

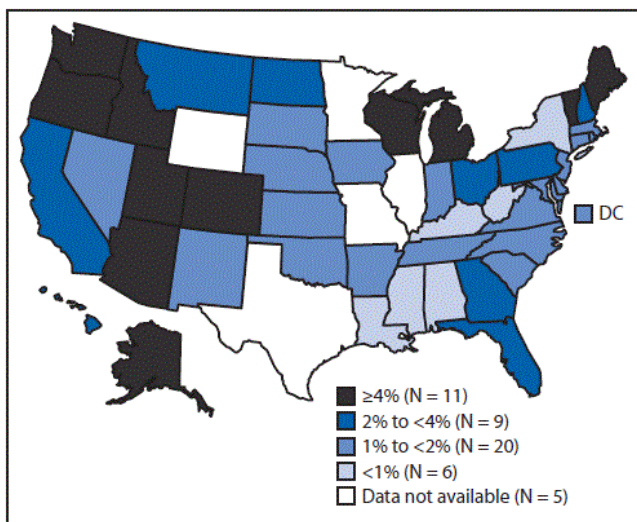
## Autism Spectrum Disorder Still Not Linked to the MMR Vaccine: A Review of the Studies since the 1998 Wakefield Study

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The Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition (DSM-V) has reclassified autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder (PDD) into a collective diagnosis now referred to as Autism Spectrum Disorder (ASD).<sup>1</sup> ASD is characterized by early-onset impairments in social interaction and restricted and repetitive physical and cognitive behaviors such as with movements, interests, and activities.<sup>2</sup> The prevalence of ASD diagnoses continue to increase, though it is unclear how much increase is due to increased awareness of the disorder and improved DSM-V classifications. The Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) network estimates that 1 in 68 children in the United States (U.S.) is diagnosed with ASD and disproportionately affects males.<sup>3</sup> The cause (or causes) of ASD remain unknown despite an abundance of research. The research has, however, provided some clarity to what is not associated with ASD.

Concerns about possible associations between vaccines and ASD remain a topic of private and public debate despite several studies that have refuted the conclusions of a small (n=12), uncontrolled and retracted 1998 study by former gastroenterologist Andrew Wakefield that attempted to show an association between ASD and the measles, mumps and rubella (MMR) vaccine.<sup>5</sup> The ramifications of the study, despite its retraction from the *Lancet* several years ago, are still apparent. A CDC report (see Image 1) of children in kindergarten during the 2014-2015 academic year found that Oregon has the second highest vaccine exemption rate in the nation at 6.0%.<sup>4</sup>

**Image 1: Estimated percentage of children enrolled in kindergarten during 2014-15 academic year exempt from receiving one or more vaccines, by state.**<sup>4</sup>



### Measles, Mumps, and Rubella Vaccine and its Debunked Association to Autism Spectrum Disorder

The 1998 *Wakefield* study led to immunization hesitation and increased nonmedical vaccine exemptions despite that the study was a small case-series of 12 children (mean age 6 years [range, 3 to 10 years]) with inflammatory bowel disease (IBD) and already had a history of PDD. Parents of 8 of the children felt the onset of behavioral impairment occurred around the time of immunization with the MMR vaccine. The study speculatively concluded that there was a pattern of IBD in children with developmental disorders, and that in most cases, the onset of symptoms occurred after MMR immunization.<sup>5</sup>

Wakefield's findings were perpetuated by another study that found an association between measles infection and a variant of IBD found in children with developmental disorders;<sup>6</sup> however, an association between the MMR vaccine and ASD was never established. Immediately after Wakefield's publication, epidemiological data began to refute any link between MMR vaccination and ASD.<sup>7,8</sup> Indeed, the logic of a perceived association after the Wakefield study was published was immediately questioned since MMR vaccination occurs in early childhood, around the same time of life ASD is typically diagnosed. Eventually, 10 of the 12 investigators involved in the Wakefield study retracted the original conclusions as by stating in 2004,

*We wish to make it clear that in this paper no causal link was established between MMR vaccine and autism as the data were insufficient.*<sup>9</sup>

In 2010, the *Lancet* retracted the publication after it had become clear that the study had provided false information and there were critical conflicts of interest and methodological concerns not previously disclosed.<sup>10</sup> The *British Medical Journal* has published a series of articles on the exposure of the fraudulent study, which was accomplished with journalistic investigation, and not academic vigilance.<sup>11-13</sup>

### Clarity Lies in the Data

Several studies have been published that have found no association between the MMR vaccine and ASD. The first of these studies was an epidemiologic study, which identified 498 children with an ASD diagnosis born after 1979.<sup>7</sup> The study looked at trends in prevalence of ASD after the introduction of the MMR vaccine in 1988.<sup>7</sup> The study concluded that although there was a steady increase in ASD throughout the time period studied, there was no increased trend of reported cases around the time of introduction of the MMR vaccine; nor was there any evidence to support a sudden increase of ASD diagnoses in the years following the introduction of the MMR vaccine.<sup>7</sup>

In 1982, the National Board of Health and National Public Health Institute launched a long-term vaccination project directed at eliminating MMR diseases in Finland.<sup>14</sup> Data were collected prospectively from the vaccination project to review the development of gastrointestinal (GI) symptoms after the receipt of the MMR vaccine and its possible link to ASD. By the end of 1996, the institute had data on 3 million vaccinations and only 31 patients had gone on to develop GI symptoms.<sup>14</sup> Time from MMR vaccine to onset of symptoms varied from 20 hours to 15 days. These 31 patients were followed for a mean period of 9 years and none of them went on to develop ASD.<sup>14</sup> From these data, no association between the MMR vaccine and PDD or IBD could be found.<sup>14</sup>

