Vaccine Adverse Event Reporting System (VAERS)
Standard Operating Procedures for COVID-19
(as of 4 December 2020)

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Disclaimer

This document is a draft planning document for internal use by the Centers for Disease Control and Prevention, with collaborating contractors. Numerous aspects (including but not limited to specific adverse events to be monitored, timeframes for report processing, data elements to be reported, and data analysis) are dynamic and subject to change without notice.

Executive Summary

CDC and FDA will perform routine VAERS surveillance to identify potential new safety concerns for COVID-19 vaccines. This surveillance will include generating tables summarizing automated data from fields on the VAERS form for persons who received COVID-19 vaccines (e.g., age of vaccinee, COVID-19 vaccine type, adverse event).

Enhanced surveillance (i.e., automated data and clinical review) will be implemented after reports of the following adverse events of special interest (AESIs): death, COVID-19 disease, Guillain-Barre Syndrome (GBS), seizure, stroke, narcolepsy/cataplexy, anaphylaxis, vaccination during pregnancy, acute myocardial infarction, myopericarditis, coagulopathy (including thrombocytopenia, disseminated intravascular coagulopathy [DIC], and deep venous thrombosis [DVT]), Kawasaki's disease, multisystemic inflammatory syndrome in children (MIS-C), multisystemic inflammatory syndrome in adults (MIS-A), and transverse myelitis. Abstraction of medical records associated with reports of these conditions will be performed using an internal CDC website (i.e., behind CDC's firewall). Data entered into the abstraction website will be stored on CDC servers and used to populate data tables, from which automated reports will be generated and analyzed on a periodic basis. Enhanced surveillance (i.e., automated data and clinical review) will also be implemented after reports of pregnancy complications, stillbirths, congenital anomalies, and vaccination errors. However, abstraction of medical records after these conditions will be performed on an as needed basis. These efforts will assist in CDC's efforts to monitor the safety of COVID-19 vaccines.

1.0 Introduction

The Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) use the Vaccine Adverse Event Reporting System (VAERS) as a front-line system to monitor the safety of vaccines licensed for use in the United States. In addition to conducting general surveillance, each year VAERS activities focus on new formulations and types of vaccine, new populations who may be vaccinated because of changes in licensed indications or Advisory Committee on Immunization Practices (ACIP) recommendations, and any new safety concerns identified. This Standard Operating Procedures (SOP) document describes the following activities for COVID-19 vaccine safety monitoring:

1) Approach for CDC-FDA VAERS monitoring
2) Plans for coordinating with FDA VAERS staff, particularly around data mining and VAERS data interpretation
3) Overall COVID-19 vaccine safety monitoring coordination for The VAERS Team within CDC's Immunization Safety Office (ISO)

This SOP does not describe details of FDA surveillance procedures for COVID-19 vaccine safety or CDC surveillance or evaluation of COVID-19 vaccines in systems other than VAERS.

[Placeholder for section describing individual COVID-19 vaccines when available]

For each adverse event of special interest (AESI), the rationale for enhanced monitoring, case definitions (if available), and references are provided in Table 1:

Table 1: Adverse Events of Special Interest, with case definitions (if available)

Adverse Event of Special Interest	Rationale for enhanced monitoring	Case definition (if available)*	References
Acute myocardial infarction (AMI)	• Has been reported as a presenting sign of COVID-19 disease and could indicate VAED	• International consensus case definition available at https://www.ahajournals.org/doi/epub/10.1161/CIR.0000000000000617	• https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7179991/

Anaphylaxis	• Can represent a severe allergy of life-threatening severity •	• Brighton Collaboration case definition available at https://www.sciencedirect.com/science/article/pii/S0264410X07002642?via%3Dihub	• https://www.sciencedirect.com/science/article/pii/S00916749193002 0X?via%3Dihub
Coagulopathy	• Thrombocytopenia, DIC, and DVT have all been reported as part of COVID-19 disease and could indicate VAED	• Brighton Collaboration case definition for thrombocytopenia available at https://www.sciencedirect.com/science/article/pii/S0264410X0700268X?via%3Dihub • Scientific Standardization Committee of the International Society of Thrombosis and Haemostasis scoring for DIC available at https://www.tandfonline.com/doi/full/10.1080/17474086.2018.1500173 • Modified Wells' score (widely acknowledged standard for DVT/PE) available at https://academic.oup.com/clinchem/article/57/9/1256/5620938	• https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(20)30151-4/fulltext

COVID-19 disease	• COVID-19 disease can be an indication of vaccine failure • Severe COVID-19 disease can be an indication of vaccine-enhanced disease (VAED)	• CSTE case definition for COVID-19 available at https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/08/05/ • Pre-publication Brighton case definition for VAED available at https://brightoncollaboration.us/vaed/	• https://www.nature.com/articles/d41587-020-00016-w
Death	• Public interest in deaths after vaccination, especially in children (<18 years of age) and recipients of newly licensed vaccines	• Report of death certificate or autopsy report	• https://academic.oup.com/cid/article/61/6/980/451431
GBS	• Is a vaccine-associated adverse event of historical interest	• Brighton Collaboration case definition available at https://www.sciencedirect.com/science/article/pii/S0264410X1000798X?via%3Dihub	• https://www.cdc.gov/vaccinesafety/concerns/guillain-barre-syndrome.html
Kawasaki's disease	• Could be confused with MIS-C, which could be an indication of VAED	• CDC case definition available at https://www.cdc.gov/kawasaki/case-definition.html	• https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e2.htm

