

## ***Maternal Gestational Tdap Vaccination and Autism: A Critique of Becerra-Culqui et al. (2018)***

James Lyons-Weiler<sup>1</sup>, Alison Fujito<sup>1</sup>, and Bernadette Pajer<sup>2</sup>

<sup>1</sup>The Institute for Pure and Applied Knowledge (Michigan Office), St. Clair Shores, MI 48080; [jim@ipaknowledge.org](mailto:jim@ipaknowledge.org), tel. 412-728-8743 (corresponding author)

<sup>2</sup> Informed Choice Washington

### **ABSTRACT**

We report flaws and inconsistencies in a critically important study of autism risk following maternal Tdap vaccination. The authors of the 2018 study, *Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination and Autism Spectrum Disorder* (BC18), concluded that Tdap gestational vaccination is not associated with increased autism risk and claimed to provide “evidence supporting the ACIP’s recommendation to vaccinate pregnant women”. Our observations, based on information from the study itself, challenge these conclusions. We find evidence of a peculiar study design and approach to data analysis forcing outcomes by arbitrary data adjustments, overlooked variables of importance such as *Bordetella pertussis* infection prevalence and vaccine injury rates, insufficient consideration of likely interactions between multiple historical medical challenges by vaccines and other interventions on their participants, exclusion from the study individuals likely at risk of vaccine intolerance due to genetics, and indications that the study samples were not representative of the general population. Their first-year data show a concerning spike in ASD rates, and their findings and conclusions did not hold up to real-world data, which currently reports 3.8% ASD rate in California. Our observations, based on information from the study itself, challenge the conclusions of Becerra-Culqui et al, 2018.

**Keywords:** *acellular pertussis vaccine, Advisory Committee on Immunization Practices (ACIP), California Department of Developmental Services (CDDS), diphtheria vaccine, maternal immune activation (MIA), Tdap vaccine, tetanus vaccine, vaccine efficacy (E), vaccine injury (VI), vaccine negative efficacy (NE), vaccine utility (U)*

### **Introduction**

Becerra-Culqui et al. (2018) analyzed the risk of autism spectrum disorder (ASD) diagnosis in children of mothers vaccinated with Tdap during pregnancy (Becerra-Culqui et al., 2018; henceforth, BC18). They found no link to autism and concluded that their study “supports ACIP’s recommendation for Tdap use during pregnancy”. We challenge that conclusion for reasons which are enumerated in this paper.

#### *Study Design and Data Analysis Protocol*

While the primary variable studied was Tdap vaccination during pregnancy, the study involved two populations in which other vaccine-related variables were involved but unaccounted for by BC18. Post-natal vaccination exposure in the offspring was not considered in the study design but was instead dismissed by

the blanket statement that “there is consistent evidence supporting that vaccines administered in childhood and their preservatives do not cause ASD”. On the contrary, there is a significant body of independent research literature not funded by vested interests in the vaccine industry, disputing the claim that vaccinations are unrelated to neurological disorders including autism (Gallagher & Goodman, 2010; Tomljenovic & Shaw, 2011; Mumper, 2013; Mawson et al., 2017), including a 2015 white paper, that lists ASD among the 43 chronic health issues determined to be biologically plausible outcomes from vaccine exposure (Glanz et al., 2016).

Additionally, CDC's own scientists have acknowledged the potential for environmental factors, including vaccines, to play a role in autism: “The possibility that immunologic stimulation from vaccines during the first 1-2 years of life could be related to the development of ASD is not well supported by the known neurobiology of ASD, which tends to be genetically determined with origins in prenatal development... although possible effects in early infancy cannot be ruled out completely. It can be argued that ASD with regression, in which children usually lose developmental skills during the second year of life, could be related to exposures in infancy, including vaccines” (Destefano et al., 2013).

The “known neurobiology of ASD” has advanced since 2013, nonetheless, the concluding statements by DeStefano et al. (2013) leave open the influence of environmental exposures to the genetically susceptible during prenatal development and during the first two years of life.

The fact that necessary and specifically relevant studies have not been conducted that would unequivocally test the hypothesis of a causal relationship between childhood neurological disorders and vaccines cannot be ignored. Most current vaccines and vaccination combinations, including DTaP and Tdap, have never been critically examined in well-designed studies that include a fully non-vaccinated control group in respect to autism or any other childhood disorders, even though vaccines are increasingly suspected of being involved, and in specific cases have been judged to be causally involved (Edlich et al., 2007). Nevertheless, in 2012, the Institute of Medicine (IOM) said that “the evidence is inadequate to accept or reject a causal relationship” between receipt of diphtheria-tetanus-pertussis containing vaccines and autism (Institute of Medicine & Committee to Review Adverse Effects of Vaccines, 2011).

Given that the focus of the BC18 study was prenatal (gestational) vaccination, and that the exposure to immunization stimuli *in utero* and after birth involve interconnected biological pathways, vaccination during gestational development and post-natal vaccination cannot reasonably be regarded as unrelated variables. The vaccination of the mother during the baby's gestational development and post-birth vaccinations must all be considered as relevant variables on account of the known toxic effects of all the injections and challenges presented to the developing babies. The interaction term between post-natal vaccination and prenatal Tdap vaccination should have been examined, including the specific post-natal vaccines received as well as the number of post-natal vaccines. The study also should have addressed whether some of the mothers who did not receive Tdap during pregnancy were in that category because their babies were born prematurely, precluding vaccine administration in the third trimester.

It is already known that the combination of premature birth and postnatal vaccination increases the risk of ASD (Mawson, Bhuiyan, et al., 2017) and that certain vaccines recommended for pregnant women substantially increase the likelihood of pre-birth injuries or babies born dead. All this came out in a classic study by Eaton et al. (2018) revealing, on careful scrutiny, that the combined congenital anomalies and morbidities attributable to either of two flu vaccines administered during pregnancies, specifically, the H1N1 vaccine and the Trivalent Influenza Vaccine (TIV), accounted for 71.19 and 67.93 birth irregularities per 1,000 administrations, respectively (Oller, 2020, pp. 286-287). Quoting from that study, note the division of injuries into eight subcategories — shown in the numbers we have added in square brackets. The negative impact of the two about equally toxic exposures that are both obviously harming the developing unborn

child is effectively minimized by splitting the damages into multiple smaller quantities as shown in the added bracketed numbers (Eaton et al., 2018, p. 2733):

Results did not vary significantly between groups. Comparing H1N1 with TIV, incidence were similar for [1] preterm births (6.37 vs 6.28/100 births), [2] very preterm births (5.30 vs 8.29/1000 births), [3] LBW (4.19 vs 2.90/100 births), [4] very LBW (4.54 vs 5.52/1000 births), [5] small for gestational age (9.99 vs 9.24/1000 births), [6] spontaneous abortion (7.10 vs 6.83/1000 pregnancies), [7] stillbirths (7.10 vs 4.57/1000 pregnancies), and [8] congenital anomalies (2.66 vs 2.43/100 births).

