Supplementary Material

Insufficient Power in Critical Studies Used in Historical Policy-Making on the Autism/Vaccine Question

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Abstract

Vaccine studies are at the core of public health policies and practices in the US and worldwide. The vaccine science evidence base including safety as well as efficacy is the basis for these policies and practices. The consideration of vaccine safety studies by the Institutes of Medicine in 2012 resulted in finding serious flaws in 17/22 studies. It is widely understood that studies should have sufficiently large sample size (sufficient statistical power) - to detect real effects of factors when they do, in fact, exist. Studies found to be acceptable by the Institutes of Medicine were examined to determine whether they could detect a realistic positive association between autism rates and MMR vaccination. The studies for which power calculations were not already available were found to be unlikely to be able to detect association between the MMR vaccine and autism. Without the ability to detect positive association, faulty paradigms of knowledge have arisen that now represent serious threats to public health (vaccine programs agnostic of risk). Because of inherent conflicts of interest, agency-conducted vaccine safety research should be eschewed; independent, extramural research is needed on the question of vaccines and autism immediately. Independently-conducted research must be sufficiently powered – and all studies of vaccine safety should be required to publish *a priori* power analyses. Review committees, including IRBs, must insist on *a priori* power calculations demonstrating high power before a single subject is recruited, before more harm than good is done to public health through unethical, weakly-powered science.

Introduction

Statistical power analysis is an essential step that should be executed in the planning stage of any study designed to detect a significant association between putative causal factors and disease, or disease state diagnosis. The power of any statistical test is defined as the probability of finding a significant result when there is, in fact, a true difference or association that should be detected. For any study, power is a function of the interplay among factors in the design of that study, and in the execution of data analysis. Variables that influence power are well-known, and include sample size, variability (variance) in the data, and the level of Type I error risk (α). If insufficient numbers of patients are included in a study, the probability of failing to detect a true association is increased, making it likely that an important association might be missed.

Sufficient statistical power is essential for meaningful research inquiry. It is surprising, therefore that these essential analyses are rarely conducted and published in epidemiological studies focused on the question of which putative causal factors may contribute to psychiatric and neurological developmental disorders (Button et al., 2013). This is surprising because understanding a given conditions' causal factors is key to prevention and to discovering potential treatments. The problem of low statistical power is nearly ubiquitous in epidemiological studies that touch on neurodevelopmental disorders. Button et al., 2013 found low statistical power to be "an endemic problem in neuroscience". Namasivayam et al. (2015) found that only 6-10% of studies in psychological journals reported *a priori* power analysis, and reported similar levels from other disciplines. Stanley et al. (2017) suggest that low powered studies create significant bias in meta-analyses, and that the influence of such studies should be minimized. They also report a stunning fact that "the majority of meta-analyses of medical research do not contain any studies with adequate power". Cuijpers (2016) found that nearly all comparative outcome studies of treatments for adult depression are underpowered, concluding that "individual trials are heavily underpowered and do not even come close to having sufficient power for detecting clinically relevant effect sizes".

The problem of low-powered studies is so widespread that Fraley and Vazire derived an "N-pact factor" to rank journals based on the sample sizes of the epidemiological studies they publish – and reported that the average power of studies in social-personality psychology was 0.50. The American Psychological Association has advocated the reporting of effect sizes (ES), confidence intervals (CIs), and statistical power analysis to complement null hypothesis statistical testing results to provide a more comprehensive understanding of research findings. However, when null hypothesis testing is underpowered, ecological (correlation) studies are more susceptible to the effects of entrenched biases (sometimes called "demonic intrusions"), which are not revealed by confidence intervals. This can include retrospective association studies.

Due to possibility of Type II errors, the use of a sufficiently robust and powerful study design is required before the results of a study can be used to rule out specific causes of disease conditions. Given their importance for establishing public health policies on vaccines, it would be expected that any studies used to test association of medical, environmental, and genetic contributors to the incidence in autism spectrum disorders would be carefully designed with sufficiently large sample sizes to avoid a series of misleading, self-confirming false negative results.

In direct response to Congressional inquiries (Congress of the United States of America, 2003), the US CDC was tasked with conducting studies and examining the available scientific evidence on the question of the link between vaccines and autism at the population level. Rep. Dan Burton entered in the Congressional Record (ibid):

"To date, studies conducted or funded by the CDC that purportedly dispute any correlation between autism and vaccine injury have been of poor design, under-powered, and fatally flawed."

The CDC has not changed their approach to vaccine safety science and autism since 2003. In fact, as part of their response, the Institute of Medicine established a committee to examine the bulk of the evidence for links between vaccines and a wide variety of medical conditions,

including autism. A total of 22 studies were identified as potentially contributing to the answer to the question; of these, IOM found serious flaws in 17 studies, and therefore excluded them from further consideration:

> "The five (sic) remaining controlled studies (Farrington et al., 2001; Madsen et al., 2002; Mrozek-Budzyn et al., 2010; Smeeth et al., 2004; Taylor et al., 1999) contribute to the weight of the epidemiologic evidence and described below".

This left four studies (Table 1, from which the committee drew the weight of the evidence upon which the question of the link between vaccines and autism was balanced. Notably, one of the studies rejected by the IOM committee as flawed was the Destefano et al. (2004) study, which is increasingly under fire due to the statement of Dr. William Thompson on the mismanagement of the data analysis plan for that study, which led to the exclusion of positive association results from both African American male and for "isolated" autism subgroup analyses while Dr. Thompson was on administrative leave for taking his concerns to then CDC Director Julie Gerberding (Thompson pers. comm. to Brian Hooker). Dr. Gerberding is now employed by Merck, Inc.

After consideration of the four studies, the IOM concluded that there was insufficient evidence to conclude that vaccines cause autism, and that therefore, a causal determination was not warranted. This conclusion came in spite of a dearth of studies in 2012 to consider, in part because as a result of the IOM's 2004 report. When the CDC's DeStefano et al. (2004) paper was published, the IOM called for an unprecedented cessation on any further research between vaccines and autism. This recommendation was boldly stated in a press release (National Academy of Sciences, 2004). Thus, future studies, or their non-occurrence, were strongly influenced by a combination of the CDC's arbitrary removal of positive association results due to the fact, according to Dr. Stefano, they did not "believe" them, and the IOM giving large weight to the Destefano et al. (2004) results in their 2004 report.