Multisystem Inflammatory Syndrome in Children (MIS-C)	• Could be an indication of VAED	• Interim case definition available at https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e2.htm	• https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e2.htm
Multisystem Inflammatory Syndrome in Adults (MIS-A)	• Could be an indication of VAED	• Interim case definition available at https://www.cdc.gov/mmwr/volumes/69/wr/mm6940e1.htm	• https://www.cdc.gov/mmwr/volumes/69/wr/mm6940e1.htm
Myopericarditis	• Has been reported as part of COVID-19 disease pathology and could indicate VAED	• Joint Smallpox Vaccine Safety Working Group of the Advisory Committee on Immunization Practices (ACIP) and the Armed Forces Epidemiology Board (AFEB) case definition available at https://www.cdc.gov/mmwr/PDF/wk/mm5221.pdf (p. 494)	• https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7199677/
Narcolepsy/ Cataplexy	• Has been alleged as an adverse event associated with some adjuvanted vaccines; some COVID-19 vaccines might employ adjuvants	• Brighton Collaboration case definition available at https://www.sciencedirect.com/science/article/pii/S0264410X12017811?via%3Dihub	• https://www.cdc.gov/vaccinesafety/concerns/history/narcolepsy-flu.html • https://www.hhs.gov/about/news/2020/07/31/hhs-dod-partner-sanofi-gsk-commercial-scale-manufacturing-demonstration-project-produce-millions-covid-19-investigational-vaccine-doses.html

Vaccination during pregnancy	• Public interest and concern over adverse pregnancy events and fetal outcomes	• Report of vaccinated person being pregnant (during or after vaccination)	• http://www.sciencedirect.com/science/article/pii/S000293781001105 1 •
Seizure	• Is a vaccine-associated adverse event of historical interest • In young patients (i.e., 5 years and younger) might indicate febrile seizure	• Brighton Collaboration case definition available at https://www.sciencedirect.com/science/article/pii/S0264410X03006613?via%3Dihub	• https://www.cdc.gov/vaccinesafety/concerns/febrile-seizures.html
Stroke	• Has been reported with COVID-19 disease and might therefore be an indication of VAED • Was also reported in a COVID-19 vaccine prelicensure clinical trial	• American Heart Association/American Stroke Association consensus definition available at https://www.ahajournals.org/doi/epub/10.1161/STR.0b013e318296aeca	• https://jamanetwork.com/journals/jamaneurology/fullarticle/2768098 • https://www.washingtonpost.com/health/2020/10/23/jj-vaccine-trial-to-resume/
Transverse myelitis	• One report of transverse myelitis observed in prelicensure clinical trial of ChAdOx1 nCoV-19 vaccine.	• No case definition exists; will track on the basis of physician diagnosis	• https://www.npr.org/sections/coronavirus-live-updates/2020/09/12/912281381/astrazeneca-resumes-its-covid-19-vaccine-trials-in-the-u-k

For details on the background, historical perspective and specific aims of VAERS surveillance, access https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html.

* Draft case definitions for some conditions under development by the Brighton Collaboration

In addition, selected AESIs will be monitored for awareness but not abstracted. These AESIs and available case definitions are listed in Table 2:

Table 2: AESIs to monitor (but not abstract), with definitions and available case definitions

AESIs to monitor but not abstract*	Reference definitions and available case definitions
Acute Respiratory Distress Syndrome (ARDS)	https://www.thoracic.org/professionals/career-development/residents-medical-students/ats-reading-list/adult/ards.php
Autoimmune disorders	Appendix 4.6 lists specific disorders to monitor
Other clinically serious neurologic AEs:	
Acute disseminated encephalomyelitis (ADEM)	Sejvar et al (2007)
Multiple sclerosis (MS)	NIH (last updated 5 Aug 2019)
Optic neuritis (ON)	Guier et al (last updated 10 Aug 2020)
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Gogia et al (last updated 9 Oct 2020)
Encephalitis	Sejvar et al (2007)
Myelitis	Sejvar et al (2007)
Encephalomyelitis	Merriam Webster (last accessed 7 Nov 2020)
Meningoencephalitis	Merriam-Webster (last accessed 7 Nov 2020)
Meningitis	CDC (last updated 21 Jan 2020)
Encephalopathy	NIH (last updated 27 Mar 2019)
Ataxia	Johns Hopkins Medicine Dept of Neurology and Neurosurgery (last accessed 7 Nov 2020)
Non-anaphylactic allergic reactions	Varies with specific symptom; see Appendix 4.6
Vaccination errors	See Section 4.4

* Will be specified by a list of MedDRA PTs (see Appendix 4.6, p. 27)

2.0 Overview of VAERS Surveillance Activities

The specific tasks and frequency of these tasks for surveillance will be adjusted to meet public health needs, with consideration of staff time and resources. For example, in the event of a significant increase in the number of adverse events (AEs) reported to VAERS that warrant clinical review, additional ISO staff will be assigned to perform reviews. An algorithm of the process to monitor vaccine AEs is shown in Appendix 4.1.

CDC will perform clinical reviews for AESIs listed in Table 1. Results from automated data assessment will identify additional conditions potentially warranting further clinical review.

CDC will perform Proportional Reporting Ratio (PRR) analysis (see section 2.3.1, p. 14), excluding laboratory results, to identify AEs that are disproportionately reported relative to other AEs.

FDA routinely reviews all serious* and other medically important condition (OMIC) reports daily and performs data mining.

* *Serious reports are defined by Code of Federal Regulations (FDA CFR 1997) if at least one of the following was reported: death, hospitalization, life-threatening illness, permanent disability and /or prolonged hospitalization, and congenital anomaly.*

Summaries (or other deliverables, as needed) will be based on data processing, coding and follow-up, automated data, and clinical review, as well as field investigations as appropriate. COVID-19 vaccine safety coordination meetings among ISO team members and FDA will be scheduled weekly (or more frequently, as needed) to discuss results of the automated data and (if indicated) clinical review.

2.1 Data processing and coding and follow-up

The CDC contractor for VAERS receives, processes, and manages VAERS reports. The contractor receives reports online and by mail, fax, or telephone. Using standard procedures, contractor staff will review each U.S. report following COVID-19 vaccines and assign standard codes to each reported sign, symptom, and diagnosis using Medical Dictionary for Regulatory Activities terminology [10]. The staff will enter all MedDRA terms and other information from each VAERS report form into a computerized database. Vaccine type codes in the VAERS database are shown in Appendix 4.2.

Trained contractor staff will request additional information including hospital records and autopsy reports when appropriate (Appendices 4.3 and 4.4). Medical records are routinely requested for all serious reports, including deaths.

