coating removal to professional users in the UK, given the requirements for limited access that are in place there?

IV. Request for Comment and Additional Information

EPA is seeking comment on all information outlined in this ANPRM and any other information, which may not be included in this notice, but which you believe is important for EPA to consider.

EPA specifically invites public comment and any additional information in response to the questions and issues identified in Unit III. Instructions for providing written comments are provided under **ADDRESSES**, including how to submit any comments that contain CBI. No one is obliged to respond to these questions, and anyone may submit any information and/or comments in response to this request, whether or not it responds to every question in this notice.

V. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

1. EPA. TSCA Work Plan Chemicals. *http://www.epa.gov/sites/production/files/2014-02/documents/work_plan_chemicals_web_final.pdf*. Retrieved February 25, 2016.
2. EPA. TSCA Work Plan Chemical Risk Assessment Methylene Chloride: Paint Stripping Use. CASRN 75–09–2. EPA Document# 740–R1–4003. August 2014. Office of Chemical Safety and Pollution Prevention. Washington, DC. *https://www.epa.gov/sites/production/files/2015-09/documents/dcm_opptworkplanra_final.pdf*.
3. EPA. Summary of Stakeholder Engagement, Proposed Rule Under TSCA § 6 Methylene Chloride and NMP in Paint and Coating Removal. 2016.
4. EPA. Final Report of the Small Business Advocacy Review Panel on EPA's Planned Proposed Rule on the Toxic Substances Control Act (TSCA) Section 6(a) as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act for Methylene Chloride and N-Methylpyrrolidone (NMP) in Paint Removers. Office of Chemical Safety and Pollution Prevention. Washington, DC. 2016.
5. Public Comment. Comments submitted by Lindsay McCormick, Chemicals and Health Project Manager, on behalf of Environmental Defense Fund. EPA–HQ–OPPT–2016–0231–0912.
6. Public Comment. DoD Comments on MeCl and NMP 19 Jan 17 Notice of Proposed Rulemaking Methylene Chloride and N-Methylpyrrolidone; Rulemaking under TSCA Section 6(a). EPA–HQ–OPPT–2016–0231–0519.
7. Halogenated Solvents Industry Alliance. Responsibly Regulating Methylene Chloride in Paint Removal Products: an Alternative Approach to Flawed Proposal Published by EPA on January 19, 2017.
8. EPA. How to Get Certified as a Pesticide Applicator. *https://www.epa.gov/pesticide-worker-safety/how-get-certified-pesticide-applicator*. Accessed December 18, 2018.
9. REACH Restriction. Annex XVII to REACH—Conditions of restriction. Entry 59 Dichloromethane containing Paint Strippers. *https://echa.europa.eu/documents/10162/0ea58491-bb76-4a47-b1d2-36faa1e0f290* (Accessed December 18, 2018).
10. *The Reach Enforcement (Amendment) Regulations* 2014 (SI 2014/2882). *http://www.legislation.gov.uk/uksi/2014/2882/made*.
11. EPA. Economic Analysis of Final Rule TSCA Section 6 Action on Methylene Chloride in Paint and Coating Removal (EPA Docket EPA–HQ–OPPT–2016–0231; RIN 2070–AK07). Office of Pollution Prevention and Toxics. Washington, DC.

VI. Statutory and Executive Order Reviews

Under Executive Order 12866 (58 FR 51735, October 4, 1993) and Executive Order 13563 (76 FR 3821, January 21, 2011), this action was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

Since this document does not impose or propose any requirements, and instead seeks comments and suggestions for the Agency to consider in possibly developing a subsequent proposed rule, the various other review requirements that apply when an agency imposes requirements do not apply to this action. Nevertheless, as part of your comments on this document, you may include any comments or information that you have regarding the various other review requirements.

In particular, EPA is interested in any information that could help the Agency to assess the potential impact of a rule on small entities pursuant to the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*); to consider voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA) (15 U.S.C. 272 note); to consider environmental health or safety effects on children pursuant to Executive Order 13045, entitled ''Protection of Children from Environmental Health Risks and Safety Risks'' (62 FR 19885, April 23, 1997); or to consider human health or environmental effects on minority or low-income populations pursuant to Executive Order 12898, entitled ''Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations'' (59 FR 7629, February 16, 1994).

The Agency will consider such comments during the development of any subsequent proposed rule as it takes appropriate steps to address any applicable requirements.

List of Subjects in 40 CFR Part 751

Environmental protection, Chemicals, Export notification, Hazardous substances, Import certification, Methylene chloride, Recordkeeping.

Dated: March 15, 2019.

Andrew Wheeler,

Administrator.

[FR Doc. 2019–05865 Filed 3–26–19; 8:45 am]

BILLING CODE 6560–50–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 100

National Vaccine Injury Compensation Program: Statement of Reasons for Not Conducting Rulemaking Proceedings

AGENCY: Office of the Secretary, Department of Health and Human Services (HHS).

ACTION: Denial of petition for rulemaking.

SUMMARY: In accordance with the Public Health Service Act, notice is hereby given concerning the reasons for not conducting rulemaking proceedings to add autism, asthma, and tics as injuries associated with vaccines to the Vaccine Injury Table (Table). Also, this document provides reasons for not conducting rulemaking proceedings to add Pediatric Infection-Triggered, Autoimmune Neuropsychiatric Disorder (PITAND) and/or Pediatric Autoimmune Neuropsychiatric Syndrome (PANS); Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) as injuries associated with pertussis, pneumococcal conjugate and Haemophilus influenza type b vaccines; and Experimental Autoimmune Encephalomyelitis/Acute Demyelinating

Encephalomyelitis as injuries associated with pertussis vaccines to the Table.

DATES: Written comments are not being solicited.

FOR FURTHER INFORMATION CONTACT: Dr. Narayan Nair, MD, Director, Division of Injury Compensation Programs (DICP), Healthcare Systems Bureau, Health Resources and Services Administration, 5600 Fishers Lane, Room 8N146B, Rockville, Maryland 20857, or by telephone at 800–338–2382 or by email: *VaccineCompensation@hrsa.gov.*

SUPPLEMENTARY INFORMATION: The National Childhood Vaccine Injury Act of 1986 (the Vaccine Act), Title III of Public Law 99–660, as amended (42 U.S.C. 300aa–10 *et seq.*) established the National Vaccine Injury Compensation Program (VICP) for persons thought to be injured by vaccines. Under this Federal program, petitions for compensation are filed with the United States Court of Federal Claims (Court). The Court, acting through special masters, makes findings as to eligibility for, and amount of, compensation. To gain entitlement to compensation under the VICP for a covered vaccine, a petitioner must establish a vaccine-related injury or death in one of the following ways (unless another cause is found): (1) By proving that the first symptom of an injury or condition, as defined by the Qualifications and Aids to Interpretation, occurred within the time period listed on the Vaccine Injury Table (Table), and, therefore, is presumed to be caused by a vaccine; (2) by proving vaccine causation, if the injury or condition is not on the Table or did not occur within the time period specified on the Table; or (3) by proving that the vaccine significantly aggravated a pre-existing condition.

