2021 HOUSE HUMAN SERVICES

HB 1306

2021 HOUSE STANDING COMMITTEE MINUTES

Human Services Committee
Pioneer Room, State Capitol

HB 1306
1/19/2021

To provide for a legislative management study of the interrelationship between sudden infant death syndrome, vaccines, and autism spectrum disorder in children

Ch**airman Weisz** opened the hearing at 4:40.

Representatives	Attendance
Representative Robin Weisz	P
Representative Karen M. Rohr	P
Representative Mike Beltz	P
Representative Chuck Damschen	P
Representative Bill Devlin	P
Representative Gretchen Dobervich	P
Representative Clayton Fegley	P
Representative Dwight Kiefert	P
Representative Todd Porter	P
Representative Matthew Ruby	P
Representative Mary Schneider	P
Representative Kathy Skroch	P
Representative Bill Tveit	P
Representative Greg Westlind	P

Discussion Topics:

- Vaccine autism study
- Public health study proposal
- Behavioral therapy

Rep. Jeff Hoverson, District 3 (4:40) introduced the bill and testified in favor.

Dr. Ted Fogarty MD, Bismarck North Dakota (4:52) testified in favor and submitted testimony #1626.

Kolette Kramer (5:01) testified in favor.

Alexis Wangler, Co-Founder & President Health Freedom North Dakota (5:08) testified in favor and submitted testimony #1454.

Tara Dukart, Hazen North Dakota (5:11) testified in favor.

Rebecca Bakke, Pediatrician - Fargo (5:14) testified in opposition and submitted testimony #1421.

Paul Carson, Center for Immunization Research and Education – North Dakota State University (5:25) testified in opposition and submitted testimony #1590.

Additional written testimony: #1070, #1080, #1215, #1324, #1330, #1426, #1430, #1431, #1484, #1490, #1492, #1495, #1525, #1543, #1547, #1575, #1602, #1607, #1617, #1620, #1621, #1649, #1650, #1651, #1652, #1684

Chairman Weisz adjourned at 5:32 p.m.

Tamara Krause, Committee Clerk

Written Testimony of Edward F. Fogarty, MD in regards to HB1307, HB1320 and HB1306 prepared for the North Dakota House Human Services Committee 01/19/2021.

Dear HHS Committee Members,

I am strongly in favor of the passage of HB1307, HB1320 and HB1306. These there bills revolve around the matters of protection of our citizens from participation in fraudulent medical and healthcare marketplaces in my opinion as a physician.

My experience as a North Dakota physician who has been a leading researcher in hyperbaric medicine and recovery of various forms of acute and chronic brain injury also informs my opinion on the importance of these bills who's passage would serve as a firewall to greater potential harms of our citizenry from product liabilities of vaccines of any sort.

Our federal government in 1986 gave immunity to all vaccine manufacturers for liability of any sort relating to their products. This has led to an entire industry running amok on matters of safety. In 2020, with our nation in a declared state of war on SARS-CoV2, I believe we have all seen how powerful the medical/pharmaceutical lobby really is and its impact on our public health department in ND as well as the very governance of our state through the executive branch.

These three bills will provide some "relief" for the encroachment of the amalgams of government/public health and global pharmaceutical companies into our most sacred decision making over our own health and immune system modifications as well as those of our children's health, well being and development.

HB1307 provisions prohibiting public facilities to demand proof of vaccination is critically important to prevent the further encroachment for what many see as a medical tyranny fed by the current pandemic. Proof of IMMUNITY rather than proof of compliance in a corrupt marketplace is the more medically sound course for any of these considerations. The marketplace of healthcare does not want to lose the opportunity to "over-vaccinate" American populations who may already be immune to diseases such as COVID19 through prior infection or vaccination. Sadly many of my own colleagues in medicine fail to understand that diagnostic laboratory studies can show that a particular vaccine is not only unnecessary but a fraudulent waste of health care resources. I addressed some of these concerns in a Bismarck Tribune Opinion piece on 03/23/2008:
https://bismarcktribune.com/news/opinion/mailbag/a-proposal-on-vaccinations/article_e41b2f91-d75f-511d-92d7-eeef199e8f91.html

HB320 is extremely important for North Dakota's citizens as state and local government mandates on vaccination might technically be unconstitutional under the laws of North Dakota itself in regards to the employment doctrine set forth in our constitution. The ND Constitution under Article VIII, section 1 indicates that all public schools are open to all children of the state. Our citizens who see the corruptions of medicine, government and law at the federal level in these matters, should be afforded the sanctuary of refusal of vaccination under prior ND laws giving philosophical, medical and religious exemptions in this arena. Behavioral economics issues have begun to show our nation and our state that we have significant percentage of people questioning the safety and need for some of these medical products that have no liability for causing harm. I believe we need this law in ADDITION to the free will provisions of exemptions, this law will send a message to government bodies who would rather their needs whether honest or fraudulent be met before the people of North Dakota's rights are protected.

I have seen MANY coercive manipulations of my fellow North Dakotans in these matters of vaccine mandates. There is a nurse in Jamestown who has loss of consciousness with every vaccination for influenza, ostensibly this person is going through this safety racket to keep her job?

I fear that many of you on this committee may have family members or yourself as well placed under duress for standing up for your right to medical decision making over vaccines and in the future, now that we have a class of vaccines that is manipulating genomics at the ribosomal level, when will the state/medical/industrial complex start mandating even greater modifications of our very being in service to the "greater good" or indirectly the billionaire cronies of elected officials? On February 20, 2019, I published this Open Letter to the State of Washington which also reiterates that state officials ought to be careful regarding their own needs to protect their own health freedoms in this realm.
https://informedchoicewa.org/education/an-open-letter-from-edward-f-fogarty-md/

It should be noted that I also called into question the use of ND taxpayer dollars for the "aid package through ND Public Health" in the containment of the 2019 Washington measles outbreak. Why did our state tax dollars go to another state's response to a measly generally non-fatal disease of childhood that engendered infection "parties" in the 1960s which some of you no doubt are old enough to have participated in for contracting mother natures version of an important immunological conditioning agent. Mayo Clinic is working on research to use measles infections therapeutically against untreatable cancers. Merck, which makes MMR under FDA licensure in America has been in a decade long battle for maintaining this licensure as the live attenuated corporate viruses here are not provoking a strong enough repsonse anymore to maintain the licensure under scientific titer checking protocols that many US physicians are now using in their clinical practices. Yes, many of my Integrative Medicine colleagues around the country are doing titer checks on the MMR series and finding that the mumps component is not provoking a safe level of antibodies after 2 doses. This is the crux of a Federal False Claims Act lawsuit in Eastern Pennsylvania filed by whistleblower scientists and several physicians against Merck.
https://www.courthousenews.com/class-says-merck-lied-about-mumps-vaccine/

The news piece above is from June of 2012. As some of you who may have read many of my emails to you and the Governor in the last 3 months may know, I am a proponent of education of many issues in the interface of law, medicine and government. One of th emore important SCOTUS decisions in this nation's history is that of Throckmorton (1878) wherein the doctrine of 'fraud vitiates all" was introduced. Please stand strong for yourselves, your families and your fellow North Dakotans and pass all three of these bills. HB1306 is needed for your grandchildren and great grandchildren to develop under a more natural milieu. As the leading state expert who is a physician/scientist that has reversed cognitive declines in a few of our state's elders via a gentle detoxification process of mild hyperbaric air and oxygen therapies, I can show you dozens of scientific studies that show infant mammals have an exquisitely sensitive respiratory drive center that lies in close proximity to the bloodstream for carbon dioxide sampling. When CO2 levels increase in the bloodstream, babies especially have a fine tuned response to increasing the respiratory rate so that CO2 (a metabolic toxin) is off-gassed to the atmosphere quickly through the lungs. As the sampling of science below shows, mammalian infants can have other toxins, including aluminum and mercury from vaccines interfere with the development of the tiny cluster of important neurons developing in these respiratory center drives.

But if you cannot understand the science below (see appendix), that is okay as we have a grand opportunity from the 2020 pandemic experiences to see how many SIDS deaths did not occur in 2020 during the pandemic as 0-12 month old American children were, on the whole basically in a delayed CDC vaccination schedule. This experiment by the hand of God and mother nature has already happened and we should now commit some limited funds to a simple epedimiology study (IN THE RIGHT HANDS) that can show the decline of SIDS rates in our children corresponding to the delay of vaccinations in our family's children. A paired relative risk could be obtained temporally by looking at the 2017, 2018, and 2019 birth cohorts on a month by month basis. The null hypothesis would be that the ND Babies born in April of the 3 years prior had the same risk of SIDS as though born in April 2020, and the other major months of access restrictions to medical facilities in 2020 for moms and their newborns would likely disprove the "null" hypothesis.

In summary, as many of you surely may have guessed from my communications with you over the last 3 months, I believe as a physician who's understanding of economic wellness that carries into my practice of medical education, communication and real world procedural and diagnostic medicine - we would be remiss as a political body to fail our grandchildren by failing to pass all three of these bills. Thank you for your time and attention.

Respectfully submitted,

Edward "Ted" Fogarty, MD
800 MUNICH DR
BISMARCK, ND
01/19/2021
1245 PM

APPENDIX:
https://ecf.cofc.uscourts.gov/cgi-bin/show_public_doc?2013vv0611-73-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170075/
https://pubmed.ncbi.nlm.nih.gov/28918379/

https://bismarcktribune.com/news/opinion/mailbag/a-proposal-on-vaccinations/article_e41b2f91-d75f-511d-92d7-eeef199e8f91.html

Now that the courts have recognized a link between vaccinations and autism, we need to revisit public policy. Individual vaccines can't get much safer, but vaccine protocols can. The 2008 Centers for Disease Control protocol for pediatric vaccines is not the safest way to accomplish the goal of immunity to multiple infectious diseases in an individual.
A vast majority of children will not be affected by the administration of vaccinations. But if epidemiological purposes can be met with a more directed approach, there is no reason to endanger a genetically vulnerable child with unneeded boosters. Titer checking protocols are inherently safer for individuals, especially in the at-risk families for autism.

A simple lab test to check titers can tell you whether an additional "booster" is needed. The vast majority of kids, 95 percent, are immune for life to measles-mumps and rubella after one dose. Multi-shot vaccine protocols are a boon to vaccine companies, not North Dakota families. Pediatricians using titer checks would shift resources from multinational vaccine corporations to North Dakota hospitals via laboratory services utilization.

The argument against this approach has always been, "It's too troublesome," and "What if we lose the patient to follow-up?" These are legitimate concerns, but is it fair to make the social assumptions that no one in this state sees their pediatrician after the first few months of a baby's life?

As the art moves forward in vaccinomics, the future will show how easily we can do this better. We now have simple finger-stick titer checking technology for HIV antibodies. This could be ported into titer checking systems for vaccine efficacy, and the University of North Dakota School of

Medicine could be the institution that leads the charge on this innovative research. It will take some time to calibrate such systems, but we can do it here better than anywhere because of our high compliance with vaccination in this state and our close-knit medical and governmental communities. Even current policy needs some modification in light of the growing public concerns in vaccine safety due to the Hanna Poling case. She is the child of parents who hold M.D., Ph.D., R.N. and J.D. degrees. They would probably advocate as I, after their experience, that parents need to be made aware of better ways to vaccinate. The first modification of law and policy that should occur is a disclosure on consent forms for vaccine boosters. A child may already be immune for life in certain series after one dose of vaccine (live virus vaccines have incredible long-lived titers and high first response rates). A titer check can obviate the need for an unneeded booster; shouldn't the public be made away of this? This is particularly important in families with high rates of autoimmune disease.

In my own experience, I lost my vaccine records, and in order to get into medical school, I had a whole series titer (antibody) check to prove that I was immune to the diseases we all need protection from in this incredibly helpful arm of medicine.

To ensure that this is done appropriately for your child is to be a loving parent, and to push your colleagues in medicine and government is to be a certain kind of patriot. To fail to educate parents on this option is engendering the socialistic mentality of a cradle-to-grave caretaker federalist system. Governments and school districts would be better served to require titer levels, not written records of vaccine shots. Titer levels are scientific evidence of immunity. A vaccine record actually isn't, as it can be forged.

All U.S. physicians and state legislators should thoroughly read the Simpsonwood Transcripts (www .nationalautismassociation.org /library.php). This is the most honest assessment of the relationship of vaccines to autism and shows a clear signal of "uncertain" strength.

The CDC conveniently "forgets" to publish the transcript as part of the timeline of understanding the relationship of vaccines to autism. This is clearly a lack of transparency at the federal level of health policy, a timely discussion in light of John Irby's front-page piece in the March 16 Tribune. Federal mandates turn a blind eye to the at-risk child harmed by vaccines. We are abusing the molecular machinery of some of our more fragile children to protect vaccine companies, it's a deal with the devil that all of us in medicine hate having to make; I make it every day as a member of the medical specialty, radiology, that deals the most heavy metals and known teratogens to U.S. citizens.

The integrity and smarts of our state level public health officers is getting usurped by the federal government whose agencies are drunk on the influence of multinational corporations, especially in medicine and pharmaceuticals. As a father of an autistic child, I will fight the federal government's continuing to abuse certain vulnerable children in this nation's war against disease. We don't send everyone to the front line of other wars, why aren't we more discriminating in this one?

North Dakota physicians know how to better vaccinate the children of this state than the CDC. We all need to get behind the pediatrics and public health community of North Dakota to improve this art in scientific ways. It may be a decade before that happens, but we can do it.

(*Dr. Edward "Ted" Fogarty is a Bismarck radiologist. - Editor*)

https://informedchoicewa.org/education/an-open-letter-from-edward-f-fogarty-md/

Excerpts below:

"This is not only a costly loss of worker productivity, influenza vaccines are a yearly unethical experiment because of the lack of any safety studies on these medical products. Influenza vaccines are distributed within weeks of their development and have repeatedly been found contaminated aftermarket release in the last 20 years. Our national healthcare security through the workforce of physicians, nurses, laboratory and radiology technologists is placed at risk for political espionage even as more vaccines are manufactured in jurisdictions that could use these products as Trojan horses for slow viruses or prions. Epidemiologically, my colleagues in public health, Neurology or Infectious Disease will need years and many exposures to identify a signal if such covert biological warfare is occurring even now."

"We do not have the ability to easily understand who is at risk of vaccine injury in children, especially our newborns, we pour billions into individualized care of the legislative-age crowd on pharmacogenomic safety studies so that products like Vioxx do not destroy lives of our learned elders. As we have never done anything of the sort in public health and policy for our most developmentally and eugenically vulnerable wildcards of mixed genes in American families, we practice tacit genetic discrimination in the access to public education. Our school budgets are skyrocketing on the increasing numbers of special needs children.

"If removing philosophical exemptions to participation in fraudulent unregulated markets are what your collective actions bring to bear in your state, you may find liabilities that you did not anticipate. I can say this without reservation, the most pervasive molecular crime against humanity in the last 20 years has been the use of aluminum injections on day one of life which have no medical indication. Diagnostic medicine has long ago marked the crime of medical assault on American babies whose mothers' obstetric laboratory panels have shown millions of times over that they are delivering antibodies against the Hep B vaccine itself to their fetuses. There is no medical indication for a vaccine on day one of life outside of active infection of the mother. The rest of my colleagues in medicine would be sued or lose their license for serial billing of the state or insurance companies on completely worthless un-indicated interventions like Hep B on day one, or for that matter, at 2 months of life.

“With growing whistleblower cases coming out of the woodwork in scientific fraud are you really ready to cast this lot towards your constituents’ children and families. The U.S. Department of Justice has a case against Merck in Pennsylvania for the scandalous corporate racketeering of scientists that were told to spike the data for mumps to pass the bar of 95% efficacy, ostensibly so that Merck would not lose the monopoly on MMR in this country. I believe you can all see now that the only check and balance in the system against fraud in vaccine science is a public consumer (parents) becoming aware within our nation discourse regarding these issues. Please hold the line on the philosophical exceptions for the greater good of Washington’s political well-being. Forcing your youngest citizens to participate in a fraud and racketeering scheme is a violation of basic human rights. We first need ethical corporate leadership in the vaccine industry before we can trust our genetically-disabled to the gross negligence of entire generations of humans being treated like cattle. Thank you for your time and attention, may the wisdom of the great decision makers of history help you discern the best for your state regarding philosophical exemptions.”

2/20/2019

EFF3MD

HOUSE HUMAN SERVICES
ROBIN WEISZ, CHAIRMAN JANUARY 19, 2021

TESTIMONY BY
ALEXIS WANGLER
RE: HOUSE BILL NO. 1306

Mr. Chairman and members of the House Human Services, my name is Alexis Wangler. I am the Co-Founder and President of the 501(c)(3) nonprofit Health Freedom North Dakota. This is my written testimony in regard to House Bill No. 1306.

I am strongly in favor of this bill. I think it would be an interesting and quite possibly a jaw-dropping study of the interrelationship among sudden infant death syndrome, vaccines, and autism spectrum disorder. There are numerous doctors, books, & peer-reviewed journals, etc. that have associated vaccines with sudden infant death syndrome and autism spectrum.

A couple of books come to mind One is called The Age of Autism by Mark Blaxill. The other is called How to End the Autism Epidemic by J.B. Handley. In How to End the Autism Epidemic, Handley lists eleven groundbreaking discoveries in separate, but related scientific fields that, taken together, reveal the cause of autism.

Discovery #1: In 2004 Dr Carlos Pardo-Villamizar at Johns Hopkins University discovers that autism brains are permanently inflamed.

Discover #2: In 2005 Dr. Paul Patterson at the California Institute of Technology discovers that immune activation events lead to autism.

Discovery #3: The cytokine interleukin-6 is the key biomarker for immune activation.

Discovery #4: Immune activation can take place after birth.

Discovery #5: Aluminum adjuvant in vaccines produces behavior and motor function deficits.

Discovery #6: Aluminum adjuvant in vaccines, injected into the body, can be carried to the brain by microphages.

Discovery #7: Aluminum adjuvant stays in the brain for much longer than anyone realized.

Discovery #8: Small doses of aluminum adjuvant are actually more dangerous.

Discovery #9: Aluminum causes immune activation in the brain.

Discovery #10: Hepatitis B vaccine induces IL-6 in postnatal rats.

Discover #11: High levels of aluminum are uniquely located in the brain tissue of people with autism.

There are a few of studies I would like to mention that highlight the interrelationship between vaccines and sudden infant death syndrome:

One of the first studies to offer an explanation was published in 2006 in the international journal of pathology, Virchow's Archives titled, "Sudden infant death syndrome (SIDS) shortly after hexavalent vaccination: another pathology in suspected SIDS?". The study discussed how previous expert analysis performed by the European Agency for the Evaluation of Medical Products in 2003, following an investigation they conducted into the emergence of a link between hexavalent vaccines and 5 cases of infant deaths that occurred, paid little attention "to examination of the brainstem and the cardiac conduction systems on serial sections, nor was the possibility of a triggering role of the vaccine in these deaths considered." The study goes on to report on the autopsy findings of a 3-month old female infant who died suddenly and unexpectedly immediately after the administration of the hexavalent vaccine. The autopsy revealed "The cardiac conduction system presented persistent fetal dispersion and resorptive degeneration." The author hypothesized, "The unexpected death of this vulnerable baby (infant with bilateral hypoplasia of the arcuate nucleus) could have been triggered by the hexavalent vaccination. This case is consistent with the triple-risk model of SIDS, a hypothesis comprising an underlying biological vulnerability to exogenous stressors and some triggering factors in a critical developmental period." https://www.ncbi.nlm.nih.gov/pubmed/16231176

In 2011, a study was published in Statistics in Medicine titled "A modified self-controlled case series method to examine association between multidose vaccinations and death," found that based on the review of 300 unexplained sudden unexpected deaths (uSUD) following either penta- or hexavalent, "a 16-fold risk increase after the 4th dose could be detected with a power of at least 90 per cent," and "A general 2-fold risk increase after vaccination could be detected with a power of 80 per cent." https://www.ncbi.nlm.nih.gov/pubmed/21337361

Another 2011 study published in PLoS titled "Sudden unexpected deaths and vaccinations during the first two years of life in Italy: a case series study," investigated a signal of an association between vaccination in the second year of life with a hexavalent vaccine and sudden unexpected deaths (SUD) in the two-day window following vaccination, which was reported in Germany in 2003. The Italian study sought to establish whether hexavalent vaccines increased the short-term risk of SUD in infants. The study analyzed 604 infants who died of SUD, 244 (40%) of whom had received at least one vaccination. Four deaths occurred within two days from vaccination with the hexavalent vaccines, representing a 50% increase in relative risk. The relative risk for SUD for the risk periods 0-7 and 0-14 days were 100% [2.0 RR] and 50% [1.5 RR] higher, respectively. The study concluded that there was a 120% [2.2 RR] increased risk associated with the first dose of hexavalent vaccine. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0016363

Good Afternoon Chairman Weisz and members of the Human Services Committee. My name is Becca Bakke, and I am here to testify in opposition to House Bill 1306..

I have been a board-certified pediatrician for 10 years. I am also a mother of four and native North Dakotan, and I am so grateful to have legislators who care about the health and well-being of the children in our state. SIDS and autism are two issues that are close to the heart of every pediatrician and really everyone who cares about kids. But this bill will do nothing to prevent SIDS or treat autism, and the money and time can be better used to support the children and families of North Dakota.

First, SIDS, or Sudden Infant Death Syndrome, falls under a larger umbrella of infant death known as SUID or Sudden Unexplained Infant Death. SIDS is a sudden death in infants that occurs during unobserved sleep for which a cause cannot be found. Diagnosis of SIDS requires an investigation that includes evaluation of the scene, autopsy and thorough review of the baby's medical history. 90% of SIDS deaths occur before 6 months of age, and on a personal note, I will add that SIDS cases are among the most devastating cases I have ever been involved in as a physician. I was a medical student when I first cared for a baby who died from SIDS, and it was horrific. I will never forget it.

By its very definition, we don't know what causes SIDS. But we do have ways to prevent it. In 1992, the American Academy of Pediatrics recommended that babies be placed to sleep in the supine position in what became known as the "Back to Sleep" campaign. This single intervention reduced the number of yearly SIDS cases by more than 50%. There are additional interventions that we know make a difference too, including having babies sleep alone on a firm, flat surface, breastfeeding, not smoking during or after pregnancy and staying up-to-date on vaccines. I'm going to repeat that last one. Vaccines. Numerous studies, I will include a list for your reference, have shown that vaccines do not increase a baby's risk of SIDS, and several have actually shown that babies who are vaccinated have a DECREASED risk of unexplained death. If we want to prevent SIDS in this state, and we do, we should be encouraging parents to vaccinate their kids on time. We should not spend precious resources looking for a link that multiple studies have already shown does not exist.

Next, let's talk about autism, which is a common neurodevelopmental disorder. Autism is defined by 2 main characteristics. The first is a deficit in social communication and interaction, and the second characteristic is a pattern of repetitive and restrictive behaviors. The symptoms of autism spectrum disorder truly present on a spectrum, with some persons able to live an essentially normal life with some mild challenges, to severe cases, in which affected individuals require assistance in even the most basic activities of daily living. Concern for a link between autism and vaccines dates back to 1998, when a man named Andrew Wakefield published a case series in a medical journal called the Lancet suggesting that the MMR vaccine caused autism. Subsequently, the rates of MMR vaccination declined throughout the western world, and we began to see measles outbreaks. It was later discovered that Mr. Wakefield had done invasive research on children without obtaining appropriate ethical clearance; he actually drew blood from children attending his son's 10th birthday party. Wakefield also falsified data, was funded by lawyers who had plans to sue the vaccine manufacturing companies., and had a patent pending on a measles only vaccine prior to publishing his case series. The Lancet retracted his

paper, and Mr. Wakefield lost his medical license. Multiple studies later showed that MMR vaccine is not associated with an increased risk of autism in children. Other proposed links between autism and vaccines, including the theory that it is caused by the preservative thimerosol and the idea that "too many vaccines too soon" cause autism have also been thoroughly rebuffed in large, reproducible studies.

We do have some ideas of what causes autism, and both genetics and environment seem to play a role. The risk of autism is increased in children who have a sibling with autism. Children born prematurely, children with older parents, and children with certain genetic disorders also have an increased risk of being diagnosed with autism.

To best support children with autism and their families, they need therapy, which usually includes speech therapy, occupational therapy, and a special kind of therapy called Applied Behavioral Analysis, or ABA. ABA therapy has been shown in multiple studies to increase positive behaviors and teach social and adaptive skills to children with autism. When started early in life and done intensely, ABA can increase a child's independence and decrease the need for special services later in life. ABA saves money and heartache in the long run. It is also a therapy that families have to fight to obtain for their children, because therapists can be difficult to find and it is often not well covered by insurance.

Vaccines are safe. They do not cause SIDS or autism. Spending additional time and money on investigating these issues is akin to doing additional studies to prove that smoking causes lung cancer. To prevent SIDS, promote safe sleep, breastfeeding and smoking cessation. To treat autism, fund ABA therapy. These questions surrounding vaccines have been asked and answered. We need to move on. Thank you.

Vaccines and SIDS

1. Yang YT and Shaw J. Sudden infant death syndrome, attention-deficit/hyperactivity disorder and vaccines: longitudinal population analyses. Vaccine 2018;36:595-598.
   The authors analyzed six years of vaccine uptake data for 3-month-olds from the National Immunization Survey and state-level National Vital Statistics SIDS reports and found vaccination coverage for routinely used childhood vaccines was not associated with an increased risk of SIDS.
2. Moro PL, Arana J, Cano M, Lewis P, Shimabukuro TT. Deaths reported to the Vaccine Adverse Event Reporting System, United States, 1997-2013. CID 2015;61:980-987.
   The authors examined deaths reported to VAERS in the United States during a 16-year period, with nearly half of the deaths attributed to SIDS. As with the previous 2001 study, SIDS reports progressively decreased over time, during

which the addition of seven-valent pneumococcal vaccine and rotavirus vaccine were added to the recommended vaccine schedule, and the DTaP-HepB-IPV combination vaccine was licensed for use.

3. Traversa G, Spila-Alegiani S, Bianchi C, Ciofi degli Atti M, Frova L, et al. Sudden unexpected deaths and vaccinations during the first two years of life in Italy: a case series study. PLoS ONE 2011;6(1):e16363.
   The authors found no increased risk for sudden unexplained death (SUD) and any vaccination in the time windows of 0-7 days or 0-14 days after vaccine receipt.
4. Vennemann, MMT, Butterfab-Bahloul T, Jorch G, et al. Sudden infant death syndrome: no increased risk after immunisation. Vaccine 2007;25: 336-340.
   The authors investigated the risk of SIDS with immunization in the first year of life, particularly with a hexavalent vaccine containing 15 different antigens. They found no increased risk of SIDS in the 14 days after immunization. As with previous studies, patients with SIDS were vaccinated less frequently and later than those infants without SIDS.
5. Eriksen EM, Perlman JA, Miller A, Marcy SM, Lee H, et al. Lack of association between hepatitis B birth immunization and neonatal death: A population-based study from the Vaccine Safety Datalink Project. Pediatr Infect Dis J 2004;23:656-661.
   The authors evaluated more than 360,000 births during a five-year period to determine if a correlation existed between hepatitis B vaccine receipt at birth and neonatal death. The authors found no relationship between hepatitis B vaccine receipt at birth and neonatal death, and the proportion of deaths from unexpected causes (e.g., SIDS) was not different between vaccinated and unvaccinated infants.
6. Fleming PJ, Blair PS, Platt MW, Tripp J, Smith IJ, et al. The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study. BMJ 2001;322:1-5.
   In the early 1990s, the schedule for routine infant immunizations in the United Kingdom was accelerated to give the vaccines at an earlier age. The authors found that the accelerated immunization program did not increase the risk of SIDS in a study population of 17.7 million infants. Immunization uptake was lowest among the infants who died from SIDS.
7. Jonville-Bera AP, Autret-Leca E, Barbeillon, Paris-Llado J and the French Reference Centers for SIDS. Sudden unexpected death in infants under 3 months of age and vaccination status – a case-control study. Br J Clin Pharmacol 2001;51:271-276.
   The authors conducted a two-year prospective study on the vaccination status of

infants with SIDS who died between 1 and 3 months of age to assess whether vaccination increased the risk of SIDS in this population in France. The authors found DTPP ± Hib immunization did not increase the risk of SIDS.

8. Silvers LE, Ellenberg SS, Wise RP, Varricchio FE, Mootrey GT, et al. The epidemiology of fatalities reported to the Vaccine Adverse Event Reporting System 1990-1997. Pharmacoepidemiol Drug Saf 2001; 279-285.
   The authors examined fatalities reported to VAERS in the United States during a seven-year period and found that reports peaked in 1992-1993 and then declined, with nearly half of the deaths attributed to SIDS. The trend in decreasing SIDS rates correlated with the 1992 American Academy of Pediatrics recommendation for infants to sleep on their side or back and the National Institute of Child Health and Human Development "Back to Sleep" campaign in 1994. The authors concluded that these data support findings of past controlled studies showing that the temporal association between infant vaccination and SIDS is coincidental and not causal.
9. Griffin MR, Ray WA, Livengood JR, Schaffner W. Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. New Engl J Med 1988;319(10):618-623.
   The authors evaluated recent immunization with DTP as a possible risk factor for SIDS during a 10-year period in Tennessee. They found no increase in the risk of SIDS after immunization with DTP vaccine and no correlation between SIDS and age at first immunization. Additionally, the rate of SIDS decreased in the first week after immunization.
10. Hoffman HJ, Hunter JC, Damus K, Pakter J, Peterson DR, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors. Pediatrics 1987;79:598-611.
    The authors investigated the possible association between diphtheria-tetanus-pertussis (DTP) immunization and subsequent occurrence of sudden infant death in the United States using data from a national SIDS epidemiological database. They found no temporal association between SIDS and DTP vaccine receipt. Infants with SIDS were less likely to have been immunized than infants without SIDS.
11. Keens TG, Davidson Ward SL, Gates EP, Andree DI, Hart LD. Ventilatory pattern following diphtheria-tetanus-pertussis immunization in infants at risk for sudden infant death syndrome. AJDC 1985;139:991-994.
    The authors evaluated the effects of DTP immunization on the ventilatory pattern

during sleep in infants at increased risk for SIDS, including those with unexplained apnea and those who were siblings of SIDS victims. Overnight pneumograms were recorded the night before and the night following DTP immunization. The authors found that DTP immunization did not increase abnormalities of the ventilatory pattern in infants at increased risk for SIDS.

Autism

Literature Reviews: Autism and Vaccines

1. Measles, Mumps, Rubella Vaccination and Autism: A Nationwide Cohort Study
   PDF available here
   Annals of Internal Medicine
   March 2019
   The study strongly supports that MMR vaccination does not increase the risk for autism, does not trigger autism in susceptible children, and is not associated with clustering of autism cases after vaccination. It adds to previous studies through significant additional statistical power and by addressing hypotheses of susceptible subgroups and clustering of cases.
2. Autism Occurrence by MMR Vaccine Status Among US Children With Older Siblings With and Without Autism
   http://jama.jamanetwork.com/article.aspx?articleid=2275444
   The Journal of the American Medical Association
   April 2015
   In this large sample of privately insured children with older siblings, receipt of the MMR vaccine was not associated with increased risk of ASD, regardless of whether older siblings had ASD. These findings indicate no harmful association between MMR vaccine receipt and ASD even among children already at higher risk for ASD.
3. Safety of Vaccines Used for Routine Immunization of U.S. Children: A Systematic Review
   http://www.ncbi.nlm.nih.gov/pubmed/25086160
   Pediatrics
   August 2014
   We found evidence that some vaccines are associated with serious AEs; however, these events are extremely rare and must be weighed against the protective benefits that vaccines provide.

4. Vaccines are Not Associated with Autism: An Evidence-Based Meta-Analysis of Case-Control and Cohort Studies
   http://www.ncbi.nlm.nih.gov/pubmed/24814559
   Vaccine
   June 2014
   Findings of this meta-analysis suggest that vaccinations are not associated with the development of autism or autism spectrum disorder. Furthermore, the components of the vaccines (thimerosal or mercury) or multiple vaccines (MMR) are not associated with the development of autism or autism spectrum disorder.
5. On-time Vaccine Receipt in the First Year Does Not Adversely Affect Neuropsychological Outcomes
   http://pediatrics.aappublications.org/cgi/content/abstract/125/6/1134
   Pediatrics
   Smith, M and Woods, C
   June 2010
   Timely vaccination during infancy has no adverse effect on neuropsychological outcomes 7 to 10 years later. These data may reassure parents who are concerned that children receive too many vaccines too soon.
6. Vaccines and Autism: A Tale of Shifting Hypotheses
   http://www.journals.uchicago.edu/doi/full/10.1086/596476
   Clinical Infectious Diseases
   Offit, Paul and Gerber, Jeffrey S.
   February 2009
   Twenty epidemiologic studies have shown that neither thimerosal nor MMR vaccine causes autism. These studies have been performed in several countries by many different investigators who have employed a multitude of epidemiologic and statistical methods. The large size of the studied populations has afforded a level of statistical power sufficient to detect even rare associations. These studies, in concert with the biological implausibility that vaccines overwhelm a child's immune system, have effectively dismissed the notion that vaccines cause autism. Further studies on the cause or causes of autism should focus on more-promising leads.
7. Immunization Safety Review: Vaccines and Autism
   http://www.iom.edu/reports/2004/immunization-safety-review-vaccines-and-autism.aspx
   Institute of Medicine
   May 2004

8. Adverse Effects of Pertussis and Rubella Vaccines: A Report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines
   http://www.nap.edu/catalog/1815/adverse-effects-of-pertussis-and-rubella-vaccines
   Institute of Medicine
   1991

Too Many Too Soon?

9. Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?
   http://pediatrics.aappublications.org/cgi/content/full/109/1/124
   Pediatrics
   Offit, Paul A., Quarles, Jessica, et al.
   2002
   Current studies do not support the hypothesis that multiple vaccines overwhelm, weaken, or "use up" the immune system. On the contrary, young infants have an enormous capacity to respond to multiple vaccines, as well as to the many other challenges present in the environment. By providing protection against a number of bacterial and viral pathogens, vaccines prevent the "weakening" of the immune system and consequent secondary bacterial infections occasionally caused by natural infection.
10. Immunization Safety Review: Multiple Immunizations and Immune Dysfunction
    http://www.iom.edu/reports/2002/immunization-safety-review-multiple-immunizations-and-immune-dysfunction.aspx
    Institute of Medicine
    February 2002
11. Cellular Immune Responses in Neonates
    http://www.ncbi.nlm.nih.gov/pubmed/10763708
    International Reviews of Immunology
    Fadel S, Sarazotti M.
    2000
12. Neonatal and Early Life Vaccinology
    http://www.ncbi.nlm.nih.gov/pubmed/11348697
    Vaccine
    Siegrist CA.
    2001
13. The Problem with Dr. Bob's Alternative Vaccine Schedule
    http://pediatrics.aappublications.org/content/123/1/e164.abstract

Pediatrics
Offit, Paul A. and Moser, Charlotte A.
January 2009

Thimerosal and Autism Studies

14. Neuropsychological performance 10 years after immunization in infancy with thimerosal-containing vaccines.
    https://pediatrics.aappublications.org/content/123/2/475?
    Pediatrics
    Tozzi AE, Bisiacchi P, Tarantino V, De Mei B, D'Elia L, Chariotti F, Salmaso S.
    January 2009
    Given the large number of statistical comparisons performed, the few associations found between thimerosal exposure and neuropsychological development might be attributable to chance. The associations found, although statistically significant, were based on small differences in mean test scores, and their clinical relevance remains to be determined.
15. Continuing Increases in Autism Reported to California's Developmental Services System
    http://archpsyc.ama-assn.org/cgi/content/full/65/1/19
    Archives of General Psychiatry
    Robert Schechter, MD, MSc and Judith K. Grether, PhD
    January 2008
    The DDS data do not show any recent decrease in autism in California despite the exclusion of more than trace levels of thimerosal from nearly all childhood vaccines. The DDS data do not support the hypothesis that exposure to thimerosal during childhood is a primary cause of autism.
16. Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years
    http://content.nejm.org/cgi/content/full/357/13/1281
    New England Journal of Medicine
    Thompson WW, Price C, Goodson B, et al.
    September 2007
17. Lack of Association Between Rh Status, Rh Immune Globulin in Pregnancy and Autism
    http://www3.interscience.wiley.com/cgi-bin/abstract/114264055/ABSTRACT
    American Journal of Medical Genetics
    Judith H. Miles and T. Nicole Takahashi
    May 2007

18. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16079072&query_hl=1
Environmental Health Perspectives
Thomas M. Burbacher, PhD
April 2005
The results indicate that MeHg is not a suitable reference for risk assessment from exposure to thimerosal-derived Hg. Knowledge of the toxicokinetics and developmental toxicity of thimerosal is needed to afford a meaningful assessment of the developmental effects of thimerosal-containing vaccines.
19. Thimerosal Exposure in Infants and Developmental Disorders: A Prospective Cohort Study in the United Kingdom Does Not Support a Causal Association
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15342824&query_hl=5
Pediatrics
John Heron and Nick Andrews, PhD and Jean Golding, DSc
September 2004
We could find no convincing evidence that early exposure to thimerosal had any deleterious effect on neurologic or psychological outcome.
20. Neurotoxic Effects of Postnatal Thimerosal Are Mouse Strain Dependent
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15184908&query_hl=10
Molecular Psychiatry
M Hornig, M
June 2004
21. Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Database
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14595043&query_hl=59
Pediatrics
Thomas Verstraeten, MD
November 2003
No consistent significant associations were found between TCVs and neurodevelopmental outcomes. Conflicting results were found at different HMOs for certain outcomes. For resolving the conflicting findings, studies with uniform

neurodevelopmental assessments of children with a range of cumulative thimerosal exposures are needed.

22. Association Between Thimerosal-Containing Vaccine and Autism
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14519711&query_hl=16
    Journal of the American Medical Association
    Anders Hviid, MSc
    October 2003
    The results do not support a causal relationship between childhood vaccination with thimerosal-containing vaccines and development of autistic-spectrum disorders.
23. Thimerosal and the Occurrence of Autism: Negative Ecological Evidence from Danish Population-Based Data
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15496004&query_hl=19
    Pediatrics
    Kreesten M. Madsen, MD
    September 2003
24. "Autism and Thimerosal-Containing Vaccines: Lack of Consistent Evidence for an Association"
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12880876&query_hl=21
    American Journal of Preventive Medicine
    Paul Stehr-Green, DrPh, MPH
    August 2003
    The body of existing data, including the ecologic data presented herein, is not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines is responsible for the apparent increase in the rates of autism in young children being observed worldwide.
25. Thimerosal and Autism?
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12612255&query_hl=22
    Pediatrics
    Karen Nelson, MD
    March 2003
26. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: A descriptive study

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12480426&query_hl=30
The Lancet
Michael Pichichero, MD
November 2002
Administration of vaccines containing thiomersal does not seem to raise blood concentrations of mercury above safe values in infants. Ethylmercury seems to be eliminated from blood rapidly via the stools after parenteral administration of thiomersal in vaccines.

Measles-Mumps-Rubella (MMR) Vaccine and Autism Studies

27. Examination of the Safety of Pediatric Vaccine Schedules in a Non-Human Primate Model: Assessments of Neurodevelopment, Learning, and Social Behavior
    http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2015/2/ehp.1408257.acco.pdf
    Environmental Health Perspectives
    February 2015
28. Early Exposure to the Combined Measles-Mumps-Rubella Vaccine and Thimerosal-Containing Vaccines and Risk of Autism Spectrum Disorder
    http://www.ncbi.nlm.nih.gov/pubmed/25562790
    Vaccine
    January 3, 2015
    No convincing evidence was found in this study that MMR vaccination and increasing thimerosal dose were associated with an increased risk of ASD onset.
29. Lack of Association Between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study
    http://www.plosone.org/article/info%3Adoi/10.1371/journal.pone.0003140
    PLoS One
    Hornig M, Briese T, Buie T, Bauman ML, Lauwers G, et al.
    September 2008
    This study provides strong evidence against association of autism with persistent MV RNA in the GI tract or MMR exposure. Autism with GI disturbances is associated with elevated rates of regression in language or other skills and may represent an endophenotype distinct from other ASD.
30. Measles Vaccination and Antibody Response in Autism Spectrum Disorders
    https://adc.bmj.com/content/93/10/832.abstract?
    Archives of Disease in Childhood

Gillian Baird, F.R.C.Paed.
February 2008
No association between measles vaccination and ASD was shown.

31. Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16818529&query_hl=2&itool=pubmed_docsum
Pediatrics
Eric Fombonne, MD
July 2006
The prevalence of pervasive developmental disorder in Montreal was high, increasing in recent birth cohorts as found in most countries. Factors accounting for the increase include a broadening of diagnostic concepts and criteria, increased awareness and, therefore, better identification of children with pervasive developmental disorders in communities and epidemiologic surveys, and improved access to services. The findings ruled out an association between pervasive developmental disorder and either high levels of ethylmercury exposure comparable with those experienced in the United States in the 1990s or 1- or 2-dose measles-mumps-rubella vaccinations.
32. MMR Vaccination and Pervasive Developmental Disorders: A Case-Control Study
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15364187&query_hl=38
The Lancet
Liam Smeeth, MRCGP
September 11, 2004
Our findings suggest that MMR vaccination is not associated with an increased risk of pervasive developmental disorders.
33. Association of Autistic Spectrum Disorder and the Measles, Mumps, and Rubella Vaccine
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12860782&query_hl=40
Archives of Pediatrics & Adolescent Medicine
Kumanan Wilson, MD, MSc, FRCP
July 2003
The current literature does not suggest an association between ASD and the MMR vaccine; however, limited epidemiological evidence exists to rule out a link between a rare variant form of ASD and the MMR vaccine. Given the real risks of

not vaccinating and that the risks and existence of variant ASD remain theoretical, current policies should continue to advocate the use of the MMR vaccine.

34. Neurologic Disorders After Measles-Mumps-Rubella Vaccination
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12415036&query_hl=64
    Pediatrics
    Annamari Makela, MD
    November 2002
    We did not identify any association between MMR vaccination and encephalitis, aseptic meningitis, or autism.
35. No Evidence for a New Variant of Measles-Mumps-Rubella-Induced Autism
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11581466&query_hl=66
    Pediatrics
    Eric Fombonne, FRCPsych
    October 2001
    No evidence was found to support a distinct syndrome of MMR-induced autism or of "autistic enterocolitis." These results add to the recent accumulation of large-scale epidemiologic studies that all failed to support an association between MMR and autism at population level. When combined, the current findings do not argue for changes in current immunization programs and recommendations.

Dear Chairman Weisz and Members of the Human Services Committee,

My name is Paul Carson. I am a physician who specializes in the area of infectious diseases, and am a Professor at North Dakota State University in the Dept. of Public Health, where I am the Medical Director of the Center for Immunization Research and Education. However, my comments today are not on behalf of NDSU.

I am testifying today in opposition to HB 1306 as I believe it is unnecessary, and would be a misuse of ND taxpayer money.

What I want to briefly address with you today, is how do we as scientists establish that something causes something else, in particular, how do we establish that something we do (e.g. receive a vaccine) may cause something bad to happen (e.g. autism or SIDS)? This is more difficult than you might think, as it is often very hard to separate out the item in question, (e.g. vaccines) from all the other things that could influence a particular outcome. We use what is called the "hierarchy of evidence", which assigns studies to a level based on the quality of their results obtained from research.

To illustrate this, I'm going to use a few examples.

Let me start with a brief, true story that was written about and published. It concerns a young physician in PA, who decided to bring his 8-month-old son to a big flu blitz clinic for his first flu shot. He stood in a long line, and it was late in the afternoon, and after a while, he decided the wait was too long, so he decided to put it off for another day. Tragically, his son died of SIDS that night. This physician then realized had he completed his mission of getting his son vaccinated that day, and observed the tragedy of his son's death that night, almost nothing would have shaken him from the belief that the vaccine caused his son's death. And this would have been a completely fair, reasonable, and understandable conclusion. But of course, had he done that, his conclusion would have been completely wrong. This story illustrates what we call the lowest level of evidence, anecdotal observation. It is compelling, but by its very nature, it is anecdotal and prone to error.

The idea that vaccines may cause problems like autism and SIDS, gained traction with the publication of a paper in 1998 by a British researcher named Andrew Wakefield. In that paper he speculated a possible connection between autism and the receipt of the MMR vaccine. The paper had seismic effects, which now ripple outward even to this committee decades later. His study was a very small case-series of only 8 children, a little better than anecdotal data, but in the research world, still considered pretty weak. To make matters worse, his research was subsequently found by an investigative reporter to have falsified data, not gotten proper research approval, and did not disclose major financial conflicts of interest. His co-researchers asked to be removed from the paper, the paper was eventually retracted, and the physician lost his medical license over the debacle.

The next level up in research quality is what we call ecological studies. These are studies that compare populations overall, e.g. "countries that give more vaccines tend to have higher rates of autism". But you do not need to be a research scientist to recognize that there might be all kinds of other reasons for that association (like, countries that give more vaccines might have more sophisticated surveillance for problems like autism). And we don't give vaccines to countries or populations overall, we give them to individuals. The example I teach in my class is the very real observation that rising autism rates have

very closely paralleled rising sales in organic foods. Frankly a much tighter correlation than with vaccines. But this lacks biologic plausibility, another thing we look for when trying to establish causality.

Anecdotal cases, case series, and ecological studies are all useful in that they can raise questions, but they do not answer the question. The question this bill seeks to answer has been raised already, numerous times, and it has been addressed by doing the hard and costly work of much higher quality research… those with a control group. It is imperative to look at studies with control groups, to see if the variable in question (vaccines) causes more problems than in a control group that does not receive that exposure. And this has already been done….. a lot!

The Cochrane group is an objective, non-conflicted, multi-national research group that uses the highest standards of evidence-based medicine to review a number of controversial health topics. They have reviewed this issue on several occasions, most recently last year, and collected and summarized 138 studies involving over 23 million children worldwide, the vast majority being case-control, and prospective cohort studies (the best study designs we have short of RCTs), and have found no evidence of any connection with MMR or Varicella vaccines and autism. Here is their summary infographic: https://www.cochrane.org/sites/default/files/public/uploads/mrrvaccvisabs_final_-_all_slides_pdf.pdf Similar reviews have been done on studies looking at the association with vaccines and SIDS, almost all showing either no association, or an actual decline in SIDS in association with vaccination.

It would be very difficult for North Dakota to be able to make a meaningful contribution to this research given our size and ability to fund anything close to the scale of what has already been done. Given the enormous amount of high-quality research that has already been conducted on this issue, and the growing knowledge of what are much more plausible explanations for these conditions, please vote no on using ND tax dollars to do this unnecessary study.

The idea that autism is caused by vaccines has been proven again and again by scientific studies. This information is widely and easily available.

More importantly, the diseases that we vaccinate against are deadly. A world without vaccines is a world with a lower childhood survival rate. It is irresponsible to chase after imaginary risks when doing so introduces real ones.

This bill assumes that it is better to be dead than to be autistic. As a teacher who works with many autistic teenagers, I can assure you this is not the case. Many people with autism contribute their community in valuable ways. Autistic people are responsible for many of the advances in society, and our world would be poorer without them. Even those individuals who are not able to contribute in tangible ways deserve to live, because every human being has worth. This bill is ableist.

My name is Melyssa Howry, and I am a resident of New Town, North Dakota. I am testifying in support of HB1306. It has long been said that vaccines are “safe and effective” and that the “science is settled”. This is commonly proclaimed without real data, because in this case, the truth would be an inconvenient one. Doctors and scientists have been willing to risk their reputations in order to seek the truth. Recently, Dr. Paul Thomas conducted two studies in his practice of over 15,000 patients comparing vaccinated children to unvaccinated children. Because of his honesty and transparency, the Oregon medical board has sought to censor him and has called him “anti-vaccine”, even though that is untrue. He administers vaccines at his practice, which is why he is able to do a comparative study. He does encourage a slower, more spread out schedule than what the CDC recommends, but he still advocates in favor of vaccines. This tells me that it is worth looking into. I have attached links that describe both studies that Paul Thomas has done. I think they speak for themselves. The evidence is overwhelming, and I believe that we are long overdue for an investigation into these uncomfortable, and yet extremely important discussions. Are we causing harm while trying to prevent it? Do the risks of vaccines outweigh the benefits? We will never know if we do not do the work. There needs to be transparency, accountability, and honesty in regards to vaccines. As we have seen over the past year, we cannot always trust government agencies to tell us the truth about what is best for our health. We must advocate for ourselves, and this is an important way to do just that. Thank you for reading!

1) https://childrenshealthdefense.org/news/real-life-data-show-that-the-cdc-vaccine-schedule-is-causing-harm/

2) https://childrenshealthdefense.org/defender/unvaccinated-children-healthier-than-vaccinated-children/

Biotechnology Innovation Organization

January 19, 2021

Representative Karen M. Rohr
Chair, Human Services Committee
North Dakota Legislative Assembly
600 East Boulevard
Bismarck, ND 58505

Senator Judy Lee
Vice Chair, Human Services Committee
North Dakota Legislative Assembly
600 East Boulevard
Bismarck, ND 58505

Dear Chair Rohr, Vice Chair Lee, and Members of the Human Services Committee,

I am writing today on behalf of the Biotechnology Innovation Organization (BIO), a national trade association for the biotechnology industry, representing over 900 companies and academic institutions involved in the research and development of innovative healthcare, agriculture, industrial, and environmental biotechnology products. BIO membership includes vaccine developers and manufacturers who have worked closely with the public health community to support policies that help ensure access to innovation and life-saving vaccines for all individuals.

BIO and our member companies would like to express our **opposition to HB 1306, HB 1307, and HB 1320**, as these bills put North Dakotans at risk of preventable diseases.

Legislative efforts related to vaccines should focus on continuing to extend protection from these diseases and their side effects to all North Dakotans. The Legislature serves a critical function in passing laws to protect the people of North Dakota. Decisions to change the immunization laws should be held to high standards of evidence-based scientific deliberation. Prohibiting the State, employers, and schools from implementing any immunization requirements will have a detrimental effect on public health in North Dakota, particularly in the middle of a pandemic. North Dakota has experienced a high toll from the COVID-19 pandemic, particularly when cases spiked to a 16% positivity rate in November and December.[1] As COVID-19 vaccination begins and there is hopefully an end to the pandemic coming soon, we must remain vigilant against other infectious diseases. Removal of vaccine requirements risks outbreaks of measles,

[1] https://www.health.nd.gov/diseases-conditions/coronavirus/north-dakota-coronavirus-cases

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6301 F
bio.org

pertussis, and influenza. Such outbreaks put lives at risk and are accompanied by great economic costs to the State[2] and society.[3]

HB 1305 is based upon false claims that vaccines are linked to sudden infant death syndrome (SIDS) and autism spectrum disorder (ASD). Potential links between vaccines and these conditions have been extensively studied, with no association found. In fact, studies have found that immunization may have a *protective* impact against SIDS. A metanalysis of existing research in 2007 found that immunizations were associated with *halving* the risk of SIDS.[4] Similarly, a 2001 study in the United Kingdom found immunization lowered the odds of SIDS[5] and a 1995 study in New Zealand found unimmunized infants had a higher risk of SIDS[6]. Additionally, more than nine studies have been conducted to investigate any possible connection between vaccines and ASD, all finding no association.[7] Thimerosal, the vaccine preservative alleged to cause autism was removed from all pediatric vaccines between 1999 and 2001, yet autism rates continue to rise.[8] Rather than continuing to look for a connection to vaccines, research should be done investigating the actual causes of these conditions.

HB 1307 and HB 1320 would restrict the ability of employers and schools to implement vaccination requirements. North Dakota's school entry requirements allow for freedom of choice by offering exemptions based upon personal beliefs. However, the choice to delay or reject some vaccines entirely is not just a personal decision. When we choose to not receive vaccines or vaccinate our children, we put ourselves and others in our community at risk for serious disease. Putting others, such as those who are immunocompromised or too young to receive vaccines, at risk for vaccine-preventable disease arguably presents a challenge to their personal freedom to go to the store, to school, or anywhere else they come into contact with their community without the possibility of contracting a dangerous, preventable illness. All North Dakotans deserve the right to freedom from preventable infectious diseases.

Individuals understandably have concerns about the unprecedented pace of development of COVID-19 vaccines. Time has been saved through prioritization of resources toward COVID-19, novel technologies that have been more efficient, public-private collaboration, and clinical trial phases happening in parallel rather than in sequence. These vaccines enrolled the same number of individuals in clinical trials as trials for other vaccines and the FDA and CDC have maintained their high standards. Therefore, individuals should be confident that there have not been shortcuts in testing

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[2] https://www.cdc.gov/mmwr/volumes/66/wr/mm6646a3.htm
[3] https://www.worldbank.org/en/news/feature/2020/06/08/the-global-economic-outlook-during-the-covid-19-pandemic-a-changed-world#:~:text=Businesses%20might%20find%20it%20hard,by%20almost%208%25%20in%202020
[4] https://www.ncbi.nlm.nih.gov/pubmed/17400342
[5] https://www.bmj.com/content/322/7290/822.short
[6] https://adc.bmj.com/content/73/6/498
[7] https://www.cdc.gov/vaccinesafety/pdf/cdcstudiesonvaccinesandautism.pdf
[8] https://www.cdc.gov/vaccinesafety/concerns/autism.html

the safety and efficacy of these vaccines and such concerns should not lead to overreaching policies that impact the use of all vaccines.

Vaccinations have led to steep decreases and eradication of many significant infectious diseases such as polio, measles, mumps, pertussis, and haemophilus influenza type B (Hib). Immunizations are our best protection against preventable disease and can help North Dakotans live longer, healthier lives.

BIO and our member companies urge the Committee to oppose HB 1306, HB 1307, and HB 1320. We stand ready to help in any discussion of legislation to strengthen immunizations and to share our knowledge of activities and initiatives from around the country.

Sincerely,

/s/

John Gregory Hoke

Director, State Government Affairs

cc: Rep. Jeff A. Hoverson
Rep. Dwight Kiefert
Rep. Lisa Meier
Rep. Matthew Ruby
Rep. Mary Schneider
Rep. Kathy Skroch
Rep. Bill Tveit
Rep. Greg Westlind
Sen. JoNell A. Bakke
Sen. Dick Dever
Sen. Kathy Hogan
Sen. Tim Mathern
Sen. Jessica Unruh-Bell

I am writing in opposition of HB 1306, which seeks “a legislative management study” of the “interrelationship between Sudden Infant Death Syndrome (SIDS), autism and vaccines.

I’m not sure where the sponsors of this bill have been for the last 15 years or so, but there is a distinct lack of scholarly, peer-reviewed evidence for this theory. Even a simple Google search will turn up references to hundreds of studies —world-wide, with thousands of subjects, peer reviewed, published in reputable publications—that refute the idea that vaccines are in any way linked to autism and SIDS.

Why is the current legislature so ignorant of established scientific theory? I expect more from my elected representatives than a pandering to junk science.

Jan Macdonald Russell

NORTH Dakota | Health
Be Legendary.™

House Bill 1306
Industry, Business and Labor
January 19, 2021, 2:45 p.m.

Good Morning Chairman Weisz and members of the House Human Services Committee. My name is Molly Howell and I am the Immunization Director of for the North Dakota Department of Health. I do not have testimony for HB1306 but want to let you know I am available virtually to answer questions, if needed. Additionally, attached is a list of studies that have been previously published regarding vaccines, autism and SIDS. Thank You.

NORTH Dakota | Health
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Vaccine-Related Science: Autism and SIDS

No Causal Association Found

Autism

Literature Reviews: Autism and Vaccines

1. Measles, Mumps, Rubella Vaccination and Autism: A Nationwide Cohort Study
   PDF available here
   Annals of Internal Medicine
   March 2019
   The study strongly supports that MMR vaccination does not increase the risk for autism, does not trigger autism in susceptible children, and is not associated with clustering of autism cases after vaccination. It adds to previous studies through significant additional statistical power and by addressing hypotheses of susceptible subgroups and clustering of cases.
2. Autism Occurrence by MMR Vaccine Status Among US Children With Older Siblings With and Without Autism
   http://jama.jamanetwork.com/article.aspx?articleid=2275444
   The Journal of the American Medical Association
   April 2015
   In this large sample of privately insured children with older siblings, receipt of the MMR vaccine was not associated with increased risk of ASD, regardless of whether older siblings had ASD. These findings indicate no harmful association between MMR vaccine receipt and ASD even among children already at higher risk for ASD.
3. Safety of Vaccines Used for Routine Immunization of U.S. Children: A Systematic Review
   http://www.ncbi.nlm.nih.gov/pubmed/25086160
   Pediatrics
   August 2014
   We found evidence that some vaccines are associated with serious AEs; however, these events are extremely rare and must be weighed against the protective benefits that vaccines provide.
4. Vaccines are Not Associated with Autism: An Evidence-Based Meta-Analysis of Case-Control and Cohort Studies

http://www.ncbi.nlm.nih.gov/pubmed/24814559
Vaccine
June 2014
Findings of this meta-analysis suggest that vaccinations are not associated with the development of autism or autism spectrum disorder. Furthermore, the components of the vaccines (thimerosal or mercury) or multiple vaccines (MMR) are not associated with the development of autism or autism spectrum disorder.