In fact, as in many studies supposedly showing the “safety and effectiveness” of whatever vaccines happen to be in focus, the manufacturers choose to compare one known toxicant cocktail against another of about equal potency. Then, if no difference is found, as in the case of Eaton et al., the conclusion reached is that both exposures are safe and should continue to be recommended for pregnant women or for whomever the vaccine might be intended in the first place. Eaton et al. did not follow up to study impact on the babies exposed *in utero* to the H1N1 or TIV vaccines, nor have any studies been done by the promoters, for example, of the HPV vaccines for post-birth consequences of surviving offspring as discussed in this journal by DeLong (2021a, 2021b). However, the toxic impact of the increasing number of vaccine exposures to pregnant women and their babies before and after their birth, in general, is demonstrated dramatically even in studies such as Eaton et al. These studies are designed to render an “all is well” with mother and baby after vaccine exposures regardless of whether their data support the opposite conclusion, or do not even address the question of safety for some populations. In the study by the BC18 authors, they plainly state the biases of the manufacturers of the vaccines up front before they conduct their studies. In the end they circle around and, unsurprisingly, repeat the presumptions with which they began, in their published conclusions. The top and bottom lines are the same: the vaccines are presumed to be unrelated to the study’s documented undesirable outcomes, which are euphemized as “side effects”, and the conclusion to be reached at the end is that the vaccines remain “safe and effective” for all the intended consumers.

More specifically, in the BC18 study, another anomaly that works in favor of the conclusion presumed and explicitly stated at the start, is their adjustment for certain arbitrary variables. The IPTW-Adjusted Hazard Ratio (HR) is 0.85, whereas the Unadjusted HR is 0.98. The authors adjusted for maternal influenza vaccination — which according to the results of Eaton et al. (2018) is a powerful negative factor. In keeping with the known levels of toxicity of influenza vaccination, in their Figure 2, it has the second largest standardized difference revealing, as should be expected, that influenza vaccination is a major source of variation in ASD risk for the vaccinated mother’s baby. The adjustment to the HR involved many different factors, but in clinical practice, Tdap vaccine is given during pregnancy without considering or adjusting for risk based on other toxic exposures from, for instance, flu vaccines. It is therefore apparent that the foregone conclusion could not be supported if the BC18 authors did not “adjust” for the hugely impactful influenza vaccination in particular. If it were not eliminated as an effective vaccination risk-raising-variable, the BC18 conclusion, implying the “safety and effectiveness” of the Tdap, could not reasonably be claimed. The influenza vaccine exposure of the pregnant women should, logically speaking, instead, have been taken as one of the co-predictors of the magnitude of risk involved with vaccinations in general. Since none of the variables of interest can be definitively ruled out as a potential causative factor in an eventual ASD outcome, they must be considered as additive — or even multiplicative as the toxicology shows (Haley, 2005; N. Z. Miller & Goldman, 2011; Seneff et al., 2015; Kennedy et al., 2016) — increasing risk of adverse vaccination outcomes leading to autism and/or related neurological disorders such as Attention Deficit Hyperactivity Disorder (ADHD).<sup>1</sup>

---

<sup>1</sup> It is troubling that the same authors have more recently published another, similarly flawed study, Becerra-Culqui et al. (2020), that is nearly identical in its beginning, ending, and internal design to their BC18 report. As in the study under critical scrutiny

The authors' use of Inverse Probability of Treatment Weighting Adjustment can only lead to an introduction of error falsely named to imply some kind of "correction". The only error being committed is to regard a known toxicant as if it were a negligible placebo or something of that sort. Specifically, if the distribution of attributes (e.g., received influenza vaccination) is, in fact, representative given the sampling process, and any initial differences are not due to bias, no such adjustment is warranted, and it is the very opposite of a correction. Alternatively, if the sampling is biased by factors, and IPTW is applied for the incorrect or irrelevant factors in a manner that ensures the skewing of results toward the presupposed conclusion, then the conclusion that the vaccines are safe for pregnant women and their unborn children is assured by adjustment factor selection. IPTW will also obviously lead to warping of any association test if the functional relationships among the variables are, in fact, different from those assumed and adjusted for by the investigators. Such so-called "corrections" should be based on prior knowledge, not on undesirable observed differences popping up in the data being analyzed. We note that the same inverse weighting scheme for variables was not used by Becerra-Culqui et al., in similar past analyses, notably a study of ozone exposure in ambient air pollution and ASD (Becerra et al., 2013), and a survey study on experiences with ASD services and treatments (Becerra et al., 2017).<sup>2</sup>

