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Overview of the Clinical Consult Case Review of Adverse Events Following Immunization: Clinical Immunization Safety Assessment Network (CISA) 2004-2009

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Abstract

Background—In 2004 the Clinical Consult Case Review (CCCR) working group was formed within the CDC-funded Clinical immunization Safety Assessment (CISA) Network to review individual cases of adverse events following immunizations (AEFI).

Methods—Cases were referred by practitioners, health departments, or CDC employees. Vaccine Adverse Event Reporting System (VAERS) searches and literature reviews for similar cases were performed prior to review. After CCCR discussion, AEFI were assessed for a causal relationship with vaccination and recommendations regarding future immunizations were relayed back to the referring physicians. In 2010, surveys were sent to referring physicians to determine the utility and effectiveness of the CCCR service.

Results—CISA investigators reviewed 76 cases during 68 conference calls between April 2004 and December 2009. Almost half of cases (35/76) were neurological in nature. Similar AEFI for the specific vaccines received were discovered for 63 cases through VAERS searches and for 38 cases through PubMed searches. Causality assessment using the modified WHO criteria resulted in classifying 3 cases as definitely related to vaccine administration, 12 as probably related, 16 as possibly related, 18 as unlikely related, 10 as unrelated, and 17 had insufficient information to assign causality. The physician satisfaction survey was returned by 30 (57.7%) of those surveyed and a majority of respondents (93.3%) felt that the CCCR service was useful.

Disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position or views of the Centers for Disease Control and Prevention.

Conclusions—The CCCR provides advice about AEFI to practitioners, assigns potential causality, and contributes to an improved understanding of adverse health events following immunizations.

Keywords

Adverse; Event; Following; Immunization; Causality

Introduction

Vaccines are one of the greatest public health achievements in the history of medicine. Throughout the past century, vaccines have helped to greatly reduce the disease burden from both bacterial and viral infections [1-8]. However, as with any medication, vaccines are not without risk. Several well documented adverse events have been associated with specific vaccines [1, 9-14]. Thus, it is the responsibility of the public health community to continuously evaluate potential adverse events following immunization (AEFI), to repeatedly assess the risk-benefit profile of each vaccine, and to inform the public if additional risks are identified [15-21].

In 2001, the Centers for Disease Control and Prevention established the Clinical Immunization Safety Assessment (CISA) Network, a national consortium of six academic medical centers with expertise in immunization safety [22]. CISA goals were: (1) to study the pathophysiologic basis of adverse events following immunization; (2) to study individual risk factors associated with developing an adverse event following immunization; (3) to serve as a vaccine safety resource for consultation on complex clinical vaccine safety issues; and (4) to assist domestic and global vaccine policy makers in developing guidance for individuals who may be at increased risk for AEFIs [23].

To address the third objective, the CISA Clinical Consult Case Review (CCCR) working group was established in 2004. The working group meets monthly to address specific questions from practitioners regarding individual clinical cases of potential AEFI after administration of a licensed vaccine. The CCCR working group consists of investigators and research coordinators from each CISA network site, CDC representatives, and subspecialists who convene to discuss specific case(s) via regularly scheduled telephone conferences. The primary goals of the CCCR are twofold: (1) to provide guidance to medical providers regarding subsequent vaccinations, and (2) to provide expert opinion as to the probability that the event could have been causally related to vaccination using modified World Health Organization (WHO) causality guidelines [18, 24]. (Table 1) The objective of this overview is to describe the scope of the cases reviewed, the process of causality determination, and to explore the usefulness of this service for health care providers.

Methods

Case Evaluation and Presentation

The CISA network includes investigators from the medical centers of Boston University, Columbia University, Johns Hopkins University, Northern California Kaiser Permanente

Vaccine Study Center, Stanford University and Vanderbilt University. In addition, board certified allergists and neurologists frequently participated in the teleconferences.