The Vaccine Act provides for the inclusion of additional vaccines in the VICP when they are recommended by the Centers for Disease Control and Prevention (CDC) for routine administration to children and/or pregnant women. See section 2114(e)(2) and (3) of the PHS Act, 42 U.S.C. 300aa–14(e)(2) and (3). Consistent with section 13632(a)(3) of Public Law 103–66, the regulations governing the VICP provide that such vaccines will be included in the Table as of the effective date of an excise tax to provide funds for the payment of compensation with respect to such vaccines, 42 CFR 100.3(c)(8). The statute establishing the VICP also authorizes the Secretary to create and modify a list of injuries, disabilities, illnesses, conditions, and deaths (and their associated time frames) associated with each category of vaccines included on the Table. See sections 2114(c) and 2114(e)(2) and (3) of the PHS Act, 42 U.S.C. 300aa–14(c) and 300aa–14(e)(2) and (3). Finally, section 2114(c)(2) of the PHS Act, 42 U.S.C. 300aa–14(c)(2) provides that any person, including the Advisory Commission on Childhood Vaccines (the Commission) may petition the Secretary to propose regulations to amend the Vaccine Injury Table. Unless clearly frivolous, or initiated by the Commission, any such petition shall be referred to the Commission for its recommendations. Following receipt of any recommendation of the Commission or 180 days after the date of the referral to the Commission, whichever occurs first, the Secretary shall conduct a rulemaking proceeding on the matters proposed in the petition or publish in the **Federal Register** a statement or reasons for not conducting such proceeding.

During 2017, private citizens submitted documents to HHS and the Advisory Commission on Childhood Vaccines (Commission) requesting that certain injuries be added to the Table. These documents are considered petitions to the Secretary of HHS to propose regulations to amend the Table to add these injuries associated with vaccines on the Table. Below are summaries of these petitions.

- On April 3, 2017, a private citizen sent an email requesting to add food allergies, asthma and autism as injuries to the Table. The citizen did not specify vaccines associated with these alleged injuries in the petition.
- Letters dated March 16, 2017, and May 4, 2017, sent from a second private citizen requested to add tics as an injury to the Table. The citizen did not specify the vaccine associated with this alleged injury in the petition.
- Two letters dated February 20, 2017, and March 20, 2017, from a third private citizen, requested that the following be added to the Table: Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorder (PITAND) and/or Pediatric Autoimmune Neuropsychiatric Syndrome (PANS), and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Group A Streptococcal Infections (PANDAS) as injuries associated with pertussis, pneumococcal conjugate, and Haemophilus influenza type b (Hib) vaccines; and Experimental Autoimmune Encephalomyelitis (EAE)/Acute Demyelinating Encephalomyelitis (ADEM) as injuries associated with pertussis vaccines.

Pursuant to the VICP statute, these petitions were referred to the Commission on December 8, 2017. The Commission voted unanimously to recommend that the Secretary not proceed with rulemaking to amend the Table as requested in the petition to add asthma to the Table. The Commission voted 4–1 to recommend that the Secretary not proceed with rulemaking to amend the Table as requested in the other petitions. A petition to add food allergies to the Table was discussed at a previous ACCV meeting and the Commission recommended not to add this injury to the Table at that time. On March 29, 2016, the Secretary of HHS published a **Federal Register** notice stating reasons for not conducting rulemaking proceedings to add food allergies as an injury associated with vaccines to the Table.[1]

Autism and Asthma

On April 3, 2017, a private citizen sent an email requesting to add food allergies, asthma and autism as injuries to the Table. As mentioned above, the petitioner's request to add food allergies to the Table was previously addressed in a **Federal Register** notice published on March 29, 2016 (81 FR 17423–01). The requests to add autism and asthma to the Table are discussed below.

Autism

The National Institute of Child Health and Human Development states that autism or autism spectrum disorder (ASD) refers to a group of complex neurodevelopment disorders characterized by repetitive and characteristic patterns of behavior and difficulties with social communication and interaction. The symptoms are present from early childhood and affect daily functioning.[2] The exact cause of ASD is unknown but it is thought that the environment and genetics both play a role. While no specific environmental factors have been definitively identified as causes of ASD, a number of genes have been identified that are associated with ASD.[3] Numerous scientific studies have found that neither vaccines nor vaccine ingredients cause ASD.[4] [5] [6]

To support the claim that autism is caused by vaccines, the petitioner

[1] 81 FR 17423 (Mar. 29, 2016); *https://www.gpo.gov/fdsys/pkg/FR-2016-03-29/pdf/2016-06666.pdf.*

[2] National Institutes of Health, *About Autism, https://www.nichd.nih.gov/health/topics/autism/conditioninfo/Pages/default.aspx* (accessed May 3, 2018).

[3] National Institutes of Health, ''Autism Spectrum Disorder Fact Sheet,'' *https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Autism-Spectrum-Disorder-Fact-Sheet#3082* 5 (accessed May 3, 2018).

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

[5] *https://www.cdc.gov/ncbddd/autism/research.html.*

[6] *https://effectivehealthcare.ahrq.gov/topics/vaccine-safety/research.*

references a non- peer-reviewed article that he wrote and published online.[7] The article does not describe any epidemiologic evidence that vaccines cause autism but refers to another article authored by the petitioner. This article proposed a theory that milk antigens in vaccines can cause autism. No clinical data are provided to support this theory.

The Court considered and denied claims alleging that vaccines cause autism as part of the Omnibus Autism Proceeding (OAP). Starting in 2001, parents began filing petitions for compensation under the VICP, alleging that certain childhood vaccinations might be causing or contributing to autism. Specifically, they alleged that the measles, mumps, and rubella (MMR) vaccines and thimerosal-containing vaccines can combine to cause autism and that thimerosal-containing vaccines alone can cause autism. The Court created the OAP to adjudicate these claims.

By 2010, over 5,600 cases had been filed, and over 5,000 pending cases were divided among the three presiding special masters. In decisions released in 2009 and 2010, and affirmed without exception on appeal, the Court found there is no credible evidence that the MMR vaccines in combination with thimerosal-containing vaccines, or that thimerosal-containing vaccines alone, cause autism. These decisions mirror the current body of scientific evidence, including the 2001 Institute of Medicine (IOM) report, ''Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders.'' [8]

During 2012, the Institute of Medicine (IOM) published a report, ''Adverse Effects of Vaccines: Evidence and Causality,'' which reviewed the medical and scientific evidence on vaccines and adverse events to update the Table. The IOM committee concluded, ''the evidence favors rejection of a causal relationship between MMR vaccine and autism.'' In addition, since the Court's OAP decisions and the IOM's findings, several studies have also found that vaccines are not associated with autism.[9] [10] [11] Furthermore, a number of professional and international organizations have reviewed the evidence and also concluded that there is no association with vaccines and autism. These organizations include: the American Academy of Pediatrics, American Medical Association, American Academy of Family Physicians, Canadian National Advisory Committee on Immunization, and the Department of Health of the United Kingdom. In summary, current scientific evidence does not support a causal association between vaccinations and autism.

Asthma

Asthma is a chronic inflammatory disorder contributing to hyperresponsive airways, decreased airflow, breathing difficulties (such as wheezing and shortness of breath), and disease chronicity. It is thought that asthma develops in individuals who have a combination of certain host and environmental factors. There are several risk factors for developing asthma, including genetic and prenatal factors, lung size in infancy, exposure to environmental factors (*i.e.,* microbial organisms, smoke, and pollution), viral infections, obesity, and atopy (tendency to produce immunoglobulin E (IgE) antibodies). Individuals who develop allergic-type asthma are usually sensitized, or first develop IgE (Immunoglobulin E) antibodies when they come into contact with an allergen through the respiratory route. When they are re-exposed to the sensitized allergen in their airways, IgE antibodies will react and bind to the specific allergen, causing an allergic reaction.