Contractor clinical staff will summarize data and assign additional MedDRA codes for symptoms, signs, and diagnoses identified from the requested additional information.

They will then add these additional codes to the data originally entered into the database for the specific VAERS report.

Table 3 lists the AESIs for which medical records will be requested and reviewed. Manual review of serious reports is routinely performed by FDA (a more in-depth clinical review will be performed by CDC as indicated).

Table 3: AESIs for which medical records will be requested and reviewed

<table>
<tr><th>AESI</th><th>Medical and vaccination records obtained by contractor</th><th>Clinical review by CDC*</th></tr>
<tr><td>Acute Myocardial Infarction (AMI)</td><td rowspan="11">All reports (including manufacturer reports)</td><td rowspan="11">All reports (including manufacturer reports)</td></tr>
<tr><td>Anaphylaxis</td></tr>
<tr><td>Coagulopathy</td></tr>
<tr><td>COVID-19 disease</td></tr>
<tr><td>Death</td></tr>
<tr><td>GBS</td></tr>
<tr><td>Kawasaki’s disease</td></tr>
<tr><td>Multisystem Inflammatory Syndrome in Children (MIS-C)</td></tr>
<tr><td>Multisystem Inflammatory Syndrome in Adults (MIS-A)</td></tr>
<tr><td>Myopericarditis</td></tr>
<tr><td>Narcolepsy/ Cataplexy</td></tr>
<tr><td>Non-Death Serious</td><td>All reports (including manufacturer reports)</td><td>As needed</td></tr>
<tr><td>Pregnancy and Prespecified Conditions</td><td rowspan="4">All reports (including manufacturer reports)</td><td rowspan="4">All reports (including manufacturer reports)</td></tr>
<tr><td>Seizure/Convulsion</td></tr>
<tr><td>Stroke</td></tr>
<tr><td>Transverse myelitis</td></tr>
</table>

*Includes review of VAERS form and available medical records by primary ISO staff. Initial review will be performed and documented within CDC internal COVID-19 medical abstraction website. More detailed review will be performed as needed

All COVID-19 vaccine reports will be entered into the VAERS database and assigned a unique identifying (ID) VAERS number during normal business hours. The contractor will send daily e-mail alerts (Daily Priority Reports) to CDC/FDA with a list of VAERS ID numbers for all serious and non-serious reports of adverse events of special interest (AESIs) after COVID-19 vaccines. Reports of AESIs will be identified in the Daily Priority Reports and in a daily table (to be constructed, as described in section 2.4). Appendix 4.3 provides details on how the prespecified conditions will be identified by the contractor.

2.1.1 Jurisdiction-specific data in VAERS reports after COVID-19 vaccines

ISO will make selected VAERS data available to Vaccine Safety Coordinators (VSCs) in requesting jurisdictions on a weekly basis via Epi-X. The selected data will include the following:

- Unredacted initial report data for reports of residents* within the VSC's jurisdiction (i.e., local, state, or territorial health department) who experience AEs after receiving COVID-19 vaccines; report data of state or territorial jurisdictions will include unredacted report data of local jurisdictions within that state or territory. These unredacted data will not be accessible by other jurisdictions. These unredacted data will be refreshed on Epi-X weekly.

- Cumulative counts of VAERS reports after vaccination with COVID-19 vaccines, cross-tabulated in the following manner:

    - Rows listing each jurisdiction by total cumulative counts, stratified by seriousness (non-serious, serious non-death, and death)
    - Rows listing selected AESIs by total cumulative counts among all jurisdictions combined (to avoid small cell counts and potential unintended identification of affected persons), stratified by age group, in years (0–4, 5–17, 18–49, 50–64, 65–74, ≥75, not reported, and total)
    - These cumulative counts will include all reports to date and will be refreshed on Epi-X weekly.

* Residency will be assigned in the following hierarchy: 1) state or territory of reported patient residency; if not available, 2) state or territory where COVID-19 vaccine was administered; if not available, 3) state or territory of person making the VAERS report; absent these data, residency will be decided per standard contractor business rules. Residence within a local jurisdiction will be determined in similar fashion, based upon city and ZIP code information comprising the local jurisdiction.

Weekly redacted data will be made available publicly via CDC WONDER (https://wonder.cdc.gov/), HHS (https://vaers.hhs.gov), and Epi-X on the same date. Case counts on Epi-X and public websites should be equal; any differences in case counts may result from data processing (e.g., data cleaning) and will be reconciled as the data mature.

2.1.2. Vaccination Errors

Reports of vaccination errors will be identified by conducting an automated search using MedDRA preferred terms (PTs) and organized into vaccination error groups shown in Appendix 4.5.

- Some reports that use the MedDRA PT codes in Appendix 4.5 do not always document a vaccination error.

- If ACIP does not recommend vaccination with COVID-19 vaccines during pregnancy, reports where vaccination was contraindicated due to pregnancy, but still performed, will be captured under "contraindication to vaccination." A previous review of reports coded as pregnancies revealed that for many reports, no vaccination error occurred. The PTs "exposure during pregnancy," "fetal exposure during pregnancy," and "maternal exposure during pregnancy" are not included in Appendix 4.5.

Vaccination errors will be summarized by vaccination error group based on automated data and include any error involving COVID-19 vaccines and any other coadministered vaccine(s). Clinical review of VAERS reports will be performed for vaccination error reports that are classified as serious (see p.11) , and vaccination error PTs with elevated PRRs.

The data from this automated search will be provided as a weekly automated table that will be reviewed as described below in sections 2.4 and 3.0.

2.2 Automated tables:

A series of tables will be generated using the VAERS automated data.

2.2.1 VAERS daily table

A version of the cumulative count tables from section 2.1.1 will be refreshed daily for internal use (i.e., inside ISO). This version will be generated independently of the jurisdictional Epi-X/CDC WONDER data and will be almost identical in appearance and content, except that the data will be presented in aggregate and not at the local level.. Because this internal version will use supplemental data not for public release, counts may vary from counts on Epi-X/CDC WONDER.

