

Systematic Review of Historical Epidemiologic Studies Influencing Public Health Policies on Vaccination

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Abstract

a. Background. Studies used to inform on public health policies on vaccination are represented are rigorous.

b. Methods. To examine the quality of the science used in high-profile sources on the question of vaccines and autism, an objective evaluation score (OES) was designed that provides a rapid, reproducible assessment of any retrospective or prospective clinical study focused on vaccine safety. The OES was determined for forty-eight "Key Studies" on the question of vaccines and autism association present to the President of United States in 2017, and on the question of the safety of thimerosal us in vaccines present by the US CDC as representative.

c. Results. Of the forty-eight studies, only one had a positive score (+4); the rest had zero or negative scores, with an average OES of -6.61. Moreover, a search of the literature revealed that the list of studies was in fact as biased selection of studies, with the selected studies yielding an average odds ratio of 0.80 (average for ASD-focused studies 0.756); the average odds ratio of studies not cited by these sources was 4.01.

d. Conclusions. Clearly, public health policies focused on low-quality underpowered retrospective correlation studies, which only measure association and do not measure causality, must be replaced with more rigorous, sufficiently powered randomized prospective clinical trials. The safety of vaccines cannot be assumed and used as justification for not performing rigorous science. (Extended Abstract supplied in text.)

What is already known on this subject?

It is widely believed that studies of the question of vaccines and autism are rigorous and have thoroughly tested for a causal link.

What does this study add?

This study provides an impartial, multi-component objective evaluation score on the key studies listed as demonstrating no link between vaccines and autism, and find that all fall short of ideal and robust.

Extended Abstract

Objective: Numerous agency authorities, resources, and publications cite numerous epidemiological studies as demonstrating a lack of evidence of association between vaccines and autism. Prior analyses have revealed that key studies used by the Institutes of Medicine lack sufficient statistical power to

provide confidence that their negative results, i.e., lack of association, could reasonably be due to the combined effects of an inability to detect an association due to low power (attributed to small sample sizes) and to healthy user bias (a form of self-selection in which patients who have previously experienced negative reactions to vaccines opted out of the single vaccine for which association was sought). In this systematic review, 48 “Key Studies” cited by organizations such as the American Association of Pediatrics, or listed by CDC and two reviews as evidence of no association between “Vaccines” and autism, or allegedly demonstrating the “safety” of thimerosal-containing vaccines (TCV), are independently and collectively reviewed.

Method: An objective 11-subscore evaluation score (Objective Evaluation Score; OES) was designed that can be applied to any vaccine safety study; the ideal score for any study is +12; the average score for the Key Studies was -6.61. Only two of the forty-eight Key Studies had a non-negative OES.

Results: The studies evaluated fell far short of high-quality science: twenty did not estimate ASD prevalence; twenty-two did not study “Vaccinated vs. Unvaccinated”; thirty-two only examined association of a single vaccine; twenty publications studied thimerosal containing vs. non-thimerosal containing vaccines; at least twenty-one studies had insufficient statistical power; thirty-three had evidence of flawed study design; twenty-eight had flaws in the design of analysis, in some cases leading to false negatives on the question of association; thirty-four made unwarranted conclusions about negative results given the sample size and type of study. All but one study were retrospective studies; none were blinded, prospective randomized clinical trials. All fall into the category of correlational analyses. Due to cohort effects and myriad ingrained flaws, correlation studies fail to provide credible evidence capable of definitively falsifying the hypothesis of causality of vaccines and autism and are at the risk of temporal confounding and cohort effects. Studies of single vaccines obviously fail to provide a sufficient level of evidence permitting a generalization to all vaccines or the CDC pediatric vaccination schedule. Studies that did not measure rates or risks of autism were found to be irrelevant to the question. Studies of TCV vs non-TCV found increased health risks due to non-TCVs, but uniformly attributed the result to a mysterious, previously unknown (ad-hoc) health benefit of thimerosal. The three largest studies fall into the categories of single-vaccine studies or TCV-vaccines. Many studies adjusted for covariates that should have been considered risk factors; none examined interaction terms between vaccines and plausible co-factors. Combined, these studies have been cited by over 6500 other studies or reviews and form the basis of public health policy and practices. The single meta-analysis conducted included low-powered studies that had already been rejected by the IOM as flawed. None of the studies were designed to test the hypothesis that a heterogeneous subgroup of humans carries susceptibility to neurodevelopmental disorders compared to the general population, nor did any of the studies conducted determine whether such individuals could be detected prior to vaccination. The bolus of studies cited by CDC and AAP conspicuously exclude studies that show a positive association of neurodevelopmental disorders and vaccines. Co-signing organizations and recipients of the AAP statement letter to POTUS will be interested to know that the average odds ratio of studies cited was 0.80 (average for ASD-focused studies 0.756); the average odds ratio of studies not cited by these sources was 4.01.

Conclusion: Low-powered association studies cannot be used to provide definitive negative evidence for hypotheses of causality, and single-vaccine studies likely suffer from Healthy User Bias. No studies exist that definitively falsify the vaccine/autism link, and the evidence presented as demonstrating no link and the alleged safety of thimerosal is both extremely weak and has not been provided to policy makers in an unbiased manner.

Introduction

Most questions about vaccine safety and efficacy elicit a media response that hearkens the question of whether vaccines contribute to risk of autism (autism spectrum disorder diagnosis), even when the question is not central to the specific question at hand. An example is the recent spate of outbreaks transmission of mumps virus involving individuals who had been fully vaccinated. The question of the cause of the loss of efficacy is not usually specifically addressed; as mumps is an RNA virus, with much higher baseline mutation rate than DNA viruses and bacteria, the vaccine types and the circulating wild types can be expected to evolve away from other, weakening immunogenicity. The standard modus operandi of media coverage is to cite the study by Wakefield and colleagues, which was a pilot study in which Dr. Wakefield and colleagues posed the hypothesis of a new form of autism involving GI disruption, potentially caused by lingering measles infection. Dr. Wakefield's medical license was stripped by the General Medical Council of the United Kingdom, who nevertheless went on to exonerate Wakefield's colleague, Dr. John Walker-Smith and to quash the suspension of Dr. Walker-Smith's license. The media coverage may also cite studies conducted to exonerate vaccines of any role in ASD risk, but they never cite studies that have found increased risk of ASD following vaccination. Examples of those studies are provided here (Table 1).

Medical associations, led by the AAP, sent President Donald J. Trump a letter in which they cite specific studies they claim demonstrate a lack of association between vaccines and autism (AAP, 2017). The US Centers for Disease Control and Prevention (CDC) also lists studies on their website, which reads "Vaccines Do Not Cause Autism" (CDC, 2018a). ASD rates (four years ago) are 1 in 59 kids by age 8; in boys, the rate was 1 in 34 (CDC, 2018b)[1].

Table 1. Examples of Studies Relevant to the Vaccine/Neurodevelopment Disorder Question Not Cited by AAP or CDC

Avella-Garcia et al., 2016[2]

Bauer et al, 2013[3]

Gallagher and Goodman, 2010[4]

Nevison, 2014[5]

Shultz et al. 2008[6]

Geier and Geier et al., 2003[7]

Geier et al, 2018[8]

Goldman and Yazbak, 2004[9]

In 2010, Shoffner et al., (2010)[11] found that 71% of kids with regressive autism had an episode of fever > 101°F In 33% of these cases, the fever occurred right after vaccination – and none showed regression into autism unless fever had occurred.

The AAP letter, evidently authored by HealthyChildren.org and provided to the AAP and co-signers for signature, and the CDC website both neglect to cite studies in favor of rejection of the null hypothesis of no association (Table 1). The bolus of studies themselves therefore may represent an example of confirmation bias in action; they have "cherry-picked" studies from the literature, leaving out any that lend support to the possibility that vaccine contribute to neurodevelopmental disorders. The US CDC is closely affiliated with vaccine manufacturers, receiving over hundreds of millions of dollars per year via

the CDC Foundation. A review of the publications by CDC ACIP committee members reveals universally shared financial conflicts of interest with a single exception.

