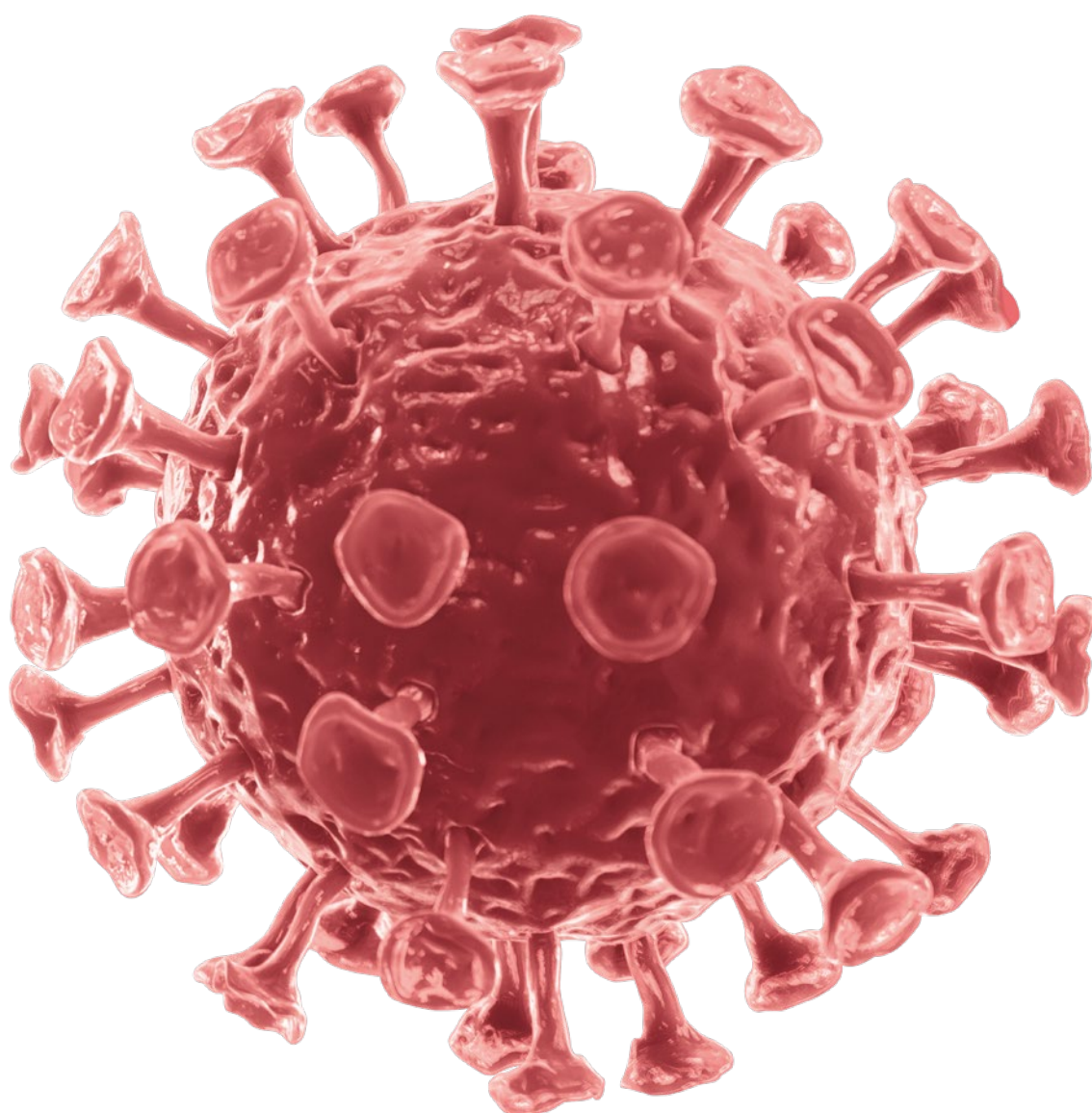


COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

**SAFETY DATA MANAGEMENT
SYSTEMS, METHODS OF
POST-INTRODUCTION
EVALUATION AND ASSESSING
PERFORMANCE IN COUNTRIES
USING COVID-19 VACCINES**

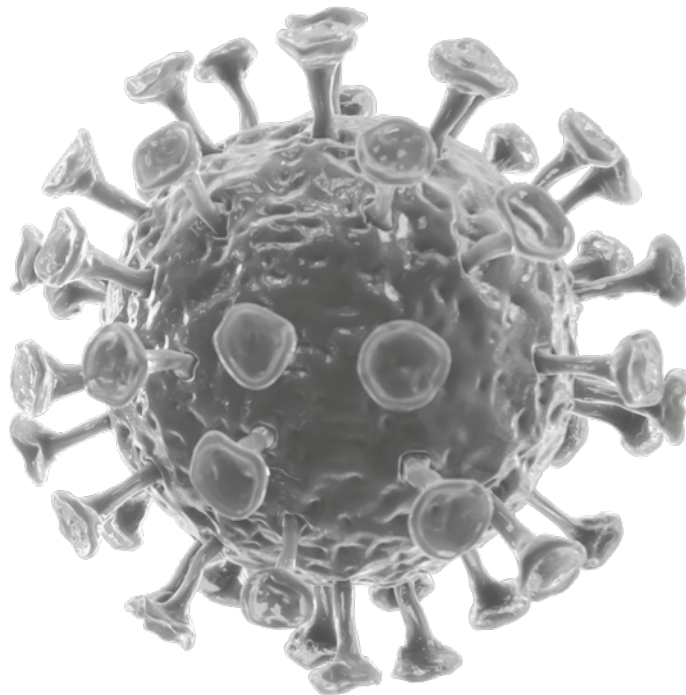


World Health
Organization

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

**SAFETY DATA MANAGEMENT
SYSTEMS, METHODS OF
POST-INTRODUCTION
EVALUATION AND ASSESSING
PERFORMANCE IN COUNTRIES
USING COVID-19 VACCINES**



**World Health
Organization**

Covid-19 vaccines: safety surveillance manual

ISBN 978-92-4-001828-0 (electronic version)

ISBN 978-92-4-001829-7 (print version)

© World Health Organization 2020

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

Suggested citation. Covid-19 vaccines: safety surveillance manual. Geneva: World Health Organization; 2020. Licence: [CC BY-NC-SA 3.0 IGO](#).