Cases were referred to CISA network sites by local providers who were aware of the CCCR service, state health departments or the CDC. Additionally, cases were also collected by CISA investigators during their clinical responsibilities and presented to the CCCR. Each CISA site was responsible for selecting individual cases to present to the group and to collect additional clinical data when indicated. These cases were then presented by the CISA site on a scheduled teleconference. When available, the provider seeking the consultation presented the case to the CCCR and/or actively participated in the discussion. Separate CISA working groups for Guillain-Barré syndrome and hypersensitivity existed and reviewed those specific adverse events separately. Standardized templates, developed in January of 2006, were completed for each case, including a brief description of the case and the results of both Vaccine Adverse Event Reporting System (VAERS) database and PubMed medical literature searches. VAERS is the national adverse event reporting system available to the public to monitor vaccine safety [25]. Reports to VAERS may indicate instances of temporal association of the vaccine and AEFI, but are not evidence of causality [25]. For each referred clinical case, we conducted VAERS searches including the specific vaccine(s), individually or in combination if applicable, linked with the diagnosis or main symptoms of the adverse event. Medical literature searches via PubMed were conducted for the diagnosis or primary symptom associated with the specific vaccine(s). All documents were available on a secure website for participants to review prior to each call.

The CCCR group reviewed the assembled documents and attempted to reach consensus regarding causality and recommendations for further immunizations. For some cases, the group determined that additional expert opinion or more patient information was needed; these cases were discussed again after this information was obtained.

Causality Assessment

WHO causality guidelines were published in 2000 [18] (Table 1), but these were previously modified by CISA investigators to more appropriately address AEFI by including supporting evidence of a causal association and expanding the criteria regarding biological plausibility and likelihood of other known causes for the event. The original and modified WHO causality criteria are presented in Table 1 [18, 24].

Recommendations

The recommendations of the working group were summarized in written correspondence to the consulting party. Causality assessment and the recommendations regarding future vaccinations were included.

Follow-up Survey

During the summer of 2010, each site sent standardized letters and a brief survey to the providers who had consulted the CCCR to obtain feedback regarding outcomes of the patients discussed, to assess whether the recommendations for future immunizations were followed, and to determine whether the review and recommendations by the CCCR were

helpful. Three weeks were allowed to receive responses by mail, phone or electronic mail. If no response was received, two more attempts were made to contact parties by telephone.

Illustrative cases

Case 1

A 10 month old female infant developed status epilepticus 18 hours after concomitantly receiving her third dose of the combination diphtheria and tetanus toxoid, acellular pertussis (DTaP), recombinant hepatitis B (Hep B), and inactivated poliovirus (IPV) vaccine, and a separate injection of seven-valent pneumococcal conjugate vaccine. She was previously healthy with the exception of a one week history of mild cough and rhinorrhea prior to vaccination. Her family history was positive in that her father had childhood febrile seizures. At the vaccination visit she had a normal physical exam, was afebrile and playful. Approximately 18 hours later she developed generalized tonic-clonic seizures. She was taken to the emergency department by ambulance where she was found to be febrile to 101.3 F and continued to have seizures, resulting in intubation and admission to the pediatric intensive care unit (PICU). Upon PICU admission, the child was hypertonic and hyperreflexic with no focal findings. Otherwise the physical exam was normal. She was treated with anticonvulsants, acyclovir, and ceftriaxone and stabilized rapidly.

Laboratory evaluation included a normal complete blood count, metabolic panel, and cerebrospinal fluid (CSF) analysis. Blood, urine and CSF bacterial cultures were negative. She had a normal head MRI and CT scan, negative pertussis direct fluorescent antibody and culture, and negative fluorescent antibody test for adenovirus, RSV, and influenza. Serology was negative for arboviruses, EBV, and mycoplasma. CSF was negative for HSV and enterovirus by polymerase chain reaction.

A search of VAERS revealed reports of febrile seizures following routine administration of the combination vaccine (DTaP-IPV-HepB) and pneumococcal conjugate vaccine, and reports in the literature also supported this association [26]. When this case was reviewed in January of 2006, the CCCR working group assessed this case as probably causally related to the vaccines due the following details: the vaccine was administered before the adverse event, the temporal relationship was compatible with a known biological mechanism, there was some evidence in the literature for a causal relationship, and other known causes were excluded or unlikely. The working group suggested (1) the use of prophylactic antipyretics following future vaccinations given the severity of her febrile reaction and evidence that prophylactic antipyretics may decrease febrile reactions[27], even though this may not reduce the risk of recurrent febrile seizure, and (2) administering the next scheduled vaccines separately to more clearly identify the causal vaccine if a similar event were to occur again [28]. The group also recommended that the provider offer education regarding febrile seizures and how this type of seizure may result from multiple causes other than vaccines.

