Vaccine 30 (2012) 7253–7259

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Causality assessment of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS)

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ARTICLE INFO

Article history:
Received 11 April 2012
Received in revised form
26 September 2012
Accepted 29 September 2012
Available online 9 October 2012

Keywords:
Causality
Vaccine safety
VAERS

ABSTRACT

Adverse events following immunization (AEFI) reported to the national Vaccine Adverse Event Reporting System (VAERS) represent true causally related events, as well as events that are temporally, but not necessarily causally related to vaccine.

Objective: We sought to determine if the causal relationships between the vaccine and the AEFI reported to VAERS could be assessed through expert review.

Design: A stratified random sample of 100 VAERS reports received in 2004 contained 13 fatal cases, 19 cases with non-fatal disabilities, 39 other serious non-fatal cases and 29 non-serious cases. Experts knowledgeable about vaccines and clinical outcomes, reviewed each VAERS report and available medical records.

Main outcome measures: Modified World Health Organization criteria were used to classify the causal relationship between vaccines and AEFI as definite, probable, possible, unlikely or unrelated. Five independent reviewers evaluated each report. If they did not reach a majority agreement on causality after initial review, the report was discussed on a telephone conference to achieve agreement.

Results: 108 AEFIs were identified in the selected 100 VAERS reports. After initial review majority agreement was achieved for 83% of the AEFI and 17% required further discussion. In the end, only 3 (3%) of the AEFI were classified as definitely causally related to vaccine received. Of the remaining AEFI 22 (20%) were classified as probably and 22 (20%) were classified as possibly related to vaccine received; a majority (53%) were classified as either unlikely or unrelated to a vaccine received.

Conclusions: Using VAERS reports and additional documentation, causality could be assessed by expert review in the majority of VAERS reports. Assessment of VAERS reports identified that causality was thought to be probable or definite in less than one quarter of reports, and these were dominated by local reactions, allergic reactions, or symptoms known to be associated with the vaccine administered.

Adverse events following immunization (AEFI) may occur by chance or may be causally related to the vaccine; distinguishing the two is challenging. To determine whether the AEFI is causally related to the vaccine, two questions arise. First, *can* the vaccine cause the AEFI? Second, *did* the vaccine cause the AEFI in this instance? The answer to the first question is based on the strength of the available scientific evidence supporting a causal relationship. This evidence is assessed using established principles: establishment of a temporal relationship, examination of biologic plausibility, quality of research producing this evidence, strength of the association between the vaccine and the AEFI, consistency of this association, specificity of the association, and coherence of the evidence [1,2]. In the United States, the Institute of Medicine (IOM) has periodically assessed the strength of evidence for the assessment of causality between vaccines and AEFIs [3–11]. The second question is answered by examining the facts of the individual case, including an assessment of the timing and nature of the AEFI and

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http://dx.doi.org/10.1016/j.vaccine.2012.09.074

by identifying if other illness or health event may have cause the adverse event.

In the United States, the Vaccine Adverse Event Reporting System (VAERS) is the largest database of AEFI reports. VAERS receives approximately 28,000 reports annually of AEFI following receipt of a licensed vaccine in the United States [12–14]. The role of VAERS is to detect unexpected or unusual patterns of AEFI, especially rare AEFI unlikely to be recognized in pre-licensure clinical trials [15,16]. Sometimes a VAERS signal suggests an association between a vaccine and an AEFI, but subsequent studies using additional data do not corroborate the initial signal [17–19].

As a passive reporting system, VAERS is limited by underreporting, variable data quality, the absence of defined diagnostic criteria, absent denominator information, and reporter bias [14]. Although VAERS is not designed to assess whether a vaccine caused an AEFI, expert review of VAERS reports and, when available, associated medical records, may provide the information necessary to assess the causal association between a vaccine and AEFI in an individual vaccinee. The Clinical Immunization Safety Assessment network (CISA), a collaboration between Centers for Disease Control and Prevention (CDC) and six academic sites [20], has recently assessed the causality of reports after influenza vaccines [21,22].

In 1994, a Canadian Advisory Committee on Causality Assessment reviewed individual AEFI following vaccines using a World Health Organization (WHO) structured causality assessment with six causality classifications – very likely/certain, probable, possible, unlikely, unrelated and unclassifiable [23,24]. We modified these WHO criteria making them suitable for the review of historical VAERS reports [25]. Our study's goals were to review a sample of VAERS reports, using a structured adjudication approach, and to determine the extent to which causal relationships between the vaccine and the AEFI could be classified.