The cumulative effects of the IOM's reports and stated public position also had a major impact on public health policy on vaccination in the US, and worldwide. There is no evidence that either the IOM, or the authors of the studies in question actually calculated the power of their study designs to determine the Type II error risk. An exception are the self-controlled case series studies by the Farrington et al., team (Farrington et al., 2001; Taylor, 1999), who published power analysis and methodological evaluation of his self-controlled case series study design (Musonda et al., 2006; Whitaker et al., 2009). The power of these studies is of massive importance given the goal of the IOM considerations at the time to assess whether sufficient evidence existed to determine (yes/no) whether vaccines were casually related to autism at the population level. This includes, by definition, autism resulting in any portion of the population. No one had, or had posited that vaccines might cause autism in every child receiving vaccines – and thus the clinically relevant results could have included effect sizes from very small (e.g., OR = 1.01) to moderate (OR 1.3). Further, the individual contributions of different vaccines has never been given full consideration, with most studies focused on the measles, mumps and rubella (MMR) vaccine. This, along with the reliance on retrospective correlations, has led to major obstacles to the creation of well-posed study designs that *could have* yielded sufficient evidence leading to conclusions of causality.

Numerous serious problems exist in modern biomedical research in the area of powering studies. Estimation of power of study designs for vaccines routinely focus primarily on efficacy (e.g., Diakite et al, 2016) with scant attention paid to the power of large retrospective studies required to detect adverse events. A body of theoretical work has been developed on real-time retrospective monitoring (e.g., Nelson et al., 2016; Cai et al., 2017), however, as the analyses reported here will show, the retrospective paradigm (so called "pharmacovigilance") is fatally flawed.

Limitations of knowledge due to low observed statistical power are heeded in other vaccine studies. Hutcheon et al. 2016 found that reported "benefits" to the fetus from influenza vaccination was not likely due to the vaccine, because the expected decrease in risk was so small that enormous sample sizes would be required to for detection. Instead, they attribute the results to healthy user bias. Li et al. (2016) compared the power of two types of self-controlled case series study designs, and detected risk of febrile seizure following seasonal influenza vaccine in the 2010-2011 season. Vincenzo, reviewing the science on the long-term efficacy and safety of human papillomavirus vaccines, found that one study (HPV-023) has not been sufficiently powered to detect some important outcomes, including the ability to detect any effect on rates of CIN 2+, a prime outcome indicator of efficacy. It is generally known that because adverse events occur to a subset of vaccinated patients; power for risk and adverse event will uniformly be lower than power to detect efficacy, and yet overt a priori power analyses are absent from nearly every study conducted on vaccine state.

Here we review the question of whether the four studies used by the IOM in 2012 were sufficiently powered to detect a positive association between vaccines and autism if it does, in fact, exist.

What the IOM Report Concluded

In their 2012 report, the IOM concluded:

> *"The committee has a high degree of confidence in the epidemiologic evidence based on four studies with validity and precision to assess an association between MMR vaccine and autism; these studies consistently report a null association."*

Thus, in their assessment of the results from these four studies, the IOM relied on a null result (specifically, failure to reject the null hypothesis of no association). If these null results were, in fact, due to a lack of association at the population level, the conclusion would be warranted. If the studies were underpowered, however, the samples might not be reflective of the larger population, and the result in each study could be due to low power. At small sample sizes, the probability of failing to reject the null when it should, in fact be rejected is high if the effect size (the magnitude of association in this case) is modest.

Why – and How - Post-Hoc Power Analysis is Appropriate for this Question

It is sometimes claimed that *post-hoc* power analyses are in a way an exercise in circular reasoning. This is true if a specific effect size is determined during the initial analysis (Goodman and Berlin, 1994), or if post-hoc probabilities are employed in the derivation of the calculation of power. Further, the circularity argument relies on the use of a reported (estimated) effect size in the calculation of statistical power. If those values were included in a post-hoc power assessment, clearly the resulting inference would be circular. When this occurs, the post-hoc power calculations are considered tautological.

In 2012, the IOM could not find evidence sufficient to support or refute the hypothesis of a link between vaccines and autism. In 2012, their review used four studies that failed to reject the null hypothesis of no association. However, when a study fails to reject a null hypothesis, and the authors also fail to conduct and report the results of an a priori power analysis, then clearly the question of whether low power due to faulty study design was likely to contribute to the result is in order, as long as the power calculations use probabilities derived independent of the result of the study in question, or over a range of possible outcomes to ask the general question "was this study sufficiently powered to detect *any* realistic positive association?" Critical to asking this question is the use of effect sizes that do not derive from the analysis in question. For example, post-hoc power analysis of a study's ability to detect a range of expected odds ratios can be achieved without circularity because the power analysis can be conducted in a manner that employs study group sample sizes, and prevalence from the control population, but not the prevalence in the case population nor the odds ratio from the study in question. To clarify communication on these issues, these ends, O'keefe (2007) recommends the use of the useful term "Observed Power" for power calculated that uses posterior (study-derived) probabilities and effect size estimates, and other forms of post-hoc power that do not. Post-hoc power considerations not focused on "Observed" or "Achieved" power can be very useful in determining what the outcome of studies the same size as the study in question would likely be, and, by deduction, provide relevant information on the study in question.

In the current analyses, no specific value of an effect size is of interest, rather, the question is whether these studies were sufficiently powered to detect *any* positive effect size, and, if so, whether that detectable effect size seems warranted given the prevalence of ASD in the populations under study. We are therefore explicitly not estimating "observed Power" or "achieved power" sensu O'keefe (2007). The power calculations used in this study specifically do not use any size of association (odds ratio or relative risk ratio) from the published results, nor from any re-analysis of the data to derive an estimate. Because these analyses are designed to determine whether each study could have found *any* level of positive association, a completely objective use of power analysis is possible. The question is relevant for the specific studies currently under question and well beyond. The broader way to look at the question is: could ANY study, with X cases and Y controls, with a prevalence of P in the unaffected group, be expected to detect a positive association?

This result can then be considered in comparison to the plausible effect size, or a range of effect size, given the prevalence of the disorder in the overall population (the expected effect size range). If no range of plausible effect size results in a sufficient power given the constraints of the study, the post-hoc analysis can be said to have shown the lack of sufficient power to detect a reasonable effect size. This is achieved most simply by exploring the range of OR or RR for no effect (1.0) to a very, but unexpected, large positive effect (2.0). The study design parameters

taken from each study were explored using two publicly available resources (Glaziou, 2005; Ausvet 2017) to determine sample sizes required to achieve Power = 0.80 at Type 1 error risk of 0.05 over a minimum odds ratio (or relative risk ratio) range of 1.1-2.0. These resources differ in that the latter assumes equal sample sizes.