Subsequent to the CCCR discussion, a large study reported no association between acellular pertussis vaccine receipt and an increased risk of seizure, even when administered concurrently with other vaccines. Thus, if this case were reviewed by our experts at a later

date, the causal assessment may have been different. This case demonstrates the difficulty of causality assessment and the importance of expert evaluations of AEFI who can apply the most current evidence of association for these reviews.

Case 2

A 4 year old male with a previous history of mild allergic rhinitis developed a very large local reaction of the left upper arm within 6 hours following the fifth DTaP vaccine and first hepatitis A (Hep A) vaccine in that arm, and the second measles, mumps and rubella vaccine (MMR) in his right arm. The next day, a physician diagnosed left arm cellulitis and treated with cefprozil. The following day, another provider reevaluated him and discontinued the antibiotics. The localized swelling reaction lasted approximately 5 days, and thereafter the child began experiencing intermittent painful wheal and flare eruptions in the same area of the left arm. At his next scheduled vaccine visit, the provider elected to give boosters of Hep A and IPV in the right arm only. Within 6 hours, he again developed a large local reaction in the same area of the left arm, despite having not received any vaccines there. This reaction was larger and more painful than the initial one and lasted 1-2 days. Afterwards, he continued to have wheal and flare eruptions in the left arm 1-2 times per month, usually when he was overheated or exposed to the sun. At the time of the CCCR consult, the patient was 12 years of age and had received varicella vaccine without incident, but his parents were hesitant to agree to the tetanus, diphtheria, and acellular pertussis (Tdap) booster and the meningococcal conjugate vaccine. Family history revealed that the patient's sister had experienced very similar reactions following vaccines, including intermittent painful eruptions at the site of initial large local reactions.

The provider had diagnosed this condition as recall urticaria. However, during the CCCR evaluation, a pediatric allergist/immunologist suggested that the reaction was more consistent with a fixed-drug reaction to alum, a common adjuvant used in the vaccines given prior to the initial reactions in both siblings[29]. The working group recommended intradermal testing with aluminum and evaluation of the child's antibody levels to the target diseases to determine if additional doses were needed. Intradermal testing with meningococcal vaccine and Tdap and use of topical steroids in the event of a recurrence was also recommended. Finally the group reassured the primary care physician that a severe, immediate anaphylactic type reaction was unlikely with further vaccination. Although fixed-drug reactions to substances other than vaccines were reported in the literature [30], there were no reports of a fixed-drug reaction or recall urticaria related to alum or the specific vaccines administered. Therefore, in accordance with the criteria for causality used by the working group, this AEFI was assessed as most likely a fixed drug reaction that was possibly causally related to the vaccination because the vaccine was given prior to the event, the medical literature did not establish or refute a causal relationship, and other known causes of the event that were more likely were excluded. This case demonstrates the value of including subject matter experts in the review of complex AEFI.

Results

Demographics and Characteristics of Case Population

From April 14, 2004 until December 31, 2009, 76 AEFI were reviewed on 68 CCCR calls. One patient experienced two separate and different adverse events after two different immunizations and both were evaluated separately. The age of patients ranged from 2 days to 85 years with 52.6% female. (Table 2)

A past medical history was available in 71 of 76 cases (93.4%). (Table 2) Of these 71, 27 were previously healthy and the other 44 had current or chronic medical conditions, or were receiving relevant treatments for chronic illnesses. Geographically, 12 states were represented with 30 cases from Tennessee, 19 from California, 8 from New York, 4 from Maryland, 3 from Colorado, 2 each from Pennsylvania, Florida, and Georgia, and one each from Michigan, Ohio, Arkansas, South Carolina, Utah and Texas. There was one case where the geographical location of the patient was unknown.