5. On-time Vaccine Receipt in the First Year Does Not Adversely Affect Neuropsychological Outcomes
   http://pediatrics.aappublications.org/cgi/content/abstract/125/6/1134
   Pediatrics
   Smith, M and Woods, C
   June 2010
   Timely vaccination during infancy has no adverse effect on neuropsychological outcomes 7 to 10 years later. These data may reassure parents who are concerned that children receive too many vaccines too soon.
6. Vaccines and Autism: A Tale of Shifting Hypotheses
   http://www.journals.uchicago.edu/doi/full/10.1086/596476
   Clinical Infectious Diseases
   Offit, Paul and Gerber, Jeffrey S.
   February 2009
   Twenty epidemiologic studies have shown that neither thimerosal nor MMR vaccine causes autism. These studies have been performed in several countries by many different investigators who have employed a multitude of epidemiologic and statistical methods. The large size of the studied populations has afforded a level of statistical power sufficient to detect even rare associations. These studies, in concert with the biological implausibility that vaccines overwhelm a child's immune system, have effectively dismissed the notion that vaccines cause autism. Further studies on the cause or causes of autism should focus on more-promising leads.
7. Immunization Safety Review: Vaccines and Autism
   http://www.iom.edu/reports/2004/immunization-safety-review-vaccines-and-autism.aspx
   Institute of Medicine
   May 2004

8. Adverse Effects of Pertussis and Rubella Vaccines: A Report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines
http://www.nap.edu/catalog/1815/adverse-effects-of-pertussis-and-rubella-vaccines
Institute of Medicine
1991

Too Many Too Soon?

9. Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?
http://pediatrics.aappublications.org/cgi/content/full/109/1/124
Pediatrics
Offit, Paul A., Quarles, Jessica, et al.
2002
Current studies do not support the hypothesis that multiple vaccines overwhelm, weaken, or "use up" the immune system. On the contrary, young infants have an enormous capacity to respond to multiple vaccines, as well as to the many other challenges present in the environment. By providing protection against a number of bacterial and viral pathogens, vaccines prevent the "weakening" of the immune system and consequent secondary bacterial infections occasionally caused by natural infection.
10. Immunization Safety Review: Multiple Immunizations and Immune Dysfunction
http://www.iom.edu/reports/2002/immunization-safety-review-multiple-immunizations-and-immune-dysfunction.aspx
Institute of Medicine
February 2002
11. Cellular Immune Responses in Neonates
http://www.ncbi.nlm.nih.gov/pubmed/10763708
International Reviews of Immunology
Fadel S, Sarazotti M.
2000
12. Neonatal and Early Life Vaccinology
http://www.ncbi.nlm.nih.gov/pubmed/11348697
Vaccine

Siegrist CA.
2001

13. The Problem with Dr. Bob's Alternative Vaccine Schedule
    http://pediatrics.aappublications.org/content/123/1/e164.abstract
    Pediatrics
    Offit, Paul A. and Moser, Charlotte A.
    January 2009

Thimerosal and Autism Studies

14. Neuropsychological performance 10 years after immunization in infancy with thimerosal-containing vaccines.
    https://pediatrics.aappublications.org/content/123/2/475?
    Pediatrics
    Tozzi AE, Bisiacchi P, Tarantino V, De Mei B, D'Elia L, Chariotti F, Salmaso S.
    January 2009
    Given the large number of statistical comparisons performed, the few associations found between thimerosal exposure and neuropsychological development might be attributable to chance. The associations found, although statistically significant, were based on small differences in mean test scores, and their clinical relevance remains to be determined.
15. Continuing Increases in Autism Reported to California's Developmental Services System
    http://archpsyc.ama-assn.org/cgi/content/full/65/1/19
    Archives of General Psychiatry
    Robert Schechter, MD, MSc and Judith K. Grether, PhD
    January 2008
    The DDS data do not show any recent decrease in autism in California despite the exclusion of more than trace levels of thimerosal from nearly all childhood vaccines. The DDS data do not support the hypothesis that exposure to thimerosal during childhood is a primary cause of autism.
16. Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years
    http://content.nejm.org/cgi/content/full/357/13/1281
    New England Journal of Medicine
    Thompson WW, Price C, Goodson B, et al.
    September 2007

17. Lack of Association Between Rh Status, Rh Immune Globulin in Pregnancy and Autism
    http://www3.interscience.wiley.com/cgi-bin/abstract/114264055/ABSTRACT
    American Journal of Medical Genetics
    Judith H. Miles and T. Nicole Takahashi
    May 2007
18. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16079072&query_hl=1
    Environmental Health Perspectives
    Thomas M. Burbacher, PhD
    April 2005
    The results indicate that MeHg is not a suitable reference for risk assessment from exposure to thimerosal-derived Hg. Knowledge of the toxicokinetics and developmental toxicity of thimerosal is needed to afford a meaningful assessment of the developmental effects of thimerosal-containing vaccines.
19. Thimerosal Exposure in Infants and Developmental Disorders: A Prospective Cohort Study in the United Kingdom Does Not Support a Causal Association
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15342824&query_hl=5
    Pediatrics
    John Heron and Nick Andrews, PhD and Jean Golding, DSc
    September 2004
    We could find no convincing evidence that early exposure to thimerosal had any deleterious effect on neurologic or psychological outcome.
20. Neurotoxic Effects of Postnatal Thimerosal Are Mouse Strain Dependent
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15184908&query_hl=10
    Molecular Psychiatry
    M Hornig, M
    June 2004
21. Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Database
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dop

t=Abstract&list_uids=14595043&query_hl=59
Pediatrics
Thomas Verstraeten, MD
November 2003
No consistent significant associations were found between TCVs and neurodevelopmental outcomes. Conflicting results were found at different HMOs for certain outcomes. For resolving the conflicting findings, studies with uniform neurodevelopmental assessments of children with a range of cumulative thimerosal exposures are needed.

22. Association Between Thimerosal-Containing Vaccine and Autism
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14519711&query_hl=16
Journal of the American Medical Association
Anders Hviid, MSc
October 2003
The results do not support a causal relationship between childhood vaccination with thimerosal-containing vaccines and development of autistic-spectrum disorders.
23. Thimerosal and the Occurrence of Autism: Negative Ecological Evidence from Danish Population-Based Data
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15496004&query_hl=19
Pediatrics
Kreesten M. Madsen, MD
September 2003
24. "Autism and Thimerosal-Containing Vaccines: Lack of Consistent Evidence for an Association"
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12880876&query_hl=21
American Journal of Preventive Medicine
Paul Stehr-Green, DrPh, MPH
August 2003
The body of existing data, including the ecologic data presented herein, is not consistent with the hypothesis that increased exposure to Thimerosal-containing

vaccines is responsible for the apparent increase in the rates of autism in young children being observed worldwide.

25. Thimerosal and Autism?
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12612255&query_hl=22
    Pediatrics
    Karen Nelson, MD
    March 2003
26. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: A descriptive study
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12480426&query_hl=30
    The Lancet
    Michael Pichichero, MD
    November 2002
    Administration of vaccines containing thiomersal does not seem to raise blood concentrations of mercury above safe values in infants. Ethylmercury seems to be eliminated from blood rapidly via the stools after parenteral administration of thiomersal in vaccines.

Measles-Mumps-Rubella (MMR) Vaccine and Autism Studies

27. Examination of the Safety of Pediatric Vaccine Schedules in a Non-Human Primate Model: Assessments of Neurodevelopment, Learning, and Social Behavior
    http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2015/2/ehp.1408257.acco.pdf
    Environmental Health Perspectives
    February 2015
28. Early Exposure to the Combined Measles-Mumps-Rubella Vaccine and Thimerosal-Containing Vaccines and Risk of Autism Spectrum Disorder
    http://www.ncbi.nlm.nih.gov/pubmed/25562790
    Vaccine
    January 3, 2015
    No convincing evidence was found in this study that MMR vaccination and increasing thimerosal dose were associated with an increased risk of ASD onset.

29. Lack of Association Between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study
http://www.plosone.org/article/info%3Adoi/10.1371/journal.pone.0003140
PLoS One
Hornig M, Briese T, Buie T, Bauman ML, Lauwers G, et al.
September 2008
This study provides strong evidence against association of autism with persistent MV RNA in the GI tract or MMR exposure. Autism with GI disturbances is associated with elevated rates of regression in language or other skills and may represent an endophenotype distinct from other ASD.
30. Measles Vaccination and Antibody Response in Autism Spectrum Disorders
https://adc.bmj.com/content/93/10/832.abstract?
Archives of Disease in Childhood
Gillian Baird, F.R.C.Paed.
February 2008
No association between measles vaccination and ASD was shown.
31. Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16818529&query_hl=2&itool=pubmed_docsum
Pediatrics
Eric Fombonne, MD
July 2006
The prevalence of pervasive developmental disorder in Montreal was high, increasing in recent birth cohorts as found in most countries. Factors accounting for the increase include a broadening of diagnostic concepts and criteria, increased awareness and, therefore, better identification of children with pervasive developmental disorders in communities and epidemiologic surveys, and improved access to services. The findings ruled out an association between pervasive developmental disorder and either high levels of ethylmercury exposure comparable with those experienced in the United States in the 1990s or 1- or 2-dose measles-mumps-rubella vaccinations.
32. MMR Vaccination and Pervasive Developmental Disorders: A Case-Control Study
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15364187&query_hl=38

The Lancet
Liam Smeeth, MRCGP
September 11, 2004
Our findings suggest that MMR vaccination is not associated with an increased risk of pervasive developmental disorders.

33. Association of Autistic Spectrum Disorder and the Measles, Mumps, and Rubella Vaccine
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12860782&query_hl=40
Archives of Pediatrics & Adolescent Medicine
Kumanan Wilson, MD, MSc, FRCP
July 2003
The current literature does not suggest an association between ASD and the MMR vaccine; however, limited epidemiological evidence exists to rule out a link between a rare variant form of ASD and the MMR vaccine. Given the real risks of not vaccinating and that the risks and existence of variant ASD remain theoretical, current policies should continue to advocate the use of the MMR vaccine.
34. Neurologic Disorders After Measles-Mumps-Rubella Vaccination
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12415036&query_hl=64
Pediatrics
Annamari Makela, MD
November 2002
We did not identify any association between MMR vaccination and encephalitis, aseptic meningitis, or autism.
35. No Evidence for a New Variant of Measles-Mumps-Rubella-Induced Autism
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11581466&query_hl=66
Pediatrics
Eric Fombonne, FRCPsych
October 2001
No evidence was found to support a distinct syndrome of MMR-induced autism or of "autistic enterocolitis." These results add to the recent accumulation of large-scale epidemiologic studies that all failed to support an association between MMR and autism at population level. When combined, the current

findings do not argue for changes in current immunization programs and recommendations.

36. Vaccines for Measles, Mumps, rubella and varicella in children
    Vaccines for measles, mumps, rubella, and varicella in children - Di Pietrantonj, C - 2020 | Cochrane Library
    Cochrane Review
    Di Pietrantonj, C, et al.
    April 2020
    This study assessed currently available literature and analyzed the evidence regarding how effective MMR, MMR+V and MMRV vaccines are and if they cause unwanted effects. They found 138 studies with more than 23 million children to analyze. Overall, the studies found that MMR, MMRV, and MMR+V vaccine did not cause autism (2 studies 1,194,764 children). Our review shows that MMR, MMRV and MMR+V vaccines are effective in preventing the infection of children by measles, mumps, rubella and chickenpox, with no evidence of an increased risk of autism or encephalitis and a small risk of febrile seizure.

Vaccines and SIDS

1. Yang YT and Shaw J. Sudden infant death syndrome, attention-deficit/hyperactivity disorder and vaccines: longitudinal population analyses. Vaccine 2018;36:595-598.
   The authors analyzed six years of vaccine uptake data for 3-month-olds from the National Immunization Survey and state-level National Vital Statistics SIDS reports and found vaccination coverage for routinely used childhood vaccines was not associated with an increased risk of SIDS.
2. Moro PL, Arana J, Cano M, Lewis P, Shimabukuro TT. Deaths reported to the Vaccine Adverse Event Reporting System, United States, 1997-2013. CID 2015;61:980-987.
   The authors examined deaths reported to VAERS in the United States during a 16-year period, with nearly half of the deaths attributed to SIDS. As with the previous 2001 study, SIDS reports progressively decreased over time, during which the addition of seven-valent pneumococcal vaccine and rotavirus vaccine were added to the recommended vaccine schedule, and the DTaP-HepB-IPV combination vaccine was licensed for use.

3. Traversa G, Spila-Alegiani S, Bianchi C, Ciofi degli Atti M, Frova L, et al. Sudden unexpected deaths and vaccinations during the first two years of life in Italy: a case series study. PLoS ONE 2011;6(1):e16363.
The authors found no increased risk for sudden unexplained death (SUD) and any vaccination in the time windows of 0-7 days or 0-14 days after vaccine receipt.
4. Vennemann, MMT, Butterfab-Bahloul T, Jorch G, et al. Sudden infant death syndrome: no increased risk after immunisation. Vaccine 2007;25: 336-340.
The authors investigated the risk of SIDS with immunization in the first year of life, particularly with a hexavalent vaccine containing 15 different antigens. They found no increased risk of SIDS in the 14 days after immunization. As with previous studies, patients with SIDS were vaccinated less frequently and later than those infants without SIDS.
5. Eriksen EM, Perlman JA, Miller A, Marcy SM, Lee H, et al. Lack of association between hepatitis B birth immunization and neonatal death: A population-based study from the Vaccine Safety Datalink Project. Pediatr Infect Dis J 2004;23:656-661.
The authors evaluated more than 360,000 births during a five-year period to determine if a correlation existed between hepatitis B vaccine receipt at birth and neonatal death. The authors found no relationship between hepatitis B vaccine receipt at birth and neonatal death, and the proportion of deaths from unexpected causes (e.g., SIDS) was not different between vaccinated and unvaccinated infants.
6. Fleming PJ, Blair PS, Platt MW, Tripp J, Smith IJ, et al. The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study. BMJ 2001;322:1-5.
In the early 1990s, the schedule for routine infant immunizations in the United Kingdom was accelerated to give the vaccines at an earlier age. The authors found that the accelerated immunization program did not increase the risk of SIDS in a study population of 17.7 million infants. Immunization uptake was lowest among the infants who died from SIDS.
7. Jonville-Bera AP, Autret-Leca E, Barbeillon, Paris-Llado J and the French Reference Centers for SIDS. Sudden unexpected death in infants under 3 months of age and vaccination status – a case-control study. Br J Clin Pharmacol 2001;51:271-276.
The authors conducted a two-year prospective study on the vaccination status of infants with SIDS who died between 1 and 3 months of age to assess whether

vaccination increased the risk of SIDS in this population in France. The authors found DTPP ± Hib immunization did not increase the risk of SIDS.

8. Silvers LE, Ellenberg SS, Wise RP, Varricchio FE, Mootrey GT, et al. The epidemiology of fatalities reported to the Vaccine Adverse Event Reporting System 1990-1997. Pharmacoepidemiol Drug Saf 2001; 279-285.
   The authors examined fatalities reported to VAERS in the United States during a seven-year period and found that reports peaked in 1992-1993 and then declined, with nearly half of the deaths attributed to SIDS. The trend in decreasing SIDS rates correlated with the 1992 American Academy of Pediatrics recommendation for infants to sleep on their side or back and the National Institute of Child Health and Human Development "Back to Sleep" campaign in 1994. The authors concluded that these data support findings of past controlled studies showing that the temporal association between infant vaccination and SIDS is coincidental and not causal.
9. Griffin MR, Ray WA, Livengood JR, Schaffner W. Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. New Engl J Med 1988;319(10):618-623.
   The authors evaluated recent immunization with DTP as a possible risk factor for SIDS during a 10-year period in Tennessee. They found no increase in the risk of SIDS after immunization with DTP vaccine and no correlation between SIDS and age at first immunization. Additionally, the rate of SIDS decreased in the first week after immunization.
10. Hoffman HJ, Hunter JC, Damus K, Pakter J, Peterson DR, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors. Pediatrics 1987;79:598-611.
    The authors investigated the possible association between diphtheria-tetanus-pertussis (DTP) immunization and subsequent occurrence of sudden infant death in the United States using data from a national SIDS epidemiological database. They found no temporal association between SIDS and DTP vaccine receipt. Infants with SIDS were less likely to have been immunized than infants without SIDS.
11. Keens TG, Davidson Ward SL, Gates EP, Andree DI, Hart LD. Ventilatory pattern following diphtheria-tetanus-pertussis immunization in infants at risk for sudden infant death syndrome. AJDC 1985;139:991-994.

The authors evaluated the effects of DTP immunization on the ventilatory pattern during sleep in infants at increased risk for SIDS, including those with unexplained apnea and those who were siblings of SIDS victims. Overnight pneumograms were recorded the night before and the night following DTP immunization. The authors found that DTP immunization did not increase abnormalities of the ventilatory pattern in infants at increased risk for SIDS.

January 19, 2021

Testimony by: Malinda Weninger
1919 Tahoe Drive, Bismarck, ND

58504

Dear Members of the Human Services Committee:

I am writing regarding HB1306.

HB1306 – would establish an interim committee to study the interrelationship between sudden infant death syndrome, vaccines, and autism spectrum disorder in children.

- I support this bill. I believe there is so many interrelationships between vaccines and sudden infant death syndrome and autism and not mentiond is just different illness such as bacterial blood infections in infants and constant ear infections.
- My own daughter who experienced illnesses and ear infections her entire growing up years and then finally a very bad reaction from the HPV vaccine – made me realize that she was having reactions her entire life – but I just didn't realize it.

- Many people that I know have had children die from Sudden Infant Death Syndrome (SIDS), ironically a week or two after a vaccination. This correlation needs to be studied.

- With a child that had a vaccine injury I have seen first hand the direct relationship.

North Dakota needs to be a leader and not a follower and pass HB1306.

To: Legislative Assembly of North Dakota

From: Heather Miller,
Mandan, ND

Date: January 18, 2021

RE: Testimony in favor of HB 1306

Ladies and gentlemen, my name is Heather Miller and I am a resident of Mandan, North Dakota. I hereby give testimony about House Bill 1306 which would establish an interim committee to study the interrelationship between sudden infant death syndrome, vaccines, and autism spectrum disorder in children. I support this bill.

House Bill 1306 needs to pass because many parents whose children were previously healthy and developing normally have observed that vaccines were given in close proximity to the death of their children. House Bill 1306 needs to pass because many parents whose children were previously healthy and developing normally have observed that vaccines were given in close proximity to their child's state of being transformed into the autism spectrum disorder. In my quest to restore healing to my vaccine-injured son, I have heard many stories of vaccine tragedies. I have also experienced the lack of support of the medical community to provide assistance and resources once vaccine injury occurs. Parents need North Dakota to do an unbiased honest look at vaccines and incidences of sudden infant death syndrome. Parents need North Dakota to do an unbiased honest look at vaccines and incidences of autism spectrum disorder in children. Thank you for your consideration.

I support HB 1306 for the legislature to study the relationship if sudden infant death syndrome/sudden unexplained death syndrome with vaccines and autism spectrum disorder in children. With increasing rates in these areas we need to look at the one thing that has also increased over the the years- vaccines. We cannot continue with the continued rhetoric of “safe and effective” until it is studied truthfully. Our children’s lives and futures depend on this.

Thank you.

Testimony at House Human Services Committee

January 19, 2021 2:45 pm

Testimony ND HB 1306,

Chairman Weisz, Vice Chairman Rohr and members of the House Human Services Committee.

I am Mary Ann Sens from Grand Forks, ND. I appear today IN OPPOSITION to ND HB 1306, requesting a legislative management study to explore any interrelationship between SIDS, vaccines, and autism.

My background: I am a North Dakota Physician, pathologist and researcher. I am Professor and Chair of Pathology at the University of North Dakota School of Medicine and Health Sciences. I am a forensic pathologist, so I directly witness the tragedy of sudden infant death in my profession. It is a profoundly sad event, forever tearing the family soul with the deaths of these babies. In forensic pathology, we deal with autism less commonly, but it is just as heartbreaking when an autistic child dies, usually in dangers they do not perceive. I also have autism in my family, so I know of the lifelong struggle of parents with these precious and special children.

In my professional background, I have over 120 peer-reviewed manuscripts, many on sudden death in infants. I have written 11 book chapters and just finished a 600 page book on Forensic Pathology. I have both a PhD in Inorganic Physical Chemistry and an MD degree. I am board certified in Anatomic and Forensic Pathology, serve as the Executive Vice President of the National Association of Medical Examiners and am active in many medical and pathology organizations.

I chose to study sudden death in infants under a very rigorous and scientific protocol involving over 50 experts from the National Institute of Health, Boston (Harvard), New York (Columbia University), Sanford Health / Avera (Dr. Elliott), South Africa (Stellenbosch University) and forensic pathologists in North and South Dakota and Capetown, SA. We studied 12,000 pregnancies, any miscarriages or sudden deaths and the health of the babies that resulted. Within the geographic areas, we also enrolled SIDS infants who were not in the initial cohort. We studied sudden death in infants in the most comprehensive study ever and discovered it is a complex disease or series of diseases. These diseases are affected by pre-natal environment, even paternal genetics. They are largely controlled by environmental factors, some preventable, others not. I am heavily involved with CDC efforts to identify risks and reduce sudden infant deaths, as demonstrated by several scientific papers. Our office has arranged for voluntary and consented collaboration with the renowned Lieber Institute for Brain Development. When a death is referred to our office, the next of kin for acceptable cases are offered the opportunity to donate their loved ones brain IF THEY DESIRE. There is no change in our service to the family and no delays, regardless of the family decision. It is just an opportunity that may help advance knowledge in autism, PTSD, reactions to psychoactive drugs and other missions of Lieber institute that we cannot offer here. Autism is an extremely complex disease; this small action may assist in ultimately understanding, treating and preventing it.

Why I oppose this bill: There are numerous studies on vaccines, vaccine safety and reviewing claimed association with autism, SIDS and other disease. None have demonstrated credible evidence of a relationship with vaccines and SIDS or autism. The original and sensational paper by Andrew Wakefield in 1998 claiming a link between autism and vaccine administration in eight children, had serious flaws as written and should never have been published. The entire paper is now totally discredited, financial conflicts with authors identified, mistreatment of developmentally challenged children documented and elements of the manuscript fabricated. Mr. Wakefield had the most severe repercussions against him by British Medical Society, the stripping of his qualifications, he is no longer recognized as a physician in the UK.

In the wake of this article, which parents understandably grasped as a simple solution for this grave, lifelong and unknown disease their children had, numerous studies initially tried to repeat the findings, hoping to solidify a cure for autism, then began to question the entire premise when no reported data could be repeated. PubMed lists over 1,000 studies; none have demonstrated any causal link from vaccines to autism or SIDS. These studies are NOT just from CDC, not just from drug companies, not just from "one side" of this debate. The highest medical recognition is invitation to the National Academy of Medicine, formerly the Institute of Medicine. Fewer than 50 people across the world are asked to join each year and they conduct the highest level of thought and research findings. They challenged and changed medicine with noting preventable errors, demanding electronic records and checks, involving patients / parents in decision-making and many other medical questions of the highest order. They HAVE studied many aspects of vaccines. The NAM/IOM uniformly assert that there is no relationship with vaccines and two of the most complex diseases affecting our babies and children – Sudden death and autism. The simple "solution" of a vaccine has NOTHING to do with either of these conditions. This is repeatedly from the best medical and scientific minds on earth – with no government, drug or political connections. This group DOES identify other complications of vaccines and have detailed reports of the risks and complications of vaccination, including timing of vaccination. Vaccines DO NOT cause SIDS, SUDC, USDI and autism nor does vaccination change any risk for these conditions.

Further studying a phenomenon that has been rigorously studied without any shred of evidence of validity is a waste of resources and time but more importantly, it is cruel to parents and families of these precious children. We need to tract these so we can look for solutions – the DOH is doing that. Those of us in research and forensic attempt to link families with the ability of consented studies whenever possible. Public health looks for trends. Bioinformatics scans for genes. Those of us in the fields realize how very complex these diseases are and continually strive to identify the complex environmental, pre-natal, genetic and epigenetic contributions.

In closing, I wish it were as simple as a shot. It is not. We cannot detract from public health efforts, science, genetics and painstaking review of cases for answers. We need finances for programs to console families with SIDS /SUDC losses. We need more programs for education, treatment and understanding of autism. We need to allow these precious children, like my nephew, to thrive their own way in our society. We need to advance science and real support programs, not a shot theory, disproven several times over.

AUTISM & ALUMINUM ADJUVANTS IN VACCINES

How Aluminum Adjuvants in Vaccines Can Cause Autism

ICAN
Informed Consent Action Network

Published: August 18, 2017 (Version 1.0)

The Centers for Disease Control (CDC) asserts that vaccines and vaccine ingredients have been disproven as potential causes of autism. Statements by the CDC are generic and encompass all vaccines and vaccine ingredients. For example, the CDC states:

> *"Vaccines Do Not Cause Autism" "There is no link between vaccines and autism." "...no links have been found between any vaccine ingredients and autism spectrum disorder." (CDC website, August 2017)*

These statements are not supported by available science. The CDC's evidence supporting these statements is limited to the MMR vaccine (Taylor 2014), thimerosal preservative (Taylor 2014) and vaccine antigen exposure (DeStefano 2013).

Dr. Frank DeStefano of the CDC's Immunization Safety Office is co-author of a paper (Glanz 2015) which states:

> *"To date, there have been no population-based studies specifically designed to evaluate associations between clinically meaningful outcomes and non-antigen ingredients, other than thimerosal."*

This statement applies to, among other vaccine ingredients, aluminum adjuvant. Studies of MMR vaccine cannot be used as evidence of safety for other vaccines, for example vaccines that contain aluminum adjuvant. The overly-broad, generic assertions that no vaccines and no ingredients cause autism are thus not supported by scientific evidence. In fact, the CDC statements are contradicted by a large, consistent and growing body of scientific evidence, including:

1) studies showing neurotoxic and neuroinflammatory effects (e.g. microglial activation) from dosages of aluminum adjuvants lower than or approximately equal to dosages received by infants according to the CDC vaccine schedule (Crepeaux 2017, Petrik 2007, Shaw 2013, Shaw 2009);

2) studies linking vaccines to immune activation brain injury (Zerbo 2016, Li 2015);

3) studies showing that early-life immune activation is a causal factor in autism and other neurodevelopmental disorders and mental illnesses (e.g. schizophrenia) (Meyer 2009, Deverman 2009, Estes 2016, Kneusel 2014, Careaga 2017, Meyer 2014).

The accumulating evidence indicates that vaccine-induced immune activation, and aluminum adjuvants in particular, may cause mental illnesses and neurodevelopmental disorders, including autism.

In this paper, we present scientific evidence that aluminum adjuvants can cause autism and other brain injuries. Also, we explain why the studies allegedly supporting the safety of aluminum adjuvants do not show safety for adverse neurological outcomes.

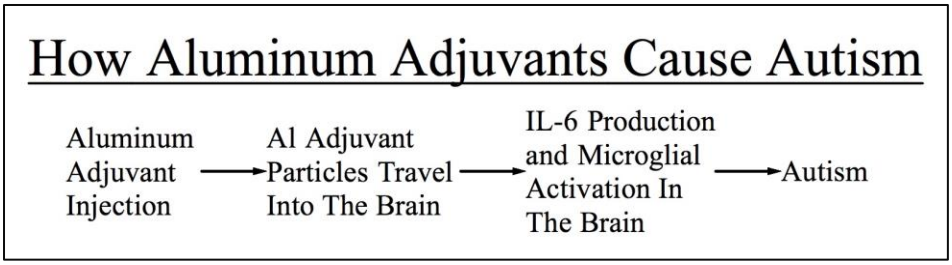

Fig 1: Proposed mechanism for how aluminum adjuvants cause autism. Each step is supported by replicated scientific studies.

Immune Activation: A Cause of Autism and Mental Illness

The term "immune activation" describes the activation of the cellular components of the immune system. The developing brain can be injured by immune activation, with life-long consequences (Meyer 2009, Deverman 2009, Estes 2016, Kneusel 2014, Careaga 2017, Meyer 2014). Immune activation injury is linked to autism, schizophrenia, depression and other mental illnesses or neurodevelopmental disorders. Immune activation effects on the brain are mediated by immune system signaling molecules, especially cytokines (Estes 2016, Meyer 2014, Smith 2007, Choi 2016, Pineda 2013).

It is generally accepted that immune activation (e.g., from infection) during pregnancy is a risk factor for autism and schizophrenia in the offspring (Ciaranello 1995, Atladottir 2010, Brown 2012). The intensity and duration of immune activation and cytokine expression appear to be important factors influencing autism risk (Meyer 2014). Intense immune activation is associated with greater risk of autism (Careaga 2017, Atladottir 2010). Chronic inflammation is associated with greater risk of autism (Jones 2016, Zerbo 2014). However, there is no evidence that short-duration, low-intensity immune activation resulting from common childhood illnesses increase autism risk. Timing of immune activation in relation to stages of brain development is also an important factor (Meyer 2006, Meyer 2009).

Animal experiments have tested the effects of immune activation during pregnancy and postnatally on the development of offspring (Meyer 2009, Deverman 2009, Estes 2016, Kneusel 2014, Careaga 2017, Meyer 2014). In these experiments, pregnant animals (mice, rats and monkeys) or neonates are injected with a non-infectious immune activating substance such as "poly-IC" (which mimics a viral infection) or lipopolysaccharide (LPS, which mimics a bacterial infection). These substances cause immune system activation without infection. They induce fever and cytokine production and can have substantial effects on brain development if activation is sufficiently intense or prolonged and if exposure occurs during vulnerable developmental stages.

Immune activation has been demonstrated in mice to cause the three core behavioral symptoms of autism: decreased socialization and communication, and increased repetitive behaviors (Malkova 2012). Immune activation has also been shown to cause neuropathology (Weir 2015) and behavioral abnormalities in monkeys that resemble behaviors in human schizophrenia and autism (Bauman 2014, Machado 2015). See Fig. 2.

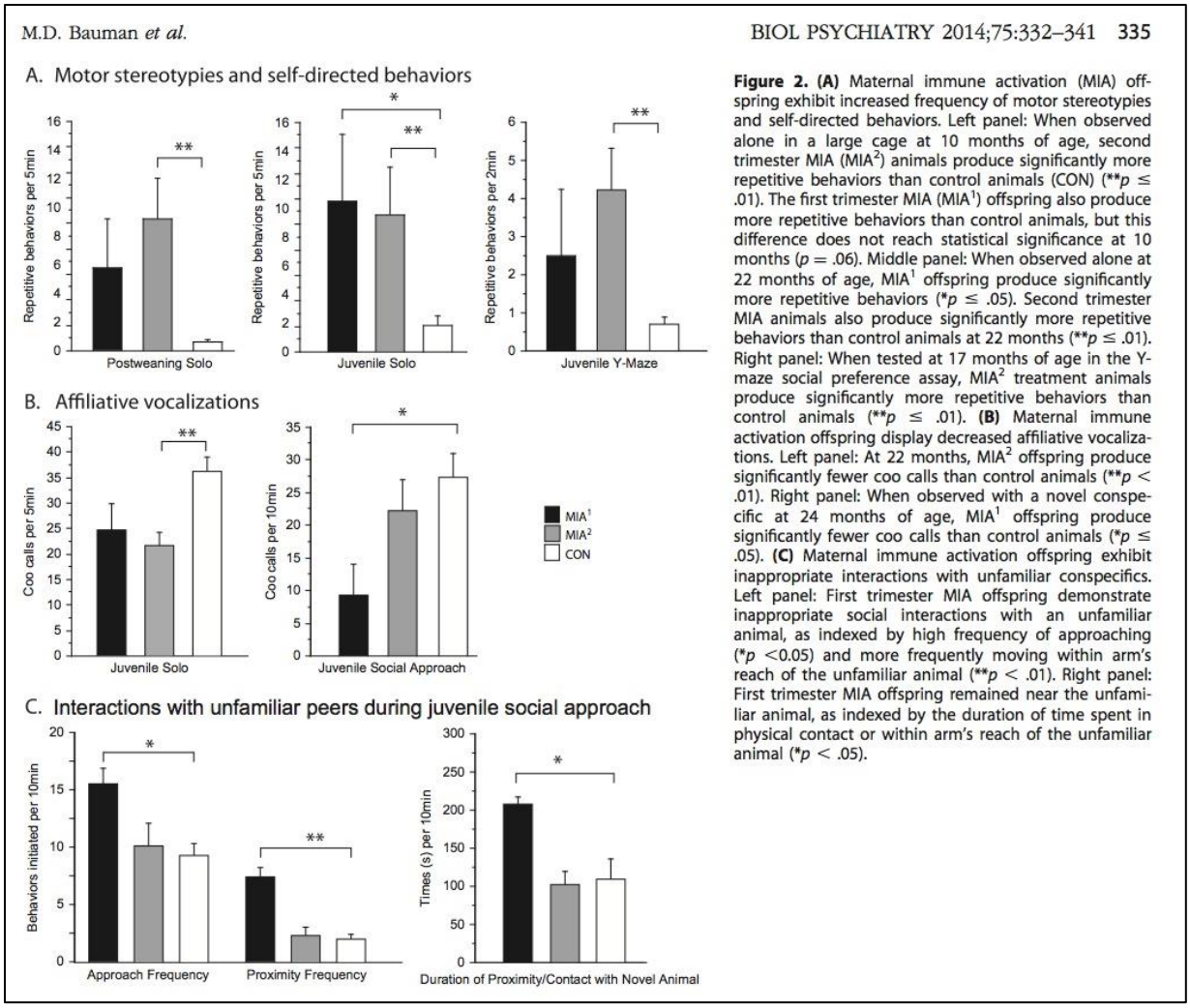

Figure 2. (A) Maternal immune activation (MIA) offspring exhibit increased frequency of motor stereotypies and self-directed behaviors. Left panel: When observed alone in a large cage at 10 months of age, second trimester MIA (MIA^2) animals produce significantly more repetitive behaviors than control animals (CON) (**$p \leq .01$). The first trimester MIA (MIA^1) offspring also produce more repetitive behaviors than control animals, but this difference does not reach statistical significance at 10 months ($p = .06$). Middle panel: When observed alone at 22 months of age, MIA^1 offspring produce significantly more repetitive behaviors (*$p \leq .05$). Second trimester MIA animals also produce significantly more repetitive behaviors than control animals at 22 months (**$p \leq .01$). Right panel: When tested at 17 months of age in the Y-maze social preference assay, MIA^2 treatment animals produce significantly more repetitive behaviors than control animals (**$p \leq .01$). **(B)** Maternal immune activation offspring display decreased affiliative vocalizations. Left panel: At 22 months, MIA^2 offspring produce significantly fewer coo calls than control animals (**$p < .01$). Right panel: When observed with a novel conspecific at 24 months of age, MIA^1 offspring produce significantly fewer coo calls than control animals (*$p \leq .05$). **(C)** Maternal immune activation offspring exhibit inappropriate interactions with unfamiliar conspecifics. Left panel: First trimester MIA offspring demonstrate inappropriate social interactions with an unfamiliar animal, as indexed by high frequency of approaching (*$p < 0.05$) and more frequently moving within arm's reach of the unfamiliar animal (**$p < .01$). Right panel: First trimester MIA offspring remained near the unfamiliar animal, as indexed by the duration of time spent in physical contact or within arm's reach of the unfamiliar animal (*$p < .05$).

Fig 2: Maternal immune activation in monkeys caused behavioral abnormalities in juvenile offspring resembling behaviors in both autism and schizophrenia. MIA1 (Black)= first trimester immune activation; MIA2 (grey) 2nd trimester immune activation; CON (white) saline control. From Bauman et al. 2014

Immune activation also causes non-behavioral effects associated with human autism (citations here link immune activation with these effects):

1) reduction in Purkinje cells (Shi 2009);
2) mitochondrial dysfunction (Giulivi 2013);
3) increase in brain volume (from IL-6 exposure, Wei 2012(b)) and neuron density in the brain (Smith 2012);
4) long term chronic brain inflammation (Garay 2012); and
5) microbiome disruption (dysbiosis) (Hsiao 2013).

These non-behavioral similarities further support the relevance of the immune activation models to human autism. The non-behavioral (e.g., physiological) effects of immune activation have been reviewed (Labouesse 2015).

The cytokines interleukin-6 (IL-6) and interleukin-17a (IL-17) have been identified as mediating the behavioral effects of immune activation (Smith 2007, Malkova 2012, Choi 2016, Pineda 2013, Wei 2012(a), Wei 2013, Parker-Athill 2010, Wei 2016). The IL-6 findings have been replicated by different researchers using a variety of experimental methods. For example, in an experiment with

poly-IC, abnormal behavior is almost completely prevented by simultaneous administration of IL-6-blocking antibody (Smith 2007, Pineda 2013). Injection of IL-6 by itself causes abnormal behavior that closely matches behavior resulting from poly-IC immune activation (Smith 2007). Inhibition of IL-6 signaling in a genetic autism model (BTBR mice) normalized social and repetitive behavior (Wei 2016). These results demonstrate that IL-6 is responsible for causing abnormal autism-like behavior.

The Patterson laboratory at CalTech was the first to report that IL-6 is responsible for causing the autism-like behavioral effects of immune activation (Smith 2007). Two papers from this research group state:

> *"IL-6 is central to the process by which maternal immune activation causes long-term behavioral alterations in the offspring." (Smith 2007)*

> *"…blocking IL-6 prevents >90% of the changes seen in offspring of poly(I:C)-injected females, showing that gene expression changes, as well as behavioral changes, are normalized by eliminating IL-6 from the maternal immune response." (Smith 2007)*

> *"IL-6 is necessary and sufficient to mediate these effects since the effects…are prevented by injection of pregnant mice with poly-IC combined with an anti-IL-6 antibody, and are mimicked by a single maternal injection of IL-6." (Garay 2013)*

Brain exposure to elevated IL-6 by engineered virus showed that IL-6 exposure, initiated after birth, caused autism-like behaviors (Wei 2012(a)). The Wei 2012(a) paper states:

> *"We demonstrated that IL-6 is an important mediator of autism-like behaviors. Mice with an elevated IL-6 in brain developed autism-like behaviors, including impaired cognition ability, deficits in learning, abnormal anxiety-like trait and habituation, as well as a decreased social interaction initiated at later stages. These findings suggest that an IL-6 elevation in the brain could modulate certain pathological alterations and contribute to the development of autism." (Wei 2012(a))*

More recent evidence shows that IL-17 acts downstream of IL-6 to cause autism-like behavioral abnormalities and atypical cortical development in mice (Choi 2016). Blocking either IL-6 or IL-17 prevents the autism-like behavior; an injection of IL-17 by itself causes the autism-like behavior (Choi 2016). IL-6 is known to induce IL-17 by promoting the development of Th17 cells which produce IL-17.

Immune activation animal models appear to be valid models for human neurological/psychiatric disorders, including autism (Estes 2016, Careaga 2017, Meyer 2014). The Estes 2016 review argues for the validity of the immune activation models to humans:

> *"These MIA (maternal immune activation) animal models meet all of the criteria required for validity for a disease model: They mimic a known disease-related risk factor (construct validity), they exhibit a wide range of disease-related symptoms (face validity), and they can be used to predict the efficacy of treatments (predictive validity)." (Estes 2016)*

Evidence suggests a mediating role for IL-6 and IL-17 in human autism. For example, IL-6 is significantly elevated in the cerebellum in human autism (Wei 2011) and is highly elevated in some brain regions of some autistic individuals (Vargas 2005). Treatment of human autistics with the anti-inflammatory flavonoid luteolin improves autistic behaviors in the individuals that also experience a decline in IL-6 blood levels (Tsilioni 2015). This result is consistent with a causal role for IL-6 in human autism. Also, IL-17 is elevated in human autism (Akintunde 2015, Al-Ayadhi

2012, Suzuki 2011). Vitamin D reduces IL-17 production (Bruce 2011, Wobke 2014, Drozdenko 2014) and improves autistic behaviors in humans (Saad 2016, Jia 2015). The vitamin D findings are consistent with a causal role for IL-17 in human autism.

IL-6 functioning appears to be similar or identical in mice and humans. No mouse-human differences in IL-6 functioning are described in a 2004 review (Mestas 2004). IL-6 functioning is quite conserved across species (Brown 2014). Central nervous system development in rodents and humans is governed by the same principles (Brown 2014). Hence, the fact that IL-6 causes autism-like behavioral abnormalities in animal models deserves a presumption of validity to humans.

Immune activation is a risk factor for autism, schizophrenia and other neurological/psychiatric disorders. The cytokines IL-6 and IL-17 are responsible for mediating the autism-like behavioral effects of immune activation in the animal models. The available evidence supports a causal role for IL-6 and IL-17 in human autism.

Maternal vs. Postnatal Immune Activation

The timing of immune activation is an important factor influencing effects on the brain. The developing brain is vulnerable to immune activation injury; the mature, adult brain is apparently not nearly as vulnerable. Sensitivity to immune activation likely declines as the brain matures (Meyer 2014, Meyer 2007).

In most immune activation experiments, the offspring are exposed to immune activation during gestation (by stimulating the maternal immune system). In contrast, most vaccines are administered postnatally. This raises the question of whether postnatal immune activation can have similar effects on the brain as maternal immune activation. Diverse evidence indicates that the brain can be adversely affected by postnatal immune activation. Postnatal immune activation experiments, human case reports, and consideration of brain development timelines suggest that the human brain is vulnerable to immune activation injury for years after birth.

In the maternal immune activation experiments, inflammatory signaling and some cytokines (e.g. IL-6) traverse the placenta into the fetus. Consequently, immune activation in the mother causes immune activation and elevated cytokines in the fetus, and in the fetal brain (Oskvig 2012, Ghiani 2011).

Postnatal immune activation can have adverse neurological effects, including increased seizure susceptibility (Chen 2013, Galic 2008), learning and memory deficits (Harre 2008), and an increase in excitatory synapse formation (Shen 2016). Seizure disorders, learning and memory dysfunction, and elevated excitatory signaling are associated with autism.

Elevated IL-6 in the brain in the postnatal period causes neuronal circuitry imbalance and mediates autism-like behaviors in mice (Wei 2012(a)). The circuitry imbalance observed in Wei 2012(a) was an excess of excitatory synapses and a deficit of inhibitory synapses. See Fig. 3. Excessive excitatory signaling is observed in human autism (Robertson 2016, Freyberg 2015). In fact, an imbalance between excitatory and inhibitory signaling (towards excess excitation) has been posited as a central characteristic of autism (Robertson 2016, Freyberg 2015).

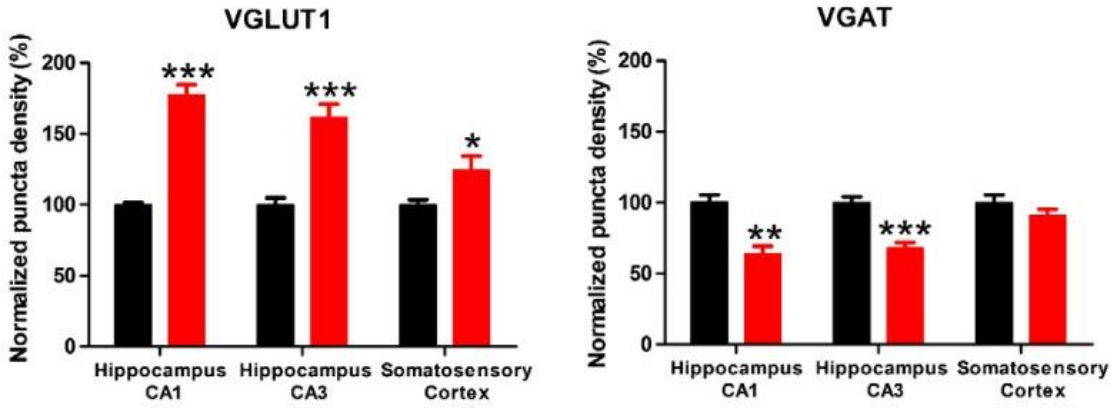

Fig 3: Elevation of IL-6 in the brains of mice (initiated shortly after birth) caused an increase in excitatory synapses (VGLUT1) and a decrease in inhibitory synapses (VGAT). Excessive excitatory signaling is observed in human autism. Red=Elevated IL-6; Black=Control. VGLUT1=excitatory synapses; VGAT=inhibitory synapses. *P<0.05, **P<0.01 and ***P <0.001. Adapted from Wei et al 2012(a).

In a maternal immune activation experiment with mice (Coiro 2015), autism-relevant behavior and dendritic spine abnormalities (relevant to autism and schizophrenia) were ameliorated by administering an anti-inflammatory drug postnatally. The drug was started at birth and continued for 2 weeks, which roughly corresponds to age 2 in humans (Semple 2013). This result indicates that brain development is affected by postnatal inflammation, at times corresponding to when vaccines are given to humans.

Several case reports describe previously-healthy children that displayed sudden-onset autistic behavior during or subsequent to infection in the brain. All the cases had signs of intense brain inflammation. Here are brief descriptions:

Delong 1981: describes 3 children, ages 5, 7 and 11 with full-blown autistic behavior associated with brain inflammation. Brain inflammation was presumed in two cases and confirmed in one. The 5 and 7 year olds recovered completely, and the 11-year recovered partially.

Marques 2014: describes a previously healthy 32-month-old girl that suffered autistic regression from a viral central nervous system infection with associated brain inflammation.

Ghaziuddin 2002: describes a previously healthy 11-year-old boy that suffered permanent autistic regression after sudden onset herpes brain infection with associated brain inflammation.

Gillberg 1986: describes a previously healthy 14-year-old girl with permanent autistic regression from herpes brain infection with associated brain inflammation.

The most parsimonious explanation for these cases is that autistic behavior resulted from intense inflammation and cytokine production in the brain. Accordingly, these cases indicate that the human brain remains vulnerable to immune activation injury well into childhood, though the vulnerability almost certainly decreases with maturation. The susceptibility of older children to inflammation-induced autistic behavior strongly suggests that younger infants, of 0-2 years of age, are also vulnerable. It is not reasonable to claim, and there is no evidence to suggest, that the age range of 0-2 years (when most vaccines are given) is uniquely resistant to immune activation

injury. All the available evidence indicates the opposite.

The immune activation experiments and case reports are consistent and indicate that immune activation and elevated cytokines in the postnatal period can cause brain injury.

The next critical question to consider is whether vaccines can cause immune activation and elevated cytokines in the brain.

Postnatal Vaccination Affects Brain Development in Animal Model

The first study to test the effect of postnatal vaccination on brain development was published in 2015 (Li 2015). In this experiment, neonatal rats were administered bacillus calmette-guerin (BCG) vaccine, hepatitis B (HBV) vaccine or a combination (BCG+HBV) timed to imitate human infant vaccination schedules. BCG and HBV vaccines produced opposite effects on the brain. Specifically, BCG enhanced synaptic plasticity and long-term potentiation (LTP, the basis for learning and memory); HBV inhibited synaptic plasticity and LTP. BCG and HBV vaccines also caused opposite changes in some synapse protein levels.

HBV vaccine (but not BCG vaccine) increased IL-6 gene expression in the brain; increased gene expression likely indicates an elevation in brain IL-6. The HBV vaccine contains aluminum adjuvant, and the BCG does not contain aluminum adjuvant. Hence, the aluminum adjuvant may be the ingredient responsible for the elevated IL-6 gene expression. See Fig. 4.

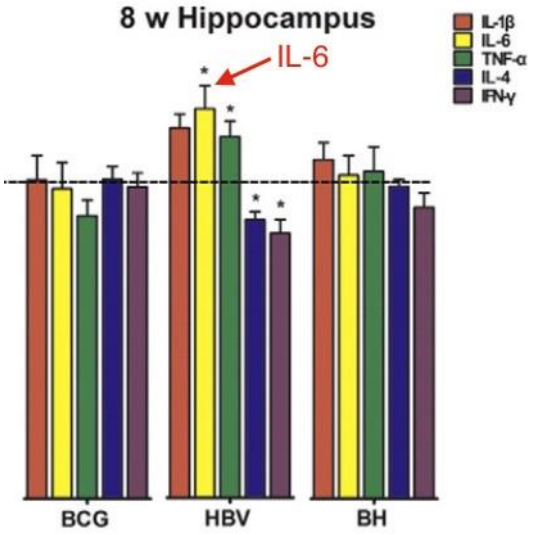

Fig. 4: Hepatitis B vaccine, but not BCG vaccine, increased IL-6 gene expression in the brain at 8 weeks after neonatal vaccination. Hepatitis B vaccine contains aluminum adjuvant; BCG vaccine does not. Elevated IL-6 causes autism-like behaviors in animal models. *P<0.05 Adapted from Li et al 2015.

The Li et al study showed that the vaccines caused other changes in the brain, including 1) changes in long-term potentiation (LTP) (Hep B decreased LTP), 2) changes in dendritic spines, and 3) changes in synapse protein expression. Changes in synapse proteins and dendritic spines have been observed in human brain disorders.

Li et al. attribute the brain effects to changes in cytokine levels and immune polarization (Th1/Th2 polarization) induced by the vaccines. Aluminum adjuvants cause

Th2 polarization. Li et al. state that the results suggest vaccines can interact by way of immune activation effects:

> *"…our data suggested that combinations of different vaccines can mutually interact (enhance or counteract). The mechanism of synaptic plasticity modulation through neonatal BCG/HBV vaccination may be via systemic Th1/Th2 bias accompanied by a specific profile of cytokines and neurotrophins in the brain." (Li 2015)*

Li 2015 demonstrates that vaccines affect brain development by an immune activation mechanism. Further, since aluminum adjuvants induce Th2 activation and long term Th2 polarization, the Li 2015 results suggest that all aluminum-adjuvanted vaccines may cause adverse effects similar to the HBV vaccine. Accordingly, the Li 2015 results suggest that studies showing that immune activation causes neurological/psychiatric disorders are relevant to vaccine adverse effects.

Vaccines Are Given During Synaptogenesis

Another way to answer the question of brain vulnerability to immune activation is to consider the types of brain development processes occurring when vaccines are administered. Vaccines are given primarily in the first 18 months after birth. The human brain undergoes intense and rapid development during this period. Synaptogenesis (formation of synapse connections between neurons) is especially intense in this period.

The vulnerability of the developing brain to immune activation is apparently related to the specific types of brain development processes occurring (Tau 2010, Meyer 2006, Meyer 2007). Such processes include migration (movement of neurons to final locations in the brain), adhesion (formation of chemical-mechanical attachments between brain cells), and synaptogenesis (formation of synapse connections between neurons), among others (neurogenesis, gliogenesis, myelination etc).

Cytokines affect brain development processes. For example, elevated IL-6 affects migration, adhesion and synaptogenesis (Wei 2011). Elevated IL-6 in the postnatal period promotes an excess of excitatory synapses and a deficit of inhibitory synapses, and mediates autism-like behaviors (Wei 2012(a)).

In humans, a dramatic increase in synaptogenesis begins around the time of birth, and continues until about age 3 (Huttenlocher 1997, Tau 2010, Stiles 2010, Semple 2013). Vaccines are administered during this intense synaptogenesis. See Figs. 5-6. Elevated brain IL-6 induced by vaccination during synaptogenesis may cause an excitatory-inhibitory imbalance, towards excitation. An excitatory imbalance has been observed in human autism (Robertson 2016, Freyberg 2015).

Synaptogenesis tapers off through childhood and adolescence. This fact may explain why some older children and teens can suffer autistic regression after intense brain inflammation, but apparently become less vulnerable to immune activation brain injury with age.

Intense synaptogenesis occurs at ages 0-18 months, when many vaccines are administered. Consequently, vaccines may adversely impact synaptogenesis if they induce inflammation or IL-6 in the brain.

The timing of brain development processes in humans supports the idea that the human brain is vulnerable to immune activation and cytokines in the first few years after birth, when vaccines are administered. Disruption of synaptogenesis by vaccine-induced immune activation is a particular concern.

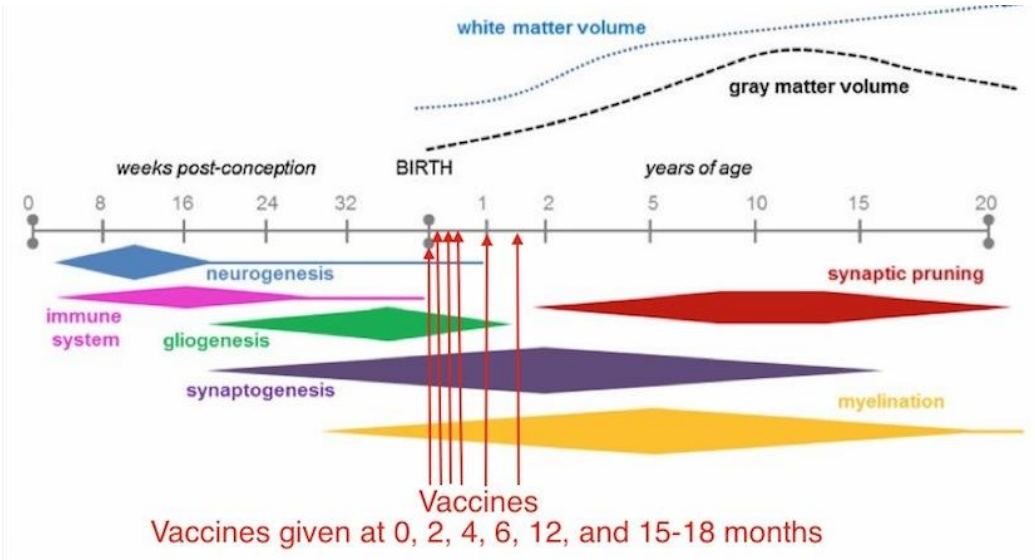

Fig. 5: Timeline of specific brain developmental processes in humans. Synaptogenesis is most intense during the first couple years of life, when vaccines are administered. Timing of vaccination according to the CDC vaccine schedule is shown. Elevated IL-6 during synaptogenesis may cause an excitatory-inhibitory synapse imbalance, towards excitation. Adapted from Semple 2013.

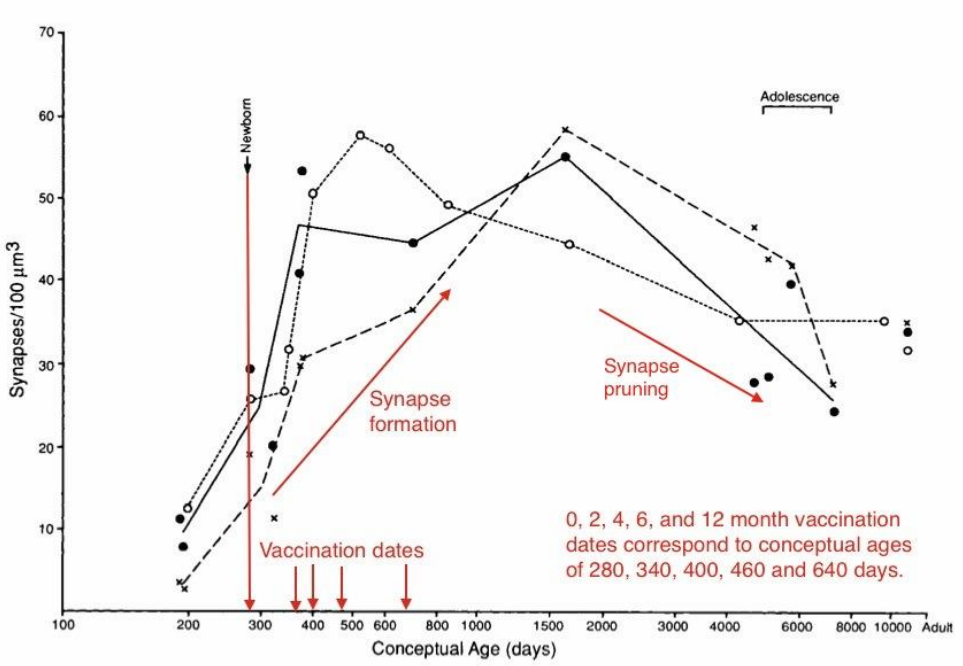

Fig. 2. Mean synaptic density in synapses/100 µm^3 in auditory, calcarine, and prefrontal cortex at various ages. Open circles, visual cortex (area 17); filled circles, auditory cortex; x, prefrontal cortex (middle frontal gyrus).