Study 1. Taylor et al., 1999/Farrington et al. (2001)

This study was actually one data set analyzed twice, with both results yielding little insight on the question posed. While power analyses had been conducted for this self-controlled case series study (Musondo et al., 2006), that design is not demonstrated to be robust the intrusion of unknown confounding variables, which can be expected to contribute to either Type I or Type II error (depending on the direction of the confounding). Indeed, a major conclusion of Farrington et al. (2001) was that the timing of the onset of autism was difficult to determine, which jeopardizes the validity of their conclusion. While we accept Farrington et al.'s power estimates, the power analysis design does not employ design approaches to protect external generalizability due to the absence of control for cohort effect.

Study 2. Mrozek-Budzyn et al. (2010)

This study was rated by the IOM Committee as having "serious limitations because it did not provide information on medical conditions among the controls and relied on medical record abstraction for immunization dates and autism diagnosis dates". It had a very small sample size as well. It is a surprise, therefore that the committee included this study in their weight of evidence. The IOM described the study thusly:

"Mrozek-Budzyn et al. (2010) conducted a case-control study in children identified in the general practitioner records in the Malopolska Province of Poland. The study included 96 cases and 192 matched controls. The cases were diagnosed with childhood or atypical autism by a child psychiatrist according to the ICD-10 criteria. Two controls were matched to each case on year of birth, gender, and physician's practice. Vaccination histories and the date of autism diagnosis were extracted from the physician's records. Date of onset of symptoms was derived from parental interview. If MMR or single-antigen measles vaccination preceded the onset of symptoms, cases were classified as vaccinated. Controls were considered vaccinated if they received an MMR or single-antigen measles vaccine before the age of symptom onset observed in the matched case. The analysis adjusted for mother's age, medication during pregnancy, gestation time, perinatal injury, and 5-minute Apgar scale score. The adjusted odds ratio for autism diagnosis after MMR vaccination was 0.17 (95% CI, 0.06–0.52). The adjusted odds ratio for autism diagnosis after single-antigen measles or MMR vaccination was 0.28 (95% CI, 0.10–0.76). The authors concluded that administration

of MMR or single-antigen measles vaccine is not associated with an
increased risk of autism in children.

Mrozek-Budzyn et al. (2012) was a retrospective association study and employed a conditional logistic regression with confidence intervals to determine significance. Sample sizes needed for Power=0.8 were calculated over the range of OR from 1.1 to 2.0, with 2 controls per case, using two public resources (Glaziou, 2005; Ausvet, 2017). These resources rely on the prevalence of the disease in the control group, and the numbers of patients in each group, and specifically do not require the use of any post-hoc odds or risk ratio. Ausvet (2017) assumes equal sample sizes, whereas Sampsize (Glaziou, 2005) does not.

Mrozek-Budzyn et al. (2012) reported 99.4% exposure to the MMR in the control group. The effects of sample size, ratio of controls: cases, and proportion of controls exposed determined the outcome of the power estimates, and therefore the sample size estimates are relevant for any such study, whether statistical control for other variables was attempted or not. Mrozek-Budzyn et al. (2012) actually used this small data set to study both MMR vs. no MMR, and an inquiry into the role of a single-antigen MMR vs. combined antigen MMR using an even smaller subset of the data. It is not clear if they were aware of the effects of multiple hypothesis testing on performing multiple comparisons in the same study; however, the small sample size would, in any estimation, put this study in the category of "pilot study".

Power assessment: Both power analysis resources indicate that this study should have used between 10,000 and 680,000 patients overall to robustly test the hypothesis of positive association (Fig 1). Nowhere in the positive RR range examined did the value of the number of patients needed achieve power of 0.8 come anywhere close to 288 patients overall. **Conclusion:** Mrozek-Budzyn et al. (2012) was woefully underpowered to detect a positive association, and its result was likely strongly influenced by its very small sample size. The IOM should not have included their result as valid, as the null finding was most likely to do the fact that the study was underpowered.

Study 3. Smeeth et al. (2004)

The IOM described this study thusly:

"Smeeth et al. (2004) conducted a case-control study in children (born
between 1973 and 1999) enrolled in the General Practice Research Database
(GPRD) from June 1987 through December 2001. The study included
991 cases with a recorded diagnosis of autism and 303 cases with other
pervasive developmental disorder diagnosis. A total of 4,469 controls were
individually matched to cases on year of birth (within 1 year), sex, and
general practice. The study excluded cases and controls that were not enrolled
in the database for at least 12 months before the diagnosis or index
date (date that control was same age as matched case at time of diagnosis).

*MMR vaccination data were abstracted from the GPRD records, and the
case or control status was concealed during the assessment. The unadjusted
odds ratio for autism diagnosis after MMR vaccination was 0.77 (95%
CI, 0.60–0.98). After adjustment for the age at which participants joined
the GPRD, the odds ratio was 0.88 (95% CI, 0.67–1.15). The authors
concluded that MMR vaccination is not associated with an increased risk
of autism."*

The study was focused on the population-wide effect of a single vaccine on autism rates. This matched case-control study of 5,761 individuals asked the question of whether MMR vaccination was associated with autism or other pervasive developmental disorder. There were 4,467 controls and 1,294 cases. Of the controls, 82.1% received the MMR vaccination prior to the age at which their matched case received first diagnosis, while 78.1% of the cases received the vaccine prior to the age of first diagnosis. Both study populations also had received various other vaccines prior to MMR and prior to the diagnosis of autism.

Power assessment: For a medium to large effect size (2.0 > OR > 1.3), the number of samples needed for Power > 0.8 approached the number of patients in the study. From OR 1.1 – 1.2, the number of samples needed vastly exceeded the number of patients in the study. An OR of 1.3 would require a 30% difference in the rate of ASD due to MMR. That would mean that 30% of children who received MMR would have a diagnosis of ASD. That does not fit a realistic expected effect size given that ASD at the time was between 1-2% overall, and most of the population being studied received MRR. The study was designed to test one vaccine in a population receiving many different vaccines, and if the effects of vaccines on ASD risk are cumulative, the effect size can be expected to be low.