Description of Case Data Collected

The primary organ system involved with the AEFI was determined. The neurological system was the most commonly affected organ system among these cases and represented a broad range of diagnoses, including transverse myelitis, meningitis, Bell's Palsy, and seizures. (Table 3) Other organ systems included 11 multisystem, 11 dermatologic, 6 hematologic, 5 musculoskeletal, 3 cardiac, 2 gastrointestinal, 2 psychiatric and one each endocrine, lymphatic, and vascular. The reviewed AEFI were associated with all routinely recommended vaccines. (Table 3) In 50% of cases reviewed, multiple vaccines were given simultaneously during the vaccine visit prior to the event.

For each AEFI, the working group considered whether another cause for the event could be identified (e.g., concurrent viral illness, current medication with similar adverse event profile). In 41 cases (54.0%) another known or likely cause of the adverse event was identified, in 25 (32.9%) there was no other explanation for the event, and in 10 (13.2%) there was insufficient information to assess other possible causes. VAERS searches identified similar AEFI associated with the specific vaccine(s) in 63 (82.9%) cases and the PubMed literature search resulted in similar AEFI reports with the same vaccine in 38 (50.0%) cases. Two cases did not have sufficient information to allow a specific PubMed search.

Causality Assessment and Recommendations

According to the modified WHO criteria (Table 1), causality was classified as definite in 3 cases (3.9%), probable in 12 cases (15.8%), possible in 16 cases (21.1%), unlikely in 18 cases (23.7%), and unrelated in 10 cases (13.2%). In 17 cases (22.4%), the working group had insufficient information to assess causality. Among 15 cases with definite or probable causality assessments, 2 were related to yellow fever vaccine (viscerotropic disease and multi-system failure) [31-32], 2 were localized abscesses [33], 2 involved systemic febrile and localized swelling reactions [33], and 2 involved infections with a vaccine strain (disseminated varicella and chronic diarrhea due to rotavirus) [34-35]. (Table 4) A case

involving seizures, cerebral edema, and hepatic abnormalities after MMR and hepatitis B-Hib combination vaccine was judged to be probably related to a prolonged febrile seizure [36]. Other cases assessed as probable included neuritis following DTaP and Hep B vaccines [37-38], febrile reaction and myalgia associated with DTaP [39], complex regional pain syndrome following Td vaccine [40], and cerebellar ataxia associated with varicella vaccine [41].

Among the 36 neurologic cases, eight met our criteria for possibly vaccine-related, with an appropriate temporal relationship, the literature did not confirm or refute the causal relationship, and more likely known causes were excluded. (Table 3) For example, one case of transverse myelitis occurred 2 weeks after receipt of DTaP, seven-valent pneumococcal (PCV-7), and Hib vaccines. However, the child also had a prior infection and there was not enough evidence to determine if this infection would be considered a “more likely” cause [42]. Another case of prolonged inconsolable crying following the administration of DTaP was assessed as possibly causally related to vaccine since there is evidence of a causal association between prolonged crying and the pertussis component of the previously recommended DTP vaccine [43], but less evidence of such an association with DTaP [44].

Survey response

Follow up surveys were returned by 30 of 52 (57.7%) providers. Of these, 28 (93.3%) described the service as helpful. Two providers were dissatisfied; one cited too long of a waiting period for recommendations following consultation and the other did not feel they received enough information regarding risk for revaccination. We also asked whether case patients experienced further adverse events after future vaccinations or whether they refused them. Three respondents reported that the subjects planned to forego further immunizations because of the adverse event. Eleven case-patients received additional immunizations without problems, but the specific vaccines administered were not necessarily those associated with the original event. Ten survey responders were uncertain as to whether the patients received additional vaccines and two responded that there was no need for additional vaccines.

Discussion

The primary goal of the CCCR was to create an accessible team of experts to examine AEFI and provide recommendations to the consulting party regarding future immunization risks and the likelihood of causal association between the vaccine and the AEFI. Although we were presented with cases affecting all organ systems, many of the cases were related to the neurological system. (Table 3) The large number of neurological cases likely resulted from selection and reporting bias due to the severity of these cases and previously reported relationships between vaccination and specific neurologic AEFI in the literature [11, 13] [45]. Also, reports of hypersensitivity and Guillian-Barré syndrome were evaluated separately by two other specific CISA working groups

We determined that another cause rather than the vaccination was “possible” in half of the cases referred to the CCCR. However, there was often not enough information to fully evaluate other causes. In half of cases reviewed, multiple vaccines were administered

simultaneously, making it difficult to determine which vaccine might have been associated with the AEFI. Although others have reported that the administration of multiple vaccines simultaneously or in fixed combinations has not been shown to increase AEFI over single administrations, it complicated the evaluation [45-46].