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Design and Layout: Agence Gardeners

Contents

Key points	iv
1. Introduction	1
2. Sharing COVID-19 vaccine safety data	1
2.1 Rationale for data sharing	2
2.2 Ethics in safety data sharing and collaboration	2
2.3 Generic data sharing model	3
2.4 Stakeholder mapping for AEFI data sharing	3
2.5 Data sources	5
2.5.1 Individual case safety reports (individual AEFI case reports)	5
2.5.2 Aggregated safety data from different sources	5
2.5.3 Ad-hoc research	5
2.6 Data standards	5
2.7 Data transformation	6
2.8 Repositories	6
3. Methods for rapid post-introduction evaluation of COVID-19 vaccine safety	7
3.1 Study population	7
3.2 Signal detection	7
3.3 Vaccine exposure	9
3.4 Analytic approaches for signal detection on electronic health record data	9
3.4.1 Rapid cycle analyses for suspected adverse events	9
3.4.2 Time-to-onset analysis	10
3.4.3 Ecological methods	11
3.4.4 Data mining for unexpected adverse events	11
3.4.5 Signal evaluation	11
3.5 Ongoing surveillance while signals are being evaluated and refined	12
3.6 Impact of change in health care use and provision on AESI identification and temporal trends	12
3.7 Vaccine-associated enhanced disease	12
4. Performance indicators	14
5. Appendices	16
Appendix 5.1: Indicators and targets for monitoring the performance of pharmacovigilance systems in COVID-19 context	16
Appendix 5.2: Indicators and targets for monitoring the quality of pharmacovigilance systems in COVID-19 context	17

Key points

- Data sharing at all levels is important to increase knowledge rapidly that can inform decisions about COVID-19 vaccine introduction and continuation strategies
- Key ethical considerations for data sharing include data confidentiality, data security, autonomy, sovereignty and benefits for those providing and sharing data
- Vaccine safety surveillance systems are for all vaccines, not just the COVID-19 vaccine and that routine vaccination will continue during COVID-19 deployment
- The WHO global database VigiBase, which contains ICSRs for adverse events following immunization (AEFIs) from all Member States in the WHO Programme for International Drug Monitoring, can be used to detect signals and safety concerns at national, regional and global levels
- Safety data will be also be available as aggregated data from various local data bases and from ad hoc research
- Data will have to be stored using agreed international standards or data transformation will have to performed to ensure compatibility for successful data sharing
- There are many examples of repositories that are collecting and processing information on AEFIs that can be used for data necessary for decision making at national, regional and global levels
- Countries should verify the performance of their safety data collection and assessments using either adaptations of existing indicators or COVID-19-specific immunization indicators

01 Introduction

WHO's global manual on surveillance of adverse events following immunization (AEFIs)¹ provides guidance on the purpose of data analysis at different levels. For example, who should analyse data, how it should be analysed and interpreted and its use for estimating relative and attributable risks. In the context of COVID-19 vaccine AEFI surveillance, the same principles and approaches should be applied, with some adaptation to allow for different vaccination strategies, vaccine target populations, types of vaccines and the surveillance systems available in different countries.

Guidance on vaccine safety surveillance systems and responding to AEFIs and adverse events of special interest (AESIs) to address the unique challenges from COVID-19 vaccine introduction is given in separate modules ([AEFI](#) and [AESI](#) modules). Once surveillance systems are operational, the efficiency and effectiveness of the system will be determined by the outputs and outcomes from the system. First, the raw data generated by the system needs to be collated, then transmitted, processed and interpreted and, finally, responded to systematically and scientifically. This module will provide guidance on how COVID-19 vaccine safety data should be processed and made actionable.

02 Sharing COVID-19 vaccine safety data

To guarantee the integrity and validity of the generated COVID-19 vaccine safety data, data loss and duplication should be minimized. This can be achieved through data sharing between stakeholders such as national immunization programmes (NIPs) and expanded programmes on immunization (EPIs), national regulatory agencies (NRAs), pharmacovigilance centres, Ministries of Health (MoHs), AEFI committees, private sector, vaccine manufacturers.² Data in some countries will be reported through multiple channels, with programmes obtaining data from the same patients and sometimes via the same health care worker, but with different goals and pathways.

¹ World Health Organization. Global Manual on Surveillance of AEFI. Available from: https://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf. Accessed 29 October 2020.

² For the purpose of this document, manufacturer also means marketing authorization holder.

At regional and global levels, data sharing maximizes resources and capacity to enable efficient responses and decision-making. Data sharing also increased signal detection capacity and the ability to detect and analyse very rare adverse events. Data transformation is usually required to facilitate data sharing from different sources.