2.2.2 VAERS weekly tables

Data tables demonstrating frequency, reporting ratios and general characteristics will be generated automatically using pre-defined variables populated by VAERS data. The data in these tables will be summarized by whether the AE is classified as serious and by age group and sex, and will be presented in weekly and cumulative formats.

The following weekly tables will be available every Monday (data as of the previous Friday):

Table 1. All reports following COVID-19 vaccines by severity and selected manufacturer/brand name

AESI tables

Table 2. Top 25 most frequently reported AEs

Table 3. Reports of the following AESIs after vaccination with COVID-19 vaccines, stratified by age group (ages <18 years, 18–49 years, 50–64 years, 65–74 years, 75+ years, unreported):

- Death
- COVID-19 Disease
- Guillain Barre Syndrome (GBS)
- Seizure
- Stroke
- Narcolepsy/Cataplexy
- Anaphylaxis
- Acute Myocardial Infarction
- Myopericarditis
- Coagulopathy
- Transverse Myelitis
- Multisystemic Inflammatory Syndrom in Adults (MIS-A)

Table 4. Reporting trends of the following AESIs after vaccination with COVID-19 vaccines, stratified by age group (<12 months, 12–35 months, 36–59 months, 5–11 years, 12–20 years, >20 years, unreported)

- Kawasaki Disease
- Multisystemic Inflammatory Syndrom in Children (MIS-C)

Table 5. Reporting trends of VACCINATION DURING PREGNANCY following vaccination with COVID-19 vaccines stratified by age group (ages <18 years, 18–29 years, 30–39 years, 40–49 years, ≥50 years, unreported)

Table 6. Reporting trends of Autoimmune Disorders by System Organ Class following vaccination with COVID-19 vaccines by age group (ages <18 years, 18–49 years, 50–64 years, 65–74 years, 75+ years, unreported)

Table 7. Reporting trends of AESIs to monitor but not abstract (Table 2, p. 8), following vaccination with COVID-19 vaccines by age group (ages <18 years, 18–49 years, 50–64 years, 65–74 years, 75+ years, unreported)

Table 8. Vaccination errors

Table 9, 10, etc. PRRs (number of tables TBD)

2.3 Signal detection methods and data analyses

The analyses for COVID-19 vaccine safety signals will focus on identifying deviations from preliminary safety data, and possibly from other vaccines, using disproportionality analyses and comparisons of reporting rates.

Two main approaches to data mining are Proportional Reporting Ratios (PRRs) and Empirical Bayesian Geometric Means [11–13]. Both have published literature suggesting criteria for detecting "signals" [14]. PRR will be used at CDC for potential signal detection; Empirical Bayesian data mining will be performed by FDA.

After initial licensure or approval of COVID-19 vaccines in the United States, initial reports may be too few to allow for data mining immediately. As the data mature, PRR and Empirical Bayesian data mining can then be used.

2.3.1 Proportional Reporting Ratio (PRR)

CDC will perform PRR data mining on a weekly basis or as needed. PRRs compare the proportion of a specific AE following a specific vaccine versus the proportion of the same AE following receipt of another vaccine (see equation below Table 4). A safety signal is defined as a PRR of at least 2, chi-squared statistic of at least 4, and 3 or more cases of the AE following receipt of the specific vaccine of interest.

CDC will apply appropriate comparator vaccines (e.g., adjuvanted vaccines like Shingrix and/or Fluad for adjuvanted COVID-19 vaccines) and adjust for severity and age distributions where applicable.

Table 4. Calculation of Proportional Reporting Ratio (PRR)

	Specific AE	**All other AE**
Specific vaccine	**A**	**B**
All other vaccines	**C**	**D**

$$PRR = \frac{[a/(a+b)]}{[c/(c+d)]}$$

2.3.2 Data mining

FDA will perform data mining at least biweekly (with stratified data mining monthly) using empirical Bayesian data mining to identify AEs reported more frequently than expected following vaccination with COVID-19 vaccines, using published criteria [12, 14]. Vaccine product-specific AE pairs following specific COVID-19 vaccines with reporting proportions at least twice that of other vaccines in the VAERS database (i.e., lower bound of the 90% confidence interval of the Empirical Bayesian Geometric Mean [EB05] >2) will be evaluated. Data mining runs can be adjusted and/or stratified by possible confounding variables such as age, sex, season of administration, and type of vaccines. FDA and CDC will share and discuss results of data mining analyses and signals.

2.3.3 Crude reporting rates

If needed for internal purposes, crude reporting rates will be calculated based on COVID-19 vaccine doses distributed, when a source of doses distributed data becomes available.

2.4 Review of VAERS forms, medical records, and automated tables for reports of interest

- Daily priority reports will provide VAERS ID numbers and associated AESIs; these reports can be reviewed by VAERS personnel for initial information.

- Daily line list will provide VAERS ID numbers, associated AESIs, and assigned medical abstractor names. Medical abstractors will then access the VAERS VPN, review available medical records, and complete abstraction using the internal abstraction website (Figure).

    - Data from these medical abstractions will be used for supplemental tables to provide additional information on the automated summary tables (i.e., the cumulative daily data described in section 2.2.1.)

- Automated tables referenced in section 2.2.2 will be reviewed weekly for potential safety signals.

