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Review

Communicating science to the public: MMR vaccine and autism

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Abstract

Media attention and consequent public concerns about vaccine safety followed publication of a small case-series of children who developed autism after receipt of the measles–mumps–rubella (MMR) vaccine. Many well-controlled studies performed subsequently found no evidence that MMR vaccine causes autism. However, despite these studies, some parents remain concerned that the MMR vaccine is not safe. We will discuss the origins of the hypothesis that the MMR vaccine causes autism, studies performed to test the hypothesis, how these studies have been communicated to the public, and some suggested strategies for how this communication can be improved.

Keywords: MMR; Autism; Intestinal inflammation

"Popular induction depends upon the emotional interest of the instances, not on their number." Bertrand Russell (1927)

1. Introduction

In 1998, Wakefield et al. [1] published a report of eight children in the United Kingdom with regressive autism following receipt of the MMR vaccine. As a consequence of media coverage of this report, MMR-immunization rates in England fell from 94 to 75% and cases of measles increased [2–4]. Concerns about MMR vaccine spread to the United States. Some parents now refuse or delay administration of the MMR vaccine or ask their physician to administer the measles, mumps, and rubella vaccines separately.

We will describe studies examining the relationship between MMR vaccine and autism. In addition, we will offer some suggestions as to how the public can be informed about the basic tenets of causality, the importance of study design, and the strengths and limitations of the scientific method.

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2. The hypothesis

2.1. MMR vaccine causes intestinal disease and consequent autism

Wakefield et al. [1] described 12 children with regressive developmental disorders and chronic enterocolitis; 10 of these children had autism. In eight of these children, the onset of regressive neurologic symptoms was linked either by the child's parent or physician to receipt of MMR vaccine. The average length of time between receipt of MMR vaccine and onset of neurologic symptoms was 6.3 days (range: 1–14 days). In addition, nine of these 12 children had lymphoid nodular hyperplasia in the terminal ileum as determined by endoscopy. The authors concluded that a unique disease process might be caused by MMR vaccine. To explain how MMR vaccine causes autism, the authors proposed the following sequence of events: (1) MMR vaccine causes intestinal inflammation; (2) intestinal inflammation results in a change in intestinal barrier function that allows for the entrance of gut-derived peptides that exert an 'opioid effect' on the brain; and (3) gut-derived peptides cause a dysregulation of the endogenous opioid system and subsequent disruption of normal brain development.

In response to the Wakefield et al.'s report, the popular press in London published headlines claiming that a new

'study' found that the MMR vaccine was linked to autism. However, Wakefield et al. had published their hypothesis—a study had not been performed. To study the hypothesis, the effect of the MMR vaccine must be tested in children, with or without autism, who either did or did not receive the vaccine. Wakefield et al.'s report did not include these controls.

3. Origins of the hypothesis

3.1. MMR vaccine causes intestinal disease

The origin of the hypothesis that MMR vaccine might cause intestinal symptoms (and consequent autism) stems from studies of the relationship between measles virus and inflammatory bowel disease (IBD). Using a monoclonal antibody, Wakefield et al. detected measles virus nucleoprotein in biopsy specimens from patients with Crohn's disease [5,6]. However, subsequent studies found that the monoclonal antibody preparation used was directed against a host, not viral, protein, [7,8] and bound to intestinal tissues obtained from patients with or without IBD [8]. Additional studies, using a technique that detected measles virus genome (i.e. polymerase chain reaction), did not detect measles virus in the intestines of patients with IBD [9–12].

3.2. MMR vaccine should be administered as three separate vaccines

On 12th November 2000, the CBS program *60 Minutes* aired a segment on the controversy surrounding the MMR vaccine and autism. CBS correspondent Ed Bradley asked Dr. Wakefield whether he would give his children the MMR vaccine. Dr. Wakefield responded, "No, I wouldn't. I would most certainly vaccinate them. I would give them the single measles, mumps, and rubella vaccines." What is the genesis of the hypothesis that autism can be avoided by separating the MMR vaccine into its three component parts?

