Global Vaccine Data Network®

Global Vaccine Data Network™

Observed versus expected analyses of COVID-19 vaccine adverse events of special interest

Study protocol

Version 1.4
18 October 2022

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THE GLOBAL VACCINE DATA NETWORK

The Global Vaccine Data Network™ (GVDN®) constitutes a multinational network of sites conducting globally coordinated active surveillance epidemiologic studies of the safety of vaccines, including COVID-19 vaccines. The GVDN network currently consists of 22 partners across 18 countries and is expanding. The GVDN is supported by the Global Coordinating Centre (GCC), hosted by UniServices at University of Auckland, Waipapa Taumata Rau in New Zealand. Through international collaboration with capacity for data linkage, it is now possible to have a large enough population to conduct robust analyses of rare events following vaccination.

GLOBAL **CO**VID **V**ACCINE **S**AFETY (GCoVS) PROJECT

Through UniServices, the GVDN was awarded a federal grant from the CDC/HHS to implement, host and manage a project titled "Assessing the safety of COVID-19 vaccines across large and diverse populations using the 17-country Global Vaccine Data Network Consortium", which is referred to as the **G**lobal **Co**VID **V**accine **S**afety (GCoVS) project.

FUNDING

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PROTOCOL DEVELOPMENT

This protocol was developed as one component of the GCoVS project, by the Background Rates and Observed vs. Expected Work Group. Members of the Work Group were associates of the GCoVS project partner sites who volunteered their time and expertise to develop a protocol suitable for use by multiple international sites, to harmonise collected data that could be amalgamated to increase study power by the GVDN. Expertise and administrative support were provided by the GVDN Global Coordinating Centre team, who are primarily based in Auckland, New Zealand.

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HISTORY OF PROTOCOL VERSIONS

Version number	Date	Summary of changes
0.1	16 November 2021	Protocol created
0.2–1.1	22 November 2021–28 February 2022	Protocol drafted by work group lead and members
1.2	21 March 2022	Protocol finalised by work group lead and members for review by GCoVS sites
1.3	5 April 2022	Minor amendments made to protocol wording in response to feedback from GCoVS sites
1.4	18 October 2022	Protocol formatted for publication and open access from the GVDN website

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ABBREVIATIONS

Abbreviation	Term
AESI	adverse event of special interest
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease due to SARS-CoV-2
ED	emergency department
GCC	Global Coordinating Centre for the Global Vaccine Data Network
GCoVS	Global COVID-19 Vaccine Safety project
GVDN	Global Vaccine Data Network
HHS	U.S. Department of Health and Human Services
HREC	Human Research Ethics Committee
ICD-10	International Classification of Diseases 10th revision
ID	identification number
IEC	Independent Ethics Committee
IRB	Institutional Review Board
O/E	observed vs. expected
PYRS	person-years
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMR	standardised morbidity ratio
vs.	versus

PROTOCOL SYNOPSIS

Title

Observed versus expected analyses of COVID-19 vaccine adverse events of special interest

Background

Comparison of background rates and post-vaccination rates is a rapid and useful tool for the surveillance of vaccine adverse events of special interest (AESI). Countries with access to immunisation registers can provide post-vaccination rates, which allows for observed versus (vs.) expected comparisons of AESI. Such comparisons have the potential to investigate early safety concerns, inform vaccination policies and can be conducted rapidly; well before a more sophisticated analysis can be planned and carried out.

Aim and objectives

The aims and objectives are to calculate the observed rates of specified, consistently defined AESI outcomes according to vaccine brand and vaccination dose profile, and post-vaccination period for population subgroups (age and sex) by site since the introduction of COVID-19 vaccination, and compare these with the expected rates for 2015–2019, from implementation of the GVDN Background rates of adverse events of special interest following COVID-19 vaccination study protocol in the same populations. Where possible, observed counts from multiple sites will be aggregated and summed to increase study power.

Study design

This is an observational retrospective study designed to estimate the association between selected AESIs and COVID-19 vaccination.

Population

Participants are individuals vaccinated with COVID-19 vaccines presenting to site healthcare facilities (hospital inpatient, outpatient, emergency department, and primary care) during the period of the study.

Study period

The study period is from the start date of the site-specific COVID-19 vaccination programme with no specified end date to provide long term active COVID-19 vaccine safety monitoring.

