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VACCINES AND AUTISM

MMR vaccine and autism: a review of the evidence for a causal association

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The hypothesis that combined measles-mumps-rubella (MMR) vaccine may cause autism was advanced by Wakefield and colleagues in a report describing 12 patients with inflammatory bowel conditions and regressive developmental disorders, primarily autism.[1] The authors hypothesized that MMR vaccine may have been responsible for the bowel dysfunction which subsequently resulted in the neurodevelopmental disorders.

Autism has a strong genetic component and associated neurological defects probably occur early in embryonic development. Therefore, in most cases, it is unlikely that a vaccination that is given after birth could cause autism. In a minority of cases, a child can appear to be developing completely normally but then regress and develop autistic characteristics. Theoretically, for cases of regression a biologically plausible link with vaccination could be made. A recent study by Nelson, however, has identified abnormal levels of certain growth factors at birth among children who developed autism, including the subgroup with regression.[2]

The original cases reported by Wakefield had all been referred for evaluation at the author's gastroenterology clinic. The main evidence of an association with vaccination was that for eight of the 12 cases the child's parents or pediatrician suspected that MMR vaccine may have contributed to the onset of behavioral problems. The authors speculated that persistent measles virus infection of the gastrointestinal tract could have resulted in pathologic changes that allowed gastrointestinal absorption of toxic neuropeptides which then caused central nervous system damage and neurodevelopmental regression.[1]

There are a number of limitations to evidence from the case reports. First, the small number of cases referred to a gastroenterology clinic may well have been a biased sample and not representative of children with autism. Second, there was no unaffected comparison group. Third, the possibility of a coincidental, but not causal, temporal association with MMR vaccination was not addressed. Fourth, the postulated link between bowel disease and autism was tenuous, as there was no confirmatory laboratory evidence (ie, measles virus was not detected in bowel) and bowel disease did not precede onset of autism in any of the cases.

Subsequent studies by Wakefield and colleagues were also not supportive of their hypothesis. For example, Wakefield's group (as well as other researchers) published that highly specific laboratory assays in patients with inflammatory bowel disease—the proposed link between autism after MMR—are negative for measles virus.[3] Moreover, a recent study in the US found no association between MMR vaccine and risk of inflammatory bowel disease.[4] Wakefield and colleagues have since proposed a new syndrome consisting of milder inflammatory bowel disease (eg, ileocolonic lymphonodular hyperplasia and mild intestinal inflammation) associated with behavioral regression.[5] They have reported identifying laboratory evidence of measles virus genome in the white blood cells[6] and intestines[7] of some of these patients.

To evaluate Wakefield's hypothesis, Taylor and colleagues identified all 498 known cases of autism spectrum disorders in a district of London born since 1979 and linked them to a regional vaccination registry.[8] The study found that, although the number of cases of autism disorders had been increasing since 1979, there was no sharp increase after the introduction of MMR vaccine in 1988. Also, cases vaccinated before 18 months of age, after 18 months of age, or not vaccinated, all had similar ages at diagnosis, indicating that vaccination does not result in earlier expression of autism. In addition, at age 2 years the MMR vaccination coverage among the autism cases was nearly identical to coverage in children in the same birth cohorts in the whole district. Taylor and colleagues then employed a case series methodology to assess the relative incidence of autism within pre-defined time periods after vaccination. No statistically significant associations were found, except for a small increased relative incidence (1.48) for the association of MMR vaccination and initial parental concern. The inability to find a temporal relationship between vaccination and onset of regression, in particular, provides persuasive evidence against the hypothesis that MMR may cause autistic regression or exacerbate autistic symptomatology.

Indirect evidence of a lack of association between MMR vaccine and autism also comes from recent ecological studies conducted in Great Britain[9] and California.[10] Each of these studies compared temporal trends in measles vaccination coverage with corresponding trends in autism prevalence. Neither found a positive correlation.

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A follow-up study of a national MMR vaccination program in Finland indicates that children who experience gastrointestinal symptoms shortly after vaccination are not at increased risk of neurodevelopmental problems.[11] Out of about 3 million vaccine doses administered, reports of gastrointestinal complaints were received from 31 recipients. These individuals were traced 1–15 years (median 10 years) later and none had developed autism. Although the small number of individuals with gastrointestinal problems precludes making firm conclusions about the risk of autism in people experiencing gastrointestinal reactions, the results indicate that any possible association following MMR vaccination would have to be extremely rare.

In conclusion, the initial case reports by Wakefield and colleagues raised a hypothesis that MMR vaccination may cause autistic regression. The one study published to date that addressed this hypothesis found no association between MMR vaccine and onset of regression or the development of autism. Data on temporal trends of autism occurrence and MMR vaccination coverage in different populations also have not revealed an association. The biological plausibility of the association is tenuous because, in most cases, the neuroanatomic abnormalities of autism probably develop *in utero* and recent evidence suggests that this is likely to be true for regression as well. The laboratory findings of measles virus genome in biological samples of some patients all emanate from one group and there has been no independent verification by other investigators in other populations. Moreover, the relevance of the laboratory findings is not clear because no association has been established between vaccination and autism or inflammatory bowel disease. Therefore, the hypothesis that MMR vaccine may cause regression or the onset of autism has little support. The weight of the currently available epidemiological and related evidence argues against a causal association. The possibility of an idiosyncratic reaction in certain susceptible individuals cannot be ruled out, but such occurrences would have to be too rare to cause detectable increased risks on a population level. A review committee of the Institute of Medicine reached similar conclusions.[12]

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