Viral infections trigger up to 85 percent of asthma exacerbations in school-aged children and up to 50 percent of exacerbations in adults and may also contribute to asthma onset. This is likely mediated by IgE. Factors such as exercise, intense emotions, and cold air, among others, can cause an exacerbation through a non-allergic pathway. Atopy, the genetic predisposition for developing an IgE-mediated response to common allergens, is the strongest identifiable predisposing factor for developing asthma.

The petitioner asserts that the injection of food allergen-contaminated vaccines ''or pathogen associated vaccine antigens'' causes sensitization and subsequently asthma.

To support the theory that vaccines cause asthma, the citizen references a non-peer-reviewed article that he wrote and published online citing 15 references.[12] The individual also provided four additional articles, two of which he wrote and published online without peer review. [13] [14] [15] [16] Three of the latter references did not discuss asthma.

In the article, he asserts that vaccines cause allergy-induced asthma by at least two mechanisms. First, individuals can develop IgE-mediated sensitization by injection of food proteins in vaccines. Second, when they inhale the sensitized food particles, they can suffer asthma symptoms. The petition alleges that individuals can also become sensitized to ''pathogen associated vaccine antigens'' via IgE. Upon inhalation of these particles, such as influenza viral particles and pertussis bacterial particles, they will develop asthma symptoms. He cites 15 articles to support his theory. However, nine of these articles discuss general immunology, atopic dermatitis, food

[7] Vinu Arumugham, ''Medical muddles that maim our children with allergies, asthma and autism,'' *ResearchGate,* February 2017, *https://www.researchgate.net/publication/313918596_Medical_muddles_that_maim_our_children_with_allergies_asthma_and_autism?ev=publicSearchHeader&_sg=BKfNvl584X7Rf80bZHRyAldVr-GGf85U4THDmg_7BrJ72PtrZMkhMKIXZQOWWm9cOPjEJRtLCOeqyCI* (accessed May 3, 2018).

[8] Institute of Medicine (IOM) Report (2001), ''Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders.''

[9] Shahed Iqbal, John P. Barile, William W. Thompson, Frank DeStefano, ''Number of antigens in early childhood vaccines and neuropsychological outcomes at age 7–10 years,'' *Pharmacoepidemiology Drug Safety* 22, no. 12 (2013): 1263–70.

[10] Luke E. Taylor, Amy L. Swerdfeger, Guy D. Eslick, ''Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies,'' *Vaccine* 32, no. 29 (2014): 3623–9.

[11] Frank DeStefano, Cristofer S. Price, Eric S. Weintraub, ''Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism,'' *The Journal of Pediatrics* 163, no. 2 (2013): 561–567.

[12] Arumugham, ''Medical muddles that maim our children with allergies, asthma and autism.''

[13] Vinu Arumugham, ''Strong protein sequence alignment between autoantigens involved in maternal autoantibody related autism and vaccine antigens,'' *ResearchGate,* May 2017, *https://www.researchgate.net/profile/Vinu_Arumugham/publication/316785758_Strong_protein_sequence_alignment_between_autoantigens_involved_in_maternal_autoantibody_related_autism_and_vaccine_antigens/links/59115a620f7e9bfa06d43d5e/Strong-protein-sequence-alignment-between-autoantigens-involved-in-maternal-autoantibody-related-autism-and-vaccine-antigens.pdf?origin=publication_list* (accessed May 3, 2018).

[14] Vinu Arumugham, ''Significant protein sequence alignment between Saccharomyces Cerevisiae Proteins (a Vaccine Contaminant) and Systemic Lupus Erythematosus Associated Epitopes,'' *ResearchGate,* May 2017, *https://www.google.com/search?q=Significant+protein+sequence+alignment+between+Saccharomyces+Cerevisiae+Proteins+%28a+Vaccin* e+Contaminant%29+and+Systemic+Lupus+Erythematosus+Associated+Epitopes&ie=utf-8&oe=utf-8 (accessed May 3, 2018).

[15] Elizabeth Fox-Edmiston and Judy Van de Water, ''Maternal anti-fetal brain IgG autoantibodies and autism spectrum disorders: current knowledge and its implications for potential therapeutics,'' *CNS Drugs* 29, no. 9 (2015): 715–724.

[16] Maryline Fresquet, Thomas A. Jowitt, Jennet Gummadova, et al., ''Identification of a Major Epitope Recognized by PLA2R Autoantibodies in Primary membranous Nephropathy,'' *Journal of the American Society Nephrology* 26, no. 2 (2015): 302–13.

allergies, and anaphylaxis rather than asthma.[17] [18] [19] [20] [21] [22] [23] [24] [25]

One study referenced by the citizen found children had IgE anti-pertussis antigens after immunization, but no generalized further increase in IgE to food or inhalant antigens to which they were already sensitive. There was no suggestion that IgE to food or bacterial antigens would be a trigger for asthma and the author concluded, ''modifications of vaccine formulation aimed at preventing IgE production do not seem warranted.'' [26] Another study by Holt et al. found greater increases in IgE in patients immunized with acellular pertussis-containing vaccines compared to those immunized with whole cell pertussis containing vaccines. They suggested that the IgE antibody against those viruses could contribute to the respiratory symptoms during acute infection, but did not discuss the development of chronic asthma.[27] Another study referenced in the citizen's article, Smith-Morowitz et al. found persistence of IgE anti-influenza antibody for 2 years after immunization, suggesting that rather IgE may be associated with protective antibodies.[28]

The citizen also cited a study by Kuno-Sakai et al. This study evaluated whether gelatin in the MMR vaccine caused an acute allergic reaction. MMR, varicella, and some influenza vaccines continue to contain hydrolyzed gelatin, but acute reactions are rare as is the incidence of gelatin allergy in the general population, suggesting that vaccines are not a likely cause of widespread allergy to gelatin. No evidence was provided that inhalation of gelatin causes asthma.[29]

The 2012 IOM report reviewed asthma exacerbation or reactive airway disease episodes in children and adults after inactivated influenza vaccine, and asthma exacerbation/reactive airway disease episodes, in both children younger than 5 years of age and in persons 5 years of age or older after live attenuated influenza vaccine (LAIV). The IOM reached the following conclusions:

- The evidence favors a rejection of a causal relationship between inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults;
- The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age; and
- The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older.

The IOM did not evaluate evidence regarding a causal association between other vaccines and asthma. Aside from influenza vaccines, the IOM does not comment on the strength of the epidemiologic or mechanistic evidence regarding asthma and vaccination. Therefore, the IOM report does not support the petitioner's position for adding asthma to the Table for the influenza vaccine.[30]

In addition to assessing the evidence submitted in the petition, HHS assessed expert reviews pertinent to asthma etiology. During 2007, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health published, ''Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma: Clinical Practice Guidelines.'' A panel consisting of 18 experts commissioned by the National Asthma Education and Prevention Program Coordinating Committee and coordinated by the NHLBI developed this report. It discusses the causes of asthma, but vaccines are not considered as a potential cause.[31] Additional expert reviews on the etiology of asthma published in the literature do not mention vaccines as a risk factor or potential risk factor.[32] [33] [34] [35]

In addition to considering submitted evidence, HHS conducted a literature search of major medical databases for any articles linking vaccination and the development of asthma, specifically, reviewing numerous studies published during 2000 or later in peer-reviewed English language publications, which directly or tangentially evaluated the development of asthma after vaccination.