Wakefield et al. performed a study of children born in England during 1 week in 1970 by evaluating histories of childhood infections and their relationship to IBD [13]. An increased risk for IBD was observed for children who were infected with measles and mumps viruses in the same year. The study was limited for two reasons: (1) only 17 cases of patients with ulcerative colitis and 20 patients with Crohn's disease were evaluated and (2) histories of childhood infections were obtained by questionnaires 4–10 years after their occurrence, and estimations of exact ages of infection might have been incorrect. However, the hypothesis that IBD was caused by contemporary infections with wild-type measles and mumps viruses was born and eventually extrapolated to the hypothesis that MMR vaccine causes IBD (and subsequent autism).

The hypothesis that separate administration of the measles, mumps, and rubella vaccines would decrease the risk for autism has not been studied.

4. Testing the hypothesis

4.1. MMR vaccine causes intestinal disease

Risk factors in 142 patients with IBD with 432 controls matched for sex, age, and birth year were compared in a carefully constructed study using data derived from four large health maintenance organizations [14]. Immunization with MMR was not a risk factor for Crohn's disease (odds ratio (OR), 0.4; 95% confidence interval (CI), 0.08–2.0), ulcerative colitis (OR, 0.8; 95% CI, 0.18–3.56), or IBD (OR, 0.59; 95% CI, 0.21–1.68). Further, the risk for IBD was not increased in children vaccinated with MMR at less than 12 months of age as compared with children vaccinated between 12 and 18 months of age.

4.2. MMR vaccine causes autism

Subsequent to Wakefield et al.'s publication [1], several investigators studied the hypothesis that MMR causes autism.

Taylor et al. [15] performed a population-based study of children in eight health districts in the North Thames region of the United Kingdom. Children with autistic spectrum disorder (ASD) born after 1979 were identified from computerized registries and school records. The authors identified 498 children with ASD that included typical autism, atypical autism, or Asperger's syndrome. Three statistical analyses were performed. First, using a time-series analysis, an increase in cases of ASD did not occur soon after the MMR vaccine was first used in England in 1988. Second, among children with ASD born after 1987, the proportion that received MMR vaccine was similar to that found for children in the general population. Third, there was not a significant clustering of cases of ASD at various intervals up to 1 year after receipt of MMR vaccine. A second study by Taylor and co-workers [16] expanded their original observations. They studied children who received one and two doses of MMR and evaluated longer intervals between receipt of vaccine and the onset of autism, but again found no evidence for a causal association between MMR and autism.

To evaluate whether MMR vaccine was associated with a new form of autism that included intestinal symptoms, two large, well-controlled, retrospective studies were performed. Taylor et al. [17] found that the proportion of children with developmental regression (25%) or bowel symptoms (17%) did not change significantly between 1979 and 1998, a period that included introduction of the MMR vaccine. Similarly, a study of 262 patients with autism found no evidence for the emergence of a new form of the disease that included intestinal symptoms following widespread use of the MMR vaccine [18].

Several subsequent studies supported the findings by Taylor and co-workers that MMR vaccine did not cause autism. One study examined trends in autism and MMR immunization rates in California between 1980 and 1994

[19]. While a substantial increase in the number of autism cases occurred during that time, immunization rates remained about the same. Similarly, a second study, using population-based data from the United Kingdom, found that although the incidence of autism increased about four-fold from 1988 to 1993, the prevalence of MMR vaccination remained constant [20]. A retrospective study, based on linkage of individual MMR vaccination data with a hospital discharge register, was conducted among 535,533 children 1–7 years old vaccinated in Finland between 1982 and 1986. No clustering of hospital visits for autism within 3 months of vaccination was observed [21].

Finally, Madsen et al. [22] performed a retrospective cohort study of all children born in Denmark between 1991 and 1998. The study included 537,303 children representing 2,129,864 person-years. Approximately 82% of children had received the MMR vaccine. The cohort was selected from the Danish Civil Registration System, vaccination status was obtained from the Danish National Board of Health, and children with autism were identified from the Danish Central Register. The relative risk of autism or ASD in the group of vaccinated children as compared with unvaccinated children was 0.92 (95% CI, 0.68–1.24) and 0.83 (95% CI, 0.65–1.07), respectively. Furthermore, there was no association between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of autism.