2.1 Rationale for data sharing

Data sharing at all levels is important to increase knowledge rapidly that can inform decisions about COVID-19 vaccine introduction and continuation strategies. Uncertainty about the frequency AEFIs and clinical presentation will be expected due to the fast-track development processes for COVID-19 vaccines, with short time frames for data collection and regulatory review. The rationale for sharing data from four main sources is outlined below:

- **Data from passive and enhanced passive AEFI surveillance systems:** to detect signals, monitor safety aspects of immunization programme activities, monitor events that could be related to defective, non-authorized or counterfeit COVID-19 vaccines.
- **Data from active surveillance systems:** to verify and confirm the post-authorization safety profiles of COVID-19 vaccines, test hypotheses (epidemiologic associations between AEFIs and COVID-19 vaccines), detect signal with an accelerated time frame from reporting to detection.
- **Data from COVID-19 vaccine manufacturers:** bi-directional sharing³ of data with COVID-19 vaccine manufacturers will help ensure that data collection is complete and will avoid double counting of events. In addition, the manufacturers may be aware of data from other countries or sources that can help in the evaluation of AEFIs.
- **Data from other sources such as disease surveillance data, vaccine distribution and utilization data:** can help generate rapid alerts to trigger common responses from a geographical territory, provide knowledge about the implementation level and the quality of surveillance at the national level to plan for improvement strategies, understand the distribution of different COVID-19 vaccines and to compare with distribution of the disease for interpreting patterns observed during data analysis.

2.2 Ethics in safety data sharing and collaboration

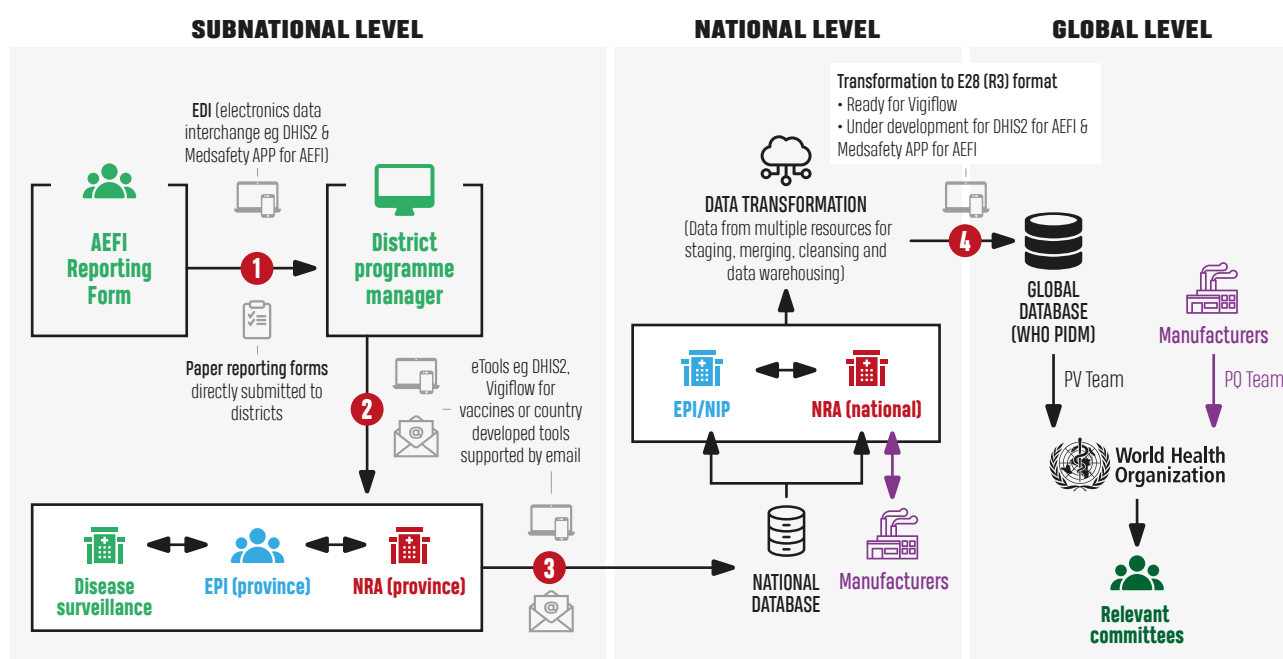
The key ethical considerations for data sharing include data confidentiality, data security, autonomy, sovereignty and benefits for those providing and sharing data.

³ Vaccine manufacturers inform the NRAs of the AEFI occurring in other parts of the world and the NRA needs to share AEFI data from their country with the vaccine manufacturers.

2.3 Generic data sharing model

Fig 1 shows a schematic representation of the structure of a generic model for data sharing at the local, subnational, national and global levels. Each country must adapt the generic systems to their local context.

Fig 1: Schematic representation of the structure for data sharing at the subnational, national and global levels



AEFI: adverse event following immunization; DB: database; EPI/NIP: expanded programme for immunization/national immunization programme; NRA: national regulatory authority.

2.4 Stakeholder mapping for AEFI data sharing

The potential stakeholder mapping is summarized in **Table 1**. It is important to consider who will be producing or managing COVID-19 vaccine AEFI data when a data sharing strategy will be developed.

