SafeMinds Critique of Schechter & Grether Paper on California's Autism DDS Data and Thimerosal Exposure

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Background

A paper[1] was published this week on autism rates and thimerosal exposure. The authors, Robert Schechter and Judith Grether, used the California Department of Developmental Disabilities Services (DDS) data on autism enrollments over time and compared them to recent thimerosal exposure rates. Stating that thimerosal has been removed from vaccines while DDS enrollments continue to rise, they conclude that "the DDS data do not support the hypothesis that exposure to thimerosal during childhood is a primary cause of autism."

Analysis Summary

The SafeMinds analysis of this paper examines the DDS data set, the thimerosal exposure information in the paper, and Schechter and Grether's interpretation of the findings as summarized in their concluding statement above. Subsequent to this analysis, SafeMinds has determined that the data can equally support thimerosal exposure as a primary causative role, if autism causation is multifactorial. Vaccine components and environmental mercury, as well as other toxicants, are additional likely candidates. Deficiencies of the DDS data as an epidemiology resource and imprecise thimerosal exposure assumptions make determination of the contribution of thimerosal to autism rates difficult. The increase in autism cases reported by Schechter and Grether since the 1980s highlights the urgency of the autism epidemic and the need to institute a rigorous and comprehensive environmental factors research program.

Analysis

DDS Data Assessment

While the DDS data have many strengths, imprecision in the data prevents an accurate characterization of autism trends, beyond the broad trend of rapidly increasing numbers for birth cohorts from the late 1980s to 2000. For the most critical timeframe relevant to thimerosal removal, that of the 3-5 year olds born 2001-2003, upon which the main argument of the Schechter & Grether paper is based, the numbers are more problematic. The authors present the data in a commendable manner (by birth year)[2] and describe some of the problems, but omit a number of limitations.

DDS enrollments have risen rapidly for each birth year since the late 1980s (Figure 1 in the Schechter & Grether paper). The authors observe that among 6 year olds born in 2000, the rate for classic or full syndrome autism, which is the only type of autism that

the DDS reports, was 4.5 per 1000. DDS does not track other forms of autism – Asperger and PDD-NOS – which collectively with classic autism, are called the broader syndrome or autism spectrum disorder (ASD). The DDS classic autism rates can be compared with those derived from studies conducted by the CDC.

- A CDC study[3] of 8 year olds born in 1992 was conducted in 6 states. The average prevalence for the 6 sites for 1992 births was 6.7 per 1000 for the broader autism syndrome, ranging from 4.5 to 9.9 per 1000, depending on the site. The sources for case ascertainment were medical and education records. This methodology does not allow breakouts for each of the ASD subtypes (classic autism, Asperger, PDD-NOS), a major limitation.
- A second CDC study[4] using the same methodology but encompassing 14 states (the original 6 plus 8 more) looked at 8 year olds born in 1994. It found an average prevalence rate of 6.6 per 1000 for the broader autism spectrum disorder. The range was 3.3 to 10.6 per 1000, depending on the site. While the multi-site average for the 1992 and 1994 birth seemed the same, 6.7 versus 6.6, in fact, when only the same 6 sites repeated in each study are compared (an apples to apples comparison), the prevalence for the 1994 births was 7.4 per 1000 versus the 6.7 for 1992 births, a 10% increase in just 2 years.[5]
- A CDC study in Brick Township, New Jersey[6] used active case finding rather than administrative records. It found a rate of 6.7 for the broader syndrome among children age 3-10 and born 1988-1995. For earlier 1988-1991 births (7-10 year olds), the rate was just 4.4; for later births 1992-1994 (4-6 year olds) the rate was 10.2, a large, statistically significant increase. Tellingly, the rate for the 1992-1994 births of 10.2 was similar to the New Jersey rate for the multi-site studies described above: 9.9 in 1992 and 10.6 in 1994, giving validity to the prevalence rates for the broader syndrome for this time period, particularly for New Jersey.
- The Brick Township study, to its credit, broke out rates separately for classic autism and for Asperger/PDD-NOS. The classic autism rate averaged 4.0 for 1988-1995 births, versus 2.7 for Asperger/PDD-NOS, or a ratio of 1.5 to 1.0. The classic autism rate was 7.0 for 6 year olds born 1992 and just 2.0 for 8 year olds born 1990.[7]
- If the DDS system is only capturing classic autism, its prevalence should be compared with the Brick classic autism rates. The DDS rate for 6 year olds/1992 births is ~1.4, and for 8 year olds/1990 births it is ~0.8. If we assume a constant ratio of 1.5 to 1.0 for classic autism versus Asperger/PDD-NOS, the DDS classic autism rate of ~2.3 for 8 year olds/1994 births would translate into a broader syndrome rate of ~3.5, compared to the New Jersey rate of 10.2.