1. Methods and materials

A panel of 10 CISA physician investigators with expertise in vaccinology and the evaluation of AEFI were enlisted to review VAERS reports. Prior to the start of the study, the reviewers were trained and the instruments were pilot tested and revised as necessary.

1.1. Sample selection

A study investigator selected a blocked, stratified random sample of 200 reports from the 15,722 publically accessible reports received by VAERS during 2004 [26]. The sample was stratified to over-sample serious reports (75%) including those reporting deaths and permanent disability; the remaining 25% of the sample was comprised of non-serious reports. Reports to VAERS are classified as serious based the code of federal regulation and include reports of death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [27]. Routinely, VAERS staff request additional records for serious non-manufacturer reports and VAERS medical officers review all serious reports and associated documentation. The principal investigator obtained electronic images of the selected VAERS reports from the CDC. Research staff at Boston Medical Center redacted the reports and indexed the supplemental documents. Supplemental documents such as medical records, laboratory reports, discharge summaries and autopsy reports, if available, were included with the reports for review. No panel member provided care for any case reviewed. We did not seek additional information.

In the order they were selected, two hundred redacted VAERS reports were distributed to the CISA panel for review. The first 100 reports were reviewed prior to an interim analysis. Five of the 100 reports were excluded; one was a duplicate record, 2 were illegible electronic reports, and 2 were reports that did not match the report selected from the public access database. The excluded reports included 1 non-fatal serious, 1 death, 2 disability, and 1 non-serious event. These reports were replaced by the next 5 randomly selected reports that included 3 non-fatal serious reports, 1 death report and 1 report of disability. The findings of the interim analysis met the aims of the study. The investigators agreed that enough data had been gathered to summarize the evidence for causal association in VAERS reports, and the case review was stopped.

1.2. Causality evaluation

Each VAERS report was assigned to 5 reviewers. Unless documentation supported a different diagnosis, reviewers were instructed to accept the diagnosis of the adverse event described in the VAERS report. However, if documentation supported a diagnosis other than the one listed on the VAERS reports, the reviewer could list the diagnosis that was supported by the evidence. Reviewers completed their causality assessment independently. The assessment form (see Appendix) prompted the reviewer to (1) identify the adverse event; (2) evaluate the adequacy of the information in the VAERS report and medical records for assessing causality; (3) examine evidence of reoccurrence of the adverse event with re-challenge; (4) examine available evidence for causes for the adverse event other than the vaccine; (5) document the temporal relationship between vaccination and the adverse event; and (6) review the medical literature for supportive evidence for a causal relationship between the vaccine(s) and the AEFI. The form listed each vaccine received and their components separately and prompted the reviewers to state if there was a known causal relationship between vaccine and the adverse event reported in the literature and/or if there was a plausible biological mechanism indicative of a causal relationship between vaccine and adverse event. Lastly, the reviewers were instructed to classify the causal association between vaccines received and the AEFI, using the modified WHO criteria. The causality classification was not vaccine specific. It documents a relationship between AEFI and any of the vaccines an individual received. The reviewers entered their findings into a web-based, data-entry tool. Data were stored and analyzed at Boston Medical Center.

1.3. Causality criteria definitions

Definitions for causality assessment were modeled after the Canadian Advisory on Causality Assessment, also known as the WHO causality criteria [23,24]. For this review, the WHO criteria were modified slightly (Table 1). The tenor of the definitions stayed the same; both criteria required that the temporal relationship between vaccine and AEFI be established and that the AEFI could not be explained by concurrent disease or drug. The modified criteria asked the reviewer to determine if the temporal relationship was consistent with a biological mechanism and to consider the strength of evidence in the medical literature previously demonstrating a causal relationship between vaccine and the AEFI; making these criteria more conservative.

1.4. Agreement scores

The causality classification was assigned by majority agreement. Agreement scores ranged from 5, indicating that five of five reviewers classified the report the same way; to 1, indicating that none of the five reviewers agreed. A score of 3 (3 of 5 reviewers agreed on the same classification) or above met the criteria for a majority.

Table 1
The modified WHO causality criteria definitions used in VAERS case review.