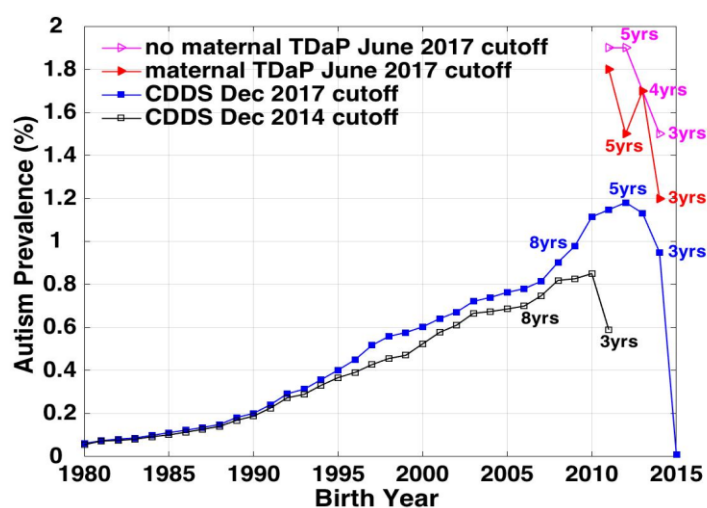


Figure 1. ASD prevalence reported by Becerra-Culqui et al.<sup>1</sup>, resolved by birth year using the reported June 30, 2017, diagnosis cut-off date (red and magenta triangles). The Becerra-Culqui data are compared to prevalence data from the California Department of Developmental Services (CDDS), resolved by birth year with a December 2017 diagnosis cut-off date (blue squares) (Nevison et al., 2018)<sup>12</sup>. CDDS focuses on the more severe cases of autism, so the CDDS values are lower than the Becerra-Culqui values. The dip in prevalence for the Becerra-Culqui data on 5-year-olds born in 2012 to Tdap-vaccinated mothers (red triangles) shows an odd age structure that is difficult to reconcile with the 2017 CDDS data. Also shown are the CDDS prevalence data with a late 2014 diagnosis cut-off (black squares), illustrating the much lower prevalence for 8-year-olds born in 2006 compared to post-2010 birth cohorts. CDDS curves show the rapid increase in autism prevalence over time while illustrating the rollover in the prevalence vs. birth year curve that occurs due to under-ascertainment in very young children. The 2014 diagnosis cut-off is included for comparison to the recent US Centers for Disease Control and Prevention (CDC) 2018 report<sup>13</sup> on 8-year-olds born in 2006.

here, the starting premise for their 2020 paper also happens to come out as their conclusion as well. As in their BC18 study on Tdap and autism risk, the authors in 2020 also used "adjusted" risk analyses. To see what is wrong about such reasoning we follow with detailed analysis of what they did in BC18. It is similar to how Eaton et al., in comparing two known vaccines with known adverse reactions (H1N1 and Trivalent Flu Vaccine), chose to split the negative impact on birth outcomes into multiple parts to minimize the numbers.

<sup>2</sup>Given that BC18 was published in a journal supported and maintained by funds coming from the manufacturers and promoters of the very vaccines supposedly under critical examination, we can only speculate about the pressure to reach a conclusion favorable to those vested interests. It is for that very reason that our critique was never considered by the journal where the BC18 study originally appeared; they would not even review a much earlier communication to them. It is crucial that critical examination of studies can appear in independent outlets not under the censorship and control of the global government, pharmaceutical, and media interests of the mainstream academic/medical journals (see Shaw, 2020).



Both cohort effects and incomplete and/or inaccurate ASD diagnosis appear likely in the study design. The authors report that about 80% of the ASD cases in the study were diagnosed among children who were only 2-4 years old; some were only 1-2 years old, which experts consider to be too young for a firm diagnosis (Ozonoff et al., 2015). The prevalence rates reported in BC18 (their Table 2) also show a non-representative age structure, particularly for the Tdap group, when compared to contemporaneous data from the California Department of Developmental Services (Figure 1). Since the CDDS data are widely considered the most reliable dataset of autism prevalence in the U.S. (Nevison et al., 2018), the comparison in Figure 1 raises questions about the accuracy of the ASD diagnoses used by BC18.

The study age restrictions and diagnostic timing create a misleading framework wherein a significant group in the later birth cohorts — those diagnosed with ASD only after school entry — were entirely missed. The study was restricted to children born between January 1, 2011, and December 31, 2014, and diagnosed with ASD by June 30, 2017. The maternal Tdap vaccination rate was 26% for the early part of the cohort (who had until age 6 to be diagnosed) and increased to 79% for the cohort born in 2014. Some of the children born to this later, more heavily vaccinated, group were under 3 years old by the June 2017 diagnosis cutoff. Even among those born in 2011, that cutoff would have excluded the significant cohort that receives an autism diagnosis after entering school (age 6.5-8.9; Nevison et al., 2018). The median age of diagnosis in the US is 4 years, even for severe ASD, while milder forms of ASD like Asperger's have a mean age of diagnosis of 8 years (Lingam et al., 2003; CDC, 2022).

Another concern is that children were included in the study if they remained under continuous medical coverage for at least 90 days after turning one year of age; it is unclear how many early-exiting children were included in the final results with their status recorded as it was when leaving the medical system, whether their departures were related to medical conditions potentially attributable to gestational vaccination (e.g., pre-term birth), or if the exiting subgroup had different rates of later diagnosis of autism or vaccine reaction. The authors acknowledge that they likely did not capture some children with ASD if they were born in later study years but assert that this is not a concern because their unstratified and cohort-stratified analyses yielded similar results. This assertion may not be correct given the potential for age-independent departure from the Kaiser-Permanente healthcare system after diagnosis with autism, or, importantly, based on the decay of health provider/patient relations following parents' refusal of vaccination and health care provider's insistence, which is becoming more widespread. The authors do not acknowledge these critical issues that indicate the potential for selection bias.

The overall prevalence reported in the study group of 1.6% inappropriately aggregates 2-6-year-old children, who vary widely in diagnostic ascertainment. It also ignores the rapid increase in prevalence with each new birth cohort in recent years (Nevison et al., 2018). Similarly, the assertion of BC18 that this average rate of 1.6% among 2-6 year olds born in 2011-2014 is "comparable to the estimated 1.7% prevalence" among 8-year old children" born in 2006 (based on CDC, 2018) is not supported, because those 8-year olds were likely to have been more thoroughly assessed and ascertained for ASD than the 2-6 year olds but at the same time represent a birth cohort likely to have substantially lower rates of ASD than those born in 2011-2014 (Figure 1).

The recent rapid increase in ASD prevalence began around birth year 2007, after a period of relative flattening among the birth cohorts of the late 1990s and early 2000s (Nevison et al., 2018). The acceleration in ASD diagnosis coincided with dramatic increases in maternal exposure to both influenza and Tdap vaccines (Baxter et al., 2017; Shakib et al., 2016). While correlation cannot sufficiently test causation, maternal immune activation (MIA) is a well-understood process that can induce autism or autism-like symptoms (Baxter et al., 2017b; Lombardo et al., 2018). Increased MIA due to maternal vaccination is thus a

plausible causal mechanism for the observed uptick in ASD prevalence among recent birth cohorts (Figure 1); as such, it merits careful and objective scrutiny.