This study should have used a minimum of 8,000 to 120,000 patients to robustly test the hypothesis of association at a low to medium effect size (Fig 2). **Conclusion:** The study by Smeeth et al., 2004 was underpowered to detect positive effect sizes from 1.01 up to 1.2, but could have detected a very strong effect size. If the effects of vaccines on the rate of autism is small, as is reflected by the low overall prevalence in the vaccinated population, the Smeeth et al. result was likely strongly influenced by its sample size. It is not surprising that the sample size used was insufficient in this study to detect a relevant population-wide shift autism rates due to a single vaccine when the population in general had received also up to six vaccines prior to the MMR.

Study 4. Madsen et al. (2002)

This study is sometimes touted as being definitive given its relatively large sample size (e.g., Gerber and Offit 2009).

*"Madsen et al. (2002) conducted a retrospective cohort study in children
born in Denmark from January 1991 through December 1998. The
children were enrolled from the Danish Civil Registration System, which*

*stores personal identification information for all residents, and linked records
to five other national registries. MMR vaccination data were obtained
from the National Board of Health; autism diagnosis was derived from the
Danish Psychiatric Central Register. The National Hospital Registry and
Danish Medical Birth Registry provided birth weight and gestational age information,
and data on socioeconomic status and mother's education came
from Statistics Denmark. Autism diagnoses were based on criteria from the
ICD-10; the diagnostic codes were separated into cases of autistic disorder
or other autistic-spectrum disorders. Children with congenital rubella or
an inherited genetic condition (fragile X syndrome, Angelman's syndrome,
or tuberous sclerosis) were excluded from the analysis. A total of 537,303
children were included in the cohort, of which 316 had an autistic disorder
diagnosis and 422 had an autistic-spectrum disorder diagnosis. Follow-up
began at 1 year of age and continued through December 31, 1999, or the
date of autism diagnosis, diagnosis of other associated conditions, emigration,
or death. Children who were vaccinated with MMR contributed
1,647,504 person-years of follow-up, and those not vaccinated contributed
482,360 person-years. Relative risks were calculated and adjusted for age,
calendar period, sex, birth weight, gestation age, mother's education, and
socioeconomic status. The adjusted relative risk of autism diagnosis after
MMR vaccination was 0.92 (95% CI, 0.68–1.24) and of other autistic
spectrum disorders after MMR vaccination was 0.83 (95% CI, 0.65–1.07).
The authors concluded that MMR vaccination is not associated with an
increased risk of autistic disorder or other autistic-spectrum disorders."*

The IOM report also included the following footnote regarding this study:

*"One of the authors of this article, P. Thorsen, was indicted for embezzlement on April 13,
2011. The implications for the integrity of the study are unknown at this time."*

This study compared relative risk of Autism Spectrum Disorder (ASD) in children vaccinated with MMR vaccine and children not exposed to MMR vaccine born in Denmark between 1991 and 1998. Of the 537,303 children in the cohort, 82% had been exposed to the MMR vaccine. The authors reported that they identified 316 children with a diagnosis of autism and 422 with a diagnosis of "other ASDs". They reported no association between the development of autism or ASD and the age at vaccination, the time interval since vaccination, or the calendar period at the time of vaccination.

Children were vaccinated at **15 to 17 months** and catch up vaccination was given to older children when the vaccine was introduced in 1987. Almost all children were vaccinated before the age of 3 years. The mean age at diagnosis for autism was **4 years, 3 months, and for autistic spectrum disorders 5 years, 3 months.**

Power Assessment: We started our power analysis on males. Using the standard Type 1 error risk of 0.05, and the reported proportion at baseline of 0.001, the number of subjects in the exposed group (226,042) and the number in the unexposed (49,680), we were surprised to find that the study was precisely powered to detect a relative risk (in the test of proportions) of 2.000 at Power = 0.8. The OR power was slightly higher at 2.002.

These RR and OR values are very high and would require that vaccines DOUBLED the risk of autism in males. That is, the rates of autism in the general population would have to be precisely double in the MMR-vaccine exposed group compared to the unexposed group. The fact that these study-derived values for males led to a power calculation of precisely 2.000 is very suspicious, as it suggests that power calculations were in fact used in the design of the study, at least for the male subgroup analysis, but were not reported, and were used instead to ensure that no association could be found.

The authors had reported that "The power of the study is reflected in the narrow 95 percent confidence intervals." However, if the MMR in fact doubled the risk of autism, the rates of autism in the population would be much higher in the general population, and the effects would have been obvious. Clearly, the actual relative risk of autism due to MMR, if it exists, lies somewhere between 1.0 and 2.0.

Given this, two related fair questions to ask of the study are

(1) "What would the effect size have to have been (measured as OR > X) to have been detected at the studies' sample size", and
(2) "How strongly does the distribution of patients among classes influence the minimum detectable effect size of studies with this configuration of patients"?

In this setting, we can explore the number of additional patients that would have to be added the vaccinated, autism group ("a" in Table 2) to achieve the apparently surmised RR of 2.0. This would represent the number of patients either with mislabeled diagnoses, or that were surreptitiously moved to the "b" group (No ASD(Control), MMR exposure). To study this possible influence on the final design, we calculated an Expected OR [E(OR)] from N, prevalence of autism in the MMR non-exposed group, and other input parameters. Of the four study group classes (Table 2), this required us to adjust a and b (moving patients from group b to group a), keeping c and d constant. We conducted this numerical exercise from 0 added patients until a and E(OR) of 2.0 was achieved, and discovered that if the number of patients in the ASD, vaccinated group were doubled, the study could have achieved E(OR) = 2.0 (Fig 3). This is consistent with someone in the Madsen (2002) study changing group

assignment of nearly precisely half of the vaccinated, ASD patients to achieve a Power of nearly 0.0 (OR 1.0) for detecting association between MMR vaccination status and autism in the males.

Table 2. Study Groups Defined in the Madsen et al. (2002) study.

	ASD Cases	No ASD
MMR Exposed	a	b
No MMR Exposure	c	d

The odds of the study being powered precisely at 1.0 at the given distribution of patients seems very, very low. This is clear fingerprint of fraud. It is extremely unlikely that precisely the number of males in the unvaccinated group would have an error in diagnosis, or incorrect vaccination records to achieve an exact halving of the E(OR). The alternative explanation, that half of the patients in the no ASD, MMR group (c) somehow had an incorrect diagnosis leading to precisely Power of 0.8 for OR = 2.000 in males is unlikely. It is reasonable to conclude that fraud in form of manipulation of the class assignments during the study "design" is responsible.