1. Definite: The report clearly states that the vaccine was given before the onset of the signs and symptoms and the temporal relationship is consistent with known biological mechanism or published literature; and there is substantial prior evidence[a] in the medical literature establishing a causal relationship between the vaccine and the event; and other known causes of the event have been excluded
2. Probable: The report clearly states that the vaccine was given before the onset of signs and symptoms and that the temporal relationship is consistent with a biologic mechanism and/or evidence in the literature; and there is some evidence in the medical literature for a causal relationship between the vaccine and the event; and other known causes of the event had been excluded or are unlikely
3. Possible: The report documents that the vaccine was given before the onset of signs and symptoms; and the medical literature does not establish or refute a causal relationship between the vaccine and the event; and known causes that are more likely associated with event had been excluded
4. Unlikely: The report clearly states that the vaccine was given before the onset of signs and symptoms; and the medical literature does not establish or refute a causal relationship between the vaccine and the event; and there were other known causes of the event that were more likely and have not been excluded
5. 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 is 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 mechanism of clinical syndrome (event), for example a hypersensitivity reaction after a prolonged interval since vaccine administration

[a] Substantial prior evidence for a causal association meant that the association between vaccine and the AEFI had been reported in the medical literature from comparative studies that assess features such as the strength, consistency, and specificity of the association; and the temporal relationship, biologic plausibility, and coherence of the evidence.

1.5. Resolving discrepancies

Reviewers' classifications were tabulated and reports with agreement scores less than 3 were discussed on conference calls. Goals of these discussions were to (1) reach agreement on the diagnosis, if necessary, (2) discuss pathogenesis and clinical documentation of each adverse event, (3) share relevant findings from literature, (4) discuss the biological plausibility of any vaccine–adverse event relationship in the individual case and (5) facilitate reviewers coming to agreement about the causality classification.

1.6. Analysis methods

A description of the 100 reports reviewed included frequency of reports by age and gender, severity and type of AEFI, vaccine formulations, interval between immunization and onset of adverse event, and length of the report. The primary analysis was to determine the distribution of causal classifications and the frequency of agreement scores for each causal assessment. The frequency of causal classification and agreement score are reported for both the initial reviews and for all reports after discrepancies were resolved.

1.7. Human subject review

The study was reviewed and exempted by the Boston Medical Center's institutional review board (IRB). As subcontractors to the CDC, CISA investigators have all signed an assurance of confidentiality, assuring the protection of participants' privacy.

2. Results

The 100 VAERS reports described 13 deaths, 19 permanent disabilities, 39 other serious reports, and 29 non-serious reports (Table 2). Forty-seven reports included only the VAERS form, while 53 provided supplemental documents. Consistent with VAERS procedures, additional medical records were not available for the 29 non-serious reports. Of the 53 reports with supplemental documents, 34 included a medical record section, 26 included a hospital admission note, 12 had a specialist consult, 30 had laboratory results and 20 had imaging studies related to the AEFI evaluation. Among the 13 deaths, 6 had an autopsy report, and 3 had death certificates. Only 5 of 100 reports contained patients' lifetime immunization history.

Of the 100 reports, 57 AEFI had onset within 1 week of vaccination, 10 occurred 2–8 weeks after vaccination, and 16 occurred more than 8 weeks after vaccination (Table 3). For 20 reports, the interval between immunization and adverse event could not be calculated, yet for 5 of these the timing could be inferred from details in the report. Four of the remaining 15 reports indicated a vaccine failure, and timing of vaccine administration and onset of illness were not explicit. Eleven of 15 were accounts of illnesses that occurred 4 or more years after the last documented immunizations. Demographic characteristics of cases and description of number of antigenic components in vaccines received are summarized in Table 3.

VAERS reports have a space for the reporter to enter one or more AEFI. The reviewers sometimes specified the AEFI differently, or identified other signs and symptoms that were considered separate AEFI. Therefore, one report could have more than one AEFI, and the causality of each AEFI was considered separately. The reviewers identified 108 distinct AEFI in the 100 VAERS reports. One hundred three of the 108 AEFI following vaccine could be assessed after initial review; 90 (87%) yielded a majority agreement, a score of 3 or above (Fig. 1). Full agreement was achieved for 7 of these events. Of these 7, one adverse event was deemed probably causal, and 6 were classified as unrelated to vaccine. Initially, no majority was reached in 18 (17%) AEFI. Of these, 13 required discussion to resolve the discrepancy. Five AEFI were not specified by all 5 reviewers; each of these AEFI was presented to the panel before classification could be assigned (see Fig. 1).