Table 1: Potential stakeholder mapping of COVID-19 vaccine AEFI data sharing

Stakeholder	Current data mapping (variable depending on context)
Subnational level	
Health care institutions	<ul style="list-style-type: none"> — Individual Case AEFI reports — Case Report Forms for ad-hoc studies
Disease surveillance offices	<ul style="list-style-type: none"> — Investigation information to complete Individual Case AEFI reports — Data on local epidemiological behaviour of infectious diseases

Stakeholder	Current data mapping (variable depending on context)
Immunization programme offices	<ul style="list-style-type: none"> — Data on immunization activities — Individual Case AEFI reports
National level	
Disease surveillance responsible	<ul style="list-style-type: none"> — Data on infectious and non-infectious diseases — Data on AEFI surveillance
National immunization programmes / expanded programmes on immunization	<ul style="list-style-type: none"> — Data on immunization activities: administrative data and distribution activities — Data on AEFI surveillance.
National regulatory authorities	<ul style="list-style-type: none"> — Data on AEFI surveillance from primary health care workers and citizens — Data on AEFI surveillance from manufacturers — Data on adverse event reports from clinical trials — WHO global database of ICSRs including adverse drug reactions and AEFIs
Health information systems units	<ul style="list-style-type: none"> — Data from all sources in the country
Research institutions/clinical research organization	<ul style="list-style-type: none"> — Individual case safety (adverse events) reports from clinical trials — Data on diseases considered as AESI/AEFI
Vaccine manufacturers	<ul style="list-style-type: none"> — Individual Case AEFI reports — Periodic safety update reports
Clinical research sponsors	<ul style="list-style-type: none"> — Suspected unexpected serious adverse reactions (SUSAR) from clinical trials
Regional and global levels	
WHO regional offices	<ul style="list-style-type: none"> — WHO/UNICEF Joint Reporting Form (JRF)⁴ — Individual case reports on infectious disease surveillance — Access to WHO global database of individual case safety reports (ICSRs) including adverse drug reactions (ADRs) and AEFIs⁵
WHO headquarters	<ul style="list-style-type: none"> — WHO-UNICEF JRF — Individual case reports on infectious disease surveillance — Access to WHO global database of ICSRs⁵ including ADRs and AEFIs
WHO Programme for International Drug Monitoring /VigiBase (maintained by UMC)	<ul style="list-style-type: none"> — Individual Case AEFI reports — WHO global database of ICSRs including ADRs and AEFIs

⁴ WHO/UNICEF Joint Reporting Process. Available from: https://www.who.int/immunization/monitoring_surveillance/routine/reporting/en/. Accessed 9 December 2020.

⁵ VigiBase. Available from: <https://www.who-umc.org/vigibase/vigibase/>. Accessed 9 December 2020.

2.5 Data sources

There are different data sources with different data formats that can be used in COVID-19 vaccine pharmacovigilance. Some considerations for country capacity for data sharing include:

- timely availability of individual AEFI case reports with at least the 25 core variables;
- data centralization in a database with variables coded using a pre-defined data standard;
- completeness and accuracy of data (quality);
- technology available to implement safe data transfer; and
- data governance frameworks that define rules for data sharing with external institutions.

2.5.1 Individual case safety reports (individual AEFI case reports)

Different levels of information systems exist in different countries. This information is usually collected from passive AEFI surveillance systems, however, it could also be collected from active sentinel surveillance sites. Individual reports could also come from COVID-19 vaccine trials that would be assessed by a specific study scientific committee established for the purpose. The WHO global database [VigiBase](#), contains ICSRs and AEFIs from all Member States in the WHO Programme for International Drug Monitoring (PIDM). The source can be used to perform quantitative calculations at national, regional and global levels to detect signals and safety concerns.

2.5.2 Aggregated safety data from different sources

All countries routinely share aggregated safety data to help characterize vaccine safety e.g. WHO-UNICEF JRF, situation reports (SITREPs), integrated disease surveillance and response (IDSR), networks reports from regulatory authorities and academic initiatives.

2.5.3 Ad-hoc research

Ad hoc research projects or specific studies could be performed by networks of health care institutes using data transferred to national institutes and to the data warehouse of the institute doing the final analysis. The platform selected by the study coordination and described in the study protocol will have an impact on the database. It is necessary to assess the data available for the event and its quality, and the availability of information about the vaccination status of the patients to be included in the study before initiating ad-hoc studies. Patient diagnosis registration systems and vaccination registries should be available.

2.6 Data standards

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standardizes the definition of the data elements used in electronic transmission of different types of Individual Case Safety Reports (ICSRs), regardless of source

and destination. The standard adopted by the ICH for electronic transmission of ICSRs is described in the [ICH E2B\(R3\) message standard](#). Additional information is available at <https://www.ich.org/page/electronic-standards-estri>.

Data should satisfy agreed international standards for successful data sharing, so that both the transmitter and the receiver have identical information. Multiple data standards are available for specific coding and for whole database structures and data formats. For clinical diagnosis coding, some standards have been developed e.g. Medical Dictionary for Regulatory Activities ([MedDRA](#)) and [ICD](#). It is important to use a standard for identifying the specific vaccine that is being evaluated. Whenever available, the anatomical therapeutic chemical (ATC) standard⁶ should be used. For active surveillance systems, data standards are defined by the study protocols.

2.7 Data transformation

If the database used by the country does not comply with a standard as outlined above, data transformation is essential before data can be shared. The [ICH E2B\(R3\) message standard](#) should be used for data transformation and transmission in a standard transmission format. This requires coding as outlined in [MedDRA](#) and Identification of Medicinal Products ([IDMP](#)). Data science techniques should be applied for converting the source database format into the target format of the international database, using tools such as, ETL (extract, transform and load). Countries are encouraged to contact WHO country offices for guidance if needed.

2.8 Repositories

The following are examples of repositories that are collecting and processing information on AEFIs and enabling decision making at national, regional and global levels:

- examples of national databases: [Vaccine Safety Datalink](#) (US), Canadian Adverse Event Following Immunization Surveillance System ([CAEFISS](#)) and [Vigiflow](#), maintained by UMC;
- example of regional databases: [EudraVigilance](#);
- example of global databases:
 - for aggregate data: the WHO/UNICEF [Joint Reporting Process](#);
- example of national, regional and global datasets:
 - for case-based data, the WHO global database of individual case safety reports, [Vigibase](#), maintained by UMC.