Fig. 6: Measurements of synapse density in human cadavers of various ages indicate a dramatic increase in synapses in the first few years of life. Vaccines are administered during intense synapse formation. Elevated IL-6 during synaptogenesis may cause an excitatory-inhibitory synapse imbalance, towards excitation. Image adapted from Huttenlocher and Dabholkar 1997.

Aluminum Adjuvants: Neurotoxic At Vaccine Dosages

Aluminum (Al) adjuvants have an essential role in many vaccines: to stimulate immune activation. Without Al adjuvants, these vaccines would have greatly reduced efficacy.

Aluminum adjuvants comprise sub-micron particles (primary particles) of aluminum compounds, typically AlOH, AlPO4, AlSO4 or mixtures. The primary particles are typically agglomerated into larger particles with sizes of about 2-20 microns (Harris 2012). The Al adjuvant materials have low solubility in water and body fluids. Al adjuvant particles are biopersistent and can remain in the body for months or years (Flarend 1997, Khan 2013, Gherardi 2001).

Aluminum ingested in the diet has low oral absorption (about 0.3%), is rapidly excreted by the kidneys, is (mostly) excluded from the brain by the blood-brain barrier, and is in a solubilized, Al3+ ionic form (not particulate). These defenses are adequate for protecting the brain from natural levels of aluminum exposure. These protective mechanisms are unable to protect the brain from injected aluminum adjuvant particles. Al adjuvant particles are too large to be removed by the kidneys, and are carried across the blood-brain barrier by macrophages.

Dosages of aluminum adjuvants received by infants according to the CDC vaccination schedule are:

Birth (Hep B):
74 mcg/kg (250 mcg for 3.4 kg infant)

2 month:
245 mcg/kg (1225 mcg for 5 kg infant)

4 month:
150 mcg/kg (975 mcg for 6.5 kg infant)

6 month:
153 mcg/kg (1225 mcg for 8 kg infant)

These are maximum-possible dosages (because different vaccine products have different amounts) for average-weight infants.

Accumulating evidence shows that aluminum adjuvants have adverse neurological effects at dosages lower than or approximately equal to dosages infants receive from vaccines. These effects appear to depend on the particulate nature and biopersistence of the aluminum adjuvant. Injected Al adjuvant has adverse effects that are apparently mediated by the particles and independent of solubilized Al3+ ions released by the slowly dissolving particles (Crepeaux 2017).

Al adjuvant injections in mice cause adverse effects at vaccine-relevant dosages of 100, 200, 300 and 550 mcg/Kg body weight (Crepeaux 2017, Shaw 2009, Petrik 2007, Shaw 2013). These include deficits in learning and memory (Shaw 2009), deficits in neuromuscular strength/function (Petrik 2007), and changes in locomotor activity and/or gait (Shaw 2009, Shaw 2013). Autism is associated with gait and movement abnormalities (Kindregan 2015) and memory dysfunction (Williams 2006).

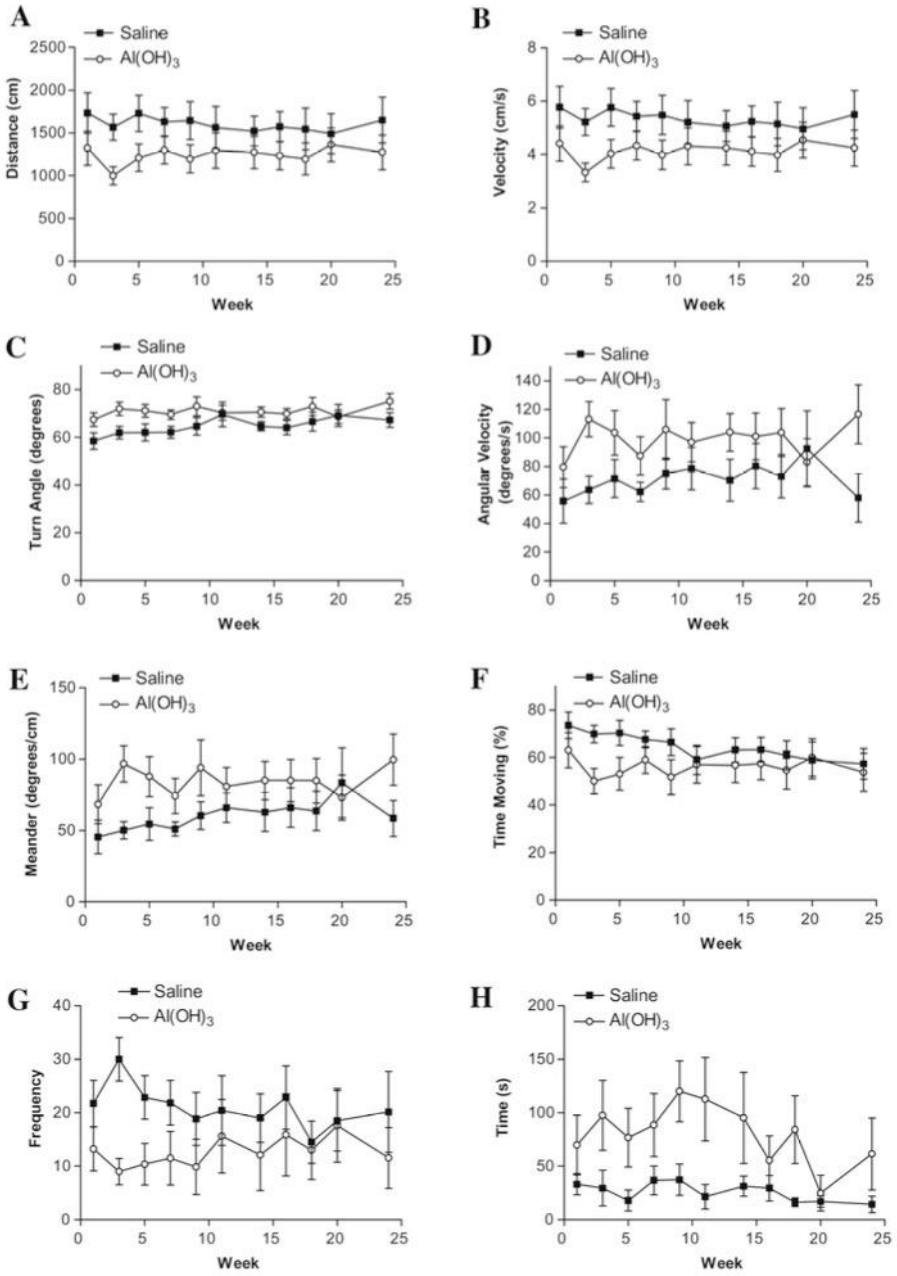

Fig. 4.
Open field movement analysis as an assessment of spontaneous activity and anxiety in control mice vs. mice injected six times with aluminum hydroxide. Aluminum hydroxide injected mice showed the following behavioural changes: (A) Shorter distances moved (***$p < 0.0001$). (B) Slower movement (***$p < 0.0001$). (C) Greater mean turn angle (***$p < 0.0001$). (D) More rapid turning (***$p < 0.0001$). (E) Greater meander (***$p < 0.0001$). (F) Smaller percentage of time in overall movement (**$p = 0.0030$). (G) Fewer entries into the centre of the open field (***$p < 0.001$). Late entry into centre (***$p < 0.0001$). (All measures, two-way ANOVA).

Fig. 7: Dosage of 300mcg/Kg AlOH adjuvant caused large and persistent changes in exploratory behavior and movement in open field tests. This is an indicator of neurotoxicity. Human autistics also display abnormal movement and exploratory behavior. Adapted from Shaw and Petrik 2009.

Al adjuvant dosages of 200mcg/Kg (as 3 x 66mcg/Kg) (Crepeaux 2017) and 300mcg/Kg (as 6 x 50mcg/Kg) (Shaw 2009) increased microglial activation in the ventral forebrain and lumbar spinal cord, respectively. The elevated microglial activation was measured about 6 months after Al adjuvant injection, which suggests that the microglial activation is chronic. Activated microglia indicate an ongoing inflammatory process and suggest the presence of elevated cytokines. Human autistics have activated microglia and elevated cytokines throughout the brain (Vargas 2005, Suzuki 2013, Li 2009).

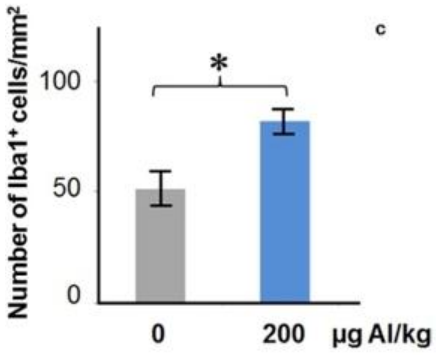

Fig. 8: Al adjuvant (200mcg/Kg) caused an increase in microglial activation in the brain of mice. The protein iba1 indicates activated microglia. Measurements were performed 6 months after Al adjuvant injection, indicating that the microglial activation is a chronic condition. * P<0.05. From Crepeaux et al., 2017.

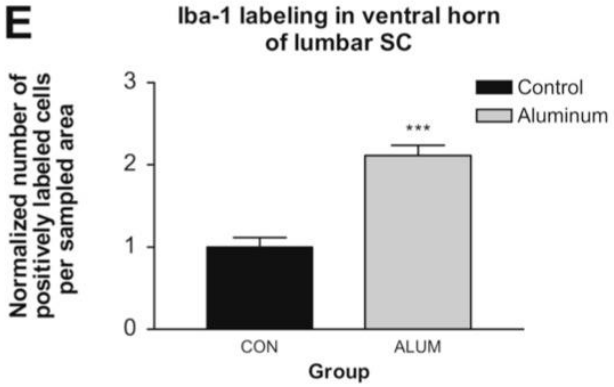

Fig. 9: Al adjuvant (300mcg/Kg) caused an increase in microglial activation in the lumbar spinal cord of mice. The protein iba1 indicates activated microglia. Measurements were performed 6 months after Al adjuvant injection, indicating that the microglial activation is a chronic condition. ***$p < 0.001$, one-way ANOVA. From Shaw and Petrik 2009.

Activated microglia are implicated as a causal factor in autism, because microglia mediate inflammation in the brain. Microglia can produce IL-6 when in an activated state. A recent review on microglia and autism (Takano 2015) states:

> *"…any factors that alter the number or activation state of microglia either in utero or during the early postnatal period can profoundly affect neural development, thus resulting in neurodevelopmental disorders, including autism." (Takano 2015)*

Microglia appear to play an important role in the causation of autism (Takano 2015, Kneusel 2014). Hence, the microglial activation caused by aluminum adjuvants suggests a role in autism.

Several studies show that Al adjuvants increase brain aluminum content (Crepeaux 2017, Flarend 1997, Shaw 2009, Khan 2013, Crepeaux 2015). A dosage of 200 mcg/Kg Al adjuvant caused a 50-fold increase in brain aluminum content in mice, from 0.02 ug/g to 1.0 ug/g dry weight of brain (Crepeaux 2017). These measurements were performed 6 months after the final injection, indicating that the Al persists in the brain long-term (Crepeaux 2017). See Fig. 10. Al adjuvants have been found to accumulate in the brain of mice up to one year after injection (Khan 2013). Crepeaux 2015 demonstrated persistence and increasing accumulation of Al adjuvant particles up to 270 days in spleen and lymph nodes of mice. Increasing accumulation of Al in distant organs over time suggests that toxic effects may increase with time, and may be delayed by months or years after exposure.

The 400 and 800 mcg/Kg doses used in the Crepeaux 2017 study did not cause adverse effects or elevated brain aluminum. The authors attribute this surprising inverted dose-response relationship to granulomas induced by the higher dosages. Granulomas trap the Al adjuvant at the injection site, thereby preventing its transport into the brain and other sensitive tissues. Granulomas occur after about 1% of vaccinations (Bergfors 2014). This is cause for concern because it indicates that, for 99% of vaccinations, the Al adjuvant can be transported around the body. It is not confined to a granuloma. See Fig. 11.

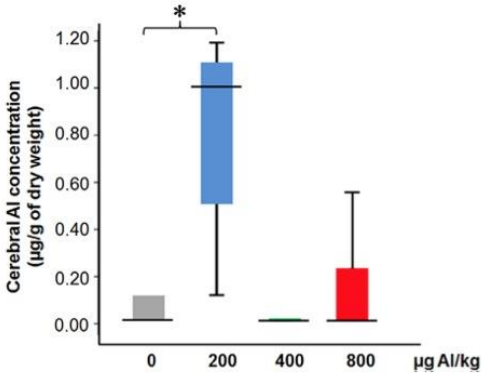

Fig. 10: Dosage of 200 mcg/Kg Al adjuvant caused a 50-fold increase in brain aluminum content, from 0.02 to 1.00 ug/g dry weight, in mice. Higher dosages (400 and 800 mcg/Kg) did not increase brain Al content, presumably because the higher dosages caused a granuloma at the injection site. A granuloma traps the Al adjuvant at the injection site, thereby preventing systemic dispersal and transport into the brain. These measurements were performed 6 months after the final injection, indicating that the Al persists in the brain long-term. *P<0.05. From Crepeaux et al., 2017.

Proposed Mechanism For Inverse Dose-Toxicity Relationship:

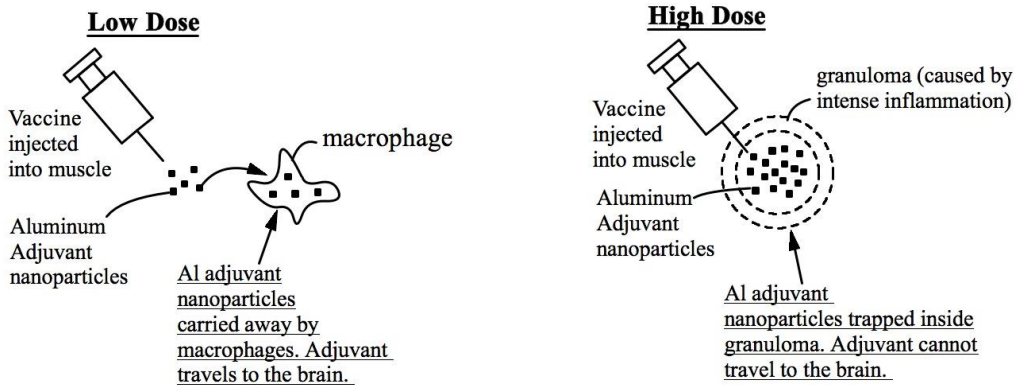

Fig. 11: High dose Al adjuvant injection into the muscle causes a granuloma, which traps the Al adjuvant and prevents it from traveling into the brain. Low dose does not form a granuloma. Hence, the lower dose is free to travel to the brain. Consequently, the lower dose is more toxic than the higher dose. This mechanism explains the surprising inverted dose-toxicity results of Crepeaux et al. 2017.

Particle Transport and Macrophage Chemotactic Protein (MCP-1)

Aluminum adjuvants travel into the brain (Khan 2013, Crepeaux 2015, Crepeaux 2017, Shaw 2009, Flarend 1997). Al adjuvant particles are carried through the blood-brain barrier and into the brain by macrophages (Khan 2013). Transport is promoted by macrophage chemotactic protein-1 (MCP-1) (Khan 2013). MCP-1 causes macrophages to travel around the body and into the brain. Particle transport into the brain by macrophages is well-established and has been investigated for therapeutic applications (Choi 2012, Pang 2016).

MCP-1 is elevated in the brains of human autistics (Vargas 2005) and is elevated in the blood of neonates later diagnosed with autism (Zerbo 2014). This suggests that neonates with high MCP-1 will experience elevated Al adjuvant transport into the brain when injected with Al adjuvanted vaccines. This is consistent with Al adjuvants causing autism by inducing immune activation and elevated cytokines in the brain.

Aluminum Induces IL-6 Expression In The Brain

Water-soluble aluminum salts (e.g. $AlCl_3$, Al lactate) induce elevated IL-6 in the brain and other tissues. In fact, aluminum appears to selectively induce IL-6 (Viezeliene 2013). Studies of aluminum exposure and IL-6 expression in the brain include:

Cao 2016: Ingestion of 30 or 90 mg/kg/day aluminum (as $AlCl_3$) for 90 days significantly increased gene expression of IL-6 and other cytokines in the brain (hippocampus).

Alawdi 2016: Ingestion of 3.4 mg/kg/day aluminum (as $AlCl_3$) for 6 weeks caused a 4-fold increase in IL-6 in the brain (hippocampus). This dosage is far lower than the outdated "no observed adverse effects level" (NOAEL) oral dosages (26 and 62 mg/kg/day) used as benchmarks for toxicity threshold (Mitkus 2011, Offit 2003).

In fact, other experiments show that oral dosages of 3.4, 4, 5.6, 6, and 20.2

mg/Kg/day aluminum cause numerous adverse effects in mice or rats and hence the NOAEL for orally ingested Al is currently unknown (Alawdi 2016, Dera 2016, Sethi 2008, Sethi 2009, Bilkei-Gorzo 1993).

The induction of IL-6 may occur because aluminum strongly induces oxidative stress (Exley 2003). Oxidative stress induces IL-6 expression (Viezeliene 2013).

CDC Website Cites Fatally Flawed Study Of Al Adjuvants (Mitkus 2011)

Dosages of Al adjuvants received by infants increased dramatically as the vaccine schedule was expanded in the 1980s and 1990s. However, as the vaccine schedule expanded, the increasing dosages of Al adjuvants were not tested for safety. Government agencies (HHS, NIH, CDC, FDA) have not pursued any new experimental work on Al adjuvant toxicity.

To support the safety of Al adjuvants at today's higher dosages, the CDC cites a 2011 FDA study of aluminum exposure from vaccines (Mitkus 2011). This study is the only scientific evidence cited by the CDC and FDA websites to support the safety of Al adjuvants.

The Mitkus 2011 study is a theoretical modeling study of Al adjuvant kinetics; it contains no new data concerning Al adjuvant toxicity (from animal models or epidemiology). Mitkus 2011 calculates a body burden of aluminum resulting from the slow dissolution of Al adjuvant particles, and compares the dissolved-aluminum body burden to a "minimal risk level" (MRL). The MRL is derived from a study of ingested Al toxicity in mice (Golub 2001). The Golub 2001 study provides the NOAEL (26 mg/kg/day ingested), which is converted into the MRL for human infants (based on 1mg/kg/day ingested) by using a safety factor of about 30.

The Mitkus study is fatally flawed for these reasons:

1) MITKUS ASSUMES AL ADJUVANT PARTICLES ARE HARMLESS

Mitkus makes an unstated assumption that Al adjuvants have zero toxicity while in particulate form. Mitkus only considers the potential toxicity of aluminum ions (Al3+) released by the slowly-dissolving Al adjuvant particles.

Al adjuvants comprise low-solubility and biologically-persistent microscopic particles. The Mitkus analysis assumes that the particles are absolutely nontoxic and perfectly harmless, even when present in the brain and other organs. Mitkus provides no justification for this unstated assumption. Further, the assumption is contradicted by recent findings on Al adjuvant toxicity (Crepeaux 2017) and particulate toxicity generally. Particles can have toxic effects mediated by surface chemistry (e.g. surface charge and surface catalytic activity) and particle shape, among other characteristics of solid particles (Sharifi 2012, Podila 2013).

Several studies show injected Al adjuvants cause behavioral abnormalities, abnormal weight gain, learning and memory impairment, motor neuron death/apoptosis, neuromuscular strength deficits, chronic microglial activation/brain inflammation, and large (e.g. 50X) increases in brain and spinal cord aluminum content (Petrik 2007, Shaw 2009, Shaw 2013, Crepeaux 2017). These adverse effects occur at dosages less than or approximately equal to dosages received by infants according to the CDC vaccine schedule.

2) NEW RESEARCH SHOWS INGESTED AL HARMFUL AT DOSAGES LOWER THAN 26 MG/KG/DAY

Mitkus assumes that Al adjuvant toxicity is mediated exclusively by solubilized Al (Al3+ ions) released by the slowly-dissolving Al adjuvant particles. To establish a threshold toxicity level from the solubilized Al, Mitkus relies on a mouse feeding study (Golub 2001) reporting a "no-observed adverse effects level" (NOAEL) oral dosage of 26 mg/Kg/day ingested aluminum. Mitkus

used a 30X safety factor for applying this dosage to humans, which is reasonable.

However, other experiments show that much lower oral dosages of 3.4, 4, 5.6, 6, and 20.2 mg/Kg/day aluminum cause adverse effects in mice or rats (Alawdi 2016, Dera 2016, Sethi 2008, Sethi 2009, Bilkei-Gorzo 1993). The adverse effects include chronic brain inflammation, learning and memory impairment, and kidney inflammation. So, the Mitkus analysis is wrong because 26 mg/kg/day is not a NOAEL. The "minimal risk level" (MRL) determined by Mitkus is too high by a factor of at least 26/3.4 = 7.6. Using a corrected NOAEL of 3.4 mg/Kg/day (based on Alawdi 2016) results in vaccine aluminum exposure exceeding the MRL for AlPO4 adjuvant, and approximately matching the MRL for AlOH adjuvant. The new, corrected MRL lines indicate that Al phosphate adjuvant (Fig. 12) and Al hydroxide adjuvant (Fig. 13) from the CDC vaccine schedule may cause toxicity from the solubilized Al per se.

Since 3.4mg/Kg/day is not a NOAEL (adverse effects were observed at this dosage) the true NOAEL is less than 3.4/mg/Kg/day. See Figs. 12-13.

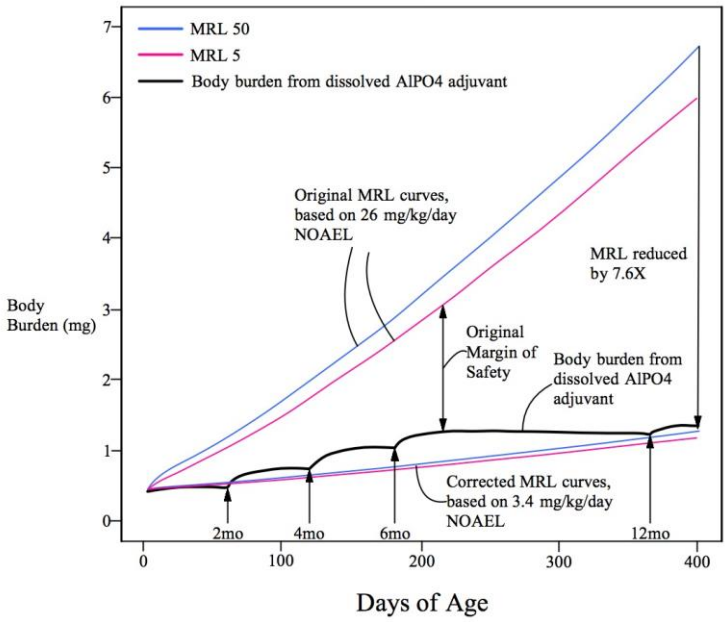

Fig. 12: Body burden vs. MRL comparison chart for Al <u>phosphate</u> adjuvant (AlPO4) corrected in accordance with the new discovery (Alawdi 2016) that ingestion of 3.4 mg/kg/day Al causes adverse effects. The body burden exceeds the corrected MRL curve for almost the entire first year of life, indicating toxicity. The toxicity of Al adjuvant <u>particles</u> is a separate, additional issue. MRL 50 and MRL 5 refer to two different infant growth rates. Adapted from Mitkus et al., 2011.

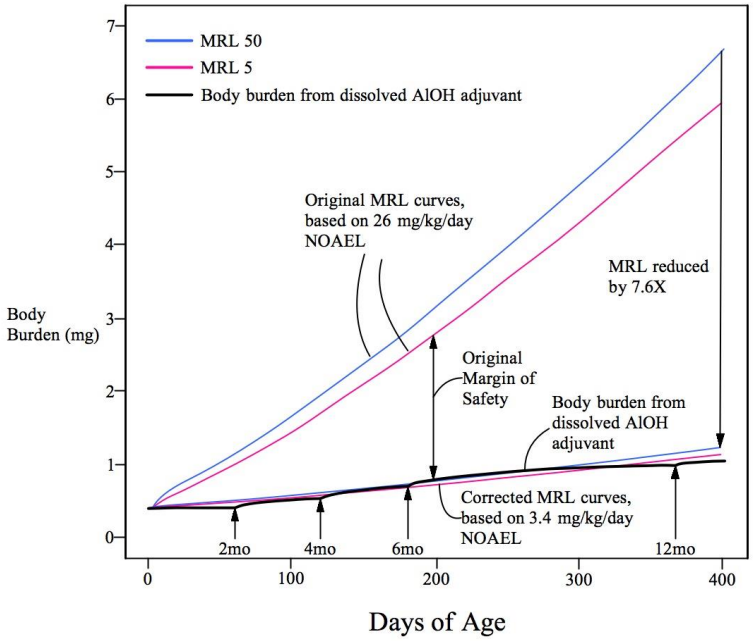

Fig. 13: Body burden vs. MRL comparison chart for Al hydroxide adjuvant (AlOH), corrected in accordance with the new discovery (Alawdi 2016) that ingestion of 3.4 mg/kg/day Al causes adverse effects. The body burden overlaps the new, corrected MRL, indicating borderline toxicity. The margin of safety is gone. MRL 50 and MRL 5 refer to two different infant growth rates. The toxicity of Al adjuvant particles is a separate, additional issue. Adapted from Mitkus et al., 2011.

3) NO AL ADJUVANT TOXICITY DATA CITED, DESPITE AVAILABILITY

Mitkus does not cite any toxicity data for injected Al adjuvants. Mitkus instead uses toxicity data for ingested, non-particulate, water-soluble Al (Golub 2001, which used Al lactate) to derive the MRL. This data comes from a single study (Golub 2001).

So, remarkably, Mitkus claims a safe level of injected Al adjuvant exposure, without citing any Al adjuvant toxicity data. The error is unnecessary and neglectful because at least two animal studies of injected Al adjuvant toxicity were available prior to the Mitkus publication in 2011 (Petrik 2007, Shaw 2009). These papers were not cited or mentioned by Mitkus 2011.

Each of these three flaws is fatal for the validity of the Mitkus study in establishing the safety of aluminum adjuvants. Hence, the CDC is completely lacking valid evidence for the safety of Al adjuvants. This is especially true for safety regarding neurological and long-term outcomes, because other available studies of Al adjuvant safety (e.g., Jefferson 2004) do not consider (or are incapable of detecting) these outcomes.

CDC Fails To Investigate Toxicity of Al Adjuvants

The CDC has conducted no epidemiological studies on long term safety (e.g. considering neurological outcomes) of Al adjuvants. There is one ecological study of country-level data, which reported an association between Al adjuvant exposure and autism (Tomljenovic 2011). However, being an ecological study, it is highly susceptible to confounding and biases.

Dr Frank DeStefano of the CDC's Immunization Safety Office is co-author of a

feasibility study (Glanz 2015) on using the Vaccine Safety Datalink (VSD) to investigate the safety of individual vaccine ingredients. The paper focuses on Al adjuvants. It acknowledges that thimerosal is the only vaccine ingredient studied for autism or neurological safety, and that a possible association between Al adjuvants and autism has not been explored in epidemiological studies. Glanz 2015 states:

> *"To date, there have been no population-based studies specifically designed to evaluate associations between clinically meaningful outcomes and non-antigen ingredients, other than thimerosal."*

The CDC has not investigated Al adjuvant safety concerns, despite the accumulating scientific evidence of harm and evidence linking Al adjuvants to immune activation mechanisms of brain injury.[1]

Conclusion

The science reviewed here tells a consistent and compelling story: that vaccines may cause autism by stimulating immune activation and elevated cytokines in the brain. Al adjuvants are implicated as a cause of autism because they can be transported into the brain, because they cause microglial activation at vaccine-relevant dosages, and because aluminum induces IL-6 in the brain.

In statements asserting no vaccine-autism link, the CDC cites scientific evidence that is not relevant to Al adjuvant safety or is incapable of disproving an Al adjuvant-autism link (Taylor 2014, DeStefano 2013, Mitkus 2011). In support of claims for Al adjuvant safety, the CDC relies on a profoundly flawed theoretical modelling study (Mitkus 2011). There is little scientific evidence supporting the safety of Al adjuvants, especially in relation to autism and other long term neurological outcomes.

[1] However, the Glanz paper notes that studies of aluminum adjuvants are problematic because of expected small differences in exposures in the low and high exposure groups. Glanz 2015 concludes: "*…children below the 10th percentile would be exposed to between 0 mg and 3.1mg, while children above the 90th percentile would be exposed to between 4.8 mg and 5.3 mg of aluminum from vaccines. It is unclear if such differences in aluminum exposure would be biologically meaningful.*" (Glanz 2015). So, epidemiological studies may not provide reliable evidence for safety or harm. Controlled, prospective human trials of aluminum adjuvant exposure from vaccines will likely be prohibited for ethical reasons. Also, Al adjuvants are essential ingredients for Al adjuvanted vaccines. Consequently, it will be challenging to design studies of long term adverse effects of Al adjuvants in humans. Experiments in animal models can provide valuable information. Al adjuvants should be tested for effects on: 1) excitatory/inhibitory imbalance; 2) core symptoms of autism (social, communicative and repetitive/stereotyped behaviors); 3) IL-6, IL-17, and other cytokine levels in the brain; 4) other physiological abnormalities associated with autism (e.g. mitochondrial dysfunction, microbiome dysbiosis, Purkinje cell loss, cerebellum abnormalities etc); and 5) microglial activation and immune activity in the brain. Investigating these outcomes can provide valuable information concerning the safety of Al adjuvants.

References

Akintunde et al., 2015 Increased production of IL-17 in children with autism spectrum disorders and co-morbid asthma, Journal of Neuroimmunology 286 (2015) 33-41.

Al-Ayadhi et al., 2012 Elevated serum levels of interleukin-17A in children with autism, Journal of Neuroinflammation 2012, 9:158.

Alawdi et al., Neuroprotective Effect of Nanodiamond in Alzheimer's Disease Rat Model: a Pivotal Role for Modulating NF-κB and STAT3 Signaling, Molecular Neurobiology, 54 (3):1906-1918.

Atladottir et al., Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders, Journal of Autism and Developmental Disorders, 2010 Dec;40(12):1423-1430.

Bauman et al., 2014 Activation of the Maternal Immune System During Pregnancy Alters Behavioral Development of Rhesus Monkey Offspring, Biological Psychiatry, 2014;75: 332–341

Bergfors et al., 2014 How common are long-lasting, intensely itching vaccination granulomas and contact allergy to aluminium induced by currently used pediatric vaccines? A prospective cohort study, European Journal of Pediatrics, 173:1297–1307.

Bilkei-Gorzo, 1993, Neurotoxic effect of enteral aluminum, Food and Chemical Toxicology, 31(5):357-361.

Brown et al., 2014 Metabolic consequences of interleukin-6 challenge in developing neurons and astroglia, Journal of Neuroinflammation, 11:183.

Brown et al., Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism, Developmental Neurobiology, 2012 October ; 72(10): 1272–1276.

Bruce et al., 2011 Converging pathways lead to overproduction of IL-17 in the absence of vitamin D signaling, 2011 Aug; 23(8): 519–528.

Careaga et al 2017 Maternal Immune Activation and Autism Spectrum Disorder: From Rodents to Nonhuman and Human Primates, Biological Psychiatry, March 1, 2017; 81:391–401.

Chen et al., Postnatal systemic inflammation exacerbates impairment of hippocampal synaptic plasticity in an animal seizure model, Neuroimmunomodulation, 2013;20(4):223-32.

Choi et al., 2012, Delivery of nanoparticles to brain metastases of breast cancer using a cellular Trojan horse, Cancer Nanotechnology, 3:47–54.

Choi et al., 2016 The maternal interleukin-17a pathway in mice promotes autismlike phenotypes in offspring, Science, 2016 Feb 26; 351(6276): 933–939.

Ciaranello et a The Neurobiology of Infantile Autism, The Neuroscientist, 1:361-367

Coiro et al., Impaired synaptic development in a maternal immune activation mouse model of neurodevelopmental disorders, Brain, Behavior, and Immunity, Nov;50:249-258.

Crepeaux et al., 2015 Highly delayed systemic translocation of aluminum-based adjuvant in CD1 mice following intramuscular injections, Journal of Inorganic Biochemistry, 152:199-205.

Crepeaux et al., 2017 Non-linear dose-response of aluminium hydroxide adjuvant particles: Selective low dose neurotoxicity, Toxicology, 375 (2017) 48–57.

DeLong et al., 1981 Acquired reversible autistic syndrome in acute encephalopathic illness in children, Archives of Neurology, 36:191-194.

Dera 2016, Protective effect of resveratrol against aluminum chloride induced nephrotoxicity in rats, Saudi Medical Journal, 37 (4).

DeStefano et al., 2013 Increasing Exposure to Antibody-Stimulating Proteins and Polysaccharides in Vaccines Is Not Associated with Risk of Autism, The Journal of Pediatrics, 163 (2).

Deverman and Patterson, 2009 Cytokines and CNS Development, Neuron 64:61-78.

Drozdenko et al., 2014 Oral vitamin D increases the frequencies of CD38+ human B cells and ameliorates IL-17-producing T cells, Experimental Dermatology, 23: 107-112.

Estes and McAllister, 2016 Maternal immune activation: implications for neuropsychiatric disorders, Science, 353 (6301) 772-777.

Exley, 2003 The Pro-Oxidant Activity of Aluminum, Free Radical Biology and Medicine, 36(3): 380-387.

Flarend et al., 1997 In vivo absorption of aluminum-containing vaccine adjuvants using 26 Al, Vaccine, 15(12/13):1314-1318.

Freyberg et al., 2015 Reduced perceptual exclusivity during object and grating rivalry in autism, Journal of Vision, 15(13):11, 1–12.

Galic et al., 2008 Postnatal Inflammation Increases Seizure Susceptibility in Adult Rats, The Journal of Neuroscience, 2008, 28 (27) 6904-6913.

Garay et al., 2013 Maternal immune activation causes age- and region-specific changes in brain cytokines in offspring throughout development, Brain, Behavior, and Immunity, 31: 54-68.

Ghaziuddin et al., 2002 Autistic symptoms following herpes encephalitis, European Child and Adolescent Psychiatry, Vol. 11, No. 3:142-146.

Gherardi et al., 2001 Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle, Brain, 124:1821-1831.

Ghiani et al., 2011 Early effects of lipopolysaccharide induced inflammation on foetal brain development in rat, ASN Neuro, 3 (4): 233-245.

Gillberg 1986 Brief Report: Onset at Age 14 of a Typical Autistic Syndrome. A Case Report of a Girl with Herpes Simplex Encephalitis, Journal of Autism and Developmental Disorders, VoL 16, No. 3:369-375.

Giulivi et al 2013 Gestational Exposure to a Viral Mimetic Poly(I:C) Results in Long-Lasting Changes in Mitochondrial Function by Leucocytes in the Adult Offspring, Mediators of Inflammation, Vol 2013:609602.

Glanz et al., 2015, Cumulative and episodic vaccine aluminum exposure in a population-based cohort of young children, Vaccine 33:6736–6744.

Golub et al., 2001 Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior of Swiss Webster mice, Neurotoxicology and Teratology 23 (2001) 365–372.

Gupta et al., 1998 Th1- and Th2-like cytokines in CD4+ and CD8+ T cells in autism, Journal of Neuroimmunology, 85:106-109.

Harre et al., 2008 Neonatal inflammation produces selective behavioural deficits and alters *N*-methyl-D-aspartate receptor subunit mRNA in the adult rat brain, European Journal of Neuroscience, 2008 Feb; 27(3): 644–653.

Harris et al., 2012 Alhydrogel® adjuvant, ultrasonic dispersion and protein binding: A TEM and analytical study, Micron, 43:192-200.

Hsiao et al., 2013 The microbiota modulates gut physiology and behavioral abnormalities associated with autism, Cell, 155(7): 1451-1463.

Huttenlocher and Dabholkar, 1997 Regional Differences in Synaptogenesis in Human Cerebral Cortex, Journal of Camparative Neurology, 387:167–178 (1997).

Jefferson 2004 Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence, The Lancet 4:84-90.

Jones et al., 2016 Autism with Intellectual Disability is Associated with Increased Levels of Maternal Cytokines and Chemokines During Gestation, Molecular Psychiatry, 22(2):273-279.

Khan et al., 2013 Slow CCL2-dependent translocation of biopersistent particles from muscle to brain, BMC Medicine, 11:99.

Kindregan et al., 2015 Gait Deviations in Children with Autism Spectrum Disorders: A Review, Autism Research and Treatment, ID:741480.

Knuesel et al., 2014, Maternal immune activation and abnormal brain development across CNS disorders, Nature Reviews 10:643-660.

Labouesse et al., 2015, Long-term pathological consequences of prenatal infection: beyond brain disorders, American Journal of Physiology, 309:1.

Li et al. 2009 Elevated Immune Response in the Brain of Autistic Patients, Journal of Neuroimmunology, 207(1-2): 111–116.

Li et al., 2015 Neonatal vaccination with bacillus Calmette–Guérin and hepatitis B vaccines modulates hippocampal synaptic plasticity in rats, Journal of Neuroimmunology, 288 (2015) 1-12.

Machado et al., 2015 Maternal Immune Activation in Nonhuman Primates Alters Social Attention in Juvenile Offspring, Biological Psychiatry, 2015 May 1;77(9):823-32.

Malkova et al., 2012 Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism, Brain Behaviorand Immunity, 2012 May ; 26(4): 607–616.

Marques et al., 2014 Autism Spectrum Disorder Secondary to Enterovirus Encephalitis, Journal of Child Neurology, 2014, Vol. 29(5) 708-714.

Mestas et al., 2004 Of Mice and Not Men: Differences between Mouse and Human Immunology, Journal of Immunology, 0022-1767:2731-2738.

Meyer et al., 2006 The Time of Prenatal Immune Challenge Determines the Specificity of Inflammation-Mediated Brain and Behavioral Pathology, The Journal of Neuroscience, 26(18):4752– 4762.

Meyer et al., 2007 The neurodevelopmental impact of prenatal infections at different times of pregnancy: the earlier the worse?, Neuroscientist, Jun;13(3):241-56.

Meyer et al., 2009 In-vivo rodent models for the experimental investigation of prenatal immune activation effects in neurodevelopmental brain disorders, Neuroscience and Biobehavioral Reviews, 33 (2009) 1061–1079.

Meyer 2014, Prenatal Poly(I:C) Exposure and Other Developmental Immune Activation Models in Rodent Systems, Biological Psychiatry, 75:307-315.

Mitkus et al., 2011 Updated aluminum pharmacokinetics following infant exposures through diet and vaccination, Vaccine 29 (2011) 9538–9543.

Offit et al., 2003 Addressing Parents' Concerns: Do Vaccines Contain Harmful Preservatives, Adjuvants, Additives, or Residuals? Pediatrics, 112(6): 1394-1401.

Oskvig et al., 2012 Maternal immune activation by LPS selectively alters specific gene expression profiles of interneuron migration and oxidative stress in the fetus without triggering a fetal immune response, Brain Behavior and Immunity, 2012 May ; 26(4): 623–634.

Pang et al., 2016 Exploiting macrophages as targeted carrier to guide nanoparticles into glioma, Oncotarget 7(24):37081.

Parker-Athill and Tan, 2010 Maternal Immune Activation and Autism Spectrum Disorder: Interleukin-6 Signaling as a Key Mechanistic Pathway, NeuroSignals, 2010;18:113–128.

Petrik et al., 2007 Aluminum Adjuvant Linked to Gulf War Illness Induces Motor Neuron Death in Mice, NeuroMolecular Medicine, Vol. 9, 83-100.

Pineda et al., 2013 Maternal immune activation promotes hippocampal kindling epileptogenesis in mice, Annals of Neurology, 2013 July ; 74(1): 11–19.

Podila et al., 2013 Toxicity of Engineered Nanomaterials: A Physicochemical Perspective, Journal of Biochemical and Molecular Toxicology, 2013 January ; 27(1): 50–55.

Robertson et al., 2016 Reduced GABAergic Action in the Autistic Brain, Current Biology, 26, 1-6.

Saad et al., 2016 Vitamin D status in autism spectrum disorders and the efficacy of vitamin D supplementation in autistic children, Nutritional Neuroscience, 19 (8) 346-351.

Semple et al., 2013 Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species, Progress in Neurobiology, Jul-Aug;106-107:1-16.

Sethi et al., 2008 Aluminium-induced electrophysiological, biochemical and cognitive modifications in the hippocampus of aging rats, Neurotoxicology 29, 1069-1079.

Sethi et al., 2009 Curcumin attenuates aluminium-induced functional neurotoxicity in rats, Pharmacology, Biochemisatry, and Behavior 93:31-39.

Shen et al., 2016 Postnatal activation of TLR4 in astrocytes promotes excitatory synaptogenesis in hippocampal neurons, Journal of Cell Biology, 215(5):719-734.

Sharifi et al., 2012 Toxicity of Nanomaterials, Chemical Society Reviews, 2012 Mar 21; 41(6): 2323–2343.

Shaw and Petrik, 2009 Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration, Journal of Inorganic Biochemistry 103 (11).

Shaw and Tomljenovic, 2013 Administration of aluminium to neonatal mice in vaccine-relevant amounts is associated with adverse long term neurological outcomes, Journal of Inorganic Biochemistry, 128 (2013) 237–244.

Shi et al., 2009 Activation of the Maternal Immune System Alters Cerebellar Development in the Offspring, Brain, Behavior, and Immunity, January, 23(1): 116–123.

Smith et al., 2007 Maternal Immune Activation Alters Fetal Brain Development through Interleukin-6, Journal of Neuroscience, 2007 October 3; 27(40).

Smith et al., 2012, Maternal Immune Activation Increases Neonatal Mouse Cortex Thickness and Cell Density, Journal of Neuroimmune Pharmacology, 7(3):529-532.

Stiles et al., 2010 The Basics of Brain Development, Neuropsychology Reviews (2010) 20:327–348.

Suzuki et al., 2011 Plasma Cytokine Profiles in Subjects with High-Functioning Autism Spectrum Disorders, PloS ONE 6(5).

Suzuki et al., 2013 Microglial Activation in Young Adults With Autism Spectrum Disorder, JAMA Psychiatry 70(1): 49-58.

Takano 2015 Role of Microglia in Autism: Recent Advances, Developmental Neuroscience, 37:195-202.

Tau and Peterson, 2010 Normal Development of Brain Circuits, Neuropsychopharmacology, (2010) 35:147–168.

Taylor et al., 2014 Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies, Vaccine, 32:3623-3629.

Tomljenovic and Shaw, 2011 Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? Journal of Inorganic Biochemistry 105.

Tsilioni et al., 2015 Children with autism spectrum disorders, who improved with a luteolin-containing dietary formulation, show reduced serum levels of TNF and IL-6, Translational Psychiatry, 5, 647.

Vargas et al., 2005 Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism, Annals of Neurology, 2005;57:67–81.

Viezeliene et al., 2013 Selective induction of IL-6 by aluminum-induced oxidative stress can be prevented by selenium, Journal of Trace Elements in Medicine and Biology, 27:226-229.

Wei et al., 2011 IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration and synaptic formation, Journal of Neuroinflammation 2011, 8:52.

Wei et al., 2012 (a) Brain IL-6 elevation causes neuronal circuitry imbalances and mediates autism-like behaviors, Biochimica et Biophysica Acta, 1822 (2012) 831–842.

Wei et al. 2012 (b) Alteration of brain volume in IL-6 overexpressing mice related to autism, International Journal of Developmental Neuroscience, 30:554-559.

Wei et al., 2013 Brain IL-6 and autism, Neuroscience 252 (2013): 320–325.

Wei et al., 2016 Inhibition of IL-6 trans-signaling in the brain increases sociability in the BTBR mouse model of autism, Biochimica et Biophysica Acta, 1862(10):1918-1925.

Weir et al., 2015 Preliminary evidence of neuropathology in nonhuman primates prenatally exposed to maternal immune activation, Brain, Behavior, and Immunity, 48,139–146.

Williams et al., 2006 The Profile of Memory Function in Children With Autism, Neuropsychology, 20(1): 21-29.

Wobke et al., 2014 Vitamin D in inflammatory diseases, Frontiers in Physiology, 5: 244.

Zerbo et al., 2014 Neonatal cytokines and chemokines and risk of Autism Spectrum Disorder: the Early Markers for Autism (EMA) study: a case-control study, Journal of Neuroinflammation, 11:113.

Zerbo et al., 2017 Association Between Influenza Infection and Vaccination During Pregnancy and Risk of Autism Spectrum Disorder, JAMA Pediatrics, 171(1).

VACCINE SAFETY

Introduction to Vaccine Safety Science & Policy in the United States

ICAN
Informed Consent Action Network
Published: October 2, 2017 (Version 1.0)
Address for correspondence: whitepaper@icandecide.org

This white paper provides an introduction to vaccine safety science and policy in the United States.

Section "I" discusses how Congress granted pharmaceutical companies immunity from liability for vaccine injuries and transferred all responsibility for vaccine safety to the United States Department of Health & Human Services (**HHS**) and its agencies, including the Food & Drug Administration (**FDA**), the Centers for Disease Control (**CDC**) and the National Institutes of Health (**NIH**).

Section "II" discusses how most pediatric vaccines were licensed based on inadequate clinical trials, including follow-up periods too brief to capture adverse outcomes, and illegitimate placebos (e.g., other vaccines).

Section "III" discusses the CDC's deficient post-licensure vaccine safety surveillance.

Section "IV" discusses the conflicts of interest at HHS regarding vaccine safety, including the issues resulting from placing HHS in charge of vaccine safety and the conflicting duty of promoting and defending vaccines against any claim of injury.

Until a frank conversation is possible regarding vaccine safety, children susceptible to vaccine injury will not be protected from such injury. Nor will children injured by vaccines be able to access the services they need. We can do better in protecting and serving children who are susceptible or succumb to serious injuries from vaccination.

The first step in avoiding vaccine injuries and helping those already harmed is understanding the state of vaccine safety science and policy in America. This paper provides this understanding and highlights areas in need of improvement.

I. Who is responsible for vaccine safety?

Unlike nearly every other company in America, pharmaceutical companies have almost no liability for injuries caused by their vaccine products. How did this happen? As explained by the Institute of Medicine (**IOM**)[1], by 1986, the "litigation costs associated with claims of damage from vaccines had forced several companies to end their vaccine

[1] In 2016, the IOM formally changed its name to the National Academies of Sciences, Engineering, and Medicine.

research and development programs as well as to stop producing already licensed vaccines."[2] Instead of letting market forces compel vaccine makers to create safer vaccines, Congress granted pharmaceutical companies financial immunity from injuries caused by vaccines recommended by the CDC.[3] Congress did so by passing the National Childhood Vaccine Injury Act (the **1986 Act**).[4]

By granting immunity from actual or potential liability from injuries caused by vaccines, Congress eliminated the market forces that are generally relied upon to assure the safety of all other products. As the 1986 Act expressly provides: "No person may bring a civil action … against a vaccine administrator or manufacturer in a State or Federal court for damages arising from a vaccine-related injury or death."[5]

The 1986 Act even shields vaccine makers from liability where it is clear and unmistakable that the vaccine in question could have been designed safer.[6] As recently explained in a U.S. Supreme Court opinion:

> *[N]o one—neither the FDA nor any other federal agency, nor state and federal juries—ensures that vaccine manufacturers adequately take account of scientific and technological advancements. This concern is especially acute with respect to vaccines that have already been released and marketed to the public. Manufacturers ... will often have little or no incentive to improve the designs of vaccines that are already generating significant profit margins.*[7]

Recognizing that the 1986 Act eliminated the incentive for vaccine makers to assure the safety of their vaccine products, the 1986 Act explicitly places this responsibility in the hands of the United States Department of Health & Human Services (**HHS**).[8]

As provided in the 1986 Act, HHS is responsible for "research ... to prevent adverse reactions to vaccines," "develop[ing] the techniques needed to produce safe ... vaccines," "safety ... testing of vaccines," "monitoring ... adverse effects of vaccines," and "shall make or assure improvements in ... the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, ... and research on vaccines in order to reduce the risks of adverse reactions to vaccines."[9]

Since passage of the 1986 Act, the number of required pediatric vaccines has grown rapidly. In 1983, the CDC's childhood vaccine schedule included 11 injections of 4 vaccines.[10] As of 2017, the CDC's childhood vaccine schedule includes 56 injections of 30 different vaccines.[11]

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[2] https://www.nap.edu/read/2138/chapter/2#2
[3] 42 U.S.C. § 300aa-1 et seq.
[4] Ibid.
[5] 42 U.S.C. § 300aa-11
[6] Bruesewitz v. Wyeth LLC, 562 U.S. 223 (2011)
[7] Ibid.
[8] 42 U.S.C. § 300aa-2; 42 U.S.C. § 300aa-27
[9] Ibid.
[10] https://www.cdc.gov/vaccines/schedules/images/schedule1983s.jpg
[11] https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html (note that the influenza vaccine is different every year)

CDC Childhood Immunization Schedule[12]		
1986	2017	
DTP (2 months)	Influenza (pregnancy)	Influenza (18 months)
Polio (2 months)	TDaP (pregnancy)	Influenza (2 years)
DTP (4 months)	Hepatitis B (one day)	Influenza (3 years)
Polio (4 months)	Hepatitis B (one month)	Influenza (4 years)
DTP (6 months)	DTaP (2 months)	DTaP (4 years)
MMR (15 months)	Polio (2 months)	Polio (4 years)
DTP (18 months)	Hib (2 months)	MMR (4 years)
Polio (18 months)	PCV (2 months)	Varicella (4 years)
DTP (4 years)	Rotavirus (2 months)	Influenza (5 years)
Polio (4 years)	DTaP (4 months)	Influenza (6 years)
Tetanus (14 years)	Polio (4 months)	Influenza (7 years)
	Hib (4 months)	Influenza (8 years)
	PCV (4 months)	Influenza (9 years)
	Rotavirus (4 months)	Influenza (10 years)
	DTaP (6 months)	HPV (11 years)
	Polio (6 months)	Men (11 years)
	Hepatitis B (6 months)	TDaP (11 years)
	Hib (6 months)	Influenza (11 years)
	PCV (6 months)	HPV (11 ½ years)
	Rotavirus (6 months)	Influenza (12 years)
	Influenza (6 months)	HPV (12 years)
	MMR (12 months)	Influenza (13 years)
	Varicella (12 months)	Influenza (14 years)
	Hib (12 months)	Influenza (15 years)
	Hepatitis A (12 months)	Men (16 years)
	PCV (12 months)	Influenza (16 years)
	DTaP (15 months)	Influenza (17 years)
	Hepatitis A (18 months)	Influenza (18 years)

It is only when the CDC adds a vaccine to its recommended vaccine schedule that the manufacturer is granted immunity from liability for vaccine injuries. And due to a federal funding scheme, CDC recommended vaccines are then made compulsory to American children under state laws and subsidized by the Federal government for children unable to afford the vaccine.[13]

The end result is that under the 1986 Act, every pediatric vaccine recommended by the CDC creates for its manufacturer a liability-free captive market of 78 million children with guaranteed payment. This incentive structure is unequal in the marketplace and eliminates the normal market forces driving product safety. Hence the 1986 Act transferred essentially all responsibility for vaccine safety from the pharmaceutical companies to HHS.

II. Pre-Licensure Vaccine Safety Review

HHS, through the FDA, licenses all vaccines used by the American public.

All non-vaccine drugs licensed by the FDA undergo long-term multi-year double-blind safety studies during which the rate of adverse reactions in the group receiving the drug under review is compared to the rate of adverse reactions in a group receiving an inert placebo, such as a sugar pill or saline injection.

For example: Enbrel's pre-licensure trials followed subjects up to 80 months and controls received a saline injection.[14] Lipitor's pre-licensure trials lasted a median of 4.8 years and controls received a sugar pill.[15] Botox's pre-licensure trials lasted a median of 51 weeks and controls received a saline injection.[16] And even with these long-term studies, drugs are still often recalled.

While most drugs, like the ones above, are given to sick adults, pediatric vaccines are typically given universally to babies and toddlers. And while pharmaceutical companies remain liable for injuries caused by their

[12] The rapid growth of CDC's vaccine schedule is excepted to accelerate since there were 271 new vaccines under development in 2013 and far more currently under development. http://www.phrma.org/press-release/medicines-in-development-vaccines (listing 2,300 trials in search for "vaccines" between 2013 and 2017)

[13] See Section IV below.

[14] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf

[15] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf

[16] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf

non-vaccine drugs, as discussed above, they have no liability for injuries caused by their vaccines. One would therefore expect that pre-licensure safety testing for vaccines would be more rigorous than that conducted for drugs.

Unfortunately, unlike all non-vaccine drugs licensed by the FDA, vaccines are *not* required to undergo long-term double-blind inert-placebo controlled trials to assess safety. In fact, not a single one of the clinical trials for vaccines given to babies and toddlers had a control group receiving an inert placebo. Further, most pediatric vaccines currently on the market have been approved based on studies with inadequate follow-up periods of only a few days or weeks.

For example, there are two Hepatitis B vaccines licensed for one day old babies in the United States – one manufactured by Merck and the other by GlaxoSmithKline. Merck's Hepatitis B vaccine was licensed by the FDA after trials which solicited adverse reactions for *only five days* after vaccination.[17] Similarly, GlaxoSmithKline's Hepatitis B vaccine was licensed by the FDA after trials which solicited adverse reactions for *only four days* after vaccination.[18]

Follow-up periods of 4 or 5 days are not nearly long enough to detect possible adverse effects such as autoimmune or neurological disorders, seizures, or death. Worse is that since neither of these clinical trials used a control group, it was impossible to scientifically determine if any adverse reaction in the limited four or five day safety review period was even caused by the Hepatitis B vaccine being evaluated.

Similarly, the HiB vaccines manufactured by Merck and GlaxoSmithKline were licensed by the FDA based on trials in which adverse reactions were monitored for only three days and four days, respectively, after vaccination.[19] The only stand-alone polio vaccine in the United States was licensed after a mere 48-hour follow-up period.[20]

Even more amazing is that unlike every drug licensed by the FDA, the control groups in these vaccine trials did not receive an inert placebo.[21] Rather, the control group was given one or more previously licensed vaccines as the "placebo."[22] This means each new vaccine need only be roughly as safe as one (or in some cases numerous) previously licensed vaccines. Such flawed and unscientific study designs cannot establish the actual safety profile of any vaccine. The real adverse event rate for a vaccine can only be determined by comparing subjects receiving the vaccine with those receiving an inert placebo. Yet, this study design, required for every drug, is never required before or after licensing a vaccine.

It is unacceptable that the FDA licensing process for vaccines fails to assess the safety profile of each vaccine. It is also unacceptable that the FDA does not require the use of inert placebo controls to assure the integrity of even the minimal safety review conducted. As HHS's own paid experts, the

[17] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf
[18] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224503.pdf
[19] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM253652.pdf; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM179530.pdf
[20] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM133479.pdf
[21] Ibid. (prior two footnotes)
[22] Ibid.

IOM, explains: "Because [vaccine] trials are primarily … for determination of efficacy, conclusions about vaccine safety derived from these trials are limited."[23]

III. Post-Licensure Surveillance of Vaccine Safety & the Known and Unknown Risks of Vaccination

HHS also fails to conduct proper post-licensure monitoring and studies of vaccine safety.

1. CDC Blocks Automation of Vaccine Adverse Events Reporting

The paucity of pre-licensure safety reviews for vaccines (see discussion above) leaves the assessment of adverse reactions to the post-licensing period when they are being administered to children in the "real world."