Of the 90 with majority consensus after initial reviews, 7 (8%) were unanimous, 58 (64%) had responses that spanned 2 contiguous categories (e.g., probable-possible or unlikely-unrelated), 17 (19%) had responses that spanned 3 contiguous categories, and 8 (9%) had responses that spanned 4 or more categories. The classifications were more disparate for the 13 AEFI where no majority was achieved initially. Of these, 7 (54%) had classification that spanned 3 contiguous categories (4 of 7 were in the same direction, e.g., definite–probable–possible) and 6 had classifications that spanned 4 or more categories.

Before discussion, only one AEFI was classified as definitely caused by vaccine. After the resolution of all 108 AEFI, two additional AEFI were classified as definitely causal. These three events included one serious report (anaphylaxis), one disability report (pain and stiffness of injected arm), and one non-serious report (localized injection site reaction). The 22 AEFI deemed probably-related included 10 non-fatal serious events, 1 death, 1 disabling event and 10 non-serious events; these involved 12 injection site reactions, 6 hypersensitivity reactions, one pneumonitis, one thrombocytopenia, one viral-like illness, and one screaming episode. The case of pneumonitis with subsequent death mentioned previously involved a 14-month-old child with an immunodeficiency who had received MMR and varicella vaccine. Three (3%) of all 108 AEFI were considered to be unclassifiable by a majority, including 2 non-serious and 1 disabling AEFI. Overall, 47 of the 108 AEFI were classified as possibly related (20%), probably related (20%), or definitely related (3%) to vaccination, and 58 AEFI were deemed either unlikely related (20%) or unrelated (33%) to vaccination (Fig. 1).

Table 2
Description of VAERS cases by severity category.

Serious status of report[a]	Number of reports (total = 100)	108 AEFI identified in the 100 reports[b]	
Death	13	5 sudden infant deaths	
		2 cardiopulmonary arrest	1 lung cancer
		1 hemolytic-uremic syndrome	2 pneumonia/pneumonitis
		1 liver inflammation with sepsis	1 seizure
Serious resulting in permanent disability	19	6 autism	
		4 Lyme disease with arthritis	1 Grave's disease
		4 arthritis/joint pain and/or arthralgia with paresthesia	1 Henoch-Schonlein purpura
		3 injection site reactions	1 neurodevelopmental injury
		1 chest pain	1 transverse myelitis
		1 depression	1 viral like illness
Other serious (not fatal or resulting in permanent disability)	39	8 seizures and 2 possible seizures	
		6 injection site reactions	1 premature ventricular contractions and palpitations
		5 immune-mediated or hypersensitivity reactions[c]	1 pallor and weakness
		4 vaccine failures	1 respiratory syncytial virus infection
		3 pneumonia	1 transverse myelitis
		2 Guillain-Barré Syndrome	1 Methicillin-resistant *Staphylococcus aureus* sepsis
		2 thrombocytopenia	1 coronary artery disease
		1 fever with leukocytosis	
		1 systemic lupus erythematosis	
Non-serious reports	29	11 immune mediated or hypersensitivity reactions[c]	3 Influenza-like symptoms
		8 injection site reactions	1 "feeling weird"
		5 vaccine failures	1 fussiness
			1 lethargy/fever/headache
			1 screaming episode

[a] Serious status was assigned by VAERS. Reports to VAERS are classified as serious based the code of federal regulation and include reports of death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability. For this review and for report selection the investigators classified serious reports into 3 groups: death, serious resulting in permanent disability or other serious reports. Non-serious AEFI included all other AEFI.

[b] Some VAERS reports had more than one adverse event either reported or identified by reviewer. The 108 AEFI identified are listed in Table 2. These were 3 reports with disabling events: (1) depression and arthritis; (2) an injection site reaction (swelling in shoulder) and arthralgia with paresthesia; and (3) chest pain, viral like illness and Grave's disease. There was one "other serious" report having lupus erythematosis and pneumonia. There were two non-serious reports: (1) rash, lip-face swelling; and (2) bruising and depersonalization "feeling weird".