In testimony to the United State Congress (excerpted and referenced in the Appendix to this study), Dr. Spitzer, a world-class epidemiologist made it clear that fatal flaws existed with the Madsen et al. (2002) study included unwarranted and mysterious and unwarranted movement of patients:

"…why did Madsen and lOM do an adjustment to the subcohort that removed six autistic (sic) and a total of 13 cases of progressive developmental disorder cases from the vaccinated subcohort and then place them in the unvaccinated one?

This single adjustment reduces relative risks of autism due to MMR vaccination by 17 percent, from 1.26 to 1.09…"

Dr. Spitzer had lauded the study for having sufficient power; however, he reported that the power analyses were not provided by the authors. Further, his assessment of the power of the study did not include the consideration that the effect of MMR on autism may be cumulative to the effects of the other vaccines, and thus the study would have had to have been powered for a small positive effect size from one vaccine. The widespread reporting of negative ORs in association studies at this time is most reasonably explained in part due to healthy user bias, in which parents refused MMR vaccination due to earlier negative effects of vaccines on the health of their child. Thus, ignoring the effects of past vaccination health outcomes on the study groups in these studies and focusing exclusively on MMR (as opposed to cumulative exposures to vaccines) was a serious design flaw.

Others had previously found serious problems with Madsen et al., (2002), including Blaxill (SafeMinds, 2013), who found, independent of this analysis, evidence that patients w/ASD were moved to the unvaccinated group and Stott et al. (2004), who concluded that adjusting for age was inappropriate. A Cochrane Report in 2005 concluded that the length of time to diagnosis was too long, that the data were in many ways incomplete, and that interpretation was made difficult due to the use of the date of diagnosis instead of age of first symptoms.

Examining the power of the entire study, with N1=440,655, and N2=96,648, at alpha = 0.05, the power analysis resulted in a finding that the samples sizes are too small to detect any P1 > P0 with Power = 0.80. In other words, the study was too small given the low baseline prevalence and the high exposure to detect any positive increase in risk of autism from vaccines – even without moving patients among groups.

Thus, in contrast to the study authors' conclusions of high power, this study, although large, was clearly underpowered. In the study of males, with N = 275,722, we determined that at least 909,073 to 935,744 males would have been needed to detect a moderate, positive association of 1.1. For the entire study, given the lower prevalence, the study would have had to use data from 1,943,339 to 1,997,911 patients to detect a moderate positive association. Further, if the effects of vaccines are cumulative, since the Madsen study effective studied an expected 6 vs. 7 vaccines, the effect size of the MMR itself would likely have been 0.01-0.1, not 0.2, and certainly not 2.0. For these reasons, **fraud or not, the study authors could not have detected a positive association at the reported sample sizes.**

Previous serious criticisms of the Madsen et al. (2002) study have fallen on robustly deaf ears. Suissa (cited in Stott et al., 2004) pointed out that when the data from the study are analyzed using time after vaccination instead of age, the association between MMR vaccination and autism is detected (45% risk increase). The NEJM declined to publish this important submitted response. Goldman (2004) 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. Importantly, the "age-adjustment" used by Madsen et al. (2002) would not have been able to undo the strong effects of this type of confounding.

The Madsen (2002) analysis should have used "time since vaccination", which in other studies has reversed the conclusions using their data. Stott et al. (2004), demonstrated the same logic flaw in Taylor et al.'s (1999) 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) 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 delay diagnosis in many of the patients, also draw the Taylor et al's (1999) conclusions into further doubt. Finally, Madsen et al., (2002) did 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 interpretation of the results of the Madsen study (2002), and any mere retrospective correlation study, impossible.

Previous Exposure Bias, a form of Healthy User Bias

Other confounding may be a play in any study of "MMR" vs "no MMR". Parents whose children experience early adverse events related to vaccines may have opted out of MMR vaccine due to the increase in reports of adverse events, and due to media coverage of original findings of Dr. Wakefield and colleagues. These children may have nevertheless been given other previous vaccines, and still regressed. This is not inconceivable given that the effects of thimerosal are nefarious and we know now include specific inhibition of ERAP1 (Stamogiannos et al., 2016) with consequent negative consequences on both the adaptive and innate immune systems, and the effects of aluminum on cellular detoxification pathways (e.g., Rizvi et al., 2014). However, healthy user bias and thimerosal exposure are less likely than fraud to explain the results in the Madsen et al. (2002) study, because neither of these factors explain the precise value of Power = 2.000 for the study design for males.

Overinterpreted Results

Clearly, studies of "MMR" vs. "No MMR:" are not "Vaccinated" vs. "Unvaccinated". We conclude, therefore, that Farrington et al., thus over-interpreted their results when they concluded that their analysis reduces the likelihood that "vaccines" are a contributing factor in the rates of autism. Similarly, any public health policy agency that pronounces that "Vaccines Do Not Cause Autism" overinterprets the results available because not all vaccines in the CDC schedule, for example, have been tested for association with autism.

Consequences for Meta-Analysis and Public Policy Statements

Two meta-analyses conducted since 2012 considered the result of these and other studies on the question of a role of MMR vaccination and autism (Taylor et al., 2014). This result is often touted for using data from over 1.3 million individuals (e.g., Wessel, 2017). The emphasis on the total number of participants in all studies in a meta-analysis is unwarranted, however, because meta-analyses do not overcome the issue of low power or bias in the studies they incorporate. The low power of the studies included in those meta-analyses cast serious doubt on the validity of the conclusions of those meta-analyses as well. Turner et al. (2013) found that none of the meta-analyses they studied were sufficiently powered, and paradoxically suggested that such low-power studies could be excluded from meta-analysis. A better recommendation would have been to insist on sufficient power in clinical studies in the first place.

More importantly, the existence of healthy-user bias likely drives the studies included in Taylor et al. (2014) into the negative. Instead, numerous individuals have offered the interpretation of OR around 0.8 as a signal of some type of protection from vaccines against ASD. It is more likely that the credit for this decreased risk is due to a combination of the use of the wrong type of study (retrospective instead of prospective), parental concern over second or third adverse events from vaccines (healthy user bias), and, as the power analysis of the male

subgroup in Madsen et al. (2002) hints, fraud. See Hooker et al. (2014) for additional serious issues with the design of the analysis of this study, including arbitrary exclusion of 2001 incidence numbers which showed a decline in autism, a trend shift that could have been attributed to the removal of Thimerosal from vaccines. Hooker et al. (2014) excerpted an email between Dr. Coleen Boyle (CDC) and Poul Thorsen implicating both in the editing of these results, which obviously biased the final published study away from attributing autism to vaccines; HHS is seeking extradition for the latter for embezzling over $1.2 million dollars that was supposed to go to autism research. Scientific fraud is generally recognized as data fabrication, falsification, or omission. Arbitrary data omission of key data that weighs in on a primary hypothesis in a study is universally seen as an especially serious offense.