In order to capture adverse events that may arise from vaccination in the "real world," the 1986 Act established the Vaccine Adverse Events Reporting System (**VAERS**) operated by HHS and co-sponsored by the CDC and FDA.[24] VAERS is a passive, not mandatory, reporting system.[25] Anyone, including health care providers, on a voluntary basis, may report adverse vaccine reactions to VAERS.[26] HHS compiles these adverse reaction reports in VAERS and the CDC uses VAERS as a "safety signal detection and hypothesis generating system" to identify potential injuries caused by vaccines.[27]

In 2016, VAERS received 59,117 reports of adverse reactions following vaccination including 432 deaths, 1,091 permanent disabilities, 4,132 hospitalizations, and 10,284 emergency room visits.[28]

A problem with VAERS is that it is a passive reporting system, relying on voluntary, rather than mandatory, reporting.[29] As such, numerous reviews of VAERS have found that only a tiny fraction of vaccine adverse events are reported. For example, an HHS-funded review of vaccine adverse events over a three-year period by Harvard Medical School involving 715,000 patients found that "fewer than 1% of vaccine adverse events are reported."[30] A U.S. House Report similarly stated: "Former FDA Commissioner David A. Kessler has estimated that VAERS reports currently represent only a fraction of the serious adverse events."[31]

Assuming VAERS captures 1 percent of adverse events (which is more than is estimated), then the number of adverse events reported to VAERS in 2016 would reflect for that year 5,911,700 adverse events, 43,200 deaths, 109,100 permanent disabilities, 413,200 hospitalizations, and 1,028,400 emergency

[23] https://www.nap.edu/read/13563/chapter/4
[24] https://wonder.cdc.gov/vaers.html
[25] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/
[26] Ibid.
[27] Ibid.
[28] https://wonder.cdc.gov/vaers.html
[29] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/
[30] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[31] https://www.congress.gov/106/crpt/hrpt977/CRPT-106hrpt977.pdf

room visits. If accurate, these figures are very troubling.

Of course, these figures are merely estimates. It would be far better if adverse events reports were automatically created and submitted to VAERS to avoid the issue of underreporting. Automated reporting would provide invaluable information that could clarify which vaccines might cause which harms and to whom, potentially allowing us to avoid these injuries and deaths.

The idea of automating adverse event reporting to VAERS is not new or even difficult to achieve.[32] The Agency for Healthcare Research and Quality, an agency within HHS, sought to do exactly that in 2007 when it provided an approximately $1 million grant to automate VAERS reporting at Harvard Pilgrim Health Care.[33] The result was the successful automation of adverse event reports at Harvard Pilgrim:

> *Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions ... were identified.*[34]

These results should have been startling to HHS since they show that over only a three-year period, there were 35,570 reportable reactions in just 376,452 vaccine recipients. Given HHS's statutory mandate to assure safer vaccines, it should have rushed forward with automating VAERS reporting. However, this is not what happened.

After automating adverse event reports at Harvard Pilgrim, the developers of this system asked the CDC to take the final step of linking VAERS with the Harvard Pilgrim system so that these reports could be automatically transmitted into VAERS. Instead, the CDC refused to cooperate. As the Harvard grant recipients explained:

> *Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed with testing and evaluation.*[35]

After three years and spending $1 million of taxpayers' money, the CDC refused to even communicate with the HHS' Harvard Medical School grant recipients.

While HHS generally strongly supports automating public health surveillance systems, when it comes to vaccine safety, the CDC has only supported projects that would limit VAERS to passive surveillance.[36] Automation would improve safety and address many of the long-standing issues and limitations raised by CDC regarding VAERS.[37]

Capturing "fewer than 1% of vaccine adverse events" thirty years after the passage of the 1986 Act is unacceptable – and potentially deadly.

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[32] https://healthit.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system
[33] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[34] Ibid.
[35] Ibid.
[36] http://www.ajpmonline.org/article/S0749-3797(12)00249-8/pdf; https://www.ncbi.nlm.nih.gov/pubmed/26209838; https://www. ncbi.nlm.nih.gov/pmc/articles/PMC4632204/
[37] Ibid.

2. CDC Ignores IOM's Calls to Identify Injuries Caused by Vaccines

The IOM was formed in 1863 by congressional charter, to "provide expert advice on some of the most pressing challenges facing the nation and the world."[38] The IOM further claims its "members are among the world's most distinguished scientists, engineers, physicians, and researchers; more than 300 members are Nobel laureates."[39]

Under the 1986 Act, the IOM was charged with issuing reports on injuries from vaccination. In 1991, the IOM examined 22 commonly reported serious injuries following the DTP vaccine.[40] The IOM concluded the scientific literature supported a causal relationship between the DTP vaccine and 6 of these injuries: acute encephalopathy, chronic arthritis, acute arthritis, shock and unusual shock-like state, anaphylaxis, and protracted inconsolable crying.[41]

While this picture was troubling enough, equally concerning was that the IOM found that the scientific literature was insufficient to conclude whether or not the DTP vaccine can cause 12 other serious injuries commonly reported from this vaccine:

> *Aseptic meningitis (serious inflammation of the brain); Chronic neurologic damage; Learning disabilities and attention-deficit disorder; Hemolytic anemia; Juvenile diabetes; Guillain-Barre syndrome; Erythema multiforme; Autism; Peripheral mononeuropathy (nerve damage); Radiculoneuritis and other neuropathies; Thrombocytopenia; Thrombocytopenic purpura*[42]

These commonly reported serious injuries *could* be caused by this vaccine – the IOM just couldn't determine one way or another due to a lack of science.

The IOM lamented that it "encountered many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines."[43] The IOM also remarked on the poor design of the few vaccine studies that had been conducted, stating these "studies are too small or have inadequate length of follow-up to have a reasonable chance of detecting true adverse reactions."[44] Moreover, the IOM reported that "existing surveillance systems of vaccine injury have limited capacity to provide persuasive evidence of causation."[45]

The IOM thus cautioned in its 1991 report that: "If research capacity and accomplishment in this field are not improved, future reviews of vaccine safety will be similarly handicapped."[46]

As charged under the 1986 Act, the IOM issued another report in 1994 entitled *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causation.*[47] This second IOM Report examined the scientific literature for evidence that could either prove or disprove a causal link between 54

[38] http://www.national-academies.org/about/whoweare/index.html
[39] Ibid.
[40] https://www.nap.edu/read/1815/chapter/2#7
[41] Ibid.
[42] Ibid.
[43] https://www.nap.edu/read/1815/chapter/2#8
[44] https://www.nap.edu/read/1815/chapter/9
[45] Ibid.
[46] Ibid.
[47] https://www.nap.edu/read/2138/chapter/1

commonly reported serious injuries and vaccination for diphtheria, tetanus, measles, mumps, polio, hepatitis B, and Hib.[48]

For this Report, the IOM located sufficient science to support a causal connection between these vaccines and 12 injuries, including death, anaphylaxis, thrombocytopenia, and Guillain-Barre syndrome.[49]

Again, as with the IOM Report from 1991, for "the majority of vaccine-adverse event pairs the evidence was considered inadequate to accept or reject causality."[50] The problem that basic scientific studies had not been done continued to persist. The IOM could not determine whether there was a causal connection between vaccination and 38 of the most common serious injuries parents reported their children experienced following these vaccines, including:

> *Demyelinating diseases of the central nervous system, Sterility, Arthritis, Neuropathy, Residual seizure disorder, Transverse myelitis, Sensorineural deafness, Optic neuritis, Aseptic meningitis, Insulin-dependent diabetes mellitus, SIDS*[51]

This means that of the 54 vaccine-injury pairs studied, there was sufficient science to find a causal relationship of harm for 12, and to reject a relationship for 4.[52] But for the remaining 38, there was insufficient science to reach any conclusion.[53]

As in 1991, this IOM Report from 1994 again stated: "The lack of adequate data regarding many of the adverse events under study was of major concern to the committee. Presentations at public meeting indicated that many parents and physicians share this concern."[54]

Another acute concern raised by the IOM in 1994 was the potential risks posed by combining vaccines. The IOM noted that this subject simply had not been studied: "The committee was able to identify little information pertaining to the risk of serious adverse events following administration of multiple vaccines simultaneously. This is an issue of increasing concern as more vaccines and vaccine combinations are developed for routine use."[55]

In 2011, HHS paid the IOM to conduct another assessment regarding vaccine safety.[56] This Report, entitled *Adverse Effects of Vaccines: Evidence and Causality*, was the culmination of the largest review by the IOM regarding vaccine safety since the IOM's reports from 1991 and 1994.[57]

This third IOM Report reviewed the 158 most common vaccine injuries claimed to have occurred from vaccination for varicella, hepatitis B, tetanus, measles, mumps, and/or rubella.[58] The IOM located science which "convincingly supports a causal relationship" for 14 of these serious injuries, including pneumonia, meningitis, hepatitis, MIBE (deadly brain inflammation a year after vaccination), febrile seizures, and

[48] https://www.nap.edu/read/2138/chapter/2#12
[49] https://www.nap.edu/read/2138/chapter/2#12
[50] https://www.nap.edu/read/2138/chapter/1#vi
[51] https://www.nap.edu/read/2138/chapter/2#12
[52] Ibid.
[53] Ibid.
[54] https://www.nap.edu/read/2138/chapter/12
[55] https://www.nap.edu/read/2138/chapter/12#307
[56] https://www.nap.edu/read/13164/chapter/2#2
[57] Ibid.
[58] Ibid.

anaphylaxis.[59] The review found sufficient evidence to support "acceptance of a causal relationship" for 4 additional serious injuries.[60]

The IOM, however, found the scientific literature was insufficient to conclude whether or not those vaccines caused 135 other serious injuries commonly reported after their administration, including:

> *Encephalitis (brain inflammation), Encephalopathy (gradual degeneration of brain function, including memory, cognitive ability, concentration, lethargy, and eventually consciousness), Infantile Spasms, Afebrile Seizures, Seizures, Cerebellar Ataxia (inflammation of and/or damage to the cerebellum), Ataxia (the loss of full control of bodily movements), Acute Disseminated Encephalomyelitis (brief but widespread attack of inflammation in the brain and spinal cord that damages myelin – the protective covering of nerve fibers), Transverse Myelitis (neurological disorder caused by inflammation across both sides of one level, or segment, of the spinal cord that typically results in permanent impairments), Optic Neuritis (inflammation of the optic nerve and symptoms are usually unilateral, with eye pain and partial or complete vision loss), Neuromyelitis Optica (body's immune system over time repeatedly mistakenly attacks healthy cells and proteins in the body, most often those in the spinal cord and eyes resulting in permanent disability), Multiple Sclerosis, Guillain-Barre Syndrome (body's immune system attacks part of the peripheral nervous system), Chronic Inflammatory Demyelinating Polyneuropathy (auto-immune inflammatory disorder of the peripheral nervous system resulting in loss of nerve axons), Brachial Neuritis (auto-immune reaction against nerve fibers of the brachial plexus), Amyotrophic Lateral Sclerosis (rapidly progressive, invariably fatal neurological disease that attacks the nerve cells responsible for controlling voluntary muscles), Small Fiber Neuropathy (damage to the small unmyelinated peripheral nerve fibers), Chronic Urticaria (chronic hives), Erythema Nodosum (skin inflammation in the fatty layer of skin), Systemic Lupus Erythematosus (autoimmune disease in which the body's immune system mistakenly attacks healthy tissue), Polyarteritis Nodosa (inflammation resulting in injury to organ systems), Psoriatic Arthritis, Reactive Arthritis, Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Arthralgia (joint pain), Autoimmune Hepatitis, Stroke, Chronic Headache, Fibromyalgia, Sudden Infant Death Syndrome, Hearing Loss, Thrombocytopenia, Immune Thrombocytopenic Purpura*[61]

Thus, out of the 158 most common serious injuries reported to have been caused by the vaccines under review, the evidence "convincingly supports a causal relationship" for 14, "favors acceptance of a causal relationship" for 4, and "favors rejection of a causal relationship" for only 5 of them.[62] For the remaining 135 vaccine-injury pairs, over 86 percent of those reviewed, the IOM found

[59] https://www.nap.edu/read/13164/chapter/2#3
[60] Ibid.
[61] Ibid.
[62] Ibid.

that the science simply had not been performed.[63]

3. CDC Ignores IOM's Calls to Identify Children Susceptible to Vaccine Injury

Compounding the lack of adequate science to simply ascertain whether the most commonly reported serious adverse reactions following vaccination are caused by vaccines, the IOM Reports discussed above have consistently acknowledged there is individual susceptibility to serious vaccine injuries.

The IOM has also acknowledged that research on such susceptibility must be done on an individual basis, considering a child's personal genome, behaviors, microbiome, intercurrent illness, and present and past environmental exposure.[64] Unfortunately, HHS has not conducted this research.

In 1994, the IOM, building on concerns raised in its 1991 Report, stated: "The committee was able to identify little information pertaining to why some individuals react adversely to vaccines when most do not."[65] The IOM urged that "research should be encouraged to elucidate the factors that put certain people at risk."[66]

Yet, seventeen years later, in 2011, the IOM acknowledged this research had still not been done:

> *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 as suggested graphically in Figure 3-1.*
>
> *Some of these adverse reactions are specific to the particular vaccine, while others may not be. Some of these predispositions may be detectable prior to the administration of vaccine. … [M]uch work remains to be done to elucidate and to develop strategies to document the immunologic mechanisms that lead to adverse effects in individual patients.*

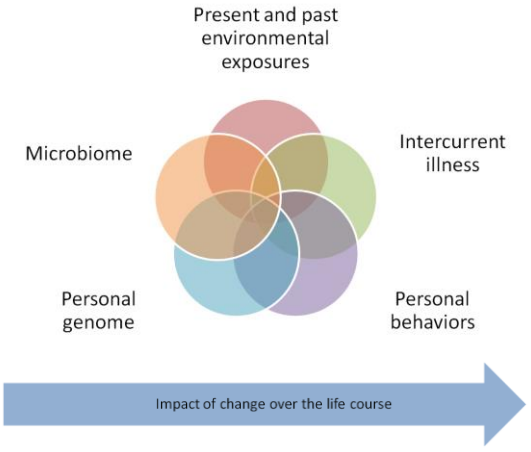

FIGURE 3-1 Present and past environmental exposures.[67]

In 2013, HHS commissioned the IOM to review the safety of the entire vaccine schedule.[68] The IOM again explained that while "most children who experience an adverse reaction to immunization have preexisting susceptibility," the IOM:

[63] Ibid.
[64] https://www.nap.edu/read/13164/chapter/5#82
[65] https://www.nap.edu/read/2138/chapter/12#307. *See also* https://www.nap.edu/read/1815/chapter/9
[66] Ibid.
[67] https://www.nap.edu/read/13164/chapter/5#82
[68] https://www.nap.edu/read/13563/chapter/1

> *found that evidence assessing outcomes in sub populations of children who may be potentially susceptible to adverse reactions to vaccines (such as children with a family history of autoimmune disease or allergies or children born prematurely) was limited and is characterized by uncertainty about the definition of populations of interest and definitions of exposures and outcomes.*[69]

HHS had failed to even define the terminology for the study of susceptible subpopulations; hence IOM admonished HHS to "develop a framework that clarifies and standardizes definitions of ... populations that are potentially susceptible to adverse events."[70] While every vaccine brand is the same, it is plain that every child is different.

The IOM correctly points out in 2011 that given the "widespread use of vaccines" and "state mandates requiring vaccination of children … it is essential that safety concerns receive assiduous attention."[71] This is the same call for diligent attention that the IOM made in 1991 and 1994. Unfortunately, all of these calls for action have gone unheeded. The critical scientific inquiry to identify individuals susceptible to serious vaccine injury has simply never commenced.

Since the IOM's first call for this science in 1991, HHS has spent tens of billions promoting and purchasing vaccines, and vaccine makers have accumulated hundreds of billions in vaccine revenue.[72] Yet, during this time, no material funds have been allocated to identify susceptible subpopulations, let alone what injuries are caused by vaccines.[73]

4. CDC Views Vaccine Safety as a Public Relations Issue

The CDC, unfortunately, has treated vaccine safety as a public relations issue rather than a public health imperative. For example, the CDC claims on its website that "Vaccines Do Not Cause Autism" even though this broad claim is plainly not supported by the scientific literature.[74]

Indeed, as part of the IOM's 2011 review of vaccine safety, it was asked by HHS whether there is a causal relationship between autism and the DTaP vaccine administered to children at two, four, six, and fifteen months of age.[75] The IOM could not locate a single study supporting that DTaP does not cause autism.[76] The IOM therefore concluded: "The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism."[77] The IOM's full explanation for this finding is as follows:

[69] https://www.nap.edu/read/13563/chapter/9#130
[70] Ibid.
[71] https://www.nap.edu/read/13164/chapter/3#28
[72] https://www.hhs.gov/about/budget/index.html#previous; https://www.statista.com/statistics/265102/revenues-in-the-global-vaccine-market/; https://www.ft.com/content/93374f4a-e538-11e5-a09b-1f8b0d268c39
[73] For example, while in 2016 vaccine makers reported over $33 billion from vaccine sales and the CDC reported spending over $5 billion promoting and purchasing vaccines (Ibid.), the CDC Immunization Safety Office's budget is apparently only around $20 million. http://www.ajpmonline.org/article/S0749-3797(15)00314-1/pdf
[74] https://www.cdc.gov/vaccinesafety/concerns/autism.html
[75] https://www.nap.edu/read/13164/chapter/2#2
[76] https://www.nap.edu/read/13164/chapter/12#545
[77] Ibid.

AUTISM

Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of autism after the administration of DTaP vaccine. This one study (Geier and Geier, 2004) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism.

Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of autism after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

Weight of Mechanistic Evidence

The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism as lacking.

Causality Conclusion

Conclusion 10.6: The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and autism.[78]

It is troubling that the only study the IOM could locate regarding whether DTaP causes autism, (Geier and Geier, 2004), concluded there *was* an association between DTaP and autism.[79] No research has been published since 2011 that could change the IOM's conclusion. Based on the foregoing, the CDC cannot validly make the blanket assertion that "Vaccines Do Not Cause Autism."

As with DTaP, there are also no published studies showing that autism is not caused by Hepatitis B, Rotavirus, Hib, Pneumococcal, Inactivated Poliovirus, Influenza, Varicella, or Hepatitis A vaccines – all of which HHS recommends babies receive by one year of age.[80]

Instead, HHS's claim that "Vaccines Do Not Cause Autism" relies almost entirely upon studies exclusively studying only one vaccine, MMR (which is administered no earlier than one year of age), or only one vaccine ingredient, thimerosal, with regard to autism.[81] Putting aside the controversy surrounding these studies, studies which focus on only one vaccine and one ingredient while ignoring the entire balance of the CDC's pediatric vaccine schedule cannot support the

[78] Ibid.

[79] Ibid. Ironically, this study was disregarded "because it provided data from a passive surveillance system [VAERS] and lacked an unvaccinated comparison population," which would be true of any study using VAERS data.

[80] https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent. html

[81] https://www.cdc.gov/vaccinesafety/concerns/autism.html

CDC's overarching declaration that "Vaccines Do Not Cause Autism."

As for the MMR vaccine, the CDC's senior scientist for its seminal MMR-autism study has recently revealed that the CDC concealed an association between MMR and autism. Dr. William Thompson has been a scientist at CDC for nearly two decades and is the CDC's Senior Scientist on dozens of the CDC's peer-reviewed publications, including the core group of the CDC's vaccine-autism safety studies.[82]

Dr. Thompson recently provided a statement through his attorney that the CDC "omitted statistically significant information" showing an association between the MMR vaccine and autism in the first and only MMR-autism study ever conducted by the CDC with American children.[83]

Dr. Thompson, in a recorded phone call in 2014, described how the CDC concealed a finding indicating that healthy children who received the MMR vaccine may be eight times more likely to develop autism than those without the vaccine.[84] He stated: "Oh my God, I can't believe we did what we did. But we did. It's all there. It's all there. I have handwritten notes."[85] Dr. Thompson stated that "If I were forced to testify or something like that, I'm not gonna lie ... I basically have stopped lying."[86] Expressing contrition for concealing the MMR-autism association, Dr. Thompson stated:

> *I have great shame now when I meet families with kids with autism because I have been part of the problem … the CDC is so paralyzed right now by anything related to autism. They're not doing what they should be doing because they're afraid to look for things that might be associated. So anyway there's still a lot of shame with that. … I am completely ashamed of what I did.*[87]

Dr. Thompson also provided the following statement explaining the CDC's concealment of the autism-MMR association with regard to African-American males:

> *My primary job duties while working in the immunization safety branch from 2000 to 2006, were to later co-lead three major vaccine safety studies. … We hypothesized that if we found statistically significant effects at either 18 or 36 month thresholds, we would conclude that vaccinating children early with MMR vaccine could lead to autism-like characteristics or features. We all met and finalized the study protocol and analysis plan ... [and after implementing this plan we found] the adjusted race effect statistical significance was huge.*
>
> *All the authors and I [therefore] met and decided ... to exclude reporting any race effects. The co-authors scheduled a meeting to destroy documents related to the study. The remaining four co-authors all met and brought a big garbage can into the meeting room, and reviewed and went through all the hardcopy documents that we had thought we should discard, and put them into a huge garbage can. However,*

[82] https://www.ncbi.nlm.nih.gov/pubmed/?term=Thompson+WW%5BAuthor%5D
[83] http://www.rescuepost.com/files/william-thompson-statement-27-august-2014-3.pdf
[84] https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio
[85] Ibid.
[86] Ibid.
[87] Ibid.

> *because I assumed it was illegal and would violate both FOIA and DOJ requests, I kept hardcopies of all documents in my office, and I retain all associated computer files. I believe we intentionally withheld controversial findings from the final draft of the Pediatrics paper.*[88]

Hence, for the only vaccine (MMR) actually studied by the CDC with regard to autism, it appears the CDC concealed an association between that vaccine and autism.

When the former Director of the National Institutes of Health, Dr. Bernadine Healy, was asked about whether public health authorities are correct to claim that vaccines do not cause autism, she answered: "You *can't* say that."[89] When asked again, Dr. Healy explained: "The more you delve into it – if you look at the basic science – if you look at the research that's been done, in animals – if you also look at some of these individual cases – *and*, if you look at the evidence that there *is* no link - what I come away with is: *The question has not been answered*."[90]

Former NIH Director Dr. Healy goes on to explain:

> *This is the time when we do have the opportunity to understand whether or not there are susceptible children, perhaps genetically, perhaps they have a metabolic issue, mitochondrial disorder, immunological issue, that makes them more susceptible to vaccines plural, or to one particular vaccine, or to a component of vaccine. … A susceptible group does not mean that vaccines are not good. What a susceptible group will tell us is that maybe there is a group of individuals, or a group of children, that shouldn't have a particular vaccine or shouldn't have vaccine on the same schedule. …*
>
> *I think the government, or certain health officials in the government, are - have been too quick to dismiss the concerns of these families without studying the population that got sick. I haven't seen major studies that focus on - three hundred kids, who got autistic symptoms within a period of a few weeks of a vaccine.*
>
> *I think that the public health officials have been too quick to dismiss the hypothesis as irrational, without sufficient studies of causation. I think that they often have been too quick to dismiss studies in the animal laboratory, either in mice, in primates, that do show some concerns with regard to certain vaccines. …*
>
> *The reason why they didn't want to look for those susceptibility groups was because they're afraid if they found them—however big or small they were—that that would scare the public away. First of all, I think the public's smarter than that; the public values vaccines. But, more importantly, I don't think you should ever turn your back on any scientific hypothesis because you're afraid of what it might show!* [91]

The CDC's claim that "Vaccines Do Not Cause Autism" also fails to address the

[88] https://www.c-span.org/video/?c4546453/senator-posey-calls-investigation-cdc-fraud
[89] http://www.cbsnews.com/news/the-open-question-on-vaccines-and-autism/
[90] Ibid.
[91] Ibid.

science supporting a link between vaccines and autism.[92] For example, the CDC has not addressed a study which found a 300% increased rate of autism among newborns receiving the hepatitis B vaccine at birth compared to those that did not.[93] Nor a recent and first ever vaccinated vs. unvaccinated pilot study which found vaccinated children had a 420% increased rate of autism and that vaccinated preterm babies had an even higher rate of autism.[94] There is also a persuasive body of science supporting a connection between aluminum adjuvants in vaccines and autism which the CDC has, despite request, failed to directly or persuasively address.[95]

The CDC also failed to address the fact that a review of vaccine injuries compensated by HHS, through the vaccine injury compensation program established by the 1986 Act, "found eighty-three cases of autism among those compensated for vaccine-induced brain damage."[96]

The CDC ignores all the foregoing and continues to rely on its prior MMR-autism studies which, even putting aside Dr. Thompson's claims of concealment, are not applicable to any of the 25 doses of seven vaccines the CDC advised doctors to inject into babies during the first year of life.[97]

The critical need for the CDC to properly engage in vaccine safety science regarding autism is made even more vital by the fact that vaccine makers are immune from liability for vaccine injury and vaccines are not safety-tested prior to licensure to assess whether they cause autism. Without proper *long-term* safety studies comparing those receiving the vaccine to a true placebo group, it is impossible to know prior to licensure whether these products cause autism. There are also no follow-up studies which compare vaccinated to unvaccinated individuals and hence no supportable basis to claim that vaccines do not cause any cases of autism. For the CDC to make this claim, it must demonstrate that a child receiving the entire vaccine schedule is at no greater risk of becoming autistic than a child that is unvaccinated. No such study has ever been done.

The IOM Report referenced above has confirmed that the CDC cannot make this claim even for children receiving only the DTaP, let alone the entire vaccine schedule. It is thus plain that the CDC cannot validly claim that "Vaccines Do Not Cause Autism." The truth is, the CDC, at best, does not know.

5. CDC & IOM Ignore Massive Body of Science Supporting Vaccine Injuries

While the 2011 IOM Report has 75 pages of citations to peer-reviewed sources, there are far more peer-reviewed articles documenting vaccine injuries apparently not even considered by the 2011 IOM Report. Resources for references to these citations can be provided upon request.

[92] https://www.cdc.gov/vaccinesafety/concerns/autism.html
[93] http://hisunim.org.il/images/documents/scientific_literature/Gallagher_Goodman_HepB_2010.pdf
[94] http://www.cmsri.org/wp-content/uploads/2017/05/MawsonStudyHealthOutcomes5.8.2017.pdf
[95] http://vaccine-safety.s3.amazonaws.com/WhitePaper-AlumAdjuvantAutism.pdf
[96] http://digitalcommons.pace.edu/cgi/viewcontent.cgi?article=1681&context=pelr
[97] Further, studies of MMR and autism are simply erroneous because of healthy user bias, which has been emphasized as a serious source of error in epidemiological vaccine safety studies by the CDC's own scientists. https://www.ncbi.nlm.nih.gov/pubmed/1415136

A major theme among these peer-reviewed vaccine papers is the connection between vaccination and chronic disease, mainly autoimmunity and immune mediated neurological disorders and injuries. As detailed above, in the last 30 years, the CDC's childhood vaccine schedule has rapidly increased from 11 injections of 4 vaccines in 1986 to 56 injections of 30 vaccines in 2017. This upsurge has occurred in lock step with the precipitous increase in childhood chronic illness and developmental disabilities which have, during this same period, risen among American children from 12.8% to 54%.[98]

Many of the same disorders that have sharply risen during this period, including neurological and autoimmune disorders, are associated with vaccination as reflected in VAERS[99], manufacturer inserts for vaccines[100], and claims in the Vaccine Injury Compensation Program[101].

The causal mechanisms of these disorders are increasingly understood, and increasingly implicate vaccine exposure during early development.[102] For example, it is now known that early life immune activation can cause autism, mental illnesses, and immune disorders.[103] Vaccines and vaccine adjuvants (particularly in cases of adverse reactions) can cause the types of immune activation known to cause these disorders later in life.[104] Accordingly, there is an urgent and long-overdue need for higher quality vaccine safety research looking at long term neurological and immune outcomes.

Nonetheless, the 2011 IOM Report makes it clear that little has been ruled out with regard to what injures are caused by vaccines. In 2013, the IOM was again engaged by HHS to review the safety of the entire vaccine schedule on a population level.[105] The "committee's literature searches and review were intended to identify health outcomes associated with some aspect of the childhood immunization schedule."[106] "Allergy and asthma, autoimmunity, autism, other neurodevelopmental disorders (e.g., learning disabilities, tics, behavioral disorders, and intellectual disability), seizures, and epilepsy were included as search terms."[107]

Instead of answers, the IOM found that no studies had been conducted to validly assess the safety of the entire vaccine schedule or even portions of the vaccine schedule:

> *[F]ew studies have comprehensively assessed the association between the entire immunization schedule or variations in the overall schedule and categories of health outcomes, and no study … compared the differences in health outcomes … between entirely unimmunized populations of children and fully immunized children. Experts who addressed the committee pointed not to a body of evidence that had been overlooked but rather to the fact that existing research has not been designed to test the entire immunization schedule. …*

[98] https://www.ncbi.nlm.nih.gov/pubmed/20159870
[99] https://wonder.cdc.gov/vaers.html
[100] https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm; See also Section III(7) below.
[101] http://www.uscfc.uscourts.gov/aggregator/sources/7; See also Section IV(4) below.
[102] https://www.ncbi.nlm.nih.gov/pubmed/27540164
[103] https://www.ncbi.nlm.nih.gov/pubmed/25311587
[104] https://www.ncbi.nlm.nih.gov/pubmed/26531688; https://www.ncbi.nlm.nih.gov/pubmed/27908630
[105] https://www.nap.edu/read/13563/chapter/1
[106] https://www.nap.edu/read/13563/chapter/2#5
[107] Ibid.

> *[Also,] studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted.*[108]

While most of the 78 million children in America follow the CDC's childhood vaccine schedule, currently at 56 injections, no science has been done to confirm the safety of this schedule.[109] Even more alarming is that the IOM acknowledges that science does not yet even know "if there is a relationship between short-term adverse events following vaccination and long-term health issues."[110]

Due to the lack of science regarding the safety of the CDC vaccine schedule, the best the IOM could do was conclude: "There is no evidence that the schedule is not safe."[111] Left unsaid, but equally true: There is no evidence that the schedule is safe.

6. CDC Refuses to Conduct Vaccinated vs. Unvaccinated Study

The best and most efficient way to answer a large portion of the questions raised regarding vaccine safety would be a long-term, properly powered (*i.e.*, sized) study comparing the overall health outcomes of vaccinated and completely unvaccinated children. Parents and safety advocacy groups have been demanding for decades that HHS perform such a study. Even the CDC's internal vaccine committee recognizes that assessing "adverse events require more detailed epidemiologic studies to compare the incidence of the event among vaccinees to the incidence among unvaccinated persons."[112]

HHS has nonetheless consistently refused to study health outcomes of the completely unvaccinated. There have been, however, small-scale studies performed outside of HHS comparing vaccinated with completely unvaccinated children. And these smaller studies have consistently reported that the unvaccinated have much better health outcomes.

Dr. Peter Aaby is renowned for studying and promoting vaccines in Africa with over 300 published studies.[113] In 2017, he published a study finding children vaccinated with DTP were 10 times more likely to die in the first 6 months of life than the unvaccinated.[114] Dr. Aaby's study therefore concluded that: "All currently available evidence suggests that DTP vaccine may kill more children from other causes than it saves from diphtheria, tetanus or pertussis."[115] More disturbing is that children vaccinated with DTP were dying from causes never associated with this vaccine, such as respiratory infections, diarrhea, and malaria.[116] This indicated that while DTP

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[108] Ibid.
[109] Ibid.
[110] https://www.nap.edu/read/13563/chapter/5#45
[111] https://www.nap.edu/read/13563/chapter/2#12
[112] https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm
[113] https://www.ncbi.nlm.nih.gov/pubmed/?term=PETER+AABY%5BAuthor+-+Full%5D
[114] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/ Dr. Aaby's study was more reliable than other vaccine safety studies because the subjects were accurately matched. An increasingly recognized problem in vaccine safety studies is that subjects are typically not well-matched. People with pre-existing health problems are reluctant to receive a vaccine, and are therefore unwittingly used as controls. When this happens, the control group is sicker than the vaccine-exposed group at the outset of the study. Studies with this problem give wrong results, and make the vaccine look much safer than it really is. Dr. Aaby's study was one of the few specifically designed to avoid this error.
[115] Ibid.
[116] Ibid.

reduced the incidence of diphtheria, tetanus, and pertussis, it increased susceptibility to other infections.[117]

It is equally troubling that Dr. Aaby's study was based on data that had been collecting dust for over 30 years.[118] This begs the question: what other serious vaccine injuries are we missing because of neglect to conduct proper vaccine safety science?

A pilot study comparing 650 vaccinated and unvaccinated homeschooled children in the United States provides a glimpse of the potential scope of vaccine harm.[119] The study found that, compared to completely-unvaccinated children, fully-vaccinated children had an increased risk of 390% for allergies, 420% for ADHD, 420% for autism, 290% for eczema, 520% for learning disabilities, and 370% for any neuro-developmental delay.[120] Fully-vaccinated pre-term infants had an increased risk of 1,450% for a neurodevelopmental disorder, which includes a learning disability, ADHD or autism, compared to completely unvaccinated preterm infants.[121]

Another recent study compared children receiving the flu shot with those receiving a saline injection in a prospective randomized double-blind study.[122] Both groups had the same rate of influenza but the group receiving the flu shot had a 440% increased rate of non-influenza infection.[123] Like the DTP study, the flu vaccine increased susceptibility to other infections.

As a final example, the CDC in 2001 unwittingly conducted a narrow vaccinated versus unvaccinated study comparing children receiving the Hepatitis B vaccine during the first month of life versus those who did not.[124] The results of this study were never released by the CDC, and an abstract of the study was only recently obtained under a FOIA request.[125] Children vaccinated with Hepatitis B vaccine in the first month of life, compared to children receiving no vaccines in the first month of life, had an increased risk of 829% for ADHD, 762% for autism, 638% for ADD, 565% for tics, 498% for sleep disorders, and 206% for speech delays.[126]

The foregoing limited studies should have raised alarm bells at the CDC regarding the urgency of a proper vaccinated versus unvaccinated study that stakeholders have been demanding the CDC perform for over 20 years. The IOM has even confirmed such a study can be conducted using the CDC's VSD, a database of health records for almost ten million individuals maintained by the CDC.[127] As explained by the IOM: "It is possible to make this comparison [between vaccinated and unvaccinated children] through analyses of patient information contained in large databases such as VSD."[128] Such a retrospective epidemiological study would be quick, cheap and efficient; CDC could literally

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[117] Ibid.
[118] Ibid.
[119] http://www.oatext.com/pdf/JTS-3-186.pdf
[120] Ibid.
[121] http://www.oatext.com/pdf/JTS-3-187.pdf
[122] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[123] Ibid.
[124] http://vaccine-safety.s3.amazonaws.com/CDC_FOIA_Response_UnpublishedStudy.pdf The CDC's study abstract discusses comparing thimerosal exposure by one month of age. Since the only vaccine recommended by one month of age was Hepatitis B, and since only thimerosal containing Hepatitis B vaccine was available at the time of this study, this study primarily compared children receiving Hepatitis B with children that did not receive this vaccine.
[125] Ibid.
[126] Ibid.
[127] https://www.nap.edu/read/13563/chapter/2#13
[128] Ibid.

conduct this study using the VSD in a matter of minutes. Yet it has never, as far as the public knows, been done. [129]

Every year tens of millions of American children are compelled to receive pediatric vaccines. Yet a large-scale study with completely-unvaccinated controls has never been performed to assess the long-term safety of the CDC's recommended vaccine schedule.[130] When vaccine makers are generating over $33 billion in vaccine revenue annually and the CDC is spending over $5 billion annually to promote and purchase vaccines, there is no justification for not performing this study.[131]

7. CDC Ignores Vaccine Manufacturer Disclosures of Potential Adverse Reactions

Vaccine makers are required by law to report to the FDA complaints they receive from consumers of serious adverse reactions from their vaccines.[132] A partial list of these serious adverse reactions is detailed below. While studies have been conducted for a few of these to confirm whether they are in fact caused by vaccines, the CDC has failed to conduct such studies for most of them.

Meningitis *(acute inflammation of protective membranes covering the brain and spinal cord)*; Thrombocytopenia *(low blood platelet count which can result from autoimmune action)*; Stevens-Johnson's Syndrome *(severe autoimmune reaction in which the top layer of skin is burned off and dies)*; Alopecia Areata *(autoimmune skin disease resulting in the loss of hair on the scalp and elsewhere on the body)*; Arthritis *(painful and disabling autoimmune disease that includes joint pain, swelling and progressive stiffness in the fingers, arms, legs and wrists)*; Rhinitis *(irritation and inflammation of nasal mucous membranes impacting ability to breathe properly)*; Insomnia; Lupus Erythematosus *(autoimmune disease in which immune system attacks healthy tissue, including skin, joint, kidney, brain, and other organs)*; Hypotension *(abnormally low blood pressure)*; Guillian-Barre Syndrome *(autoimmune disease that attacks the nerves in the legs, upper body, arms and/or face)*; Polyarteritis Nodosa *(systemic vasculitis that affect medium-sized and small muscular arteries resulting in ruptures and other damage)*; Encephalitis *(inflammation of the brain, which can result in permanent injury)*; Bell's Palsy *(disfiguring paralysis or weakness on one side of the face)*; Radiculopathy *(compressed or pinched nerve)*; Myelitis *(inflammation of spinal cord that can involve nerve pain, paralysis and incontinence)*; Multiple Sclerosis *(immune system attacks nerve fibers, causing them to deteriorate)*; Optic Neuritis *(inflammation*

[129] The CDC's inaction does not appear to be mere neglect since CDC Senior Scientist, Dr. Thompson, recently stated that a proper large scale vaccine safety study "needs to be done" but that the CDC is "not doing what they should be doing because they're afraid to look for things that might be associated." https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio Dr. Thompson even explained that they have the data to conduct such a study and that "we're insane to be sitting on this data and not have an independent group" conduct this study but that it will not happen because "they don't really want people to know that this data exists." Ibid.

[130] In fact, due to the CDC's refusal to act, bills have been proposed in Congress to require such a study, but, the political clout for passage could not be mustered. *See, e.g.,* H.R. 1757 (2013) and H.R. 1636 (2015) ("to conduct or support a comprehensive study comparing total health outcomes ... in vaccinated populations in the United States with such outcomes in unvaccinated populations in the United States").

[131] https://www.hhs.gov/sites/default/files/fy2017-budget-in-brief.pdf; https://www.bccresearch.com/market-research/pharmaceuticals/vaccine-technologies-markets-report-phm014f.html

[132] 21 C.F.R. § 600.80(c)

causing eye pain and partial or complete vision loss); Aplastic anemia *(damage to the bone marrow which slows or shuts down the production of new blood cells)*; Aseptic Meningitis *(acute inflammation of the brain and spinal cord which can lead to death)*; Henoch-Schonlein purpura *(abnormal immune response resulting in inflammation of microscopic blood vessels which can result in multiple organ damage)*; Myalgia *(muscle pain that can become chronic)*; Radial nerve and recurrent nerve paralysis *(nerve injury to the radial nerve that can cause weakness or difficulty moving the wrist, hand or fingers)*; Encephalopathy with EEG disturbances *(damage or malfunction of the brain with severity ranging from altered mental status to dementia, seizures and coma)*; Grand Mal Convulsion *(loss of consciousness and violent muscle contractions)*; Sudden Infant Death Syndrome *(sudden death of infant in good health)*; Diabetes mellitus *(chronic, lifelong condition effecting ability to use energy found in food)*; Pancreatitis *(pancreas attacks its own digestive enzymes)*; Encephalomyelitis *(inflammation of the brain and spinal cord)*; Transverse myelitis *(autoimmunity causing inflamed spinal cord which may result in paralsis)*; *Pneumonitis (inflammation of lung tissue)*; Ocular Palsies *(damage to the nerve of the eye that controls eye movement)*; Ataxia *(brain damage resulting loss of full control of bodily movement, impaired speech, eye movement, and swallowing)*; Retrobulbar Neuritis *(inflammation and damage to the optic nerve between the back of the eye and the brain)*; Epididymitis *(inflammation testicle tube which can lead to abscess formation, testicular pain, painful urination, tissue death, and decreased functionality of gonads)*; Orchitis *(inflammation of one or more testicles that can cause infertility, testicular atrophy, pain, and severe pain)*; Nerve Deafness *(hearing loss from damage to the nerve that runs from the ear to the brain)*.[133]

IV. CONFLICTS OF INTEREST IN VACCINE SAFETY

The 1986 Act created a system in which vaccines are licensed, recommended, encouraged, subsidized, and defended by HHS (the **Vaccine Program**).

The lack of evidence supporting vaccine safety is partially the result of the 1986 Act's unfortunate scheme which places the same agency, HHS, in charge of two conflicting duties. On the one hand, HHS is responsible for vaccine safety. On the other hand, HHS is simultaneously required to promote vaccine uptake and defend against any claim that vaccines cause any harm.

Regrettably, it appears that HHS has chosen to focus almost entirely on its vaccine promotion and defense responsibilities to such a degree that it has essentially abandoned its vaccine safety responsibility.

The Vaccine Program has transformed what should be a government watchdog over the pharmaceutical industry with regard to vaccines into an industry partner, with the same interests of promoting and literally defending, with the Department of Justice (**DOJ**) as its defense firm, against any claim of

[133] See vaccine products inserts at https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm

vaccine injury. The result – as reflected in scathing reports by Congress and the HHS Inspector General – is that the Vaccine Program is fraught with pervasive conflicts of interests both structurally and literally with pharmaceutical company insiders.

Usually, when a government watchdog becomes ineffective or conflicted, consumers turn to the last line of recourse against harm caused by a product: class action and product liability attorneys. But in the case of vaccines, even they have been neutered because of the immunity from financial lability given to pharmaceutical companies for harms caused by their vaccines.

The Vaccine Program created by the 1986 Act has unfortunately resulted in a complete lack of accountability for vaccine safety.

1. HHS Licenses Vaccines

The introduction of a new vaccine begins with its licensure by the FDA. A committee at the FDA, the Vaccines and Related Biological Products Advisory Committee (**VRBPAC**), "advises the FDA on whether or not to license new vaccines for commercial use."[134] In reality this committee effectively decides whether a new vaccine gets licensed since its recommendations for licensure are almost always accepted by the FDA. Unfortunately, the members of this board are often pharmaceutical insiders and, as discussed in Section II above, they license vaccines with virtually no safety data.

By the year 2000, most pediatric vaccines on the CDC's vaccine schedule were already licensed by the FDA. That same year, the U.S. House of Representatives' Committee on Government Reform (the **Committee**) issued a report revealing serious conflicts of interest in the VRBPAC.[135] The Committee "determined that conflict of interest rules employed by the FDA and the CDC have been weak, enforcement has been lax, and committee members with substantial ties to pharmaceutical companies have been given waivers to participate in committee proceedings."[136] The Committee further explained that:

> *Perhaps one of the major problems contributing to the overall influence of the pharmaceutical industry over the vaccine approval and recommendation process may be the loose standards that are used by the agency in determining whether a conflict actually exists. In many cases, significant conflicts of interest are not deemed to be conflicts at all.*[137]

For instance, the Committee found that "3 out of 5 FDA advisory committee [VRBPAC] members who voted to approve the rotavirus vaccine in December 1997 [then the most recently approved vaccine by the VRBPAC] had financial ties to pharmaceutical companies that were developing different versions of the vaccine."[138]

Among these five VRBPAC members present and voting to license the rotavirus vaccine: one member's employer had a $9,586,000 contract for a rotavirus vaccine;

[134] http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf
[135] http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf
[136] Ibid.
[137] Ibid.
[138] Ibid.

another member was the principal investigator for a grant from Merck for the development of a rotavirus vaccine; two other members received almost $1,000,000 from vaccine manufacturers toward vaccine development; and even the "consumer advocate" member (an ardent vaccine supporter) had received honoraria, in addition to travel expenses, from Merck.[139]

These members voted to approve this pediatric vaccine even though a temporary voting member raised the following concern: "I would ask the FDA to work with the sponsor to further quantitate what these serious side effects are – specifically the adverse effects, driven in particular by febrile illness – is inducing hospitalizations and what is that level of access. I still don't feel like I have a good grasp of that at this point."[140]

Regarding the VRBPAC, the Committee concluded: "The overwhelming majority of members, both voting members and consultants, have substantial ties to the pharmaceutical industry."[141] Hence, even putting aside the astonishing lack of safety review prior to licensure, extensive conflicts were found to pervade the HHS committee that largely determined whether to license the pediatric vaccines currently on the market.

2. HHS Recommends Vaccines

After a pediatric vaccine is licensed with virtually no safety data by an HHS committee rife with conflicts of interest, another HHS committee, the CDC's Advisory Committee on Immunization Practices (**ACIP**), decides whether to recommend the vaccine for all children in America.

ACIP is the only federal entity to make vaccination recommendations and these recommendations are consistently approved by the CDC.[142] A recommendation by ACIP "for routine use of a vaccine is tantamount to a Federal mandate for vaccine use."[143] This is because "HHS regulations require that all grants for childhood immunizations are subject to the States' implementation of procedures to ensure routine vaccination ... [and] vigorous enforcement of school immunization laws."[144]

ACIP-recommended vaccines are also subsidized by the federal government.[145] In fact, 41% of the entire childhood vaccine market is purchased through ACIP resolutions.[146] This currently amounts to over $4 billion paid to vaccine makers by the CDC, accounting for a third of the CDC's current budget.[147]

Putting all this together: as a result of the 1986 Act, **when the ACIP votes to recommend a pediatric vaccine for general use, the pharmaceutical industry is handed a liability-free, captive market of 78 million children with guaranteed payment**. It is not surprising that with this economic incentive,

[139] Ibid.
[140] Ibid.
[141] Ibid.
[142] Ibid.
[143] Ibid.
[144] Ibid.
[145] https://doi.org/10.1086/420748
[146] Ibid. (Once ACIP votes to add a vaccine to the Vaccine for Children program, payment is provided to vaccine makers without needing additional Congressional appropriations. As pointed out by the CDC: "It is unusual that a federal advisory committee has the power and authority to add benefits to an entitlement program." It is also noteworthy that another 11% of the pediatric vaccine market is purchased through other Congressional appropriations and another 5% from state and local government funding.)
[147] https://www.hhs.gov/sites/default/files/fy2017-budget-in-brief.pdf

the vaccine market has catapulted from $170 million in 1982 to over $33 billion in 2016.[148]

Given these economic incentives, it is obvious that the ACIP should be scrupulously shielded from even an apparent – let alone actual – conflict of interest with vaccine makers. Unfortunately, government reports have found the exact opposite.

The ACIP is comprised of 15 voting members that are *not* federal government employees. Fourteen of these voting members must be medical professionals in the area of immunization.[149] There are also eight non-voting members who represent federal agencies with responsibility for immunization programs and an additional 26 non-voting members of liaison organizations, many of which receive financial support from vaccine makers.[150] As the U.S. House Committee on Government Reform concluded:

> *The absence of any consumer advocates on the ACIP has resulted in an advisory committee that is inherently not 'fairly balanced.'*[151]

Far worse than the structural conflicts in ACIP's composition are the actual conflicts of interests of its members. These conflicts have been highlighted by multiple government reports but due to gridlock and disparate influence on Congress by pharmaceutical companies, Congress has never moved to fix the issues and conflicts it has identified.

One investigation by the U.S. House Committee on Government Reform resulted in a June 15, 2000 report entitled *Conflicts of Interest in Vaccine Policy Making*.[152] The Committee found that ACIP members routinely fail to disclose conflicts with vaccine manufacturers.[153] Moreover, as a matter of routine, "[t]he CDC grants blanket waivers to the ACIP members each year that allow them to deliberate on any subject, regardless of their conflicts, for the entire year."[154] In the congressional inquiry, legal counsel for the ACIP *conceded* that even when serious conflicts are identified, "we generally give them [waivers] to everyone ... we give them out freely."[155] The Committee on Government Reform was troubled:

> *The CDC's policy of issuing annual waivers creates an environment where people do not take the conflict of interest issue as seriously as they should. This policy, in concert with sloppy monitoring of the completeness of members' financial disclosure statements, allows for a clubby environment where ethical concerns are downplayed.*[156]

As an example of this "clubby environment," the Committee found: "Members of the ACIP are allowed to vote on a recommendation for one company's vaccine even if they have

[148] https://www.bccresearch.com/market-research/pharmaceuticals/vaccine-technologies-markets-report-phm014f.html; https://www.ncbi.nlm.nih.gov/books/NBK216815/
[149] https://www.cdc.gov/vaccines/acip/committee/downloads/nominations.pdf
[150] https://www.cdc.gov/vaccines/acip/committee/acip-charter-2016.pdf
[151] http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf
[152] Ibid.
[153] Ibid.
[154] Ibid.
[155] Ibid.
[156] Ibid.

financial ties to a competing firm developing a similar vaccine."[157]

Highlighting these conflict issues, the Committee drew focus on the vaccine most recently approved by the ACIP, a rotavirus vaccine, and whatever conflicts they could identify for the eight members of the ACIP that voted to approve that vaccine for routine pediatric use.[158] The Committee's findings were damning: (1) The chairman served on Merck's Immunization Advisory Board; (2) another member, who shared the patent on a rotavirus vaccine, had a $350,000 grant from Merck to develop the vaccine, and was a consultant for Merck; (3) another member was under contract with the Merck Vaccine Division and received funds from various vaccine makers including Pasteur, and was a principal investigator for SmithKline; (4) another member received a salary and other payments from Merck; (5) another member participated in vaccine studies with Merck, Wyeth, and SmithKline; and (6) another member received grants from Merck and SmithKline.[159]

The Committee was deeply troubled that these members were nonetheless allowed to vote to recommend a pediatric vaccine for universal use.[160]

The Committee was further concerned by its finding that "ACIP liaison representatives have numerous ties to vaccine manufacturers."[161] The Committee found that these liaison members, through whom third-party organizations are permitted to provide opinions regarding a vaccine under review, "provide more than just the opinions."[162] The Committee found them "more like" a voting member of ACIP "than an advisory representative."[163] The advice of these liaison representatives "is solicited frequently by CDC personnel on issues where their organization has a financial interest."[164]

The ACIP also routinely forms subcommittees (called "working groups") which convene behind closed doors and whose recommendations are typically rubber stamped by the ACIP.[165] The Committee was troubled by extensive and routine use of working groups since the participants in these working groups often had conflicts which would have prohibited them from voting during an actual ACIP meeting.[166] The Committee explained: "The ACIPs prolific use of working groups to draft vaccine policy recommendations outside the specter of public scrutiny opens the door to undue special interest access."[167] Regarding the ACIP's most recent working group recommending approval of a vaccine, the Committee found:

> *The working group has ten members, seven of whom have identifiable conflicts of interest with vaccine manufacturers or vaccine interest groups. The group's meetings were held in private with no minutes or records of the proceedings taken. It appears that members who were not allowed to vote because of conflicts of interest ... were allowed to work*

[157] Ibid.
[158] Ibid.
[159] Ibid.
[160] Ibid.
[161] Ibid.
[162] Ibid.
[163] Ibid.
[164] Ibid.
[165] Ibid.
[166] Ibid.
[167] Ibid.

extensively on the recommendation for a long period of time in the working group.[168]

The Committee's damning overall conclusion was that ACIP's process for recommending a vaccine reflected "a system where government officials make crucial decisions affecting American children without the advice and consent of the governed."[169]

After the Committee's scathing report in 2000, one would expect nothing less than drastic reform of ACIP – something that would differentiate it from a biased and self-interested pharmaceutical company board so that the interests of American children are placed ahead of the companies with the resources to influence government. This expectation unfortunately has not been fulfilled.

Indeed, in December 2009, the HHS Office of Inspector General issued another report after an extensive review of the conflicts of CDC's advisory committee members, known as Special Government Employee (**SGEs**), with the first among these committees being the ACIP.[170] The Inspector General found that the "CDC had a systemic lack of oversight of the ethics program for SGEs."[171] For example, the Inspector General found that: "Most of the experts who served on advisory panels in 2007 to evaluate vaccines for flu and cervical cancer had potential conflicts that were never resolved."[172]

The Inspector General reached this conclusion after reviewing the conflict forms, Form 450's, filed by SGEs at the CDC. CDC "must obtain from SGEs" a completed Form 450, which includes "assets, sources of income, and non-income-earning activities."[173] Then, "[b]efore permitting SGEs to participate in committee meetings, CDC must review these forms and certify them to indicate that they are complete and that it has identified and resolved all conflicts of interest."[174] Reviewing CDC's compliance with these requirements, the Inspector General found that nothing had changed in the years since the scathing Congressional Committee on Government Reform report in 2000.[175]

Indeed, the Inspector General found that "CDC certified OGE Forms 450 with at least one omission in 2007 for 97 percent … of SGEs."[176] Almost all of these "had more than one type of omission."[177] Compounding this problem, the Inspector General found that "58 percent … of SGEs had at least one potential conflict of interest that CDC did not identify."[178] Splicing down this 58% of unidentified conflicts, 40% involved employment or grants, 13% involved equity ownership, and 5% involved consulting.[179]

These conflicts are serious, and the CDC "did not inform the SGEs that they would violate the criminal conflict-of-interest statute if they participated in committee work regarding particular matters affecting their specific employers' financial interests."[180]

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[168] Ibid.
[169] Ibid.
[170] https://oig.hhs.gov/oei/reports/oei-04-07-00260.pdf
[171] Ibid.
[172] http://www.nytimes.com/2009/12/18/health/policy/18cdc.html?mcubz=0
[173] https://oig.hhs.gov/oei/reports/oei-04-07-00260.pdf
[174] Ibid.
[175] Ibid.
[176] Ibid.
[177] Ibid.
[178] Ibid.
[179] Ibid.
[180] Ibid.

The Inspector General further concluded that even when the CDC actually identified a conflict, the CDC improperly granted broad waivers despite already being castigated for this improper practice in 2000.[181] Even worse, "32 percent … of SGEs with certified forms had at least one potential conflict of interest that CDC identified but did not resolve."[182] Amazingly, 13 percent of SGEs were allowed to participate in committee meetings without even having a Form 450 on file.[183]

In sum, even after the blistering 2000 Committee on Government Reform report, and numerous damning Congressional hearings before that committee regarding CDC's conflicts with vaccine makers, little changed.[184] Instead of resolving and avoiding these conflicts, the "incestuous relationship" between the CDC and vaccine makers has apparently become even more hardened and enmeshed.[185]

Since an ACIP vote to recommend a vaccine hands a vaccine maker a liability-free market of 78 million American children with guaranteed payment, an ACIP vote must be completely insulated from any influence by pharmaceutical companies. Instead, the ACIP and its working groups, are inundated with conflicts of interest and ties to these companies.

3. HHS Promotes Vaccines

Not only is the process for licensing and recommending vaccines riddled with conflicts, so is HHS's process for promoting vaccines.

While the CDC states on its website – not less than 130 times – that "CDC does not accept commercial support," this is simply not true.[186] For example, in reviewing this very issue, the British Medical Journal, which it asserts is "one of the world's most influential and widely read medical journals," reported in 2015:

> *The CDC's image as an independent watchdog over the public health has given it enormous prestige, and its recommendations are occasionally enforced by law. Despite the agency's disclaimer, the CDC does receive millions of dollars in industry gifts and funding, both directly and indirectly, and several recent CDC actions and recommendations have raised questions about the science it cites, the clinical guidelines it promotes, and the money it is taking.*[187]

Explaining the concern with CDC receiving industry funding, the Journal described this as "classic stealth marketing, in which industry puts their message in the mouths of a trusted third party [here the CDC]."[188] The Journal quoted a methodologist and emeritus professor of medicine at UCLA stating, "Most of us were shocked to learn the CDC takes

[181] Ibid.
[182] Ibid.
[183] Ibid.
[184] *Compare* http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf *with* Ibid.
[185] https://cdn.voiceamerica.com/health/010278/arranga040814.mp3
[186] https://search.cdc.gov/search?query=%22cdc+does+not+accept+commercial+support%22&utf8=%E2%9C%93&affiliate=cdc-main
[187] http://vapers.org.uk/wp-content/uploads/2015/05/CDC-Industry-Funding.pdf
[188] Ibid.

funding from industry," adding that, "it is outrageous that industry apparently is allowed to punish the CDC if the agency conducts research that has the potential to cut into profits."[189]

As another example, Congress expressly created a private foundation, the "CDC Foundation," through which private entities, such as pharmaceutical companies, can support programs at the CDC, endow positions at the CDC, and even place individuals to work at the CDC, paid through "private funding."[190]

Since 1995 the CDC Foundation has raised $620 million to pay for 824 programs at the CDC.[191] In 2015 alone, the CDC Foundation raised $157 million for privately funded programs at the CDC, which then obtain the stamp of legitimacy of the CDC.[192] Merck, for example, funded an $832,916 program through the CDC Foundation to "expand CDC's ... viral hepatitis prevention and vaccination activities."[193] As a result, the CDC is reliant on the CDC Foundation for the continued funding of these projects, and even for the services of the staff placed at the CDC by the CDC Foundation, since the CDC is only permitted to use these funds as expressly directed by the CDC Foundation.[194] This foundation even funds and thus directs CDC "management training courses."[195]

Worse, the promotion track for CDC management extends into vaccine makers. The most prominent example is former CDC Director Dr. Julie Gerberding who headed the CDC from 2002 to 2009. Dr. Gerberding oversaw several controversial studies regarding vaccines produced by Merck, including notably the MMR vaccine, which sought to silence those calling for an increase in the safety profile of those vaccines. When she left the CDC she was rewarded with the position of President of Merck Vaccines in 2010 with a reported estimated $2.5 million annual salary and lucrative stock options.[196]

In contrast, the few CDC officials who have attempted to blow the whistle on how vaccine safety research is conducted and treated at the CDC have become targets of character assassination. For example, following revelations of Dr. Thompson's statements regarding the CDC's improper conduct[197] (some of which was discussed above), he soon found himself marginalized and publicly maligned, despite the CDC's prior reliance on him for over a decade to produce most of its core vaccine safety science.[198]

As Congressman Bill Posey explained in 2014 after investigating the CDC's approach to vaccine safety: the CDC and vaccine industry's "media network [will] twist the truth to disparage, to malign, to vilify, to denigrate anybody who wants any kind of accountability" and added that his review of CDC emails discussing vaccine safety "will make you absolutely sick to your stomach."[199]

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189 Ibid.
190 42 U.S.C.A. §§ 280e-11(h)(1), (2)
191 http://www.cdcfoundation.org/FY2015
192 Ibid.
193 Ibid.
194 42 U.S.C.A. § 280e-11(h)(2)(a)), (7)(b)
195 https://www.cdcfoundation.org/sites/default/files/upload/pdf/CDCF-Form990-2014.pdf
196 https://www.sec.gov/cgi-bin/own-disp?action=getowner&CIK=0001628884
197 https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio
198 https://www.ncbi.nlm.nih.gov/pubmed/?term=Thompson+WW%5BAuthor%5D
199 https://cdn.voiceamerica.com/health/010278/arranga040814.mp3

4. HHS Defends Vaccines

After HHS licenses, effectively mandates, and promotes a vaccine to 78 million American children with virtually no safety data, *this very same government agency is mandated to defend against any claim that the vaccine caused harm*. There is no other product where the very agency responsible to regulate a product and assure its safety is statutorily required to defend against any claim it causes harm.