[c] Immune mediated or hypersensitivity reactions include anaphylaxis, angioedema, urticaria, and skin eruptions judged to be probable hypersensitivity.

3. Discussion

Using a structured adjudication process, we found that causality could be classified in the majority (97%) of VAERS reports; most were classified unrelated or unlikely to be related to vaccine(s). An AEFI was classified as definitely caused by vaccine in 3% of the reports only. Forty percent of the AEFI reported were deemed probably or possibly caused by vaccine. Despite the overall inability to classify an event as having a definite causal association with vaccine(s), we found that a majority did agree on a causal classification, with 83% agreement after initial independent review without further discussion.

VAERS reports have variable data quality and may contain clinical information that is incomplete or cannot be validated [14,17]. VAERS data are intended to be used to generate hypotheses regarding vaccine exposure and clinical outcomes, and generally cannot address the question: "can a vaccine cause an adverse event?" However, when an AEFI is reported to VAERS that has a known causal relationship to that vaccine, for example thrombocytopenia after Measles–Mumps–Rubella vaccine [28], then causality can more often be assigned, answering the question: "did the vaccine cause the AEFI in this particular case?"

There is no "gold standard" for determining causality. We chose to replicate a process used to assess AEFI in clinical trials, and that was used in the 1994 Canadian Advisory Committee on Causality Assessment [23,24,29]. As in the Canadian assessment, causality classification was assigned by a majority agreement. In the Canadian assessment only a small proportion of the serious or unusual events were deemed very likely related (8.7%) or probably (8.7%) related to immunization. A moderate proportion of their AEFI (16%) were considered possibly related, and 41% of events were considered unlikely related or unrelated to immunization [23]. Recently, Rosenberg et al. used modified WHO criteria to assess 104 serious AEFI following trivalent inactivated influenza vaccine (TIV) in children 6–23 months of age [21]. Causality was classified by two independent reviewers and discrepancies were adjudicated by the third member of the research team. The authors reported high agreement, 92%, after initial review and complete concurrence after discussion. This is expected given only 2 reviewers assessed reports, and a single vaccine for a specific age group was considered. In that study, no reports were deemed definitely caused by vaccine, while seven (6.7%) and 54 (51.2%) were considered probably or possibly associated with vaccine, respectively [27]. In our study, even after refining the causality criteria in advance and completing several practice reviews, the panel found that causality assessments of VAERS reports was challenging. However, both the concordance of responses across causality classifications for individual AEFI and the proportion of times a majority agreed on classification after initial review were reassuring.

There are several limitations to consider when interpreting these results. First, there is a paucity of scientific literature to establish or refute causal relationships for many AEFI. In our assessment, this lack of evidence provided a rationale for classifying an AEFI as unlikely related to the vaccine. When scientific evidence is lacking, the causality classification is less certain. The classification of an individual event could change, if more research became available to prove or disprove a causal relationship. The second limitation is the stipulation that the diagnosis of the AEFI as reported on the

Figure 1. The causality assessment of the 108 distinct adverse events following immunization (AEFI) identified in the 100 randomly selected VAERS reports.