#### *Inclusion/Exclusion Criteria*

The inclusion/exclusion criteria used in the study further draw into question the generalizability of the conclusions. Specifically, women with pregnancies induced by *in vitro* fertilization were excluded without rationale. It is now suspected that many cases of low fertility involve autoimmunity (Busnelli et al., 2016); maternal autoimmunity is also a suspected risk factor for adverse events from vaccines in infants, as well as for autism, with repeated and long-known findings of anti-brain protein antibodies (Zimmerman et al., 2007; Fox et al., 2012; Braunschweig et al., 2013; Piras et al., 2014). The study also excluded infants with <90 days continuous enrollment, which could bias the overall result if parents witnessed vaccine adverse events and left in order to seek alternative treatment. They also excluded children with chromosomal abnormalities; however, in clinical translation, karyotypic analysis is not routinely consulted prior to vaccination, and those groups receive all vaccinations on schedule.

BC18's decision to exclude children with congenital and chromosomal issues resulted in eliminating 2.8% of their study subjects. That is nearly twice the number of study subjects diagnosed with autism. It is crucial to know how many of those anomalies were in children of the vaccinated mothers, and thus potentially caused or triggered by the vaccine. Surely it would be unethical for a safety review of any intervention to eliminate a group of test subjects specifically because they share the same injury status that arguably might have been caused by the intervention being studied. If autism has both genetic *and* environmental causal components (which it almost certainly does; Lyons-Weiler, 2018), BC18 may have removed from their study most of the individuals susceptible to issues with detoxification of vaccine excipients and susceptible to "rare" vaccine adverse events.

#### **Human Subjects Research Ethics**

The women in the study were part of a cohort who had received Tdap vaccination during pregnancy without having been provided appropriate and required consent for enrollment in a clinical study of the safety of a vaccine. In fact, from the first and quite recent recommendations of giving Tdap vaccine during pregnancy, pregnant women have never been told of the experimental nature of this recommendation. While it is clearly documented in the package inserts for both the Boostrix and Adacel vaccines, vaccine package inserts are not routinely provided to patients, and the "Vaccine Information Sheets" do not provide this information to patients considering vaccination options (Kay et al., 2014).

Vaccine safety (like drug safety and device safety) must never be assumed, especially during safety trials, and that assumption cannot be used as justification to skip over the step of getting consent before placing patients in clinical research studies. Because the safety of Tdap vaccine use in pregnancy has never been fully established in prospective studies, the paradigm that individuals in subsequent post-marketing surveillance studies are not properly informed of potential risks of vaccination is unethical.

It is remarkable that the study authors concluded that Tdap was safe when their data (their Table 1) point to at least one important problematic secondary outcome: hard selection against males. This risk should be considered for the Vaccine Information Sheets provided to women prior to vaccination during pregnancy and should be clearly communicated to patients as well.

### *Potential for Negative Efficacy*

Any reasonable definition of utility of a given vaccine would be a complex function of the reduction in mortality and morbidity due to vaccination (Efficacy, E) minus any tendency of the vaccine to lead to spread of the wild-type pathogen anywhere in the population (negative efficacy, NE) minus any increase in morbidity and mortality due to vaccine injury (vaccine injury, VI), or

$$U = f(E + NE - VI) \quad \text{Equation (1)}$$

Studies of vaccine safety should explicitly address all the inputs to utility, with costs and benefits both internal and external to the medical industry included, which is especially difficult for pertussis vaccination. Newborn pertussis risk is extremely small. BC18 cite Baxter et al. (2017) in their introduction and report the improvement in relative risk among babies of vaccinated mothers. However, the Baxter et al. data provide an absolute risk reduction (ARR) in infants of just 0.02%, i.e., 15 pertussis cases out of 79,292 unvaccinated mothers vs. 1 case out of 68,168 mothers vaccinated at least 8 days prior to giving birth. Baxter et al. limited the birth mothers to those born prior to 1996 for the purpose of ensuring all mothers had received the whole-cell pertussis primary series, so even this small ARR may not be afforded to infants born to women who received acellular vaccines as their primary series. Further, Baxter et al. did not address the fact that the highest rate of pertussis in their study was in infants born to mothers vaccinated with Tdap within 7 days of giving birth (1 case out of 1,521 vaccinated mothers, or 0.06%).

Acellular pertussis vaccines are understood to protect the vaccinated individual from symptoms only, as noted by the FDA in 2013; they do not prevent asymptomatic colonization and active transmission of *B. pertussis* upon subsequent exposure to wild-type strain (Fine, 1997; Kay et al., 2014; Warfel et al., 2014; Cherry, 2015). Acellular pertussis vaccines protect the vaccinated individual from symptoms only, as noted by the FDA in 2013. If women are vaccinated during pregnancy with Tdap and are later exposed to pertussis, they may be asymptotically colonized and transmit *B. pertussis* to their own family, including the newborn. Furthermore, during subsequent prenatal or postnatal care, they may unwittingly transmit infection to other patients, as well as the medical staff, who may in turn infect other patients. The problem of persistent circulation of pertussis in highly vaccinated pediatric and adult populations, which led Cherry (2015) to label Tdap a “failed vaccine”, is likely to follow the use of acellular pertussis vaccines in the population of children, adolescents, and pregnant women. In this setting, symptom-based diagnosis is insufficient to estimate prevalence.

Waning immunity (as far as protection from typical whooping cough symptoms is concerned) was acknowledged by BC18 as a reason for rising pertussis incidence, but the inability for acellular pertussis vaccine to prevent colonization and transmission was not; yet it is this much-studied aspect that contributes the most to NE. Vaccine Injury (VI) the final component we have enumerated in Eqn 1, was insufficiently addressed in the present study in part because the developmental fates of those exiting the practice is unknown, and thus, the overarching conclusion that Tdap use in pregnancy is safe and is protective is not supported.

Baxter et al (2017) state: “Without pertussis vaccination during pregnancy, maternal pertussis antibodies in the infant decline substantially by 6 weeks of age and become undetectable by about 4 months of age.” They fail to report whether antibody levels between 6 weeks and 2 months (which is when infants are vaccinated for pertussis) are below a level necessary to prevent infection. In fact, a specific cut-off level does not seem to have been established. Baxter et al (2017), cited Ladhani et al (2016), who found that unvaccinated infants had high pertussis antibody concentrations pre-immunization, and also concluded: “Antenatal pertussis immunization results in high infant pre-immunization antibody concentrations, but blunts subsequent responses to pertussis vaccine and some CRM-conjugated antigens.”