The Vaccine Injury Compensation Program (**VICP** or **Vaccine Court**) is effectively the only legal recourse in America to obtain compensation for a pediatric vaccine injury.[200] The injured must file a claim in the VICP and litigate against HHS and the DOJ in a quasi-judicial process filed under seal where the injured child effectively cannot obtain documents from or depose vaccine makers to prove how the vaccine caused injury.[201] There is no jury, nor even a judge; special masters play the role of trial judges, with the final say.[202] DOJ and HHS have the government's vast resources while the injured must secure a private attorney.[203] Moreover, an injured child's damages are limited to $250,000 for death and pain and suffering.[204]

Worst of all, despite these limitations, the injured child must *still* almost always prove "causation" – the biological mechanism by which the vaccine caused the claimed injury. Requiring an injured child to prove causation adds insult to injury because, sadly, had HHS conducted the vaccine safety science it demands as proof in the VICP before licensing a vaccine, the child's injury may have been avoided altogether.

There is a disconnect in requiring a child receiving a compulsory pharmaceutical product to medically prove how the vaccine caused his or her injury, where the science to understand vaccine injuries is not being done by the government agency tasked with this job.[205] As confirmed by the IOM, HHS has not conducted the basic science needed to even determine whether commonly claimed vaccine injuries are caused by vaccines.[206] It has failed to conduct even one properly sized study comparing vaccinated to unvaccinated children, despite all the resources at its disposal.[207] It therefore may not be surprising that the Federal Circuit Court of Appeals found, medical science is "a field bereft of complete and direct proof of how vaccines affect the human body."[208]

The Committee on Government Reform explained the devastating consequences suffered by families when children are injured by a vaccine:

> *Every year, a number of children are seriously injured by adverse reactions to vaccines. When such a tragedy befalls a family, they are faced with devastating emotional and financial consequences. As the devastation of adverse reactions can lead to paralysis, permanent disability and death, families without adequate insurance can face enormous expenses, including*

[200] 42 U.S.C. § 300aa-10 et seq.
[201] 42 U.S.C. § 300aa-12
[202] Ibid.
[203] 42 U.S.C. § 300aa-15
[204] Ibid.
[205] See Sections II and III above.
[206] See Section III(2) above.
[207] See Section III(6) above.
[208] *Althen v. Secretary of Health and Human Services*, 418 F.3d 1274 (Fed. Cir. 2005)

> *residential care, therapy, medical equipment, and drugs.*[209]

Yet it is left to the injured child to prove the physiological mechanics by which the vaccine caused injury.[210]

Moreover, Congress left HHS with the authority to set the rules for the VICP and so HHS has used this authority to shortcut its defense of claims for vaccine injuries by changing the rules in its favor. Indeed, the 1986 Act created a Vaccine Injury Table (the **Table**) which quickly compensated certain common injuries associated with each vaccine.[211] If the petitioner suffered an injury on the Table, the burden would shift to HHS to prove the vaccine did not cause the injury.[212] After passage of the 1986 Act, almost 90 percent of claims were Table claims and were quickly settled.[213] Soon after, in 1995 and 1997, HHS amended the Table such that 98% of new claims are off-Table.[214] This change greatly increased the difficulty of obtaining compensation for vaccine injuries.

While HHS changes the VICP rules in its favor, the Committee on Government Reform found "DOJ attorneys make full use of the apparently limitless resources available to them," "pursued aggressive defenses in compensation cases," and "establish[ed] a cadre of attorneys specializing in vaccine injury" and "an expert witness program to challenge claims."[215] The Committee even noted a VICP decision which stated:

> *In the special master's view, [HHS's] counsel's abrasive, tenacious, obstreperous litigation tactics were inappropriate in a program that is intended to be less adversarial; and hindered greatly a fair, expeditious resolution of the case. In addition, counsel lacks simply tact and compassion. Quite frankly; the special master is embarrassed that [HHS's] counsel and ... life care planner represented the United States Government in this case.*[216]

The length of time it has taken to adjudicate claims has also multiplied such that over half of claims now take over five years.[217]

Even with all the foregoing barriers to obtaining compensation for a vaccine injury – notably requiring injured children to prove causation and capping damages for pain and suffering and death at $250,000 – the VICP has paid over $2.1 billion dollars for vaccine injury claims since 2007 and over $3.7 billion since 1986.[218] Just a few of the serious vaccine injuries for which the VICP has paid include:

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[209] https://www.congress.gov/106/crpt/hrpt977/CRPT-106hrpt977.pdf

[210] Further compounding the above issues, babies are unable to describe their symptoms which may explain why most VICP claims are filed by adults. Most adults bring claims for injury after a single flu shot. (https://www.hrsa.gov/vaccinecompensation/data/vicpmonthlyreporttemplate8_1_17.pdf) In contrast, babies receive between five and seven injections of numerous vaccine doses at two months, four months, six months, etc. (See Section I above.) If babies could talk, they may be able to explain why they are crying inconsolably, have decreased activity/lethargy, drowsiness, irritability, fussiness, and loss of appetite – reactions that are considered "normal" side effects of vaccination. (See vaccine product inserts at https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm) But since babies can't talk, the symptoms which would explain a neurological injury, for example, are not knowable until later in life when it is too late to assert a claim.

[211] https://www.hrsa.gov/vaccinecompensation/vaccineinjurytable.pdf

[212] 42 U.S.C. § 300aa-13

[213] Stevens v. Secretary of the Department of Health & Human Services, No. 99-594V (Office of Special Masters 2001)

[214] http://www.gao.gov/assets/670/667136.pdf

[215] https://www.congress.gov/106/crpt/hrpt977/CRPT-106hrpt977.pdf

[216] Ibid.

[217] http://www.gao.gov/assets/670/667136.pdf

[218] https://www.hrsa.gov/vaccinecompensation/data/vicpmonthlyreporttemplate8_1_17.pdf; 42 U.S.C.A. § 300aa-15(a)(2), (4)

> *Guillain-Barre Syndrome, Transverse Myelitis, Encephalopathy (disease altering brain function), Seizure Disorder, Death, Brachial Neuritis, CIDP (inflammation damaging the brain and spinal cord), Acute Disseminated Encephalomyelitis, Premature Ovarian Failure, Bell's Palsy, Idiopathic Thrombocytopenic Purpura (ITP) (autoimmune disease of the blood), Juvenile Diabetes, Rheumatoid Arthritis, Multiple Sclerosis, Fibromyalgia, Infantile Spasms, Anaphylaxis, Ocular Myasthenia Gravis (autoimmune condition causing visual impairments), Hypoxic Seizure*[219]

Recognizing the depths of the foregoing issues and conflicts, in 2006 a bi-partisan group of seven congressmen proposed a bill to create an entirely new government agency solely devoted to vaccine safety.[220] The primary sponsor of this bill explained the need for this bill as follows:

> *Federal agencies charged with overseeing vaccine safety research have failed. They have failed to provide sufficient resources for vaccine safety research. They have failed to fund extramural research. And, they have failed to free themselves from conflicts of interest that serve to undermine public confidence in the safety of vaccines.*
>
> *The American public deserves better and increasingly parents and the public at large are demanding better.*
>
> *I'm a physician. … When I first began working on this issue about seven years ago, I was shocked at the dearth of resources dedicated to vaccine safety research. …*
>
> *When I first tasked my staff with investigating this issue we got a lot of confused responses from federal agencies. The FDA told us to check in with the CDC, saying CDC did most of the vaccine safety research. The CDC referred us over to the NIH. Then, the NIH referred us back to the CDC. …*
>
> *Several issues relating to vaccine safety have persisted for years. The response from public health agencies has been largely defensive from the outset and the studies plagued by conflicts of interest. …*
>
> *Presently, vaccine safety research is an in-house function conducted predominantly by the CDC – the very agency that makes vaccine*

[219] *See, e.g.*, *Kuperus v. Sec'y of the HHS*, No. 01-0060V, 2003 U.S. Claims LEXIS 397 (Fed. Cl. Oct. 23, 2003) (Acute Disseminated Encephalitis from DTaP); *Lerwick v. Sec'y of HHS*, No. 06-847V, 2010 U.S. Claims LEXIS 398 (Fed. Cl. May 26, 2010) (Acute Disseminated Encephalitis from DTaP); *Price v. Sec'y of HHS*, No. 11-442V, 2015 U.S. Claims LEXIS 1554 (Fed. Cl. Oct. 29, 2015) (Anaphylaxis from DTaP); *Rodriguez v. Sec'y of the HHS*, No. 06-559V, 2007 U.S. Claims LEXIS 685 (Fed. Cl. Sep. 14, 2007) (Death from DTaP); *Harry Tembenis & Gina Tembenis v. Sec'y of HHS*, No. 03-2820V, 2010 U.S. Claims LEXIS 950 (Fed. Cl. Nov. 29, 2010) (Death from DTaP); *Agresti v. Sec'y of HHS*, No. 05-0752V, 2009 U.S. Claims LEXIS 517 (Fed. Cl. Mar. 17, 2009) (Encephalopathy from DTaP); *Corzine v. Sec'y of the HHS*, No. 01-230V, 2004 U.S. Claims LEXIS 116 (Fed. Cl. Apr. 23, 2004) (Hypoxic seizure leading to Death from DTaP); *Loving v. Sec'y of HHS*, No. 02-469V, 2013 U.S. Claims LEXIS 1570 (Fed. Cl. Sep. 20, 2013) (Infantile Spasms and Seizure Disorder from DTaP); *Herrell v. Sec'y of the HHS*, No. 08-123V, 2009 U.S. Claims LEXIS 577 (Fed. Cl. Jan. 6, 2009) (Idopathic Thrombocytopenic Purpura from MMR); *Zatuchni v. Sec'y of HHS (In re Snyder)*, No. 94-58V, 2006 U.S. Claims LEXIS 127 (Fed. Cl. May 10, 2006) (Fibromyalgia leading to death from MMR); *Francis v. Sec'y of the HHS*, No. 99-520V, 2007 U.S. Claims LEXIS 172 (Fed. Cl. May 23, 2007) (Ocular Myasthenia Gravis from Varicella).

[220] https://www.congress.gov/bill/109th-congress/house-bill/5887

> *recommendations and promotes their uptake. This should not be.*[221]

This bill did not get out of committee, a fact which likely reflects the ratio of over 1,000 pharma lobbyists in Washington D.C. to virtually no vaccine safety lobbyists.

Many parents, doctors and scientists, as well as politicians, are legitimately concerned about the process whereby vaccines are licensed, recommended, promoted and defended by the same department. This is not because of any conspiracy, or belief in an insidious intent. Rather, the problem is with the structural conflicts and incentive scheme this system creates. There is no incentive for research to uncover which long-term chronic conditions, including which immune and neurological disorders – which *can* clearly result from the current vaccination schedule – are caused by vaccines. Even worse is the disincentive to uncover susceptible populations to vaccine injury. The burden of judging whether a vaccine will seriously injure a child therefore falls on the child's parents. But unless parents can identify with scientific accuracy how a vaccine will injure their child, parents cannot obtain a medical exemption from vaccinating their child. Worse, when a child is injured, the burden again falls on the parent to prove how the vaccine injured their child. This system is inherently unfair and unjust.

CONCLUSION

We can do better. With hundreds of vaccines in the pipeline we must do better. Children susceptible to vaccine injury are as deserving of protection as any other child. Avoiding injury to these children is not only a moral and ethical duty, but will, in fact, strengthen the Vaccine Program. Every parent that does not witness their child suffer a serious reaction after vaccination, such as a seizure or paralysis, is another parent that will not add their voice to the growing chorus of parents opposed to the Vaccine Program due to safety concerns.

These parents and their kindred doctors, scientists and politicians, are also in fact correct that the system for vaccine safety is broken. While we know that vaccines can cause serious adverse reactions, the studies to quantify the rate at which it causes these harms have never been done. While we know that certain children are predisposed to serious injury from vaccines, the studies to identify which children are so disposed have never been done. While we know that valid pre-licensure safety trials take years and must use an inert placebo control, such pre-licensure safety trials are never done for any vaccine. While we know that post-licensure surveillance of vaccines captures less than one percent of adverse reactions, the CDC refused to cooperate to automate VAERS reporting.

In the zeal to protect the Vaccine Program the primary objective of protecting every child to the greatest extent possible from

[221] http://vaccine-safety.s3.amazonaws.com/Weldon_Statement_Vaccine_Safety_final.pdf

harm has been lost. Every child susceptible to a vaccine injury or injured by a vaccine deserves better.

The good news is that fixing this system is not complicated and would require a tiny fraction of the resources already devoted to the Vaccine Program. The quickest solution would be to repeal the 1986 Act and let normal market forces drive vaccine safety. Alternatively, the following actions would immediately correct many of the issues identified in this white-paper:

Reduce Conflicts

1. Prohibit any conflict waivers for members of HHS's vaccine committees.[222]

2. Prohibit HHS vaccine committee members or employees from accepting any compensation from a vaccine maker for twenty years.

3. Require that vaccine safety advocates comprise at least half of HHS's vaccine committees.

Increase Safety Profile

4. Conduct prospective double-blind saline-placebo controlled studies of each vaccine recommended by the CDC as well as the entire CDC vaccine schedule.

5. Conduct properly sized and controlled retrospective and prospective safety studies comparing total health outcomes between vaccinated children and completely unvaccinated children.

6. Create a vaccine safety agency independent of HHS with a budget equal to 50% of HHS's budget for promoting and purchasing vaccines.

7. Automate creation and transmission of adverse reactions reports at hospital/clinic to VAERS.

[222] HHS's vaccine committees include the Advisory Committee on Immunization Practices (ACIP), the Vaccine and Related Biological Products Advisory Committee (VRBPAC), the National Vaccine Advisory Committee (NVAC), and the Advisory Commission on Childhood Vaccines (ACCV).

APPENDIX: Vaccine Ingredients

Most pediatric vaccines do not contain live viruses.[223] For example, (i) polio vaccine (IPV) only contains a killed virus, (ii) hepatitis b vaccine contains a portion of a killed virus, and (iii) diphtheria vaccine contains only a modified toxin released by the diphtheria bacteria.[224] These pieces of killed bacteria or virus or modified toxins are commonly referred to as "antigens." An injection of antigen alone, with nothing more, produces a weak immune response insufficient for creating long-term immunity.[225]

Therefore, many vaccines also contain an "adjuvant," an immune-stimulating substance that increase the immune response to the antigen, so that immunity is created. Aluminum compounds are by far the most commonly used adjuvants in vaccines. They are made of particles of aluminum hydroxide, aluminum phosphate or aluminum sulfate, or mixtures thereof.[226]

It is universally accepted that aluminum is a potent neurotoxin, and toxic to all life.[227] Accordingly, the FDA has established strict limits for aluminum in intravenous feeding solutions (.000005 grams per kg body weight per day). Exposure in infants exceeding this limit causes long term cognitive impairment.[228]

A significant safety problem with aluminum adjuvants is that, because they are made of microscopic particles, they can travel into the brain.[229] Once in the brain, aluminum adjuvants cause long term chronic inflammation.[230] Inflammation in the brain is a cause of neurodevelopmental disorders (e.g. autism) and mental illnesses (e.g. schizophrenia).[231] The resulting mental illness can occur years or decades after the inflammation starts.[232]

Exposure to aluminum adjuvants has increased dramatically in the last 50 years, in parallel with the increasing incidence of neurodevelopmental disorders in children.[233]

Some vaccines also contain other biological matter, both intended and unintended.[234] These include cell lines from aborted human fetuses and biological material from animal tissue.[235] Before being killed in the vaccine manufacturing process, the virus, disease, or toxin (against which the vaccine is supposed to protect) is grown on these human and biological mediums.[236]

Human cell portions in vaccines disclosed by the CDC include "human albumin, human diploid cell cultures (WI-38), human embryonic lung cultures, WI-38 human diploid lung fibroblasts, MRC-5 (human diploid) cells, MRC-5 cells, residual components of MRC-5 cells including DNA and protein, [and] recombinant human albumin."[237] These human cell portions also include billions of strands of human DNA from these aborted fetal cells lines that are of a length capable of inserting themselves into DNA to which they are exposed.[238]

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[223] https://www.vaccines.gov/basics/types/index.html
[224] Ibid.
[225] https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html
[226] Ibid.
[227] https://www.ncbi.nlm.nih.gov/pubmed/2940082; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2819810/; https://www.ncbi.nlm.nih.gov/pubmed/23932735
[228] https://www.ncbi.nlm.nih.gov/pubmed/9164811
[229] https://www.ncbi.nlm.nih.gov/pubmed/23557144
[230] https://www.ncbi.nlm.nih.gov/pubmed/27908630; https://www.ncbi.nlm.nih.gov/pubmed/19740540
[231] https://www.ncbi.nlm.nih.gov/pubmed/27540164; https://www.ncbi.nlm.nih.gov/pubmed/25311587
[232] Ibid.
[233] https://www.cdc.gov/vaccines/schedules/past.html; https://www.ncbi.nlm.nih.gov/pubmed/20159870
[234] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf
[235] Ibid.
[236] Ibid.
[237] Ibid.
[238] http://soundchoice.org/research/dna-fragments-research/; http://soundchoice.org/wp-content/uploads/2012/08/DNA_

The CDC's list of ingredients for the vaccines also includes the following animal parts:

> *monkey kidney cells, vero (monkey kidney) cells, embryonic guinea pig cell cultures, lactose, chick embryo cell culture, bovine calf serum, bovine serum albumin, calf serum protein, fetal bovine serum*[239]

These fragments of cultured human tissue and animal tissue, which have also been found to include various monkey, retro and other unintended viruses, are injected into the muscle tissue of babies and children, along with the adjuvant intended to generate a sustained immune response to the biological matter in the vaccine.[240]

Contaminants_in_Vaccines_Can_Integrate_Into_Childrens_Genes.pdf

[239] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf

[240] https://www.fda.gov/biologicsbloodvaccines/scienceresearch/biologicsresearchareas/ucm127327.htm; https://www. ncbi.nlm.nih.gov/pubmed/20375174. Vaccines also contain, among other ingredients, the following: *2-phenoxethanol, complex fermentation medium, detergent, 5rdimethyl 1-beta-cyclodextrin, Eagle MEM modified medium, enzymes, formaldehyde, gelatin, glutaraldehyde, hemin chloride, hydrolyzed galtin, lactalbumin hydrolysate, Medium 199, Minimum Essential Medium, modified Mueller's growth medium, modified Stainer-Scholte liquid medium, neomycin, neomycin sulfate, phenol polymyxin B, polymyxin B sulfate, polysorbate 80, soy peptone, Stainer-Scholte medium, streptomycin, yeast, yeast protein*

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House Bill 1306
Human Services Committee
January 19, 2021, 2:45 p.m.

Good Morning Chairman Weisz and members of the House Human Services Committee. My name is Mandy Slag and I am the Inafant and Child Death Services Program Director of for the North Dakota Department of Health. I do not have testimony for HB1306 but want to let you know I am available virtually to answer questions, if needed. Thank You.

January 19th, 2021

Dear ND House Human Services Committee Members,

I am writing this morning to urge you to support and pass:

HB 1307 that would enact a law that prohibits places of public accommodation from refusing services, goods, or access to facilities to individuals who refuse vaccination.

HB 1320 that would prohibit state and local government from mandating vaccination and would prohibit making the receipt of a vaccine a condition for entry, education, employment, or services.

HB 1306 that would establish an interim committee to study the interrelationship between sudden infant death syndrome, vaccines, and autism spectrum disorder in children.

I am a retired pharmacist having worked 32 years in hospital, community, and compounding pharmacies. Having done so, I have been eyewitness to vaccine injury over the years and have grave concerns over the SARS-COV2 vaccine. New pharmaceutical drugs commonly take 7-8 years to come on the market because of extensive animal and human trials done first to ensure safety of the drug and thereby ensure the pharmaceutical manufacturer will not face exorbitant damage liability. However, as you likely know, vaccine manufacturers are exempt from damage liability. Though it is amazing that this vaccine has been formulated in a short amount of time, it has not passed the test of time and trials to determine safety. I also oppose this vaccine because it is a mRNA vaccine with the possibility of being incorporated into one's genetic code. Also, the use of cell lines from aborted babies is highly problematic for religious reasons.

Last September, I was sick with what appeared to be COVID and recovered without incident. I have had numerous bouts of influenza in my lifetime which were worse. My observation has been that people with symptoms have not been treated adequately in the early stages of the disease, especially when complaining of shortness of breath. I know of MD's who successfully treat people with Vitamin C, D, and Zn, Quercetin, HCQ or Ivermectin, and Budesonide for inhalation. These treatments were vilified by the powers that be who likely stood to benefit from the emergency authorization of the vaccines. Herd immunity will happen without vaccines. The number of deaths due to COVID is dropping weekly. I would encourage you to keep that statistic before you, and not the number of cases which is determined by a test with dubious false positives. Also, the study of the 30 million people in Wuhan showed that there is not asymptomatic spread of the virus.

Finally, I believe that implementation of a laws to prevent people without the vaccine from enjoying their rights as citizens of the United States of America is unconstitutional. For most, this disease is not worse than the common flu and draconian measures to attempt to vaccinate everyone with an untested vaccine is reckless and suspect. Thank you so much for your time and consideration of my concerns.
Regards,

Maureen Bratten
827 19th St E
Dickinson, ND

I am in support of this bill due to the incomplete science of the long term health effects of vaccinations. Where there is inherent risk, there should also be choice.

These bills regarding personal health freedoms have been brought to our attention. We would hope that you would support these bills to prevent discrimination against those who choose, for many different reasons not to vaccinate.
We have a voting-age son who has a documented reaction to a childhood vaccine and currently has a medical exemption for several vaccines. Knowing the things that can be triggered in a persons body by an immunization has caused us to be quite leery of many vaccines. We are certainly not “anti-vaxxers”, as our son and other family members have received certain other vaccines since his reaction. This term and the

negative attitude that go along with it are proof of the discrimination, shaming and bullying that already is happening to those choose to not vaccinate.
If doctors would not be so afraid to learn the truth about vaccine-triggered illnesses and be honest about them, people would have far more trust.
Ourselves and many, many people we have talked to are choosing to wait on receiving any covid vaccine until short & long term effects are known. Part of the problem is that we have already seen the denial by doctors of injuries/ negative reactions. Obviously resulting in lack of trust.
The thought of mandatory vaccines and the refusing of services/

discrimination to those who refuse is absolutely appalling and I would have never believed it could happen here in the United States of America, certainly not here in North Dakota. This should not be a partisan issue in any way. All you need to do is imagine yourselves or a loved one being forced to receive any sort of medical treatment that you don't want. The idea of taking away personal rights is a dangerous path to go down. We would ask that you support these bills and stand up for the personal health freedom of North Dakota residents!

Sincerely,

Patricia and Tyrone Unruh

Sykeston, ND

HB 1306 Testimony
Human Services Committee
January 19, 2021 2:45 p.m.

Good afternoon, Chairman Weisz and members of the Human Services Committee. My name is Kylie Hall, and I am here to testify in opposition to this bill. I have a Master's Degree in Public Health and have worked at the North Dakota State University Center for Immunization Research and Education for the past 5 and 1/2 years. I would like to make clear that my comments today are not on behalf of NDSU.

The studies on vaccines and autism have been done. We've looked at vaccines and any relationship they may have to SIDS. The studies tell us there is no association between vaccines and autism and vaccines do not cause SIDS. We need to stop putting time and energy into a question that has been answered, and as a society, we need to refocus. We are learning more about autism and its causes every day, but there's more to learn. Let's study that. We are also learning more about SIDS, its causes, and ways to prevent it. Let's keep moving this initiative forward, too.

As a ND taxpayer, I encourage you to oppose this bill. Instead of using taxpayer dollars to fund this study, I would like to see our state legislature act to support those with autism spectrum disorder and support programs that are proven to reduce SIDS, like programs that promote safe sleeping practices.

Thank you.

I support HB1306. Autism has skyrocketed alongside of the skyrocketing number of vaccines. Vaccine manufacturers are liability free. Safety studies for vaccines are not double blind placebo studies, so we really have no idea if this pharmaceutical product is safe or not. They get away with this because vaccines are categorized as biologics.

THE DANGER OF ELIMINATING VACCINE EXEMPTIONS & CURTAILING VACCINE CRITICISM

ICAN
Informed Consent Action Network

Prior to any medical procedure, the U.S. Department of Health & Human Service ("**HHS**") explains that the "voluntary consent of the human subject is absolutely essential."[1] **Coercion invalidates informed consent.**[2] Infringing this right by eliminating vaccine exemptions and curtailing criticism is unethical and un-American given the following facts:

PHARMA HAS NO INCENTIVE TO ASSURE VACCINE SAFETY

1. Immunity from Liability for Vaccine Harms. By the early 1980s, pharmaceutical companies were facing crippling liability for injuries to children caused by their vaccines.[3] Instead of letting these market forces drive them to develop safer vaccines, Congress passed the National Childhood Vaccine Injury Act (the "**1986 Act**") which eliminated pharmaceutical company liability for injuries caused by their vaccine products.[4]

2. Pharmaceutical Company Misconduct. Since 1986, Merck, GSK, Sanofi and Pfizer have paid billions of dollars for misconduct and injuries related to their drug products.[5] These same companies manufacture almost all childhood vaccines, but because of the 1986 Act, cannot similarly be held accountable for misconduct and injuries related to their vaccine products.

HHS CONFLICTED FROM ASSURING VACCINE SAFETY

3. HHS Must Defend Against Any Claim of Vaccine Injury. After eliminating liability for pharmaceutical companies, the 1986 Act established the Vaccine Injury Compensation Program ("**Vaccine Court**"), part of the U.S. Court of Federal Claims, to compensate people injured by vaccines.[6] Under the 1986 Act, HHS is the defendant in Vaccine Court and is legally obligated to defend against any claim that a vaccine causes injury.[7] There is no right to discovery in Vaccine Court and HHS is represented by the formidable resources of the U.S. Department of Justice ("**DOJ**").[8] In nearly every case the injured person bears the burden to prove causation.[9] Despite these hurdles, since 1986, HHS has paid over $4 billion for vaccine injuries.[10]

4. HHS Incriminates Itself if it Publishes or Admits a Vaccine Can Cause a Harm. If HHS publishes any study supporting that a vaccine causes a harm, that study will then be used against HHS in Vaccine Court.[11] This greatly limits HHS's incentive to publish safety studies.

5. CDC's Childhood Vaccine Schedule Was Created by Pharma Insiders. Congress has repeatedly found that the members of the FDA and CDC committees responsible for approving most of the currently licensed and recommended childhood vaccines had serious conflicts of interests with pharmaceutical companies.[12]

VACCINE SAFETY: CONCERNS & LIMITATIONS

6. HHS Fails to Perform Basic Vaccine Safety Requirements. After eliminating the market forces that assured vaccine safety, Congress made HHS directly responsible for vaccine safety pursuant to a section of the 1986 Act entitled the "Mandate for safer childhood vaccines."[13] As HHS recently

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[1] https://ori.hhs.gov/chapter-3-The-Protection-of-Human-Subjects-nuremberg-code-directives-human-experimentation

[2] https://www.utcomchatt.org/docs/biomedethics.pdf

[3] https://www.nap.edu/read/2138/chapter/2#2 ("The litigation costs associated with claims of damage from vaccines had forced several companies [by 1986] to end their vaccine … programs as well as to stop producing already licensed vaccines.")

[4] 42 U.S.C. § 300aa-11 ("No person may bring a civil action for damages in the amount greater than $1,000 or in an unspecified amount against a vaccine administrator or manufacturer in a State or Federal court for damages arising from a vaccine-related injury or death."); Bruesewitz v. Wyeth LLC, 562 U.S. 223, 243 (2011) ("the National Childhood Vaccine Injury Act preempts all design-defect claims against vaccine manufacturers brought by plaintiffs who seek compensation for injury or death caused by vaccine side effects")

[5] https://www.citizen.org/sites/default/files/2408.pdf

[6] 42 U.S.C. § 300aa-12 ("In all proceedings brought by the filing of a petition [in Vaccine Court] the Secretary [of HHS] shall be named as the respondent."); https://www.congress.gov/106/crpt/hrpt977/CRPT-106hrpt977.pdf (HHS amended the Vaccine Court rules to make it extremely difficult to obtain compensation and "DOJ attorneys make full use of the apparently limitless resources available to them," "pursued aggressive defenses in compensation cases," "establish[ed] a cadre of attorneys specializing in vaccine injury" and "an expert witness program to challenge claims.")

[7] Ibid.

[8] Ibid.

[9] The 1986 Act created a Vaccine Injury Table (the "**Table**") which was intended to permit the Vaccine Court to quickly compensate certain common vaccine injuries. 42 U.S.C. § 300aa-12. For Table injuries, the burden shifts to HHS to prove the vaccine is not the cause. 42 U.S.C. § 300aa-13. After passage of the 1986 Act, almost 90% of claims were Table claims and quickly settled. Stevens v. Secretary of HHS, No. 99-594V (Office of Special Masters 2001). However, in the 1990s, HHS amended the Table such that now 98% of new claims are off-Table. http://www.gao.gov/assets/670/667136.pdf. As a result, injured children "must prove that the vaccine was the cause" in almost all cases. https://www.ncbi.nlm.nih.gov/nlmcatalog/101633437

[10] https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/data/monthly-stats-february-2019.pdf

[11] *See fn.* 6 and 9.

[12] http://vaccinesafetycommission.org/pdfs/Conflicts-Govt-Reform.pdf

[13] 42 U.S.C. § 300aa-27

conceded in federal court, it has not performed even the basic requirements of this section, such as submitting reports to Congress on how HHS has improved vaccine safety.[14]

7. Pediatric Vaccine Clinical Trials (i) Lack Placebos and (ii) Are Too Short. The pivotal clinical trials relied upon to license childhood vaccines do not include a placebo-control group and safety review periods in these clinical trials are typically only days or months.[15] The safety profile for a pediatric vaccine is therefore not known before it is licensed and routinely used in children.[16]

8. Post-Licensure Safety. After licensure and use by the public, federal law requires that the package insert for each vaccine include "*only* those adverse events for which there is some basis to believe there is a *causal* relationship between the drug and the occurrence of the adverse event."[17] Inserts for childhood vaccines include over one hundred serious immune, neurological and other chronic conditions that their manufacturers had a basis to believe are caused by their vaccines.[18]

9. Prevalence of Vaccine Harm. The CDC's Vaccine Adverse Events Reporting System ("**VAERS**"), to which doctors and patients may *voluntarily* report adverse vaccine events, received 58,381 reports in 2018, including 412 deaths, 1,237 permanent disabilities, and 4,217 hospitalizations.[19] An HHS-funded three-year review by Harvard Medical School of 715,000 patients stated that "fewer than 1% of vaccine adverse events are reported" to VAERS.[20] This could mean there are a hundredfold more adverse vaccine events than are reported to VAERS. The CDC has nonetheless refused to mandate or automate VAERS reporting.[21]

10. Children Susceptible to Vaccine Injury. While the Institute of Medicine ("**IOM**") has explained that "most individuals who experience an adverse reaction to vaccines have a preexisting susceptibility," HHS and CDC have failed to conduct studies to identify children susceptible to vaccine harms while at the same time recommending vaccines for all children.[22]

11. Carcinogenicity, Mutagenicity & Infertility. Most vaccines have never been evaluated for their potential to cause cancer, mutate genes or cause infertility.[23]

12. Autism. Autism is the most controversial of the claimed vaccine injuries and the one HHS and CDC declare they have thoroughly studied. Most parents with autistic children claim vaccines (including DTaP, Hep B, Hib, PCV13, and IPV, each injected 3 times by 6 months) are a cause of their child's autism.[24] The CDC tells these parents that "Vaccines Do Not Cause Autism."[25] However, there is no science to support this claim for almost all vaccines. For example, reports from the IOM in 1991 and 2012, and HHS in 2014, tried but failed to identify any study to support that DTaP does not cause autism.[26] The same is true for Hep B, Hib, PCV 13, and IPV.[27] The only vaccine actually studied with regard to autism is MMR, and a Senior CDC Scientist claims the CDC did find an increased rate of autism after MMR in the only MMR/autism study ever conducted by the CDC with American children.[28] Moreover, HHS's primary autism expert in Vaccine Court recently provided an affidavit explaining that vaccines can cause autism in some children.[29] Given the lack of studies regarding vaccines and autism, it should come as no surprise that there is a dearth of scientific studies that support the CDC's other claims regarding vaccine safety.

13. HHS Refuses to Conduct Vaccinated Vs. Unvaccinated Studies of Vaccine Schedule. A true epidemic in the U.S. is the fact that 1 in 2 children have an autoimmune, developmental, neurological, or chronic disorder.[30] These conditions have sharply

[14] http://icandecide.org/government/ICAN-HHS-Stipulated-Order-July-2018.pdf
[15] https://icandecide.org/hhs/ICAN-Reply.pdf (see Section I)
[16] Ibid.
[17] https://icandecide.org/hhs/ICAN-Reply.pdf (see Appendix B)
[18] Ibid.
[19] https://wonder.cdc.gov/vaers.html
[20] https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf
[21] https://icandecide.org/hhs/ICAN-Reply.pdf (see Section III)
[22] https://icandecide.org/hhs/ICAN-Reply.pdf (see Section V)
[23] https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm
[24] https://www.ncbi.nlm.nih.gov/pubmed/16685182; https://www.ncbi.nlm.nih.gov/pubmed/25398603; https://www.ncbi.nlm.nih.gov/pubmed/16547798; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1448378/
[25] https://www.cdc.gov/vaccinesafety/concerns/autism.html
[26] https://www.nap.edu/read/1815/chapter/2#7; https://www.nap.edu/read/13164/chapter/12?term=autism#545; https://www.ncbi.nlm.nih.gov/books/NBK230053/pdf/Bookshelf_NBK230053.pdf
[27] https://icandecide.org/hhs/ICAN-Reply.pdf (see Section VI)
[28] http://www.rescuepost.com/files/william-thompson-statement-27-august-2014-3.pdf; https://soundcloud.com/fomotion/cdc-whistle-blower-full-audio; https://www.c-span.org/video/?c4546421/rep-bill-posey-calling-investigation-cdcs-mmr-reasearch-fraud
[29] http://icandecide.org/documents/zimmerman.pdf
[30] https://www.ncbi.nlm.nih.gov/pubmed/21570014

risen in lock-step with the increases in the CDC's recommended vaccine schedule.[31] That schedule has risen from 7 injections of just 2 vaccines in 1986 to the current total of 50 injections of 12 different vaccines.[32] The need to compare health outcomes of vaccinated and unvaccinated children is urgent. In 2017, a seminal study found that babies receiving the DTP vaccine died at 10 times the rate of unvaccinated babies.[33] In another study, children received influenza vaccine or a saline placebo; while both groups had a similar rate of influenza, the vaccinated group had a 440% increased rate of non-influenza infections.[34] A recent pilot study from the School of Public Health at Jackson State University found that 33% of vaccinated preterm babies had a neuro-developmental disorder compared to 0% of the unvaccinated preterm babies; and vaccinated children in this study had an increased risk of 290% for eczema, 390% for allergies, 420% for ADHD, 420% for autism, and 520% for learning disabilities.[35] Nonetheless, HHS and CDC refuse to publish any studies comparing the health outcomes between vaccinated and unvaccinated children.[36]

MMR VACCINE

14. Measles is a Mild Childhood Illness. The mortality rate from measles declined by over 98% between 1900 and 1962 as living conditions improved in this country.[37] In 1962, a year before the first measles vaccine, the CDC reported a total of 408 deaths.[38] That amounts to 1 in 500,000 Americans at a time when measles infected nearly every American.[39]

15. Eliminating Measles Has Increased Cancer Rates. Eliminating measles has increased cancer rates. For example, the International Agency for Research on Cancer found that individuals who never had measles had a 66% increased rate of Non-Hodgkin Lymphoma and a 233% increased rate of Hodgkin Lymphoma.[40] Combined, these cancers killed 20,960 Americans in 2018.[41] As another example, individuals who never had measles, mumps or rubella had a 50% increased rate of ovarian cancer.[42] In 2018, ovarian cancer killed 14,070 Americans.[43] Eliminating measles in this country has caused more deaths from cancer.

16. Eliminating Measles Has Increased Heart Disease. A 22-year prospective study of over 100,000 individuals in Japan revealed that "measles and mumps, especially in case of both infections, were associated with lower risks of mortality from atherosclerotic CVD [heart disease]."[44] Heart disease killed 610,000 Americans in 2018.[45] Eliminating our ecological relationship with measles, mumps and rubella has had serious unintended consequences.

17. Side effects from MMR vaccine. The MMR vaccine has serious risks. For example, the MMR vaccine causes seizures in about 1 in 640 children, five times the rate from measles, as well as "thrombocytopenic purpura," "chronic arthritis," and "brain damage."[46] However, because the MMR was not licensed based on a placebo-controlled clinical trial and post-licensure studies are limited, there are many suspected harms the CDC has yet to confirm or rule out, such as those listed on Merck's package insert for the MMR.[47]

18. Waning Immunity. While the vaccination rate for measles in the United States has been stable over the last 20 years, what has changed is that Americans who have had measles (which confers lifetime immunity) are being replaced by those vaccinated with MMR (which does not typically confer lifetime immunity).[48] MMR produces no immunity in 2% to 10% of vaccinees; and 22 years after two doses of MMR approximately 33% of vaccinees are again

[31] https://www.ncbi.nlm.nih.gov/pubmed/20159870
[32] https://www.cdc.gov/vaccines/schedules/images/schedule1983s.jpg; https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf
[33] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/
[34] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/
[35] http://www.oatext.com/pdf/JTS-3-186.pdf; http://www.oatext.com/pdf/JTS-3-187.pdf
[36] https://icandecide.org/hhs/ICAN-Reply.pdf (see Section VII)
[37] https://www.cdc.gov/nchs/data/vsus/vsrates1940_60.pdf; https://www.cdc.gov/nchs/data/vsus/VSUS_1962_2A.pdf
[38] https://www.cdc.gov/nchs/data/vsus/VSUS_1962_2A.pdf
[39] Ibid.; https://www.census.gov/library/publications/1962/compendia/statab/83ed.html
[40] https://www.ncbi.nlm.nih.gov/pubmed/16406019
[41] https://seer.cancer.gov/statfacts/html/nhl.html; https://seer.cancer.gov/statfacts/html/hodg.html
[42] https://www.ncbi.nlm.nih.gov/pubmed/16490323
[43] https://seer.cancer.gov/statfacts/html/ovary.html
[44] https://www.ncbi.nlm.nih.gov/pubmed/26122188
[45] https://www.cdc.gov/heartdisease/facts.htm
[46] https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf; https://www.cdc.gov/vaccines/hcp/vis/vis-statements/mmr.pdf; https://physiciansforinformedconsent.org/measles/vrs/ (since the measles death from 1959 to 1962 was appx. 400 per 4 million cases https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/e/reported-cases.pdf and death to seizure ratio is appx. 3.25 https://www.cdc.gov/vaccines/pubs/pinkbook/meas.html this amounts to 1 seizure in 3,095 measles cases).
[47] https://www.fda.gov/downloads/BiologicsBloodVaccines/UCM123789.pdf
[48] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/G/coverage.pdf

potentially susceptible to measles.[49] The proportion after 30 years is even higher.[50] Yet the only focus is on children whose parents have reason to believe the MMR may cause them harm, while ignoring the efficacy issues with this vaccine.

OTHER VACCINES

19. DTaP Vaccine. According to the FDA, those vaccinated with DTaP will have fewer symptoms of pertussis, but will become infected and transmit pertussis, and "will be more susceptible to pertussis throughout their lifetimes."[51] This means the children vaccinated for pertussis are more likely to catch and spread pertussis as asymptomatic carriers, while the unvaccinated are less likely to catch pertussis (and when they do will have symptoms and know to stay home).[52] Since pertussis is very common and more of a concern than measles, as long as children vaccinated for pertussis are permitted to attend school, children not vaccinated for measles should also be permitted to attend school. In any event, the immunity provided by DTaP for pertussis, tetanus, and diphtheria wanes within a few years.[53]

20. Inactivated Polio Vaccine. For the last 20 years, the only polio vaccine used in the U.S. is inactivated polio vaccine ("**IPV**"), which is injected intramuscularly, after it was determined that the oral polio vaccine can cause paralysis.[54] Polio is spread through fecal to oral contamination, and IPV does not prevent colonization and transmission of polio; it only potentially prevents polio from traveling to the spinal column.[55] Hence, those vaccinated or not vaccinated with IPV can equally become infected and transmit polio; but, it is the vaccinated who are considered less likely to have symptoms and thus more likely to spread polio.

21. Chicken Pox Vaccine. Children vaccinated for chicken pox can spread chicken pox virus for six weeks after vaccination.[56] Moreover, the immunity from this vaccine wanes and, absent natural boosting from exposure to chicken pox virus, can lead to shingles.[57] The increased risk of shingles from use of this vaccine is why countries, such as the United Kingdom, have not added it to their routine vaccine schedule.[58]

22. Note. There are additional efficacy and safety issues with the above vaccines and other vaccines not addressed due to space constraints. For example, aluminum adjuvant particles in vaccines, which animal studies reveal deposit in brain and bones, or the millions of snippets of human DNA cultured from the cell lines of aborted fetuses in certain vaccines.[59]

ADDITIONAL INFORMATION

The foregoing highlights a few of the vaccine safety and efficacy issues necessitating the need for informed consent for vaccination and the ability to openly criticize our vaccine policies.

At the least, the following should occur before censoring concerns regarding vaccine safety:

a. Vaccine safety duties should be removed entirely from HHS and placed into an independent board;

b. Pharmaceutical companies should be liable for injuries caused by their vaccine products; and

c. The childhood vaccine schedule and each vaccine should be safety tested in a properly sized long-term placebo-controlled clinical trial.

For additional information or to arrange a presentation, please contact Cat Layton at cat@icandecide.org

[49] https://www.ncbi.nlm.nih.gov/pubmed/17339511
[50] Ibid.
[51] https://www.ncbi.nlm.nih.gov/pubmed/24277828; https://www.ncbi.nlm.nih.gov/pubmed/30793754; https://www.ncbi.nlm.nih.gov/pubmed/29180031 ("neither DTP, nor DTaP or Tdap prevent asymptomatic infection and silent transmission of the pathogen")
[52] Ibid.
[53] Ibid.
[54] http://polioeradication.org/polio-today/polio-prevention/the-vaccines/ipv/
[55] Ibid.
[56] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142813.pdf
[57] https://www.ncbi.nlm.nih.gov/pubmed/22659447; https://www.ncbi.nlm.nih.gov/pubmed/24275643
[58] https://www.nhs.uk/common-health-questions/childrens-health/why-are-children-in-the-uk-not-vaccinated-against-chickenpox/
[59] http://vaccinepapers.org/wp-content/uploads/vaccine_papers_brochure_8.5x11.pdf; https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf; https://www.ncbi.nlm.nih.gov/pubmed/5949788; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC274969/; https://www.ncbi.nlm.nih.gov/pubmed/29108182

1-19-21

To whom it may concern,

One of my children received two vaccinations at the same time in his left arm, as was recommended by our pediatrician. He received the vaccinations and within hours his arm swelled up to 3-4 times its normal size, was red, hot, and he was in severe pain. We brought him back in to the clinic and they indicated he was having an allergic reaction to one of the vaccinations but were unable to differentiate which one it to was to as he had received 2 in the same arm. They also informed us "that there is no way to know for certain that it was a result of his vaccination." We brought him in to the clinic 4 times over the next 2 weeks from his symptoms not improving. They were only able to state, "There is nothing we can do." The response to us choosing to put something in our son's body, at a recommendation from our pediatrician, was our son being at risk of losing his arm. Thankfully, he did not, but the realty existed if his allergic response did not improve. We have since stopped vaccinating our children. I believe It should be a parent's right to decide if their child should or should not be vaccinated as we are the ones that assume the "risk of or death" as it states in the medical data sheets when getting the vaccinations. Along with our son having this allergic reaction to the vaccination, out of our 7 children, we have 1 that has severe allergies, it happens to be this same child. Up until the time he was vaccinated as an infant he tolerated eating all the foods we ate. Once vaccinated he has around 20+ allergies, some of them to the point of needing to have an epi-pen to protect his life. Is this a coincidence or is it a result of his vaccinations? We will never truly know the answer to that question and again were told, There is not way to know for certain that it is a result of his vaccination." We are the ones that have to sign a document stating we will not hold pharmaceuticals accountable for our choice. So, shouldn't it be our choice to vaccinate or not? I support HB 1320 as no individual should be forced to get vaccinated against their wishes. I support HB1306 as more research should be done to see if there is a relationship between vaccinations and injury to children. I believe my child was injured and there is nothing that was ever done to study the possibility of a link in his body. Recently through testing we discovered he has severely high levels of aluminum in his hair follicles, is this a coincidence or could it be related to his vaccinations from about 10 years ago? I urge our government to step up to doing more research and to put a stop to forcing parents to possibly cause harm to our own children through possible vaccine mandates.

Sincerely,

Erica Hanson

Lisa Pulkrabek
4795 Co Rd 82
Mandan, ND 58554
701-595-4264
wadenlisa@aol.com
Jan 19, 2021

Members of the House Human Services Committee,

I am writing to you today in support of HB 1306. A BILL for an Act to provide for a legislative management study of the interrelationship between sudden infant death syndrome, vaccines, and autism spectrum disorder in children.

I believe that children that die of SIDS and those who don't die, but have the symptoms of autism are poisoned by adjuvants included in childhood vaccines. Mainly these adjuvants are mercury and aluminum, which are both heavy metals that cross the blood brain barrier and cannot be detoxed out of the body naturally. When too much of these metals accumulates in the brain, it causes neurological disorders, disease and death.

I believe that a study comparing non vaccinated children against vaccinated children and the death and disease / disorders they have and do not have, would be very informative for this state. Children's lives are at stake and this subject deserves to be studied.

I strongly urge a DO PASS on this bill.

Thank you for your time and consideration.

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Relative Incidence of Office Visits and Cumulative Rates of Billed Diagnoses Along the Axis of Vaccination

James Lyons-Weiler [1,*] and Paul Thomas [2]

[1] The Institute for Pure and Applied Knowledge, Pittsburgh, PA 15101, USA
[2] Integrative Pediatrics, Portland, OR 97225, USA; paulthomasmd@drpaul.md
* Correspondence: jim@ipaknowledge.org

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Abstract: We performed a retrospective analysis spanning ten years of pediatric practice focused on patients with variable vaccination born into a practice, presenting a unique opportunity to study the effects of variable vaccination on outcomes. The average total incidence of billed office visits per outcome related to the outcomes were compared across groups (Relative Incidence of Office Visit (RIOV)). RIOV is shown to be more powerful than odds ratio of diagnoses. Full cohort, cumulative incidence analyses, matched for days of care, and matched for family history analyses were conducted across quantiles of vaccine uptake. Increased office visits related to many diagnoses were robust to days-of-care-matched analyses, family history, gender block, age block, and false discovery risk. Many outcomes had high RIOV odds ratios after matching for days-of-care (e.g., anemia (6.334), asthma (3.496), allergic rhinitis (6.479), and sinusitis (3.529), all significant under the Z-test). Developmental disorders were determined to be difficult to study due to extremely low prevalence in the practice, potentially attributable to high rates of vaccine cessation upon adverse events and family history of autoimmunity. Remarkably, zero of the 561 unvaccinated patients in the study had attention deficit hyperactivity disorder (ADHD) compared to 0.063% of the (partially and fully) vaccinated. The implications of these results for the net public health effects of whole-population vaccination and with respect for informed consent on human health are compelling. Our results give agency to calls for research conducted by individuals who are independent of any funding sources related to the vaccine industry. While the low rates of developmental disorders prevented sufficiently powered hypothesis testing, it is notable that the overall rate of autism spectrum disorder (0.84%) in the cohort is half that of the US national rate (1.69%). The practice-wide rate of ADHD was roughly half of the national rate. The data indicate that unvaccinated children in the practice are not unhealthier than the vaccinated and indeed the overall results may indicate that the unvaccinated pediatric patients in this practice are healthier overall than the vaccinated.

Keywords: pediatrics; vaccines; adverse events; relative incidence of office visit

1. Introduction

Vaccines are widely regarded as safe and effective within the medical community and are an integral part of the current American medical system. While the benefits of vaccination have been estimated in numerous studies, negative and nonspecific impact of vaccines on human health have not been well studied. Most recently, it has been determined [1,2] that variation exists in individual responses to vaccines, that differences exist in the safety profile of live and inactivated vaccines, and that simultaneous administration of live and inactivated vaccines may be associated with poor outcomes. Studies have not been published that report on the total outcomes from vaccinations, or the increase or decrease in total infections in vaccinated individuals.

Pre-licensure clinical trials for vaccines cannot detect long-term outcomes since safety review periods following administration are typically 42 days or less [3]. Long-term vaccine safety science relies on post-market surveillance studies using databases such as the US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC's) Vaccine Adverse Events Reporting System (VAERS) and the Vaccine Safety Datalink. VAERS [4] is a passive reporting system in which, according to Ross 2011 [5], "fewer than 1% of vaccine adverse events are reported." The Vaccine Safety Datalink (VSD) can, in principle, according to the Institute of Medicine (IOM, 2013) [6], be used to compare outcomes of vaccines and unvaccinated children. Based on the IOM's recommendation, in 2016, the CDC published a white paper (CDC, 2016 [7]; Glanz et al., 2016 [8]) on studying the safety of their recommended pediatric vaccine schedule. Unfortunately, to date, no studies have been published comparing a diversity of outcomes of vaccinated and unvaccinated children using the VSD.

There are serious limitations inherent to long-term vaccine safety studies as currently implemented. Post-licensure studies on vaccine safety typically employ an "N vs. $N + 1$" design of analysis, meaning they compare fully vaccinated children with fully vaccinated children missing only one vaccine. Despite reports of increases in vaccine cessation, virtually none of the post licensure-vaccine safety studies have included comparisons to groups completely unexposed to vaccines.

A few independent (non-CDC) studies do exist that have compared outcomes between vaccinated and unvaccinated children. A small survey study of 415 families with homeschooled children by Mawson et al., 2017 [9] that compared vaccinated with completely unvaccinated children reported increased risk of many diagnoses among the vaccinated children including (condition, fold-increase): allergic rhinitis (30.1), learning disabilities (5.2), attention deficit hyperactivity disorder (ADHD) (4.2), autism (4.2), neurodevelopmental disorders (3.7), eczema (2.9), and chronic illness (2.4). The increased risk of neurodevelopmental disorders appeared to be higher in cases of preterm births. A study from Germany (Schmitz et al., 2011) [10] reported no increases in adverse outcomes other than atopy.

A limitation of both of these studies is that they relied on parental surveys, and both had a small unexposed group. A further limitation in the German study [10] is that they also defined a child as unexposed to vaccines even if they received vaccination for varicella, rotavirus, pneumococcal, meningococcal, influenza, and/or others; the study, therefore, is not "vaccinated vs. unvaccinated". Studies of Diphtheria, Pertussis, and Tetanus (DTP) vaccine that had an unexposed group found an increased risk of mortality (Mogensen et al., 2017) [11] and asthma (McDonald et al., 2008) [12] in the vaccine exposed group. Gallagher and Goodman, 2008 [13] reported increased ASD in a hepatitis B vaccine-exposed group. Studies funded by the pharmaceutical industry or conducted by the CDC typically tend to find no harm associated with vaccination, while studies conducted without pharmaceutical industry funding have often found harm.

Hooker and Miller 2020 [14] recently found an increase in odds ratio (OR) in developmental delay (OR 2.18), asthma (OR 4.49), and ear infection (OR 2.13) in vaccinated children compared to unvaccinated children in a study using data from three practices. In the current study, we assess the total outcomes of patients ranging in age from 2 months to 10.4 years of all children in a pediatric practice that have not been vaccinated compared to those who have been variably vaccinated based on medical records using a novel measure, the Relative Incidence of Office Visit (RIOV), and compare results from that measure to results obtained using odds ratios of incidence of diagnoses.

2. Materials and Methods

2.1. Data Source and Provenance

A detailed proposal for a retrospective study was submitted to an Institutional Review Board (IRB), and was approved (Pro00031853 letter dated 7 May 2019). The data source for this study was all billing and medical records of Integrative Pediatrics, a private pediatric practice located in Portland, Oregon. Data collected from True North Data (Mill Creek, WA, USA) were de-identified by trained and honest brokers with the Institute for Pure and Applied Knowledge (IPAK) affiliation

who were certified to de-identify patient data as required under the Health Insurance Portability and Accountability Act (HIPAA), thus ensuring that the data analysts never saw identified data. Outcomes were represented by International Classification of Diseases (ICD) codes (See Supplementary Materials Table S1). Coded data were matched back to the identified medical and billing record to provide a data parity check by our honest brokers team.

2.2. Inclusion/Exclusion Criteria

All patients that were born into the practice between 1 June 2008 and 27 January 2019, with a first visit before 60 days of life and a last visit after 60 days. All inclusion/exclusion criteria applied are outlined in Figure 1.

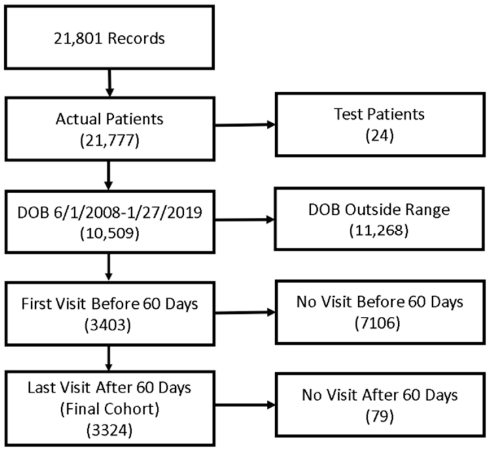

Figure 1. Inclusion criteria diagram.

2.3. Study Population

The inclusion/exclusion criteria lead to 3324 patients, of which 2763 were variably vaccinated, having received 1 to 40 vaccines (Figure 1).

2.4. Demographics

The study population had similar proportions of males and females (Table 1). Nearly all patients had been breastfed in both the vaccinated (96.6%) and the unvaccinated (98%) conditions. Among the vaccinated, 25.16% had a family history of autoimmunity, whereas among the unvaccinated, 31% had the same characteristic. Functionally, this also likely reflects the net effects of decisions between the patient/doctor dyad in determining risk of long-term poor outcomes sometimes associated with vaccination.

Table 1. Demographic variables in the analyzed data set.