5. Communicating science to the public

The hypothesis that MMR vaccine causes autism has been evaluated now in six separate studies performed in England, Finland, Denmark, and the United States [15,16,19–22]. All six studies reached the same conclusion—when autism followed receipt of MMR vaccine, it occurred at a rate that would have been predicted by chance alone. Conversely, no studies have found that autism occurs in vaccinated children at a rate greater than that found in unvaccinated children. However, most parents of children with autism, and many parents fearful that their children might develop autism, have not been reassured. How can the scientific community make the results of these studies compelling to parents who are concerned about the safety of MMR vaccine?

5.1. Engaging the news media

Most people learn about medicine and science from newspaper and magazine stories, radio reports, the World Wide Web, and television programs. As a consequence, the news media influences the public's perception of diseases, their causes, and their importance. For example, Combs and Slovic [23] examined the reporting of 41 causes of death in two newspapers in Eugene, Oregon and New Bedford, Massachusetts in the late 1970s. These reports were then compared to actual causes of death in the United States. Common causes of death such as diabetes, emphysema, heart disease, stroke, and cancer were reported far less frequently than relatively uncommon causes of death such as homicides, tornadoes, fires, drownings, and floods. The news media were more likely to report causes of death that were uncommon, dramatic, and sensational. As a result, people reading these newspapers overestimated the importance of relatively infrequent causes of death and underestimated the importance of common causes of death [24].

Similarly, news reports about MMR vaccine and autism have been more interesting than informative—reports often include emotional and dramatic stories of parents concerned that their children were harmed by MMR vaccine rather than details of specific scientific studies. For example, CBS correspondent Ed Bradley began the segment on *60 Minutes* by interviewing a family from Evans City, Pennsylvania. Mr. Bradley stated: "Nicholas appeared perfectly normal until just after his first birthday, when he received the MMR vaccine. Within a week, according to his parents, he began to change." The parents, fighting back tears, then told the story of a child who was happy, playful, and interactive until he received the MMR vaccine. The mother stated: "I should never had him have that vaccine." The report included a lengthy interview with Andrew Wakefield during which time he discussed his concern that MMR vaccine caused autism. Unfortunately, Brent Taylor, who by that time had published the first of what were to be many studies showing that MMR vaccine did not cause autism, was not interviewed nor were his data discussed. Dr. Taylor's data did not include any personal and compelling stories and would have required a somewhat lengthy explanation of methods and analyses.

The challenge to healthcare professionals is to make the story that the MMR vaccine does not cause autism at once informative, personal, emotional, and compelling. One possible strategy would be to convey to the media what is at stake if the results of these studies are not made available to the public. For example, the media's influence on the public caused a drop in immunization rates in England and a consequent increase in the incidence of measles infection [2–4]. Immunization rates do not have to fall very far for outbreaks of measles to occur. In the late 1980s and early 1990s outbreaks of measles in the United States caused approximately 11,000 hospitalizations and 120 deaths [25]. At the time, about 70% of young children were immunized with measles-containing vaccine. Children who have suffered from measles, families who have experienced hospitalizations from measles, and physicians who have witnessed children die from measles can tell stories that are quite compelling and dramatic.

5.2. Explaining the difference between causal and coincidental associations

Parents of children with autism face the very difficult challenge of raising a child with special needs. At the very least it would be comforting to know what causes autism. To state that MMR doesn't cause autism only disregards parent's

observations that symptoms began soon after receipt of the vaccine and doesn't offer a suitable alternative explanation. Some parents may never be convinced that MMR vaccine is safe or that the MMR vaccine did not cause autism in their child. However, many parents trust science, but need to be informed about how scientific studies determine whether one event causes another.

To determine whether a vaccine causes a particular disease, you need the four pieces of information that are represented in boxes a, b, c, and d of the table below.

	Disease	No disease
Vaccine	a	b
No vaccine	c	d

It is reasonable that a parent, observing symptoms of autism soon after receipt of an MMR vaccine, would be concerned that the vaccine had caused the disease. But the observation includes only information represented in 'box a'. Determination of causality depends on knowing the risk of the disease in a vaccinated group ($a/a+b$) and comparing it with the risk of disease in an unvaccinated group ($c/c+d$).