The majority of the reviewed articles found no potential causality between vaccinations covered by the VICP and the development of asthma. The search did not identify any peer-reviewed articles that evaluated or discussed the possible role of food allergen

[17] Arthur M. Silverstein, ''Clemens Freiherr von Pirquet: Explaining immune complex disease in 1906,'' *Nature Immunology* 1, no. 6 (2000): 453–5.

[18] H. Gideon Wells, ''Studies on the Chemistry of Anaphylaxis,'' *The Journal of Infectious Diseases* 5, no. 4 (1908): 449–483.

[19] H. Gideon Wells, ''Studies on the Chemistry of Anaphylaxis (III). Experiments with Isolated Proteins, Especially Those of the Hen's Egg,'' *The Journal of Infectious Diseases* 9, no. 2 (1911): 147–71.

[20] H. Gideon Wells and Thomas B. Osborne, ''The biological reactions of the vegetable proteins,'' *The Journal of Infectious Diseases* 8, no. 1 (1911): 66–124.

[21] Kate Grimshaw, Kirsty Logan, Sinead O'Donovan, et al., ''Modifying the infant's diet to prevent food allergy,'' *Archives of Disease Childhood* 102, no. 2 (2017): 179–186.

[22] George Du Toit, Graham Roberts, Peter H. Sayre, et al., ''Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy,'' *The New England Journal of Medicine* 372, no. 9 (2015): 803–813.

[23] Vinu Arumugham, ''Evidence that Food Proteins in Vaccines Cause the Development of Food Allergies and its Implications for Vaccine Policy,'' *Journal of Developing Drugs,*'' (October 2015), *https://www.researchgate.net/publication/285580954_Evidence_that_Food_Proteins_in_Vaccines_Cause_the_Development_of_Food_Allergies_and_Its_Implications_for_Vaccine_Policy?_sg=_2GjOVUyCyFmiLl1OWGBk6iBA3OnpAlN-gTrpR1QpTn0ZRXL0Vn1P6pO6f6zk9mKp0aVRVOS09R9tmY* (accessed May 3, 2018).

[24] Tetsuo Nakayama, Takuji Kumagai, Naoko Nishimura, et al., ''Seasonal split influenza vaccine induced IgE sensitization against influenza vaccine,'' *Vaccine* 33, no. 45 (2015): 6099–105.

[25] Ake Davidsson, Jens-Christian Eriksson, Stig Rudblad, Karl Albert Brokstad, ''Influenza Specific Serum IgE is Present in Non-Allergic Subjects,'' *Scandinavian Journal of Immunology* 62, no. 6 (2005): 560–1.

[26] E.J. Ryan, L. Nilsson, N.I.M. Kjellman, et al., ''Booster immunization of children with an acellular pertussis vaccine enhances Th2 cytokine production and serum IgE responses against pertussis toxin but not against common allergens,'' *Clinical and Experimental Immunology* 121, no. 2 (2000): 193–200.

[27] Patrick G. Holt, Tom Snelling, Olivia J. White, et al., ''Transiently increased IgE responses in infants and pre-schoolers receiving only acellular Diphtheria–Pertussis–Tetanus (DTaP) vaccines compared to those initially receiving at least one dose of cellular vaccine (DTwP)—Immunological curiosity or canary in the mine?'' *Vaccine* 34, no. 35 (2016): 4259–4261.

[28] Tamar Smith-Norowitz, Darrin Wong, Melanie Kusonruksa, et al., ''Long Term Persistence of IgE Anti-influenza Virus Antibodies In Pediatric and Adult Serum Post Vaccination with Influenza Virus Vaccine,'' *International Journal of Medical Sciences* 8, no. 3 (2011): 239, 241–243.

[29] Harumi Kuno-Sakai and Mikio Kimura, ''Removal of gelatin from live vaccines and DTaP—an ultimate solution for vaccine-related gelatin allergy,'' *Biologicals* 31, no. 4 (2003): 245–249.

[30] Institute of Medicine (IOM), *Adverse Effects of Vaccines: Evidence and Causality* (Washington, DC: The National Academies Press, 2012), 356.

[31] National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma: Clinical Practice Guidelines.* (Bethesda, MD: National Heart, Lung, and Blood Institute (NHLBI), 2007): 11–34.

[32] Augusto Litonjua and Scott T Weiss. ''Risk Factors for Asthma,'' *UptoDate,* last updated May 3, 2018, *https://www.uptodate.com/contents/risk-factors-for-asthma* (accessed May 3, 2018).

[33] George Guibas, Spyridon Megremis, Peter West, and Nikolas G. Papadopoulos, et al., ''Contributing factors to the development of childhood asthma: working toward risk minimization,'' *Expert Review of Clinical Immunology* 11, no. 6 (2015): 721–35.

[34] George Guibas, Alexander G. Mathioudakis, Marina Tsoumani, and Sophia Tsabouri, ''Relationship of Allergy with Asthma: There Are More Than the Allergy ''Eggs'' in the Asthma ''Basket'','' *Frontiers in Pediatrics* 5 (2017): 92.

[35] Padmaja Subbarao, Allan Becker, Jeffrey R. Brook, et al., ''Epidemiology of asthma: risk factors for development,'' *Expert Review of Clinical Immunology* 5, no. 1 (2009): 77–95.

contaminated vaccines or ''pathogen associated vaccine antigens'' in the development or exacerbation of asthma. Vaccines studied in the published articles included diphtheria, pertussis, and tetanus (DPT), MMR, measles, oral polio virus (OPV), Prevnar 13, Hib, and Hepatitis B. Fifteen studies found no association between vaccinations and asthma.[36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] Some studies found a protective effect suggesting that asthma risk was reduced with vaccination.[49] [50] [51]

Three studies had mixed results with two of them possibly having confounding variables. A study by Laubereau showed Hib-vaccinated children had a slightly higher risk for asthma. The authors of the study stated, ''results have to be interpreted with caution. Biological evidence to support a causal association is not available.'' Some of the questions the authors posed regarding the results dealt with the validity of parental reports and possible recall bias.[52]

A study by Benke, et al. of 3,200 22–44 year old individuals in Australia showed no difference in the risk of asthma among subjects who received DTP, Hepatitis B, measles, MMR, and OPV. However, an analysis of individuals who had received all three MMR, OPV and DTP vaccines showed an increased risk of asthma. Authors state there is ''relatively weak support . . . (that) vaccinations may lead to increased risk of asthma, but caution is advised due to possible recall bias.'' They write that typically studies of young adults who self-report vaccination histories may be subject to significant recall bias. In this study, childhood vaccination was based entirely on subject recall. In addition, as noted by the authors, associations for atopy and vaccinations appeared consistently weak for all vaccines investigated. Since atopic asthma has a strong association with atopy, this also does not suggest that vaccines led to the increase in asthma.[53]

A study by Thomson, et al. demonstrated conflicting results. OPV and MMR vaccines decreased the risk of asthma at age 2, and OPV decreased the risk of asthma at age 6. Also, the diphtheria and tetanus (DT) vaccine that was administered in the first year of life increased the risk of asthma at 6 years. However, this study had significant limitations. Nearly 21 percent of the subjects were lost to follow-up. Only children with a previous reaction to DPT vaccine were given DT suggesting that this may be an at-risk group. In addition, there was a small sample size and there was no control group.[54]

Another study by McDonald, et al. demonstrated an association between timing of DPT receipt and risk of asthma. This study consisted of 11,531 children born in Manitoba during 1995 who received at least four doses of DPT. The researchers looked at timing of vaccine receipt and the development of asthma and found that delaying the first dose of DPT by greater than 2 months decreased risk of asthma by 50 percent. They identified several potential confounding factors, including the fact that the reason for immunization delay was unknown. Children without asthma may visit a physician less often with fewer opportunities to be vaccinated. This may lead to self-selection. Also, there was not a comparison control (unvaccinated) group.