Category	Unvaccinated (N = 561)	Vaccinated (N = 2763)	χ^2	*p*
Male (N,%)	279 (49.7%)	1432 (51.8%)	0.819	0.365
Female (N,%)	282 (50.3%)	1331 (48.2%)		
Breastfed (N,%)	550 (98%)	2670 (96.6%)	3.037	0.081
			T-test	
FHA (any)	174 (31%)	695 (25.16%)	28.239	<0.00001
Mean DOC	741	1525	17.69	<0.00001
DOC matched	741	741 (N = 561)	0	1.0
Mean BW (kg) unmatched	3.3	3.28	0.509	0.305

DOC = "Days of Care" = (day of age at last record − day of age at first record); FHA = family history of autoimmunity (at least one condition); Mean BW = average body weight (day 1). The "**T-test**" is in bold in the table because it is a column subheader.

2.5. Variation in Vaccination

The study population has a great diversity in vaccination uptake (Figure 2), reflecting the combined outcome of the patient/physician dyad considering vaccine risk information leading to informed consent on the part of the patients in the practice.

Given the potential of a cohort effect leading to time-based trends in vaccination and to protect against health-care seeking behavior, we calculated for each patient the number of days of care (DOC) as the number of days between the last and first office visits. Importantly, DOC is the range from first to last recorded visits for each patient and is not expected to be influenced overall by healthcare seeking behavior. Among the vaccinated, the mean DOC was 1525 days; among the unvaccinated, the mean DOC was 741 days. This reflects age of patient, not healthcare seeking behavior (prior to matching, unvaccinated: min age, 2 months, mean age 2 years 1 month, and max age 10 years 1 month; vaccinated: min age 2 months, mean age 4 years 3 months, and max age 10 years 6 months; after DOC matching, average age in the vaccinated was also 2 years 1 month). The difference in DOC between the vaccinated and unvaccinated groups was highly significant prior to DOC matching (Student's t, $p < 0.0001$). The patient populations did not differ in mean predicted birthweight (unvaccinated 3.3 kg; vaccinated 3.28 kg, $p = 0.61$ (Student's t)).

From this analysis, only DOC could be a potential confounding variable, potentially collinear with patient age, given full consideration by a matched analysis (see below).

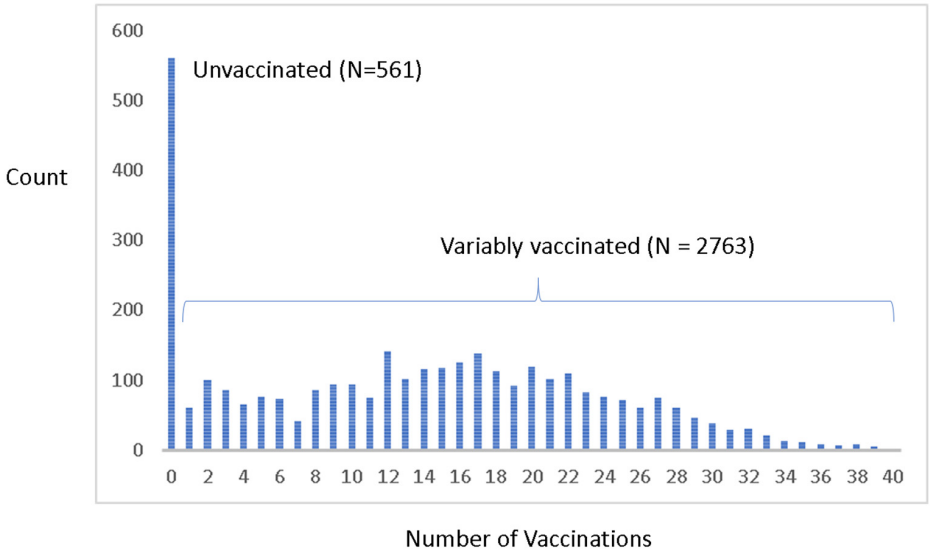

Figure 2. Distribution of vaccination across the patient cohort.

2.6. Analysis 1. Relative Incidence of Average Billed Visitation Rates in Percentile Vaccinating vs. Unvaccinated (Aka "Whole Cohort" Analysis: Unblocked and Unmatched)

2.6.1. Relative Incidence of Office Visit (RIOV)

Typical retrospective analyses of association of outcomes and vaccine exposure rely on the incidence of conditions, which is the percentage of a group with a particular diagnosis of interest. This is the equivalent of "at least one billed office visit", which is a specific form of "at least n office visits" related to a diagnosis. Use of incidence-only is therefore an arbitrary decision on data representation. We generalized the approach by considering the incidence of office visits over each patients' record related to a diagnosis. First, patients were ranked by the number of vaccines accepted. For controls, the average incidence of billed visitations per conditions was calculated within percentiles ranging from the 5th (least vaccinated) to the 90th percentile of vaccination acceptance (Figure 3). For the study outcomes, data were represented as quartiles.

Average incidence of office visit ratio (RIOV) plots for the vaccinated (OV_V) and unvaccinated (OV_{UV}) groups were used to provide assurance of the robustness of the results in the study design and design of analysis. In some cases, the percentile groups in the non-vaccinating end of the immunization axis had zero patients; in those cases, the value of the least vaccinating percentile was used as the denominator for the relative incidence to avoid division by zero. In contrast therefore to "most vaccinated" ("MV") to "unvaccinated" ("UV"), such analyses were therefore "most vaccinated" vs. "least vaccinated" ("LV") patients. This modification had to be applied to the billed diagnoses of "developmental speech delay" and "pain". The *y*-axis in the graphical representation of the data in the percentile analysis is the average incidence of related visitations per condition at a given percentile of vaccination/the average incidence of the related visitations per condition in the unvaccinated (OV_V/OV_{UV}). Incidence ratios were calculated as a ratio of average incidence per patient in each percentile compared to the un- or least-vaccinated group (the latter to avoid division by zero, e.g., ADHD); they are equivalent to an expression of relative risk of diagnosis for each study outcome.

2.6.2. Natural Positive and Negative "Controls"

It is well known that "fever" is a side effect of vaccination. In this analysis, we therefore used incidence of "fever" as positive controls on trends in the data. Similarly, "Well Child" visits can be considered a type of negative control given that they were regularly scheduled events and that they set a comparator value of RIOV for other outcomes (Figure 3).

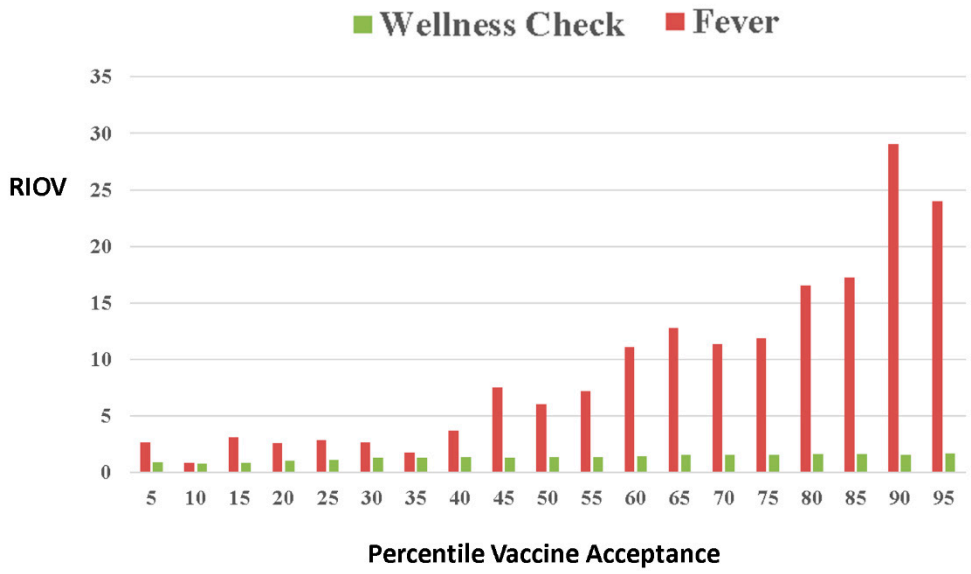

Figure 3. Relative Incidence of Office Visit (RIOV) percentile vaccinated vs. unvaccinated design of analysis: power decreases from left to right; thus, a stable trend (increase or decrease) becomes noteworthy. The data shown are for the Relative Incidence of Office Visits (RIOVs) to average incidence ratio of billed office visits related to fever in the vaccinated compared to the unvaccinated (OV_V/OV_{UV}) conditions and for "Well Child" visit on the right. For all the clinical conditions studied, RIOV reflects the total number of billed office visits per condition per group, reflecting the total disease burden on the group and the population that it represents.

2.7. Analysis 2. Odds Ratio Analysis of Incidence of Diagnoses

For comparison to the RIOV method, the same data were also analyzed using a classical odds ratio of incidence of diagnoses using the rates of diagnosis of each condition in the vaccinated and unvaccinated groups using 95% confidence interval testing. Odds ratios per each ith diagnosis were calculated as the standard ratio of the rate of exposure in those with the diagnosis ($p_{1,i}$) to the rate of exposure in those without diagnosis ($p_{2,i}$), i.e.,

$$OR_i = \frac{p_{1,i} \Big/ (1 - p_{1,i})}{p_{2,i} \Big/ (1 - p_{2,i})} \quad (1)$$

Relative risk ratios for each of the ith conditions with n_{1i} vaccinated in D_1 diagnosed and n_{2i} vaccinated among D_2 without diagnosis was calculated as

$$RR_i = \frac{n_{1,i} \Big/ (D_{1,i})}{n_{2,i} \Big/ (D_{2,i})} \quad (2)$$

Z-tests of proportion were conducted to provide p-values. Effect size was estimated with absolute risk difference (ARD), calculated as (vaccinated diagnosis rate − unvaccinated diagnosis rate).

2.8. Analysis 3. Days-of-Care (DOC)-Matched Vaccinated vs. Unvaccinated RIOV Analysis

Because this is an observational retrospective study, a potential limitation of the time-agnostic analysis is that more recent and younger patients' parents in the practice have opted to vaccinate less frequently and, being younger, have fewer office visits. Thus, fewer diagnoses may be expected to be related to lower exposures due to the combined effects of age (less time) and vaccine choice behaviors. Given this shift occurring in vaccination choices over time, it is possible that a false signal may be embedded due to temporal population-wide shifts due to unmeasured factors, such as cultural shifts in attitudes toward vaccination unrelated to personal outcomes or specific risk. Therefore, an additional analysis was conducted to assess the signal in Days-of-Care (DOC)-matched groups. For each unvaccinated patient, a patient with identical or closest DOC values was selected (without bias) from among the more numerous vaccinated patients. RIOV analysis was conducted on the resulting two groups.

2.9. Analysis 4. DOC-Matched OR on Incidence of Diagnoses. Vaccinated vs. Unvaccinated

As a comparison to analysis 3, odds ratios of incidence using diagnoses were calculated on the same data resulting from the matching of patients for DOC.

2.10. Analysis 5. Cumulative Office Visit Risk (COV Relative Risk)

To provide another view on the data considering the dimension of time, we calculated for all vaccinated patients and separately for the unvaccinated the number of diagnoses of all of the conditions studied at each day of life considering the vaccinated patients born into the practice (N = 2763) compared to the unvaccinated patients (N = 561). We also then calculated the cumulative office visits per each day of life. It is important to note that, in these analyses, a patient can have office visits related to the same diagnosis multiple times. These two representations of the data provide a clear graphical representation of the comparison of the vaccinated and unvaccinated and seem to also provide some insight into the typical timing of onset of a study outcome. Cumulative incidence of risk of office visit (RIOV) would be the cumulative numbers divided by the number of patients per group and would thus also reflect age-specific cumulative probabilities (risk of diagnosis-related office visit). Due to the imbalance in study design, the COV curve for the unvaccinated are expressed as the adjusted number

of office visits expected if the study had been balanced with equal numbers to make the two curves directly comparable in scale when expressed as numbers of office visits (multiplier factor 4.9).

2.11. Analysis 6. Family History Blocked RIOV Analysis

Data on family history of autoimmune disorders or autism were used to block patients into those who had a family history on record (FH+) and those who did not (FH−; blocked design). Average RIOV ratios were calculated to determine whether increased vaccination was associated with increased relative incidence of office visitations in both clinical groups (similar to analysis 1), given family history (FH+ and FH−). The results are not otherwise matched or blocked.

2.12. Analysis 7. RIOV vs. OR Incidence of Diagnoses Power Simulation Comparison

A comparison of the power of the test statistics RIOV and OR on incidence is provided to demonstrate the relative power of RIOV to detect differences and associations compared to odds ratio of diagnoses. Poisson variables drawn from distinct theoretical populations were analyzed using both RIOV (full values of x_i) and OR on incidence ($x_i > 0$). For the simulation, 1000 measurement sets $X = \{x_1, x_2, x_3 \ldots x_n\}$ drawn from a Poisson distribution of 400,000 random values were used to simulate two groups (each of size N = 400) for each Poisson λ value ranging from 1 to 1.1 (step 0.01). The null data ($\lambda = 1$) were used to represent the unvaccinated with no effect.

We simulated an increased effect of vaccines on office visits by increasing λ from 1.01 to 1.1 (step 0.01), with 400,000 values at each level of λ. Increased levels of λ represent increased numbers of office visits due to negative effects of vaccines. The data were analyzed using OR of incidence counting each individual value of $x_i > 0$ as a positive diagnosis and again using RIOV, leaving the generated values of x_i in both simulated groups intact.

2.13. Analysis 8. Gender Blocks

We blocked the cohort data into gender blocks (males and females). RIOV analysis was conducted on the vaccinated vs. unvaccinated in both gender blocks.

2.14. Analysis 9. Age (Youngest Third and Oldest Third) Blocks

One of the honest brokers ranked the patients by date of birth and sent a set of age-ranked identifiers to the analyst (J.L.-W.). The data were blocked into the youngest 1/3 and the oldest 1/3. RIOV analysis was conducted on the vaccinated vs. unvaccinated in both age blocks.

2.15. Analysis 10

We compiled and presented the number of diagnoses for infections targeted by vaccines (considering the CDC pediatric schedule) in the vaccinated and unvaccinated groups in the full cohort. We evaluated each vaccine targeted infection individually and analyzed the association between vaccination status and overall occurrence of vaccine-targeted infections using vaccine-targeted diagnoses. We studied the incidence of vaccine-targeted diagnoses in the vaccinated and unvaccinated groups using the χ^2 test.

3. Results

The overall full-cohort RIOV analysis of the vaccinated (N = 2763) vs. unvaccinated (N = 561) groups are presented in Table 2. There were no cases of ADHD in the unvaccinated group.

Table 2. RIOV and test of proportions of office visits per condition for the fully vaccinated (N1 = 2763) vs. (never) unvaccinated (N2 = 561) groups comparison: these results are not adjusted for days of care. CI = confidence interval.

Condition	Vaxxed	Unvaxxed	RIOV	95% CI	Z	*p*
Fever	759	17	9.065	8.801	12.476	<0.0001
"Well Child" Visits	32,826	4987	1.336	1.149	6.540	<0.0001
Ear Pain	269	16	3.414	3.232	5.310	<0.0001
Otitis media	3105	216	2.919	2.518	23.441	<0.0001
Conjunctivitis	1018	87	2.376	1.935	9.783	<0.0001
Eye Disorders (Other)	277	31	1.814	1.586	3.350	0.0008
Asthma	336	13	5.248	5.065	6.693	<0.0001
Allergic Rhinitis	405	12	6.853	6.662	8.158	<0.0001
Sinusitis	107	5	4.345	4.240	3.566	0.00036
Breathing Issues	621	44	2.866	2.561	7.898	<0.0001
Anemia	979	36	5.522	5.181	13.603	<0.0001
Eczema	512	23	4.520	4.281	8.479	<0.0001
Urticaria	174	17	2.078	1.908	3.027	0.00244
Dermatitis	742	105	1.435	0.992	4.034	<0.0001
Behavioral Issues	343	17	4.097	3.900	6.087	<0.0001
Gastroenteritis	688	30	4.656	4.374	6.543	<0.0001
Weight/Eating Disorders	1115	90	2.515	2.056	10.264	<0.0001
Seizure	43	8	1.091	0.985	0.229	0.8181

RIOVs were calculated using the number of patients as the sample size in each group (Vaxxed and Unvaxxed) with the exception of well-child visits and otitis media visits, both of which were greater in number than the number of patients.

3.1. Analysis 1 Results, Unmatched and Unblocked

RIOV analysis views across deciles provide a graphical view on the trends in the data (e.g., Figure 3). Recalling that the data are represented as the average incidence of billed office visits for patients in each percentile of the vaccine acceptance/unvaccinated groups, the statistic is the incidence of office visits in each percentile relative to the non-vaccinating portion of the population, but it is not relative risk of diagnosis. Results for outcomes were presented by study outcome cluster in quartiles for clarity.

Examination of the unmatched, unblocked results shows widespread increased RIOV among outcomes with all but seizures, and the developmental delay outcomes were significant. Those results are consistent with low power due to low overall incidence in the cohort. These results are not adjusted for days of care.

R1.1. Group A: Autoimmune Respiratory Illnesses. Large increases in office visits were found among the vaccinated group in this group of respiratory illnesses. Our quartile representation shows consistent increases in the incidence of office visits for allergy, allergic rhinitis, asthma, sinusitis, and breathing issues with increased vaccine acceptance compared to the unvaccinated group (Figure 4A). In the most vaccinated quartile compared to unvaccinated comparison, the relative risks (and lower CI) of office visits related to these conditions were estimated for asthma (16.01), allergic rhinitis (20.64), sinusitis (11.32), and breathing issues (6.52); all were highly significant in univariate analysis ($p < 0.0001$).

R1.2. Group B: Attention Deficit/Hyperactive Disorder and Behavioral Issues. Because there were no cases of ADHD in the unvaccinated group, the quartile analysis uses a comparison to the least vaccinated decile to avoid division by zero. Large increases were found in office visits among the vaccinated compared to the unvaccinated groups in outcomes in this group as well. The quartile representation shows large increases in ADHD and moderately large increases in behavioral issues (Figure 4B). Both of these conditions had highly significant relative incidences of office visit (ADHD, RIOV = 53.74; behavioral issues, 10.28) ($p < 0.00001$).

R1.3 Group C: Ear Pain, Otitis media, and Eye Disorders. Issues with the ear showed a range of increases with vaccine acceptance over the quartiles; in the last quartile, the differences were all

significant (ear pain (RIOV = 10.37), otitis media (RIOV = 7.03), and eye disorders (5.53) (Figure 4C) ($p < 0.00001$).

R1.4. Group D: Autoimmune Conditions of the Skin and Blood. Skin reactions commonly observed and sometimes attributed to vaccination showed consistent, moderate increases in RIOV in the last quartile of eczema (2.315), urticaria (4.81), and dermatitis (2.72) (Figure 4D); $p < 0.0001$.

R1.5. Group E: Gastroenteritis, Weight/Eating Disorders, and Seizure. The RIOV of both gastroenteritis and weight/disorders increased over the quartiles with increased vaccine uptake, as did seizure (Figure 4E).

R1.6. Group F: speech, language, social, and learning delays showed variable but nonsignificant response over the axis of vaccination. Autism was only significant at the third quartile (Figure 4F).

Sensitivity analysis for multiple hypothesis testing in the full cohort data did not change the outcome of analyses for most comparisons. Specifically, an increase of the critical value of Z on the test of proportions from 9.98 to 18 resulted in no loss of significance except for seizure; when increased to 19, dermatitis and behavioral issues lost significance.

Associations were found comparing the most vaccinated quartile for most of the outcomes (Table 3) with the exception of developmental delays and autism spectrum disorders (Figure 4). Following the same analysis protocol for all other conditions, the rate of autism was found to be higher at the third quartile of vaccine uptake compared to unvaccinated (Figure 4F). This is expected given that families with children with autism may be inclined to opt out of the vaccination program, potentially reflecting a signal of informed choice by families excluding them from the higher vaccinated quartile.

Table 3. RIOV analysis of outcomes of the vaccinated vs. unvaccinated groups, matched for Days of Care (DOC) matched comparison (N1 = 561 and N2 = 561).

					Test of Proportions	
Condition	**Vaxxed**	**Unvaxxed**	**RIOV**	**95% CI**	**Z**	**P(Z)**
Fever	78	17	4.596	4.412	6.547	<0.00001
"Well Child" Visit	5204	4989	1.045	1.041	2.156	0.0307
Ear Pain	18	16	1.127	1.022	0.354	0.726
Otitis media	355	216	1.646	1.001	8.312	<0.00001
Conjunctivitis	113	87	1.301	1.023	2.042	0.04136
Eye Disorders—Other	38	31	1.228	1.076	0.877	0.3788
Asthma	20	13	1.541	1.437	1.317	0.186
Allergic Rhinitis	21	12	1.753	1.649	1.600	0.1096
Sinusitis	6	5	1.202	1.143	0.306	0.756
Breathing Issues	75	44	1.708	1.502	3.015	0.00252
Anemia	130	36	3.618	3.361	7.912	<0.00001
Eczema	64	23	2.788	2.613	4.581	<0.00001
Urticaria	14	17	0.825	0.925	−0.541	0.5892
Dermatitis	86	105	0.821	1.090	−1.459	0.1443
Behavioral Issues	54	17	3.182	3.026	4.452	<0.00001
Gastroenteritis	89	30	2.972	2.763	5.728	<0.00001
Weight/Eating Disorders	147	92	1.601	1.288	4.023	<0.00001
Seizure	10	8	0.798	0.067	0.874	0.6312
Respiratory Infection	703	382	2.682	1.134	51.85	<0.00001

The calculation of Z for "Well Child" visits compared the proportion of number of office visits per group to the total number of days of care (length of time in practice; per group: vaccinated = 416,101, unvaccinated 416,056) in this DOC-matched analysis.

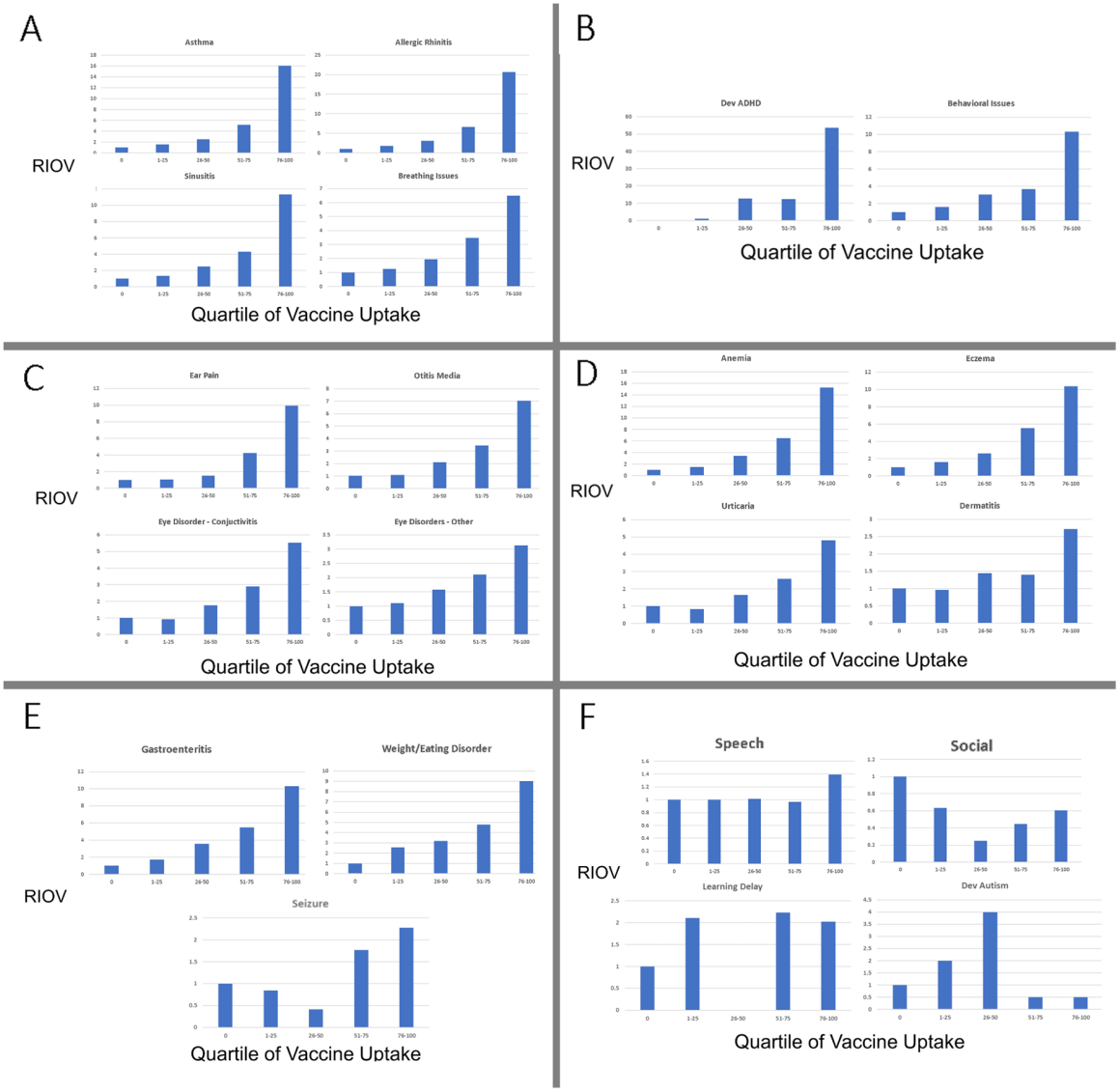

Figure 4. RIOV axis of vaccination percentile vaccine uptake analysis: incidence of study outcome-related office visits relative to that found in the 2763 variably vaccinated compared to the 561 unvaccinated groups for each percentile of vaccine uptake on the *x*-axis. (**A**) Autoimmune respiratory illnesses; (**B**) attention deficit/hyperactive disorder and behavioral issues; (**C**) ear pain, otitis media, and eye disorders; (**D**) autoimmune conditions of the skin and blood; (**E**) gastroenteritis, weight/eating disorders, and seizure; and (**F**) development delays in speech, learning, and social interactions and autism spectrum disorder.

3.2. Analysis 2 Results. Odds Ratio on Incidence of Diagnoses

When the data are represented as the number of patients in each group who had at least one record of an office visit related to a given condition, the signals remain (Table 4). Incidence of diagnoses of each condition was compared between the 561 unvaccinated and the 2763 vaccinated individuals. This result is similar overall to the RIOV analysis; we present the odds ratio, relative risk, lower than 95% of each, along with the absolute risk difference (vaccinated − unvaccinated) in Table 4. Among all of the outcomes, allergic rhinitis and anemia had the highest OR; anemia, weight/eating disorders, and respiratory infection showed the highest absolute risk difference (ARD; all increased in the vaccinated).

Table 4. Incidence of diagnoses of conditions in the vaccinated vs. unvaccinated groups in the population under study.

Outcome	OR	RR	Relevant 95% CI	ARD *	Significant
Fever	9.57	8.08	5.35/7.45	0.15	+/+
Ear Pain	4.11	3.87	2.22/3.40	0.06	+/+
Otitis media	3.11	2.2	2.49/2.11	0.12	+/+
Otitis externa	3.832	3.756	1.395/3.000	0.02	+/+
Conjunctivitis	2.67	2.21	2.04/2.08	0.15	+/+
Eye Disorders (Other)	1.9	1.82	1.24/1.61	0.04	+/+
Ear Disorders	2.359	2.32	1.08/1.86	0.02	+/+
Asthma	3.496	3.361	1.77/2.87	0.04	+/+
Allergic Rhinitis	6.479	5.595	3.31/5.31	0.08	+/+
Sinusitis	3.529	3.451	1.42/2.79	0.02	+/+
Breathing Issues	2.46	2.238	1.74/2.04	0.08	+/+
Anemia	6.334	4.482	4.68/4.6	0.21	+/+
Eczema	4.763	4.301	2.86/3.89	0.09	+/+
Urticaria	2.258	2.183	1.29/1.87	0.03	+/+
Dermatitis	1.591	1.482	1.22/1.37	0.06	+/+
Behavioral Issues	3.13	1.8	1.80/2.60	0.05	+/+
Gastroenteritis	4.479	3.587	2.98/3.56	0.13	+/+
Weight/Eating Disorders	3.146	2.489	2.41/2.35	0.183	+/+
Allergy—Food	2.24	2.23	0.52/1.47	0.004	−/+
Pain	2.569	2.236	1.759/2.147	0.0754	+/+
Respiratory Infection	1.716	1.365	1.351/1.255	0.131	+/+

* ARD = absolute risk difference, calculated as (vaccinated diagnosis rate − unvaccinated diagnosis rate). Odds ratios and relative risk ratios were calculated as described in the Methods section (Equations (1) and (2), respectively). The +, − symbols represent the significance of the OR and RR statistics for each condition for the relevant (upper or lower) 95% CI.

3.3. Analysis 3 Results. Days of Care (DOC) Matched Vaccinated vs. Unvaccinated RIOV Analysis

Due to the likelihood of confounding on DOC, DOC-matched results inform on the robustness of associations. DOC matching also led to matching by age; the average rank of age in both the vaccinated and unvaccinated groups was nearly identical (Student's t, $p = 0.919$). Average age at last office visit was also not significantly different (Student's t, $p = 0.95$). The average age of first office visit differed only by 2 days (6 days vs. 8 days, Student's t, $p < 0.001$).

3.4. Analysis 4 Results. DOC-Matched Incidence

In the analysis of days-of-care-matched data represented as incidence, many of the conditions for which associations were found in the RIOV analysis were found to be undetectable by OR and Relative Risk analysis (Table 5). This included ear pain, eye disorders, ear disorders, asthma, allergic rhinitis, sinusitis, and urticaria (Table 5). Otitis externa, anemia, and respiratory virus infection had the highest absolute risk differences.

While RIOV is reduced in the DOC-matched analysis, the significance of an increased proportion of cases in the vaccinated individuals compared to unvaccinated individuals remains for most outcomes. Risk of seizure was significant for confidence interval testing in this matched analysis but not for Z-test ($p = 0.6321$). Some comparisons had too few counts in the DOC-matched analysis to be reliable (e.g., food allergy had 1 case in the vaccinated group and 2 in the unvaccinated group).

Table 5. Analysis 4: DOC-matched incidence analysis.

Outcome	OR	RR	95% CI	ARD	Significance
Fever	3.88	3.66	2.02/2.75	0.057	+,+
Ear Pain	1.559	1.57	0.723/0.966	0.01	−,−
Otitis media	1.551	1.4	1.17/1.22	0.078	+,+
Otitis externa	2.01	1.996	0.602	1	+,+
Conjunctivitis	1.323	1.273	0.942/1.05	0.033	−,+
Eye Disorders—Other	1.25	1.24	0.729/0.879	0.011	−,−
Ear Disorders	1.29	1.28	0.476/0.671	0.003	−,−
Asthma	1.224	1.22	0.503/0.679	0.003	−,−
Allergic Rhinitis	1.452	1.44	0.615/0.842	0.007	−,−
Sinusitis	1.2	1.2	0.364/0.540	0.008	−,−
Breathing Issues	1.614	1.549	1.504/1.217	0.037	+,+
Anemia	3.216	2.865	2.098/2.368	0.103	+,+
Eczema	2.822	2.682	1.57/2.01	0.047	+,+
Urticaria	1	1	0.471/0.595	0	−,−
Dermatitis	0.884	0.898	1.27/1.13	−0.012	+,+
Behavioral Issues	2.13	2.067	1.11/1.45	0.0266	+,+
Gastroenteritis	2.785	2.572	1.74/2.054	0.073	+,+
Weight/Eating Disorders	1.915	1.721	1.386/1.47	0.089	+,+
Allergy—Food	0.498	0.499	5.51/3.53	−0.001	−,−
Seizure	1.756	1.746	0.511/0.836	0.0053	−,−
Infection—Respiratory	1.716	1.365	1.351/1.255	0.131	+,+
Pain	1.274	1.255	0.783/0.927	0.014	−,−

The symbols "+, – " denote the significance of the relevant (upper or lower) 95% CI analysis for OR and RR.

3.5. Analysis 5 Results. Cumulative Office Visits

The visual impact of the cumulative office visit plots is striking; more so than other plots, the time element (day of life) provides an index by which to compare the accumulation of human pain and suffering from potential vaccine side effects (Figure 5). These results are worth studying closely and noticing the variation among the cumulative office visits per condition and the stark differences between the rates of billed office visits in the most and unvaccinated patients born into the practice.

False discovery sensitivity analysis performed by increasing of the critical of value of Z (test of proportions) from 9.98 to 18 caused a loss of significance for ear and eye conditions only. All other conditions were robustly significant to $Z_{crit} < 19.2$ (behavioral issues). The remainder of the conditions retained significance well beyond $Z_{crit} = 24$.

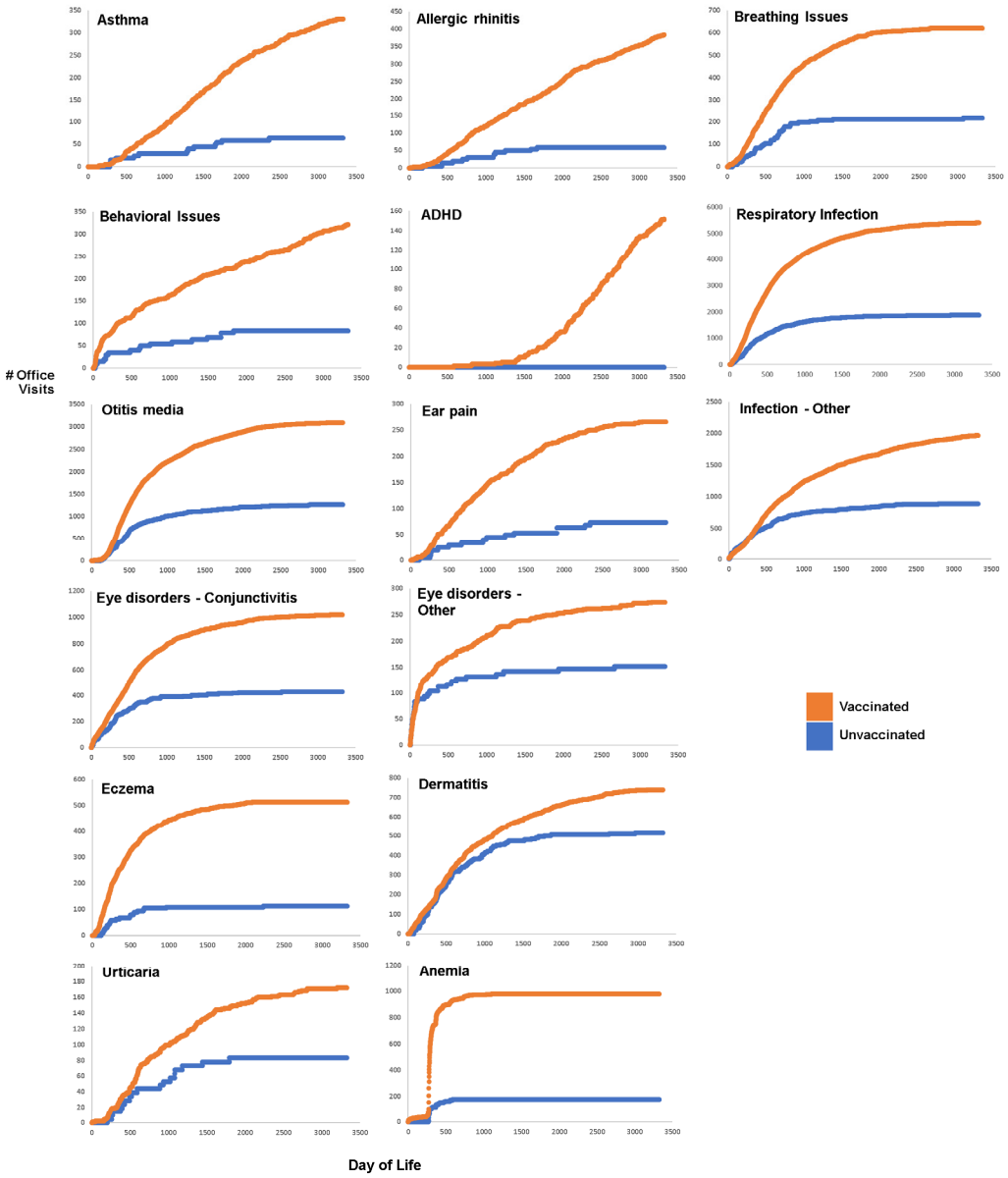

Figure 5. Analysis 5. Cumulative office visits in the vaccinated (orange) vs. unvaccinated (blue) patients born into the practice: the clarity of the age-specific differences in the health fates of individuals who are vaccinated (2763) compared to the 561 unvaccinated in patients born into the practice over ten years is most strikingly clear in this comparison of the cumulative numbers of diagnoses in the two patient groups. The number of office visits for the unvaccinated is adjusted by a sample size multiplier factor (4.9) to the expected value as if the number of unvaccinated in the study was the same as the number of vaccinated.

3.6. Analysis 6 Results. Family History-Blocked RIOV Analysis

The relative incidence of visitation per condition for patients with family history of autoimmune conditions and those patients with no record of family history of autoimmune conditions indicate variation among conditions in the likelihood of family history playing a role, either biologically or by influencing patient choice, in the association of vaccine uptake and outcome (Table 6). Within the pattern (Score FH+ >> Score FH−), family history of autoimmunity itself is consistent with a biological risk factor of the outcome. This was the pattern for fever, sinusitis, and potentially anemia. Within the pattern (Score FH+ << Score FH−), this is consistent with the signal of vaccine choice, implying that further vaccine uptake may have increased the risk of the condition in the unvaccinated. This was

the case in otitis externa, asthma, allergic rhinitis, and dermatitis. In this analysis: FH + N1 = 175 vaccinated, N2 = 88 unvaccinated; FH−, N1 = 385 vaccinated, and N2 = 186 unvaccinated.

Table 6. RIOV score blocked by family history and implication for co-factor status.

Condition	FH+	FH−	Pattern *	Consistent w/Risk Cofactor? **
Fever	21.826	3.818	+,+	yes
"Well Child" Visit	2.690	1.009	+,−	yes
Ear Pain	10.500	13.427	+,+	no
Otitis externa	0.988	9.242	−,+	yes
Otitis media	30.500	21.715	+,+	maybe
Conjunctivitis	19.266	13.443	+,+	maybe
Other Eye Disorder	2.343	3.902	+,+	maybe
Asthma	8.143	19.030	+,+	yes
Allergic Rhinitis	18.382	54.339	+,+	yes
Sinusitis	27.316	8.282	+,+	yes
Breathing Issues	9.524	10.188	+,+	no
Anemia	29.302	20.027	+,+	maybe
Eczema	17.292	13.718	+,+	maybe
Urticaria	4.135	4.404	+,+	no
Dermatitis	1.470	4.922	−,+	yes
Sezure	0.989	0.634	−,−	no
Respiratory Infection	4.556	5.396	+,+	no

* +,+ CI testing significant in both comparisons, +,− significant under FH+ block but not FH- block, etc. ** Yes = FH is a likely co-risk factor for outcome. Numerators (N1 and N2) for both groups were adjusted in fever and "Well Child" visits by a factor of 20; Otitis externa, anemia, and Otitis externa (factor of 2) and Otitis media (factor of 3). This does not change the RIOV score but allows the Z-test score to estimated.

3.7. Analysis 7 Results. Power Simulation

The resulting 1000 comparison sets at each value of λ (N1 = 400 λ = 1.0 vs. N2 = 400 $\lambda = 1.x$ for each $\{x = 0.01, 0.02, 0.03 \ldots 0.50\}$ were analyzed twice, first as an odds ratio of "diagnosis" ("0" = no diagnosis vs. ">0" = diagnoses). The second analysis conducted was a ratio of relative incidence of office visits, with each groups' sum of values within each comparison group representing the total number of office visits being compared.

The simulations were not intended to precisely model the data from the current study; instead, it is intended to demonstrate the principle that the loss of information caused by using the incidence of health condition rather than the more sensitive measure of the number of office visits results in a loss of power to detect adverse events.

Over the range studied, the average increase in power achieved from the analysis using RIOV compared to the odds ratio of diagnoses was doubled over that of odds ratio on incidence of diagnoses (133%) (Figure 6). RIOV was more powerful compared to OR on rates of diagnosis over the simulated range. Our results demonstrate that drug and vaccine safety studies should employ RIOV rather than OR on rates of diagnosis of health conditions that might be attributable to the treatment, therapy, or vaccine.

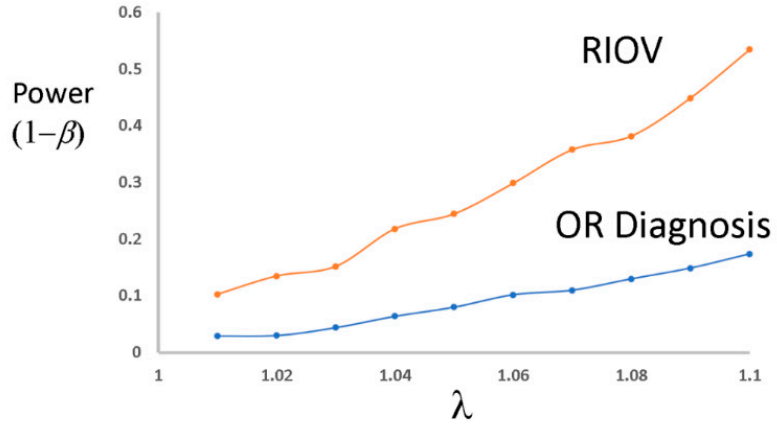

Figure 6. Simulated demonstration of increased power of RIOV (number of office visits) relative to the power of odds ratio of incidence of diagnoses (at least one office visit).

3.8. Analysis 8. Gender Blocks

In the gender block analysis, the following conditions were significant in both the male and female ROIV comparisons: fever, "Well Child" visits, ear pain, otitis media, conjunctivitis, eye disorders (other), asthma, sinusitis, breathing issues, anemia, eczema, behavioral, gastroenteritis, and weight/eating disorder. The developmental delays were largely underpowered for robust analysis due to low overall rates in the practice, but two conditions were significantly lower in the vaccinated females (autism) and males (social development). These results, provided as a table with RIOV values and exact *p*-values of Z in Supplementary Materials Table S2, were not DOC- or age-matched.

3.9. Analysis 9 Age Blocks: Oldest Third and Young Third Blocked Analysis

The following conditions were significantly increased ($p < 0.05$) in the vaccinated group in both age blocks: fever, otitis media, conjunctivitis, sinusitis, breathing issues, anemia, gastroenteritis, and weight/eating disorder. The following conditions were significantly increased in the vaccinated group in the younger (more recent) age block only: asthma and allergic rhinitis. The following conditions were significantly increased in the older age block only: "Well Child" visit and eczema. None of the developmental delay categories were significantly increased in either the older or younger age blocks, likely due to low power. Social delay was significantly increased in the unvaccinated older age block. Two health outcomes, pain and respiratory infection, were increased in the unvaccinated group under the older block but were not significantly different in the younger block. These results, requested by a peer reviewer, demonstrate robustness of many associations to blocking by age and by gender and are provided as tables in Supplementary Materials Table S3 (including RIOV values and exact *p*-values of Z).

3.10. Analysis 10 Results—Vaccine-Targeted Diagnoses

There was a total of 41 vaccine-targeted diagnoses in patients born into the practice, mostly (by far) in varicella (29) and less so in pertussis (10). Overall, the groups show differences in vaccine-targeted diagnoses (Table 7; $\chi^2 = 0.292$, $p = 0.588$). The rates of any diagnosis were vaccinated, 7/2647 (0.00264) and unvaccinated, 34/561 (0.0499). The odds ratio of having a diagnosis of any vaccine-targeted infection (Dx_V/Dx_{UV}) was 0.054 (0.114), *Z*-score, 7.155, $p < 0.0001$. Relative risk of any vaccine-targeted diagnosis was 0.053 (0.119), $Z = 7.117$, $p < 0.0001$, number needed to treat (NNT) = 21.15 (17.72 to 26.225 (benefit)).

Table 7. Incidence of vaccine-targeted diagnoses in the study cohort.

Vaccine Targeted Diagnosis	Vaccinated	Unvaccinated	Deaths
Diphtheria	0	0	0
Hepatitis A	0	0	0
Hepatitis B	0	0	0
HiB *	0	0	0
Measles	0	0	0
Meningococcus	0	0	0
Mumps	0	0	0
Pertussis	1	9	0
Pneumococcal	0	0	0
Rotavirus	0	2	0
Rubella	0	0	0
Tetanus	0	0	0
Varicella	6	23	0
Total **	7	34	0

* Haemophilus influenzae type B; ** Overall for all $\chi^2 = 99.51$. $p < 0.00001$.

The overall probability (risk) of a vaccine-targeted diagnosis in the unvaccinated, however, was only 0.0123, among 13 conditions. It is important to note that zero deaths have been attributed to any vaccine-targeted diagnosis in this practice over the study period.

4. Discussion

The analysis of total outcomes related to vaccine and drug exposures is rarely conducted. It is made complex due to factors such as changes in trends in vaccine or drug acceptance, and the very signal sought—indication of adverse events from vaccines—can be changed by decisions made to avoid vaccine injury by those at risk. We have shown that the outcome of observational studies is sensitive to the choice of test of association and have presented a test (RIOV) more powerful than odds ratios on incidence (Figure 6).

Matching on DOC provides protection against healthcare-seeking behavior because each patient in the vaccinated group is matched to a person in the unvaccinated group with nearly identical length of records in the practice. This also led to matching on age, adding protection against incidental temporal confounds in changes over time in vaccination trends or schedules: both the vaccinated and unvaccinated matched samples are representative of the entire age range of the study cohort. Most of the differences in ratios persist comparing the full cohort analysis when the data were matched for DOC (Analysis 2; Table 3). All RIOV were >1, indicating increased risk of office visit for a specific outcome, except seizure, urticaria, and dermatitis. The change in direction of seizure likely points to "cessation of vaccination signal" following initial events. The difference between the vaccinated and unvaccinated groups was no longer significant for dermatitis following matching for DOC.

The variation in vaccination was the outcome of the final decisions on the part of the patients after consulting with their physicians in the practice. This adherence to the tenets of informed consent, as required by federal regulations for both medical practice and for post-market surveillance studies, is also a key element built into "The Vaccine Friendly Plan" (VFP), developed in a manner to space aluminum-containing vaccines out and to avoid aluminum-containing vaccines (ACVs) whenever a non-ACV is available. The net effects of these changes on aluminum accumulation in children is described in [15]. Children on the CDC schedule would have on average received more vaccines in total; considering the most vaccinated of the VFP compared to the CDC schedule reveals that CDC-scheduled children receive 14 more vaccines by age 2 compared to those most vaccinated on the VFP; by age 5 years, children receive 4 more vaccines (CDC 6, VFP 2), and by ten years, children receive six more vaccines under the CDC schedule compared to the VFP (CDC + 8, VFP, +2). This represents a

total of 24 additional vaccines those on the CDC schedule would have received in 2019 compared to the most vaccinated individuals in this retrospective study. Children on the CDC schedule also would have received more instances of more than one ACV per visit and a larger number of ACVs.

We have found higher rates of office visits and diagnoses of common chronic ailments in the most vaccinated children in the practice compared to children who are completely unvaccinated. The data clearly show different odds of developing many of these adverse health conditions. We have demonstrated in many ways that most of the statistical associations found tend to be robust to age in cohort (days of care), vaccination range, and family history. The first of these is the contrast in the increase in fever cf. "Well Child" visit (Figure 3). The second is robustness of the results to adjustment to days of care provided and of course robustness to the age-matched design as well.

Vaccination appears to have had the largest impact on anemia and respiratory virus infection on the number of office visits in the vaccinated compared to the unvaccinated groups. Due to a small number of cases and corresponding low power, neurodevelopmental conditions and seizures are not well studied using the data available. Autism, at a study-wide rate of 8 per 1000, is far lower than the national rate (18.5–21 per 1000). Speech, learning, and social delays were found to have different full-cohort practice-wide incidences of 0.023, 0.003. and 0.009, respectively. Future studies with less restrictive inclusion criteria that also avoid temporal confounding by matched DOC may help us better characterize these populations in the practice.

Our family history of autoimmune conditions analysis points to numerous conditions likely carrying a genetic risk of vaccine-related adverse health effects. This, however, is only one study from data from a single practice, so any absence of a pattern consistent with a genetic risk of adverse health effects should not be taken as evidence of absence of a role of genetic risk. Larger studies able to estimate the interaction term between family history and vaccine exposure should be undertaken.

Previous studies such as the Mawson study (2017) [9] reported high odds ratios for allergic rhinitis (30.1), learning disabilities (5.2), ADHD (4.2), autism (4.2), neurodevelopmental disorders (3.7), eczema (2.9), and chronic illness (2.4) but were limited because they were based on survey data. While not necessarily fatal to a study, the highly charged nature of the vaccine risk research brings a special concern over survey respondents who might, for the sake of advocacy, seek or unintentionally emphasize their unvaccinated child's lack of diagnoses or amplify their vaccinated child's larger number of diagnoses. Recall bias is a potential factor in this setting, and therefore, our results go a long way to validate those on the Mawson (2017) [9] study. The age range in that study was also restricted to 6- to 12-year-olds, precluding the comparison of the cumulative rates from day 1 of life. Survey studies in the future should obtain HIPAA permissions to access at least a portion of patients' medical records to at least estimate the accuracy of responses compared to medical records from a sample. Despite limitations of survey studies, our results validate many of these results.

Numerous studies conducted in the past have found an association of vaccination with adverse health effects. Numerous studies reporting an association of individual vaccines with adverse study outcomes are too numerous to cite here; many more such studies are reviewed online [16]. For example, a prior study reported a vaccination association with asthma and allergy (e.g., Hurwitz and Morgenstern, 2000) [17].

Concerned over healthy user bias (HUB), i.e., healthier individuals accepting more vaccines leading to differences in study outcome are alleviated in this practice, the physicians and patients overtly came to a joint decision on whether to vaccinate on a patient-by-patient and vaccine-by-vaccine basis. As originally described, if "healthy user bias" was the explanation problem, we would see more illness in the unvaccinated; we found the opposite. We do see the potential signal of informed avoidance of vaccine injury with informed consent and without coercion potentially weakening associations of vaccine injury. This type of effect has historically been interpreted as a form of healthy user bias, but it can be equally interpreted as the signal of avoidance of vaccine injury due to informed consent. Our design of analysis allows the detection of some potential instances (e.g., autism, in which

some individuals at risk of adverse outcome who otherwise would have been in quartiles 3 and 4 stopped vaccinating).

Glanz et al., 2003 [18] found that parents who tended to not accept all vaccines or who delayed vaccines were 2 times more likely to report that they began thinking about vaccines before their child was born and were also 8 times more likely to report that they constantly reevaluate their vaccine decisions than parents who accepted all vaccines. Notably, the signal of change in vaccination behavior following adverse events via informed consent would appear to be detectable as a reduction in the overall incidence of adverse outcomes in the unvaccinated group and fewer office visits related to those outcomes. This opposing trend is the opposite of the expectation that physicians may be more likely to admit the unvaccinated for health issues than the vaccinated (described by [18]). Lifestyle differences between the vaccinated and unvaccinated groups in this practice cannot explain the large difference in outcomes, and if they do, then it would be objective to conclude that everyone should adopt the lifestyle followed by the unvaccinated if they want healthier children. That lifestyle choice includes, for many families, avoiding some or all vaccines, and thus, the lifestyle choice concern is inextricably linked to vaccine exposure.

Because we are considering the potential effects of cumulative vaccination, the potential problem of reverse temporal association with appropriately juxtaposed association is undefined in our study. The RIOV design of analysis makes the reverse temporal association irrelevant, as in the vaccinating population, the cumulative number of vaccinations over the course of a decade is the independent variable. For reverse temporal association concern to manifest, all or most of the diagnoses would have had to had occur prior to the first vaccine, which is extremely unlikely (and are not at all what our data show). Our accumulation diagrams make clear the general tendencies toward requiring medical attention for outcomes in vaccinated vs. unvaccinated segments of the patient population in a distinctly age-specific manner. We have focused on the cumulative effects of vaccines on overall health and therefore, this concern cannot logically apply to the study as it is designed.

4.1. Caveat on Applicability of Results (Generalizability)

Data from this single and unique practice provides a unique opportunity to examine variation in outcomes associated with variation in vaccination. A number of unique factors may limit the generalizability of these findings to other practices, including the fact that patients in the practice appear to be, on average, becoming healthier over time with less chronic illness and seem to have lower frequencies of certain health issues compared to national trends. Under the Vaccine Friendly Plan, parental choice leads to cessation of vaccination more frequently if certain health indications present following vaccination, leading, by observation, to a reduction in identifiable adverse health conditions. Therefore, our results may or may not generalize to other practices but could be expected to apply to practices that adopt the Vaccine Friendly Plan over the next ten years. Our results are likely conservative compared to practices that do not screen actively for patients who might experience further health complications due to vaccines. We conducted our analyses and present our results and interpretation with these caveats in mind.

We have been keenly aware of the brewing political controversies around vaccination studies, including the public's increased awareness of the dearth of long-term randomized prospective clinical studies that use inert placebos such as saline. Many studies have failed to detect the association of vaccines with adverse outcomes; however, they have mostly used correlative retrospective studies focused on odds ratios of mere incidence and have largely been agnostic to intrinsic methodological power. A white paper for conducting retrospective studies on vaccines [6,7] suggests adjusting/correcting for variables that correlate with vaccination status and/or outcomes. This is an incorrect and risky strategy; in a situation with highly collinear independent variables, adjusting for co-risk factors can remove variation in the model important to finding accurate interpretive context of the main variable of interest and prevents the development of risk models to avoid adverse vaccine outcomes. The CDC's white paper has fostered the widespread practice of selecting a subset of available

variables as confounders for adjusted analyses when the functional relationships among collinear variables are not well established, a feat that Vansteelandt et al., 2010 [19] consider "impossible". The protocol introduces serious risks of model misspecification due to adjusting for variables that correlate with outcomes and overadjustment of highly and sometimes multicollinear variables without formal model selection protocols and should be discontinued.

The use of objective criteria for model selection is rare, and the common practice of arbitrary selection of potential confounders could conflate signals when study outcome measures or measurements collinear with study outcome measures are treated as confounders. This increases the risk of overadjustment bias (See Schisterman et al., 2009 [20]). Not all potential confounders are in fact confounders; they may in fact represent a co-risk factor that could be used to predict risk of adverse events. "Adjusting" for risk factors of vaccine adverse events would undo signals expected to be functionally related to risk of vaccine toxicity; these include birthweight, gestational age, mother's income, and mother's age, all variables that are likely multicollinear and may well be important functional indicators of specific risk to vaccine adverse events. Repeated rounds of analysis of the same data set following observation of results to achieve a desired result (toward or away from statistical significance) without showing all the stages of analysis is now understood to increase the likelihood of bias and can be seen as "*p*-hacking" (George et al., 2016) [21] or "results-peeking". Such activities undertaken to achieve a desired result and failure to bring forward the full set of alternative or interim results should be discouraged by scientific journals publishing any type of observational research studies on any subdiscipline of research.

We recommend stratification and blocking with RIOV, which makes explicit the robustness of the association in different subpopulations. It also makes transparent the effect of subgroup sample size on power. Underpowered designs and methods should not yield presented hypothesis testing results (negative or positive) as definitive as they can have misleading and potentially disastrous effects on public health policies.

Given the massive abundance of electronic medical record data, the dearth of independent studies such as ours on vaccine safety is conspicuous. The value of any vaccination program must be seen as a product of the total net health effects of the individual vaccines in the program, and negative findings should provide an agency for a shift in their use, respect for patient choice, and regulation of their excipients and vaccine formulation.

It is little appreciated that the results of observational studies—including retrospective vaccine safety studies—can depend to a large degree on the statistical method(s) selected and the variables used to "adjust for" variation as found in an observational data set. We have introduced a new measure—RIOV—as a more powerful alternative to the commonly used odds ratios of incidence of diagnosis. We have shown OR on incidence of diagnosis to be, via our simulations (Analysis 7), a less powerful test than RIOV. OR on incidence is in fact a de facto lossy transform (binarization of a continuous variable office visits) of RIOV. Office visits carry more information than diagnoses; specifically, measures based on the number of office visits will carry information on severity in addition to the number of yes/no ever-diagnoses. Our days-of-care-matched incidence (diagnosis only) analysis appears to be the least powerful analysis when odds ratio using incidence is considered; reduced power of OR on incidence relative to RIOV analysis may explain the failure of many prior studies to detect an association between exposure to vaccines and adverse health effects. The realization that studies of the relative occurrence of office visits is a more powerful measure than incidence of diagnoses means that future vaccine studies can be made more capable of detecting real associations of adverse outcomes associated with vaccination.

