by regression and bowel symptoms, is associated with MMR. The authors stated that if there were a new phenotype of autism, at least one of the following six predictions would have to 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" (p. 1). Three samples of children were used: the main sample (96 children born between 1992 and 1995 with a pervasive developmental disorder diagnosis, 99% received the MMR vaccine thus called a "post-MMR sample") and two comparison samples (comparison sample 1-68 children born between 1987 and 1996 with a diagnosis of PDD, most of these children were likely to have been exposed to the MMR vaccination, thus called "post-MMR sample"); comparison sample 2-99 indivi-

duals born between 1954 and 1979 with a diagnosis of autism, none of them received the MMR vaccine, thus called "pre-MMR sample"). The experimenters tested the six hypotheses mentioned above and obtained the following results: 1) there was no evidence that CDD rate was increased among children who were exposed to MMR immunization, 2) there was no difference across the pre-MMR sample and the two post-MMR samples in the mean age at which parents became concerned about autistic symptoms of their child, 3) there was no evidence that regressive autism has increased in frequency, 4) 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, 5) no statistically significant difference was found between the group of children with regression and the group without regression, suggesting a great similarity for patterns and levels of autistic symptomatology, and 6) No association was found between gastrointestinal symptoms and regression. The authors concluded that there is "lack of evidence for a new phenotype of MMR-induced autism" (p. 7).

Gillberg and Heijbel (39) compared via a case series analysis proportions of autistic cases in high and low MMR coverage periods. The authors reanalyzed data obtained from a population study of autism performed in the late 1980s (43). Seventy four children (55 with the diagnosis of autistic disorder and 19 with the diagnosis of atypical autism) were divided into two groups based on era of birth, as a proxy for exposure to the MMR vaccine. The MMR vaccine was introduced for 18-month-old children in Sweden in 1982, so the pre-MMR group consisted of children born between January 1, 1975 and June 30, 1980 and the post-MMR group consisted of children born between July 1, 1980 and December 31, 1984. The authors hypothesized that the post-MMR group would be at higher risk of developing autism if there were a correlation between MMR vaccine and autism. The prediction was not correct, as the analysis showed that 47 children with diagnosed autism or atypical autism were born in the earlier period and 27 children in the later period. Thus, the authors concluded that there is not an association between MMR vaccine and autism.

Kaye at al. (40) investigated in a time series analysis the relation between increasing rates of ASD and changes in rates of the MMR vaccine coverage in the UK. The authors obtained from the general practice research data base information about 305 cases of autism among children aged 12 younger, who were diagnosed in the years 1988-1999. The MMR vaccine was introduced in the UK in 1988. The estimated annual incidence of diagnosed autism had increased sevenfold from 0.3 per 10,000 person-years in 1988 to 2.1 per 10,000 person-years in 1999. Further analyses were conducted for 114 boys born between 1988 and 1993 and diagnosed between 1990 and 1999 in an attempt to assess more precisely the possibility of a temporal association between MMR vaccine and autism. The four year risk of diagnosed autism increased nearly fourfold, from 8 per 10 000 for boys born in 1988 to 29 per 10 000 for boys born in 1993. In contrast, the rates of MMR vaccination were stable (about 97%) for each successive annual birth cohort. The authors explain that if the MMR vaccine had played a role in developing autism, the risk of autism in successive birth cohorts would be expected to stop increasing within a few years from the vaccine begin in full use. The results speak to the contrary. Thus, the authors concluded that their study provides "evidence against a causal relation between MMR vaccination and the risk of autism" (p. 462).

Taylor et al. (41) compared in a time series analyses trends in the incidence of ASD before and after the introduction of the MMR vaccine in the UK. The authors identified 498 cases of ASD among children born between 1979 and mid 1998 in eight health districts in the UK. Data on the vaccination histories of those children were also obtained. The analyses revealed that: 1) there was a steady increase in cases of autism by year of birth with no sudden change in the trend line after the introduction of MMR vaccination in 1988, 2) there was no difference in age at diagnosis between the cases vaccinated before or after 18 months of age and those never vaccinated, 3) there was no temporal association between onset of autism within 1 or 2 years after vaccination with MMR, and 4) developmental regression was not clustered in the months after vaccination. The authors conclude that "our results do not support the hypothesis that MMR vaccination is causally related to autism, either its initiation or to the onset of regression" (p. 2029).

Taylor et al. (42) conducted a time series analysis to investigate whether the MMR vaccination is related to bowel problems and developmental regression in children with autism. This work was an elaboration on the 1999 study done by the same group of researchers. Taylor et al. used 5 health districts in north east London. The authors identified via computerized registers of children with disabilities, children born between 1979 and 1998 and diagnosed with autistic disorder or atypical autism. 473 children were enrolled in the study. Information on their vaccination histories, bowel problems and regression was gathered. The authors investigated in detail the relation between exposure to MMR vaccine in relation to onset of autism and the presence of bowel symptoms or regression, with adjustment for potential confounding factors – sex, year of birth, district, age at parental concern, and type of autism. The analysis confirmed no association between MMR vaccination and regression of bowel syndromes. However, the authors found out that bowel problems were reported more often for children with regression than for those without it, which may reflect particular dietary problems leading to constipation in some children with autism who have regression. The authors concluded that the results of their study lack "to support a "new variant" form of autism, where MMR vac-

cination is associated with developmental regression and bowel problems" (p. 394).