In summary, current scientific evidence does not support a causal association between vaccinations and asthma. There is no evidence that vaccination leads to IgE antibody against the most common causes of wheezing in childhood, namely respiratory syncytial virus, and human rhinovirus. There is no evidence that individuals develop IgE sensitization by injection of food proteins in vaccines and that subsequent inhalation of these particles causes symptoms of asthma. There is no evidence that inhalation of vaccine antigens triggers asthma symptoms via an IgE mechanism. Although some studies show a possible association with asthma, these have significant lapses in methodology. The majority of studies show no association.

Tics

On March 16, 2017, and May 4, 2017, a private citizen submitted letters to HHS requesting that tics be added to the Table. The petitioner claims that two CDC employees have been quoted as believing there is evidence that vaccines can cause tics; neither the CDC nor the CDC employees have verified these comments. The petitioner mentions a study by Barile and Thompson in support of his request. The petitioner did not specify vaccine type or differentiate between thimerosal-containing versus thimerosal-free vaccines.

[36] H. Ross Anderson, Jan D. Poloniecki, David P. Strachan, et al., ''Immunization and symptoms of atopic disease in children: results from the international study of asthma and allergies in children,'' *American Journal of Public Health* 91, no. 7 (2001): 1126–9.

[37] Kristin Wickens, Julian Crane, Trudi Kemp, et al., ''A case-control study of risk factors for asthma in New Zealand children,'' *Australian and New Zealand Journal of Public Health* 25, no. 1 (2001): 44–49.

[38] Frank DeStefano, David Gu, Piotr Kramarz, et al., ''Childhood vaccinations and the risk of asthma,'' *Pediatric Infectious Disease Journal* 21, no. 6 (2002): 498–504.

[39] H. P. Roost, M. Gassner, L. Grize, et al., ''Influence of MMR-vaccinations and diseases on atopic sensitization and allergic symptoms in Swiss schoolchildren,'' *Pediatric Allergy and Immunology* 15, no.5 (2004): 401–7.

[40] Julie E. Maher, John P. Mullooly, Lois Drew, and Frank DeStefano, ''Infant vaccinations and childhood asthma among full-term infants,'' *Pharmacoepidemiology and Drug Safety* 31, no. 1 (2004): 1–9.

[41] Monique Mommers, Gerard M. H. Swaen, Michela Weishoff-Houben, et al., ''Childhood infections and risk of wheezing and allergic sensitisation at age 7–8 years,'' *European Journal of Epidemiology* 19, no. 10 (2004): 945–51.

[42] John P. Mullooly, Roberleigh Schuler, Michael Barrett, and Julie E. Maher, ''Vaccines, antibiotics, and atopy,'' *Pharmacoepidemiology and Drug Safety* 16, no. 3 (2007) 275–88.

[43] Ran D. Balicer, Itamar Grotto, Marc Mimouni, and Daniel Mimouni, ''Is childhood vaccination associated with asthma? A meta-analysis of observational studies,'' *Pediatrics* 120, no. 5 (2007): e1269–77.

[44] Ben D. Spycher, Michael Silverman, Matthias Egger, et al., ''Routine vaccination against pertussis and the risk of childhood asthma: a population-based cohort study,'' *Pediatrics* 123, no. 3 (2009): 944–50.

[45] John P. Mullooly, John Pearson, Lois Drew, et al., ''Wheezing lower respiratory disease and vaccination of full-term infants,'' *Pharmacoepidemiology and Drug Safety* 11, no. 1 (2002): 21–30.

[46] Gabriele Nagel, Gudrun Weinmayr, Carsten Flohr, et al., ''Association of pertussis and measles infections and immunizations with asthma and allergic sensitization in ISAAC Phase Two,'' *Pediatric Allergy and Immunology* 23, no. 8 (2012): 737–46.

[47] Hung Fu Tseng, Lina S. Sy, In-Lu Amy Liu, et al., ''Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children,'' *Vaccine* 24, no. 22 (2013): 2578–83.

[48] Vittorio DeMicheli, Alessandro Rivetti, Maria Grazia Debalini and Carlo Di Pietrantonj, ''Vaccines for measles, mumps and rubella in children,'' *Cochrane Database of Systematic Reviews* 15, no. 2 (2012): 4, 18, 21, 135–139.

[49] Clara Amalie, Gade Timmermann, Christa Elyse Osuna, Ulrike Steuerwald, et al., ''Asthma and allergy in children with and without prior measles, mumps, and rubella vaccination,'' *Pediatric Allergy and Immunology* 26, no. 8 (2015): 742–749.

[50] John P. Mullooly, Roberleigh Schuler, Jill Mesa, et al., ''Wheezing lower respiratory disease and vaccination of premature infants,'' *Vaccine* 29, no. 44 (2011): 7611–7.

[51] H. P. Roost, M. Gassner, L. Grize, et al., ''Influence of MMR-vaccinations and diseases on atopic sensitization and allergic symptoms in Swiss schoolchildren,'' *Pediatric Allergy and Immunology* 15, no. 5 (2004): 401–7.

[52] B. Laubereau, V. Grote, B. Holscher, et al., ''Vaccination against Haemophilus influenzae type b and atopy in East German schoolchildren,'' *European Journal of Medical Research* 7, no. 9 (2002): 387, 389–391.

[53] G. Benke, M. Abramson, J. Raven, et al., ''Asthma and vaccination history in a young adult cohort,'' *Australian and New Zealand Journal of Public Health* 28, no. 4 (2004): 337.

[54] Jennifer A. Thomson, Constance Widjaja, Abbi A. P. Darmaputra, et al., ''Early childhood infections and immunisation and the development of allergic disease in particular asthma in a high-risk cohort: A prospective study of allergy-prone children from birth to six years,'' *Pediatric Allergy and Immunology* 21, no. 7: 1076, 1079–1084.

Tics are defined as sudden, rapid, recurrent, non-rhythmic, stereotyped motor movement or vocalization.[55] They are involuntary, but can be suppressed for varying lengths of time and are markedly diminished during sleep. The onset of tics almost always occur in childhood with multiple tics and complex vocal sounds developing over time, usually peaking in severity by 10–12 years of age. The precise etiology of tics is not known, but it is thought to be due to chemical abnormalities in the brain. The risk of developing tics and the prognosis are influenced by temperamental, environmental, genetic, and physiological factors. Diagnosis of tic disorders is hierarchical and complex. Therefore, specialists typically diagnose tics and tic disorders.