As reported by ICAN (2017)[10]:

“Since 1995 the CDC Foundation has raised 620 million to pay for 824 programs at the CDC... In 2015 alone, the CDC Foundation raised 157 million for privately funded programs at the CDC, which then obtain the stamp of legitimacy of the CDC... Merck, for example, funded an 832,916 program through the CDC Foundation to “expand CDC’s ... viral hepatitis prevention and vaccination activities”... As a result, the CDC is reliant on the CDC Foundation for the continued funding of these projects, and even for the services of the staff placed at the CDC by the CDC Foundation, since the CDC is only permitted to use these funds as expressly directed by the CDC Foundation.... This foundation even funds and thus directs CDC ‘management training courses.’”

Many of the individual studies cited were funded by vaccine manufacturers, presenting a systematic conflict of interest (Kern et al 2017)[12]. HealthyChildren.org, an unofficial vaccine educator organization, receives funding from the CDC (Doshi, 2017[13]), representing a conflicted source (DeLong, 2012) [14]. CDC also owns numerous patents on vaccines, and ACIP members nearly universally have extensive financial conflicts of interest.

To date, no independent evaluation of the studies cited by AAP and by CDC has been conducted.

Context of the 48 “Key Studies”

The first study to propose that vaccines might be involved in any aspect of ASD (Wakefield et al, 1998[15]) was retracted by the Lancet after some of the authors self-retracted an interpretation. The study has been misrepresented as having concluded that vaccines cause autism. However, in the original study, authors had merely proposed the hypothesis of an MMR/ASD/colitis link and actually concluded: *“We did not prove an association between measles, mumps, and rubella vaccine and the syndrome described”*.

After Dr. Wakefield’s initial study, the question of the link between vaccines and autism was raised by the US Congress, which tasked CDC to undertake objective studies to address the question. CDC participated in numerous studies, and subcontracted others. Nearly all studies were retrospective (i.e., correlational) in nature and thus fail to actually test the hypothesis of causality. In 1986, the US Congress passed, and President Ronald Reagan signed it law, the 1986 National Childhood Vaccine Injury act, which stipulated (1) that vaccines be made safer, and (2) that individuals who are genetically susceptible to vaccine injury be found. So far, neither of these mandates have been met. CDC has conducted zero studies on the question of genetic susceptibility to vaccine injury. In the studies CDC did conduct, or fund, all were retrospective studies, i.e., correlational studies, meaning that the hypothesis of causality could not be tested. Some of the studies cited (e.g., McMahon et al., 2008) [16] used data from vaccine safety databases (such as VAERS and the VSD), which entail warnings to users on the inherent limitations of the use of the data sources to infer causality.

At around the same time, the link between thimerosal and autism was addressed by the opportunity afforded by the phasing out of Thimerosal from vaccines, ostensibly (according to CDC) due to an “abundance of caution” (CDC, 1999) [17]. In reality, the amount of mercury being injected to infants had been found to exceed the federal limits of exposure permitted by the EPA (Ball et al., 2001; Hurley et al., 2010[18,19]). Thimerosal is included as a preservative for multi-dose vials of vaccines. “Thimerosal-containing vaccine” vs. “non-thimerosal containing vaccines” were included in the evaluation because they were included in the original listings, although they received a demerit due to their inexact focus on

ASD risk. In 2002, for reasons that are unclear, the CDC began recommending that pregnant women and infants as young as 6 months preferentially receive thimerosal-containing annual flu shots at 1-2 doses each season. Gerber and Offit (2009)[20] lamented the shift of the hypothesis of causality of autism due to vaccines from ethyl mercury to “too many vaccines”; however, those observing cases of sudden onset of autism are not responsible for the vaccine schedule, nor for the formulation of vaccines, and aluminum exposures, a potent neurotoxin, is now known to exceed “safe” levels determined by an unreliable FDA modeling exercise that derived judgment of safe levels of injected forms of aluminum from dietary exposure in adult mice with arbitrary dietary MSL levels (Lyons-Weiler and Ricketson, 2018) [21]. The CDC schedule results in neurotoxic doses of aluminum in the first six months of life (Dórea and Marques, 2010; Lyons-Weiler and Ricketson, 2018) [21,22], with more aluminum exposure from vaccines than from diet (Dórea and Marques, 2010) [22]. Autism can be seen as an acquired syndrome with failed detoxification deficiency (Lyons-Weiler, 2018) [23], meaning susceptible individuals may not fare well with repeated and combined exposures of injected forms of neuro- and immunotoxic metals.

IOM Causality Determinations, Evidence of Bias, Studies of Mechanism Ignored

In 1989, 2004, and 2012, the Institute of Medicine undertook the task (via contract) to evaluate the available scientific literature on issues of vaccine safety, focused specifically on the question of whether the available evidence could, or could not support, a conclusion of causality. Unfortunately, minutes of the meetings leading to the 2012 conclusions revealed that the IOM decided to ignore available animal studies presenting mechanistic plausibility for lack of a “free weekend” (NAS-IOM, 2001)[24].

An absence of sufficient evidence due to a lack of studies was, in the original reports, used appropriately to conclude that insufficient information was available for, or against, a conclusion of causality, but in the latter reports, and in CDC usage of those reports, the conclusion was shifted slightly toward a focus on insufficient evidence to conclude that causality was not an issue. Whereas a lack of evidence for, or against causality previously had been interpreted as “insufficient evidence”, in 2012, a new logic was created that allowed the absence of sufficient evidence to be emphasized as “no evidence in favor of”. This alone is a clear breach of objective analysis and inference.

This shift has had profound and definitive impact on public health policies toward vaccination. The vaccine schedule has expanded, and a cultural phenomenon pitting physicians against parents over the objective reality of vaccine risk has taken hold. There are social consequences for exercising choice both in individuals’ personal and professional lives. Where some individuals lose close friends, others have lost employment. In 2014, six healthcare workers at Saint Vincent Hospital in Erie, PA sued their former employer for wrongful termination due to their choice to exercise their rights to refuse the influenza vaccine, and won a settlement that includes reinstatement (AHC Media, 2014) [25]. In 2014, a PBS station in Boston, MA, USA “unhired” a scientist, Mish Michaels, who had spoken out while between jobs on vaccine risk. We have to ask ourselves: Is it rational for members of our society to suffer consequences for speaking out about potential risks of a medical procedure of the source of the biased perception on the safety of that procedure is due to activities of those who stand to gain financially from vaccines as a business?

Widespread Cohort Effects: Changes in Schedule

Around the time that thimerosal was being phased out of pediatric vaccines (with exceptions), additional vaccines were being added to the schedule. Many of these were aluminum-containing vaccines (ACVs) and additional booster shots were being added. This, along with the shift in the use of TCVs during pregnancy, introduces a massive and universal cohort effect that impacts any retrospective study. When parents began to observe regression into autism after the DtaP vaccine, parents were accused of moving

the goalposts; in reality, the parents were not responsible for the addition of so many new aluminum-containing vaccines, and they began reporting what is now a widespread set of observations: of the back, a high-pitched cry from which the infant could not be consoled, head banging if >2 years old, then a sudden or gradual (over the course of days) of loss of social contact (low eye contact, use of fewer, simpler words, loss of speech) and regression into autism.