A retrospective cohort of 535,544 Finland children vaccinated for MMR between 1982 and 1986 was also analyzed.<sup>15</sup> A total of 352 children from this cohort were hospitalized and discharged with a diagnosis of ASD. Of these, 309 children had been immunized with the MMR vaccine prior to admission.<sup>15</sup> The time from MMR vaccination to onset of symptoms of ASD in 309 of the hospitalized children varied widely, from 3 days to 12.5 years, and the data did not show any evidence of clustering.<sup>15</sup> None of the hospitalizations were for IBD.<sup>15</sup> Children not hospitalized were not captured in these data, although it is worth noting that most diagnoses in Finland were made in the hospital during this time period.<sup>15</sup> The study was unable to identify an association between MMR vaccine and ASD.<sup>15</sup>

Another retrospective cohort study analyzed pooled data of all children in Denmark born between January 1991 and December 1998 and a complete vaccination registry from 1991 to 1999 to determine if an association between MMR vaccine and ASD existed.<sup>16</sup> The cohort consisted of 535,393 children

with a total follow-up of over 2 million person-years.<sup>16</sup> Of the 440,655 (82%) children that received the MMR vaccine, no increased risk for autistic disorder (n=316; adjusted relative-risk (ARR) 0.92 (95% CI 0.68 to 1.24) or ASD (n=422; ARR 0.83 (95% CI 0.65 to 1.07) was found.<sup>16</sup>

A large retrospective cohort (n=95,727) was recently reviewed to determine diagnoses of ASD by MMR vaccine status in U.S. children with older siblings with and without ASD.<sup>17</sup> Overall, the MMR vaccination rate ( $\geq 1$  dose) for children with older siblings without ASD was higher than for children with older siblings with ASD at age 2 years (84% vs. 73%) and at age 5 years (92% vs. 86%).<sup>17</sup> Compared to unvaccinated children, the cumulative incidence rate ratio (RR) of ASD for 1 dose of MMR at age 2 years among children with unaffected older siblings was 0.80 (95% CI, 0.44 to 1.46; p=0.57) and 0.44 (95% CI, 0.15 to 1.29; p=0.22) among children with older siblings with ASD.<sup>17</sup> There were also no associations found between 1 dose of MMR at ages 3, 4, and 5 years, irrespective of whether their older siblings had ASD.<sup>17</sup> Similarly, compared to unvaccinated children, for 2 doses of MMR at age 5 years, the cumulative incidence RR of ASD among children with unaffected older siblings was 0.74 (95% CI, 0.55 to 0.99; p=0.049) and 0.44 (95% CI, 0.26 to 0.75; p<0.01) among children with older siblings with ASD.<sup>17</sup> The study concluded that the MMR vaccine was not associated with increased risk of ASD in children, regardless of whether older siblings had ASD.<sup>17</sup>

### Conclusion

Vaccine refusal has reintroduced many new cases of preventable measles cases in the U.S. each year.<sup>18</sup> Since 2000, there have been 1,416 reported measles cases in the U.S.<sup>18</sup> A total of 199 cases (14.1%) involved persons who had been vaccinated against measles, whereas 805 cases (56.8%) involved persons who had not been vaccinated (in the remaining cases, vaccine history was unknown).<sup>18</sup> Of the cases where detailed vaccination history was available, 59.2% of the cases occurred in unvaccinated individuals who were age-eligible to receive the vaccine, most of which had nonmedical exemptions as opposed to a contraindication to the vaccine.<sup>18</sup> Thus, a substantial proportion of the U.S. measles cases occurred in persons intentionally unvaccinated. Perhaps more important than the number of measles cases are the potentially very serious complications associated with its spread, both to the exposed children and to public health.

Some parents remain hesitant to vaccinate their children due to uncertainty whether vaccination is necessary for rare diseases, perceived risks associated with multiple vaccinations in a short period of time, concern over adverse effects of vaccinations (such as ASD), and the unknown long-term effects of new vaccinations. Preserving parent autonomy while developing buy-in requires great motivational interviewing skills and supporting educational material. The CDC vaccination website provides great communication tools for clinicians to inform parents about the benefits of vaccination and the potential risks of vaccination exemption to their child, and the community as a whole.<sup>19,20</sup> A helpful place for providers to start is the

**Provider Resources for Vaccine Conversations with Parents** webpage, located at <http://www.cdc.gov/vaccines/hcp/conversations/index.html>

Access to several additional resources from the CDC is also available:

#### Talking to Parents about Vaccines

<http://www.cdc.gov/vaccines/hcp/conversations/conv-materials.html>

#### For Parents: Vaccines for Your Children

<http://www.cdc.gov/vaccines/parents/index.html>

#### About Vaccine Conversations with Parents

<http://www.cdc.gov/vaccines/hcp/conversations/about-vacc-conversations.html>

#### Vaccine Resources to Share with Parents

<http://www.cdc.gov/vaccines/hcp/conversations/resources-parents.html>

Helpful and up-to-date clinical information on communicable disease outbreaks, rates and trends, immunization recommendations and schedules, and laws and requirements regarding vaccinations can be found at: <http://www.cdc.gov/vaccines/><sup>21</sup>

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