The petition mentions a study by Barile without a citation. Presumably, this is the study published in the Journal of Pediatric Psychology in 2012.[56] The study's ''objective was to examine associations between thimerosal-containing vaccines and immunoglobulins early in life and neuropsychological outcomes evaluated at children aged 7–10 years.'' The study population was 1,047 children ages 7–10, born between January 1993 and March 1997. The evaluators measured seven neuropsychological outcomes during a 3-hour testing period with the child including the following: (1) Intellectual functioning, (2) speech and language, (3) verbal memory, (4) executive functioning, (5) fine motor coordination, (6) tics, and (7) behavior regulation. The authors found no statistically significant associations between thimerosal exposure from vaccines early in life in six of the seven outcomes. There was a small, statistically significant association between early thimerosal exposure and the presence of tics in boys. However, the authors concluded that this finding should be interpreted with caution because of limitations in the measurement of tics and also the limited biological plausibility regarding a causal relationship. The authors suggested additional studies were needed to examine these associations using more reliable and valid measure of tics.[57]

There are several significant limitations of the Barile study. The only training the evaluators received for tics assessment was based on a 30-minute video on the diagnosis of Tourette syndrome from 1989 and may not have been sufficient to adequately diagnose the subjects. These raters were not required to meet any criteria for skill or reliability criteria. This could have led to misdiagnosis of the study subjects. The parent's assessment of the presence or absence of tics was not concordant with the assessor's reports. The study does not provide the parents' assessment of tics. However, positive presence of tics from parent's report and the assessor's report of tics agreed only 23% of the time for motor tics and 16% of the time for phonic tics. Thus, this outcome of interest, tics, was either not noticed by, or is not consistent with, behaviors that would be observed by or concerning to parents. The response rate was low—only 30 percent of invitees agreed to participate.

The petition did not specify vaccine type or if the vaccines of concern were thimerosal-containing or not. However, according to the citizen, the Barile study mentioned in the petition specifically focused on thimerosal-containing vaccines. Thimerosal is a mercury-based preservative that is broken down into ethyl mercury after entering the body. The low levels of ethyl mercury in vaccines are broken down by the body differently and clear out of the blood more quickly than methylmercury.[58] There is no evidence of harm caused by low doses of thimerosal in vaccines, except for minor reactions like redness and swelling at the injection site. Multi-dose FDA-approved seasonal influenza vaccines contain thimerosal as a preservative however, single-dose presentations that do not contain thimerosal as a preservative are available for use in infants, children, adults, the elderly and pregnant women. All other vaccines routinely recommended for children 6 years of age or younger and marketed in the U.S. do not contain thimerosal.[59] MMR vaccines do not and never did contain thimerosal. Varicella (chickenpox), inactivated polio (IPV), and pneumococcal conjugate vaccines have also never contained thimerosal. There are numerous studies and independent reviews supporting the safe use of thimerosal in vaccines.[60 61 62 63 64 65 66 67 68 69 70 71 72 73]

An initial literature search was performed looking for articles on tics by the two CDC employees mentioned in the petition, Dr. Thompson and Dr.

[55] American Psychiatric Association, *Diagnostic and statistical manual of mental disorders (5th ed.).* (Arlington, VA: American Psychiatric Publishing, 2013): 81.

[56] John P. Barile, Gabriel P. Kuperminc, Eric S. Weintraub, et al., ''Thimerosal Exposure in Early Life and Neuropsychological Outcomes 7–10 Years Later,'' *Journal of Pediatric Psychology* 37, no. 1 (2012): 115.

[57] John P. Barile, ''Thimerosal Exposure in Early Life and Neuropsychological Outcomes 7–10 Years Later,'' 115.

[58] Centers for Disease Control and Prevention, *Understanding Thimerosal, Mercury, and Vaccine Safety,* February 2013, *https://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-thimerosal-color-office.pdf* (accessed May 3, 2018).

[59] One single dose presentation of seasonal influenza vaccine, Fluvirin's single-dose presentation, utilizes thimerosal as part of its manufacturing process, not as a preservative, and a trace remains in the final presentation.

[60] Nick Andrews, Elizabeth Miller, Andrew Grant, et al., ''Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association,'' *Pediatrics* 114, no. 3 (2004): 584–591.

[61] Eric Fombonne, Rita Zakarian, Andrew Bennett, et al., ''Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links with Immunizations,'' *Pediatrics* 118, no. 1 (2006): e139–150.

[62] Anders Hviid, Michael Stellfeld, Jan Wohlfahrt, et al., ''Association between Thimerosal-Containing Vaccine and Autism,'' *Journal of the American Medical Association* 290, no. 13 (2003): 1763–1766.

[63] Institute of Medicine, *Immunization Safety Review: Vaccines and Autism. Institute of Medicine* (Washington, DC: The National Academies Press, 2004): 145.

[64] Cristofer Price, William W. Thompson, Barbara Goodson, et al., ''Prenatal and Infant Exposure to Thimerosal from Vaccines and Immunoglobulins and Risk of Autism,'' *Pediatrics* 126, no. 4 (2010): 656–664.

[65] Robert Schechter and Judith K. Grether, ''Continuing Increases in Autism Reported to California's Developmental Services System,'' *Archives of General Psychiatry* 65, no. 1 (2008): 19–24.

[66] William Thompson, Cristofer Price, Barbara Goodson, et al., ''Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years,'' *The New England Journal of Medicine* 357, no.13 (2007): 12811292.

[67] Global Advisory Committee on Vaccine Safety, *Statement on Thiomersal* (World Health Organization, 2006): *http://www.who.int/vaccine_safety/committee/topics/thiomersal/statement_jul2006/en/* (accessed May 3, 2018).

[68] Agency for Toxic Substances and Disease Registry (ATSDR), *Toxicological Profile for Mercury.* (Atlanta, GA, 1999).

[69] American Academy of Pediatrics, *Vaccine Safety: Examine the Evidence,* April 2013, *https://www.healthychildren.org/English/safety-prevention/immunizations/Pages/Vaccine-Studies-Examine-the-Evidence.aspx?gclid=Cj0KCQjwrLXXBRCXARIsAIttmRNIMWanl3CP-P6t8eA1MPl07uJFNPpxF2dzPEJkshVq9-U5kRozmQQaAki1EALw_wcB* (accessed May 3, 2018).

[70] L. Magos, ''Review on the toxicity of ethylmercury, including its presence as a preservative in biological and pharmaceutical products,'' *Journal of Applied Toxicology* 21 no. 1, (2001): 1–5.

[71] Robert J. Mitkus, David B. King, Mark O. Walderhaug, and Robert A. Forshee, ''A Comparative Pharmacokinetic Estimate of Mercury in U.S. Infants Following Yearly Exposures to Inactivated Influenza Vaccines Containing Thimerosal,'' *Risk Analysis* 34, no. 4 (2014): 735–50.

[72] Mieszko Olczak, Michalina Duszczyk, Pawel Mierzejewski, et al., ''Lasting neuropathological changes in rat brain after intermittent neonatal administration of thimerosal,'' *Folia Neuropathologica* 48, no. 4 (2010): 258–69.

[73] Michael E. Pichichero, Elsa Cernichiari, Joseph Lopreiato, and John Treanor, ''Mercury Concentrations and Metabolism in Infants Receiving Vaccines Containing Thiomersal: A Descriptive Study,'' *The Lancet* 360, no. 9347 (2002): 1737–41.