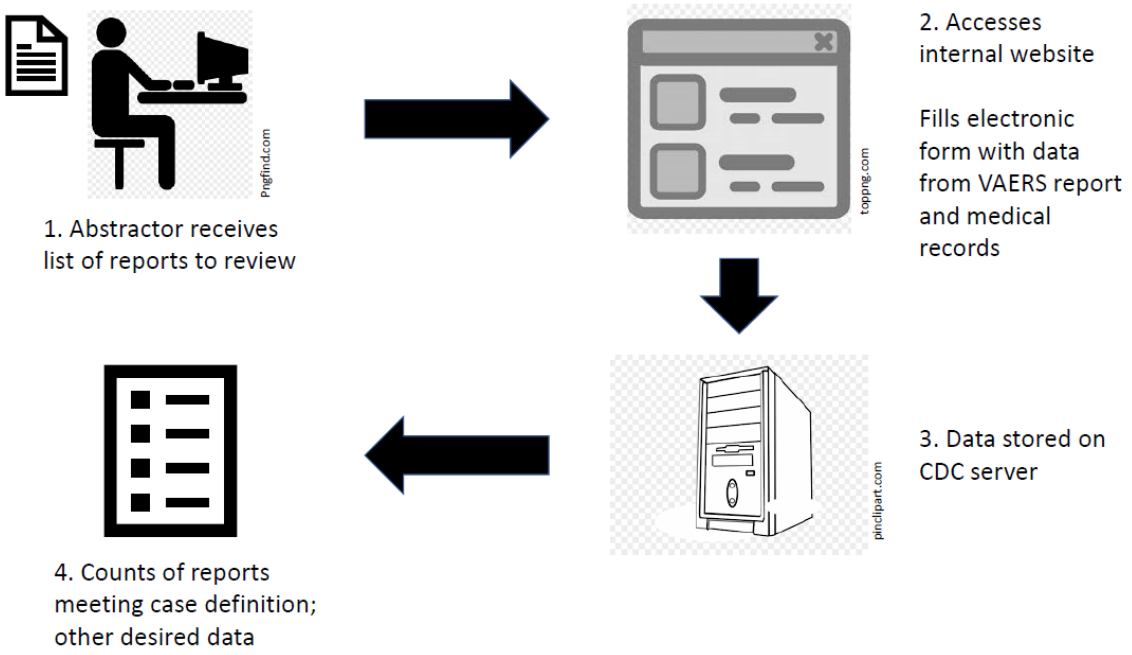


Figure: abstraction process

MedDRA terms identified as safety signals due to elevated PRR and/or a stastistically significant finding on data mining will be reviewed as appropriate. The pattern or trend of PRR and data mining results over a period of time (e.g., several weeks) will be monitored before initiating a clinical review. Other factors, such as clinical importance, whether AEs are unexpected, seriousness, and whether a specific syndrome or diagnosis is identified rather than non-specific symptoms will be considered in determining if clinical review will be performed.

Identification of a cluster of reports or unexpected AEs will be further investigated, and additional information on serious AEs will be shared with CDC leadership. A list of lot numbers of vaccines that may be of concern will be requested from FDA. In the event of review of difficult or rare cases, subject matter experts (e.g., neurologist, the Clinical Immunization Safety Assessment network) may be consulted.

Clinical review will include reviewing reports (and associated medical records) containing the identified MedDRA terms, confirming appropriate coding, confirming diagnosis (e.g., by applying a case definition), confirming time from vaccination to symptom onset, reviewing the patient history and course of illness to identify risk factors, and potentially comparing to comparable data for another vaccine.

A summary of the data review described in this section will be provided monthly, or as needed, to pertinent stakeholders (e.g., Immunization Safety Office leadership, FDA partners).

2.5 Signal assessment

Signal detection can occur in VAERS surveillance through FDA empirical Bayesian data mining, through CDC PRR data mining, and through descriptive analysis. When a potential signal is detected, ISO VAERS staff shall take a series of steps to assess the potential signal. Steps may include, but are not limited to:

- Assess if the potential signal merits further investigation (e.g., expected AEs might not warrant further analysis)
- Consult with FDA colleagues to coordinate response
- Perform quality checks on data management and data analysis that led to signal detection
- Individual report review to:
    - Confirm the accuracy of MedDRA coding
    - Confirm the AE outcome and apply a standardized case definition if appropriate
    - Confirm onset interval to assess biological plausibility
    - Assess for other risk factors that might contribute to the AE
    - Assess the clinical seriousness
- Perform comparative analysis with other vaccines (e.g., compare frequencies and proportions with influenza vaccine)
- Analyze reporting rates and compare reporting rates with other vaccines or background rates

If, after an initial assessment, VAERS investigators determine a signal warrants further investigation, the VAERS team lead will notify ISO leadership and develop a coordinated response plan. Any appropriate investigation will be conducted in collaboration with FDA. FDA will share with CDC reports of possible concern based of the data mining results and assess product-specific or lot safety as appropriate. ISO leadership will be responsible for notifying NCIRD and the CDC COVID-19 Vaccine Task Force (VTF) in a timely manner.

3.0 Coordination and Collaboration

Meetings and conference calls will be scheduled as follows, subject to change as needed:

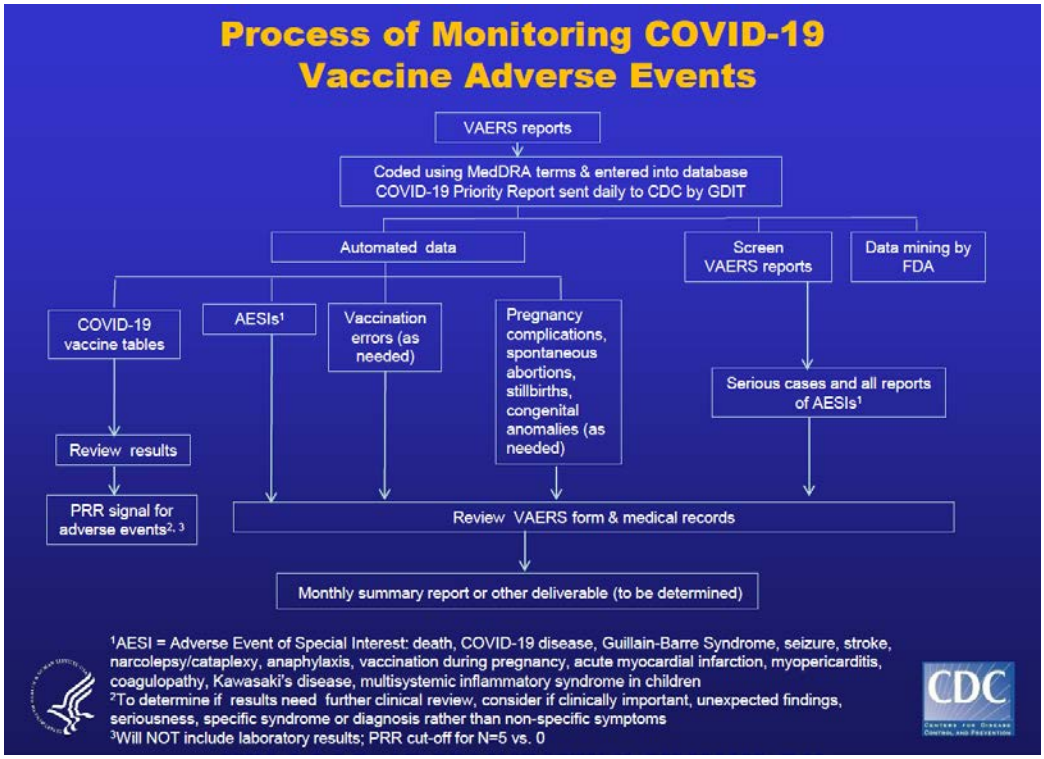
1) **Daily review by team lead and ISO leadership,** to review counts of reports and selected subgroups (e.g., deaths)