⁶ World Health Organization. The ATC/DDD Methodology. Available from: https://www.who.int/medicines/regulation/medicines-safety/toolkit_methodology/en/. Accessed 29 October 2020.

Methods for rapid post-introduction evaluation of COVID-19 vaccine safety

Before regulatory approval, results from randomized clinical trials will be used for the initial evaluation of the safety of any COVID-19 vaccine. These trials will have limited sample size, duration of follow-up and certain populations may be missing or underrepresented (e.g., elderly, people with chronic conditions, pregnant women). It is also possible that some vaccines may be introduced under an emergency use listing authorization, further limiting the data available prior to introduction. It is critical, therefore, to conduct post-introduction safety surveillance to ensure appropriate monitoring to allow rapid signal detection and assessment to evaluate the benefit-risk profile of COVID-19 vaccines. Here we propose a set of post-introduction analyses and points for consideration in the assessment of COVID-19 vaccine safety that can be applied both for signal detection or for assessment of signals detected in other data sets.

3.1 Study population

Studies should include all vaccinees for the primary analyses to provide maximum statistical power, with subgroup analyses of:

- children under the age of 19,
- elderly patients over the age 64, and
- pregnant women.

Studies should be conducted in the whole vaccine-eligible population of the country or region or in a representative sample. If the delivery of COVID-19 vaccines is initially limited (due to supply constraints) to high-risk groups such as health care workers, then the target study population for safety surveillance should be defined accordingly.

3.2 Signal detection

When we ascertain or quantify adverse events (AEs), the occurrence of the event is compared in vaccinated and non-vaccinated individuals or in exposed versus unexposed time periods for the same individual, using different types of methodologies.

For signal detection the observed AE rate is compared with the 'expected' rate which is generally inferred from data from:

- historical controls using data from the same (or a similar) population during an earlier time period;
- cohort studies which compare event rates in specific risk windows; controls may be other individuals during the same time period who did not receive the targeted vaccine but who are otherwise similar to those vaccinated;
- self-controlled studies, using a case-series, case-crossover or risk interval design, in which all data would be obtained from vaccinated individuals, comparing a post-exposure risk window with either a pre-exposure control window or with a post-exposure control window that occurs after the risk window;
- case-based studies where the vaccination rate among cases who had the AE of interest is compared with that among individuals that did not have the AE of interest, in a case-control or case-coverage design.

In most anticipated post-introduction settings, self-controlled designs will be promising and efficient study designs as they automatically adjust for between-person confounding that can be present in other study designs. However, one disadvantage of the self-controlled study design with pre-exposure control windows is potential bias due to vaccine indication or contraindications, in situations where having the adverse event increases or decreases the likelihood of being vaccinated. The most extreme form of vaccine contraindication is death, since dead people will not be vaccinated. To overcome this limitation, a post-exposure control window, occurring after the risk window, may be defined. One disadvantage of this approach is that a signal will not be detected if the risk of the AE is constant during the post-vaccination period. Moreover, AEs are not informative, and cannot contribute to a safety 'signal', until data from the post-exposure control window are available, delaying the timeliness of the analysis. This is further complicated if vaccination requires two doses of the vaccine, e.g. if a second dose is recommended 30 days after the first dose it could be difficult to specify an appropriate post-vaccination control window. Finally, for signal detection, a traditional self-control design has limited utility for diseases with a long latency, but this could be overcome by using a post-vaccination control window that occurs before the risk window. When a risk window cannot be well defined, it is possible to use the self-control temporal scan statistic, simultaneously evaluating hundreds of potential risk windows, while automatically adjusting for the multiple testing inherent in such an approach.

While automatically adjusting for between person bias, it is important to recognize that self-control designs are still subject to time-varying confounders. Examples of such confounders are concomitant vaccines, seasonal variation in the adverse event, changing diagnosis coding, and for infants, increasing age.

In a cohort design, the key challenge is to identify a control group that minimizes between person bias. The priority target groups for COVID-19 vaccines are likely to be similar to those for seasonal influenza vaccines (health care workers, the elderly, and potentially pregnant women), therefore, the use of time-varying propensity scores analysis for COVID-19 vaccine recipients and seasonal influenza recipient controls could minimize health care seeking and risk group biases in studies assessing the safety of COVID-19 vaccine. This approach could be used if seasonal influenza and COVID-19 vaccine campaigns are overlapping, providing not all individual get both vaccines at the same time. It would allow for matching on propensity scores

as well as the epidemiological week of exposure, to simultaneously control for presence of circulating wild-type virus. Another alternative would be to use influenza vaccine recipients from an earlier period. If the COVID-19 vaccine is given at times outside the influenza vaccination season, adjustment for any seasonal variation in the AE rates must be made.

Each vaccine safety study design has its different strengths and weaknesses, therefore it is often advisable to use multiple designs for the investigation of the same AE.

3.3 Vaccine exposure

Given the large variety of vaccine platform technologies used to develop COVID-19 vaccines, It is important to be able to perform vaccine-specific safety analyses. For this will be important to have complete information about the COVID-19 vaccine, such as manufacturer, brand name and batch number. While there are hopes that at least some of the new COVID-19 vaccines will be equipped with 2D barcodes which can be scanned to record this information, this is not guaranteed. Also, pilot projects with 2D barcodes in the US have revealed several hurdles slowing down that acceptance.⁷ Plans for alternative 'lower tech' means to capture the essential vaccine exposure information must therefore be made. For example, a standard data dictionary for each COVID-19 vaccine introduced for use could be maintained by Brighton Collaboration or WHODrug Global.