The predominance of children over adults in the CCCR likely reflects the larger number of vaccines children receive in comparison to adults. Our patient population was equally distributed by gender. The majority of AEFI cases lived in states with CISA sites, namely Tennessee, California, New York, and Maryland, suggesting greater awareness of the service in these areas.

Having an expert panel with subspecialty representation, particularly from neurology and allergy/immunology, to distinguish between an underlying disease process and the potential causal association with a vaccine is a beneficial component of the CCCR service [47]. For example, a provider may believe that a given vaccination was likely responsible for a temporally related exacerbation of multiple sclerosis (MS), but input from neurologic consultants could reassure the practitioner that MS exacerbations are common and that multiple studies have not supported their increased risk after vaccination [48]. Also, panel experts can clarify the most likely diagnosis, such as the fixed-drug reaction to aluminum in Case 2 and provide appropriate recommendations regarding future immunization options.

One limitation of the CCCR is that only a limited number of AEFI cases could be reviewed during monthly calls. During the recent H1N1 pandemic, the CCCR effectively responded to an increased demand by scheduling weekly CCCR calls to review AEFI following the H1N1 vaccine. Another potential limitation was that the working group accepted the case diagnoses reported by the providers in most instances. Although specific case definitions for AEFI are available through the Brighton Collaboration [49], most CCCR cases reviewed were not diagnoses with established Brighton definitions. The use of Brighton definitions in other CISA projects has proven helpful and should be considered for future CCCR cases for which a Brighton case definition exists. Also, more Brighton definitions for other common AEFI would be helpful. Additional limitations result from the retrospective nature of this review, including limited information of past medical and family history, variability in specific case data available, and the inability to reach several original consulting providers in preparation for this review. The range of cases presented was also impacted by the limited geographical location of the CISA sites and the limited national awareness of the CCCR service.

The most challenging aspect of this endeavor was and continues to be causality assessment. As clearly demonstrated in Case 1, new studies evaluating vaccine associated adverse events are continually published. Thus, our experts are charged with knowing the most recent data and applying it to their understanding of vaccine safety at the time of the case review. Overall, a significant number of cases did not have sufficient information to assign causality. Such uncertainty could be reduced, however, by more complete case histories and improved access to patient information after the initial referral.

Through our use of the modified WHO criteria for causality assessment, we identified areas where application of the criteria was problematic. The definitions for different levels of causality are often unclear and inconsistent from level to level (e.g. “temporal relationship” versus “timing of onset”). Also, the criteria for causality levels concerning “other known causes” are difficult to interpret and apply, and the criteria for evidential support lack strict definitions for each causality determination (e.g., the difference between “substantial” and “some” evidence). In spite of these limitations, knowledgeable experts in vaccine safety who were participants in the CCCR were able to assess causality based on these criteria. CISA is currently developing a more comprehensive algorithmic approach for evaluating individual cases of AEFI which will address these identified limitations.

Other countries have developed alternative methods for systematic reviews of AEFI. The “Green Channel” in one region of Italy provides a counseling service to a population of 4.5 million. This service allows local health departments to evaluate patients with a history of AEFI prior to vaccination, provides a real time consultation service regarding AEFIs with contact capabilities by telephone, fax, or e-mail, and encompasses a surveillance system similar to what is available in the US through VAERS [50-51]. Another consultation service for providers is available in Switzerland (population approximately 7.7 million). This system is e-mail based, with an “on-call” expert in vaccine safety available to respond to questions and additional access to the entire vaccine safety expert group for comment [52]. Both examples provide services for much smaller populations than the entire U.S. and a similar approach in the U.S. would prove challenging. The CCCR is only one component of an extensive vaccine safety monitoring system which serves the unique role of addressing individual cases of AEFIs, and as evidenced by our review during the H1N1 pandemic, this service could be enhanced to accommodate more cases if needed.