All of these facts call into question the assumption of the necessity for universal maternal pertussis vaccination and draw into question why BC18 did not incorporate this prior knowledge into their own study.

## Interpretation

The study results are difficult to interpret given the foregoing. In their Table 2, BC18 appear to find substantially higher rates of ASD among the unvaccinated mothers even when stratified by birth year. One possibility for the  $HR < 1$  effect is hard selection against males (unborn babies that died) that misleadingly appears to be “protective” because ASD-bound as yet unborn males may be more likely to die *in utero* due to vaccination. Another possibility is healthy user bias: non-vaccinating mothers may be actively avoiding vaccines due to bad personal past experiences, or bad experiences with their older children, or cultural transmission of vaccine avoidance due to familial/genetic susceptibility to serious adverse events, or the combined effect of all of these. This hypothesis is not new and is known to influence influenza vaccine uptake (see Shrank et al., 2011 for a primer). A third possibility is non-receipt of maternal Tdap in situations of premature birth (a high-risk group for autism, see Mawson et al., 2017) where there was insufficient time to administer Tdap to the mother in the 3rd trimester.

It is well established in the scientific literature that vaccines cause maternal immune activation (MIA) and release of inflammatory markers such as C Reactive Protein (CRP) and proinflammatory cytokines. These markers in turn are widely recognized as risk factors for autism and other adverse health outcomes in the fetus (Christian et al., 2011; Brown et al., 2014; Kay et al., 2014). Thus, there are no prior immunological or development processes by which maternal immune activation via Tdap could be truly protective against ASD. Our understanding of the relevant biology points in the opposite direction. Yet, the authors suggest that their “results potentially indicate that the maternal Tdap vaccine affects immune trajectories protecting infants against infections that would otherwise lead to neurodevelopmental alterations”. However, U.S. maternal tetanus, diphtheria, and pertussis detected infections are very rare and therefore cannot be driving the increases of neurodevelopmental disorders. Presumably, MIA from these diseases is avoidable without exposing the fetus to the risk of the vaccine, or the MIA the vaccine may activate by pre-pregnancy vaccination. Vaccination during pregnancy is not being recommended by the ACIP to protect the mother from pertussis infections — this is an off-label recommendation to protect the child after birth from an extremely rare event (neonatal pertussis). Animal models use maternal *B. pertussis* lipopolysaccharide (LPS) exposure to induce ASD in offspring (Estes & McAllister, 2016); pertussis and influenza vaccines have been found to be contaminated with LPS (Kataoka et al., 2012).

The ASD hazard ratios  $< 1$  presented by BC18 are therefore almost certainly spurious because of confounding factors that were “adjusted for” or ignored in the study. The authors acknowledge the well-known risks of MIA but make no serious attempt to address their puzzling results. They also present some peculiar secondary outcomes in the study, including a significant reduction in birth weight and a greatly increased risk of preterm birth (9% vs. 5.7%) among unvaccinated mothers. Again, BC18 offer no explanation for these outcomes. However, a plausible confounding factor that could explain all of these apparent “protective” outcomes of prenatal Tdap vaccination (against ASD, low birth weight and preterm birth) is non-receipt of prenatal Tdap due to premature birth, followed by the incumbent high risk of ASD in vaccinated premature infants (Mawson, Bhuiyan, et al., 2017).

In our view, the study supports conclusions that differ markedly from those the authors drew about the general safety of Tdap vaccination during pregnancy. The secondary outcome of hard male selection *in utero* points to risks that the authors either ignored or failed to note. The three implausible protective outcomes of maternal Tdap vaccination strongly suggest unrecognized or unacknowledged confounding influences or biases. Overall, this study does not support the authors’ conclusion of general safety, and in addition,



provides data that contradicts ACIP's reassurance of safety and recommendation to vaccinate pregnant women with Tdap for the off-label use of protecting the child after birth.

### *Sponsorship Bias*

It is well-known that studies funded by sponsors with vested interests lead to pressures and persistent biases that trend toward results favorable to the sponsor. The BC18 “conflict of interest” statement suggests the potential for sponsorship bias. This study also bases its report of utility of Tdap vaccination during pregnancy on a study (Baxter et al., 2017) that also reported conflicted sponsorship:

Drs Baxter and Klein report potential conflicts of interest relevant to this article: the pertussis vaccines purchased by Kaiser Permanente Northern California, which are the focus of this study, were manufactured by GlaxoSmithKline and Sanofi Pasteur.

## **Conclusions**

In 2011, the Institute of Medicine & Committee to Review Adverse Effects of Vaccines (2011) noted:

Both epidemiologic and mechanistic research suggest that most individuals who experience an adverse reaction to vaccines have a preexisting susceptibility. These predispositions can exist for a number of reasons — genetic variants in human or microbiome DNA — environmental exposures, behaviors, intervening illness, or developmental stage, to name just a few — all of which can interact.

Risk of each of these predispositions exist for unborn children directly, or through their parents. Given the IOM's notice, we have identified and reported serious flaws in the BC18 study that invalidate their conclusions and suggest that the research does not provide a step forward toward understanding of causality in autism and the many related conditions that come with it. We have pointed out that up to 1.9% of very young children in the Southern California HMO at issue had already been diagnosed with ASD, signifying a higher prevalence of severity on the spectrum than in previous years (Figure 1). If history is any guide, this spike foretells that total percentage across the spectrum will almost certainly grow to well over 2%, if not 3%, as these birth cohorts age and are fully diagnosed (Ozonoff et al., 2015). This result of BC18 is astonishing but is not mentioned by the authors. (Updated in proof: CDC has more recently estimated ASD rates in California of 1/26, or 3.8%; CDC, 2021).