In 2017, the American Academy of Pediatrics published a letter to the President of the United States outlining studies reporting negative results. The studies we reviewed here were included among those listed. Therefore, the AAP should update their policy position given this new information on the flaws in the study designs. CDC's public policy on vaccines also relied heavily on the original IOM report. Clearly, AAP should update their policy statement and should insist upon an *a priori* power analysis of prospective clinical studies of vaccinated vs. fully unvaccinated and prospective randomized properly controlled clinical trials to provide a rigorous test of the hypothesis of vaccine-induced encephalopathy-mediated autism given the high likelihood that their position is misinformed by bias, low power and fraud.

Conclusions

The **association study paradigm** does not provide a sufficiently well-defined test of causality; therefore, **negative results cannot demonstrate lack of causality**. Resources such as VAERS include warnings that their contents are not systematically collected, and therefore they cannot be used to infer causality. Because post-marketing surveillance systems do not represent a critical test of causality, negative results cannot be relied upon to conclude "no effect".

The association study paradigm has further failed on the question of a role of vaccines in contributing to autism risk in part due to the unseen effects of insufficient statistical power. The study authors, the reviewing journal editorial boards, and the IOM should have insisted on *a priori* power analysis for each of these studies. Alternatively, they should have conducted the power analyses themselves and helped society understand the limits of knowledge from small epidemiological studies.

Exposure bias, previous adverse event bias, healthy user bias and cohort effects and fraud may all have played a role in the near-ubiquitous negative OR results in retrospective vaccine studies on autism.

Critically, three of the four studies (Mrozek-Budzyn et al., 2010, Smeeth et al., 2004, Madsen et al, 2002) not rejected by the IOM Committee in 2012 are now shown to have been underpowered, and could not have detected a realistic positive association. Had power analyses been required of these studies prior to publication, it is highly unlikely that the IOM Committee would have found them useful for their assessment.

Taylor et al. (1999), the remaining SCCS study (which as noted may have used erroneous MMR prevalence data) would seem to have overdrawn its conclusions, and it further demonstrated, given its conclusions, that at the time the study was done, it was extremely difficult to identify the age of first onset of symptoms. This is consistent with Brian Deer's reports on parent's uncertainty of timing of first diagnosis, which fueled the fear of suspicion of Dr. Wakefield. Rather than confirm Deer's conclusions, however, if Dr. Farrington and colleagues had a difficult time discerning age at first diagnosis, their conclusions would seem to further exonerate Dr. Wakefield from wrong-doing.

Recommendations

(1) Prediction studies, not association studies, are needed. Future studies must be focused on determining which patients are likely to develop neurological and immunological disorders as a result of vaccination/other exposures. Meaningful covariates, such as patients' reasons for late vaccination or non-vaccination statuses should be routinely collected and used appropriately as predictor variables rather than factors to be corrected. Vaccination policy is cast wide in spite of restrictions and narrow clinical populations defined by past studies. Examination of interaction terms is required to determine if combined factors interact more than single independent variables. This means covariates should be considered a source of contraindications, not merely explanatory factors that might relieve vaccines of liability for adverse events. Factors such as low birth weight should therefore be used as additive or interactive (multiplicative) covariates, and the actual prediction accuracy of combined variable models tested on blinded data. Prospective, double-blind randomized clinical trials (RCTs) are needed. The ethical argument that such studies would leave some children unvaccinated completely begs the question of the study and assumes a negative result without justification and may well be contributing to the largest public health crisis in the history of humankind.

(2) No further retrospective association studies are warranted; they have proven to be too weak to detect associations that might exist and far too easy to manipulate via analysis-to-result.

(3) All vaccine safety studies should conduct and publish the results of *a priori* power analysis over a range of plausible effect size.

(4) Studies of individual vaccines should be powered to detect cumulative effect sizes, which may be small.

(5) Steps toward a viable, objective vaccine safety screening must be undertaken immediately using known risk factors. Genetic risk must be studied ASAP and phased biomarker development studies undertaken to demonstrate accuracy, sensitivity and specificity of avoiding serious adverse events.

(6) All members of the scientific and medical community should adopt a more compassionate view of the publics' concern over neurological adverse events from vaccines and change their culture before an ever more draconian reality takes hold.

(7) No practice should count individuals with medical exemptions as potentially vaccinated, and administrators need to remove the pressure on health care practitioners to meet vaccination quotas. Incentives tied to the percentage of patients vaccinated must be abolished.

The assessment that "Vaccines Do Not Cause Autism", as reported by CDC's website, is, in large part due to the IOM's reliance on the four studies that _only_ focused on the MMR vaccine and which we have shown are under-powered. The low statistical power of these studies, and the lack of randomization rule out any firm conclusions on causality. Because autism and has not been adequately and rigorously tested as a potential outcome from vaccination, the issue needs to be revisited with more appropriately designed and conducted clinical trials. The power of all studies focused on vaccine safety subsequent to these four studies should be determined, and their individual results and meta-analyses should be re-interpreted accordingly. The unethical practice of conducting and publishing vaccine safety studies without _a priori_ power analyses to enable detection of important suspected adverse events must end.

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Power Calculators

Sampsize - http://sampsize.sourceforge.net/iface/s3.html

Ausvet - http://epitools.ausvet.com.au/content.php?page=case-controlSS

Proportions – Effect Size - http://www.sample-size.net/proportions-effect-size/

Appendix: Excerpted Spoken and Written Testimony re: Madsen et al. of Dr. Testimony of Walter O. Spitzer, M.D., M.P.H., F.R.C.P.C. to UNITED STATES CONGRESS

Dr. Spitzer was Emeritus Professor of Epidemiology and Past Chairman, Faculty of Medicine, McGill University, Emeritus Editor, Journal of Clinical Epidemiology and Member of the Institute of Medicine U.S.A. at the time of this testimony.

Spoken:

"…they had allocation of cases to subcohorts of exposed and nonexposed which are difficult to understand. That's one of the two examples that I gave.

There is an unusual distribution of ages in the cohorts to which you alluded to. Dr. Geier, and they have problems with measurement of clinical phenomena, and their censoring rules are surprising or are inappropriate.

These are just five or six of the statistical issues over and above that main issue of failing to protect against hiding a phenomenon in a subgroup by looking at the 90 percent, if you wish."