Eight studies examined Hypothesis 3 (temporal association between developing ASD and having received the MMR vaccine) (38, 41, 42, 44-48). Four of those studies have been described above.

DeWilde et al. (44) conducted a case-control study in which they compared changes in the number of consultations with the general practitioner (GP) for children who were diagnosed as autistic as compared to non-diagnosed controls, before and after the MMR diagnosis. A general practice database was used to examine whether children who were subsequently diagnosed with autism had more frequent consultations following MMR vaccine than children who were not vaccinated. There were 71 cases of children diagnosed with autism identified between 1989 and 2000 using the data base. For those children, 284 controls were chosen matched for age, sex, month of MMR vaccination, and GP practice. No significant difference in numbers of consultations in the six months and two months before and after MMR between cases and controls was identified. The authors concluded that "MMR vaccination does not appear to cause any dramatic decline in the behavior of children who subsequently become autistic" (p. 227) as indicated by no difference in the consulting behavior of the parents of the children.

Farrington et al. (45) extended Taylor et al. (41) study, by conducting a self-matched case series method to test the hypothesis that the MMR vaccine may cause autism, without pre-specifying any fixed time interval after vaccination in which the risk for developing autism may be heightened. The researchers used the same group of children as Taylor et al. (41). Their results indicate that there was no increased incidence of diagnosis of ASD, developmental regression or parental concern relating to the child's level of functioning 24, 36 or 60 months after vaccination. There was also no increased likelihood of ASD, regression, or parental concern after vaccination compared with before vaccination. The authors concluded that their results combined with the results of Taylor et al. (41) "provide powerful evidence against the hypothesis that MMR vaccine, or indeed any measles-containing vaccine, causes autism at any time after vaccination" (p. 3635).

Makela et al. (46) conducted a retrospective cohort study in which linkage between individual MMR vaccination and the hospital discharge register was investigated. The researchers identified 535 544 1-to 7-yearold children who were vaccinated between November 1982 and June 1986 in Finland. Out of those children, 352 were hospitalized for autistic disorder. 309 children were hospitalized for autism after they had received vaccination. However, no distinguishable clustering was detected in the intervals from vaccination to hospitalization (the intervals ranged from 3 days to 12 years and 5 months). The number of hospitalizations remained stable during the first 3 years after vaccination followed by a decrease, which may be expected as the child becomes older. For the children with autism who were hospitalized, none was admitted due to inflammatory bowel diseases in 1982-1995. The authors concluded that their study found "no evidence for the hypothesized link between MMR vaccination, autism, and inflammatory bowel disease" (p. 961).

Patja et al. (47) is a case-series analysis identified and scrutinized reports of vaccine-related complications in Norway between 1982 and 1996. The MMR vaccination was initiated in Norway in 1982, the coverage was approximately 95% and about 1,8 indiwiduals were immunized until 1996. With the introduction of the MMR vaccination, a country-wide surveillance system was also put in place to detect serious adverse events associated with MMR. Patja and colleagues reviewed 173 serious adverse events that were identified by the surveillance system. During the 14 years of MMR vaccination surveillance, no cases of ASD were reported. The study provides evidence for lack of association between the MMR vaccine and ASD.

Finally, Hypothesis 4 (a new variant of ASD is related to the MMR vaccine) was investigated in four studies (38, 42, 46, 48). Three of those studies were described above.

Peltola et al. (48) relied on the same data base as Patja et al. (47). The researchers followed up on the 31 surveillance system reports in which children developed gastrointestinal symptoms that lasted longer than 24 hours. All children except one developed the problems after the first dose of the vaccination. The time from MMR vaccine to onset of symptoms varied from 20 h to 15 days. None of the children developed ASD. The authors concluded that their found "no data supporting the hypothesis that it (MMR vaccination) would cause pervasive developmental disorder or inflammatory bowel disease" (p. 1328).

Taken together, the available studies find "no evidence of the emergence of an epidemic of ASD related to the MMR vaccine" (35, p. 633), do "not support the hypothesis that MMR vaccine causes autism or associated disorders" (49, p. 17), provide "no evidence that MMR vaccine causes autism" (50), and find "no convincing scientific evidence to support a causal relationship between the MMR vaccine and the development of autism" (51, p. 837).

CONCLUSION

There have been over 40 epidemiological surveys of autism and other PDDs conducted since 1960s in different regions of the world. Methodological differences make it hard to compare results of those studies, however, the most recent studies provide us with a relatively good estimates on the prevalence of all PDDs combined. Such best estimate is 60 to 70 children in 10 000. This means that PDDs are much more common nowadays than even 30 years ago. Current evidence does not support the hypothesis of a secular increase in incidence of autism, and especially it does not show the cause-and-effect relation between the

MMR vaccine and autism. Rather, other factors such as changes in the diagnostic criteria used for identifying autistic individuals, service availability, increased awareness of autism among parents and professionals contribute to the rise in prevalence of the disorder. There is a need for very well designed epidemiological studies to access whether there is a true change in the underlying incidence, since this possibility should not be ruled out.

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