Further, we note ethical concerns in conducting and publishing poorly designed vaccine safety studies that focus exclusively on a single (or selected few) environmental factor(s), e.g., one or more vaccines, while ignoring genetic variation associated with autism risk, much of which may be involved in or impair cellular detoxification. Genetic variation and environmental susceptibility are especially complex *in utero* and early infancy when so much neurological development occurs. It is likewise unethical to conduct ASD gene studies that do not consider environmental factors. Studies are needed that are designed — and sufficiently powered — to measure known and suspected genetic and environment interactions. Clinical science is moving toward the use of pre-study public registration of study designs and data analysis protocols (Aveyard et al., 2013; Chambers & Munafo, 2013; Munafo et al., 2017). We suggest that *Pediatrics* could improve the quality of the studies they publish by requiring such registrations and asking reviewers to examine them for flaws and weaknesses. Reviewers also would be asked to compare those registrations, including a fixed, explicit data analysis plan and the final executed analyses to detect unwarranted deviations and thereby help *Pediatrics* avoid publishing arbitrary and biased results. Of course, it should be added that the problem is a general one for mainstream medical publishing. It is an industry deeply conflicted on account of its nearly universal control by vested interests (Liu et al., 2017; Wong et al., 2017; Dal-Ré et al., 2019; Niforatos et al., 2020) that are shaping and cherry-picking results of published studies that turn out to be mostly “false” when examined closely (Ioannidis, 2005, 2007, 2016).

## Funding Source

This work was supported in part by donations from the public to The Institute for Pure and Applied Knowledge.

## Conflict of Interest

JLW has, in the past, participated as an expert witness in the National Vaccine Compensation Program, but has no existing conflict of interest.

## Acknowledgements

The authors would like to thank Dr. Cynthia Nevison for supplying the data for Figure 1 and for input on the manuscript.

## References

- Aveyard, P., Bellgrove, M., Bertamini, M., Bestmann, S., Bishop, D., Brembs, B., & Wolfe, J. (2013). Trust in science would be improved by study pre-registration. *Strona Internetowa*: <http://www.theguardian.com/science/blog/2013/jun/05/trust-in-science-study-pre-registration>.
- Baxter, R., Bartlett, J., Fireman, B., Lewis, E., & Klein, N. P. (2017). Effectiveness of vaccination during pregnancy to prevent infant pertussis. *Pediatrics*, 139(5). <https://www.publications.aap.org/pediatrics/article-split/139/5/e20164091/38778/Effectiveness-of-Vaccination-During-Pregnancy-to>
- Becerra, T. A., Massolo, M. L., Yau, V. M., Owen-Smith, A. A., Lynch, F. L., Crawford, P. M., Pearson, K. A., Pomichowski, M. E., Quinn, V. P., Yoshida, C. K., & Croen, L. A. (2017). A Survey of Parents with Children on the Autism Spectrum: Experience with Services and Treatments. *The Permanente Journal*, 21, 16–009. <https://doi.org/10.7812/TPP/16-009>
- Becerra, T. A., Wilhelm, M., Olsen, J., Cockburn, M., & Ritz, B. (2013). Ambient Air Pollution and Autism in Los Angeles County, California. *Environmental Health Perspectives*, 121(3), 380–386. <https://doi.org/10.1289/ehp.1205827>
- Becerra-Culqui, T. A., Getahun, D., Chiu, V., Sy, L. S., & Tseng, H. F. (2018). Prenatal tetanus, diphtheria, acellular pertussis vaccination and autism spectrum disorder. *Pediatrics*, 142(3). <https://www.publications.aap.org/pediatrics/article-split/142/3/e20180120/81652/Prenatal-Tetanus-Diphtheria-Acellular-Pertussis>
- Becerra-Culqui, T. A., Getahun, D., Chiu, V., Sy, L. S., & Tseng, H. F. (2020). Prenatal tetanus, diphtheria, acellular pertussis vaccination and attention deficit hyperactivity disorder. *American Journal of Epidemiology*. <https://academic.oup.com/aje/article-pdf/doi/10.1093/aje/kwaa074/34304895/kwaa074.pdf>
- Braunschweig, D., Krakowiak, P., Duncanson, P., Boyce, R., Hansen, R. L., Ashwood, P., Hertz-Picciotto, I., Pessah, I. N., & Van de Water, J. (2013). Autism-specific maternal autoantibodies recognize critical proteins in developing brain. *Translational Psychiatry*, 3(7), e277–e277. <https://www.nature.com/articles/tp201350>
- Brown, A. S., Sourander, A., Hinkka-Yli-Salomäki, S., McKeague, I. W., Sundvall, J., & Surcel, H.-M. (2014). Elevated maternal C-reactive protein and autism in a national birth cohort. *Molecular Psychiatry*, 19(2), 259–264. <https://www.nature.com/articles/mp2012197>
- Busnelli, A., Paffoni, A., Fedele, L., & Somigliana, E. (2016). The impact of thyroid autoimmunity on IVF/ICSI outcome: A systematic review and meta-analysis. *Human Reproduction Update*, 22(6), 775–790. <https://academic.oup.com/humupd/article-abstract/22/6/775/2420584>
- CDC. (2022, March 2). *Data and Statistics on Autism Spectrum Disorder* | CDC. Centers for Disease Control and Prevention. <https://www.cdc.gov/ncbddd/autism/data.html>
- CDC, 2021 Autism Prevalence Higher in CDC's ADDM Network <https://www.cdc.gov/media/releases/2021/p1202-autism.html>
- Chambers, C., & Munafo, M. (2013). Trust in science would be improved by study pre-registration. *The Guardian*, 5.