Systematic Review Methodology

Search Strategies

Various organizations have published publication lists of studies with short summaries on epidemiological studies reported to address the question of a causal relationship between vaccines and autism. This includes governmental agencies (CDC, 2018) [26], a professional medical association (AAP, 2017[27]), and two additional compendia that selected arbitrary sets of studies from the full literature (Hotez, 2017[28]; Gerber and Offit, 2009[20]). These compendia were compiled into a master list of “Key Studies” for evaluation. This resulting bolus of a widely circulated catalog of studies are used to ostensibly show the massive amount of science that purportedly shows no association between vaccines and autism or other neurodevelopmental disorders. It is assumed that these studies are representative of the full body of literature published on the question of any connection between vaccines and autism, and on vaccine safety in general. If these studies had been selected without bias, are robust (i.e. free of sources of bias and sufficiently powered), and if the data analyses conducted are appropriate, then the claim that “Vaccines Do Not Cause Autism” listed on CDC’s website might be warranted.

As a check on the objectivity and unbiasedness of those lists, a Pubmed and internet search was for studies and reviews that mentioned “autism”, “vaccines”, and “odds ratio”. These studies were analyzed separately from the boluses provided by AAP and CDC.

Inclusion Criteria for this Review

All studies cited by AAP, by CDC and by other sources as demonstrating ‘vaccine safety’ and addressing the question of whether ‘vaccines’ cause autism were included and scored specifically for their contribution to the question of whether vaccine cause autism. As this was a systematic review of the suitability of studies cited by governmental and medical professional organizations in their statement of their public health policies and public health policy recommendations, all studies cited were subjected to evaluation.

Objective Evaluation Scoring System

Applying a systematic objective evaluation system (Table 2), the studies cited by CDC, AAP and others are evaluated. Independent of study author affiliation, the same scrutiny was applied for all criteria. The criteria were selected to reflect deviation from an ideal study (prospective randomized clinical trial of vaccinated (per schedule) vs. unvaccinated study with the outcome variable of the prevalence of ASD). The studies listed fall short of ideal in a common way (none are prospective RCTs). Based on the aims and scope, study design and design of analysis, it was possible to derive 11 evaluation criteria (Table 2). Some of the criteria are obviously not independent (underpowered studies, for example, would also have inappropriate design and may have had an inappropriate conclusion), but all criteria were applied independent of each other to each study because flaws in study design such as low power and the inappropriate use of covariates could have nevertheless been appropriately interpreted.

The scoring system was devised to facilitate rapid evaluation. Scoring proceeded as follows as outlined in Table 2. The final Objective Evaluation Score (OES) was the sum of these subscores for each study is

reported. If a particular criterion was irrelevant to a given study, the study was given a score of zero for that criterion. For example, Baird et al. (2008) [29] studied the effects of the number of doses of measles vaccines on serum titer levels in a case/control study, and therefore the criterion on measuring prevalence was irrelevant to that study. Studies of thimerosal-containing vaccines compared to non-thimerosal containing vaccines included by those listing studies were given a subscore of -1 because they universally fail to be represented by those citing them as a comparison of two periods, suffering from numerous sources of temporal confounding. The first of which thimerosal-period vaccines were given vs. thimerosal use in flu vaccine *plus* a larger number of vaccines overall; the second of which was an expansion of the overall schedule with the additional of numerous aluminum-containing vaccines; the third of which is the potential for interaction between TCVs and ACVs in the latter period.

Under this OES system, an ideal study could achieve a score of +12.

Table 2

Criterion	Subscore	Justification/Example
Examined ASD Prevalence	+1, -1	Primary hypothesis of interest vaccine injury
Comparison of Vaccinated vs Unvaccinated	+2, 0	Best study aim
Comparison of Groups Based on Single Vaccines	-2, 0	Improper science; susceptible to healthy user/accrual bias
Analysis of Trends Only	-1, 0	Weak science
RCT/Retrospective Correlation Study	+2,-2	Weak science, falls short of testing hypothesis of causality
Sufficient/Insufficient Power	+2,-2	Negative results are expected with small sample sizes
Appropriate/Inappropriate Use of Covariates	+1,-1	Adjusting/correcting for “confounders” that may actually represent risk co-factors. Inappropriate interpretation is prevalent.
Comparison of TCV vs. non-TCVs	-1, 0	Limited scope with respect to primary hypothesis of interest
Appropriate/Inappropriate Design/Aims	+2,-2	Study design must match stated aims
Appropriate/Inappropriate Analysis association “go	+1,-1	Data analysis must not be repeated exercises to make initial away”, revealing a pre-determined conclusion (“Analysis-to-Result”)
Appropriate/Inappropriate Conclusion	+1,-1	Given limited ability of correlation studies to test causality, sample size, study design and analysis, are conclusions warranted?

Study Design Evaluation

To undertake this review, standard considerations of study design were applied: suitability of design of the study to the stated study aims, representativeness of the population, potential sources of bias, and appropriateness of the study design and the design of analysis (data analysis). The study design evaluation included both whether the stated aims, design, analysis and interpretation matched as well as consideration of statistical power (sample size). For each study, a power analysis was conducted to determine whether the study had sufficiently large sample sizes to detect a biologically plausible positive

effect size given the prevalence of ASD at the time period the study examined. When possible, any other limitations of each study were noted.

Evaluation for Study Selection Bias

When available from the primary citation, odds ratios (ORs) or relative risk (RR) reported by the Key Studies were recorded and compared to other studies not cited by the authorities citing the literature. These are presented as funnel plots, which allow for objective visual inspection to determine whether a balanced representation of the literature is evident in a systematic review.

Results

All of the Key Studies were observational analytic studies, which fall short of testing causality. None were prospective randomized clinical trials. These overall results were informative by subclasses of studies, as follows:

Studies That Did Not Study Autism or Neurological Outcomes

In spite of the title of the study, Peltola et al. (1998) [30] could not analyze the prevalence of autism diagnosis because they detect zero cases of autism after 3 million instances of vaccination. This alone suggests a serious ascertainment bias. McMahon et al., 2008 [16] used VAERS data, but like other studies that employ the VAERS resource, *did not carry forward the stated limitations on its use for assessing causality*, and did not report any result relevant to the question of an autism/vaccine link. If the source reported the data are not appropriate for causality assessment, then studies conducted using the data should carry that limitation forward.

Various studies (e.g., Peltola et al., 1998; Black et al., 2002) [30,31] focused exclusively on rates of GI issues in children with, and without ASD rather than ASD association nor causality itself. Black (2002) [31] only studied the relative rates of GI issues prior to a diagnosis of autism. D'Souza et al. (2006) [32] and Hornig et al., (2008) [33] used molecular assays to study whether persistent measles virus (MV) could be detected in the GI tracts of children with autism. While they tested only one proposed mechanism of vaccine involvement in ASD (latent enteric measles virus infection), and other routes by which metals in vaccines might induce autoimmune gastroenteritis (e.g., activation of enteric microglia), and GI issues might contribute directly or reflect (common cause) sensitivity to vaccines or their excipients, these were nevertheless included in the evaluation.

Studies That Only Analyzed Trends

By definition, retrospective studies that compare the incidence of groups receiving a treatment or intervention to groups that have not received the treatment or intervention are, in a way, a consideration of trends because a key assumption is that the incidence of specific outcomes in control group rates reflect baseline rates. Unless baseline incidence data are available, the validity of the between- or across-group comparisons rely on no temporal confounding (cohort effect). In the groups of studies under consideration, two (Kaye et al., 2001; Stehr-Green et al., 2003) [34,35] were analyses of trends with no comparison group, and total of ten studies (Stehr-Green et al., 2003; Fombonne et al., 2001; Lingam et al., 2003; Andrews et al., 2004; Chen et al., 2004; McMahon et al., 2008; Tozzi et al., 2009; Price et al., 2010a; Klein et al., 2011; Taylor et al., 2014) [13,35-43] depended primarily on comparisons of trends.

An analysis of the Fombonne et al. study (2001) [36] by the Cochrane Collaboration (Demicheli et al., 2005) [44] yielded a scathing critique:

“The number and possible impact of biases was so high that interpretation of the results was difficult.”