Yeargin-Allsop. There are two additional studies related to tics that involved Dr. Thompson. One article examined early thimerosal exposure and neuropsychological outcomes in children aged 7–10 and did not find an association between tics and vaccinations containing thimerosal.[74] The second article by Iqbal et al. was designed to evaluate the association between antibody-stimulating proteins and polysaccharides from early childhood vaccines and neuropsychological outcomes at age 7–10 years. There were no adverse associations between antigens through vaccines in the first 2 years of life and neuropsychological outcomes, including tics in later childhood.[75]

HHS conducted a comprehensive literature review of the major medical databases to search for articles linking tics/tic disorders to vaccinations that do not contain thimerosal. There is a paucity of literature on tics/tic disorders as a result of vaccinations. Leslie, et al. authored one article that discussed tics. The objective of this study was to examine whether antecedent vaccinations are associated with increased incidence of obsessive compulsive disorder (OCD), anorexia nervosa, anxiety disorder, chronic tic disorder, attention deficit hyperactivity disorder, major depressive disorder, and bipolar disorder. Using claims data, the investigators compared the prior year's occurrence of vaccinations in children and adolescents with the above neuropsychiatric disorders that were newly-diagnosed between January 2002 and December 2002, as well as two control conditions (broken bones and open wounds). The investigators found children with OCD, anorexia nervosa, anxiety disorder, and tic disorder were more likely to have received influenza vaccine during the preceding 1-year period. They concluded that the onset of some neuropsychiatric disorders may be temporally-related to prior vaccinations, but stated it does not prove a causal role of vaccinations in the etiology of these conditions.[76]

This study had several limitations. It relied on administrative retrospective data rather than systematically obtained clinical data. Therefore, diagnostic misclassification may have occurred. The dates in which individuals were diagnosed do not indicate disease onset dates, which may suggest a temporal association where none exists. In addition, the control groups may not be similar enough to the disease groups. Furthermore, the influenza vaccine is given annually and is the most frequently administered vaccine. By chance, there may be many diagnoses made within a year of flu vaccination. Thus, this case-control study provides no more than a temporal association and does not give an absolute risk.

In summary, there is limited literature on tics/tic disorders and vaccinations. Childhood vaccines do not contain thimerosal and influenza vaccines have thimerosal-free formulations. Current scientific evidence does not support a causal association between thimerosal-containing or thimerosal-free vaccinations and tics/tic disorders.

PANS, PITAND, PANDAS, EAE, and ADEM

On February 20, 2017, and March 20, 2017, a private citizen submitted written petitions requesting HHS to add PANS, PITAND, PANDAS, EAE, and ADEM to the Table. The petitions assert that certain components in pertussis vaccines cause the development of PANS and/or PITAND and conjugate and polysaccharide pneumococcal vaccines and Hib vaccines cause or enable the development of PANS and/or PANDAS. However, not all pneumococcal vaccines are covered by the VICP. There are two types of pneumococcal vaccines given in the U.S. The pneumococcal conjugate vaccine (PCV13), which is administered routinely to infants and children up to age 5, and the pneumococcal polysaccharide vaccine (PPV23), which is given to adults age 65 and older and individuals of varying age with certain medical conditions making them at higher risk for pneumococcal infection. Since December 18, 1999, the VICP has covered only the pneumococcal conjugate vaccine (PCV13).

PANS, PITAND, and PANDAS

PANS, PITAND, and PANDAS are proposed conditions based on a concept that an immune basis may underlie and may trigger disorders associated with movement and behavioral abnormalities. A hypothesis is that ''neuropsychiatric syndromes may result from various etiologies, including hereditary, environmental, and inflammatory causes.''[77] It has been hypothesized that infections with group A streptococcus (GAS) and others may trigger autoimmune responses that can cause or exacerbate childhood-onset OCD or tic disorders (including Tourette syndrome). A theory proposed is that antibodies against GAS cross-react with brain antigens by molecular mimicry resulting in autoantibody-mediated neuronal cell signaling in susceptible hosts.[78] Initially researchers coined the term PANDAS and later this was modified to PANS. Neither PITAND, PANS, nor PANDAS are officially recognized disease entities and do not have diagnostic codes in either: (a) International Statistical Classification of Diseases and Related Health Problems (ICD–10, most recent revision, 2010); or (b) Diagnostic and Statistical Manual of Mental Disorders (DSM–V; most recent revision, 2013).

The diagnostic criteria proposed for PANS include abrupt onset of symptoms of OCD or food restriction (anorexia) plus two of the following:

- Anxiety, emotional lability and/or depression, irritability, aggression and/or severely oppositional behaviors, behavioral (developmental) regression, deterioration in school performance, sensory or motor abnormalities, somatic signs and symptoms (*e.g.,* sleep disturbances, enuresis, urinary frequency); and
- Symptoms not better explained by a known neurologic or medical disorder.[79]

To support the claim that PANS and/or PITAND are caused by pertussis-containing vaccines, the petition outlines a mechanism of molecular mimicry and autoantibody-mediated neuronal cell-signaling leading to symptoms. To support the claim that PANS and/or PANDAS are caused or enabled by pneumococcal and Hib vaccines, the petition outlines a mechanism of injury in which vaccination with pneumococcal/Hib vaccines results in disruption of the blood-brain barrier in a susceptible child, which then allows circulating GAS antibodies to enter the central nervous system (CNS). This results in cross-reactivity between GAS antibodies and CNS structures, which leads to symptoms of PANS/PANDAS.

[74] Thompson, ''Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years,'' 1285.

[75] Iqbal, ''Number of antigens in early childhood vaccines and neuropsychological outcomes at age 7–10 years,'' 1263, 1266.

[76] Douglas L. Leslie, Robert A. Kobre, Brian J. Richmond, et al. ''Temporal Association of Certain Neuropsychiatric Disorders Following Vaccination of Children and Adolescents: A Pilot Case-Control Study,'' *Frontiers in Psychiatry* 8, no. 3 (2017): 6.

[77] Kyle A. Williams and Susan E. Swedo, ''Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond,'' *Brain Research* 1617 (2015): 145.

[78] Albert J. Allen, Henrietta L. Leonard, and Susan E. Swedo, ''Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome,'' *Journal of the American Academy of Child Adolescent Psychiatry* 34, no. 3 (1995): 307–311.

[79] Susan E. Swedo, James F. Leckman, and Noel R. Rose, ''From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome),'' *Pediatrics & Therapeutics* 2, no. 2 (2012): 3.

The 2012 IOM report did not review any possible association between pertussis-containing vaccines or any vaccine and PANS and/or PITAND, nor did it review any possible association between pneumococcal conjugate vaccines and Hib vaccines or any vaccine and PANS and/or PANDAS. HHS gathered data from the existing medical literature in addition to the evidence submitted in the petition. A literature search of the major medical databases was conducted searching for any articles linking the development of PANS, PITAND, or PANDAS to vaccinations, including pertussis-component, pneumococcal conjugate, and Hib vaccines.

Despite an extensive search of peer-reviewed English language publications, HHS did not find any published research addressing any linkages, potential causality, or enablement between vaccinations covered by the VICP, including pertussis-containing, pneumococcal conjugate, and Hib vaccinations, and the development of PANS, PITAND, and/or PANDAS in any population. There are no published data on PANS and PITAND regarding possible specific infectious or non-infectious triggers and autoimmune mechanisms. Data on the more well-studied PANDAS are conflicting.[80] Some researchers question the autoimmune mechanism of PANDAS and no specific autoimmune antibody is agreed upon as a pathogenic mechanism for its symptoms.[81]

After an extensive literature search, HHS has not found any published study that examines anti-neuronal antibodies in children suspected of PANS or PITAND following pertussis infection or following pertussis immunization. HHS has not found any studies that examine whether pneumococcal conjugate vaccines or pneumococcal infections and Hib vaccines or Hib infections disrupt the filtering mechanism of the blood-brain barrier to allow circulating GAS antibodies to cross into the CNS in a susceptible child and, once across the barrier, to react with CNS structures to generate neuropsychiatric symptoms. In addition, HHS is not aware of any published studies concluding that PANS, PITAND, and/or PANDAS are caused by pertussis infection or pertussis, pneumococcal conjugate or Hib vaccines.