- Cherry, J. D. (2015). Epidemic pertussis and acellular pertussis vaccine failure in the 21st century. *Pediatrics*, 135(6), 1130–1132. <https://www.publications.aap.org/pediatrics/article-split/135/6/1130/75787/Epidemic-Pertussis-and-Acellular-Pertussis-Vaccine>
- Christian, L. M., Iams, J. D., Porter, K., & Glaser, R. (2011). Inflammatory responses to trivalent influenza virus vaccine among pregnant women. *Vaccine*, 29(48), 8982–8987. <https://www.sciencedirect.com/science/article/pii/S0264410X11014459>
- Dal-Ré, R., Caplan, A. L., & Marusic, A. (2019). Editors' and authors' individual conflicts of interest disclosure and journal transparency. A cross-sectional study of high-impact medical specialty journals. *BMJ Open*, 9(7), e029796. <https://doi.org/10.1136/bmjopen-2019-029796>
- Delong, G. (2021a). Receipt of HPV vaccine associated with increased prevalence of high-risk HPV infections. *International Journal of Vaccine Theory, Practice, and Research*, 2(1), 81–92. <https://ijvtp.com/index.php/IJVTPr/article/view/28>
- Delong, G. (2021b). Lowered female fertility associated with human papilloma virus vaccines. *International Journal of Vaccine Theory, Practice, and Research*, 2(1), 125–148. <https://ijvtp.com/index.php/IJVTPr/article/view/31>
- DeStefano F., Price C.S., Weintraub E.S. (2013) Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. *J Pediatr*. 163(2):561-7.
- Eaton, A., Lewis, N., Fireman, B., Hansen, J., Baxter, R., Gee, J., & Klein, N. P. (2018). Birth outcomes following immunization of pregnant women with pandemic H1N1 influenza vaccine 2009–2010. *Vaccine*, 36(19), 2733–2739. <https://doi.org/10.1016/j.vaccine.2017.08.080>
- Edlich, R. F., Olson, D. M., Olson, B. M., Greene, J. A., Gubler, K. D., Winters, K. L., Kelley, A. R., Britt, L. D., & Long, W. B. (2007). Update on the National Vaccine Injury Compensation Program. *Journal of Emergency Medicine*, 33(2), 199–211. <https://doi.org/10.1016/j.jemermed.2007.01.001>
- Estes, M. L., & McAllister, A. K. (2016). Maternal immune activation: Implications for neuropsychiatric disorders. *Science*, 353(6301), 772–777. <https://www.science.org/doi/abs/10.1126/science.aag3194>
- Fine, P. E. (1997). Adult pertussis: A salesman's dream—and an epidemiologist's nightmare. *Biologicals*, 25(2), 195–198. <https://www.sciencedirect.com/science/article/pii/S104510569790083X>
- Fox, E., Amaral, D., & Van de Water, J. (2012). Maternal and fetal antibrain antibodies in development and disease. *Developmental Neurobiology*, 72(10), 1327–1334. <https://onlinelibrary.wiley.com/doi/abs/10.1002/dneu.22052>
- Gallagher, C. M., & Goodman, M. S. (2010). Hepatitis B Vaccination of Male Neonates and Autism Diagnosis, NHIS 1997–2002. *Journal of Toxicology and Environmental Health, Part A*, 73(24), 1665–1677. <https://doi.org/10.1080/15287394.2010.519317>
- Glanz, J. M., Newcomer, S. R., Jackson, M. L., Omer, S. B., Bednarczyk, R. A., Shoup, J. A., DeStefano, F., Daley, M. F., Goddard, K., & Panneton, M. (2016). White Paper on studying the safety of the childhood immunization schedule in the Vaccine Safety Datalink. *Vaccine*, 34, A1–A29. <https://www.sciencedirect.com/science/article/pii/S0264410X1501525X>
- Haley, B. E. (2005). Mercury toxicity: Genetic susceptibility and synergistic effects. *Medical Veritas*, 2, 535–542. <https://doi.org/10.1588/medver.2005.02.0006>
- Institute of Medicine & Committee to Review Adverse Effects of Vaccines. (2011). *Adverse Effects of Vaccines: Evidence and Causality* (K. Stratton, A. Ford, E. Rusch, & E. W. Clayton, Eds.). National Academies Press (US). <http://www.ncbi.nlm.nih.gov/books/NBK190024/>
- Ioannidis, J. P. A. (2005). Why most published research findings are false. *PLoS Med*, 2(8), e124. <https://doi.org/10.1371/journal.pmed.0020124>
- Ioannidis, J. P. A. (2007). Molecular evidence-based medicine: Evolution and integration of information in the genomic era. *European Journal of Clinical Investigation*, 37(5), 340–349. <https://doi.org/10.1111/j.1365-2362.2007.01794.x>
- Ioannidis, J. P. A. (2016). The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. *Milbank Quarterly*, 94(3), 485–514. <https://doi.org/10.1111/1468-0009.12210>
- Kataoka, M., Ochiai, M., Yamamoto, A., & Horiuchi, Y. (2012). A need for careful evaluation of endotoxin contents in acellular pertussis-based combination vaccines. *Biologicals*, 40(1), 49–54. <https://www.sciencedirect.com/science/article/pii/S1045105611001977>