"…why did Madsen and IOM do an adjustment to the subcohort that removed six autistic (sic) and a total of 13 cases of progressive developmental disorder cases from the vaccinated subcohort and then place them in the unvaccinated one?

This single adjustment reduces relative risks of autism due to MMR vaccination by 17 percent, from 1.26 to 1.09…"

"Why did Madsen not simply exclude all cases involving earlier, that is, nonregressive, diagnosis of autism? If they had removed all cases diagnosed before 2 years of age from both subcohorts, the relative risk would have risen from 1.26 to 1.28."

"To age cohorts coming close to the end of the study or the end of followup, we have an average inception of the disease. It's about 3 years. If you only follow them for a year and a half, you are going to miss an awful lot of autistic cases among those exposed. So the censoring is difficult to understand, how they adjusted for it."

Written:

The paper, 'A population-based study of measles, mumps, and rubella vaccination and autism'… published on November 7, 2002 describing a very good national data linkage based upon which a cohort study was done. It was sponsored and possibly supervised by the Centers for Disease Control and Prevention of the United States of America. A group led by KM Madsen with a good reputation in Europe did the study. The main conclusion from the study is 'This study provides evidence against the hypothesis that MMR vaccination causes autism.'… The study is a major improvement over all earlier epidemiologic investigation due to an appropriate controlled design. Unfortunately, the strategic advance was not matched by some important methodological tactics in the execution of the study. That vitiates the strength of the authors' conclusions.

Without being exhaustive, this presentation reviews some of the methodological problems

Source: https://archive.org/stream/gov.gpo.fdsys.CHRG-107hhrg84605/CHRG-107hhrg84605_djvu.txt *Accessed June 9, 2017*

A very important attribute of the linked Danish national databases was that there (sic) was no selection bias, the curse of almost all observational epidemiological research. The key result published is an odds ratio of 0.92 for autistic disorders which fails to attain statistical significance as expected but with good power of 0.80 for an OR of 1.5.

The main objection is that the apparently reassuring finding is almost certainly misleading if you consider that autism is likely to be caused multifactorial and that only a small subset of autistic patients may have been affected by MMR. For instance, hypothetically, if only one subset had been identified where 1 0% of all autistics were affected by the MMR vaccination, the OR would be 4. 14 which is high for that 10% subset. But it is not a trivial subset. Conservatively, in the United States alone, 10% would result in a financial burden of suffering of 1 .25 billion dollars for the lifetime of the children in direct expenditures alone.

Further, there were several analytic shortcomings and problems. Censoring was done inappropriately particularly for the later birth cohorts. The age distribution of the children is unusual and questionable as the basis for standardization. Some important variables could not be examined at all.

As of December of 2002 1 have important unanswered questions on the study management particularly the role of the CDC.

Madsen and perhaps Canadian investigators need to replicate, verify and corroborate the initial Danish study. An important step forward has been taken. But one study does not prove or disprove any hypothesis (sic) definitely. The road of research needs to be followed. Excellent research standards need to be matched to transparent and ethical standards of management in exploring the causes of the baffling epidemic of autism."

1st author	Year	Design	Measure	Statistic	Test	Calculator	Randomiz	Concern
Farrington	2001	Retrospective SCCS	Regression, parent's first conce	Relative Incidence	Intervals	Farrington et al	No	No fixed time interval specified;
								confuses MMR vaccination status
								with "vaccinated"
Taylor	1999	Retrospective Case series	Time trend	Relative Incidence	Intervals	N/A	No	Uncertainty of diagnosis
								clinical information not updated
Madsen	2002	Retrospective Cohort	ASD diaganosis	Relative Risk	Intervals	SS	No	Small sample size
								Negative Ors indicate PNR Bias
Mrozek-Budzyn	2010	Retrospective Case/Control	ASD in MMR vs. Not	CLR	Intervals	SS, EPI	No	Small sample size, used adjusted OR
								used adjusted OR , all of which may
								reflect underlying conditions that indicate
								indicate intolerance of toxins in vaccines
								(mother's age, medication during pregnancy
								gestation time, perinatal injury
								and Apgar score)
Smeeth	2004	Matched Retrospective Case/	Vaccination in ASD vs. No ASD	OR	Intervals	SS, EPI	No	Small sample size, adjustment for age
SS = http://sampsize.sourceforge.net/iface/s3.html, EPI= http://epitools.ausvet.com.au/content.php?page=case-controlSS								joined GPRD when enrollment was
CLR = conditional logistic regression								linked to vaccination status
OR = odds ratio								(therefore in the causal pathway)

Table 1. Flaws in the Handful of Studies Cited by IOM After Rejecting 17 Other Studies as Flawed.

| Author	Year	Study Type	Sample Size Group 1	Group 2	Total N	Power > x? 0.8	0.7	0.6	Comments
Madsen	2002	Tx/Control Cohort	440655	96648	537303	N	Y	Y	evidence of fraud or very poor design
Mrozek-Budzyn	2010	Case/Control	96	192	288	N	N	N	poor design
Smeeth et al.	2004	Case/Control	1294	4467	5761	N	N	N	poor design
Taylor et al.	1999	Case series	233	64	297	Y	Y	Y	susceptible to temporal biases
Farrington et al.	2001	Case series	233	64	297	Y	Y	Y	susceptible to temporal biases