These concerns did not prevent the AAP from listing this study as if it were, indeed, considered a useful study. Similarly, a published critique of Andrews et al. (2004) [38] by Hooker et al. (2014) [45] was not referenced and the published concerns, which included the inclusion of time as covariate that would be confounded with vaccination practices.

Madsen et al. (2003) [46] found that the incidence of autism diagnosis in children between 2 and 10 years old in the Danish registry from 1971-2000 continued to increase after the removal of thimerosal from vaccines. This is usually interpreted as evidence that thimerosal in vaccines was not contributing to autism rates; however, many vaccines added after the removal of thimerosal contained aluminum hydroxide as an adjuvant. An equally plausible explanation is that autism rates would have decreased, but that the pediatric schedule conferred more risk.

Dales et al. (2001) [47] compared the percentage increase in autism diagnosis in children in California between 2 and 10 years old during the period from 1971-2000. Their rates were recorded as age-specific incidence for first day of first recorded admission with a diagnosis of autism. They found that ASD rates increased 377%, but that MMR vaccination only increased 14%. No formal statistical analysis was reported. Given their data, however, a Fisher's exact test reveals a significant association $p=0.0002$, and therefore it is puzzling why Dales et al. (2001) [47] did not report the association. This is an example of how conclusions might not match results in spite of proper execution. Instead, they reported their opinion that the rate of increase in ASD was higher than the rate of increase in MMR vaccination, which requires a linear relationship between vaccination and ASD. In reality, at highest MMR vaccination rates, the latter populations were also receiving a larger number of vaccines. The study's focus on MMR only in a setting in which other vaccination influences could also exist would require a hyperlinear model. Of course, other factors including changes in diagnosis explain *part*, but not all of the increase (Nevison, 2014) [5]. The limitation of the Dales et al. (2001) [47] study exemplifies the limitation of relying on correlation studies to inform on causality, a limitation shared by in fact all of the studies in this review.

Honda et al. (2005) [48] studied the MMR vaccination rates in Yokohama, Japan from 1988-1996. They found that MMR vaccination in the city of Yokohama declined from 1988 through 1992 and the vaccine was abandoned in 1993 and thereafter. They reported that the cumulative incidence of ASD up to age seven increased significantly between 1988-1996, with the highest increase beginning in 1993.

They concluded that autism rates could not be attributed to the MMR vaccine; however, separate measles, mumps and rubella vaccines were used at the time, i.e., vaccination did not stop. Thus, while the study could arguably be interpreted that the MMR itself might be ruled out as a cause of autism, the study did not test the hypothesis that vaccination against measles, mumps and rubella might individually or together contribute. Also, the number of other vaccines available for use in Japan increased over this time period. It is worth noting that when Japan banned vaccination of children under the age of two, deaths from crib death and meningitis ended (Cherry et al., 1988) [49], and the incidence of infantile mortality plummeted to the lowest in the world.

Madsen et al. (2003) [46], while a very large retrospective study, were found to have removed incidence data from 2001 and manipulated inpatient/outpatient data to create an artificial rise in prevalence in 1994 (Hooker et al., 2014) [45]. One of the authors on the study, Poul Thorsen, is on the HHS's most wanted list for embezzling >1.2 million CDC autism research dollars. Further limiting details of the study include that as an ecological correlation study, its design falls short of the level of evidence required to test causality; studied only one vaccine (MMR). Goldman and Yazbak (2004) [9] pointed to ascertainment bias due to the likelihood that a large portion of children born later than 1997 were too young to have received a diagnosis of autism, and some had not even received their dose of MMR when the data were

collected (1998). The average age of diagnosis in the Madsen study was 5 years. This means a large portion of children in the MMR/No Autism group had received the MMR but had not yet been diagnosed. The "age-adjustment" used by Madsen et al. would not have been able to undo the strong effects of this type of confounding. Their analysis should have used "time since vaccination". This is another example of the extreme weakness of basing public health policies that influence millions of people on mere correlation studies.

McMahon et al., 2008 [16] was a retrospective study focused on rates of reported adverse events in the Vaccine Adverse Events Reporting System (VAERS) after preservative-free (PFV), preservative-including (PIV), and preservative unknown (PUV) vaccines in reports from 7/1/2004 to 1/4/2006. Thus, the analysis was restricted to TCV vs. non-TCVs. No power analysis was conducted, and the authors noted the likely effects of underreporting. CDC does not carry forward these limitations in their representation of this study. VAERS is severely limited as a resource for tracking adverse events, not only due to underreporting, which is estimated to be limited to between 1-10% of actual recognized adverse events. Underreporting suggests insufficient power, and likely absence of some adverse events altogether from the records. ASD was not specifically studied; in fact, neurodevelopmental disorders were not explicitly studied.

Stehr-Green et al., 2003 [35] was a retrospective ecological study of autism incidence versus Thimerosal exposure in Denmark, Sweden, and California. Using "graphical ecological analyses", they compared prevalence of ASD and found it continued to increase in all three countries in spite of the alleged discontinuation of thimerosal over the time period. Two independent analyses of the Stehr-Green et al. (2003) [35] study found issues with the interpretation of changes in group designation and with study design (changing entrance criteria in ecological studies) and reporting and interpretation (not all results reported in the final publication, and changes in description of source data (Blaxill, 2004[50]; Hooker et al., 2014) [45]).

Andrews et al (2004) [38] was a retrospective study of 109,863 children who were born from 1988 to 1997 and were registered in general practices in the United Kingdom. The author sought to measure a dose correlation of the number of doses of DTP/DT received by 3 and 4 months of age, the cumulative age-specific DTP/DT exposure by 6 months, and autism diagnosis. Finding no correlation, they concluded there was "no evidence that thimerosal exposure via DTP/DT vaccines causes neurodevelopmental disorders". As a study of adverse events related to a single vaccine, the study was susceptible to healthy user bias, which has been acknowledged to confound such studies since 1992 (Fine and Chen, 1992[51]; Jain 2015[52]). Prior analyses had shown increased risk of developmental disorders with DTP/DT vaccine exposure, which has been seen as further evidence of methodological issues with this study (Hooker et al., 2014) [45].

Baird et al. (2008) [29] conducted a retrospective case/control study focused on whether children with ASD had a higher antibody response to measles virus than individuals with special education needs and neurotypical individuals. All individuals in each sample group were ages 10-12 and from the United Kingdom. All individuals were tested for measles virus and antibody response to measles in serum. Failure to find a dose-response relationship between autism symptoms and antibody concentrations could easily have been due to low power due to low sample sizes per group (N=98, 52, and 90 respectively). An alternative study design would have been the rates of high measles antibody rates between the two groups.

Fombonne et al. (2001) [3] estimated retrospectively the pervasive developmental disorder prevalence in Montreal, Canada, in cohorts born from 1987 to 1998 to evaluate the potential relationship of trends in

pervasive developmental disorder rates to three factors: (1) changes in cumulative exposure to ethylmercury (thimerosal) and (2) trends in measles-mumps-rubella vaccination use rates and (3) the introduction of a 2-measles-mumps-rubella dosing schedule during the study period.

The Fombonne et al. (2001) [36] study could not have compared thimerosal to non-thimerosal vaccine periods because thimerosal was still in use in the Hepatitis B vaccine until 2001. Thimerosal was also in use (and still is in use) in flu vaccines. Thus, the stated aims are inaccurate, and the conclusions thus cannot be supported by the study. The study actually compared the pervasive developmental disorder prevalence in a period in which thimerosal was used in vaccines and a period in which more vaccines containing aluminum were added while thimerosal was still in use. Regarding the MMR vaccination aims, issues exist with the definition of cohorts because some individuals may have received only one vaccine but not the second; such individuals were scored by the study protocol as out of compliance. Credit to these observations should be attributed to Dr. Paul King. The focus on one vaccine subjects the study to the healthy user bias, given that children who experienced earlier adverse events from any vaccine may have been excluded from the MMR vaccination program due to parental concern. The study appears to have been sufficiently powered, but statistical power does not overcome source of bias.