- Kay, A. W., Fukuyama, J., Aziz, N., Dekker, C. L., Mackey, S., Swan, G. E., Davis, M. M., Holmes, S., & Blish, C. A. (2014). Enhanced natural killer-cell and T-cell responses to influenza A virus during pregnancy. *Proceedings of the National Academy of Sciences*, 111(40), 14506–14511. <https://www.pnas.org/content/111/40/14506.short>
- Kennedy, D., Seneff, S., Davidson, R. M., Oller, J. W., Haley, B. E., & Masters, R. D. (2016). Environmental toxicants and infant mortality in America. *Peertechz Journal of Biological Research and Development*, 1(1), 36–61. <https://www.peertechzpublications.com/articles/OJBS-1-105.php>
- Lingam, R., Simmons, A., Andrews, N., Miller, E., Stowe, J., & Taylor, B. (2003). Prevalence of autism and parentally reported triggers in a northeast London population. *Archives of Disease in Childhood*, 88(8), 666–670. <https://adc.bmj.com/content/88/8/666.abstract>
- Liu, J. J., Bell, C. M., Matelski, J. J., Detsky, A. S., & Cram, P. (2017). Payments by US pharmaceutical and medical device manufacturers to US medical journal editors: Retrospective observational study. *BMJ*, 359, j4619. <https://doi.org/10.1136/bmj.j4619>
- Lombardo, M. V., Moon, H. M., Su, J., Palmer, T. D., Courchesne, E., & Pramparo, T. (2018). Maternal immune activation dysregulation of the fetal brain transcriptome and relevance to the pathophysiology of autism spectrum disorder. *Molecular Psychiatry*, 23(4), 1001–1013. <https://www.nature.com/articles/mp201715>
- Lyons-Weiler, J. (2018). Autism is an Acquired Cellular Detoxification Syndrome with Genetic Heterogeneity. *Autism Open Access* 8(1):1-15. <https://www.longdom.org/abstract/autism-is-an-acquired-cellular-detoxification-deficiency-syndrome-with-heterogeneous-genetic-predisposition-36965.html>
- Mawson, A. R., Bhuiyan, A. R., Jacob, B., & Ray, B. D. (2017). Preterm birth, vaccination and neurodevelopmental disorders: A cross-sectional study of 6- to 12-year-old vaccinated and unvaccinated children. *Journal of Translational Science*, 3(3). <https://doi.org/10.15761/JTS.1000187>
- Mawson, A. R., Ray, B. D., Bhuiyan, A. R., & Jacob, B. (2017). Pilot comparative study on the health of vaccinated and unvaccinated 6- to 12-year-old U.S. children. *Journal of Translational Science*, 3(3). <https://doi.org/10.15761/JTS.1000186>
- Miller, N. Z., & Goldman, G. S. (2011). Infant mortality rates regressed against number of vaccine doses routinely given: Is there a biochemical or synergistic toxicity. *Human & Experimental Toxicology*, 30(9), 1420–1428. <https://doi.org/10.1177/0960327111407644>
- Mumper, E. (2013). Can awareness of medical pathophysiology in autism lead to primary care autism prevention strategies? *North American Journal of Medicine and Science*, 6(3). <http://www.najms.com/index.php/najms/article/view/191>
- Munafò, M. R., Nosek, B. A., Bishop, D. V., Button, K. S., Chambers, C. D., Percie du Sert, N., Simonsohn, U., Wagenmakers, E.-J., Ware, J. J., & Ioannidis, J. (2017). A manifesto for reproducible science. *Nature Human Behaviour*, 1(1), 1–9.
- Nevison, C., Blaxill, M., & Zahorodny, W. (2018). California autism prevalence trends from 1931 to 2014 and comparison to national ASD data from IDEA and ADDM. *Journal of Autism and Developmental Disorders*, 48(12), 4103–4117. <https://link.springer.com/article/10.1007/s10803-018-3670-2>
- Niforatos, J. D., Narang, J., & Trueger, N. S. (2020). Financial Conflicts of Interest Among Emergency Medicine Journals' Editorial Boards. *Annals of Emergency Medicine*, 75(3), 418–422. <https://doi.org/10.1016/j.annemergmed.2019.02.020>
- Oller, J. W. (2020). *Human Anatomy and Physiology: An Introduction for Undergraduate Students of Speech-Language Pathology and Audiology* (2nd ed.). Sentia Publishing. <https://www.sentiapublishing.com/health-sciences/human-anatomy-and-physiology-for-speech-language-pathologists-and-audiologists-3rd-edition-oller-online-textbook/>
- Ozonoff, S., Young, G. S., Landa, R. J., Brian, J., Bryson, S., Charman, T., Chawarska, K., Macari, S. L., Messinger, D., & Stone, W. L. (2015). Diagnostic stability in young children at risk for autism spectrum disorder: A baby siblings research consortium study. *Journal of Child Psychology and Psychiatry*, 56(9), 988–998. <https://acamh.onlinelibrary.wiley.com/doi/abs/10.1111/jcpp.12421>
- Piras, I. S., Haapanen, L., Napolioni, V., Sacco, R., Van de Water, J., & Persico, A. M. (2014). Anti-brain antibodies are associated with more severe cognitive and behavioral profiles in Italian children with Autism Spectrum Disorder. *Brain, Behavior, and Immunity*, 38, 91–99. <https://www.sciencedirect.com/science/article/pii/S0889159113006053>
- Seneff, S., Swanson, N., & Li, C. (2015). Aluminum and glyphosate can synergistically induce pineal gland pathology: Connection to gut dysbiosis and neurological disease. *Agricultural Sciences*, 06(01), 42–70. <https://doi.org/10.4236/as.2015.61005>



- Shakib, J. H., Korgenski, K., Presson, A. P., Sheng, X., Varner, M. W., Pavia, A. T., & Byington, C. L. (2016). Influenza in infants born to women vaccinated during pregnancy. *Pediatrics*, 137(6). <https://www.publications.aap.org/pediatrics/article-split/137/6/e20152360/52373/Influenza-in-Infants-Born-to-Women-Vaccinated>
- Shaw, C. A. (2020). Weaponizing the Peer Review System. *International Journal of Vaccine Theory, Practice, and Research*, 1(1), 11–26. <https://ijvtp.com/index.php/IJVTPr/article/view/1>
- Shrank, W. H., Patrick, A. R., & Alan Brookhart, M. (2011). Healthy user and related biases in observational studies of preventive interventions: A primer for physicians. *Journal of General Internal Medicine*, 26(5), 546–550. <https://link.springer.com/article/10.1007/s11606-010-1609-1>
- Tomljenovic, L., & Shaw, C. A. (2011). Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? *Journal of Inorganic Biochemistry*, 105(11), 1489–1499. <https://doi.org/10.1016/j.jinorgbio.2011.08.008>
- Warfel, J. M., Zimmerman, L. I., & Merkel, T. J. (2014). Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proceedings of the National Academy of Sciences*, 111(2), 787–792. <https://www.pnas.org/content/111/2/787.short>
- Wong, V. S. S., Avalos, L. N., & Callahan, M. L. (2017). *Industry payments to physician journal editors* (e3359v1). PeerJ Inc. <https://doi.org/10.7287/peerj.preprints.3359v1>
- Zimmerman, A. W., Connors, S. L., Matteson, K. J., Lee, L.-C., Singer, H. S., Castaneda, J. A., & Pearce, D. A. (2007). Maternal antibrain antibodies in autism. *Brain, Behavior, and Immunity*, 21(3), 351–357. <https://www.sciencedirect.com/science/article/pii/S0889159106002947>

## Legal Disclaimer

The information on the website and in the *IJVTPr* is not intended as a diagnosis, recommended treatment, prevention, or cure for any human condition or medical procedure that may be referred to in any way. Users and readers who may be parents, guardians, caregivers, clinicians, or relatives of persons impacted by any of the morbid conditions, procedures, or protocols that may be referred to, must use their own judgment concerning specific applications. The contributing authors, editors, and persons associated in any capacity with the website and/or with the journal disclaim any liability or responsibility to any person or entity for any harm, financial loss, physical injury, or other penalty that may stem from any use or application in any context of information, conclusions, research findings, opinions, errors, or any statements found on the website or in the *IJVTPr*. The material presented is freely offered to all users who may take an interest in examining it, but how they may choose to apply any part of it, is the sole responsibility of the viewer/user. If material is quoted or reprinted, users are asked to give credit to the source/author and to conform to the non-commercial, no derivatives, requirements of the [Creative Commons License 4.0 NC ND](https://creativecommons.org/licenses/by-nc-nd/4.0/).