Another potential approach to the evaluation of AEFI would be to establish specific protocols for practitioners to follow such as the recently published CISA guidelines for assessment of patients with possible hypersensitivity reactions [53]. For example, obtaining viral titers and cultures and Lyme disease serology could establish that a recent infection, rather than a recently administered vaccine, was the cause of Bell's palsy. CISA maintains a sample repository and timely collection of specimens may aid in establishing causality, as well as providing biologic samples for future studies designed to further address these questions. Such protocols could include detailed instructions on obtaining specimens, conducting thorough physical examinations, and complete medical history forms, which could then be submitted to the CCCR team for a more comprehensive evaluation. The previously established CDC guidelines to evaluate possible adverse events following smallpox immunization also serves as a model for similar protocols [54].

Given the positive responses from our survey, it does appear that primary care physicians find the CCCR services beneficial. We believe that the CCCR works well in the academic environment, where the review team can call upon subspecialty experts relatively quickly. However, many providers are not aware of this service and as the CCCR becomes more recognized, it is likely that the demand would increase. Although there are no charges to the providers for this service, 3 to 4 hours of coordinator and investigator time were spent in preparing and scheduling the cases, 1 to 2 hours were spent in discussing the cases, and 1 to

2 hours were spent in providing follow up letters to outline the results and recommendations. This activity was supported through CISA funding. We believe that addressing public concerns about immunizations in an easily accessible format through a systematic process facilitates trust in immunization recommendations, adds to the vaccine safety monitoring infrastructure, and provides a forum where complex adverse events following vaccination can be thoroughly evaluated [55].

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Abbreviations

DTaP	diphtheria and tetanus toxoids and acellular pertussis
HepA	hepatitis A
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
IPV	inactivated poliovirus
LAIV	live, attenuated influenza vaccine
MCV4	quadrivalent meningococcal conjugate vaccine
MMR	measles, mumps, and rubella
MMRV	measles, mumps, rubella, and varicella
MPSV4	quadrivalent meningococcal polysaccharide vaccine
PCV	pneumococcal conjugate vaccine
PPSV	pneumococcal polysaccharide vaccine
PRP-OMB	polyribosylribitol phosphate-meningococcal outer membrane protein conjugate
Td	tetanus and diphtheria toxoids
TIV	trivalent inactivated influenza vaccine
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis
Var	varicella vaccine

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Table 1

WHO causality assessment criteria[a] compared with CISA investigator modified criteria[b] used in this report

	CISA Modified Criteria		Original WHO criteria
Definite	The report documents that the vaccine was given before the onset of the signs and symptoms and that the timing of onset was consistent with a known mechanism or published literature; there is substantial existing evidence in the medical literature establishing a causal relationship between vaccine(s) and the event, and other known causes of the event had been excluded.	***Very Likely / Certain***	Clinical event with plausible time relationship to vaccine administration, and which cannot be explained by concurrent disease or other drugs or chemicals
Probable	The report documents that the vaccine was given before the onset of symptoms and that the temporal relationship was consistent with a biologic mechanism or published literature; there is some evidence in the medical literature for a causal relationship between vaccine(s) and the event, and other known causes of the event had been excluded or were unlikely.	***Probable***	Clinical event with a reasonable time relationship to vaccine administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals
Possible	The report documents that the vaccine was given before the onset of symptoms; the medical literature does not establish or refute a causal relationship between vaccine(s) and the event, and known causes that are more likely associated with event had been excluded*.	***Possible***	Clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals
Unlikely	The report documents that the vaccine was given before the onset of symptoms; the medical literature does not establish or refute a causal relationship between vaccine(s) and the event, and there were other known causes of the clinical event that were more likely and/or had not been excluded*.	***Unlikely***	Clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could plausibly be explained by underlying disease or other drugs or chemicals
Unrelated	The onset of the event was prior to vaccine administration; or there is substantial evidence in the medical literature that the vaccine does not cause the event; or there was a co-existing disease/condition, drug, or vaccine that caused the event; or the temporal relationship between vaccination and the event was not consistent with the biological onset of clinical event.	***Unrelated***	Clinical event with an incompatible time relationship to vaccine administration, and which could be explained by underlying disease or other drugs or chemicals.