Jain et al. (2015) [52] retrospectively examined ASD occurrence in groups defined by MMR vaccine status in a large sample of US children who have older siblings with and without ASD. They found that MMR vaccine was not associated with increased risk of ASD, regardless of whether older siblings had ASD. However, because the only studied one vaccine (MMR), their results are almost certainly due to healthy user bias, which they acknowledge in their text, but for which no steps were taken to avoid.

Uchiyama et al., 2007 [53] studied the rates of MMR vaccine uptake in 904 children with regressive autism from Japan and compared it to the MMR vaccine uptake children without ASD. They found similar rates of MMR vaccine uptake between the two groups. This study is also susceptible to healthy user bias.

Zerbo et al. (2016) [54] was a retrospective cohort study of 196,929 children enrolled in Kaiser Permanente Northern California from January 1, 2000 to December 31, 2010, at a gestational age of at least 24 weeks. A total of 3,103 had a diagnosis of autism spectrum disorder, in which maternal influenza vaccination during pregnancy was concluded to not be associated with increased autism risk. However, the study initially found an association of ASD with vaccination in the first-trimester (hazard ratio (HR) = 1.2; [95% CI, 1.04-1.39], $p=0.01$). The significance of the association was lost after correction for multiple comparisons. ASD from vaccination is not a whole-population hypothesis; there appears to be a genetically susceptible subgroup, and given that the signal of ASD risk from vaccination could be both heterogeneous and dilute, the use of multiple hypothesis correction is not a strong reason to reject the association.

The study has also numerous flaws, the most important of which is that their results are dependent on adjusting for multiple collinear covariates, but rather than interpret the results as pointing to factors that could point to groups susceptible to ASD from vaccination during pregnancy. They should have analyzed the significance of the interaction terms involving vaccination and each covariate. Objective criteria for model selection were not used; rather, the authors preferred the default interpretation of no association with vaccines (overall). Correcting for covariates that are actually risk factors of vaccine injury will mislead.

Hooker (2017) [55] pointed out that the correction for multiple hypothesis testing applied by Zerbo et al. (2016) [54] requires an assumption of independence; it is not meant to be applied when testing significance of different forms of the same hypothesis. Other criteria exist for objective model selection.

Kaiser Permanente North was also a participant of the Simpsonwood meetings at which an initial association of childhood vaccine exposure and risk of any neurodevelopmental disorder, a result that has never been published, and that for which great effort was undertaken via many repeated rounds of analysis specifically to make the association “go away” after very strong risk signal of autism due to exposure to thimerosal in the first year of life (SafeMinds, 2018a,b)[56,57].

The author of the email, Dr. Thomas Verstraeten, has denied (Verstraeten, 2014) [58] that he participated in repeated rounds of analysis to achieve a desired, pre-determined result, but also notes that the study results are not definitive:

"Surprisingly, however, the study is being interpreted now as negative [where 'negative' implies no association was shown between Thimerosal and autism] by many...The article does not state that we found evidence against an association, as a negative study would. It does state, on the contrary, that additional study is recommended, which is the conclusion to which a neutral study must come...A neutral study carries a very distinct message: the investigators could neither confirm nor exclude an association, and therefore more study is required."

This denial is tenuous given the actual text of email, which implored, in the name of objective, CDC collaborators to accept a positive result, while stating that Verstraeten did not wish to appear to be fostering anti-vaccinism. Nevertheless, it is surprising, even given Verstraeten's re-interpretation to find the original study cited by CDC as exonerating thimerosal as “safe”: how does an equivocal result become a strongly supported negative result?

Barile et al. (2012) [60] studied the effects of thimerosal exposure in a retrospective study of 1,047 children ages 7–10 years and their biological mothers in which seven neurological “latent constructs” (evaluation tools) were examined. The used structural equation modeling, but did not report any analyzed interactions between covariates and thimerosal exposure. They found an association between thimerosal exposure and tics in boys, but no association between thimerosal exposure and the other six conditions.

The Barile et al (2012) [60] study is a good example of well-intended handling of covariates potentially gone wrong. They wrote:

“...Failure to adjust for these covariates can lead to the misidentification of positive associations between thimerosal exposure and neurodevelopmental outcomes...”

yet the authors do not seem aware of the value of studying and reporting interactions among covariates and the main treatment effect (in this case, thimerosal exposure) as a source of information on at-risk subgroups.

In fact, they seem to misinterpret the functional significance of covariates when the significance of the main treatment variable is lost after adjustment for a covariate. A good example is their interpretation of the results of Smith and Woods (2010) [61]:

*“a recent study found that receiving vaccines on-time (compared to delayed or not at all) was not related to any negative neuropsychological outcomes **after adjusting for thimerosal exposure** (Smith & Woods, 2010). This suggests that the timeliness of vaccination does not appear to adversely affect neuropsychological outcomes of children 7–10 years later after controlling for the level of thimerosal exposure”* (emphasis added, citations theirs).

Destefano et al., (2013) [62] concluded no association between exposure to large numbers of antigens in vaccine after employing extensive multivariate adjustment, as follows:

“Covariates for ASD models included birth weight, maternal age, birth order, duration of breastfeeding, family income, maternal healthcare-seeking behavior (ie, Kotelchuck inadequacy of prenatal care, use of cholesterol screening, use of Pap smear screening), maternal exposures during pregnancy with the study child (ie, alcohol use, folic acid use, viral infection, lead exposure), and early childhood health conditions (ie, anemia at age 6-30 months, pica before age 3 years). Covariates for AD models included birth weight, maternal age, birth order, duration of breastfeeding, family income, maternal healthcare-seeking behavior (ie, Kotelchuck inadequacy of prenatal care, use of cholesterol screening, use of Pap smear screening), maternal exposures during pregnancy with the study child (ie, folic acid use), and early childhood health conditions (ie, anemia at age 6-30 months, pica before age 3 years). Covariates for ASD with regression models included birth weight, maternal age, family income, maternal education level, and maternal exposures during pregnancy with the study child (ie, alcohol use).”

Their adjusted odds ratios hover around 1.0, but it is not reassuring to learn that multiple significant ORs become non-significant after so many adjustments, when clearly these covariates could also be interpreted as risk factors for ASD from exposure to large numbers of vaccines. First, health outcomes that could be *due* to exposures to toxins, including those like aluminum in early vaccination, could well be due to sensitivity to vaccination; both anemia and pica are health outcome that could be caused by exposure to metals in vaccines. Other variables likely interact with vaccination; e.g., lead exposure could very well interact with aluminum in vaccines, if aluminum increases the retention of lead, and birth weight can increase dose toxicity. Many of these covariates are also not independent; maternal age and family income may be related to birthweight; use of folic acid is likely also correlated with access to health care. The study is agnostic to the well-known problems of model overfit and the challenge of using highly collinear covariates.

These results are examples of inappropriate corrections or adjustments for covariates coupled with inappropriate interpretation. A bad practice is emerging in epidemiology in which ‘back-door’ factors are excluded by statistical adjustment – without sufficient a priori information on the actual functional relationships among covariates. This practice is evidenced by a white paper (Glanz et al., 2018) [64] which provides an example of correcting for confounders to avoid “back-door” influences, which are perceived as confounders. This approach is problematic because the directed acyclic graphs (DAGs) represent a particular set of presumed, or preferred function relationships, which are subjective, debatable and may be incomplete, and not every covariate imaginable can qualify as a confounder; examples include health outcomes that may also be caused by exposure to neurotoxins.