The DDS rates have been historically lower than the Brick Township rates, and lower than the multi-site CDC study states, for equivalent time periods. This could reflect a lag time in entry of cases into the DDS system or a true lower rate for California versus New Jersey and other measured states. Given the DDS methodology of voluntary enrollments and a system that sometimes tries to keep case counts low, the reason cannot be known

without more rigorous investigations. If the reason is lag time, then, while it is clear that the long term rate of autism is rising, given the CDC studies as well as the DDS data, the slope of the trend, including that of the 4-6 year olds, is impossible to know from the current DDS data set. If the reason is a true difference between California and other locations, drawing general conclusions from DDS is difficult. The difference may provide clues as to etiology, if exposures are different by state.

One of the problems in interpreting the DDS data for the most recent birth cohorts is the issue of age of ascertainment. A sizable portion of children with classic autism are not diagnosed until they are 6 years old. Thus, the rates for 3-5 year olds tend to be unstable. The trend over time has been for diagnosis to occur at earlier ages. The average age of diagnosis was 5.3 years in 1990, 4.4 years in 2000, and 3.1 years in 2006.[8] This trend suggests that younger age groups in the DDS system will create an artificial rise in prevalence over time, simply because relatively more children are enrolled in the younger age group than an older age group. Again, this circumstance makes the interpretation of the slope of the trend difficult, even though it is clear that in the long term prevalence is increasing.

Additionally, administrative changes have altered the DDS caseload, so that more recent reporting years have higher numbers not reflective of real changes in enrollment but instead due to changes in recordkeeping. The DDS website describes this recent change[9]:

> "Improvements to the reporting system in July 2002 resulted in the addition of diagnostic and evaluation information on 4,684 active consumers to the existing CDER database. These additional records are included in the September 2002 quarterly reports (i.e., Quarterly Client Characteristics Report and Quarterly Client Characteristics by County of Residence) and all subsequent reports. These records ***are not*** included in quarterly reports prior to September 2002."

DDS has not been consistent or rigorous in removing inactive cases from their database once they are entered. Although Schechter and Grether say the cases in their data set are "active cases", in fact, if the regional center has provided services for a case, it is unclear how long they will have no contact before the case is removed. The DDS web site states[9]:

> "Inactive CDER Files": Historically, the DDS policy was to exclude from the CDER reporting database all CDER records that were not current. Currency was defined as records that were either originally submitted or updated within the past three years. In July 2002, DDS changed this policy to include the CDER records of persons who are still being served by DDS, regardless of date of the most recent CDER. Through a data matching procedure, the CDER records of 1,464 active consumers were added to the CDER reporting archive system.

While the DDS seems to be diligent about enrollments, they are more lax (as they should be as service providers and not data collectors) about removals from the system. As inactive cases build up, the trend slope is impacted in unknown ways, especially after the new rule went into effect in 2002.

Although DDS only enrolls classic autism cases ("full syndrome"), the profile of the more recent cases is different from older cases. For example, Mental Retardation, which used to be the majority, is now a minority of cases.[10] Comparison of the older cases with newer cases using the same diagnostic criteria has not been done in a comprehensive way, although the MIND Institute may be doing so with their CHARGE study. [10]

Given these deficiencies, use of the DDS to determine the precise effect of thimerosal's reduction (not removal, as the author's assert; see Exposure section below) on recent autism rates is premature and findings incomplete. What can be said is the following:

- Autism continues to be diagnosed at a high level. Even among 4 year olds who are not fully diagnosed, the rate is 3.5 per 1000 for 2001 births. This high rate has implications for evaluating causation, including the role of thimerosal. (See Interpretation section below.)
- The exact comparative trend between more recent cohorts, born from 2000 and more recently, and older cohorts born in the 1990s cannot be determined from the DDS data at this point in time, also with implications for drawing conclusions about the role of thimerosal and other environmental factors.
- Autism is being diagnosed now more than the early 1980s. As such, this trend characterizes autism as an environmentally-driven disorder, not purely genetic. (See Interpretation section below);
- The fundamental problems in using an administrative data set like DDS to understand prevalence, phenotype changes and the role of diagnostic practices in autism may be insurmountable. More rigorous epidemiology studies, like a replication of the Robert Byrd study released in 2002[11] or the Brick Township Study by the CDC, are urgently needed.