Many families across the United States who are not vaccinating or who have stopped vaccinating their child or children or who choose to partially vaccinate often choose to opt out as a direct result of adverse health observations following vaccination, including health conditions that to date have not been attributed to vaccination based on epidemiological studies. Parents are almost universally told by their child's health care provider that the health issue was not due to the vaccine, in spite of growing

evidence in the scientific literature that supports both plausible mechanisms of action for chronic illnesses including epidemiological associations. It is now apparent that the commonly reported lack of association of adverse events may be due to the use of a test statistic with low intrinsic power and due to problems including model misspecification and overadjustment bias and that further research is needed to update guidelines and recommendations via additional studies.

We attribute the relative dearth of epidemiological findings similar to ours to a number of factors, including the use of incidence of diagnoses, which is clearly likely to be (on first principles) a less sensitive measure of differences in vaccine-induced disease burden. Importantly, RIOV is a readily accessible measure that likely has a higher power to detect associations than ratios of incidence or odds ratio. The underreporting of adverse events to VAERS is also a factor precluding the detection of adverse events that can be attributed to vaccines. According to the US CDC (CDC, 2020) [22] and the US Department of Health and Human Services (HHS) [23], healthcare providers should report to VAERS (a) any adverse event listed in the VAERS Table of Reportable Events Following Vaccination that occurs within the specified time period after vaccinations and (b) an adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine. Also, the CDC reports that healthcare providers are strongly encouraged to report to VAERS (a) any adverse event that occurs after the administration of a vaccine licensed in the United States, whether it is or is not clear that a vaccine caused the adverse event and (b) vaccine administration errors. Finally, the CDC reports that vaccine manufacturers are required to report to VAERS all adverse events that come to their attention; they are also required to pass on such reports to the Food and Drug Administration.

Regardless of such recommended reporting, the inquiry by Harvard Pilgrim (Ross et al., 2011) [5] on underreporting found that vaccine adverse events are underreported to VAERS by a factor of 100. If doctors are not reporting events because they believe they are not attributable to vaccines and VAERS is the primary resource by which new adverse events are detected, heretofore, undetected adverse events are not discovered. Families experiencing vaccine-induced chronic illnesses not yet recognized by science as adverse outcomes to vaccination are going to object strenuously to mandatory vaccination policies, and science will lag behind the public awareness of vaccine-induced human pain and suffering. This lag is currently undermining trust in public health vaccine policies, government regulating and licensing agencies, vaccine makers, and proponents of vaccination—including most of mainstream media in the US—who insist all vaccines are universally "safe and effective."

This study, and others, indicates that the correct path forward should include the enforceable requirement of all physicians to report all adverse health events recorded in medical records over an extended period to capture those adverse events that are latent, whether they are already recognized by the HHS or not, so as to empower users of the VAERS system to be better able to detect adverse outcomes associated with vaccination. Mandatory adoption of an ESP-VAERS-like adverse event detection system embedded in electronic medical record systems in practices and clinics would be beneficial toward a full understanding of vaccine-related morbidity and mortality in our populations and could lead to a significant increase in overall health. This study also provides information on diagnosed infections targeted by pediatric vaccines.

4.2. Strengths and Limitations

Factors such as sample size limitations, likely due to changes in vaccine acceptance following initial adverse events, limit our ability to robustly test hypotheses of association for some outcomes, especially in neurodevelopmental disorders and vaccination and seizures. If a link does exist, the absence of clear associations is likely due the small number of patients in the practice with neurodevelopmental disorders and seizures, which, ironically, may be due in part to the respect for patient preference, leading to informed choices by families at potential risk.

A related potential limitation includes that, because the data used were from billed diagnoses (in the case of outcomes) or billed vaccination, there may be some occurrences that were missed if insurance did not cover those events for a given patient (e.g., ASD diagnosed via a family

counselor/psychologist/psychiatrist). Similarly, diagnoses of developmental delay outside of the office may have not made it into the medical record for some patients. However, given that part of our data representation of such diagnoses was a per-patient count of reports of such diagnoses, the effects of these possible sampling limitations is likely mostly restricted to neurodevelopmental delays, and such an effect is more likely in outcomes related to data for a limited number of diagnoses than on vaccination data.

A criticism of association studies that detect negative health effects of vaccines is that some unknown, unmeasured confounder, or set of confounders might offer an alternative explanation. An example is the concern that our results may be explicable by other, unmeasured, healthier lifestyle choices made by families who also do not vaccinate. This seems highly unlikely given the relationships between increased adverse outcomes and vaccine acceptance, and lifestyle choices do not seem to be plausible explanations for many of the outcomes we have measured, although exposures to environmental substances such as cigarette smoke and acetaminophen (paracetamol), and malnutrition, which are known to impact negatively the immune system and development, cannot be ruled out as additive or multiplicative risk factors to vaccine adverse reactions and to the examined outcomes. The positive control outcome "fever" (Figure 3) points to a pattern expected following vaccination with no known or suspected relationship to lifestyle choices. However, if it were so, it would appear that our collective priority as a medical community should not be the pursuit of complete vaccination across the population but instead studies on what those other lifestyle choices might include and massive recommendations toward improving the lifestyle choices across the population.

Our study also has numerous strengths: the sample is fully representative of the practice population, and our design protocol had robust data provenance (parity checking) and rigorous data analysis. We avoided overadjustment bias and used a more powerful test to detect adverse events, demonstrated the robustness of the results to analysis assumptions, and have been careful to avoid overdrawn conclusions.

5. Conclusions

We could detect no widespread negative health effects in the unvaccinated other than the rare but significant vaccine-targeted diagnosis. We can conclude that the unvaccinated children in this practice are not, overall, less healthy than the vaccinated and that indeed the vaccinated children appear to be significantly less healthy than the unvaccinated.

We concur with Mawson et al., 2017 [9], who reported: "Further research involving larger, independent samples is needed to verify and understand these unexpected findings in order to optimize the impact of vaccines on children's health."

We also concur with Hooker and Miller 2020 [14], who wrote: "Further study is necessary to understand the full spectrum of health effects associated with childhood vaccination".

Other pediatric practices with variably vaccinating populations should be studied using a methodology similar to ours to attempt to refute or validate our findings and those of Mawson et al., 2017 [9], Hooker and Miller 2020 [14], and the numerous studies that have reported adverse health following vaccination. We are particularly interested in further study of the relationship between specific vaccines and combination of vaccines on specific outcomes as well as the relationship between the uptake of specific types of vaccines—inactivated, live virus, and aluminum-adjuvanted—with specific outcomes. Larger studies using electronic medical records from major medical institutions should be undertaken by research teams with no financial interest in the outcome of the studies (e.g., revenue from vaccination and from treatment of vaccine-related adverse outcomes).

Unintended and nonspecific consequences of vaccination, such as increased risk of chronic health conditions from vaccine exposures, must also be examined to determine if for any vaccine-targeted infection alternative methods of infection-avoidance or effective treatments that reduce disease sequela are available and preferable to vaccination in various circumstances, as has been reported by Cowling

et al., 2012 [24] and by Wolff (Wolff, 2020) [25]. Our findings are consistent with the concern that vaccination may increase respiratory virus infection risk, clearly a grave concern in the age of COVID-19.

Our finding of a robust signal of anemia deserves follow up: aluminum is known to bind to transferrin [26] and, in so doing, may interfere with the proper deposition of iron in the bones of children. Iron deficiency can also contribute to febrile seizures, a known side effect of some vaccines. Our society should work to identify safer vaccine schedules and safer adjuvants [27–35] and to reduce autoimmunity risk by removing unsafe epitopes—peptide sequences from pathogens or human cell line remnants in vaccines that match human proteins in sequence or structure from any tissue [36]—would seem expeditious, kind, and wise.

Future studies should now focus on the relative incidence of billed office visits, now that it has been shown to be a more sensitive and powerful measure of outcomes with a larger dynamic range than binary yes/no incidence of diagnoses.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/22/8674/s1: 'Table S1: ICD code mapping'; Table S2: 'LW and Thomas Supplemental S2 Gender Block Results 2.8.xlsx'; Table S3: 'LW and Thomas Supplemental S3 Age Blocks R2.9.xlsx'.

Author Contributions: P.T. directed the care of the patients in the study; P.T. conceived of the study concept; both J.L.-W. and P.T. designed the study; J.L.-W. designed the analysis strategy, and J.L.-W. conceived of and executed the data analysis including the power simulations and drafted the first manuscript; two anonymous honest brokers de-identified the data and provided a data parity check; all technical errors in the execution of analysis, if any, are the sole responsibility of J.L.-W. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: J.L.W. has, in the past, been but is no longer a compensated expert witness in cases in the US National Vaccine Injury Compensation Program. P.T. receives income in the form of royalties from the sale of his book, and he receives income from the sale and administration of vaccines in his practice. P.T. is the owner of Integrative Pediatrics, the population for this study, and is the author of the book "The Vaccine-Friendly Plan: Dr. Paul's Safe and Effective Approach to Immunity and Health—from Pregnancy Through Your Child's Teen Years" by Balantine Books 2016.

References

1. Benn, C.S.; Fisker, A.B.; Rieckmann, A.; Sørup, S.; Aaby, P. Vaccinology: Time to change the paradigm? *Lancet Infect Dis.* **2020**, *20*, e274–e283. [CrossRef]
2. Aaby, P.; Jensen, H.; Samb, B.; Cisse, B.; Sodemann, M.; Jakobsen, M.; Poulsen, A.; Rodrigues, A.; Lisse, I.M.; Simondon, F.; et al. Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: Reanalysis of West African studies. *Lancet* **2003**, *361*, 2183–2188. [CrossRef]
3. CDC. Report an Adverse Event to VAERS. 2020. Available online: https://vaers.hhs.gov/reportevent.html (accessed on 15 August 2020).
4. Tan, T.Q.; Gerbie, M.V.; Flaherty, J.P. The Vaccine Handbook. Oxford University Press: New York, NY, USA, 2017.
5. Lazarus, R.; Klompas, M. Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP:VAERS). Grant. Final Report, Grant ID: R18 HS 017045. 2010. Available online: https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf (accessed on 16 August 2020).

6. Institutes of Medicine (National Academy of Sciences) Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule; Board on Population Health and Public Health Practice; Institute of Medicine. *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies.* National Academies Press (US): Washington, DC, USA, 27 March 2013.
7. CDC. White Paper on Studying the Safety of the Immunity Schedule: For the Vaccine Safety Datalink 2018. Available online: https://www.cdc.gov/vaccinesafety/pdf/whitepapersafety_web.pdf (accessed on 14 August 2020).
8. Glanz, J.M.; Newcomer, S.R.; Jackson, M.L.; Omer, S.B.; Bednarczyk, R.A.; Shoup, J.A.; DeStefano, F.; Daley, M.F. White Paper on studying the safety of the childhood immunization schedule in the Vaccine Safety Datalink. *Vaccine* **2016**, *34*, A1–A29. [CrossRef]
9. Mawson, A.R.; Ray, B.D.; Bhuiyan, A.R.; Jacob, B. Pilot comparative study on the health of vaccinated and unvaccinated 6- to 12- year old U.S. children. *J. Transl. Sci.* **2017**, *3*, 1–12. [CrossRef]
10. Schmitz, R.; Poethko-Müller, C.; Reiter, S.; Schlaud, M. Vaccination status and health in children and adolescents: Findings of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Dtsch. Arztebl. Int.* **2011**, *108*, 99–104. [CrossRef]
11. Mogensen, S.W.; Andersen, A.; Rodrigues, A.; Benn, C.S.; Aaby, P. The Introduction of Diphtheria-Tetanus-Pertussis and Oral Polio Vaccine Among Young Infants in an Urban African Community: A Natural Experiment. *EBioMedicine* **2017**, *17*, 192–198. [CrossRef] [PubMed]
12. McDonald, K.L.; Huq, S.I.; Lix, L.M.; Becker, A.B.; Kozyrskyj, A.L. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. *J. Allergy Clin. Immunol.* **2008**, *121*, 626–631. [CrossRef] [PubMed]
13. Gallagher, C.; Goodman, M. Hepatitis B triple series vaccine and developmental disability in US children aged 1–9 years. *Tox. Environ. Chem.* **2008**, *5*, 997–1008. [CrossRef]
14. Hooker, B.S.; Miller, N.Z. Analysis of health outcomes in vaccinated and unvaccinated children: Developmental delays, asthma, ear infections and gastrointestinal disorders. *SAGE Open Med.* **2020**, *8*, 1–11. [CrossRef] [PubMed]
15. McFarland, G.; LaJoie, E.; Lyons-Weiler, J. Acute exposure and chronic retention of aluminum in three vaccine schedules and effects of genetic and environmental variation. *J. Trace. Elem. Med. Biol.* **2020**, *58*, 126444. [CrossRef]
16. Vaccine Safety Commission. 2020. Available online: https://vaccinesafetycommission.org (accessed on 24 August 2020).
17. Hurwitz, E.L.; Morgenstern, H. Effects of diptheria-tetanus-pertussis or tetanus vaccine on allergies and allergy-related respiratory symptoms among children and adolescents in the United States. *J. Manip. Physiol. Therap.* **2000**, *23*, 81–90. [CrossRef]
18. Glanz, J.M.; Wagner, N.M.; Narwaney, K.J.; Shoup, J.A.; McClure, D.L.; McCormick, E.V.; Daley, M.F. A mixed methods study of parental vaccine decision making and parent-provider trust. *Acad. Pediatr.* **2013**, *13*, 481–488. [CrossRef] [PubMed]
19. Vansteelandt, S.; Bekaert, M.; Claeskens, G. On Model Selection and Model Misspecification in Causal Inference. *SSRN Electron. J.* **2010**, *21*, 7–30. [CrossRef]
20. Schisterman, E.F.; Cole, S.R.; Platt, R.W. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. *Epidemiology* **2009**, *20*, 488–495. [CrossRef]
21. George, B.J.; Beasley, T.M.; Brown, A.W.; Dawson, J.; Dimova, R.; Divers, J.; Goldsby, T.U.; Heo, M.; Kaiser, K.A.; Keith, S.W.; et al. Common scientific and statistical errors in obesity research. *Obesity* **2016**, *24*, 781–790. [CrossRef]
22. CDC. Reporting Adverse Events. Available online: https://www.cdc.gov/vaccinesafety/hcproviders/reportingadverseevents.html (accessed on 24 August 2020).
23. US Department of Health and Human Services. Vaccine Adverse Event Reporting System: Report an Adverse Event to VAERS. 2020. Available online: https://vaers.hhs.gov/reportevent.html (accessed on 1 March 2020).
24. Cowling, B.J.; Fang, V.J.; Nishiura, H.; Chan, K.-H.; Ng, S.; Ip, D.K.M.; Chiu, S.S.; Leung, G.M.; Peiris, J.S.M. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. *Clin. Infect. Dis.* **2012**, *54*, 1778–1783. [CrossRef]

25. Wolff, G.G. Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017–2018 influenza season. *Vaccine* **2020**, *38*, 350–354. [CrossRef]
26. Papageorgiou, V.; Vargiami, E.; Kontopoulos, E.; Kardaras, P.; Economou, M.; Athanassiou-Mataxa, M.; Kirkham, F.J.; Zafeiriou, D.I. Association between iron deficiency and febrile seizures. *Eur. J. Paediatr. Neurol.* **2015**, *19*, 591–596. [CrossRef]
27. Crépeaux, G.; Gherardi, R.K.; Authier, F.-J. ASIA, chronic fatigue syndrome, and selective low dose neurotoxicity of aluminum adjuvants. *J. Allergy Clin. Immunol. Pract.* **2018**, *6*, 707. [CrossRef]
28. Exley, C. An aluminium adjuvant in a vaccine is an acute exposure to aluminium. *J. Trace Elements Med. Biol.* **2020**, *57*, 57–59. [CrossRef]
29. Crépeaux, G.; Eidi, H.; David, M.-O.; Baba-Amer, Y.; Tzavara, E.; Giros, B.; Authier, F.-J.; Exley, C.; Shaw, C.A.; Cadusseau, J.; et al. Non-linear dose-response of aluminium hydroxide adjuvant particles: Selective low dose neurotoxicity. *Toxicology* **2017**, *375*, 48–57. [CrossRef] [PubMed]
30. Gherardi, R.K.; Crépeaux, G.; Authier, F.-J. Myalgia and chronic fatigue syndrome following immunization: Macrophagic myofasciitis and animal studies support linkage to aluminum adjuvant persistency and diffusion in the immune system. *Autoimmun. Rev.* **2019**, *18*, 691–705. [CrossRef] [PubMed]
31. Masson, J.-D.; Crépeaux, G.; Authier, F.-J.; Exley, C.; Gherardi, R.K. Critical analysis of reference studies on the toxicokinetics of aluminum-based adjuvants. *J. Inorg. Biochem.* **2018**, *181*, 87–95. [CrossRef] [PubMed]
32. Mold, M.; Umar, D.; King, A.; Exley, C. Aluminium in brain tissue in autism. *J. Trace Elem. Med. Biol.* **2018**, *46*, 76–82. [CrossRef] [PubMed]
33. Morris, G.; Puri, B.K.; Frye, R.E. The putative role of environmental aluminium in the development of chronic neuropathology in adults and children. How strong is the evidence and what could be the mechanisms involved? *Metab. Brain Dis.* **2017**, *32*, 1335–1355. [CrossRef] [PubMed]
34. Petrik, M.S.; Wong, M.C.; Tabata, R.C.; Garry, R.F.; Shaw, C.A. Aluminum Adjuvant Linked to Gulf War Illness Induces Motor Neuron Death in Mice. *NeuroMolecular Med.* **2007**, *9*, 83–100. [CrossRef]
35. Erigolet, M.; Eaouizerate, J.; Ecouette, M.; Ragunathan-Thangarajah, N.; Eaoun-Sebaiti, M.; Gherardi, R.K.; Ecadusseau, J.; Authier, F.-J. Clinical Features in Patients with Long-Lasting Macrophagic Myofasciitis. *Front. Neurol.* **2014**, *5*, 230. [CrossRef]
36. Lyons-Weiler, J. Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. *J. Transl. Autoimmun.* **2020**, *3*, 1–5. [CrossRef]

Vaccines and Related Biological Products Advisory Committee Meeting
December 10, 2020

FDA Briefing Document

Pfizer-BioNTech COVID-19 Vaccine

Sponsor:
Pfizer and BioNTech

Table of Contents

List of Tables

List of Figures

Glossary

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	Che
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
modRNA	nucleoside-modified messenger RNA
NAAT	nucleic acid amplification-based test
PVP	Pharmacovigilance Plan
RBD	receptor binding domain
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On November 20, 2020, Pfizer and BioNTech (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older." The proposed dosing regimen is 2 doses, 30 µg each, administered 21 days apart.

The EUA request includes safety and efficacy data from an ongoing phase 3 randomized, double-blinded and placebo-controlled trial of BNT162b2 in approximately 44,000 participants. The primary efficacy endpoint is incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen. In a mid-November analysis of 36,621 participants randomized 1:1 to vaccine or placebo who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination regimen, efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.

Safety data from approximately 38,000 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. Available safety data from all participants enrolled through the November 14, 2020 data cut-off (N=43,252, which includes late enrollment of additional adolescent and adult participants), was consistent with the safety profile for the approximately 38,000 participants with median follow-up of 2 months and also did not raise specific safety concerns. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ⩾55 years of age (⩽ 2.8%) as compared to younger participants (⩽4.6%). The frequency of serious adverse events was low (<0.5%), without meaningful imbalances between study arms. Among non-serious unsolicited adverse events, there was a numerical imbalance of four cases of Bell's palsy in the vaccine group compared with no cases in the placebo group, though the four cases in the vaccine group do not represent a frequency above that expected in the general population. Otherwise, there were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations on whether:

- based on the totality of scientific evidence available, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 in individuals 16 years of age and older, and
- the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks for use in individuals 16 years of age and older.

The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

2. Background

2.1. SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of November 30, 2020, has caused more than 60 million cases of COVID-19 and claimed the lives of 1.5 million people worldwide. In the United States, over 13 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 260,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is a main target for neutralizing antibody, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain (RBD), as the immunogenic determinant.

2.2. EUA Request for the Pfizer and BioNTech COVID-19 Vaccine BNT162b2

Pfizer, in partnership with BioNTech Manufacturing GmbH, is developing a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNP). The Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2) is administered intramuscularly as a 2-dose series spaced 21 days apart at a dose of 30 μg each. The vaccine is supplied as a multi-dose vial (5 doses) containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for five 0.3 mL doses. The vaccine is preservative free.

A phase 3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. Vaccine efficacy for the primary endpoint against confirmed COVID-19 occurring at least 7 days after the second dose was 95.0% with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group. Data from about 38,000 participants randomized 1:1 with a median of 2 months of follow-up after the second dose of vaccine showed a favorable safety profile at a dose of 30 μg in participants 16 years of age and older. On November 20, 2020, Pfizer and BioNTech submitted an EUA request to FDA for its investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by SARS-CoV-2.

2.3. U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and it would be under further investigation (under an Investigational New Drug Application) until it is licensed under a Biologics License Application (BLA). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4. Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" (Appendix C, page 53) describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.

2.5. Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[6]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing phase 3 studies.

Phase 3 Follow-up

Data from phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[7] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.6. Continuation of clinical trials following issuance of an EUA for a COVID-19 vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Some developers have proposed maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[8-10]

2.7. Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session, to discuss, in general, the development, authorization and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents

- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
    - Further evaluate safety, effectiveness and immune markers of protection
    - Evaluate the safety and effectiveness in specific populations.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on December 10, 2020, to discuss and provide recommendations on whether:

- based on the totality of scientific evidence available, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 in individuals 16 years of age and older, and
- the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks for use in individuals 16 years of age and older.

The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

4. Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

4.1. Vaccine Composition, Dosing Regimen

The Pfizer-BioNTech COVID-19 Vaccine is a white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection. The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen [between -80°C to -60°C (-112°F to -76°F)] multi-dose (5-dose) vial. The vaccine must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 5 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution.

The Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 21 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. As such, FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2. Proposed Use Under EUA

The proposed indication and use of the vaccine under an EUA is “for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.”

5. FDA Review of Clinical Safety and Effectiveness Data

5.1. Overview of Clinical Studies

Data from two ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study C4591001 is a multi-center, multi-national Phase 1,2,3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study BNT162-01 is a Phase 1 study that explored various vaccine candidates and dose levels and will not be discussed in detail. A brief summary of the BNT162-01 study design and results to date is found in Appendix A, page 51.

Table 1: Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Pfizer-BioNTech COVID-19 Vaccine

Study Number/ Country	Description	BNT162b2 (30 μg)* participants (N)	Placebo participants (N)	Study Status
C4591001 USA, Argentina, Brazil, Germany, S. Africa, Turkey	Phase 1,2,3 randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 24 Phase 2/3: 21823	Phase 1: 6 Phase 2/3: 21828	Ongoing
BNT162-01 Germany	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity, dose escalation	12	0	Ongoing

N= total number of randomized participants as of November 14, 2020. Placebo: saline.
*Phase 1 studies included additional participants vaccinated with other dose levels and other mRNA vaccine candidates.
Studies C4591001 and BNT162-01 started in April 2020 (first participant, first visit).

5.2. Study C4591001

5.2.1. Design

Study C4591001 is an ongoing, randomized, placebo-controlled, phase 1/2/3 study being conducted in the US, Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a phase 1/2 study in healthy adults in the US for vaccine candidate and dosage selection, immunogenicity and preliminary efficacy, but the protocol was revised to expand the study design for inclusion of a phase 2/3 portion to evaluate clinical disease endpoint efficacy in individuals 12 years of age and older in the US and additional sites outside of the US.

In phase 1, two age groups were evaluated in separate cohorts, younger participants 18 through 55 years of age (N=45) and older participants 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received escalating dose levels with progression to subsequent dose levels and evaluation of escalating dose levels in the older age group (65 through 85 years), based on recommendations from an internal review committee that reviewed safety and immunogenicity data. For each vaccine candidate and dose

level, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from phase 1, in combination with data from Study BNT162-01 (See Section 10), supported the final vaccine candidate and dose level (BNT162b2 at 30 µg, given 21 days apart) to proceed into phase 2/3.

In phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) and a goal of 40% enrollment in the older adult age group. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study, so the age strata were revised as follows: 12 through 15 years of age, 16 through 54 years of age, and 55 years of age and older. The study population for phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19 disease, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. The phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants enrolled early-on, and these participants also contribute to the overall efficacy and safety data in the phase 3 portion. The ongoing phase 3 portion of the study is evaluating the safety and efficacy of BNT162b2 for the prevention of COVID-19 disease occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (midturbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (e.g., Cepheid; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001) Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design includes planned interim analyses of the first primary efficacy endpoint at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases), and all primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued (see Statistical Analysis section, below). Participants are expected to participate for a maximum of approximately 26 months.

Primary Efficacy Endpoints

Study C4591001 has two primary endpoints:

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Secondary Efficacy Endpoints

Study C4591001 has secondary endpoints based on different approaches to COVID-19 case evaluation criteria as follows:

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2

CDC-defined COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was the presence of at least one of the following symptoms and a positive SARS-CoV-2 NAAT within 4 days of the symptomatic period:

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

For a secondary efficacy endpoint, a second definition, which may be updated as more is learned about COVID-19, included the following additional symptoms defined by CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

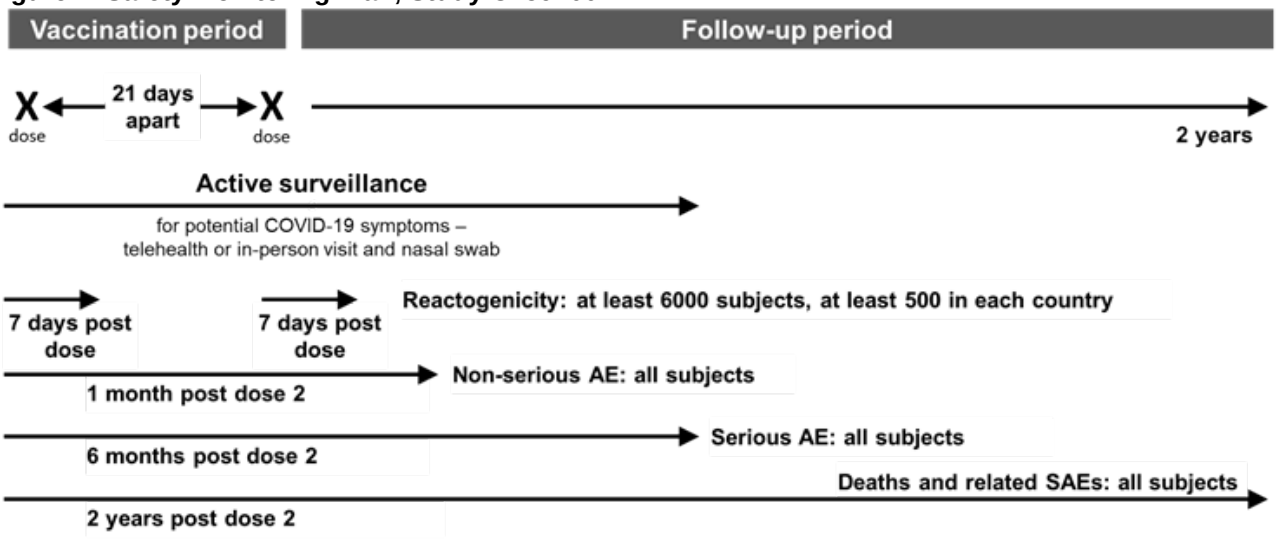
For another secondary endpoint, the case definition for a severe COVID-19 case was a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of BNT162 vaccine(s) in healthy adults after 1 or 2 doses. All phase 1 participants (n=30), and then 6653 U.S. participants (360 phase 2, 6293 phase 3) and the first ~500 phase 3 participants/per country with enrollment through October 9, 2020 (Argentina, Brazil and South Africa) recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from Dose 1 to 1 month after the last dose and serious AEs (SAEs) from Dose 1 to 6 months after the last dose. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study C4591001



Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), and antipyretic/pain medication use were recorded in an e-diary. At the data cutoff date for the EUA, reactogenicity events were not collected from adolescents 16 to 17 years of age (enrolled prior to the implementation of Protocol Amendment 9, finalized on 29 October 2020) using an e-diary but were detected and reported as unsolicited AEs. For any phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as unsolicited AEs. HIV-positive participants and adolescents 12 through 15 years of age were included in the reactogenicity subset with implementation of protocol amendment 6 (finalized on September 8, 2020) and amendment 7 (finalized on October 6, 2020), respectively. Solicited reactogenicity data in adolescents 16-17 years of age are not available for the reporting period. Reactogenicity data from a total of 100 adolescents 12 through 15 years of age enrolled in C4591001 phase 2/3 were provided in the EUA submission. However, the Sponsor did not request inclusion of this age group in the EUA because the available data, including number of participants and follow-up duration, were insufficient to support favorable a benefit-risk determination at this time. Therefore, the reactogenicity data for participants 12 through 15 years of age are not presented in this document.

Clinical laboratory tests were assessed in phase 1 at 1-week postvaccination. The planned safety follow-up for currently enrolled adolescents and adults is through 24 months after vaccination #2.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

In phase 2/3, monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants, and alert criteria were triggered when this probability was less than 11%.

Analysis Populations

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed informed consent document.
Randomized	All participants who are assigned a randomization number.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.

Phase 2/3 safety analysis populations were as follows:

- Phase 2/3 all-enrolled population: composed of a total of 43,448 (21720 vaccine, 21728 placebo) participants ≥16 years of age, regardless of duration of follow-up, for whom written informed consent was obtained. Initial enrollment included individuals 18 years and older, then included individuals as young as 16 years of age and individuals with known HIV (protocol amendment 6; finalized on September 8, 2020). As of November 14, 2020, 43.9% and 79.5% of vaccine recipients completed at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks) were similar to the vaccine group.

- Phase 2/3 safety population (median follow-up time of 2 months after vaccination #2): comprised of a total of 37586 (18801 vaccine,18785 placebo) participants >16 years of age enrolled by October 9, 2020 and received at least 1 dose of study vaccine or placebo; overall, 98.1% of participants completed the 2-dose series. As of November 14, 2020, 50.6% and 91.6% of vaccine recipients completed at least 2 months (>8 weeks) and at least 1 month (>4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (>8 weeks) and at least 1 month (>4 weeks) were similar to the vaccine group. A total of 283 (138 vaccine,145 placebo) individuals were 16 to <18 years of age. HIV-positive individuals were included in the all-enrolled population, but not the phase 2/3 safety population because the number of participants enrolled by October 9, 2020 was small (n=120) and the median duration of safety follow-up was short.

5.2.2. FDA Assessment of Phase 2/3 Follow-Up Duration

Study C4591001 initially enrolled approximately 30,000 participants and then several months later began enrollment of approximately 14,000 additional participants, including adolescents and participants with chronic, stable HIV, hepatitis B, or hepatitis C infections. Because of the gap in enrollment, the entire enrolled study population had a median follow-up of less than 2 months as of the EUA submission data cut-off date of November 14, 2020. However, the analyses submitted to support this EUA request meet the expectation for median duration of follow-up time, as follows:

- Submitted safety analyses for participants enrolled through October 9, 2020, and followed through November 14, 2020 (referred to by Pfizer and in this document as the phase 2/3 safety population and including a total of 37,586 participants), represent a median follow-up of 2 months. Additionally, this safety database is larger than for the initial planned enrollment of approximately 30,000 participants.

- The date for data cut-off for the first interim analysis for efficacy was November 4, 2020, when a total of 94 confirmed COVID-19 cases were accrued. All of the participants included in the first interim efficacy analysis had at least 7 days of follow-up after Dose 2, and thus were enrolled no later than October 7, 2020. All participants in the first interim efficacy analysis were therefore included in the phase 2/3 safety population defined above. Although the median follow-up duration for participants included in the first interim efficacy analysis was slightly less than 2 months as of November 4, 2020, these participants were also included in the final efficacy analyses with data cut-off of November 14, 2020, which extended the median follow-up for these participants to greater than 2 months. The results of the final efficacy analysis on data to November 14, 2020, indicate that the conclusions from the first interim efficacy analysis would not change when including additional follow-up to November 14, 2020.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued. As noted above, the median follow-up duration after completion of the full vaccination regimen for all participants enrolled at that time was less than 2 months for both safety and efficacy populations, due to a gap in enrollment. Because the data for the final efficacy analysis could be submitted in support of the EUA request and could provide data from a greater number of participants than from the interim analysis, FDA has focused its review on the efficacy data from the final efficacy analyses. Additional safety analyses from this larger database of all enrolled participants were also reviewed to evaluate for differences compared with the smaller phase 2/3 safety population.

5.2.3. Subject Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 2 (efficacy analysis populations) and Table 3 (phase 2/3 safety population). Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. Of 43,448 participants in the phase 2/3 all-enrolled population, 94.2% of vaccine recipients and 94.1% of placebo recipients completed 2 doses (data not shown).

Table 2. Efficacy Populations, Treatment Groups as Randomized

	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Participants without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Participants excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Participants without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Participants without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Participants excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Participants excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Participants excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

[a]n = Number of participants with the specified characteristic.
[b]These values are the denominators for the percentage calculations.
[c]Participants may have been excluded for more than 1 reason.
Note: 100 participants 12 through 15 years of age with limited follow-up are included in the randomized population (49 in the vaccine group and 51 in the placebo group). Some of these subjects were included in the denominators of efficacy analyses, depending on the population analyzed, but did not contribute primary endpoint cases and do not affect efficacy conclusions for ages 16 years and above.

Table 3. Disposition of All Randomized Participants, Phase 2/3 Safety Population

Treatment Group	BNT162b2 N=18904 n (%)	Placebo N=18892) n (%)	Total N=37796 n (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Vaccinated			
Completed 1 dose	18858 (99.8)	18849 (99.8)	37707 (99.8)
Completed 2 doses	18555 (98.2)	18533 (98.1)	37088 (98.1)
Withdrawn from Study	180 (1.0)	259 (1.4)	439 (1.2)
Reason for Withdrawal			
Adverse Event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	4 (0.0)	6 (0.0)
Withdrawal by Subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to Follow-up	80 (0.4)	86 (0.5)	166 (0.4)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)

Source: EUA 27036, amendment 3, Table 2; c4591001-safety-tables-cos-reacto.pdf, page 43.
Note: One participant was randomized but did not sign informed consent and therefore not included in any analysis population.
Note: 120 HIV-positive participants included in this table. HIV population analyses were summarized separately from analyses based on the phase 2/3 safety population, but included in the all-enrolled poplation analyses presented in this briefing document.
%:n/N. n = number of subjects with the specified characteristic. N = number of participants ≥16 years of age enrolled by October 9, 2020, including 120 HIV-positive participants, and received at least 1 dose of study vaccine or placebo. N is the denominator used for the percentage calculations.
Data analysis cutoff date: November 14, 2020

The numbers of randomized participants contributing to efficacy analyses presented in this document include 100 participants 12 through 15 years of age (49 in the vaccine group and 51 in the placebo group) who had limited follow-up at the time of the November 14, 2020 data cut-off. However, the sponsor did not include this age group in the EUA request. The numbers of participants presented and used as denominators for efficacy calculations were not adjusted to remove participants 12 through 15 years of age. Because the number of participants 12 through 15 years of age is very small relative to the overall efficacy analysis populations, and no primary endpoint COVID-19 cases occurred in this age group, the vaccine efficacy conclusions are not impacted. No participants 12 through 15 years of age are included in the safety analyses. However, the safety disposition table includes 120 HIV-positive participants who were not included in the phase 2/3 safety population analyses.

5.2.4. Demographics and Other Baseline Characteristics

Overall, the phase 2/3 evaluable efficacy population included 49.4% females, 81.9% White, 9.8% African American, 4.4% Asian participants, and <3% from other racial groups; 26.2% of participants were Hispanic/Latino; 21.4% of participants were ≥65 years of age. The median age was 51 years. The most frequently reported comorbidities were obesity (35.1%), diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-available efficacy population were similar to the evaluable efficacy population. Please refer to the table below.

Table 4. Demographic Characteristics, Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Characteristic	BNT162b2 (N[a]=20033) N[b] (%)	Placebo (N[a]=20244) N[b] (%)	Total (N[a]=40277) N[b] (%)
Sex: Female	9794 (48.9)	10107 (49.9)	19901 (49.4)
Sex: Male	10239 (51.1)	10137 (50.1)	20376 (50.6)
Age at Vaccination: Mean years (SD)	50.3 (15.73)	50.1 (15.78)	50.2 (15.76)
Age at Vaccination: Median (years)	51.0	51.0	51.0
Age at Vaccination: Min, max (years)	(12, 89)	(12, 91)	(12, 91)
Age Group: 16 to <18 years	77 (0.4)	76 (0.4)	153 (0.4)
Age Group: 16 to 55 years	11589 (57.8)	11743 (58.0)	23332 (57.9)
Age Group: >55 years	8396 (41.9)	8454 (41.8)	16850 (41.8)
Age Group: ≥65 years	4294 (21.4)	4319 (21.3)	8613 (21.38)
Age Group: ≥75 years	860 (4.3)	852 (4.2)	1712 (4.3)
Race: American Indian or Alaska Native	131 (0.7)	122 (0.6)	253 (0.6)
Race: Asian	880 (4.4)	883 (4.4)	1763 (4.4)
Race: Black or African American	1957 (9.8)	1972 (9.7)	3929 (9.8)
Race: Native Hawaiian or Other Pacific Islander	54 (0.3)	29 (0.1)	83 (0.2)
Race: White	16387 (81.8)	16619 (82.1)	33006 (81.9)
Race: Multiracial	523 (2.6)	493 (2.4)	1016 (2.5)
Race: Not reported	101 (0.5)	126 (0.6)	227 (0.6)
Ethnicity: Hispanic or Latino	5272 (26.3)	5281 (26.1)	10553 (26.2)
Ethnicity: Not Hispanic or Latino	14652 (73.1)	14847 (73.3)	29499 (73.2)
Ethnicity: Not reported	109 (0.5)	116 (0.6)	225 (0.6)
Comorbidities[c]: Yes	9278 (46.3)	9314 (46.0)	18592 (46.2)
Comorbidities: No	10755 (53.7)	10930 (54.0)	21685 (53.8)
Comorbidity: Obesity	6934 (34.6)	7093 (35.0)	14027 (34.8)

[a].N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b].n = number of participants with the specified characteristic.
[c]. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity only (BMI ≥30 kg/m^2).

Overall, the phase 2/3 safety population included 83.1% White, 9.1% African American, 4.3% Asian participants, and <3% from other racial groups; 28.0% of participants were Hispanic/Latino; 21.6% of participants were >65 years of age. The median age was 52 years, and safety data from a total of 103 participants 16 and 17 years of age were included in this submission. The most frequently reported comorbidities were obesity (35.1%), diabetes (without chronic complications, 7.8%) and chronic pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2.0% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-enrolled population were similar and were also enrolled from sites in Germany (1%) and Turkey (1%). There were no significant imbalances in demographic and other baseline characteristics between the all-enrolled population and phase 2/3 safety population with median 2-month follow-up.

Table 5. Demographics and Other Baseline Characteristics, Phase 2/3 Safety Population

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Age (years)									
Mean [SD]	16.40 [0.49]	44.99 [12.66]	68.84 [2.80]	78.07 [2.78]	16.36 [0.48]	44.78 [12.72]	68.84 [2.78]	78.10 [2.81]	50.38 [15.70]
Median	16	46	68	77	16	46	69	77	52
Min, max	16-17	18-64	65-74	75-89	16-17	18-64	65-74	75-91	16-91
Sex									
Male	33 (0.2)	7385 (39.3)	1714 (9.1)	470 (2.5)	24 (0.1)	7153 (38.1)	1724 (9.2)	498 (2.7)	19001 (50.6)
Female	20 (0.1)	7305 (38.9)	1513 (8.0)	361 (1.9)	26 (0.1)	7539 (40.1)	1511 (8.0)	310 (1.7)	18585 (49.4)
Race									
White	37 (0.2)	11895 (63.3)	2908 (15.5)	775 (4.1)	38 (0.2)	11891 (63.3)	2930 (15.6)	756 (4.0)	31230 (83.1)
African American	11 (0.1)	1477 (7.9)	186 (1.0)	20 (0.1)	7 (0.0)	1505 (8.0)	189 (1.0)	21 (0.1)	3416 (9.1)
Asian	0 (0.0)	693 (3.7)	81 (0.4)	26 (0.1)	0 (0.0)	715 (3.8)	72 (0.4)	19 (0.1)	1606 (4.3)
Multiracial	3 (0.0)	417 (2.2)	21 (0.1)	7 (0.0)	3 (0.0)	379 (2.0)	18 (0.1)	5 (0.0)	853 (2.3)
Not reported	0 (0.0)	82 (0.4)	11 (0.1)	0 (0.0)	1 (0.0)	98 (0.5)	10 (0.1)	5 (0.0)	207 (0.6)
American Indian or Alaska native	0 (0.0)	84 (0.4)	15 (0.1)	2 (0.0)	1 (0.0)	83 (0.4)	11 (0.1)	2 (0.0)	198 (0.5)
Nat. HI or other Pac. Isl.	2 (0.0)	42 (0.2)	5 (0.0)	1 (0.0)	0 (0.0)	21 (0.1)	5 (0.0)	0 (0.0)	76 (0.2)
Ethnicity									
Hispanic or Latino	6 (0.0)	4595 (24.4)	549 (2.9)	103 (0.5)	5 (0.0)	4616 (24.6)	558 (3.0)	90 (0.5)	10522 (28.0)
Non-Hispanic/non-Latino	47 (0.2)	10009 (53.2)	2658 (14.1)	722 (3.8)	44 (0.2)	10004 (53.3)	2652 (14.1)	707 (3.8)	26843 (71.4)
Not reported	0 (0.0)	86 (0.5)	20 (0.1)	6 (0.0)	1 (0.0)	72 (0.4)	25 (0.1)	11 (0.1)	221 (0.6)
Baseline Body Mass Index (BMI)									
Obese	3 (0.0)	5200 (27.7)	1079 (5.7)	248 (1.3)	14 (0.1)	5242 (27.9)	1147 (6.1)	235 (1.3)	13168 (35.0)
Overweight	14 (0.1)	4901 (26.1)	1278 (6.8)	368 (2.0)	9 (0.0)	4857 (25.9)	1255 (6.7)	340 (1.8)	13022 (34.6)

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Baseline Evidence of Prior SARS-CoV-2 Infection									
Negative	48 (0.3)	13879 (73.8%)	3109 (16.5)	805 (4.3)	47 (0.3%)	13858 (73.8%)	3115 (16.6%)	788 (4.2%)	35649 (94.8%)
Positive	3 (0.0)	473 (2.5%)	53 (0.3)	16 (0.1)	3 (0.0%)	520 (2.8%)	52 (0.3%)	5 (0.0%)	1125 (3.0%)
Missing	2 (0.0)	338 (1.8%)	65 (0.3)	10 (0.1)	0 (0.0%)	314 (1.7%)	68 (0.4%)	15 (0.1%)	812 (2.2%)
Comorbidities									
No	48 (0.3)	12353 (65.7%)	2081 (11.1)	444 (2.4)	37 (0.2%)	12412 (66.1%)	2118 (11.3%)	470 (2.5%)	29963 (79.7%)
Yes	5 (0.0)	2337 (12.4%)	1146 (6.1)	387 (2.1)	13 (0.1%)	2280 (12.1%)	1117 (5.9%)	338 (1.8%)	7623 (20.3%)
Diabetes Without Chronic Complication	0 (0.0)	814 (4.3%)	497 (2.6)	156 (0.8)	1 (0.0%)	849 (4.5%)	491 (2.6%)	132 (0.7%)	2940 (7.8%)
Chronic Pulmonary Disease	5 (0.0)	1093 (5.8%)	286 (1.5)	89 (0.5)	12 (0.1%)	1060 (5.6%)	309 (1.6%)	66 (0.4%)	2920 (7.8%)
Myocardial Infarction	0 (0.0)	82 (0.4%)	71 (0.4)	41 (0.2)	0 (0.0%)	73 (0.4%)	83 (0.4%)	31 (0.2%)	381 (1.0%)
Peripheral Vascular Disease	0 (0.0)	26 (0.1%)	67 (0.4)	31 (0.2)	0 (0.0%)	29 (0.2%)	52 (0.3%)	33 (0.2%)	238 (0.6%)
Liver Disease (mild, moderate or severe)	0 (0.0)	83 (0.4%)	34 (0.2)	7 (0.0)	0 (0.0%)	67 (0.4%)	17 (0.1%)	6 (0.0%)	214 (0.6%)
Diabetes With Chronic Complication	0 (0.0)	47 (0.2%)	36 (0.2)	15 (0.1)	0 (0.0%)	47 (0.3%)	47 (0.3%)	18 (0.1%)	210 (0.6%)
Congestive Heart Failure	0 (0.0)	44 (0.2%)	26 (0.1)	17 (0.1)	0 (0.0%)	36 (0.2%)	30 (0.2%)	16 (0.1%)	169 (0.4%)
AIDS/HIV	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Hypertension only	0 (0.0)	2569 (13.7%)	1528 (8.1)	488 (2.6)	1 (0.0%)	2621 (14.0%)	1569 (8.4%)	432 (2.3%)	9208 (24.5%)

Source: FDA-generated table.
Abbreviations: n = number of participants with the specified characteristic; N = number of participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo, N is denominator for the percentage calculations; SD = standard deviation; min, max = minimum, maximum; Nat. HI = Native Hawaiian; Pac. Isl. = Pacific Islander
Data analysis cutoff date: November 14, 2020.

5.2.5. Vaccine Efficacy

Primary Efficacy Analyses

Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 6). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.

[b] n1 = Number of participants meeting the endpoint definition.

[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

[d] n2 = Number of participants at risk for the endpoint.

[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.

[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively (Table 7). The posterior probability was >99.99% for the true VE being greater than 30%. The 95% credible interval for the vaccine efficacy was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

Table 7. Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants With And Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.9, 97.3)[e]	Yes
16 to 55 years	6 1.309 (10653)	120 1.317 (10738)	95.0 (88.7, 98.2)[f]	NA
>55 years and older	3 1.022 (7892)	49 1.028 (7956)	93.8 (80.9, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy >30% conditioning on the available data is >99.5% at the final analysis
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Subgroup Analyses of Vaccine Efficacy

Subgroup analyses of the second primary efficacy endpoint provide additional information about the VE for participants with and without evidence of infection prior to vaccination in specific populations enrolled, which is the endpoint considered to represent the general population who may receive the vaccine, as baseline evidence of prior infection may not be known by all people who might receive the vaccine. The results are displayed below in Table 8. The VE point estimates for the subgroup analyses were comparable to results for the first primary efficacy endpoint.

VE point estimates were uniformly high across the subgroups examined with the exception of participants identifying as multiracial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 cases occurred to interpret efficacy data for these subgroups. Additionally, the numbers of participants and cases in some other specific subgroups, such as the adolescent age group and racial subgroups, limits the interpretability of the VE results because of the wide credible intervals, but are displayed for completeness.

Table 8: Subgroup Analyses of Second Primary Endpoint: First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup, Participants With and Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Overall	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.6, 97.6)
Age group (years)			
16 to 17	0 0.003 (58)	1 0.003 (61)	100.0 (-3969.9, 100.0)
18 to 64	8 1.799 (14443)	149 1.811 (14566)	94.6 (89.1, 97.7)
65 to 74	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)
≥75	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)
At risk[f]			
Yes	4 1.083 (8584)	87 1.084 (8609)	95.4 (87.8, 98.8)
No	5 1.250 (9975)	82 1.261 (10099)	93.8 (85.0, 98.1)
Age group (years) and at risk			
16-64 and not at risk	5 1.012 (8172)	75 1.019 (8239)	93.3 (83.6, 97.9)
16-64 and at risk	3 0.790 (6329)	75 0.794 (6388)	96.0 (87.8, 99.2)
≥65 and not at risk	0 0.238 (1794)	7 0.241 (1849)	100.0 (29.5, 100.0)
≥65 and at risk	1 0.293 (2250)	12 0.290 (2218)	91.7 (44.2, 99.8)
Obese[g]			
Yes	3 0.810 (6445)	68 0.832 (6582)	95.5 (86.2, 99.1)
No	6 1.522 (12108)	101 1.513 (12120)	94.1 (86.7, 97.9)
Age group (years) and obese			
16-64 and not obese	5 1.163 (9380)	89 1.162 (9422)	94.4 (86.4, 98.2)
16-64 and obese	3 0.637 (5116)	61 0.651 (5199)	95.0 (84.6, 99.0)
≥65 and not obese	1 0.358 (2715)	12 0.351 (2685)	91.8 (44.7, 99.8)
≥65 and obese	0 0.172 (1328)	7 0.180 (1382)	100.0 (27.4, 100.0)
Sex			
Female	5 1.149 (9102)	84 1.176 (9366)	93.9 (85.2, 98.1)
Male	4 1.183 (9457)	85 1.170 (9342)	95.3 (87.6, 98.8)
Ethnicity			
Hispanic or Latino	3 0.637 (5074)	55 0.638 (5090)	94.5 (83.2, 98.9)

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Not Hispanic or Latino	6 1.681 (13380)	114 1.693 (13509)	94.7 (88.1, 98.1)
Race			
American Indian or Alaska native	0 0.011 (104)	1 0.010 (104)	100.0 (-3511.0, 100.0)
Asian	1 0.095 (796)	4 0.097 (808)	74.4 (-158.7, 99.5)
Black or African American	0 0.187 (1758)	7 0.188 (1758)	100.0 (30.4, 100.0)
Native Hawaiian or other Pacific Islander	0 0.006 (50)	1 0.003 (29)	100.0 (-2112.1, 100.0)
White	7 1.975 (15294)	153 1.990 (15473)	95.4 (90.3, 98.2)
Multiracial	1 0.047 (467)	1 0.042 (424)	10.4 (-6934.9, 98.9)
Not reported	0 0.010 (90)	2 0.013 (112)	100.0 (-581.6, 100.0)
Baseline SARS-CoV-2 Status			
Positive[h]	1 0.056 (526)	1 0.060 (567)	-7.1 (-8309.9, 98.6)
Negative[i]	8 2.237 (17637)	164 2.242 (17720)	95.1 (90.1, 97.9)
Unknown	0 0.039 (396)	4 0.043 (421)	100.0 (-68.9, 100.0)

[a.] N = number of participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d.] n2 = Number of participants at risk for the endpoint.
[e.] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.
[f.] At risk is defined as having at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity (BMI ≥30 kg/m^2).
[g.] Obese is defined as BMI ≥30 kg/m^2.
[h.] Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[i.] Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 9.

Table 9. Demographic Characteristics, Participants With Protocol Defined Case (Without Evidence of Infection Prior to 7 Days After Dose 2)

Characteristic	BNT162b2 (N[a]=8) N[b] (%)	Placebo (N[a]=162) N[b] (%)	Total (N[a]=170) N[b] (%)
Sex: Female	5 (62.5)	81 (50.0)	86 (50.6)
Sex: Male	3 (37.5)	81 (50.0)	84 (49.4)
Age at Vaccination: Mean years (SD)	51.4 (12.47)	47.4 (15.21)	47.6 (15.09)
Age at Vaccination: Median (years)	51	48	48
Age at Vaccination: Min, max (years)	(30, 69)	(18, 79)	(18, 79)
Age Group: 16 to < 18 years	0	0	0
Age Group: 18 to < 65 years	7 (87.5)	143 (88.3)	150 (88.2)
Age Group: ≥ 65 to < 75 years	1 (12.5)	14 (8.6)	15 (8.8)
Age Group: ≥ 75 years	0	5 (3.1)	5 (2.9)
Race: American Indian or Alaska Native	0	1 (0.6)	1 (0.6)
Race: Asian	1 (12.5)	4 (2.5)	5 (2.9)
Race: Black or African American	0	7 (4.3)	7 (4.1)
Race: Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.6)
Race: White	7 (87.5)	146 (90.1)	153 (90.0)
Race: Multiracial	0	1 (0.6)	1 (0.6)
Race: Not reported	0	2 (1.2)	2 (1.2)
Ethnicity: Hispanic or Latino	3 (37.5)	53 (32.7)	56 (32.9)
Ethnicity: Not Hispanic or Latino	5 (62.5)	109 (67.3)	114 (67.1)
Ethnicity: Not reported	0	0	0
Comorbidities[c]: Yes	4 (50.0)	86 (53.1)	90 (52.9)
Comorbidities: No	4 (50.0)	76 (46.9)	80 (47.1)
Comorbidity: Obesity	3 (37.5)	67 (41.4)	70 (41.2)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = Number of participants with the specified characteristic.
[c] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity only (BMI ≥30 kg/m^2).

Only 3% of participants had evidence of prior infection at study enrollment, and additional analyses showed that very few COVID-19 cases occurred in these participants over the course of the entire study (9 in the placebo group and 10 in the BNT162b2 group, only 1 of which occurred 7 days or more after completion of the vaccination regimen – data not shown). The placebo group attack rate from enrollment to the November 14, 2020, data cut-off date was 1.3% both for participants without evidence of prior infection at enrollment (259 cases in 19,818 participants) and for participants with evidence of prior infection at enrollment (9 cases in 670 participants). While limited, these data do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the vaccine efficacy, by comorbidity status. VE point estimates were uniformly high across the comorbidities examined, though for some interpretation of the results is limited by small numbers of participants and/or cases.

Table 10. Vaccine Efficacy: First COVID-19 Occurrence From 7 Days After Dose 2, by Comorbidity Status, Among Participants Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

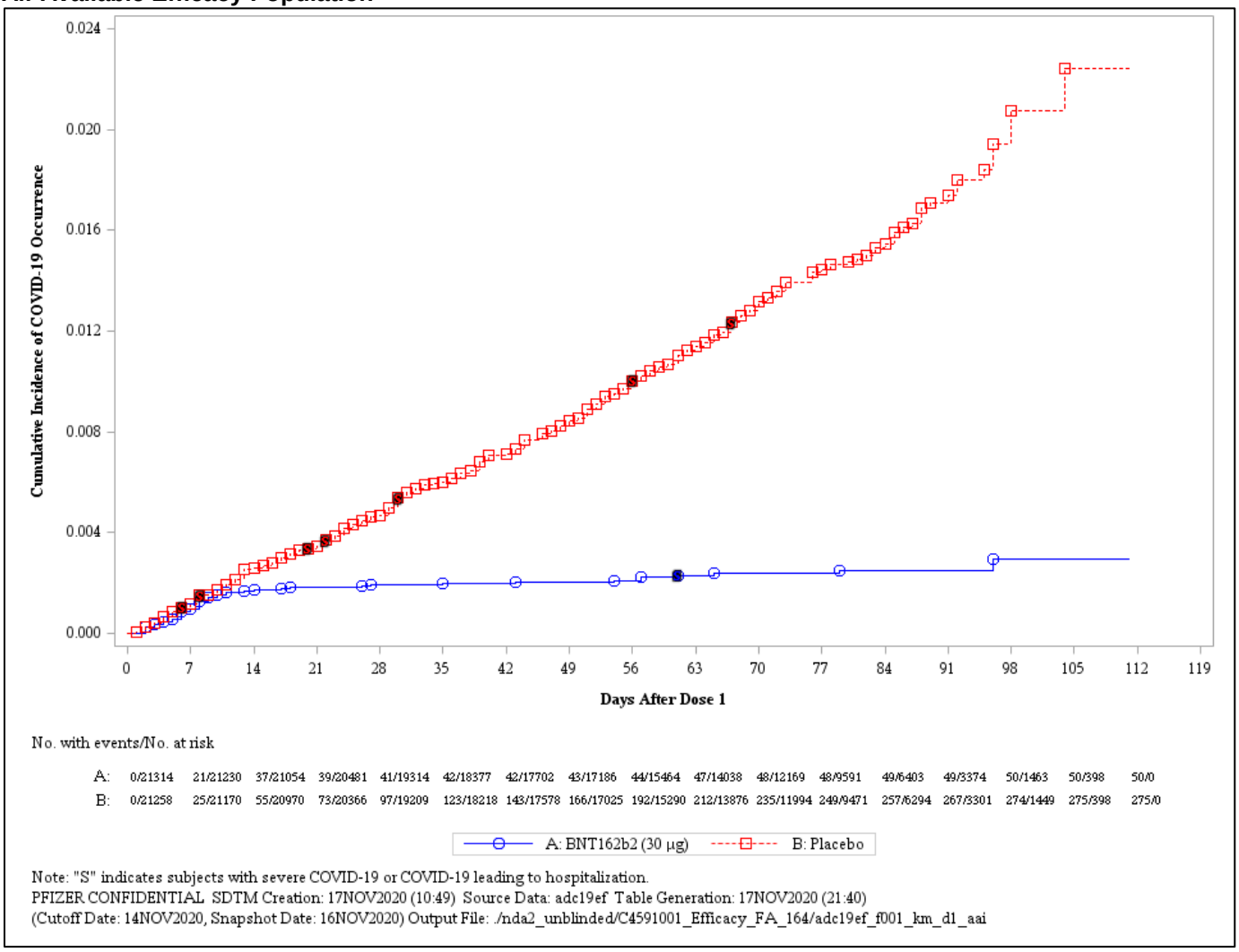
Efficacy Endpoint Subgroup	BNT162b2 (30 µg) N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Overall	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.0, 97.9)
Comorbidity			
No comorbidity	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Any comorbidity[f]	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
Any malignancy	1 0.092 (704)	4 0.090 (681)	75.7 (-145.8, 99.5)
Cardiovascular	0 0.067 (534)	5 0.062 (492)	100.0 (-0.8, 100.0)
Chronic pulmonary disease	1 0.175 (1374)	14 0.171 (1358)	93.0 (54.1, 99.8)
Diabetes	1 0.176 (1372)	19 0.176 (1374)	94.7 (66.8, 99.9)
Obese (BMI≥30.0 kg/m^2)	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
Hypertension	2 0.567 (4413)	44 0.567 (4437)	95.4 (82.6, 99.5)
Diabetes (including gestational diabetes)	1 0.177 (1381)	20 0.178 (1384)	95.0 (68.7, 99.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f] Subject who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or BMI ≥30 kg/m2.