The set of functional relationships among covariates now typically corrected for can also be seen in a different light. Some covariates may increase risk of vaccine adverse event, and thus are not confounders, but co-factors, and the interaction term should be studied. In reality, low income, birthweight and other demographic factors may well be co-factors, i.e., co-predictors of poor health outcomes due to vaccination.

The practice of over-correction for functionally related covariates is rampant in epidemiological studies of vaccine safety. Interaction terms should be studied, instead. When the significance of the main effect is lost after correcting for a covariate, two interpretations are possible; the first is that the other variable accounted for the variation in the outcome independent of the main factor being tested. The other interpretation requires specific analyses of the functional relationships between covariates, between each

covariate and the main effect, specifically the interaction term a covariate of interest and the main exposure.

When the main effect significance is lost after adjusting for a covariate, and the interaction between the primary exposure and the covariate is lost, if the interaction term is ignored, there is a risk of false positive (missed) association that can actually inform on variables that could be used to identify individuals who might not tolerate the primary exposure as well as others. Motivation for adjustment for and interpretation of covariates requires a priori functional understanding, otherwise the analysis falls into a curve-fitting exercise known as “analysis-to-result”. Examination of and powering for true interaction terms are both necessary.

This first result of better health in the earlier cohort of TCV-receiving children could be taken to suggest that thimerosal exposure modulates effects of vaccines on neuropsychological outcomes. One of the ways it could modulate it is to be a positively contributing factor. But this interpretation would require an ad-hoc biological mechanism of benefit; i.e., no such hypothesis existed prior to the study. A more direct interpretation would be that the latter vaccines incurred higher risk.

A related risk of a false negative is the arbitrary use of a large number of covariates, which can lead to model overfit. The Barile et al. (2012) [60] study adjusted for many covariates, but did not mention or report interaction terms for main effect (thimerosal exposure) and covariates. No objective measure of collinearity among the covariates was offered, and the bases of the assumption that covariates were, in fact, confounding variables, were not explicit. The covariates were not studied as potential co-predictors and their interactions with vaccines were not studied. The simultaneous consideration of independent and interaction terms is possible using SEM, including methods are evaluating indicators of a latent interaction (Batista-Foguet et al., 2004; Coenders et al., 2008[65,66]). Formal criteria for model selection available and in wide use at the time included the Akaike information criterion (AIC). The fact that the external generalizability of the models are never tested on independent test sets (i.e., the ability to predict adverse health outcomes using combinations of risk factors and vaccination status) means that model overfit has not been evaluated.

Hviid et al., (2003) [45] was a study retrospective of the rate of autism in children receiving TCVs and non-TCVs. While their sample sizes are very large, the flaws and limitations inherent to the “TCV vs. non-TCV” paradigm apply. Hooker et al. (2014) [45] identified two major sources of ascertainment bias in this study, including the use of “person-years of follow up” instead of numbers of patients per group, which given the available data per group, can induce a bias of underestimating the ASD diagnosis rate and biasing the study towards the null.

The remainder of the studies are not summarized, but instead are represented only via their OES score, and by comment in the Discussion, below.

Studies with Low Statistical Power

Low power can result from large confidence intervals due to small sample sizes rather than from large sample variation reflecting population variation. Actual calculations of statistical power for any positive association for a previously analyzed few studies shows the scale of the studies needed for whole-population association (Table 3). These particular studies were part of the IOM 2012 review, which incredibly cited negative results from a study so small that less than one case of autism would be expected in one group. For example, the sample sizes for the Mrozek-Budzyn et al. (2010) [68] study, which sought association between MMR vaccination and autism, had sample sizes $N_1=96$; $N_2=198$, and the

study was stratified by MMR and measles-only vaccines. The clear limits of small sample sizes leading to negative results due to a lack of power is not communicated by AAP nor by CDC.

Statistical power after the fact (post-hoc statistical power) is legitimate in this case because no effect sizes were estimated from the data and are routinely used to aid in the interpretation of negative results from clinical studies (e.g., Ali et al., 2018)[69]. Full descriptions of analysis of the power of the five studies cited by IOM in 2012 are provided as supplementary material, and they provide a reference point for power required by other studies.

Table 3. Power of Studies Cited by IOM (2012) Supporting No Causal Link Between Vaccines and Autism

Author	Year	Study Type	Sample Size			Power > α ?		
			Group 1	Group 2	Total N	$\alpha=0.8$	$\alpha=0.7$	$\alpha=0.6$
Madsen	2003	Tx/Control Cohort	440655	96648	537303	N	Y	Y
Mrozek-Budzyn	2010	Case/Control	96	192	288	N	N	N
Smeeth et al.	2004	Case/Control	1294	4467	5761	N	N	N
Taylor et al.	1999	Case series	233	64	297	Y	Y	Y
Farrington et al.	2001	Case series	233	64	297	Y	Y	Y

NB: Farrington et al. (2001) was a re-analysis of data from Taylor et al. (1999); neither study used an independent control group and are therefore susceptible to temporal intrusion biases.

Using these power calculations as a point of reference, out of the 48 Key Studies, only about half are estimated to have sufficient power to have detected a population-wide association of >1.1 if one, in fact, did exist. Like Mrozek-Budzyn et al. (2010)[68], six studies are so small that less than one human subject would be expected to be found to have ASD diagnosis in either one or both study groups assuming prevalence on the order of 1-2% (i.e., Hornig et al. 2008; Fombonne et al. 2001; Black, 2002; D'Souza et al. 2006; Pichichero et al. 2008; Klein et al. 2011)[31,32,33,34,42]. How such studies passed peer review is a complete mystery; all future vaccine safety studies must include a priori power analyses for the least frequent serious adverse event suspected.

Studies that Misinterpret Negative Odds Ratios

In studies that purport to examine the relative risk of ASD from a single vaccine, healthy user bias is very likely to cause any effect to disappear, or for the unvaccinated to have a higher incidence of autism than the vaccinated. Healthy user bias occurs when parents pull their children from the vaccination program due to an earlier negative experience with vaccines. A study focused on a single vaccine, such as MMR, would likely fail to detect an effect – or could find a lower risk of ASD in the vaccinated – if children who would have regressed were pulled from the vaccinated group by alert parents. This is considered a fatal flaw stemming from the use of retrospective epidemiological studies instead of using randomized clinical trials. All of the studies of the effects of single vaccines are thus compromised.

Another potential interpretation of the odds ratios <1 would be that children who received >1 vaccine to achieve the same antigen exposure as the MMR may be experiencing enhanced immune system activation (over-activation). Glickman et al. (2017) [71] provides a confirmed example in which healthy user or healthy family bias affected measurement of vaccine injury in a study.

Combined with Healthy User Bias, the consistent value averaging around $OR = 0.8$ for most studies may in fact be carrying a vaccine safety signal. Because the MMR was suspected, the overriding focus of the studies appears to have been to attempt to exonerate MMR; the study of the safety of a single multiplex

vaccine in the context of other vaccine options, and vaccine refusal, with not completely unvaccinated control group represents an intractable question.

In the case of TCV vs. non-TCV's, such results have, oddly, been used to propose ad-hoc hypotheses of a "protective" effect of thimerosal. In reality, non-TCV's are often aluminum-containing vaccines, which may point therefore to risks associated with individual exposures to aluminum and to thimerosal due to the expansion of the schedule with ACVs. We should recall that thimerosal was not, and has not, been completely removed pediatric vaccines; it is included in some influenza vaccines. Thus, the unanticipated "health benefits" of TCVs may plausibly have been due to an enhanced toxicity of thimerosal and aluminum hydroxide in children that receive different vaccines with both types of metals in the same office visit. Dosing of aluminum in the pediatric schedule needs to be revisited (Masson et al., 2018[72]; Morris et al, 2017[73]; Lyons-Weiler and Ricketson, 2018[21]).