3.4 Analytic approaches for signal detection on electronic health record data

3.4.1 Rapid cycle analyses for suspected adverse events

Outcomes: Standard vaccine AEs following immunization (AEFI) during relatively brief post-vaccination risk intervals, or adverse events of special interest (AESIs) such as Guillain-Barré syndrome (GBS), Kawasaki disease and seizures. Serious outcomes from clinical trials, even if only one event was observed. AESI lists developed by the Safety Platform for Emergency vACcines (SPEAC)⁸ or provided by WHO.⁹

Frequency: Weekly data feeds and analyses.

Statistics: Maximised sequential probability ratio test.

7 Centers for Disease Control and Prevention. Summary report. Reporting for the adoption strategies for 2D barcode project (page 36). Available from: <https://www.cdc.gov/vaccines/programs/iis/2d-vaccine-barcodes/downloads/summary-report.pdf>. Accessed 9 December 2020.

8 Brighton Collaboration. Safety Platform for Emergency vACcines (SPEAC). Available from: <https://brightoncollaboration.us/speac/>. Accessed 9 December 2020.

9 Global Advisory Committee on Vaccine Safety, 27–28 May 2020, WER. 2020;95(28):331:325-336.

Model: Can be used with any study design., e.g.:

- Poisson model with age- and sex-adjusted expected counts from the general population, with a fixed X to Y day risk interval, where X and Y depend on the outcome;
- Poisson model with day zero as the risk window, with age- and sex-adjusted expected counts from general population;
- Self-controlled Bernoulli model, with a 1 to 14 day risk window and a pre-vaccination control window of between 15 to 42 days; and
- Self-controlled temporal scan model, with 1 to 42 days¹⁰ post-vaccination follow-up and a temporal scan statistic as the risk window. A post-vaccination control period (e.g. 21 to 34 days) may also be considered to address the possibility that it may not be appropriate to use a pre-vaccination period. If this is done, then the analysis will be delayed until the end of the post-vaccination control period. An adjustment to allow for delays in recording of AEs in the database should be considered.

Case-centered logistic regression could also be used with a sequential test (either a likelihood ratio test or a Wald test, with a flat Pocock-style threshold for controlling one-sided alpha-spending at 0.05), regardless of whether the 'expected' proportion of vaccinees who experience an AEFI during a risk window is inferred from historical controls, contemporaneous controls, or other comparison windows (in self-controls).

Sample size: Analyses should start immediately with the first week of post-authorization vaccinees, even if there are only a few exposed individuals. The sequential analyses should continue until there are at least one million individuals for the primary analysis, and 200,000 for the subgroup analyses.

3.4.2 Time-to-onset analysis

Time-to-onset analysis, using Kolmogorov–Smirnov tests,¹¹ has been used in spontaneous reporting system databases to compare time-to-event distributions for AESIs with:

- the time-to-event distributions for other events following exposure to the same vaccine; and
- the time-to-event distributions of AESIs after exposure to other vaccines.

The approach has been tested in a prospective observational setting but has not yet been used for signal detection in routine health care data. If influenza vaccination occurs in late 2020 in the northern hemisphere, prior to deployment of COVID-19 vaccines, this will provide an opportunity to construct time-to-event distributions for AESIs following influenza vaccine exposure to be used to compare with corresponding distributions following COVID-19 vaccine exposure.

¹⁰ The 42-day window would have to be censored when the second vaccine dose for a two-dose regimen is received.

¹¹ Van Holle L, Zeinoun Z, Bauchau V, Verstraeten T. Using time-to-onset for detecting safety signals in spontaneous reports of adverse events following immunization: a proof of concept study. *Pharmacoepidemiol Drug Saf.* 2012;21(6):603-10. doi: 10.1002/pds.3226.

3.4.3 Ecological methods

Ecological analyses may also be informative if COVID-19 vaccination uptake is high and over a short period, in a demographic group that can easily be selected, such as the elderly. A simple interrupted-time series analysis comparing rates of selected AESIs in the pre- and post-vaccine deployment periods may be able to detect a signal for an event with a brief onset-to-event interval in a subpopulation with high vaccine coverage, assuming wild-type virus circulation is relatively stable over these periods. It may also be possible to assess time effects by comparing changes in the incidence of AESIs in vaccination targeted groups with changes in non-targeted groups. However, it is important to take into consideration the potential changing patterns in health care due to the COVID-19 pandemic.

3.4.4 Data mining for unexpected adverse events

In addition to evaluating the risk of a predetermined list of AEFIs or AESIs, it will also be necessary to search for unexpected AEFIs or AESIs. To do this, a different approach is required:

Outcomes: Would include most ICD-10 (or ICD-9) codes with removal of those for elective events, such as well-care visits, pregnancies or for conditions not of interest such as cancer.

Frequency: Monthly data feeds and analyses.

Statistics: Sequential tree-based scan statistics, using ICD-9 or ICD-10 hierarchical coding structure.

Model: Self-controlled Bernoulli model, with days 1 to 21 as the risk window, and in separate analyses, days 22 to 42 post-vaccination and days 22 to 42 pre-vaccination as control windows.

Sample size / length of surveillance: Analyses should start immediately after authorization and ideally continue until there are one million doses for the primary analysis, 200,000 each for children under the age of 19 and elderly patients over the age 64 subgroups, and 50,000 for pregnant women subgroup.

3.4.5 Signal evaluation

Any signals must be thoroughly evaluated. Steps to be considered are:

1. data quality check:
 - a. examination of electronic health record linelist of all outcomes for the patients generating the signal (i.e. who have the AE); and
 - b. examination of temporal trends for both the vaccination and the outcome.
2. medical record review to confirm cases with the outcome, if not for all, at least for a sample, to assess the positive predictive value of the case identification algorithm;
3. COVID-19 vaccine brand- and platform-specific analyses with comparison with COVID-19 vaccines of a different brand or using a different platform;

4. adequate control for confounding, using study design, matching or adjustments, as necessary; and

Following this evaluation, any signals that remain of concern should be assessed further in a full appropriately-designed epidemiological study, which ideally should be done using a different dataset to the one in which the signal was detected.