2) **Weekly VAERS Team COVID-19 Meeting** among VAERS team members
    a. To review the automated tables and clinical summary
    b. To analyze and interpret the VAERS data
    c. To discuss signals or potential events of concern

3) **Weekly (or as needed) CDC/FDA COVID-19 Safety Coordination Meeting** with ISO leadership, NCIRD representatives, and FDA
    a. To present pertinent automated data and clinical summary (e.g., AEs resulting in signals) and FDA data mining results
    b. To provide updates on ISO VAERS team and FDA COVID-19 vaccine activities (e.g., scientific projects/publications, regulations, data from other vaccine safety systems)

4.0 Appendices

4.1 Process of monitoring of COVID-19 vaccine adverse events



4.2 VAERS codes for COVID-19 vaccines [pending]

Vaccine type	CDC code	Notes
(Fill as appropriate)		

4.3 NURFU (Nurses Follow-up) Guidance: requesting additional information for selected AESIs

Criteria			Actions/ Documents Requested
Description	**Report Type**	**Vaccine Brand/Manufacturer**	
All	Serious (including manufacturer reports)	Unknown/ Not Specified	Vaccination records
		MedDRA Codes or Text Search	
Acute Myocardial Infarction	Serious/Non-serious (including manufacturer reports)	MedDRA Codes: Acute myocardial infarction Myocardial infarction Silent myocardial infarction	Clinical follow-up Vaccination records
Anaphylaxis	Serious/Non-serious (including manufacturer reports)	MedDRA Codes: Anaphylactic reaction Anaphylactic shock Anaphylactoid reaction Anaphylactoid shock	Clinical follow-up Vaccination records
COVID-19 Disease	Serious/Non-serious (including manufacturer reports)	COVID-19 Asymptomatic COVID-19 COVID-19 pneumonia	Clinical follow-up Vaccination records
Coagulopathy	Serious/Non-serious (including manufacturer reports)	MedDRA Codes: Acquired amegakaryocytic thrombocytopenia Amegakaryocytic thrombocytopenia Axillary vein thrombosis Cavernous sinus thrombosis Cerebral venous thrombosis Deep vein thrombosis Disseminated intravascular coagulation Embolism venous Hepatic vein thrombosis Immune thrombocytopenia Intracranial venous sinus thrombosis Mesenteric vein thrombosis Portal vein thrombosis Pulmonary embolism Pulmonary thrombosis	Clinical follow-up Vaccination records

		Pulmonary venous thrombosis Severe fever with thrombocytopenia syndrome Subclavian vein thrombosis Thrombocytopenia Thrombocytopenic purpura Thrombotic thrombocytopenic purpura Thrombosis Transverse sinus thrombosis Vena cava embolism Vena cava thrombosis Venous thrombosis	
GBS	Serious/Non-serious (including manufacturer reports)	<u>MedDRA Codes:</u> Guillian-Barre syndrome Miller Fisher syndrome Demyelinating polyneuropathy	Clinical follow-up Vaccination records Do NOT fill out GBS questionnaire
Kawasaki Disease	Serious/Non-serious (including manufacturer reports)	<u>MedDRA Codes:</u> Kawasaki's disease	Clinical follow-up Vaccination records
Multisystem Inflammatory Syndrome in Children (MIS-c)	Serious/Non-serious (including manufacturer reports)	Ages 0-20 AND <u>MedDRA Codes:</u> Multisystem inflammatory syndrome in children	Clinical follow-up Vaccination records
Multisystem Inflammatory Syndrome in Adults (MIS-a)	Serious/Non-serious (including manufacturer reports)	Ages 21 and older AND <u>MedDRA Codes:</u> TBA	Clinical follow-up Vaccination records
Myocarditis/Pericarditis	Serious/Non-serious (including manufacturer reports)	<u>MedDRA Codes:</u> Atypical mycobacterium pericarditis Autoimmune myocarditis Autoimmune pericarditis Bacterial pericarditis Coxsackie myocarditis Coxsackie pericarditis Cytomegalovirus myocarditis Cytomegalovirus pericarditis Enterovirus myocarditis	Clinical follow-up Vaccination records

		Eosinophilic myocarditis Hypersensitivity myocarditis Immune-mediated myocarditis Myocarditis Myocarditis bacterial Myocarditis helminthic Myocarditis infectious Myocarditis meningococcal Myocarditis mycotic Myocarditis post infection Myocarditis septic Pericarditis Pericarditis adhesive Pericarditis constrictive Pericarditis helminthic Pericarditis infective Pericarditis mycoplasmal Pleuropericarditis Purulent pericarditis Viral myocarditis Viral pericarditis	
Narcolepsy/Cateplexy	Serious/Non-serious (including manufacturer reports)	<u>MedDRA Codes:</u> Narcolepsy Cataplexy	Clinical follow-up Vaccination records
Pregnancy and Prespecified Conditions	Serious/Non-serious (including manufacturer reports)	<u>MedDRA Codes:</u> Abortion Aborted pregnancy Abortion complete Abortion early Abortion incomplete Abortion late Abortion missed Abortion spontaneous Abortion spontaneous complete Abortion spontaneous incomplete Abortion threatened Congenital anomaly	Clinical follow-up including: prenatal visit documentation, delivery records, ER/hospital records during pregnancy, well child visits, infant hospitalization records; for congenital anomalies- infant records, ultrasounds, genetic studies