Thimerosal Exposure Determinations

Although it is always made to appear by vaccine officials (Dr. Schechter works for the CA Immunization Branch) that the removal date of thimerosal from vaccines is precise and that the amount of thimerosal actually administered to children is precise, in fact, they are not. There is exposure uncertainty on both measures for the children in the DDS system.

The authors suggest that thimerosal was removed entirely except for inconsequential minute traces from routinely recommended vaccines as of 2002, almost entirely removed in 2001, largely removed in 2000 and starting to be removed in 1999. Thus, they assert that if rates of autism did not fall for birth years 1999-2003, then thimerosal was not a

major factor in autism causation. There are several areas of uncertainty in these assertions.

- The only change to practices in 1999 concerned the Hepatitis B vaccine. The birth dose was suspended for about 2 months, but given that many providers were not administering this dose anyway (according to one study,[12] the percent of children immunized ranged from 3% to 90% depending on location), it is unclear what effect the suspension had in terms of exposure to thimerosal in California in 1999. The suspension mostly resulted in a delay in vaccination, rather than failure to immunize. A new mercury-free vaccine was approved in September 1999, but it is not known how quickly this vaccine was utilized in the California population.
- Manufacturers of other vaccines began to convert to thimerosal-free or thimerosal-reduced versions in 2000, continuing into 2001, but there was a lag time between production and actual administration of the newer vaccines to children. Use of full dose thimerosal (25 micrograms) in routinely recommended U.S. infant vaccines other than the influenza vaccine may have continued until 2003.[13]
- A number of vaccines administered to children still contained reduced or trace amounts of mercury in the 2000-2003 timeframe. [14]
- The authors state that influenza was not recommended for infants until 2004, but they fail to note that ACIP "encouraged" immunization of infants as of April 2002[15], a position that fell just short of a universal recommendation only because of uncertainty over supply. The effect of the statement was to greatly expand infant immunization of thimerosal containing influenza vaccine during 2002.
- The ACIP also recommended influenza vaccine for all pregnant women beyond their first trimester. All but a small quantity of flu vaccine contained the full dose of thimerosal.

So, while the full effect of thimerosal removal in non-flu vaccines would be noticeable in 2002 births, the effect is diluted due to the increased uptake of flu vaccine. As Rick Rollens noted in his commentary on the Schechter & Grether paper, the effect of thimerosal removal will not truly be known until 2009-2010, when DDS cohorts born under the California "no thimerosal" law are tracked by DDS.[16] Nevertheless, exposure to thimerosal of some non-quantifiable lower amount is likely for California births in 2002 relative to 1994.

Dose uncertainty also arises from the number of non-U.S. born cases in the DDS system. These children would have been immunized with non-U.S. vaccines, many of which would have contained thimerosal. According to the Migration Policy Institute (http://www.migrationinformation.org/datahub/acscensus.cfm), in 2005, 1.7% of children nationwide under the age of 5 were foreign born compared to California, where 2.8% (74,868) in 2005 were foreign born. In the California DDS system, the website tab for March 2007, which is the last date they reviewed for the article, 31.54% of the children in the DDS system were listed as Hispanic. David Kirby, in a presentation in Atlanta in November 2007,[8] noted that the increase in autism cases for the Asian/Hispanic group far exceeded that for whites and accounted for a sizeable portion of the more recent increases in cases. The non-U.S. born children, not subject to estimates

about thimerosal removal from U.S. vaccines, may be modifying the more recent trends, making upward slopes steeper.

Interpretation of the Findings

The paper's premise is that if thimerosal-containing vaccines (TCVs) are the primary cause for the rise of ASD rates, then one would expect to see a sharp decline in the incidence of autism as thimerosal was removed from the vaccines. If the rate of autism continued to increase or did not fall following the removal of thimerosal, then TCVs could not be the primary cause.