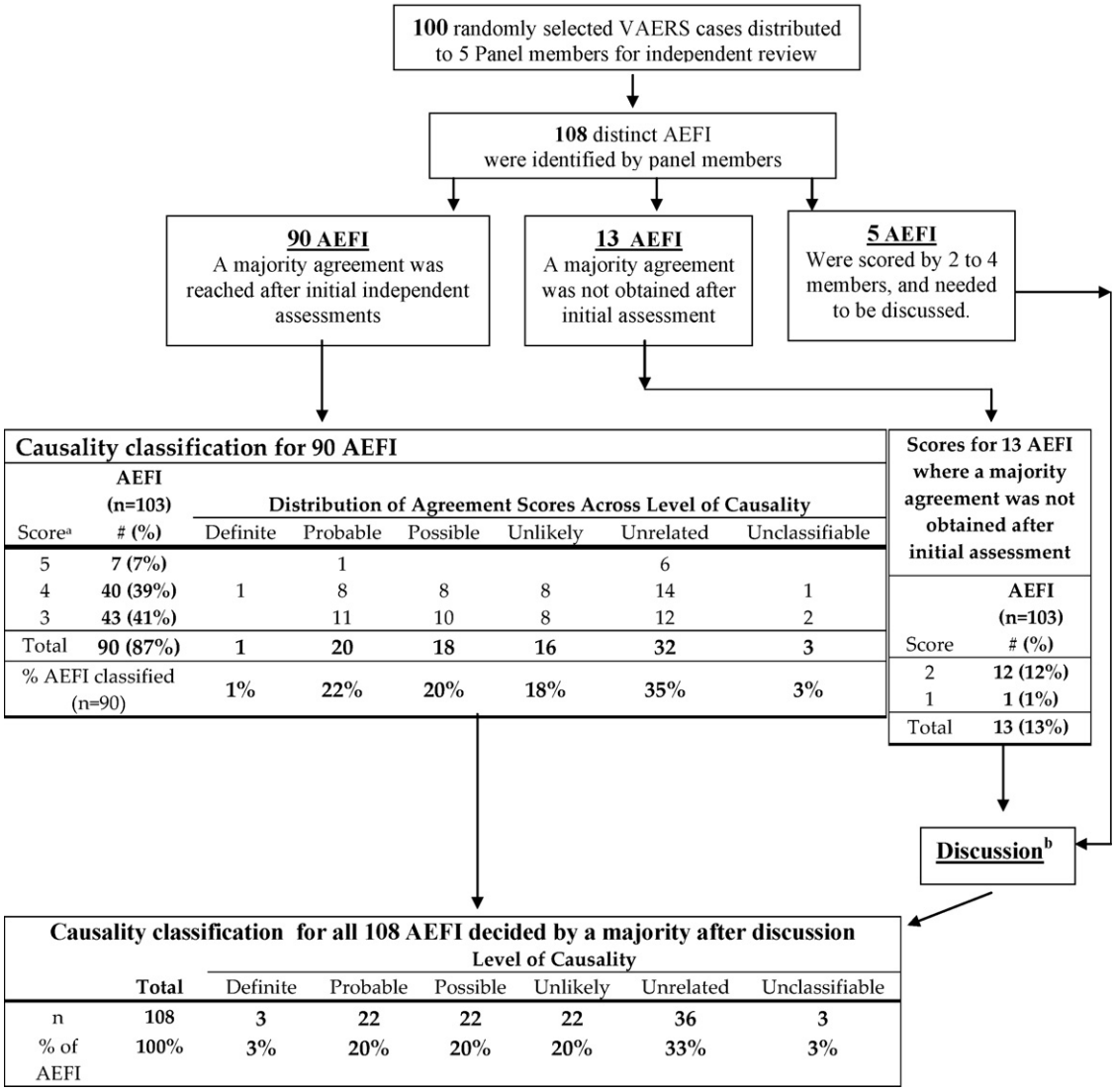

Fig. 1. The causality assessment of the 108 distinct adverse events following immunization (AEFI) identified in the 100 randomly selected VAERS reports. [a]*Score*: 5 means all five reviewers classified the report the same way; 4 means four of five reviewers classified the report the same way, and one of five classified the case differently; 3 means three of five reviewers classified the report the same way; 2 means two of five reviewers classified the report the same way; and 1 means all reviewers had different classifications. A score of 3 or above met the criteria for a majority. [b]*Discussion*: The 18 reports that required discussion included 13 (73%) serious reports and 5 (27%) non-serious reports reflective of the distribution of the cases reflected.

VAERS form be accepted unless there was evidence against raised some problems, yet this stipulation led to the classification of most AEFI rather than assigning many events to the unclassifiable category. Even with supporting documentation, often the information needed to assess causality – such as a medical history, record of concurrent illness or medication, or even the vaccine history – was incomplete or unavailable. However, in most cases (97%) we found that the information available in VAERS report was sufficient to assign causality; we did not find that the causal classification of VAERS reports with only 1 or 2 pages was substantially different from those with more extensive records in the sample of reports we evaluated (χ^2 test, $p = 0.17$ data not shown). Nonetheless, we caution those who seek to draw causal conclusions from limited data in a brief 1 or 2 page VAERS report.

The US National Vaccine Plan calls for efforts to "improve causality assessments of vaccines and related AEFI" [30]. Assessments of the relationship between an AEFI and vaccine would be improved by the use of standard case definitions, such as the AEFI defined by the Brighton Collaboration [31]. Most importantly, more research into the relationships between vaccines and AEFI and a better understanding of biologic mechanisms underlying AEFI are needed. Recently, the IOM reviewed the evidence regarding 158 specific vaccine–adverse health events relationships and their findings have been published [3]. CISA investigators work to improve the causality assessment methods and an algorithm to assist the AEFI evaluation is being developed. Recently, CISA investigators used the modified WHO causality criteria to classify serious AEFI following H1N1 vaccine in children [32] and adults [22].