		Drug exposure during pregnancy Exposure during pregnancy Foetal death Maternal exposure during pregnancy Stillbirth OR <u>Text String:</u> Preg (Text String located in symptom_text, history, prex_illness) OR Pregnant Status (2.0 form-Q8) OR Congenital anomaly outcome (2.0 form-Q21)	Vaccination records
Seizure/Convulsion	Serious/Non-serious (including manufacturer reports)	<u>MedDRA Codes:</u> Atonic seizures Atypical benign partial epilepsy Autonomic seizure Clonic convulsion Complex partial seizures Convulsion in childhood Convulsion Convulsions local Epilepsy Epileptic encephalopathy Febrile convulsion Febrile infection-related epilepsy syndrome Generalised non-convulsive epilepsy Generalised onset non-motor seizure Generalised tonic-clonic seizure Grand mal convulsion Idiopathic generalised epilepsy Myoclonic epilepsy Neonatal seizure Partial seizures with secondary generalisation Partial seizures Petit mal epilepsy Seizure anoxic	Clinical follow-up Vaccination records

		Seizure cluster Seizure like phenomena Seizure Simple partial seizures Status epilepticus Temporal lobe epilepsy Tonic clonic movements Tonic convulsion Tonic posturing	
Stroke	Serious/Non-serious (including manufacturer reports)	MedDRA Codes: Basal ganglia stroke Brain stem stroke Cerebellar stroke Cerebrovascular accident Embolic stroke Haemorrhagic stroke Haemorrhagic transformation stroke Ischaemic stroke Lacunar stroke Perinatal stroke Spinal stroke Thrombotic stroke Vertebrobasilar stroke	Clinical follow-up Vaccination records
Transverse myelitis	Serious/Non-serious (including manufacturer reports)	MedDRA Codes: Myelitis transverse	Clinical follow-up Vaccination records

4.4 VAERS triaging of reports in business days[1, 2]

Type of report	Reported Vaccine	Serious reports		Serious follow-up initiation	Non-serious reports	
		Scan within	Complete process within[3]		Scan within	Complete process within[3]
1. US Deaths[4]	COVID-19	1	1	1	N/A	N/A
2. US Deaths[4]	Non-COVID-19	2	2	2	N/A	N/A
3. US/Foreign 5-day	All	2	2	N/A	N/A	N/A
4. US 15-day	All	2	2	N/A	N/A	N/A
5. US	COVID-19[5]	2	3	3	2	5
6. US	Seasonal Influenza[6,7]	2	4	4	2	10
7. US 30-day	All	2	20	N/A	2	30
8. US	List A[6]	2	20	20	2	30
9. US	List B	2	30	20	2	45
10. Foreign Deaths	COVID-19	2	2	N/A	N/A	N/A
11. Foreign	COVID-19	2	30	N/A	5	120
12. Foreign	Non-COVID-19	5	90	N/A	5	120

1. Subject to change in response to new public health policies and/or events and/or funding availability after discussion between CDC and FDA
2. Not applicable for GBS reports where a patient is confined to facility longer than the time allowed for follow-up (e.g., patient in rehabilitation after GBS)
3. Completion includes scanning, data entry, and coding
4. If final autopsy report is not received within 2 months, make request every 2 months
5. If no records received within 5 days from the original request, make another request for Covid-19
6. If no records received within 7 days from the original request, make another request for Seasonal Influenza
7. Seasonal influenza reports will be prioritized as stated in Row 4 until March 31, 2021. On April 1, 2021, process reports as stated in Row 8.

List A	List B
HEPLISAV-B Shingrix Gardasil 9 Yellow Fever Other vaccines licensed in the U.S. for less than 12 months Seasonal Influenza reports received after March 31, 2021	All vaccines excluding List A and Seasonal Influenza

4.5 Vaccination error groups and MedDRA Preferred Terms (PTs) for COVID-19 vaccination errors

Administration Errors
- Accidental exposure to product
- Accidental exposure to product by child
- Drug administered in wrong device
- Exposure via direct contact
- Exposure via eye contact
- Exposure via skin contact
- Inadequate aseptic technique in use of product
- Incorrect product administration duration
- Incorrect product formulation administered
- Incorrect route of product administration
- Intercepted drug administration error
- Lack of administration site rotation
- Lack of injection site rotation
- Lack of vaccination site rotation
- Multiple use of single-use product
- Occupational exposure to product
- Paravenous drug administration
- Product administration error
- Product administered at inappropriate site
- Product commingling
- Product leakage
- Product use complaint
- Product use in unapproved indication
- Unintentional use for unapproved indication,
- Wrong technique in device usage process
- Wrong technique in product usage process

Contraindication to vaccination
- Contraindication to vaccination
- Contraindicated product administered
- Contraindicated product prescribed
- Documented hypersensitivity to administered product
- Labelled drug-disease interaction medication error
- Labelled drug-drug interaction medication error
- Labelled drug-food interaction medication error

Equipment
- Device connection issue,
- Device breakage
- Device defective
- Device difficult to use
- Device dislocation
- Device failure
- Device leakage
- Device issue
- Device malfunction
- Device use issue
- Device use error
- Expired device used
- Exposure to contaminated device
- Exposure via contaminated device
- Incorrect dose administered by device
- Injury associated with device
- Medical device complication
- Needle issue
- Poor quality device used
- Syringe issue
- Wrong device used

General
- Medication error
- Intercepted medication error
- Product use issue
- Vaccination error
- Unintentional use for unapproved indication

Inappropriate schedule of drug administration
- Inappropriate schedule of product administration
- Product administered to patient of inappropriate age
- Wrong schedule