Studies comparing the relative risks of diseases in vaccinated and unvaccinated people have been used to determine whether vaccines cause specific diseases. Large, well-controlled epidemiologic studies can detect even very rare associations. For example, studies determined that about 1 of every 100,000 recipients of the swine flu vaccine used in the late 1970s developed Guillan-Barré syndrome [26], that about 1 of every 4000 recipients of the inactivated polio vaccine used in April 1955 developed paralysis [27], that about 1 of every 10,000 recipients of Rotashield vaccine developed intussusception [28], and that about 1 of every 23,000 recipients of MMR vaccine developed thrombocytopenia [29].

Although information from 'box a' (e.g. parental observations or case-series reports) can be used to generate hypotheses, only large, well-controlled studies that include data from 'boxes a, b, c, and d' can be used to test hypotheses. For example, despite concerns, large epidemiologic studies found that the hepatitis B vaccine does not cause multiple sclerosis [30,31], that the *Haemophilus influenzae* type b vaccine does not cause type 1 diabetes [32], and that the whole-cell pertussis vaccine does not cause permanent neurologic damage [33–39], sudden infant death syndrome [40], asthma or allergies [41,42].

5.3. Explaining science and the scientific method

A third, and more subtle, problem concerns how scientists and clinicians communicate science and the scientific method to the media and to the public. For example, in April 2001 the Institute of Medicine (IOM) reviewed studies that evaluated the relationship between MMR vaccine and autism [43]. The IOM concluded that "evidence favors rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorder (ASD)..." [43]. However, the IOM report also included the following statement: "... the committee notes that its conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children..." [43]. The caveat stated by the IOM was probably based on concerns that (1) the scientific method does not allow for a negative proof and (2) epidemiologic studies can never be large enough to offer a definitive proof. The IOM's caveat is worth examining.

The scientific method is based on formulation of a hypothesis, establishment of specific burdens of proof, and subjection of these proofs to statistical analyses. The hypothesis is always framed in the negative (i.e. the null hypothesis). In this case, the null hypothesis is that the MMR vaccine does not cause autism. Statistical analyses of data allow for two possible outcomes—the null hypothesis either can be rejected or not rejected. However, the null hypothesis cannot be accepted. In other words, one cannot prove a negative. Therefore, the scientific method does not allow one to say that MMR vaccine does not cause autism because this would imply that MMR vaccine never causes autism—something one cannot prove.

Unfortunately, the IOM's statement that one cannot "exclude the possibility that MMR vaccine could contribute to ASD" [43] is often misunderstood by the media, and consequently the public, to mean that the door is still open and that nothing has been settled. Some parents might reason that even an extremely small risk is not worth taking.

The lack of association between MMR vaccine and autism is often communicated to the press and the public with statements such as: "There is no evidence that MMR vaccine causes autism." "Autism occurs after MMR vaccine at the same rate that it occurs in children who did not receive the vaccine." "MMR vaccine is not a major cause of autism." Out of respect for the scientific method, aware of the fact that one cannot accept the null hypothesis, and mindful of the limits imposed by the size of epidemiologic studies, we do not say "MMR vaccine does not cause autism." However, neither the media nor the public may understand the reasons for our reticence.

6. Summary

Media coverage of a small case-series published by Wakefield et al. linking the MMR vaccine to autism resulted in a loss of confidence and decreased immunization rates in England. However, many rigorously controlled studies performed in the United Kingdom, Finland, Denmark, and the United States found no evidence that MMR vaccine causes autism. Despite these studies, some parents remain concerned that the MMR vaccine is not safe.

The challenge to the healthcare community is to provide information from studies of the relationship between MMR vaccine and autism in a manner that is compelling to parents making decisions about vaccines for their children.

Suggested strategies include providing information that is at once informative and interesting to the media as well as explaining methods used by scientists and clinicians to distinguish causal from coincidental relationships. Further, healthcare professionals can help parents understand the relationship between vaccines and specific diseases by explaining that although case reports can be used to form a hypothesis, only carefully performed, well-controlled studies can be used to test a hypothesis.

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