We have outlined the limitations of using VAERS data for causal assessments, yet we support the need for systematic case-based clinical investigations, for clusters or for rare AEFI, to assure that the reported AEFI considered causally related to vaccine are consistent with the biologically plausible mechanisms proposed in the medical literature. Case-based clinical investigations, including collection of medical records and interviewing the medical provider and/or patients to gather missing information, would

Table 3
Description of VAERS cases reviewed for serious and non-serious reports.

Characteristic	Serious reports		Non-serious reports		Total %
	N	%	*N*	%	
Total number (*N*)	71		29		100
Age group (years)					
<1	21	29.6	3	10.3	24
1–5	18	25.4	14	48.3	32
6–19	3	4.2	3	10.3	6
20–39	6	8.5	5	17.2	11
40–59	13	18.3	4	13.8	17
60+	10	14.1	0	0.0	10
Gender					
Male	41	57.7	14	48.3	55
Female	30	42.3	15	51.7	45
Interval from vaccination to onset of adverse event (days)					
0	11	15.5	5	17.2	16
1–2	21	29.6	10	34.5	31
3–7	7	9.9	3	10.3	10
8–14	2	2.8	3	10.3	5
15–59	5	7.0	0	0.0	5
60–100	3	4.2	0	0.0	5
100+	5	7.0	5	17.2	10
Unknown/not reported	17	23.9	3	10.3	20
Number of antigenic components received at vaccination[a]					
1	32	45.1	11	37.9	43
2	5	7.0	1	3.4	6
3	5	7.0	3	10.3	8
4	2	2.8	4	13.8	8
5	7	9.9	2	6.9	6
6	8	11.3	2	6.9	9
7	7	9.9	2	6.9	10
8	4	5.6	3	10.3	7
10	1	1.4	1	3.4	10

[a] For example, MMR vaccine would be considered 3 antigens.

greatly improve the quality of data needed for causal assessments. Our study reminds the reader that submission of a report to VAERS cannot be interpreted as indicating that the adverse event was caused by the vaccine.

Acknowledgements

Financial support for this study was provided by the Centers for Disease Control and Prevention (contract 200-2002-00732) through America's Health Insurance Plans, this funding covered the costs of design and conduct of the study, collection, management, analysis, and interpretation of data, and the preparation, review, and approval of the manuscript. The principal investigator, Colin Marchant and first author, Anita Loughlin had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the analysis. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The CISA Causality working group includes all co-authors. Their contributions include but are not limited to (1) the refinement of study protocol and modified causality criteria definitions, (2) the review of records and participation in the adjudication process for each case report, and (3) the critical review and editing of the submitted manuscript. Co-authors' financial disclosures are the following. Elizabeth Barnett has received research support Sanofi Pasteur and Intercell; Roger Baxter has received research grants from Novartis, Sanofi Pasteur, Merck, GSK, MedImmune, and Wyeth; Steven Black is a consultant for Novartis and serves on DSMBs for GSK and Novartis; Cornelia Dekker is a member of the Scientific Advisory Board of PharmaJet; Jerome Klein has been a member of the Pediatric Scientific Advisory Committee of Merck; Nicola Klein has received research support from Merck, Sanofi Pasteur, GSK, Novartis and Pfizer. Philip LaRussa serves on DSMBs for Novartis and his laboratory receives research support from Merck & Co; Colin Marchant has received research funding, and/or has been a speaker or consultant to the following companies: GlaxoSmithKline, Merck, MedImmune, Novartis, Sanofi-Pasteur, and Pfizer. Authors without conflicts of interest are William Adams, Christine Casey, Kathryn Edwards, Kathleen Jakobs, Anita Loughlin, and Robert Sparks.

We would like to acknowledge the efforts of Scott Campbell, RN, MPH, from CDC, who was instrumental in assisting with the transfer of computerized VAERS reports; and Marissa Black, BA, Boston Medical Center, who assisted in de-identifying VAERS data, distributing cases to reviewers, and collating results.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2012.09.074.

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