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Table 2

Demographics and Characteristics of 76 Cases Reviewed, CISA Clinical Case Review, 2004-2009

Age	
Range (IQR)	2 days – 85 years (1.3 - 26)
< 18 yr, n (%)	49 (64.5%)
> = 18 yr, n (%)	27 (35.5%)
Female	40 (52.6%)
Current or chronic medical condition[a]	
Yes	44 (57.9%)
No	27 (35.5%)
Underlying known medical conditions[b]	
Atopy (asthma +/− eczema +/− allergic rhinitis +/− food allergy)	13 (17.1%)
Immune abnormality (SCID[c], cancer, Kawasaki disease, congenital neutropenia, pregnancy)	6 (7.9%)
Autoimmune disorders (psoriasis, thyroid disorder, Sjogren's syndrome)	4 (5.3%)
Previous similar reaction or event	3 (4.0%)
Multiple medical problems	9 (11.8%)
Known medical history that could be causal (i.e., specific medicine associated with event, acute worsening of previous condition)	13 (17.1%)

[a] Data on past medical history available from 71 (93.4%) cases

[b] categories are not mutually exclusive

[c] Severe Combined Immunodefiency

Table 3

Characteristics of 35 Cases with Neurological Events Reported After Immunization, CCCR 2004-2009.

Age (yrs)	Diagnosis[a]	Time interval from vaccination to symptoms (days)	Vaccine(s)	Past medical history	Causality
0.5	Brachial neuritis	7	DTaP	Healthy	Probable
0.8	Status epilepticus	0.75	HepB, IPV, DTaP (given in fixed combination), PCV-7	Healthy	Probable
1.5	Cerebellar ataxia	9	DTaP, Hib, HepB, MMR, Var	Healthy	Probable
16	Periodic myalgia	0.5	DTaP, HepB, IPV, Var	Asthma	Probable
29	Neuritis	29	HepB	Unknown	Probable
0.1	Inconsolable crying	<1	HepB, IPV, DTaP, PCV-7, Hib	Healthy	Possible
0.3	Bulging fontanelle, fussy	0.3	Hib, DTaP, HepB, IPV, PCV-7, Rotavirus	Healthy	Possible
0.6	Transverse myelitis	14	DTaP, PCV-7, Hib	Healthy	Possible
12	CIDP[c]	<21	MCV4, HepA TdaP	Healthy	Possible
13	Transverse Myelitis	18	Var, HepA	Seasonal allergies, asthma, eczema	Possible
39	Meningitis/ Meningoencephalitis	2	LAIV	Concurrent URI	Possible
54	Facial diplegia	7	TIV	Elevated cholesterol, HTN, shrimp allergy	Possible
74	Acute polyneuropathy	1	PPSV, TIV	Chronic proctitis	Possible
9	Generalized seizure	2	LAIV	Seasonal allergies	Unlikely
14	Meningitis	7	MCV4	Concussion	Unlikely
14	Primary muscular atrophy vs autoimmune polyneuropathy	90	HPV	Delayed early gross motor	Unlikely
15	Intracerebral vessel inflammation	10	HepA, MCV4	Exercise induced asthma, h/o trauma to orbit	Unlikely
18	Pseudotumor cerebri exacerbation	30	HPV	Pseudotumor cerebri, scoliosis	Unlikely
21	Amyotrophic Lateral Sclerosis vs. Pharyngeal-Cervical Brachial variant GBS	270	HPV	Developmental delay motor, hypothyroidism, h/o purpura fulminans with varicella	Unlikely
36	Temporal lobe epilepsy	11	MMR	Healthy	Unlikely
57	GBS	44	HepA, HepB, Td, TYP, YF	Healthy	Unlikely
61	Exacerbation of idiopathic inflammatory disease of CNS	10	TIV	Unknown	Unlikely
64	Encephalitis vs ADEM[c]	3	TdaP	Smoker, high cholesterol	Unlikely
1.2	Pallid infant syncope	6	MMR	Kawasaki in future	Unrelated
16	Aseptic meningitis	0.75	MCV4, TdaP, HepA	“allergies”	Unrelated
17	Aseptic meningitis	< 30	MCV4, TdaP, HepA	Healthy	Unrelated