Table 2
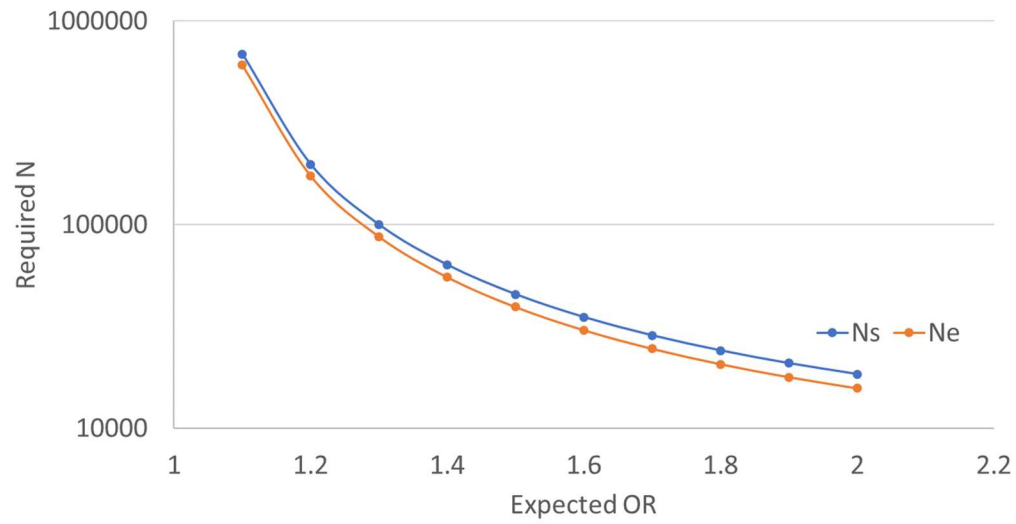
Figure 1. Post-hoc Sample Sizes Required to Achieve a Positive Association for Studies Like and Including Mrozek-Budzyn et al., 2010. Ns, Ne = Number needed to achieve Expected OR determined using the resources by Glaziou (2005) and Ausvet (2017), respectively.
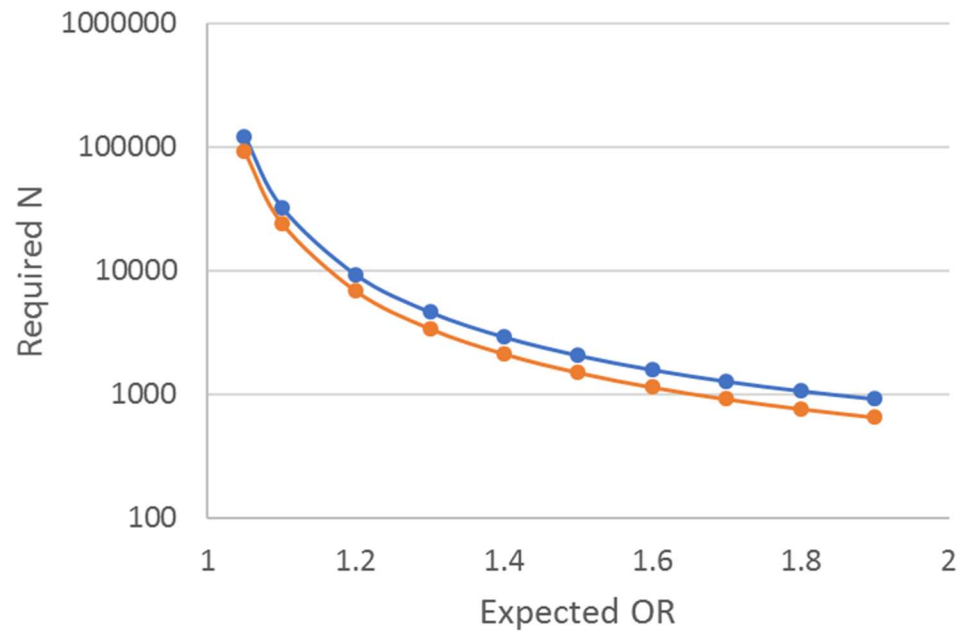
Figure 2. *Post-hoc Sample Sizes Required to Achieve a Positive Association for Studies Like and Including Smeeth et al. (2004)*
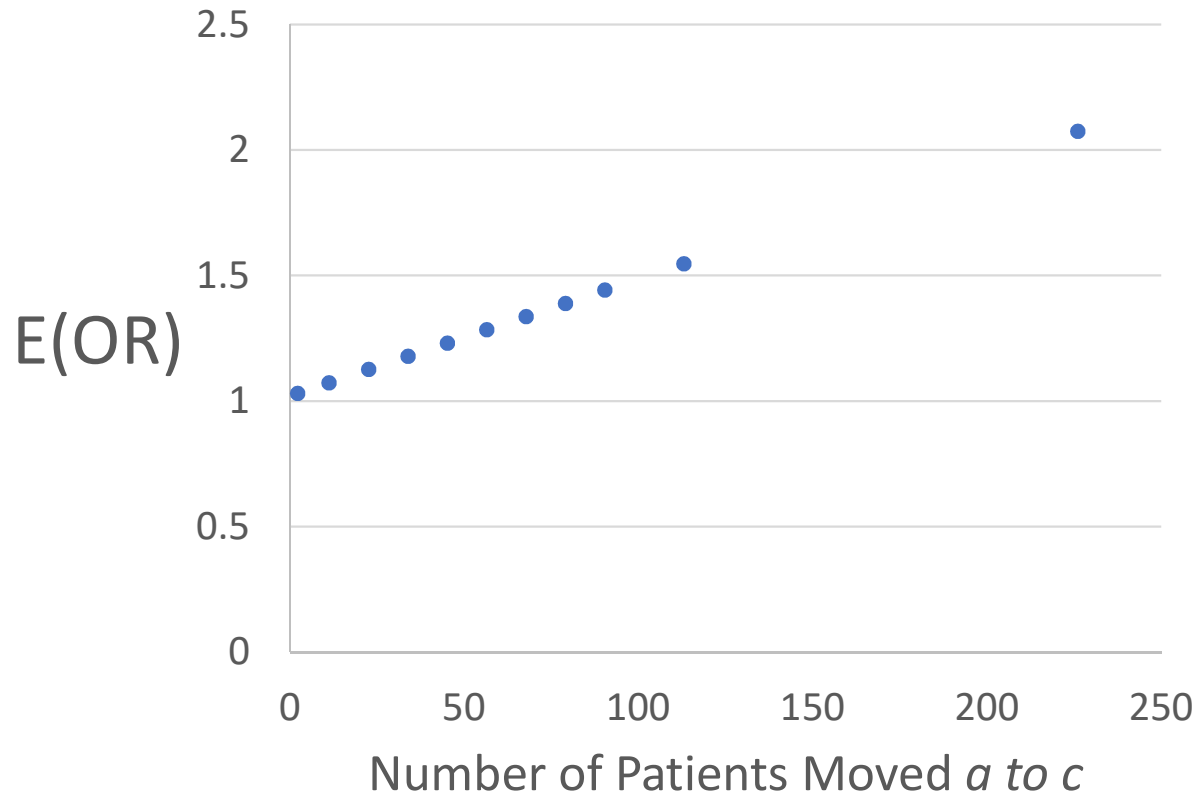
Figure 3. Hypothetical Reversal of Fraud shows that that if the number of patients moved from group a (ASD, vaccinated) to group c (ASD, unvaccinated) had been approximately half of the patients in group a, the expected OR would fall to 1.0. This would mean no power to detect any positive OR value that might exist, and the precision with which this was executed is the fingerprint of very poor science, fraud, or both.