3.5 Ongoing surveillance while signals are being evaluated and refined.

Regulators and public health agencies will not necessarily stop delivering vaccines when a safety signal exceeds a pre-defined statistical threshold. However, if this threshold is exceeded, the information will contribute to an overall analysis of vaccine's benefit-risk profile. These analyses should provide information on the magnitude of the risk and the attributable risk.

Although pre-signal statistical tests are sequential, ongoing surveillance after a signal can report nominal p-values and confidence intervals, in addition to the sequentially adjusted test that initially generated the signal. The multiplicity of outcomes under surveillance and the multiplicity of analyses of the accumulating data should continue to be reported.

3.6 Impact of change in health care use and provision on AESI identification and temporal trends

The pandemic has led to changes in health care use and provision and these changes are likely to continue into the vaccine deployment period. This may be reflected in observational data as an excess or a deficit of code counts for some AESIs or their proxies in the pandemic period. To understand these changes to the data available for analysis, it is recommended that counts and rates of both individual codes used in any AESI case-identification algorithm as well as the set(s) of codes used to identify each event be described over time both within and between databases, taking into account the type of database and the type of health care encounters typically captured (e.g. general practice vs. hospitalization). These counts and rates should be compared graphically to help to interpret the study results. It may also be possible to use historical periods to generate projected expected counts and rates in the absence of changes to health care use and provision.

3.7 Vaccine-associated enhanced disease

It has been suggested that individuals who receive a COVID-19 vaccine might be at increased risk of experiencing enhanced or more severe disease following vaccination or vaccine-

associated enhanced disease (VAED).¹² This has been suggested as a potential problem because of results in animal models with SARS-CoV-1 and MERS vaccines. Importantly, it has not been reported in animal models or in humans for any COVID-19 vaccine in advanced development. To be classified as a case of VAED, the individual would have to be a vaccine failure and also exhibit either a specific histopathology associated with advanced disease or have a specific biomarker. Unfortunately, none of the proposed patterns of histopathology have been confirmed and there is currently no known biomarker. Hence, diagnosis of VAED will require the demonstration that vaccinated individuals who develop COVID-19 disease have a higher risk of developing severe disease than non-vaccinated individuals. This assessment is further complicated by the fact that a higher risk of VAED could be expected as the levels of antibody wane with time, i.e. distant from vaccination. For this reason, it is being recommended that vaccinees be followed for an extended period, possibly for several years. A registry to follow-up participants from clinical trials who were in the control (unvaccinated) group and who choose to remain unvaccinated after vaccine introduction may be useful. It would be even more useful if they could have periodic blood draws that could be stored in biobanks for the future identification of potential biomarkers should VAED be recognized as a real AESI. It will not be possible to use of SCCS study design due to an indeterminate risk window following vaccination, therefore, a case-control design will probably be the most suitable for a study using standardized severity assessment scores for the multiple possible disease outcomes associated with COVID-19 disease to assess if the cases (vaccinated individuals with COVID-19 disease) are more likely to have severe disease than controls (unvaccinated individuals with COVID-19 disease).

12 Lambert PH, Ambrosino DM, Andersen SR, Baric RS, Black SB, Chen RT, et al. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. *Vaccine*. 2020;38(31):4783-4791. doi: 10.1016/j.vaccine.2020.05.064.

04 Performance indicators

Indicators have been adapted from existing immunization indicators, where possible, so that all countries can verify that their safety assessments for COVID-19 vaccines, but some specific indicators have been developed to respond to the current COVID-19 situation. Programme managers should take into consideration the fact that vaccine safety surveillance systems are for all vaccines, not just the COVID-19 vaccine and that routine vaccination will continue during COVID-19 deployment.

This section describes indicators obtained by extracting data on COVID-19 vaccines from pharmacovigilance monitoring and evaluation systems. The objectives of these indicators specific to COVID-19 vaccines are:

- at the national level:
 - help national AEFI committees, NRAs and NIPs/EPIs to identify any subnational programmatic issues, vaccine safety signals or any crisis in a timely manner and to make decisions for correction;
 - identify if the country's vaccine safety system is sensitive enough to identify signals and respond to them;
 - improve the quality of reporting, investigations and causality assessment; and
 - enable comparison of national safety performances with regional and global standards.
- at the subnational level:
 - help provincial governments to identify districts where surveillance is poor (low reporting);
 - identify and respond to programme and immunization errors early;
 - identify capacity gaps in specific districts, particularly those with vulnerable populations; and
 - allocate resources for building local training capacity.
- at the local level:
 - Identify zones with high COVID-19 coverage but poor AEFI reporting.

Since COVID-19 vaccines are novel, it has been suggested that a separate report should be generated monthly, based on:

- key COVID-19 vaccine pharmacovigilance indicators (**Table 2**):
 - total AEFI rate/100,000 COVID-19 vaccine doses administered/distributed;
 - serious AEFI (SAE) rate per 100,000 doses of COVID-19 vaccine administered/distributed;

- six indicators for monitoring the functionality of pharmacovigilance systems in the COVID-19 context (**Appendix 5.1**):
 - % of districts with silent COVID-19 AEFI reporting (i.e. no reports received);
 - % of districts not submitting monthly reports;
 - % of districts with >10 COVID-19 related AEFI reports / 100,000 doses of COVID-19 vaccines doses administered;
 - % of serious AEFI after COVID-19 vaccination investigated;
 - % of serious AEFI after COVID-19 vaccination investigations initiated within 2 days of notification; and
 - % of identical AEFI reports available with the NRA and the NPI/EPI (i.e. NRA reports =EPI reports).
- five indicators for monitoring the quality of pharmacovigilance systems in the COVID-19 context (**Appendix 5.2**):
 - % of case based AEFI reports shared between NRA and EPI <7 days of receipt;
 - % Completeness of AEFI reporting forms with the critical variables;
 - % of AEFIs reported within 48 hours of notification;
 - % of serious AEFI cases with causality assessed within 14 days of investigation; and
 - % of AEFI cases with causality assessment done where feedback was provided within 7 days of case classification.