Age (yrs)	Diagnosis[a]	Time interval from vaccination to symptoms (days)	Vaccine(s)	Past medical history	Causality
17	Mental status change	1	HPV, MCV4	Healthy	Unrelated
18	Chronic fatigue syndrome	18	RBV	Lyme disease, future dx of hashimoto's	Unrelated
0.5	ADEM[b]	5	DTaP, IPV, HepB (given in fixed combination), Hib, PCV-7, Rotavirus	Concurrent febrile illness	Insufficient information
26	Bell's palsy	Unknown	HPV	Healthy	Insufficient information
Mid-40s	Neuromuscular weakness	1	TIV	Healthy	Insufficient information
67	Myelopathy	35	PPV	Previous lesion on MRI	Insufficient Information
63	Bell's palsy	1	Td, HepA, HepB, YF	Unknown	Insufficient information
77	Encephalitis/aseptic meningitis/vitritis/retinitis	>60	YF	Unknown	Insufficient information
85	Bell's Palsy vs Ramsay Hunt syndrome	21	Zos	MI	Insufficient information

[a]The CCCR accepted the diagnoses as given to us by providers and made no effort to independently verify the diagnoses.

[b]Acute Demyelinating Encephalomyelopathy

[c]Chronic Inflammatory Demyelinating Polyneuropathy

Table 4

Characteristics of 15 Cases with Causality Assessments of “Definite” or “Probable”, CISA Clinical Case Review, 2004-2009

Age	Vaccine(s)	Diagnosis	Time Interval	Past Medical History	Causality
4 mo.	Rotavirus[b]	Rotavirus positive (confirmed vaccine strain) chronic diarrhea[†]	90 days	later dxwith SCID[ab]	Definite
1 yr.	MMR, Var[b], Hep B, PCV-7	Disseminated varicella[b]	23 days	reactive airway disease, prolonged hospitalization with pneumonia, dx with SCID[ab] after this illness	Definite
22 yr.	YF[b], Typ, Hep A, Td	Yellow Fever Viscerotropic Disease[b]	1 day	Asthma	Definite
16 yr.	DTaP[b], Hep B, IPV, Var	Periodic myalgia[b]	< 1 day	Asthma	Probable[c]
4 mo.	IPV, DTaP, PCV-7, Hib/Hep B	Abscess,sterile	21 days	None	Probable
6 mo.	Hep B, IPV, PCV-7	Abscess, pyogenic	7 days	Eczema	Probable
6 mo.	DTaP[b]	Brachial neuritis[b]	7 days	None	Probable
10 mo.	Hep B, IPV, DTaP[b] (combination) and PCV-7	Febrile seizure[b], status epilepticus	< 1 day	None	Probable
1 yr.	MMRV[b], HepB-Hib	Seizure[b], cerebral edema, liver and endocrine instability	8 days	Unknown	Probable
1.5 yr	DTaP, Hib, Hep B, MMR, Var[b]	Cerebellar ataxia[b]	9 days	None	Probable
29 yr.	Hep B[b]	Neuritis[b]	< 1 day	Unknown	Probable
36 yr.	Td[b]	ComplexRegional Pain Syndrome[b]	< 1 day	Obesity	Probable
67 yr.	TIV[b], Zos	Febrile illness[b], Local reaction	< 1 day	Sjogren's	Probable
70 yr.	TIV[b], Zos	Febrile illness[b], local reaction	< 1 day	None	Probable
77 yr.	YF[b], Tdap, TIV	Multisystem organ failure[b]	5 days	Factor V Leiden deficiency, hyperlipidemia, diabetes, obesity, hypertension	Probable

[a]Severe Combined Immunodeficiency

[b]Denotes a documented association between the vaccine and the adverse event (see text for explanations of unfootnoted associations). [34-35, 56-59] [33, 38-39, 41, 43, 60]

[c]Causality assessment for first occurrence only.