EAE and ADEM

EAE is not a clinical diagnosis. EAE is an animal model of autoimmune disease of the CNS.[82] As EAE does not occur in humans, it will not be discussed separately from the human diseases (which are discussed below). Pertussis toxin has been used in EAE studies due to its immunogenicity (ability to evoke an immune response). However, acellular pertussis vaccines are formulated to contain inactivated pertussis toxin and not pertussis toxin that is used in animal models of EAE.

Encephalopathy is currently an injury on the Table for vaccines containing whole cell pertussis bacteria, extracted or partial cell pertussis bacteria, or specific pertussis antigen, and vaccines containing measles, mumps, and rubella virus or any of its components. ADEM can have encephalopathy as a symptom, but ADEM and encephalopathy are two distinct conditions. The autoimmune etiology is specific for ADEM and the onset between primary exposure and development of primary antibody response is 7–10 days as opposed to 0–72 hours for the onset to meet the Table definition for encephalopathy.[83] The time period for development of ADEM is outside the 0–72 hour time period of the Table definition for acellular pertussis vaccine and encephalopathy and encephalitis. With ADEM, there is a characteristic demyelination in the CNS and a strong association with prodromal (infectious) illness that is absent in an encephalopathy as defined in the Table. These differences were significant enough that the IOM 2012 Report considered ADEM separate from encephalopathy and encephalitis.

Multiple articles were submitted by the petitioner in support of adding ADEM/EAE to the Table.[84] [85] [86] [87] [88] [89] [90] [91] [92] [93] [94] However, the studies dealing with EAE do not have relevance to pertussis vaccinations and/or ADEM. These studies do not provide any evidence that pertussis vaccinations cause ADEM.

The IOM reviewed the epidemiologic and mechanistic evidence as to whether pertussis vaccinations cause ADEM. They found the evidence inadequate to accept or reject a causal relationship between pertussis-containing vaccines and ADEM. HHS conducted a review of the literature published after the IOM report regarding ADEM and vaccination. A paper by Baxter et al. identified all cases of ADEM in the Vaccine Safety Datalink (VSD). The VSD is a collaborative project between CDC and eight health care organizations that utilizes electronic health data to monitor the safety of vaccines. The VSD study analyzed 64 million vaccine doses and calculated the risk difference of being diagnosed with ADEM for each vaccine. This study revealed two cases of ADEM after Tdap (tetanus, diphtheria, and acellular pertussis) vaccination. The study was limited with regard to assessing causality due to the small number of ADEM cases. It is also possible this finding could be due to chance alone due to multiple testing. Multiple testing refers to any instance that involves the simultaneous testing of several hypotheses.[95] [96]

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[80] Sonja Orlovska, Claus Høstrup Vestergaard, Bodil Hammer Bech, et al., ''Association of Streptococcal Throat Infection with Mental Disorders: Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study,'' *JAMA Psychiatry* 74, no. 7 (2017): 741.

[81] Williams, ''Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond,'' 145.

[82] William J. Lindsey, ''EAE: History, Clinical Signs, and Disease Course,'' in *Experimental Models of Multiple Sclerosis,* eds..Ehud Lavi and Cris Constantinescu (New York: Springer Science+Business Media, Inc., 2005): 1.

[83] IOM, *Adverse Effects of Vaccines,* 546–7.

[84] Harald H. Hofstetter, Carey L. Shive, and Thomas G. Forsthuber, ''Pertussis Toxin Modulates the Immune Response to Neuroantigens Injected in Incomplete Freund's Adjuvant: Induction of Th1 Cells and Experimental Autoimmune Encephalomyelitis in the Presence of High Frequencies of Th2 Cells,'' (animal model), *The Journal of Immunology* 169, no. 1 (2002) 117–125.

[85] B. Diamond, G. Honig, S. Mader, et al., ''Brain-Reactive Antibodies and Disease,'' *Annual Review of Immunology* 31 (2013): 345–385.

[86] Hans Lassman, ''Acute disseminated encephalomyelitis and multiple sclerosis,'' *Brain* 133 (2010): 317–319.

[87] Kristina Leuner, Tanja Schutt, Christopher Kurz, et al., ''Mitochondrion-Derived Reactive Oxygen Species Lead to Enhanced Amyloid Beta Formation,'' (animal study), *Antioxidants and Redox Signaling* 16, no. 12 (2012): 1421–1433.

[88] Dan Zhou, Rajneesh Srivastava, Stefan Nessler, et al., ''Identification of a pathogenic antibody response to native myelin oligodendrocyte glycoprotein in multiple sclerosis,'' *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* 103, no. 50 (2006): 19057–19062.

[89] Peter M. Clifford, Shabnam Zarrabi, Gilbert Siu, et al., ''Aβ peptides can enter the brain through a defective blood–brain barrier and bind selectively to neurons,'' (animal study), *Brain Research* 1142 (2007): 223–236.

[90] Ralf A. Linker and De-Hyung Lee, ''Models of autoimmune demyelination in the central nervous system: on the way to translational medicine,'' *Experimental & Translational Stroke Medicine* 1, no. 5 (2009): 1–10.

[91] Kevin O'Connor, Katherine A. McLaughlin, Philip L. De Jager, et al., ''Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein,'' *Nature Medicine* 13, no. 2 (2007): 211–217.

[92] Fabienne Brilot, Russell C. Dale, Rebecca C. Selter, et al., ''Antibodies to native myelinoligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease,'' *Annals of Neurology* 66, no.6 (2009): 833–42.

[93] Alan G. Baxter, ''The origin and application of experimental autoimmune encephalomyelitis,'' *Nature Reviews Immunology* 7 (2007): 904–912.

[94] Roberto Furlan, Elena Brambilla, Francesca Sanvito, et al., ''Vaccination with amyloid-β peptide induces autoimmune encephalomyelitis in C57/BL6 mice,'' *Brain* 126, no. 2 (2003): 285–291.

[95] Roger Baxter, Edwin Lewis, Kristin Goddard, et al., ''Acute Demyelinating Events Following

Another study by Chang that analyzed post-licensure safety for diphtheria and acellular pertussis vaccines found no statistically significant adverse events including ADEM.[97] A study by Pellegrino looked at the onset of ADEM utilizing a post-marketing study from the U.S. and Europe. The investigators found a decrease in the diagnosis of ADEM in individuals who received DTaP, IPV, and Hib vaccines.[98] In summary, EAE is not a disease in humans but rather an experimental model. The Table only lists conditions found in humans. In addition, the current literature does not support a relationship between vaccines and ADEM.

Conclusion

In light of the above, HHS has determined that there is no reliable scientific evidence of an association between vaccines and asthma, autism, tics, PITAND, PANS, PANDAS, EAE, and/or ADEM. Therefore, HHS will not add them as injuries associated with any vaccine on the Table at this time.

Dated: February 22, 2019.

George Sigounas,

Administrator, Health Resources and Services Administration.

Approved: March 15, 2019.

Alex M. Azar II,

Secretary, Department of Health and Human Services.

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