This conclusion would be valid if autism across all subgroups, time and geography is caused by only one factor. However, if it is multifactorial, then a cause that is a primary factor for one subgroup, geography or time period might not be a primary factor for another. A geographic example was described by Tony Persico,[17] whose work suggested a relationship between pesticides and autism in American subjects but not Italians, because Americans are exposed to the pesticides but Italians are not. Maternal rubella exposure is an example from a time period. Pregnant women who contracted rubella during the epidemic of the 1960s had children with a much higher rate of autism. When the epidemic resolved, no further autism cases were associated with rubella, but this does not mean that exposure to rubella while pregnant was an unimportant risk factor for autism during the 1960s rubella epidemic.

Thimerosal may well have been the primary cause of the initial cases of autism described by Kanner and Asperger among children born in the 1930s, [18] and of the rapid increase in cases seen from the late 1980s to the late 1990s.[19] However, if other compounds act on the same pathways leading to autism and exposure to these other compounds is increasing while thimerosal exposure is decreasing, then a decrease from thimerosal removal would not be detected in an imprecise prevalence trend, because the other increasing substance(s) would cancel out the decline.

A number of substances that have been implicated in autism are increasing in terms of exposures to pregnant women and infants. The following substances are of major concern:

1. Aluminum in infant vaccines. As thimerosal was removed, the aluminum content of vaccines increased, plus many more vaccines were added to the infant schedule in the late 1990s and early 2000s that contained significant amounts of aluminum. Aluminum is a metal that can produce similar biological aberrations as mercury.[20] The aluminum may interact synergistically with the remaining thimerosal in the vaccines to increase toxicity.

2. Vaccines in general: Since the late 1990s, many new vaccines have been added to the infant schedule. New routine shots include those for varicella, influenza, rotavirus, pneumococcal disease, and hepatitis A. Many of these shots are given in a series of multiple injections and contain live viruses as well as aluminum and other potentially

harmful substances. Parents of autistic children report regression into autism by their child after getting immunized. Influenza vaccination during pregnancy has also been implicated in autistic-like symptoms in the offspring from animal model studies.[21,22]

3. Mercury in general: Mercury exposure comes from a number of sources. Thimerosal is just one, albeit a very effective compound for mercury delivery into cells. Other sources include coal-burning power plants, chlorine plants, oil extraction and refining, and persistent mercurial compounds used decades ago as fungicides and herbicides and in the mining industry. The amount of environmental mercury through coal plant emissions has been increasing rapidly. Exposures can come through air, water, and food. A few preliminary studies have tied higher rates of autism with areas that have higher mercury releases.[23,24] Schechter and Grether did not look at thimerosal in the context of total mercury exposures, which overall are increasing even as the use of one type of mercury – thimerosal – has gone down.

4. Hazardous pollutants like airborne particulate matter, pesticides, plasticizers, and lead: these have been preliminarily linked to autism; exposure is increasing for most; even lead still persists despite being banned in this country. [17,24,25,26]

Conclusions

There are many more autistic children being enrolled in the DDS system in the 2000s than in the 1980s, consistent with CDC studies showing an increase in rates among children born in the 1990s. The trend among younger children and its relationship to thimerosal and other environmental exposures are still not clear. Thus, the data in the Schechter & Grether paper supports these critical points:

1. The autism epidemic is real and not solely an artifact of better diagnostic practices or changing diagnostic criteria. Autism is a national emergency and requires more government focus.

2. The increase supports a strong environmental role in autism causation. Environmental triggers are interacting with autism susceptibility genes to produce autistic symptoms. More autism research funding should be allocated to studying environmental causes.

3. This study does not rule out any causative agent. The imprecision of the DDS data and uncertainties over thimerosal dose is too great, especially for the younger age groups, on which the authors' argument rests. The imprecision argues the need for more rigorous epidemiology studies that can adequately describe autism prevalence trends from the 1980s to the present.

4. The study does not rule out thimerosal, even as a "primary" causative factor, if multiple agents are operating on different subgroups, at different time periods, or over different geographies. Thimerosal may have been a primary or important factor in the

beginnings of autism and the rapid rise in the 1990s; the DDS data are agnostic on this interpretation. Thimerosal remains a top candidate for contributing to cases from 1930 to the present and the need for it to be investigated fully remains strong.

5. Other environmental factors are being identified as playing a role in autism but none has been adequately studied.[27] The environmental causes of autism are likely to be multiple and complex. A comprehensive research agenda that systematically studies all leading candidates for environmental triggers is urgently needed.

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