Table 2: Key COVID-19 vaccine safety surveillance indicators

Indicator	Calculation	Information source	Measures	Primary collector
Total AEFI rate per 100,000 doses of COVID-19 vaccine doses administered / distributed*	No of AEFI reported at xx level / no of doses of COVID-19 vaccines administered or distributed at the same level X 100,000	Numerator: Case based AEFI reports from linelist or reporting forms Denominator: Vaccination records at the local level	If the reporting rate of AEFI differs from the ones available in clinical trials	Numerator: health care workers reporting AEFI Denominator: District immunization programme manager
Serious AEFI rate per 100,000 doses of COVID-19 vaccines doses administered / distributed*	No of serious AEFI reported at xx level / no of doses of COVID-19 vaccines administered or distributed at the same level X 100,000	Numerator: Case based serious AEFI reports from linelist or reporting forms Denominator: Vaccination records at the local level	If the reporting rate of serious AEFI differs from the ones available in clinical trials	Numerator: health care workers reporting serious AEFI Denominator: District immunization programme manager

**To consider the type of vaccine at the time of calculation.*

05 Appendices

Appendix 5.1: Indicators and targets for monitoring the performance of pharmacovigilance systems in COVID-19 context

Indicator	Target	Calculation	Information source	Measure	Main responsible
% of districts with silent (i.e. no reports received) COVID-19 AEFI reporting.	<10%	Number of districts where COVID-19 related AEFI was zero in the month of XX / No of Districts X 100	Reports submitted with zero AEFIs. during the previous month.	Identification of silent districts / areas within a province	District immunization programme manager sending periodic reports
% of districts not submitting monthly Reports	<10%	Number of districts where monthly COVID-19 related reports AEFI was not sent for a particular month / No of Districts X 100	Monthly (including zero) reports submitted by districts	Identification of delinquent reporting districts in a province	District immunization programme manager sending periodic reports
% of districts with >10 COVID-19 related AEFI reports/ 100,000 doses of COVID-19 vaccines doses administered	>80%	No of districts with > 10 AEFI reported for 100,000 doses of COVID-19 vaccines Administered / No of Districts X 100	Calculated from AEFI reporting form submitted by the districts following COVID-19 vaccination and Immunization registries	District performance on AEFI monitoring	District immunization programme manager sending AEFI reporting form and data on administered doses
% of serious AEFI after COVID-19 vaccination investigated	100%	Number serious AEFI investigated / Number of serious AEFI X 100	AEFI reporting form and AEFI investigation form	The quality of investigation of serious AEFI	District immunization programme manager coordinating the AEFI investigation

Indicator	Target	Calculation	Information source	Measure	Main responsible
% of serious AEFI after COVID-19 vaccination investigations initiated within 2 days of notification	>80%	Number serious AEFI investigations initiated within 2 days of notification / Number of serious AEFI X 100	AEFI reporting form and AEFI investigation form	The timeliness of investigation of serious AEFI	District immunization programme manager coordinating the AEFI investigation
Proportion of identical AEFI reports available with the NRA and the EPI (i.e. NRA reports =EPI reports).	1 for all months	No of AEFI reports with NRA in the month of XXXX / No of AEFI reports with EPI in the month of XXXX	AEFI reporting forms available with EPI or NRA following COVID-19 vaccination	Data sharing between the immunization programme and the regulators	Regulators and NIP/EPI programme managers

Appendix 5.2: Indicators and targets for monitoring the quality of pharmacovigilance systems in COVID-19 context

Indicator	Target	Calculation	Source of information	Measure	Main responsible
% of case based AEFI reports shared between NRA and EPI <7 days of receipt	100%	Number AEFI reports shared between NRA and EPI within 48 h of receipt / Number of AEFI reports X 100	AEFI reporting forms available with NRA and EPI or matching number of cases in linelist	Quality of data sharing	NRA and NIP/EPI programme managers
% Completeness of AEFI reporting forms with the critical variables	>80%	Number AEFI reports with complete critical variables* / Number of AEFI reports X 100	AEFI reporting forms	Quality of AEFI data collected	NIP/EPI programme managers
% of AEFIs reported within 48 hours of notification	>80%	Number AEFI reports sent to next level within 48 hours of notification / Number of AEFI reports X 100	AEFI reporting forms	Speed of response to AEFI notification	NIP/EPI programme managers

Indicator	Target	Calculation	Source of information	Measure	Main responsible
% of serious AEFI cases with causality assessed within 14 days of investigation	>80%	Number serious AEFI reports with causality assessed within 14 days of investigation / Number of serious AEFI reports X 100	AEFI reporting forms	Speed of response to AEFI investigation	NRA and NIP/EPI programme managers
% of AEFI cases with causality assessment done where feedback was provided within 7 days of case classification	>80%	Number causality assessed cases with feedback provided within 7 days of case classification / Number of AEFI reports with causality assessment done X 100	Documentation of feedback of AEFI causality assessment	Speed of response to AEFI causality assessment	NRA and NIP/EPI programme managers

* *Italics in reporting form*

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL