National Vaccine Information Center

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***** VIA EMAIL*****

August 27, 2014

Mr. Dave King, Chairman
Advisory Commission on Childhood Vaccines (ACCV)
Division Of Vaccine Injury Compensation (DVIC)
Parklawn Building, Room 11C-26
5600 Fishers Lane
Rockville, MD 20857
Email: dking@salesmotion.com

Re: Request for ACCV to reconsider encephalopathy definition recommendation relating to the Vaccine Injury Table

Dear Mr. King,

Acute and chronic encephalopathy is one of the most serious vaccine adverse events on the Vaccine Injury Table (VIT) eligible for compensation under the federal Vaccine Injury Compensation Program (VICP). The Secretary of the Department of Health and Human Services (DHHS) is the legal respondent in the vaccine injury compensation process, is defended by the Department of Justice (DOJ) in claims proceedings and DHHS officials determine eligibility, administer the Trust Fund and make compensation payments awarded by the U.S. Court of Claims. Any revision of the definition of encephalopathy by DHHS officials is of great concern to the National Vaccine Information Center (NVIC), whose co-founders worked with Congress on the National Childhood Vaccine Injury Act of 1986 [1] to help ensure that the VICP would be a non-adversarial, expedited, less traumatic and more reliable alternative to a vaccine injury lawsuit in civil court.[2] [3] [4]

NVIC requests that ACCV carefully reconsider pending recommendations to change the definition of encephalopathy, which will be used as a guide by officials at DHHS and Department of Justice (DOJ), as well as by special masters in the Claims Court, to either award or deny compensation to plaintiffs filing vaccine injury and death claims. We make this request in hopes that ACCV will reaffirm and maintain the spirit and intent of the National Childhood Vaccine Injury Act, which is to err on the side of the petitioner in order to provide an economic safety net for those for whom the risks of vaccination are 100% and to address eroding public trust in the integrity of the vaccination system.

First, it is important to put NVIC's objections to changing the definition of encephalopathy in context by reviewing the history of the 1986 National Childhood Vaccine Injury Act and the VIT.

NVIC's History with the National Childhood Vaccine Injury Act of 1986

NVIC co-founders Jeffrey Schwartz, Barbara Loe Fisher and Kathi Williams, whose children had suffered serious reactions to DPT vaccine, founded the charitable non-profit Dissatisfied Parents Together (DPT) in the spring of 1982 with the mission of "preventing vaccine injuries and deaths through public education." Subsequently, they worked for four years with parents and Congress on the

1986 law at the request of congressional legislative staff.[5] In 1989, they established the National Vaccine Information Center (NVIC) and expanded the mission to include defending the ethical principle of informed consent to medical risk-taking, including vaccine risk-taking. For the past 25 years, NVIC has called for the institution of informed consent protections in U.S. vaccine policies and laws.[6]

The participation of parents of vaccine injured children during the legislative process creating the 1986 National Childhood Vaccine Injury Act was to ensure that the legislation would balance ***prevention*** of vaccine injuries and deaths with ***compensation*** for children suffering serious injury and for families of children who died after receipt of government recommended and mandated vaccines.

Importantly, the key to creating a no-fault, non-adversarial federal compensation alternative to a civil lawsuit was that the VICP would avoid compelling most plaintiff's to prove "causation in fact," which is the standard used in personal injury and product liability lawsuits filed in the tort system. There was to be a "presumption" of causation in the absence of a more biologically plausible explanation for the child's injury or death. Compensation was also to be awarded if there was evidence that a vaccination significantly aggravated a pre-existing health condition in the child leading to a substantial deterioration of health.[7]

Presumption of causation was key to making the VICP primarily an administrative, rather than an adversarial, system in order for:

(1) parents to want to select the no-fault, non-adversarial federal compensation alternative as the preferred legal option for obtaining compensation for their vaccine injured children, thereby reducing product liability and malpractice lawsuits; and

(2) to make the VICP less burdensome than a long, contentious, expensive and emotionally draining lawsuit for families caring for a severely vaccine injured child.

In addition to securing important vaccine safety informing,[8] recording and reporting provisions[9] in the 1986 law, among the unique contributions that NVIC parent co-founders made to the Act was to secure a provision in the Act that Congress would ask the Institute of Medicine (IOM), National Academy of Sciences, to review the medical literature and publish reports evaluating evidence regarding federally recommended vaccines and brain dysfunction, immune system disorders and death.[10] Parents of vaccine injured children participating in the legislative process were very concerned that those evaluating vaccine safety science be independent from influence by pharmaceutical corporations marketing vaccines in the U.S. and federal health agencies responsible for developing, regulating, making policy for and promoting state mandated vaccine use.

The IOM was selected as the entity included in the Act for conducting review and analysis of the vaccine safety science for several important reasons. While IOM receives funding from government and industry, IOM has a history of making efforts to assemble committees with broad representation utilizing a deliberative process that includes transparency and public engagement when addressing scientific and controversial public policy issues, unlike other government and industry funded organizations.[11]

Development of the VIT

The Vaccine Injury Table (VIT) included in the 1986 law was created primarily based on published scientific evidence in the medical literature and through a collaborative process that included participation by medical trade associations, whose memberships administer vaccines to children, such as the American Academy of Pediatrics. At the time the VIT was created, there were only seven vaccines federally recommended and state mandated for children and administered between the ages

of two months and six years: diphtheria, tetanus and pertussis (DPT); measles, mumps and rubella (MMR); and oral polio vaccine (OPV).[12]

The VIT incorporated clinical symptoms of vaccine reactions, injuries and deaths published in the medical literature and time periods within which most symptoms generally appeared following receipt of DPT, MMR and OPV vaccines. The purpose of the VIT was to provide officials at DHHS, DOJ and the U.S. Court of Claims with an administrative guideline for awarding no-fault, non-adversarial compensation to those children filing claims with evidence of serious health deterioration after receipt of government recommended and mandated vaccines or to families whose children died following vaccination. Causation is presumed for conditions listed in the VIT.

Encephalopathy: The VIT Centerpiece

The centerpiece of the VIT was a list of clinical symptoms associated with acute and chronic encephalopathy because encephalopathy[13] is one of the most serious complications of vaccination and can lead to permanent brain dysfunction. Acute encephalopathy or brain inflammation (encephalitis,[14] [15] encephalomyelitis[16]) and chronic encephalopathy (persistent brain dysfunction) has been a long acknowledged serious reaction to vaccination since the first vaccines for smallpox and rabies[17] [18] were developed and used in humans.

Acute and chronic encephalopathy also has been an acknowledged reaction to pertussis vaccine, a vaccine originally developed in 1912 and administered as a single component vaccine[19] before being combined with diphtheria vaccine[20] and tetanus vaccines (DPT) in the late 1940's[21] and recommended by federal health and AAP officials for children since the early 1950s.[22] [23] [24] Acute and chronic encephalopathy is also an acknowledged reaction to measles vaccine and measles containing vaccines (MR, MMR)[25] and has been reported following receipt of other federally recommended vaccines.[26] [27]

Many of the children most in need of vaccine injury compensation have experienced acute encephalopathy with or without brain inflammation (encephalitis, encephalomyelitis) following vaccination[28] [29] [30] [31]because brain inflammation or acute encephalopathy – irrespective of the cause - can lead to chronic encephalopathy (permanent neurological dysfunction).[32] [33] [34] [35] [36] Encephalopathy or chronic brain dysfunction can result in the most serious manifestations of brain injury, including physical and mental regression and failure to meet developmental milestones; dramatic personality and behavior changes; loss of muscle control, speech and other abilities; multiple learning disabilities and ADHD/ADD; medication resistant seizure disorders; behavior disorders and profound mental retardation.

The scientific literature has long recognized that neurological symptoms of acute encephalopathy can include:

- the sudden onset of convulsions (seizures);
- high pitched screaming *(cri encephalique*) resulting from cerebral irritation;
- and altered state of consciousness.

The literature has also historically recognized that seizures may be a manifestation of acute encephalopathy and that chronic encephalopathy can include residual seizure disorders that over time can cause irreversible brain damage. Chronic encephalopathy can render the child incapable of functioning independently in society as an adult, requiring lifelong economic support. Families caring for vaccine injured children with severe brain injury have little money, time or physical and emotional energy to spend on expensive and drawn out legal proceedings and the VIT was one mechanism for making the VICP a less burdensome legal alternative for petitioners.

Below is the original VIT that was included in the 1986 National Childhood Vaccine Injury Act with definitions for encephalopathy. The original VIT definition of encephalopathy and clinical signs and symptoms indicating encephalopathy remain consistent with the definitions of encephalopathy in past and current scientific literature.

VACCINE INJURY TABLE [37]

I. DTP; P; DTP/Polio Combination; or Any Other Vaccine Containing Whole Cell Pertussis Bacteria, Extracted or Partial Cell Bacteria, or Specific Pertussis Antigen(s).	
Illness, disability, injury, or condition covered:	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration:
A. Anaphylaxis or anaphylactic shock	24 hours
B. Encephalopathy (or encephalitis)	3 days
C. Shock-collapse or hypotonic-hyporesponsive collapse	3 days
D. Residual seizure disorder in accordance with subsection (b)(2)	3 days
E. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable
II. Measles, mumps, rubella, or any vaccine containing any of the foregoing as a component; DT; Td; or Tetanus Toxoid.	
A. Anaphylaxis or anaphylactic shock	24 hours
B. Encephalopathy (or encephalitis)	15 days (for mumps, rubella, measles, or any vaccine containing any of the foregoing as a component). 3 days (for DT, Td, or tetanus toxoid).
C. Residual seizure disorder in accordance with subsection (b)(2)	15 days (for mumps, rubella, measles, or any vaccine

		containing any of the foregoing as a component). 3 days (for DT, Td, or tetanus toxoid).
	D. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable
III.	Polio Vaccines (other than Inactivated Polio Vaccine).	
	A. Paralytic polio	
	—in a non-immunodeficient recipient	30 days
	—in an immunodeficient recipient	6 months
	—in a vaccine-associated community case	Not applicable
	B. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable
IV.	Inactivated Polio Vaccine.	
	A. Anaphylaxis or anaphylactic shock	24 hours
	B. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable

(b) Qualifications and aids to interpretation

The following qualifications and aids to interpretation shall apply to the Vaccine Injury Table in subsection (a) of this section:

(1) A shock-collapse or a hypotonic-hyporesponsive collapse may be evidenced by indicia or symptoms such as decrease or loss of muscle tone, paralysis (partial or complete), hemiplegia or hemiparesis, loss of color or turning pale white or blue, unresponsiveness to environmental stimuli, depression of consciousness, loss of consciousness, prolonged sleeping with difficulty arousing, or cardiovascular or respiratory arrest.

(2) A petitioner may be considered to have suffered a residual seizure disorder if the petitioner did not suffer a seizure or convulsion unaccompanied by fever or accompanied by a fever of

less than 102 degrees Fahrenheit before the first seizure or convulsion after the administration of the vaccine involved and if—

(A) in the case of a measles, mumps, or rubella vaccine or any combination of such vaccines, the first seizure or convulsion occurred within 15 days after administration of the vaccine and 2 or more seizures or convulsions occurred within 1 year after the administration of the vaccine which were unaccompanied by fever or accompanied by a fever of less than 102 degrees Fahrenheit, and

(B) in the case of any other vaccine, the first seizure or convulsion occurred within 3 days after administration of the vaccine and 2 or more seizures or convulsions occurred within 1 year after the administration of the vaccine which were unaccompanied by fever or accompanied by a fever of less than 102 degrees Fahrenheit.

(3)(A) **The term "encephalopathy" means any significant acquired abnormality of, or injury to, or impairment of function of the brain**. Among the frequent manifestations of encephalopathy are focal and diffuse neurologic signs, increased intracranial pressure, or changes lasting at least 6 hours in level of consciousness, with or without convulsions. The neurological signs and symptoms of encephalopathy may be temporary with complete recovery, or may result in various degrees of permanent impairment. Signs and symptoms such as high pitched and unusual screaming, persistent unconsolable crying, and bulging fontanel are compatible with an encephalopathy, but in and of themselves are not conclusive evidence of encephalopathy. Encephalopathy usually can be documented by slow wave activity on an electroencephalogram.

(B) If in a proceeding on a petition it is shown by a preponderance of the evidence that an encephalopathy was caused by infection, toxins, trauma, or metabolic disturbances the encephalopathy shall not be considered to be a condition set forth in the table. If at the time a judgment is entered on a petition filed under section 300aa–11 of this title for a vaccine-related injury or death it is not possible to determine the cause, by a preponderance of the evidence, of an encephalopathy, the encephalopathy shall be considered to be a condition set forth in the table. In determining whether or not an encephalopathy is a condition set forth in the table, the court shall consider the entire medical record.

(4) For purposes of paragraphs (2) and (3), the terms "seizure" and "convulsion" include grand mal, petit mal, absence, myoclonic, tonic-clonic, and focal motor seizures and signs. If a provision of the table to which paragraph (1), (2), (3), or (4) applies is revised under subsection (c) or (d) of this section, such paragraph shall not apply to such provision after the effective date of the revision unless the revision specifies that such paragraph is to continue to apply.

Department of Health & Human Services (DHHS) Changes VIT Definition of Encephalopathy

In 1995, the Secretary of DHHS removed long recognized symptoms of acute and chronic encephalopathy, including seizures, from the VIT[38] *despite* (1) an IOM report published in 1991, which acknowledged that DPT vaccine can cause acute encephalopathy[39] and is associated with clinical symptoms such as seizures, collapse and protracted inconsolable crying (includes high pitched screaming or *encephalitic cry*) and (2) an IOM report published in 1994 that acknowledged DPT vaccine can cause chronic encephalopathy.[40]

When the 1986 law was enacted, encephalopathy was defined in the VIT as "*any acute or chronic significant acquired abnormality of, or injury to, or impairment of function of, the brain".* In 1995, DHHS rewrote the VIT definition for acute encephalopathy as "*a significantly decreased level of consciousness lasting for at least 24 hours"* and specifically excluded clinical signs and symptoms of acute encephalopathy that have been reported in the medical literature for a century.

Contrary to the IOM's definition of encephalopathy, the new VIT definition re-written by DHHS in 1995 and still in effect today states:

> "*The following clinical features alone or in combination do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness: sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy. In the absence of other evidence of an acute encephalopathy, seizures shall not be viewed as the first symptom or manifestation of the onset of an acute encephalopathy."*

Encephalopathy Defined: Institute of Medicine Reports (1991-2012)

1991: IOM Report on Adverse Effects of Pertussis and Rubella Vaccines

The 1991 IOM committee report *Adverse Effects of Pertussis and Rubella Vaccines*[41] identified a causal relationship between DPT vaccine and acute encephalopathy. This report went into great detail when describing clinical symptoms and scientific definitions of encephalopathy, with the committee noting that "acute or subacute encephalitis, encephalomyelitis and encephalopathy" were used in various published studies to describe a "constellation of symptoms and signs reflecting a generalized disturbance in brain function" that may include:

- altered levels of consciousness;
- confusion;
- irritability;
- headaches;
- changes in behavior;
- screaming attacks;
- neck stiffness;
- sudden onset of convulsions;
- visual, auditory or speech disturbances;
- motor and sensory deficit;
- other neurological abnormality of the brain.

Knowledge Gaps: The 1991 IOM report also for the first time pointed out to the medical community and the public that there is a serious lack of quality basic science research and methodologically sound epidemiological studies evaluating the biological mechanisms and frequency of vaccine adverse events and natural history of conditions, such as encephalopathy. These knowledge gaps hampered the IOM committee's investigation into reported serious health problems associated with the two federally recommended childhood vaccines (DPT, rubella). The committee stated:

> *"In the course of its review the committee found many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. Such shortcomings relate, for*

*example, to pathologic mechanisms of specific infectious agents, the molecular basis for vaccine injury, and the natural history of conditions such as **encephalopathy**, mental retardation and chronic arthritis."* [42]

1994: IOM Report on Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality

The Institute of Medicine issued two important reports in 1994 and both fell within the congressional vaccine research mandate under the 1986 law for IOM to review medical literature and other evidence that there are health risks to children associated with federally recommended vaccines.

Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality was a report that reviewed evidence related to seven federally recommended childhood vaccines: diphtheria, tetanus, measles, mumps, polio, hepatitis B and H. influenza type b (Hib) vaccines.[43]

Continuing Knowledge Gaps: For more than 30 reported serious brain and immune system problems associated with the seven federally recommended vaccines under examination, the 1994 IOM committee was unable to come to a conclusion about *whether or not* there was a causal relationship, including for **encephalopathy and residual seizure disorders** related to several vaccines. Once again, an IOM committee was frustrated by gaps in vaccine safety science and made statements such as:

> *"For the vast majority of vaccine-adverse event relations studied, the data came predominantly from uncontrolled studies and case reports."* [44]

This 1994 report echoed concerns expressed in the 1991 IOM report about lack of scientific knowledge about vaccine adverse events and why there is individual susceptibility to suffering vaccine harm:

> "*The lack of adequate data regarding many of the adverse events under study was of major concern to the committee….The committee was able to identify little information pertaining to why some individuals react adversely to vaccines when most do not."* [45]

In a concluding chapter "Need for Research and Surveillance," the committee stated:

> *"The committee found that a judgment regarding causality was often limited by the absence of background data for the occurrence of the pathologic condition (the putative adverse event) in apparently normal individuals not recently exposed to the vaccine."* [46]

This lack of background data for the occurrence of acute encephalopathy in unvaccinated children or those receiving fewer vaccines, such as learning disabilities, ADD/ADHD, seizure disorders, developmental delays and other chronic brain and immune disorders, continues today to hamper causality conclusions about encephalopathy and vaccination.

1994: IOM Report on DPT Vaccine & Chronic Nervous System Dysfunction

The second report issued by IOM in 1994, *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* was groundbreaking.[47] This report affirmed the conclusions of the *National Childhood Encephalopathy Study (NCES)* published by the British government in 1981.[48]

More than three decades after *NCES* was published, it remains the largest well-conducted prospective, case controlled study of neurological disorders in children. The *NCES* included evaluation of cases of

acute and chronic encephalopathy that developed after children received DPT or measles vaccines and, in 1981, *NCES* authors concluded that receipt of DPT vaccine was causally related to the development of acute encephalopathy (encephalitis, encephalomyelitis) and permanent brain damage in some previously healthy children enrolled in *NCES*, as well as those with underlying brain or metabolic disorders after the DPT vaccine "triggered" expression of the underlying disorder.

Attributable risk estimates in for participants in *NCES* were that:

- **1 in 110,000 DPT shots was followed by an acute encephalopathy within seven days of administration of the vaccine**; and

- **1 in 310,000 DPT shots was followed by persistent neurological damage one year later.**

It is notable that in 1981, the same year that the *NCES* was published confirming that DPT vaccine can cause acute and chronic encephalopathy, an FDA-sponsored case controlled study conducted at UCLA was published reporting the results of a head-to-head comparison of the reactivity of whole cell DPT vaccines and DT vaccines.[49] That U.S. study found that DPT vaccine was far more reactive than DT vaccine and estimated that 1 in 1,750 DPT shots was followed by a convulsion or a hypotonic-hyporesponsive episode (HHE).

In 1993, *NCES* authors published a 10-year follow up of the children, who had developed an acute encephalopathy after DPT vaccination during the study.[50] They found that many of the children were continuing to suffer clinical symptoms of neurologic, behavioral, educational, motor, sensory and self care dysfunctions, including:

- low scores for global educational abilities assessed by intelligence, vocabulary, spelling, reading and arithmetic tests;
- epilepsy/seizure disorder;
- tremor;
- fine or gross motor incoordination;
- muscle weakness or spasticity in one or more limbs;
- hearing and vision problems;
- behavioral dysfunction (problem, hyperactive or unsociable behavior);
- lack of bladder or bowel control.

The *NCES* authors said:

> ***"Our results provide good evidence that illnesses such as those studied in the national childhood encephalopathy study, including a variety of encephalopathies and severe convulsions, both febrile and afebrile, can have lasting sequelae as measured by various indices of brain function. This seems to be true for cases associated in time with diphtheria, tetanus and pertussis immunization as for other cases."*** [51]

The 1994 IOM Committee to Study New Research on Vaccines reviewed the 10-Year follow up of *NCES* and determined that, in addition to the evidence about acute and chronic encephalopathy they had collected for the 1991 IOM report on DPT vaccine, there was compelling scientific evidence to conclude that children with or without underlying brain or metabolic abnormalities can experience an acute encephalopathy within 7 days after receipt of DPT vaccine and go on to suffer chronic neurological dysfunction.

The IOM committee stated:

> ***"The NCES data are consistent with the possibility that some children without underlying brain or metabolic abnormalities might experience serious acute neurologic illness within 7 days after receiving DPT and that acute illness could have chronic nervous system sequelae. The NCES data are also consistent with the possibility that some children with underlying brain or metabolic abnormalities (which foster a "triggering" by DPT of an acute neurologic illness) might go on to develop chronic neurological dysfunction due to a DPT-triggered acute illness. Therefore, the committee concludes that the balance of evidence is consistent with a causal relation between DPT and the forms of chronic nervous system dysfunction described in the NCES in those children who experience a serious acute neurologic illness within 7 days after receiving DPT vaccine."*** [52]

[In September 2006, DHHS officials and four health maintenance organizations (HMOs) participating in the DHHS-operated Vaccine Safety Datalink Group published a retrospective study that concluded DPT and MMR vaccines do not cause encephalopathy.[53] The study has never been replicated and part of the reason may be that non-DHHS, independent scientists are unable to get access to raw data used in Vaccine Safety Datalink Group studies to confirm VSD vaccine safety findings.

In 2005, the IOM Committee on the Review of the National Immunization Program's Research Procedures and Data Sharing Program published a report, *Vaccine Safety Research, Data Access, and Public Trus*t. [54] The IOM Committee concluded that there is "limited ability of independent external researchers to conduct high quality corroborative studies or studies of new hypotheses" [55] using VSD data:

> ***"There are legitimate concerns about the independence and fairness of the implementation of review procedures applied to VSD data sharing proposals and of determination about the release of preliminary findings from VSD analyses. The lack of transparency of some of the processes also affects the trust relationship between the National Immunization Program Office (NIP) and the general public." [56]***

Prospective studies, such as NCES, are superior to retrospective studies and replication is a gold standard in science. The DHHS-conducted 2006 study rejecting a causal association between DPT and MMR vaccines and encephalopathy, a study which has never been replicated and contradicts conclusions of more transparent studies adhering to higher scientific standards, should not influence the revision of the VIT definition of encephalopathy or be used to deny compensation to those suffering encephalopathy following receipt of MMR or pertussis containing vaccines.]

The 1991 and 1994 IOM reports reaffirmed the evidence base for the definition of encephalopathy embedded in the original VIT in the VICP, including acknowledgement of the fact that some children have pre-existing identified and unidentified genetic or biological risk factors that can be triggered by administration of vaccines or have pre-existing medical conditions that can be significantly aggravated by vaccination. Appropriately, there have been vaccine injury compensation awards made to children, who were born with genetic or biological high risk factors, such as an undiagnosed brain or metabolic disorder, that increased their susceptibility to suffering harm from federally recommended vaccines.[57]

2012: IOM Report on Adverse Effects of Vaccines: Evidence and Causality

In 2012, two decades after the first congressionally mandated 1991 IOM report was published, the IOM published a report *Adverse Effects of Vaccines: Evidence and Causality*[58] again reviewing the medical literature for scientific evidence that federally recommended vaccines can cause brain and immune system dysfunction and death. The report reviewed a total of 158 vaccine-related adverse events - including **encephalitis, acute disseminated encephalomyelitis (ADEM) and encephalopathy** - reported following receipt of varicella zoster (chickenpox) vaccine; influenza vaccines; hepatitis B vaccine; human papillomavirus vaccine (HPV); tetanus toxoid-containing vaccines other than those containing the whole cell pertussis component; measles, mumps and rubella vaccines; hepatitis A vaccine; and meningococcal vaccines.

In 2009, the Health Resources and Services Administration (HRSA) had contracted with IOM to conduct what would become the largest assessment of epidemiologic, clinical and biological mechanism evidence about vaccine adverse event outcomes conducted by IOM since the 1986 Childhood Vaccine Injury Act became law and IOM published the 1991 and 1994 reports requested by Congress under the Act. The CDC and National Vaccine Program Office (NVPO) also contributed funding for the 2012 IOM study.[59]

The stated purpose of the 2012 IOM study was to provide scientific basis for review and adjudication of claims of vaccine injury by the VICP. At the study outset, HRSA presented a list of specific adverse events for the committee to review, which HRSA indicated represented the majority of adverse events listed in VICP petitioner claims. During the course of its review of the medical literature, the IOM committee added to the report the following adverse events for which epidemiological studies or case reports were identified:

- all cause mortality and seizures following influenza vaccine;
- optic neuritis following MMR, influenza, hepatitis B and DTaP vaccines;
- neuromyelitis optica following MMR vaccine;
- erythema nodosum following hepatitis B vaccine;
- stroke and small fiber neuropathy following varicella vaccine.

The 2012 IOM Committee to Review Adverse Effects of Vaccines concluded that “the evidence convincingly supports” or “favors acceptance of” a causal relationship between:

- varicella vaccine and Oka varicella zoster vaccine reactivation;
- MMR vaccine and measles inclusion body encephalitis;
- MMR vaccine and febrile seizures;
- Anaphylaxis and MMR, varicella, influenza, hepatitis B, meningococcal, HPV and tetanus toxoid vaccine;
- MMR vaccine and transient arthralgia in female adults and children;
- Any of the vaccines and syncope (sudden loss of consciousness)
- Any of the vaccines and deltoid bursitis;

However, significantly for 135 (85%)[60]***of serious adverse health outcomes associated with one or more of the federally recommended vaccines under examination there was either an absence of or too little biological mechanism evidence and/or methodologically sound epidemiologic studies related to the vaccine and reported serious adverse health outcome for the committee to make a causation conclusion.*** This lack of enough scientific evidence to make a causation

determination between a number of the vaccines being studied and a wide range of brain and immune system disorders included:

- **Encephalitis; encephalopathy; acute disseminated encephalomyelitis (ADEM);** meningitis; traverse myelitis; optic neuritis; chronic inflammatory disseminated polyneuropathy; Bell's palsy; small fiber neuropathy; Guillain Barre Syndrome GBS); afebrile seizures; infantile spasms; opsoclonus/myoclonus syndrome; ataxia; first demyelinating event in children and adults; multiple sclerosis in children and adults.

Like the previous IOM committees, this committee was unable to come to conclusions about causation for the majority of vaccine-related adverse health outcomes because of continuing gaps in scientific knowledge about the biological mechanisms for vaccine adverse effects. Chapter 3 "Evaluating Biological Mechanisms of Adverse Events" is a thoughtful description of the outstanding biological mechanism questions that need to be answered before there can be a better understanding of how and why vaccines can cause acute and chronic brain and immune system dysfunction and death.

The 2012 report highlights the lack of understanding of biological, genetic, environmental and other high risk factors, which increase an individual's susceptibility to vaccine reactions:

> ***"Both epidemiologic and mechanistic research suggest that most individuals who experience an adverse reaction to vaccines have a pre-existing susceptibility. <u>These predispositions can exist for a number of reasons – genetic variants (in human or microbiome DNA), environmental exposures, behaviors, illness or developmental stage, to name just a few, all of which can interact.</u> Some of these adverse reactions are specific to the particular vaccines, while others may not be. Some of these predispositions may be detectable prior to the administration of vaccine; others, at least with current technology and practice, are not."*** [61]

In the Preface of the published 2012 study, the IOM committee chair, Ellen Wright Clayton, M.D., stated that the committee "had a herculean task, requiring long and thoughtful discussions of our approach to analyzing the studies culled from more than 12,000 peer-reviewed articles." She said "some issues simply cannot be resolved with current available epidemiological data" and emphasized that scientific conclusions about cause and effect relationships between vaccines and reported adverse events requires a combination of biological mechanism and epidemiological evidence, particularly when it comes to identifying individual susceptibility risk factors:

> *"Even very large epidemiologic studies may not detect or rule out rare events. Subgroup analysis or more focused epidemiologic studies, informed by as yet incomplete knowledge of the biological mechanisms of vaccine-induced injury, may be required….The value of dialogue between both epidemiologic and mechanism approaches cannot be overstated. Epidemiologic studies can identify particular high risk groups, who can then be examined with more in depth testing to explore predisposing factors. The findings of such studies can then inform more focused epidemiologic research as well as efforts to reduce risks. These conversations between different types of research can be difficult, but the results are worth it."*

While the 2012 IOM Committee noted recent discoveries relating to SCN1A mutations, Dravet syndrome and encephalopathy, they were cautious in drawing any conclusions and stated:

> "This list of factors that are known to confer susceptibility is by no means definitive or exhaustive. Rather, we hypothesize that continued study of alleged vaccine-related injuries, the committee informed by epidemiologic studies that identify vulnerable populations and exploration of underlying mechanisms of susceptibility, will provide greater insight into these and other mechanisms and will identify more factors that contribute to vaccine susceptibility." [62]

More recent studies with regard to Dravet syndrome have noted de novo genetic mutations of SCN1A may occur at any time, from the embryonic premorula stage to adulthood[63] and the syndrome "encompasses different epileptic and cognitive phenotypes that probably result from both genetic and epigenetic factors."[64] Coupled with the 2012 IOM Committee's acknowledgement that fever induced by vaccines may trigger Dravet syndrome, these studies indicate that there are as yet unidentified genetic, biological and environment factors involved in expression of Dravet syndrome in some individuals and leaves open the possibility that individuals may go through their whole lifetime without exhibiting symptoms of Dravet syndrome.

In the IOM 2012 report the following statements were made regarding Dravet syndrome and whole cell pertussis vaccine:

> *"In some metabolically vulnerable children, receiving vaccines may be the largely nonspecific "last straw" that leads these children to reveal their underlying genotype. It was recently discovered that a large majority of children who developed encephalopathy after receiving whole cell pertussis vaccine have mutations in SCN1A, which are associated with Dravet syndrome or severe myoclonic epilepsy of childhood (Berkovic et al., 2006; McIntosh et al., 2010). While it seems likely that the vaccine triggered symptoms in these children by causing high fever, the particular vaccine antigens do not appear to alter the course of the disease. Rather, the ensuing phenotype could and probably would have been precipitated by multiple other fever-inducing triggers (McIntosh et al., 2010; Wiznitzer, 2010)."* [65]

At issue is the implication that "a large majority of children" who develop encephalopathy after receiving whole cell pertussis vaccine have mutations in SCN1A, when the 2006 Bercovic et al study examined only 14 patients and the 2010 McIntosh study examined 40 patients. This dataset is not large enough to make that sweeping conclusion and certainly not enough justification to change the definition of encephalopathy for the purpose of denying vaccine injury compensation to those children with that genotype.

In 2011, a study by Tro-Baumann et al retrospectively examined the relationship between vaccination and occurrence of seizures in 70 children with Dravet syndrome. The authors pointed out that 27% of patients suffered seizures post-vaccination (primarily after DPT vaccine) and in 58% vaccine-related seizures represented the first clinical manifestation. Appropriately, the study authors called for "preventive measures for seizures triggered by vaccination or fever in these children." [66]

There can be no assumption that *all* individuals with SCN1A mutations associated with Dravet, who develop encephalopathic symptoms after vaccination, including seizures, would have developed encephalopathy even if no vaccines had been given. Children born with SCN1A mutations, who develop acute and chronic encephalopathy after vaccination, should not be precluded from receiving vaccine injury compensation simply because of the genes they were born with, genes which may or may not have been expressed had one or more federally recommended vaccines not been given.

Definitions for Encephalopathy Align with IOM Findings

The IOM is not alone in their acknowledgment of signs, symptoms and definitions of encephalopathy long recognized in the medical literature.

- **The National Institutes of Health's National Library of Medicine** states encephalitis complications can lead to permanent brain damage with symptoms that can include mild fever, mild to severe headache, low energy, poor appetite, clumsiness, unsteady gait, confusion, disorientation, drowsiness, irritability, light sensitivity, stiff neck and back, vomiting, fontanel bulging (infant), loss of consciousness, stupor, coma, muscle weakness, paralysis, seizures, flat mood, inappropriate mood, memory loss that may be caused by the following vaccines: MMR, Polio, Varicella.[67]