Incorrect dose
- Accidental overdose
- Accidental underdose
- Booster dose missed
- Dose calculation error
- Extra dose administered
- Incomplete course of vaccination
- Incorrect dose administered
- Incorrect dosage administered
- Incorrect product dosage form administered
- Overdose
- Product dose omission
- Single component of two component product administered
- Underdose
- Wrong dose
- Wrong strength

Prescribing and dispensing
- Drug dispensed to wrong patient
- Inappropriate prescribing
- Intercepted drug dispensing error
- Intercepted drug prescribing error
- Intercepted product selection error
- Prescribed overdose

- Prescribed underdose
- Product dispensing error
- Product preparation error
- Product prescribing error
- Product prescribing issue
- Product selection error
- Transcription medication error

Product quality

- Expired product administered
- Discontinued product administered
- Incorrect product storage
- Poor quality product administered
- Product contamination
- Product contamination microbial
- Product contamination physical
- Product expiration date issue
- Product quality issue
- Product quality control issue
- Product preparation issue
- Product reconstitution issue
- Product reconstitution quality issue
- Product sterility lacking
- Product storage error

Product labeling/packaging

- Product barcode issue
- Product design confusion
- Product name confusion
- Product container issue
- Product dosage form confusion
- Product identification number issue
- Product label confusion
- Product label issue
- Product label on wrong product
- Product lot number issue
- Product name confusion
- Product packaging confusion
- Product packaging issue
- Product outer packaging issue
- Product packaging confusion

Wrong Product

- Interchange of vaccine products
- Intercepted wrong patient selected
- Product substitution error
- Wrong patient received product
- Wrong product administered
- Wrong drug
- Wrong product procured

Vaccination Error groups shown on this list were updated to include several new PT codes that became available in MedDRA. Reports of exposure during pregnancy, fetal exposure during pregnancy, maternal exposure during pregnancy are not included. A review of pregnancy coded reports revealed that many reports were documenting that the patient was pregnant without an error occurring. A contraindication to vaccination code has captured true vaccine contraindication reports in pregnant women.

While most reports are documenting a medical error, some reports that use the MedDRA PT codes are not necessarily vaccination errors (e.g., product quality issue, needle issue, syringe issue).

4.6 AESIs to monitor, but not abstract, and identifying PTs

VAERS COVID-19
Prespecified Condition

(The embedded Excel spreadsheet documents PTs for *all* AESIs, both abstracted and monitored, but not asbtracted.)

AESI	Identifying MedDRA PT(s)
Acute Respiratory Distress Syndrome (ARDS)	Acute Respiratory Distress Syndrome
Autoimmune disorders	[see embedded spreadsheet]
Other clinically serious neurologic AEs:	
Acute disseminated encephalomyelitis (ADEM)	Acute disseminated encephalomyelitis
Multiple sclerosis (MS)	Multiple sclerosis Multiple sclerosis relapse Primary progressive multiple sclerosis Progressive multiple sclerosis Progressive relapsing multiple sclerosis Relapsing multiple sclerosis Relapsing-remitting multiple sclerosis Secondary progressive multiple sclerosis Tumefactive multiple sclerosis
Optic neuritis (ON)	Optic neuritis
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Chronic inflammatory demyelinating polyradiculoneuropathy
Encephalitis	Encephalitis
Myelitis	Myelitis
Encephalomyelitis	Encephalomyelitis Leukoencephalomyelitis Noninfective encephalomyelitis
Meningoencephalitis	Meningoencephalitis viral
Meningitis	Meningitis Meningitis aseptic Meningitis viral
Encephalopathy	Encephalopathy Leukoencephalopathy
Ataxia	Ataxia Cerebellar ataxia Cerebral ataxia

Non-anaphylactic allergic reactions	Allergic reaction to excipient Allergy to vaccine Allergic bronchitis Allergic colitis Allergic cough Allergic cystitis Allergic gastroenteritis Allergic hepatitis Allergic keratitis Allergic pharyngitis Allergic reaction to excipient Allergic respiratory disease Allergic respiratory symptom Allergic sinusitis Conjunctivitis allergic Dermatitis allergic Encephalitis allergic Encephalopathy allergic Laryngitis allergic Nephritis allergic Pruritus allergic Rhinitis allergic Scleritis allergic

5.0 References

1. CDC. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunizations Practices (ACIP)—United States, 2019-20 influenza season. Available at https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6703a1-H.pdf. Accessed on September 11, 2018.
2. Flublok Quadrivalent [Package Insert] 2017, Protein Sciences: Meriden, CT. Available at https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619551.pdf. Accessed on September 11, 2018.
3. Flucelvax Quadrivalent [Package Insert] 2017, Seqirus: USA. Available at https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619588.pdf. Accessed on September 11, 2018.
4. Fluad [Package Insert] 2017, Sequris: USA. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM474387.pdf. Accessed on September 11, 2018.
5. Vaccine Adverse Event Reporting System (VAERS) form. Available at https://vaers.hhs.gov/uploadFile/index.jsp. Accessed on September 11, 2018.
6. Shimabukuro T, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Reporting System (VAERS). Vaccine 2015 Aug 6;33(36):4398-405.
7. Moro PL, Li R, Haber P, Weintraub E, Cano M. Surveillance systems and methods for monitoring the post-marketing safety of influenza vaccines at the Centers for Control and Prevention. Expert Opin Drug Saf 2016 Sep;15(9):1175-83.
8. Varricchio F, Iskander J, DeStefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the vaccine adverse event reporting system. Pediatr Infect Dis J 2004;23:287–94.
9. Vellozzi C**,** KR Broder**,** P Haber et al. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Events Reporting System, United States, October 1, 2009–January 31, 2010. Vaccine 2010;28(45):7248-55.
10. Medical Dictionary for Regulatory Activities terminology (MedDRA) https://www.meddra.org/.
11. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for single generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001;10:483-6.
12. DuMouchel W. Bayesian data mining in large frequency tables with an application to the FDA spontaneous reporting system. Am Stat 1999;53:177-90.
13. Almenoff JS. Innovations for the future of pharmacovigilance. Drug Saf 2007;30: 631-3.
14. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reporting system. Drug Saf 2002;25(6):381-92.