Cumulative Incidence Curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1, (Figure 2), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the BNT162b2 group, and there does not appear to be evidence of waning protection during the follow-up time of approximately 2 months following the second dose that is being evaluated at this point in time.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



Secondary Efficacy Analyses

The secondary efficacy endpoints evaluate the VE of BNT162b2 for the prevention of COVID-19 disease from 14 days after Dose 2 and based on the CDC's definition of COVID-19 disease from 7 and 14 days after Dose 2. The case splits and VE for each of these secondary efficacy endpoints were each similar to the primary efficacy endpoints described above.

Severe COVID-19 Cases

In the final analysis of the evaluable efficacy population (7 days), four participants had severe COVID-19 disease at least 7 days after Dose 2 (one subject who received BNT162b2 and three participants who received placebo). The vaccine recipient who had severe COVID-19 disease met the severe case definition because oxygen saturation at the COVID-19 illness visit was 93% on room air. The subject was not hospitalized, did not seek further medical care, and did not have risk factors for severe disease. The three placebo recipients who had severe COVID-19 disease met the severe case definition for the following reasons: one subject had an oxygen saturation of 92% on room air without other severe disease criteria, one subject was

hospitalized for noninvasive positive pressure ventilation with bilateral pneumonia, and one subject had an oxygen saturation of 92% and ICU admission for heart block. One of these placebo recipients with severe disease also had a body mass index > 30 kg/m^2 as a risk factor, while the other two participants did not have any risk factors for severe disease. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 11.

Table 11. First Severe COVID-19 Occurrence from 7 Days after Dose 2 - Evaluable Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
First severe COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection	1 2.215 (17411)	3 2.232 (17511)	66.4 (-124.8, 96.3)[e]	No

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >98.6% at the final analysis.
[a.] N = number of participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d]. n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

In the all-available efficacy population, ten participants had severe COVID-19 disease after Dose 1 (one subject who received BNT162b2 and nine participants who received placebo). Five of the remaining six placebo recipients who had severe COVID-19 disease were hospitalized, two of whom were admitted to an intensive care unit. Five of these remaining six placebo recipients who had severe disease had at least one risk factor for severe disease. The total number of severe cases is small, which limits the overall conclusions that can be drawn; however, the case split does suggest protection from severe COVID-19 disease.

Table 12. First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First severe case occurrence after Dose 1	1 4.021 (21314)	9 4.006 (21259)	88.9 (20.1, 99.7)[f]
After Dose 1 to before Dose 2	0	4	100.0 (-51.5, 100.0)
Dose 2 to 7 days after Dose 2	0	1	100.0 (-3800.0, 100.0)
≥7 Days after Dose 2	1	4	75.0 (-152.6, 99.5)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Additional Efficacy Analyses

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 2 (Table 13).

Table 13. Primary Efficacy Endpoint –All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after Dose 1 – Dose 1	50 4.015 (21314)	275 3.982 (21258)	82.0 (75.6, 86.9)[f]
After Dose 1 to before Dose 2	39	82	52.4 (29.5, 68.4)
Dose 2 to 7 days after Dose 2	2	21	90.5 (61, 98.9)
≥7 Days after Dose 2	9	172	94.8 (89.8, 97.6)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 82%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 21 days after a single dose.

Efficacy Summary

The data submitted in this EUA request were consistent with the recommendations set forth in the FDA Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 and met the prespecified success criteria established in the protocol. In the planned interim and final analyses, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the group of participants with or without prior infection. Efficacy outcomes were consistently robust (⩾93%) across demographic subgroups.

Efficacy against severe COVID-19 occurring after the first dose was 88.9% (95% CI 20.1, 99.7), with an estimated VE of 75.0% (95% CI -152.6, 99.5) (1 case in BNT162b2 group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.

Among all participants (regardless of evidence of infection before or during the vaccination regimen), 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2. The efficacy observed after Dose 1 and before Dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the time of observation is limited by the fact that most of the participants received a

second dose after three weeks. The trial did not have a single-dose arm to make an adequate comparison.

5.2.6. Safety

Overview of Adverse Events

Table 14 below presents an overview of all adverse events in the phase 2/3 safety population. A higher proportion of vaccine recipients reported adverse events compared with placebo recipients, and this imbalance was driven by reactogenicity (solicited adverse events) reported in the 7 days following vaccination and unsolicited adverse events corresponding to reactogenicity symptoms among participants not in the reactogenicity subset (see presentation of unsolicited adverse events in a later section). Proportions of participants with serious adverse events, deaths, and withdrawals due to adverse events were balanced between treatment groups.

Table 14. Study C4591001 Safety Overview- Ages 16 years and older

Participants Experiencing at Least One:	BNT162b2 n/N (%)	Placebo n/N (%)
Immediate unsolicited AE Within 30 minutes after vaccination[a]		
Dose #1	78/18801 (0.4)	66/18785 (0.4)
Dose #2	52/18494 (0.3)	39/18470 (0.2)
Solicited injection site reaction within 7 days[b]		
Dose #1	3216/4093 (78.6)	525/4090 (12.8)
Dose #2	2748/3758 (73.1)	396/3749 (10.6)
Solicited systemic AE within 7 days[b]		
Dose #1	2421/4093 (59.1)	1922/4090 (47.0)
Dose #2	2627/3758 (69.9)	1267/3749 (33.8)
From Dose 1 through 1 month after Dose 2[a]		
Unsolicited non-serious AE	5071/18801 (27.0)	2356/18785 (12.5)
SAE	103/18801 (0.5)	81/18785 (0.4)
From Dose 1 through cutoff date (safety population)		
SAE	124/18801 (0.7)	101/18785 (0.5)
From Dose 1 through cutoff date (all-enrolled)[c]		
Withdrawal due AEs	37/21621 (0.6)	30/21631 (0.5)
SAE	126/21621 (0.6)	111/21631 (0.5)
Deaths	2/21621 (0.0)	4/21631 (0.0)

Source: c4591001-safety-tables-ae3.pdf pages 216,446,459,463; c4591001-safety-tables-cos-reacto.pdf, pages 113-114.
n= number of participants with the specified reaction or AE.
[a] N: number of participants in the phase 2/3 safety population.
[b] N: number of participants in the reactogenicity subset of the phase 2/3 safety population.
[b] N: number of participants in the all-enrolled population.
Data analysis cutoff date: November 14, 2020.

Solicited Local Reactions and Systemic Adverse Events

As of the cutoff date, solicited reactogenicity data in participants 16 and 17 years of age were not collected by e-diary and are not available. Symptoms consistent with solicited reactogenicity that were reported by these participants were collected and analyzed as unsolicited adverse events and are discussed with review of those data.

Solicited Local Reactions

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of local reactions in the vaccine group was 0 (day of vaccination) to 2 days after either dose and lasted a median duration between 1 and 2 days.

For both age groups, injection site pain was the most frequent solicited local adverse reaction. After dose 2, the younger age group reported any pain more frequently than the older age group (77.8% vs 66.1%) and pain characterized as moderate (27.1% vs. 18.0%); a similar pattern was observed after Dose 1. Injection site redness and swelling after each dose were generally similar for both age groups.

Subgroup analyses by age

Table 15. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Local Reaction	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Pain[a]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)
Redness[b]				
Any	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[b]				
Any	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)

Source: adapted from EUA 27034, amendment 3, Table 17.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, >55 Years of Age and Older

Local Reaction	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Pain[a]				
Any	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)
Redness[b]				
Any	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[b]				
Any	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)

Source: EUA 27036, amendment 3, Table 21.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Solicited Systemic AEs

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of systemic AEs in the vaccine group in general was 1 to 2 days after either dose and lasted a median duration of 1 day.

The frequency and severity of systemic AEs were higher in the younger than the older age groups. Within each age group, the frequency and severity of systemic AEs was higher after Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar regardless of dose. For both age groups, fatigue, headache and new/worsened muscle pain were most common.

Subgroup analyses by age

Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Adverse Event	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Fever				
≥38.0℃	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
>38.0℃ to 38.4℃	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4℃ to 38.9℃	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9℃ to 40.0℃	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0℃	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)

Adverse Event	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Fatigue[a]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	46 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[a]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[a]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[b]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[c]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[a]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[a]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

Source: adapted from EUA 27036, amendment 3, Table 19.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 18. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population*, >55 Years of Age and Older

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
>38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[a]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)
Headache[a]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[a]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[b]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[c]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[a]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[a]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

Source: EUA 27036, amendment 3, Table 23.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Unsolicited (non-serious) AEs

A higher frequency of unsolicited, non-serious adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local reactions and systemic adverse events in subjects not in the reactogenicity subset and are consistent with solicited reactions/events reported by reactogenicity subset participants during the first 7 days following vaccination. Table 19 below presents unsolicited adverse events reported by at least 1% of participants in any treatment group for the phase 2/3 safety population.

Reports of lymphadenopathy were imbalanced with notably more cases in the vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Bell's palsy was reported by four vaccine participants and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days postvaccination) was reported as resolved with sequelae within three days after onset, and the other three were reported as continuing or resolving as of the November 14, 2020 data cut-off with ongoing durations of 10, 15, and 21 days, respectively. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and there is no clear basis upon which to conclude a causal relationship at this time, but FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories (system organ class or preferred term) of non-serious adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Table 19. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1-month After Dose 2, Phase 2/3 Safety Population*, 16 Years of Age and Older

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
General disorders and administration site conditions	3521 (18.7)	737 (3.9)	4258 (11.3)
Injection site pain	2125 (11.3)	286 (1.5)	2411 (6.4)
Fatigue	1029 (5.5)	260 (1.4)	1289 (3.4)
Pyrexia	1146 (6.1)	61 (0.3)	1207 (3.2)
Chills	999 (5.3)	87 (0.5)	1086 (2.9)
Pain	455 (2.4)	36 (0.2)	491 (1.3)
Musculoskeletal and connective tissue disorders	1387 (7.4)	401 (2.1)	1788 (4.8)
Myalgia	909 (4.8)	126 (0.7)	1035 (2.8)
Arthralgia	212 (1.1)	82 (0.4)	294 (0.8)
Nervous system disorders	1158 (6.2)	460 (2.4)	1618 (4.3)
Headache	973 (5.2)	304 (1.6)	1277 (3.4)
Gastrointestinal disorders	565 (3.0)	368 (2.0)	933 (2.5)
Diarrhoea	194 (1.0)	149 (0.8)	343 (0.9)
Nausea	216 (1.1)	63 (0.3)	279 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Subgroup analyses by age

16 and 17 years of age: the table below represents an FDA-generated summary of unsolicited AEs consistent with reactogenicity and AEs that occurred at ≥1% and higher in the BNT162b2 Vaccine Group, classified by MedDRA System Organ Class and Preferred Term.

Table 20. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 16 and 17 Years of Age

System Organ Class Preferred Term	BNT162b2 N=53 n (%)	Placebo N=50 n (%)	Total N=103 n (%)
General disorders and administration site conditions	7 (13.2)	3 (6.0)	10 (9.7)
Injection site pain	5 (9.4)	2 (4.0)	7 (6.8)
Pyrexia	5 (9.4)	0	5 (4.9)
Pain	2 (3.8)	0	2 (1.9)
Chills	1 (1.9)	0	1 (1.0)
Injury, poisoning and procedural complications	1 (1.9)	0	1 (1.0)
Concussion	1 (1.9)	0	1 (1.0)
Facial bones fracture	1 (1.9)	0	1 (1.0)
Road traffic accident	1 (1.9)	0	1 (1.0)
Investigations	1 (1.9)	0	1 (1.0)
Body temperature increased	1 (1.9)	0	1 (1.0)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 21. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 65 Years and Older

System Organ Class Preferred Term	BNT162b2 (N=4058) n (%)	Placebo (N=4043) n (%)	Total (N=8101) n (%)
General disorders and administration site conditions	577 (14.2)	118 (2.9)	695 (8.6)
Injection site pain	361 (8.9)	39 (1.0)	400 (4.9)
Fatigue	175 (4.3)	44 (1.1)	219 (2.7)
Chills	143 (3.5)	19 (0.5)	162 (2.0)
Pyrexia	148 (3.6)	10 (0.2)	158 (2.0)
Pain	60 (1.5)	7 (0.2)	67 (0.8)
Musculoskeletal and connective tissue disorders	231 (5.7)	83 (2.1)	314 (3.9)
Myalgia	125 (3.1)	23 (0.6)	148 (1.8)
Arthralgia	42 (1.0)	21 (0.5)	63 (0.8)
Pain in extremity	33 (0.8)	10 (0.2)	43 (0.5)
Nervous system disorders	179 (4.4)	87 (2.2)	266 (3.3)
Headache	127 (3.1)	45 (1.1)	172 (2.1)
Gastrointestinal disorders	127 (3.1)	72 (1.8)	199 (2.5)
Diarrhea	49 (1.2)	26 (0.6)	75 (0.9)
Nausea	40 (1.0)	13 (0.3)	53 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

FDA independently conducted standard MedDRA queries (SMQs) using FDA-developed software (MAED) to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions. The SMQs, conducted on the phase 2/3 all-enrolled safety population, revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137 [0.63%]) compared with the placebo group (111 [0.51%]). No imbalances between treatment groups were evident for any of the other SMQs evaluated.

Immediate AEs (phase 2/3 safety population)
The frequency of immediate AEs reported in the vaccine group was 0.4% after Dose 1 and <0.3% after Dose 2 and were mainly consistent with solicited reactogenicity events. In both study groups, the most frequently reported immediate AE was injection site pain (BNT162b2 vaccine 0.3%, placebo 0.2%).

Study Withdrawals due to an AE (all-enrolled population)
Of 43,448 enrolled participants, 37 (0.2%) vaccine recipients and 30 (0.1%) placebo recipients (0.1%), and no adolescents 16 to <18 years of age, withdrew from the study due to an AE. AEs in the SOC of General Disorders and Administration Site Conditions (7 vaccine, 3 placebo) was common, with injection site pain the most frequent (2 vaccine, 0 placebo).

Serious Adverse Events

Deaths

A total of six (2 vaccine, 4 placebo) of 43,448 enrolled participants (0.01%) died during the reporting period from April 29, 2020 (first participant, first visit) to November 14, 2020 (cutoff date). Both vaccine recipients were >55 years of age; one experienced a cardiac arrest 62 days after vaccination #2 and died 3 days later, and the other died from arteriosclerosis 3 days after vaccination #1. The placebo recipients died from myocardial infarction (n=1), hemorrhagic stroke (n=1) or unknown causes (n=2); three of the four deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

Non-fatal SAEs

In the all-enrolled population of (total N=43,448), the proportions of participants who reported at least 1 SAE during the time period from Dose 1 to the data cutoff date (November 14, 2020) were 0.6% in the BNT162b2 vaccine group and 0.5% in the placebo group. The most common SAEs in the vaccine group which were numerically higher than in the placebo group were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), and syncope (0.02%). Occurrence of SAEs involving system organ classes and specific preferred terms were otherwise balanced between treatment groups, including no imbalance overall in cardiovascular serious adverse events.

Appendicitis was reported as a SAE for 12 participants, and numerically higher in the vaccine group: 8 vaccine participants ([appendicitis [n=7], appendicitis perforated [n=1]) and 4 placebo participants (appendicitis [n=2], appendicitis perforated [n=1], complicated appendicitis [n=1]). All of the vaccine participants (n=8) and 2 placebo participants were younger than 65 years of age. The cases were considered unrelated to vaccination by the study investigators and occurred no more frequently than expected in the given age groups. FDA agrees that there is no clear basis upon which to suspect that this imbalance represents a vaccine-related risk.

Three SAEs reported in the BNT162 group were considered by the investigator as related to vaccine or vaccine administration: shoulder injury, ventricular arrhythmia, and lymphadenopathy. The investigator and the sponsor thought that the shoulder injury was related to vaccine administration. Two SAEs in the BNT162b2 group and none in the placebo group were considered by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally following vaccination (n=1). In FDA's opinion following review of the adverse event narratives, two of these events were considered as possibly related to vaccine: shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. For lymphadenopathy, the event was temporally associated and biologically plausible.

Among participants 16 to 17 years of age, there was 1 participant in the vaccine group who experienced an SAE of facial bones fracture, which was not considered related to study intervention by the investigator.

Suspected COVID-19 Cases

As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness. Two serious cases of suspected but unconfirmed COVID-19 were reported, both in the vaccine group, and narratives were reviewed. In one case, a 36-year-old male with no medical comorbidities experienced fever, malaise, nausea, headache and myalgias beginning on the day of Dose 2 and was hospitalized 3 days later for further evaluation of apparent infiltrates on chest radiograph and treatment of dehydration. A nasopharyngeal PCR test for SARS-CoV-2 was negative on the day of admission, and a chest CT was reported as normal. The participant was discharged from the hospital 2 days after admission. With chest imaging findings that are difficult to reconcile, it is possible that this event represented reactogenicity following the second vaccination, a COVID-19 case with false negative test that occurred less than 7 days after completion of the vaccination series, or an unrelated infectious process. In the other case, a 66-year-old male with no medical comorbidities experienced fever, myalgias, and shortness of breath beginning 28 days post-Dose 2 and was hospitalized one day later with abnormal chest CT showing a small left-sided consolidation. He was discharged from the hospital 2 days later, and multiple nasopharyngeal PCR tests collected over a 10-day period beginning 2 days after symptom onset were negative. It is possible, though highly unlikely, that this event represents a COVID-19 case with multiple false negative tests that occurred more than 7 days after completion of the vaccination regimen, and more likely that it represents an unrelated infectious process.

Among 3410 total cases of suspected but unconfirmed COVID-19 in the overall study population, 1594 occurred in the vaccine group vs. 1816 in the placebo group. Suspected COVID-19 cases that occurred within 7 days after any vaccination were 409 in the vaccine group vs. 287 in the placebo group. It is possible that the imbalance in suspected COVID-19 cases occurring in the 7 days postvaccination represents vaccine reactogenicity with symptoms that overlap with those of COVID-19. Overall though, these data do not raise a concern that protocol-specified reporting of suspected, but unconfirmed COVID-19 cases could have masked clinically significant adverse events that would not have otherwise been detected.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Female study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Twenty-three pregnancies were reported through the data cut-off date of November 14, 2020 (12 vaccine, 11 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (4 vaccine, 2 placebo), within 30 days after LMP in 8 participants (4 vaccine, 6 placebo), >30 days after LMP in 1 participant (0 vaccine, 2 placebo), and date of LMP not known in 5 participants (4 vaccine, 1 placebo). Unsolicited AEs related to pregnancy include spontaneous abortion and retained products of conception, both in the placebo group. Pregnancy outcomes are otherwise

unknown at this time.

Clinical Laboratory Evaluations

Clinical laboratory tests (hematology, chemistries) were assessed in study BNT162-01 and C4591001 phase 1. The only common laboratory abnormality reported throughout the studies was transient decreases in lymphocytes 1-3 days after Dose 1, which increased in frequency with increasing dose, were mostly Grade 1-2, generally normalized at the next laboratory assessment 6-8 days after Dose 1 and did not occur after Dose 2. Among C4591001 phase 1 participants who received the 30 µg dose of BNT162b2, transient decreases in lymphocytes post-Dose 1 occurred in 5 of 12 participants 18-55 years of age and in 4 of 12 participants 65-85 years of age. These transient hematological changes were not associated with clinical symptoms.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of BNT162b2 in the context of the proposed indication and population for intended use under EUA. The number of participants in the phase 2/3 safety population (N=37586; 18801 vaccine,18785 placebo) meets the expectations in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy, and the median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series meets the agency's expectations in FDA's Guidance on its Emergency Use Authorization for Vaccines to Prevent COVID-19. The all-enrolled population contained more participants >16 years of age, regardless of duration of follow-up (43448; 21720 vaccine, 21728 placebo). The demographic and baseline characteristics of the all-enrolled population and the safety population were similar. Although the overall median duration of follow-up in the all-enrolled population was less than 2 months, because the protocol was amended to include subpopulations such as individuals with HIV and adolescents, the data from both populations altogether provide a comprehensive summary of safety.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in adults ≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). Among adverse events of special interest, which could be possibly related to vaccine, lymphadenopathy was reported in 64 participants (0.3%): 54 (0.5%) in the younger (16 to 55 years) age group; 10 (0.1%) in the older (>55 years) age group; and 6 in the placebo group. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff. Bell's palsy was reported by four vaccine participants. From Dose 1 through 1 month after Dose 2, there were three reports of Bell's palsy in the vaccine group and none in the placebo group. This observed frequency of reported Bell's palsy is consistent with the expected background rate in the general population. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine.

A total of six deaths occurred in the reporting period (2 deaths in the vaccine group, 4 in placebo). In the vaccine group, one participant with baseline obesity and pre-existing atherosclerosis died 3 days after Dose 1, and the other participant experienced cardiac arrest

60 days after Dose 2 and died 3 days later. Of the four deaths in the placebo arm, the cause was unknown for two of them, and the other two participants died from hemorrhagic stroke (n=1) and myocardial infarction (n=1), respectively; three deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

The frequency of non-fatal serious adverse events was low (<0.5%), without meaningful imbalances between study arms. The most common SAEs in the vaccine arm which were numerically higher than in the placebo arm were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), atrial fibrillation (0.02%) and syncope (0.02%). Appendicitis was the most common SAE in the vaccine arm. There were 12 participants with SAEs of appendicitis; 8 in the BNT162b2 group. Of the 8 total appendicitis cases in the BNT162b2 group, 6 occurred in the younger (16 to 55 years) age group and 2 occurred in the older (>55 years) age group (one of the cases in the older age group was perforated). One of the 6 participants with appendicitis in the younger age group also had a peritoneal abscess. Cases of appendicitis in the vaccine group were not more frequent than expected in the general population.

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

The Sponsor plans to offer vaccination to participants ⩾16 years of age who originally received placebo and who become eligible for receipt of BNT162b2 according to local or national recommendations. The Sponsor proposes that these participants will be unblinded upon request and will have the opportunity to receive BNT162b2 as part of the study. The Sponsor also proposes that all placebo recipients ⩾16 years of age will be offered BNT162b2 after completing 6 months of follow-up after Dose 2, if they did not request and receive vaccine previously. The participants will provide consent to receive vaccination and to continue follow-up. For these participants, the Sponsor plans a total follow up period of 18 months, with one visit 1-month postvaccination and subsequent phone contacts at 1, 6, and 18 months postvaccination. Safety and efficacy monitoring during this period will include collection of AEs, SAEs, and screening and diagnosing COVID-19 cases.

7. Pharmacovigilance Activities

Pfizer submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with Pfizer-BioNTech COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. Use in pregnancy and lactation and vaccine effectiveness are areas the Sponsor identified as missing information. In addition to the safety concerns specified by the Sponsor, FDA requested that the Sponsor update their PVP to include missing information in pediatric participants less than 16 years of age.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following three planned active surveillance studies. Of note, the Sponsor will submit plans for a clinical study to assess safety and immunogenicity in pregnant women and has proposed active surveillance studies designed to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA.

- Study Protocol Number C4591008. The Sponsor proposes to survey 20,000 U.S. health care workers enrolled in the COVID-19 HERO registry as well as health care workers in certain participating health care facilities about adverse events of special interest, and other clinically significant events of interest after vaccination with the Pfizer-BioNTech COVID-19 Vaccine. Incidence rates of these events in this cohort will be compared to expected rates. The respondents would receive follow-up surveys for a 30-month period.
- Study Protocol Number C4591011. This study is an active safety surveillance evaluation conducted within the Department of Defense Health System Databases using data derived from electronic health records and medical service claims among covered U.S. military and their families. Rates of safety events of interest in vaccinated participants will be compared to unvaccinated comparators. The study will be conducted for 30 months.
- Study Protocol Number C4591012. This study is an active surveillance study for adverse events of special interest and other clinically significant events associated with the Pfizer-BioNTech COVID-19 Vaccine using the Veteran's Health Administration electronic medical record database. Vaccinated participants will be compared to unvaccinated participants or to recipients of seasonal influenza vaccine. The study will be conducted for 30 months.

Currently, the primary objective of all three proposed studies above is descriptive, and the list of adverse events in the studies has not been finalized. FDA will provide feedback on these studies after further review.

Reporting to VAERS and Pfizer, Inc.

Providers administering the Pfizer-BioNTech COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to Pfizer the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1. Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2
- Reduction in the risk of confirmed COVID-19 after Dose 1 and before Dose 2
- Reduction in the risk of confirmed severe COVID-19 any time after Dose 1

The protocol-specified 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 7 days after completion of the vaccination regimen. Additional primary efficacy analyses in the all-available efficacy population, including participants who had protocol violations, showed consistency with outcomes in the primary analysis population. Efficacy findings were also consistent across various subgroups, including racial and ethnic minorities, participants aged 65 years and older, and those with one or more of the following conditions: obesity, diabetes, hypertension, and chronic cardiopulmonary diseases. While limited, available data suggest that individuals with previous SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination.

Among participants with no evidence of COVID-19 prior to vaccination, the vaccine was effective in reducing the risk of COVID-19 and severe COVID-19 after Dose 1. Fewer severe cases were also observed in the vaccine recipients relative to recipients of placebo during the follow up period after Dose 1. The findings post Dose 1, from a post-hoc analysis, cannot be the basis to assess the potential efficacy of the vaccine when administered as a single dose because the period of observation is limited by the fact that most participants received a second dose three weeks after the first one.

8.2. Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subset of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) is too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

The primary endpoint was evaluated in individuals without prior evidence of COVID-19 disease, and very few cases of confirmed COVID-19 occurred among participants with evidence of infection prior to vaccination (although more cases occurred in the placebo group compared with the vaccine group). Therefore, available data are insufficient to make conclusions about benefit in individuals with prior SARS-CoV-2 infection. However, available data, while limited, do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Effectiveness in pediatric populations

The representation of pediatric participants in the study population is too limited to adequately evaluate efficacy in pediatric age groups younger than 16 years. No efficacy data are available from participants ages 15 years and younger. Although adolescents 16 to 17 years of age were included in the overall efficacy analysis, only one confirmed COVID-19 case was reported in this age group. However, it is biologically reasonable to extrapolate that effectiveness in ages 16 to 17 years would be similar to effectiveness in younger adults. Efficacy surveillance continued beyond November 14, 2020, and the Sponsor has represented that additional data will be provided in a BLA.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27 to November 14, 2020, in various geographical locations. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine against asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[11-14] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3. Known Risks

The vaccine has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%). Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of subjects reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs. 111 [0.51%]). Severe adverse reactions occurred in 0.0-4.6% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in older adults (>55 years of age) ($\underline{\leq}$2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination.

Serious adverse events, while uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study. Three SAEs in the BNT162b2 group were considered related by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally related following vaccination (n=1). We considered two of the events as possibly related to vaccine: the shoulder injury possibly due to vaccine administration or the vaccine itself and lymphadenopathy. Lymphadenopathy was temporally associated and biologically plausible.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Although participants 16 to 17 years of age were enrolled in the phase 3 trial, safety data for this age group is limited. However, available data are consistent with the safety profile in the adult population, and it is biologically reasonable to extrapolate the greater safety experience in adults, in particular younger adults, to the oldest pediatric age group of 16 to 17 years.

8.4. Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 16 years of age, pregnant and lactating individuals, and immunocompromised individuals.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of nearly 44,000 participants over the period of follow up at this time. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

A numerically greater number of appendicitis cases occurred in the vaccine group but occurred no more frequently than expected in the given age groups and do not raise a clear concern at this time for a causal relationship to study vaccination. Although the safety database revealed an imbalance of cases of Bell's palsy (4 in the vaccine group and none in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

9. References

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine.* 2020;382(8):727-733.
2. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2.
3. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England).* 2020;395(10224):565-574.
4. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280.e278.
5. Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb–3 and 360bbb-3b. (2011).
6. FDA. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19.

7. National Vaccine Injury Compensation Program. Vaccine Injury Table, Revised and Effective March 21, 2017. https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf.
8. International Coalition of Medicines Regulatory Authorities. Statement on continuation of vaccine trials. http://www.icmra.info/drupal/en/covid-19/statement_on_continuation_of_vaccine_trials. 2020.
9. Krause PR, Fleming TR, Longini IM, et al. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. *The New England journal of medicine.* 2020.
10. Wendler D, Ochoa J, Millum J, Grady C, Taylor HA. COVID-19 vaccine trial ethics once we have efficacious vaccines. *Science.* 2020:eabf5084.
11. Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working Group, the. Historical Comparisons of Morbidity and Mortality for Vaccine-Preventable Diseases in the United States. *JAMA.* 2007;298(18):2155-2163.
12. Verhees RAF, Dondorp W, Thijs C, Dinant GJ, Knottnerus JA. Influenza vaccination in the elderly: Is a trial on mortality ethically acceptable? *Vaccine.* 2018;36(21):2991-2997.
13. Flannery B, Reynolds SB, Blanton L, et al. Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010–2014. 2017;139(5):e20164244.
14. Rolfes MA, Flannery B, Chung JR, et al. Effects of Influenza Vaccination in the United States During the 2017-2018 Influenza Season. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2019;69(11):1845-1853.

10. Appendix A. Study BNT162-01

Design

Study BNT162-01 is an ongoing, first-in-human, phase 1 dose-level finding study conducted in Germany to evaluate the safety and immunogenicity of several different candidate vaccines, including BNT162b2. Twelve adults 18 to 55 years of age received 30ug BNT162b2.

Secondary and exploratory objectives were specified to describe the immune response, measured by functional antibody titer, antibody binding assay, and cell-mediated immune responses (cytokines associated with Th1 and Th2 responses to assess for the induction of a balanced versus Th1 or Th2 dominant immune response) at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as in study C4591001.

Results

No SAEs were reported in the BNT162-01 safety database included in the EUA submission, and the safety profile for BNT162b2 in this study was similar to that in the much larger study, C4591001.

Evaluable ELISPOT data were available from 39 participants across dose levels of BNT162b2 (data cutoff date was 17 September 2020). Evaluable intracellular cytokine staining and FACS data were available from 36 participants across dose levels of BNT162b2 (cutoff date was 04 September 2020). Data for serology results for serum neutralizing titers were available for 45 participants across dose levels of BNT162b2 (data cutoff date was 18 September 2020). Most participants who received both doses of BNT162b2 had evidence of SARS-CoV-2 S protein-specific CD4+ (39/39, 100%) and CD8+ (35/39, 89.7%) T cell responses. These T cell responses were directed against different parts of the antigen, including epitopes in the RBD, indicating the induction of multi-epitope responses by BNT162b2. Functionality and polarization of S-specific BNT162b2-induced SARS-CoV-2 T cells were assessed by intracellular accumulation of cytokines IFNγ, IL-2, and IL-4 measured after stimulation with overlapping peptide pools representing the full-length sequence of the whole SARS-CoV-2 S protein. For benchmarking, PBMC fractions from 15 convalescent patients with virologically confirmed COVID-19 were used. The Th1 polarization of the T helper response was characterized by the IFNγ and IL-2 production, and only minor IL-4, production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation. The SARS-CoV-2 neutralizing geometric mean titer (GMTs) increased over baseline after Dose 1, with a boost effect after Dose 2 that was most pronounced at the 30 µg dose level.

Thus, the immunogenicity results from Study BNT162-01 showed evidence of antibody-mediated SARS-CoV-2 neutralization and a Th1 polarization in the cell-mediated cellular immune responses in healthy adults 18 to 55 years of age, which supports the final dose selection and prospect of benefit for the enrollment of larger numbers of participants in Study C4591001.

11. Appendix B. Charlson Comorbidity Index

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, HIV/AIDS.

Reference: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

12. Appendix C. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19

Emergency Use Authorization for Vaccines to Prevent COVID-19

January 19, 2021

Representative Karen M. Rohr,
Chair, Human Services Committee
North Dakota Legislative Assembly
600 East Boulevard
Bismarck, ND 58505

Senator Judy Lee
Vice Chair, Human Services Committee
North Dakota Legislative Assembly
600 East Boulevard
Bismarck, ND 58505

Dear Chair Rohr, Vice Chair Lee, and Members of the Human Services Committee,

I am writing in support of bills HB 1306, HB 1307, and HB 1320. I have a BSN in nursing and a graduate doctoral degree in Chiropractic. I've worked in health RESTORATION for over of 12 years. I've worked in ICU work as an RN before continuing my Doctoral education. Because we take a different view of the human body (one that looks at triggers of dysfunction and why the body breaks down, as opposed to the end point-disease) I see protection from being injured is paramount in protecting people who choose to be responsible for their own health.

There are questions that need to be asked when considering coercion of health care choices.

"Are my health choices private? Will I eventually need to divulge what I eat, my exercise/fitness routine, Lab findings, Sexual orientation, and history? Will my health care choices determine my ability to access my bank accounts, To get on an airplane, or To fill gas?"

"Do vaccines do what you are taught to believe they do?"

"Who should make your health care decisions- you or your government?"

"If there are admitted, inherent dangers to a health care decision, should you be coerced into that health care decision?"

"What about people with known side effects to inoculation? Will they be treated as second rate citizens?"

For the record, I would like to enter in some important information, as coercion of health care choices is a very slippery slope. A year ago I was laughed at for saying we will be given vaccination ID's and will need to prove status for travel. Today, it has become a reality.

1. Vaccines are classified as biologics. This means that they are NOT subject to true placebo controlled studies. Rarely, if ever, are they studied against a true placebo. Almost every study uses other vaccines (example: the astrazeneca covid-19 study used the meningitis vaccine) [1] and/or the equally as risky ingredients (adjuvants like alumimum or mercury) in vaccines as a

"control" which allows them to hide expected adverse reactions with other reactions in the placebo group. Adjuvants have the capability of producing neuroinflammation which can lead to damage to the central and peripheral Nerve System.[2] Encephalopathy is a form of neuroinflammation. Encephalopathy can lead to autism and other neurologic and immune related disorders.

2. Vaccine injuries are severely underreported. Less than 1% of adverse events are ever reported. This has been researched and can be validated:[3]

> "Adverse events from drugs and vaccines are common but underreported. Although 25% of ambulatory patients experience an adverse drug event, less than 0.3% of all adverse drug events and 1-13% of serious events are reported to the Food and Drug Administration (FDA). **Likewise, fewer than 1% of vaccine adverse events are reported. Low reporting rates preclude or slow the identification of "problem" drugs and vaccines that endanger public health.** New surveillance methods for drug and vaccine adverse effects are needed. **Barriers to reporting include a lack of clinician awareness, uncertainty about when and what to report, as well as the burdens of reporting:** reporting is not part of clinicians' usual workflow, takes time, and is duplicative."[3]

This brings out the inconvenient truth that adverse events are 100 times more common than the mainstream media and medical doctors would like to admit.

I have personal experience with this, and a good example is the HPV inoculation. However as listed above, is prevalent in many more. Public marketing campaigns downplay risks and overestimate efficacy. They ignore the actual data (or lack thereof) to unduly influence the public. They will tell you that injuries are estimated to be "one in a million". However, since moving back to North Dakota 10 years ago, I have taken care of THREE teenagers in the Burleigh/Morton area alone whose severe symptomatology (diagnosed as POTS disease) began within 7 days of their HPV inoculation. Based on basic math and how many teenaged people there are in the Bismarck-Mandan area alone, along with how many I see, these numbers are massively higher than publicized. Then put into the equation that I came across these people randomly, for other reasons like sports injuries. This means the I am likely to have seen an extremely small minority of these people effected. So you have to ask, how does this happen? When questioned, the parents and patients had no idea to even ponder a link or to share with their doctor. Furthermore, not a single medical doctor had questioned them about inoculation history prior to onset of their problems. It was not until I asked the question about inoculation history that the family began to put the pieces together, and when they then inquired to their medical doctor, there was no testing or validation, nor was it reported to VAERS (the Vaccine Adverse Event Reporting System), a government entity responsible for diverting tax dollars to pay out damages caused by vaccines.

3. Drug companies are all exempt from paying out damages for vaccine damage, even though many of the biggest vaccine production companies are convicted felons for fraud and marketing—Pfizer,[4] Johnson & Johnson,[5] Astrazeneca,[6,7] and Merck all have some of the largest fines ever given out in court due to fraud, false marketing, kickbacks and bribery, false claims act related, and drug or medical equipment safety violation. (but hey, they "Pledged" transparency

in their studies, so we can trust them, right?)[8] Many, including Pfizer, Glaxo, and Sanofi are convicted felons. They have no impetus to improve vaccine safety or improve studies. Therefore, those who question safety have valid concerns.

4. Vaccines to not create health. Until recently, the US government has not bothered to study vaccinated and non-vaccinated populations. However, recently, Dr. Paul Thomas published research in his own practice in regards chronic disease prevalence in children fully vaccinated, partially vaccinated, and nonvaccinated. Because of the published findings, politically he is facing a "witchhunt" and is being targeted by the powers that be (note who is the largest lobbying company in the world—the pharmaceutical industry). Nonvaccinated children had significantly less chronic disease than the other two groups.[9] If vaccines create health, then why is the vaccinated group much sicker than the nonvaccinated group?

5. My health care choices are MY health care choices. To even INQUIRE about inoculations is an intrusion of my HIPAA privacy laws. Furthermore, where does the intrusion stop? Once the vaccine tracking digitalized system comes out, will it lead to medical martial law?

6. We also know that the covid injection has caused a large number of anaphylactic reactions. We have ZERO long term safety data, regardless of what self-appointed experts' postulate. Without vigorous, accurate tracking (which, as referenced above, has never happened) how can this even be performed? The "placebo groups" (again, many are not even a real placebo) are being given the Covid vaccine themselves. I have anaphylactic food allergies (16 of 38 foods tested via IgE blood response testing). Many people have food allergies that they are unaware of. I CANNOT take the chance of injecting myself with these dangerous chemicals. People are dying from this intervention. Whether the mainstream media, social media sites, and the medical profession and want to censor it or not, it is happening. It saddens me that we even have to have a bill protecting my RIGHT to health and health choices, and to weight my OWN risks and benefits of a procedure.

7. To coerce someone into a forced medical procedure, based on false premises is not only wrong, but it can also be considered fraudulent. First, we must delineate the difference between SARS covid-2 and "Covid-19". SARS covid-2 is the infection. Covid-19 are the symptoms of infection (like influenza vs "the flu"). The marketing of "90%-95% efficacy has NOTHING to do with ability to infect/transmit SARS-CoV-2. It refers to decreasing symptoms in a small subset of individuals. **It is unlawful under the FTC Act, 15 U.S.C. § 41 et seq., to advertise that a product or service can prevent, treat, or cure human disease unless you possess competent and reliable scientific evidence,** including, when appropriate, well-controlled human clinical studies, substantiating that the claims are true at the time they are made.

   Definitions Per the CDC: Immunity: Protection from an infectious disease. If you are immune to a disease, **you can be exposed to it without becoming infected**.
   Vaccine: A product that stimulates a person's immune system to produce immunity to a specific disease, **protecting the person from that disease**. Vaccines are usually

administered through needle injections but can also be administered by mouth or sprayed into the nose.
This is taken directly from the Pfizer phased 3 study:

8.2. Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subset of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) is too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

The primary endpoint was evaluated in individuals without prior evidence of COVID-19 disease, and very few cases of confirmed COVID-19 occurred among participants with evidence of infection prior to vaccination (although more cases occurred in the placebo group compared with the vaccine group). Therefore, available data are insufficient to make conclusions about benefit in individuals with prior SARS-CoV-2 infection. However, available data, while limited, do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine against asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[11-14] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8. Where there is clear risk, there needs to be freedom of choice. Coercion by public pressure is unethical. And we know that there will be pressure through lobbyists to coerce businesses and other entities to enforce these expectations just like they have the masking and shutdown practices.

Finally, I would like to bring up a glaring problem in society today, particularly with these HEALTH and LIFE MANDATES/COERCIONS. If this is truly about health, why is it that it always comes to drugs/injections? What about building and supporting a strong, robust, balanced immune response? What about addressing the triggers that lead to a damaged, incompetent immune response?

The cold hard fact is that there are ALWAYS going to be new viruses. Are we now setting precedence that every new virus needs an inoculation? In less than a year we are being told that there are additional strains of Coronavirus and more inoculations being developed. Guess what, they are not going anywhere. Will they just tell us we need to stay inside forever and keep giving more and more injections? The solution is not in more drugs. The solution lies in restoring normal immune function and addressing the reasons why people's immune response fails them. This is one thing that Sars Covid-2 has brought to light. 94% of people have comorbidities, the largest number being obesity and type 2 diabetes, which most have similar underlying mechanisms. Are we going to start mandating certain waist sizes as well? I have a novel idea. How about we admit that the United States is one of the most chronically ill countries and the the prescription drug culture we live in is not working. If you are truly healthy, your body handles these dis-eases as it should. Why should I as someone who studies these things daily need to follow the same path as the rest of the country, who is CLEARLY on the wrong path. If you want me to be responsible for other people's health, then let me mandate what foods people eat, how much exercise people get, what testing they do, what nutrients they consume… I hope that sounds preposterous, because this is what it sounds like to me.

Food and lifestyle factors play a MAJOR role in whether someone gets sick or stays well. IT is crucial for a balance, normal t-cell response and overall health. Why has this been all-but ignored and ridiculed for the last 10 years, especially the last 10 months. We have the burleigh-morton task force ridiculing the courageous people that have brought this up and taken a stand. Medical doctors threatening me for telling people that they need to be responsible for their own health. I've been saying that for 12 years. Covid didn't change that. It has always been a problem but now we are seeing the downstream effects and we either need to change course or sleep in the bed we make. I don't have to be part of the sick care cycle. And I should have the freedom to opt out for whatever means I feel necessary.

Thank you for your time. I would be happy to answer any of your questions.

Dr. Steve Nagel, DC

180 Health Solutions

1. https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html
2. https://www.hilarispublisher.com/open-access/vaccines-and-neuroinflammation.pdf
3. https://digital.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system
4. https://www.justice.gov/opa/pr/justice-department-announces-largest-health-care-fraud-settlement-its-history
5. https://www.usatoday.com/story/money/2019/10/09/johnson-johnson-8-billion-over-risperdal-gynecomastia-case/3916878002/
6. https://www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing
7. https://www.nytimes.com/2003/06/21/business/astrazeneca-pleads-guilty-in-cancer-medicine-scheme.html
8. https://violationtracker.goodjobsfirst.org/prog.php?parent=glaxosmithkline
9. https://www.mdpi.com/1660-4601/17/22/8674/htm

Grant Final Report

Grant ID: R18 HS 017045

Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP:VAERS)

Inclusive dates: 12/01/07 - 09/30/10

Principal Investigator:
Lazarus, Ross, MBBS, MPH, MMed, GDCompSci

Team members:
Michael Klompas, MD, MPH

Performing Organization:
Harvard Pilgrim Health Care, Inc.

Project Officer:
Steve Bernstein

Submitted to:
The Agency for Healthcare Research and Quality (AHRQ)
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Abstract

Purpose: To develop and disseminate HIT evidence and evidence-based tools to improve healthcare decision making through the use of integrated data and knowledge management.

Scope: To create a generalizable system to facilitate detection and clinician reporting of vaccine adverse events, in order to improve the safety of national vaccination programs.

Methods: Electronic medical records available from all ambulatory care encounters in a large multi-specialty practice were used. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions were evaluated for values suggestive of an adverse event.

Results: Restructuring at CDC and consequent delays in terms of decision making have made it challenging despite best efforts to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial and comparison of ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. However, Preliminary data were collected and analyzed and this initiative has been presented at a number of national symposia.

Key Words: electronic health records, vaccinations, adverse event reporting

Final Report

Purpose

This research project was funded to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS), via the following aims:

Aim 1. Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration.

Aim 2. Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS).

Aim 3. Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.

Aim 4. Distribute documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems.

Scope

Public and professional confidence in vaccination depends on reliable postmarketing surveillance systems to ensure that rare and unexpected adverse effects are rapidly identified. The goal of this project is to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS). This project is serving as an extension of the Electronic Support for Public Health (ESP) project, an automated system using electronic health record (EHR) data to detect and securely report cases of certain diseases to a local public health authority. ESP provides a ready-made platform for automatically converting clinical, laboratory, prescription, and demographic data from almost any EHR system into database tables on a completely independent server, physically located and secured by the same logical and physical security as the EHR data itself. The ESP:VAERS project developed criteria and algorithms to identify important adverse events related to vaccinations in ambulatory care EHR data, and made attempts at formatting and securely sending electronic VAERS reports directly to the Centers for Disease Control and Prevention (CDC).

Patient data were available from Epic System's Certification Commission for Health Information Technology-certified EpicCare system at all ambulatory care encounters within Atrius Health, a large multispecialty group practice with over 35 facilities. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions are evaluated for values

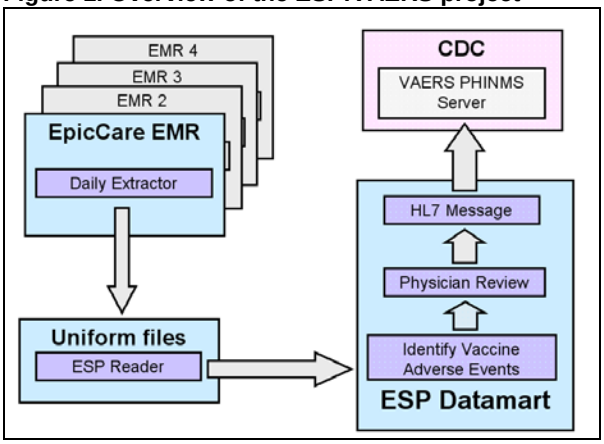
suggestive of an adverse vaccine event. When a possible adverse event was detected, it was recorded, and the appropriate clinician was to be notified electronically.

Clinicians in-basket messaging was designed to provide a preview a pre-populated report with information from the EHR about the patient, including vaccine type, lot number, and possible adverse effect, to inform their clinical judgment regarding whether they wish to send a report to VAERS. Clinicians would then have the option of adding free-text comments to pre-populated VAERS reports or to document their decision not to send a report. The CDC's Public Health Information Network Messaging System (PHIN-MS) software was installed within the facilities so that the approved reports could be securely transferred to VAERS as electronic messages in an interoperable health data exchange format using Health Level 7 (HL7).

Methods

The goal of Aim 1: *Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration,* and Aim 2: *Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS),* was to construct the below flow of data in order to support the first two Aims:

Figure 1. Overview of the ESP:VAERS project



Existing and functioning ESP components are shown on the left, and Aims 1 and 2 on the right. ESP:VAERS flags every vaccinated patient, and prospectively accumulate that patient's diagnostic codes, laboratory tests, allergy lists, vital signs, and medication prescriptions. A main component of Aim 1 was to *Develop AE criteria to assess these parameters for new or abnormal values that might be suggestive of an adverse effect.* A reporting protocol & corresponding algorithms were developed to detect potential adverse event cases using diagnostic codes, and methods were tested to identify prescriptions or abnormal laboratory values that might be suggestive of an adverse effect. These algorithms were designed to seek both expected and unexpected adverse effects.

This reporting protocol was approved by both internal & external partners. We initially prepared a draft document describing the elements, algorithms, interval of interest after vaccination, and actions for broad classes of post-vaccination events, including those to be reported immediately without delay (such as acute anaphylactic reaction following vaccination), those never to be reported (such as routine check-ups following vaccination) and those to be reported at the discretion and with additional information from the attending physician through a feedback mechanism. The draft was then widely circulated as an initial / working draft for comment by relevant staff in the CDC and among our clinical colleagues at Atrius. In addition to review by the internal CDC Brighton Collaboration liaison, this protocol has also received review & comment via the CDC's Clinical Immunization Safety Assessment (CISA) Network.

The goal of Aim 2 was the *Development of HL7 messages code for ESP:VAERS to ensure secure transmission to CDC via PHIN-MS*. The HL7 specification describing the elements for an electronic message to be submitted to Constella, the consultants engaged by CDC for this project was implemented. Synthetic and real test data was been generated and transmitted between Harvard and Constella. However, real data transmissions of non-physician approved reports to the CDC was unable to commence, as by the end of this project, the CDC had yet to respond to multiple requests to partner for this activity.

The goal of Aim 3 was to *Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.*

We had initially planned to evaluate the system by comparing adverse event findings to those in the Vaccine Safety Datalink project—a collaborative effort between CDC's Immunization Safety Office and eight large managed care organizations. Through a randomized trial, we would also test the hypothesis that the combination of secure, computer-assisted, clinician-approved, adverse event detection, and automated electronic reporting will substantially increase the number, completeness, validity, and timeliness of physician-approved case reports to VAERS compared to the existing spontaneous reporting system; however, due to restructuring at CDC and consequent delays in terms of decision making, it became impossible to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial, and compare ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. Therefore, the components under this particular Aim were not achieved.

Aim 4 *Distribution of documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems* has been successfully completed. Functioning source code is available to share under an approved open source license. ESP:VAERS source code is available as part of the ESP source code distribution. It is licensed under the LGPL, an open source license compatible with commercial use. We have added the ESP:VAERS code, HL7 and other specifications and documentation to the existing ESP web documentation and distribution resource center http://esphealth.org, specifically, the Subversion repository available at:
http://esphealth.org/trac/ESP/wiki/ESPVAERS.

Results

Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions (2.6 percent of vaccinations) were identified. This is an average of 890 possible events, an average of 1.3 events per clinician, per month. These data were presented at the 2009 AMIA conference.

In addition, ESP:VAERS investigators participated on a panel to explore the perspective of clinicians, electronic health record (EHR) vendors, the pharmaceutical industry, and the FDA towards systems that use proactive, automated adverse event reporting.

Adverse events from drugs and vaccines are common, but underreported. Although 25% of ambulatory patients experience an adverse drug event, less than 0.3% of all adverse drug events and 1-13% of serious events are reported to the Food and Drug Administration (FDA). Likewise, fewer than 1% of vaccine adverse events are reported. Low reporting rates preclude or slow the identification of "problem" drugs and vaccines that endanger public health. New surveillance methods for drug and vaccine adverse effects are needed. Barriers to reporting include a lack of clinician awareness, uncertainty about when and what to report, as well as the burdens of reporting: reporting is not part of clinicians' usual workflow, takes time, and is duplicative. Proactive, spontaneous, automated adverse event reporting imbedded within EHRs and other information systems has the potential to speed the identification of problems with new drugs and more careful quantification of the risks of older drugs.

Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed with testing and evaluation.

Inclusion of AHRQ Priority Populations

The focus of our project was the Atrius Health (formerly HealthOne) provider & patient community. This community serves several AHRQ inclusion populations, specifically low-income and minority populations in primarily urban settings.

Atruis currently employs approximately 700 physicians to serve 500,000 patients at more than 18 office sites spread throughout the greater Metropolitan Boston area. The majority of Atruis physicians are primary care internal medicine physicians or pediatricians but the network also includes physicians from every major specialty.

The entire adult and pediatric population served by Atruis was included in our adverse event surveillance system (ESP:VAERS). Atruis serves a full spectrum of patients that reflects the broad diversity of Eastern Massachusetts. A recent analysis suggests that the population served by Atruis is 56% female, 16.6% African American, 4% Hispanic. The prevalence of type 2 diabetes in the adult population is 5.7%. About a quarter of the Atruis population is under age 18.

List of Publications and Products

ESP:VAERS [source code available as part of the ESP source code distribution]. Licensed under the GNU Lesser General Public License (LGPL), an open source license compatible with commercial use. Freely available under an approved open source license at: http://esphealth.org.

Lazarus, R, Klompas M, Hou X, Campion FX, Dunn J, Platt R. Automated Electronic Detection & Reporting of Adverse Events Following Vaccination: ESP:VAERS. The CDC Vaccine Safety Datalink (VSD) Annual Meeting. Atlanta, GA; April, 2008.

Lazarus R, Klompas M Automated vaccine adverse event detection and reporting from electronic medical records. CDC Public Health Informatics Network (PHIN) Conference August 27, 2008.

Klompas M, Lazarus R ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 17th.

Lazarus R, Klompas M, Kruskal B, Platt R Temporal patterns of fever following immunization in ambulatory care data identified by ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

Linder J, Klompas M, Cass B, et al. Spontaneous Electronic Adverse Event Reporting: Perspectives from Clinicians, EHR Vendors, Biopharma, and the FDA. Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

Dear House Human Services Committee Members,

Thank you for your important service and dedication to the state of North Dakota.

I am a mother of nine children whom I homeschooled kindergarten thru high school for 32years.

I graduated from UND with a BS in Education, hold a ND teaching certificate, have my Masters in Public Health from the University of Michigan, and recently became a Certified Nursing Assistant.

After extensive careful study of vaccines, I stand in full support of the following three Bills…HB1307, HB1320, HB1306.

2020 was wrought by many albeit good intended but heavy-handed broad sweeping Public Health regulations that cancelled out so much additional effective scientific information, procedures, and practices in hasty political and financial overriding of the Truth and to personal freedom. Our Government, you, must allow us the right to choose whether to vaccinate or not without fear of losing our right to education and work! And, to continue to study the effects of vaccines is very important also.

Thank you for your consideration on this matter.

Please Vote in support of HB1307, HB1320, HB1306

Sincerely,

Julie Liffrig

District 33

2021 HOUSE STANDING COMMITTEE MINUTES

Human Services Committee
Pioneer Room, State Capitol

HB 1306
1/20/2021

To provide for a legislative management study of the interrelationship between sudden infant death syndrome, vaccines, and autism spectrum disorder in children

Chairman Weisz opened the committee meeting at 3:42 p.m.

Representatives	Attendance
Representative Robin Weisz	P
Representative Karen M. Rohr	P
Representative Mike Beltz	P
Representative Chuck Damschen	P
Representative Bill Devlin	P
Representative Gretchen Dobervich	P
Representative Clayton Fegley	P
Representative Dwight Kiefert	P
Representative Todd Porter	P
Representative Matthew Ruby	P
Representative Mary Schneider	P
Representative Kathy Skroch	P
Representative Bill Tveit	P
Representative Greg Westlind	P

Discussion Topics:

- Vaccine and autism correlation
- Vaccine and sudden infant death syndrome correlation
- Study cost

Rep. Todd Porter made a motion for a **Do Not Pass**

Rep. Bill Devlin seconded the motion

Representatives	Vote
Representative Robin Weisz	Y
Representative Karen M. Rohr	Y
Representative Mike Beltz	Y
Representative Chuck Damschen	Y
Representative Bill Devlin	Y
Representative Gretchen Dobervich	Y
Representative Clayton Fegley	Y
Representative Dwight Kiefert	Y
Representative Todd Porter	Y
Representative Matthew Ruby	Y
Representative Mary Schneider	Y
Representative Kathy Skroch	Y

Representative Bill Tveit	Y
Representative Greg Westlind	Y

Motion carried 14-0-0

Bill Carrier: Rep. Bill Devlin

Chairman Weisz adjourned at 3:47 p.m.

Tamara Krause, Committee Clerk

REPORT OF STANDING COMMITTEE

HB 1306: Human Services Committee (Rep. Weisz, Chairman) recommends **DO NOT PASS** (14 YEAS, 0 NAYS, 0 ABSENT AND NOT VOTING). HB 1306 was placed on the Eleventh order on the calendar.