- **The National Institute of Neurological Disorders and Stroke (NINDS)** uses the following definitions and symptoms for the following conditions:
    - **Encephalitis** is an inflammation of the membranes surrounding the brain and spinal cord with symptoms that can include sudden fever, headache, vomiting, light sensitivity, stiff neck and back, confusion and impaired judgment, drowsiness, weak muscles, clumsy and unsteady gait, irritability, loss of consciousness, seizures, muscle weakness, and/or sudden severe dementia. Complications can include permanent impairment or death.[68]
    - **Encephalopathy** is a condition that results in the altering of the structure or function of the brain that may include the following symptoms: altered mental state, progressive loss of memory and cognition, involuntary muscle twitching, subtle personality changes, rapid involuntary eye movement, tremor, muscle atrophy and weakness, dementia, seizures, apraxia (loss of speech), and/or inability to swallow. This condition may cause permanent changes and irreversible damage to the brain and can be fatal. [69]
    - **Acute Disseminated Encephalomyelitis** is characterized as an attack of inflammation of the brain and spinal cord that damages the protective covering of nerve fibers. This condition can result from the MMR vaccine with encephalitis-like symptoms appearing rapidly that can include fever, fatigue, headache, nausea, vomiting, seizures and coma. The damage to nerve fibers typically lead to neurological symptoms that can include vision loss, paralysis, muscular coordination difficulties. Some ADEM patients will have lifelong impairment such as cognitive difficulties, weakness, loss of vision, numbness, and can be fatal.[70]

Current VIT Language Under Consideration

The current language the ACCV is being asked to approve relating to the VIT and encephalopathy and are additions to the QAI that would stating

> "Individuals who return to their baseline neurologic state, as confirmed by clinical findings, in **less than** 6 months **from the date of vaccination** shall not be presumed to have suffered residual neurologic damage from that event…"
>
> and
>
> "…an encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by: (A) An underlying condition or systemic disease

shown to be unrelated to the vaccine (such as a malignancy, structural lesions, psychiatric illness, dementia, genetic disorder…"

This restrictive and exclusionary encephalopathy guideline change unfairly discriminates against children and adults born with certain genes or pre-existing medical conditions that may be triggered or significantly aggravated following receipt of government recommended and mandated vaccines. There is no ethical, scientific or legal justification for denying compensation to susceptible individuals because of the genes they were born with, especially in light of the fact that significant knowledge gaps about the biological mechanisms and high risk factors for vaccine injury remain. The VICP cannot and should not be a vehicle for discrimination against those most vulnerable to vaccine injury and death.

Knowledge Gaps, Biodiversity & Individual Susceptibility Being Ignored

Science is not static but continually evolves. In the coming years, there will be more information about genetic and other high risk factors that predispose some individuals to suffering vaccine induced encephalopathy and other serious, life altering brain and immune system disorders. The emerging new microbiome and epigenetics science, which is focusing on biodiversity and how it affects individual health outcomes, will change the practice of medicine.

Microbiome Individual Differences: Resident microbes add another 100 trillion cells to the 10 million cells that make up the human body and contributing 8 million genes that interact with 21,000 human genes to help our body grow, digest food, develop and mount immune responses and perform many other normal bodily functions.[71] [72] [73] In 2014, researchers in Ireland studying the microbiome, stress, health and disease observed that the microbiome is established during the first three years of life but that it evolves throughout our lives as we constantly respond to our environment and there are microbiome differences between individuals:

> *"The microbiome is a dynamic entity that is under continuous evolution throughout the host's lifetime in particular during the first three years of life during which time a stable microbiome is established. It is sensitive to a whole array of manipulations such as diet, stress, infection, pharmacological interventions and thus is it clear that the composition of the microbiota is distinct at different milestones of life."* [74]

Epigenetics & Individual Differences: Together with a better understanding of the complexity of the microbiome, the new field of epigenetics is highlighting the importance of respecting biodiversity.[75] Epigenetics, which can be defined as stimuli-triggered changes in gene expression that are inheritable and occur independent of changes to the underlying DNA sequence[76] provides compelling evidence for the urgent need to fill in knowledge gaps about individual susceptibility to vaccine reactions. Scientists have discovered that differing external environmental exposures (such as nutrients, chemicals, infections) and individual responses to trauma and fear, for example, can trigger changes in chromatin structure and gene expression to uniquely affect each individual's susceptibility to certain illnesses and disorders and these susceptibilities can be passed on to future generations.[77] [78]

Microbiome and epigenetics science highlights why there is an urgent need to acknowledge and adjust for individual differences in responses to vaccines and to respect individual susceptibilities, not ignore or punish those with them when considering awards for development of encephalopathy after vaccination. Hopefully the new science will lead to a move away from the current one-size-fits-all approach to vaccine policies and in the future fewer individuals will need to apply for vaccine injury compensation.

In the meantime, vaccine manufacturers protected from civil liability by the 1986 law should make greater efforts to better define the biological mechanisms for adverse events and potential genetic,

biological and environmental high risk factors that place some individuals at higher risk than others for suffering encephalopathy and other types of brain and immune system damage from both existing and new vaccines being developed so fewer children and adults will become vaccine injured VICP claimants.[79] [80]

NVIC urges the ACCV to vote against the DHHS recommendations for the revision of the definition of encephalopathy because it is not based on sound science and will unfairly discriminate against those most susceptible to vaccine injury and death, as well as further erode parent and public confidence in the integrity of the vaccine system.

Sincerely,

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