Studies that Lack Proper Control Groups

Among the study design considerations, the use of appropriate and independent controls is paramount. Chen et al. 2004 [39] used patients with Down's syndrome as a control group, clearly opening the study to any confounding associated with diagnosis of autism. Self-controlled case series studies Taylor et al. (1999) [75] and Farrington et al (2001) [76] may have sufficient power given the use of patients as their own controls, but they are weak in that they only analyzed trends. They are not immune from cohort effects because each patient acts as their own control there is no control over the intrusion of temporal confounding factors. The value of self-controlled case series can be over-stated; the concern over lack of control of incidental temporal confounding is real. DeSoto and Hitlan (2013) [77] outlined the problem of over-matching for the Price et al. (2010) [41] study, pointing to low variation in thimerosal exposure among exposure groups. These concerns are not relayed by the CDC.

In addition to the appropriate interpretation of increase risk of non-TCVs given in combination with thimerosal-containing influenza vaccines, other interpretations of the published results of some of the key studies are also possible:

Ethical and Plausible Alternative Interpretation of Negative Results

The studies included in this systematic review are interpreted by policy makers and vaccine stakeholders who would like their interpretation to influence public health policy. Many of these studies include results that can be interpreted as problematic for vaccine safety. For example, every study that had small sample sizes and large confidence intervals could (and perhaps should) be interpreted as insufficient for a firm negative conclusion (no association) due to low power (e.g. Pichichero et al. 2008[81]. This is problematic because a lack of evidence is not the same as negative evidence when the study has insufficient power to robustly test the hypothesis at hand.

Table 4. Smeeth et al. data (2004) [78] as a contingency table

Smeeth et al.	ASD	No ASD
MMR	1010	3671
no MMR	285	798

Positive Results Under Appropriate Analysis

Most of the epidemiological studies used odds ratios. Alternative tests of a 2 x 2 contingency, well-applied for the test of independence of vaccination status and ASD status include the Chi-square test, and

Fisher's exact test. Re-analysis of the data from Smeeth et al. (2004) [78], which reported no association, nevertheless results in a significant association (Table 4; Chi-square 11.3402, $p = 0.00076$). Their analysis included an adjustment for the age at which the patients joined the research database. Their statistical correction was, according to the authors, due to an ascertainment bias on the vaccination status, drawing the entire study into question. The average age of cases under the age of 7 was 4.5 for both cases and controls, and the MMR vaccination rate bias could either have been over- or under-estimated. Without independent means other than the vaccination rates in the controls, the logic for the adjustment was circular and would represent a form of within-study bias resulting from decisions made during the design and execution of the analysis of the data.

Test of Study Selection Bias

In an unbiased bolus of studies, say, used in a meta-analysis, studies would be selected regardless of their findings. To assess study selection bias in the 48 key studies, a Pubmed and an internet search was done for studies that mention "Autism" and "Vaccine" with "Odds ratio" to collect OR values for comparison to those studies selected by AAP and CDC.

Odds ratios and risk ratios are comparable for rare diseases (Rodrigues and Smith, 1999)[79], and thus they are averaged for studies included and excluded from the Key Studies. Standard deviations were estimated from reported confidence intervals using Chebychev's assumption (which is approximated by $SD=CI/3$). Standard errors were estimated as $(Upper\ 95\% \text{ CI} - Lower\ 95\% \text{ CI} - 0.05) / 1.96$. Funnel plots were made to compare these values for included and excluded studies.

Due to concern over bias from fraud in the Destefano et al. (2004) [85] study communicated into the Congressional Record by Congressman William Posey (Posey, 2015)[62], and statements communicated by CDC Senior Research Scientist Dr. William Thompson, the odd ratios for Destefano et al. (2004)[85] were examined separately. A statement of concern was sent to the journal over evidence of changes in the data analysis plan by Destefano et al. (2004)[85] after finding initial positive association results; the statement was ignored without reply.

The Objective Evaluation Score

The calculated OES for each study is provided in the Supplementary Material (S2) and are summarized as Figure 1. Only one study (D'Souza et al., 2006[32]) had a positive score; all others were zero or negative. The average OES score for the studies cited by AAP and CDC was -6.61.

Discussion

The first set of assumptions of statistical hypothesis testing include that the variables are a random variable from a representative set of samples. Many of the studies reviewed define the study groups retrospectively, which has been shown vastly misestimate the timing on the onset of autism (Ozonoff et al., 2018[80]). As these groups are not truly random samples, and thus, the entire practice of the use of epidemiological studies is fraught with risk.

Statistical control of covariates is important when the functional (causal) relationship between covariate pre-empts a main effect. Statistical control has been routinely misapplied, and the results misinterpreted as absolving vaccines overall instead of highlighting potentially increased risk in specific subgroups (low income, young mothers, low birth weight). Many of these variables are highly collinear, and therefore model overfit is possible; each covariate may in fact point to an increased risk of ASD from vaccination, especially if they are biological or medical covariates. Rather than attribute the entire risk of ASD to such covariates, which are often highly collinear (e.g., birthweight, age of gestation, mother's age, mother's

income, race), studies should be designed to test the interaction between covariates and vaccination. The loss of association after “correcting for” such variables requires careful consideration, especially when the study is not sufficiently powered to study interactions among variables as co-predictors with vaccination as risk. One study actually corrected for overall vaccine uptake a covariate, clearly, a contradictory strategy to the agenda to disprove that vaccines cause autism. The practice of the interpretation of the loss of significance of the main effect (vaccines) on adverse events without studying the interaction terms should end.

Prevalence is the rate of a disease or condition in a general population; incidence is the rate of a disease or condition in a population at increased risk. No studies have focused on the incidence of autism in vaccinated and unvaccinated individuals with increased genetic risk of autism. A study of the rates of autism in a prospective trial to provide direct control for covariates that thus far have been misapplied.

Infants whose mothers were not vaccinated during pregnancy who have LOF or COF genetic variation at any of the >850 genes should be randomized into two groups – one which receives vaccines, and the other which receives saline placebos. While some may object to this study as unethical because the unvaccinated would be exposed to risk of childhood diseases, the study would provide true risk rates. Two simultaneously conducted additional arms of individuals with no increased genetic risk of ASD who are vaccinated, and those who are not, would provide additional insight into the role of genetic risk.

Pichichero et al. (2008) [81] was included the AAP’s letter to President Trump as evidence of vaccine safety. The study measured blood mercury levels in 216 healthy children prior, 12 hours and 30 days after vaccination with thimerosal-containing vaccines. The study only measured blood levels, which is problematic given the tissue deposition in the brain and other organs was not measured. The study reported that blood mercury half-life 3.7 days, and that it returned to pre-vaccination levels by day 30. The blood-clearance rate is not assuring given that mercury deposited in the brain would not be measured. The observation that blood clearance of thimerosal was faster than for methylmercury –could point to a problem with ethyl mercury due to faster uptake by tissues and organs. An earlier study similarly seems obliquely unaware of the relevant measurements required to understand neurotoxicity levels of injected mercury (Pichichero et al., 2002)[81]. No specific relationship to autism risk was examined in either study. Burbacher et al (2005)[82], a study cited by CDC, found that organic mercury from thimerosal injected into monkeys stayed in the brain longer than that from methyl mercury via oral gavage.

Examples of other studies not included are Gallagher and Goodman (2010) [4], and Nevison (2014) [5]. A growing number of studies that support the hypothesis that Acetaminophen given after vaccination may increase the risk of autism (Avella-Garcia et al., 2016[2]; Bauer and Kriebel, 2013[3]; Saeedan et al., 2018[87];Schultz et al., 2008[6]) were cited neither by AAP nor by CDC. In 2010, Shoffner et al., (2010) [11] found that 71% of kids with regressive autism had an episode of fever > 101°F In 33% of these cases, the fever occurred right after vaccination – and none showed regression unless fever had occurred. Neither CDC nor AAP cite Shoffner et al. (2010) [11].

The cherry-picking, biased use of the literature stands to significantly erode the public trust in the AAP and the CDC. The bias in the ORs of the studies they cite compared to the studies they fail to cite is cause for grave concern.

Interaction Terms Missing from Study Designs

Nearly all studies had flawed designs in that interaction terms for vaccination and other variables were not tested. For example, Price et al. (2010) [41]studied the relationship (using conditional logistic regression) between thimerosal exposure from vaccines in medical records in 256 children with ASD and 752

controls. Patient accrual was conducted by physician consent. Numerous covariates were used; in the covariate-based analyses, the adjusted odds ratio decreased, again potentially pointing to the interaction between thimerosal exposure and covariates – a result not knowable given the limited sample size of the study. The study was powered for odds ratio of the main effect, but not specifically for the interaction terms, which typically requires much larger sample sizes. Interactions among the variables were not explored.

Taylor et al. (2014): Meta-analysis Cites Flawed Studies

Previous serious criticisms of the Taylor et al. (2014) [43] study has fallen on robustly deaf ears. Suissa (cited in Stott et al, 2004) [84] pointed out that when the Madsen et al. data are analyzed using time after vaccination instead of age, the association between MMR vaccination and autism is detected. Stott et al., (2004) [84] demonstrated a logic flaw in Taylor et al.'s conclusion that there was no increase in autism after 1988 because a large number of patients born before 1987 received the MMR as a part of a "catch up program". This makes the dependence of the independent variable (autism rate) difficult to assess with certainty due to unaccounted variance in the independent variable. Stott et al. (2004) [84] pointed out that an analysis of these key data that uses the timing of vaccination, rather than the year of birth as the independent variable, the increase in autism rates become clearly timed with the timing of MMR vaccination.

Incomplete diagnosis in the five-to-seven year age group, and delayed diagnosis in many of the patients in these studies, also draw the Taylor et al's (2014) [43] conclusions into further doubt. Even the largest studies like Madsen et al. (2003) [46] did not – and could not - correct for the fact that many parents of children likely to regress into autism after the MMR may have decided to forego the MMR vaccination, either due to family history, or due to a previous bad reaction on the part of the specific child (healthy user bias). These flaws make confident interpretation of the results of the Madsen study, and any mere retrospective correlation study, impossible.

The Taylor et al. meta-analysis [43] also used studies that were also found to be flawed by the IOM, including the much-scrutinized Destefano et al. (2004) [85] study. That study also should have included two set of positive association for on-time MMR for African American males and for so-called “isolated autism”, both results which were left out because, according to Destefano, the team did not believe them (Frank Destefano to journalist Sharyl Attkisson, *pers. comm.*). The uncritical acceptance of the results of studies, including many that were underpowered, and the obvious fact that Taylor et al. (2014) [43] also ignored a significant body of scientific literature available at the time of their meta-analysis is a serious flaw in their meta-analysis.

Misrepresentation of The Full Available Science by AAP and CDC

To their credit, the authors of many of these studies are forthright about the limitations of their studies. However, neither the AAP nor the CDC are forthright about the acknowledged limitations. They also ignore previously published criticisms of some of the studies they listed. Neither the AAP nor the CDC carry the stated limitations made by authors of the studies over with their listings. The Verstraeten (2014) [58] example is just one of many examples of over-interpretation; certainly, public health policies that influence millions of patients should not be based on negative results from underpowered studies.

More disturbing is the biased selection of studies in the lists provided as representative and definitive on the questions at hand. The average ORs reported in studies cited by APP, CDC and the other sources (overall) is 0.801 (0.756 for ASD-focused studies); by comparison, the average ORs reported in studies not cited is 4.01. To give an idea of the variability, estimated (pseudo) SDs and SEs are provided in

Table 5. It is worth pointing out that many of the reported 95% confidence intervals in studies reporting no association not only overlap with 1.0; many are overlap with 2.0, meaning there is insufficient evidence in those studies on whether the OR is significantly different from both zero risk and double the risk.

Table 5. Study Wide Averages Show Publication Bias

	Overall	
	<i>Cited</i>	<i>Not Cited</i>
OR	0.801	4.01
pSD	0.307	3.53
pSE	0.445	5.38

OR = odds ratio; pSD = pseudo standard deviation; pSE = pseudo standard error

The AAP and CDC also have also ignored and continue to fail to transmit published concerns over the integrity of many of the studies they listed (Hooker et al., 2014[45], Kern et al., 2017[12]) and as the current analysis demonstrates, have been selective in the studies AAP cited to POTUS and that both CDC and AAP include in their study lists. Further, the AAP document cites the National Vaccine Injury Compensation Program’s Autism Omnibus proceedings, but fails to report the Hanah Poling case, as case that was originally in the Autism Omnibus proceeding but removed after a settlement was provided. More importantly, the AAP document fails to report the PACE Law Review by Holland et al. (2011) [86] who found 81 instances in which vaccines were found to found encephalopathy, leading to autism (vaccine-induced encephalopathy-mediated autism) were given awards in the National Vaccine Injury Compensation Program. The omission of this extensive review of relevant case law is further evidence of the biased, one-sided view promulgated by the AAP document provided to the President of the United States.

Our unified and collective goal must be to understand factors that contribute to the increasing rates of ASD and other chronic illnesses of “unknown origin”, regardless of where those studies lead us. The results of retrospective ecological correlational epidemiological studies (RECE’s) are too malleable to subjective influences. Obviously, the use of retrospective ecological studies on questions of such massive importance to public health is insufficient to test hypotheses of causality. None of the studies actually attempt to determine whether they could have predicted, using genetics, or blood biomarkers, or demographic and medical variables, which children would develop ASD. Our unified goal must be to fulfil the 1986 Congressional mandate to make vaccines safer, and to identify the groups who may be at highest risk of adverse event. In this setting, the only ethical position any medical practitioner or legislator can choose is to respectfully preserve the freedom of vaccine choice by patients and by parents.

Given the extensive and serious limitations in the studies presented as best evidence of no causality, it is time to revisit the question of causality with renewed studies comparing total health outcomes in vaccine-naïve vs vaccine exposed individuals, including neurodevelopmental disorders.

Public health policies based primarily on negative evidence from correlation study predominant paradigms risk harming hundreds of thousands to millions of individuals. To assure public safety and our national well-being, regulatory agencies must be made independent of corporate financial interests.

Recent Studies

No blinded randomized clinical trials have been conducted since the AAP statement was sent to POTUS. A recently published result by Geier et al. (2018) [8] reported increased significant association of autism (odds ratio (OR) = 2.75, $p < 0.02$), developmental delay (OR = 5.39, $p < 0.01$), psychomotor disorder (OR = 2.38, $p < 0.03$), and neurodevelopmental disorder in general (OR = 2.70, $p < 0.001$) associated with the receipt of Thimerosal-containing Hib vaccine than Thimerosal-free Hib vaccine. These are retrospective studies.

Unless and until we see large independently conducted, prospective randomized trials comparing vaccinated vs. unvaccinated, a non-definitive, schizophrenic, broken scientific literature filled with correlations with little information on causality will continue to be developed. Vaccine stakeholders' position rest on a biased selection of unpowered and flawed studies. Sufficiently powered genetic studies that seek associations should include vaccine exposure and study genetic x environmental toxin exposure interaction terms. Strong evidence points to a genetic basis for sensitivity to neurotoxins and immunotoxins in vaccines (as reviewed in Lyons-Weiler, 2018 [23]). Therefore, further exclusively genetic research on autism – and on autoimmune conditions which excludes vaccines as a source of environmental toxins would be an unethical waste of national research resources.

Additional studies scored using OES but not further critiqued are listed in the references (87-93)

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Conflict of Interest Statement: The author has served in the capacity of expert witness in the National Vaccine Compensation Program on various cases, none of which involve autism.

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