Outcome event

An outcome event is any one of 13 AESI defined by harmonised ICD-10 codes occurring during the study period within a COVID-19 vaccinated individual where no previous outcome events have occurred within a washout duration of 365 days. The outcomes are the same as those in the GVDN Background rates of adverse events of special interest following COVID-19 vaccination study protocol.

Analyses

The count of observed cases per 100,000 person-years during the follow-up period for a given vaccination profile and post-vaccination period will be calculated and stratified by age group and sex. These counts will be compared with the expected number of cases identified in the age- and sex-stratified background rates for 2015–2019, from implementation of the GVDN Background rates of adverse events of special interest following COVID-19 vaccination study protocol.

Each of the age-sex-stratified person-years will be multiplied by the corresponding age-sex-stratified background rate per 100,000 person-years. The resulting expected number of cases in each stratum can then be summed to give the expected number of cases that we would expect in the observed follow-up period. 95% confidence intervals will be calculated based on the Poisson distribution of the observed counts.

Where possible, the observed number of cases per 100,000 person-years for each AESI and age-sex stratified for a given vaccination profile and post-vaccination period will be aggregated and summed across available sites.

1. BACKGROUND

Before the unprecedented global rollout of COVID-19 vaccines, a list of adverse events of special interest (AESI) was developed based on the pathophysiology of SARS-CoV-2 infection and what was known about vaccine safety issues in general. Post vaccination rollout, further events have been added in response to the safety signals of thrombosis with thrombocytopenia syndrome and myocarditis, respectively.

The estimation of background and post-vaccination rates is a rapid and useful tool for the surveillance of vaccine AESI. In the context of a global collaboration, estimation of background rates is feasible for many countries since only outcome and population estimates as denominator are required. Background rates provide important context for regulatory and public health agencies to quickly assess emerging safety signals. Countries with access to immunisation registers can also provide post-vaccination rates, which allows for observed versus (vs.) expected comparisons of AESI. Such comparisons have the potential to investigate early safety concerns, inform vaccination policies and can be conducted rapidly; well before a more sophisticated analysis can be planned and carried out.

One highly relevant example of this approach was the thrombosis with thrombocytopenia signal, which prompted the suspension of the use of Oxford/AstraZeneca COVID-19 vaccine on 11 March 2021 in Denmark and Norway. Immediately, a collaboration between Denmark and Norway was formed to provide observed vs. expected comparisons for a range of thrombotic events based on nationwide register data. The results showed an increased risk of serious thrombotic events primarily in the form of cerebral venous sinus thrombosis following vaccination with the adenoviral vector vaccine, corresponding to one case per ~40,000 vaccinations.[1] On March 25, the vaccine was removed from the Danish programme. Norway similarly removed the vaccine from the national programme on May 12. Additional studies have confirmed this vaccine risk.

2. AIM AND OBJECTIVES

2.1 Aim

The study aims to calculate, and report the observed vs. expected rates of specified, consistently defined adverse events of special interest.

2.2 Objectives

The study has three objectives:

a) Identify the rates of consistently defined AESI outcomes from different sites (countries) and vaccinated population since the introduction of COVID-19 vaccination (observed rates).
b) Calculate the expected rates of AESI outcomes using the age-sex-stratified pre-COVID-19 vaccination background rates data (2015–2019) from the same populations, collected in the GCoVS Background rates of adverse events of special interest following COVID-19 vaccination study.
c) Compare the observed vs. expected (O/E) rates according to vaccine brand and vaccination dose profile, and post-vaccination period, in the underlying population.

3. METHODS

3.1 Study design

This is an observational retrospective study designed to estimate the association between selected AESIs and COVID-19 vaccination.

3.2 Participant selection

Participants are individuals vaccinated with COVID-19 vaccines in the populations represented by the sites. Please refer below for the description of 'patient types'.

3.2.1 Patient types

Patient types include hospital inpatients, outpatients, emergency department (ED) patients, and primary care patients. Definitions will vary between countries. In some countries separate datasets exist for emergency and outpatient departments. In countries without clearly defined patient types, contact duration (if available) can be used as a proxy for patient types at discretion of the site lead(s). As an example, a contact duration of 24 hours or longer can be used as a proxy for inpatients.

3.2.2 Age group intervals

The age group interval could be 5-years (preferred interval), 10-years, or 20-years depending on the rarity of the outcome events at participating sites, refer to Table 1. Please also note that it is possible to combine different age groupings, e.g., 0–19 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–49 years, 50–59 years, 60–79 years, and 80+.

Table 1. Age group intervals

5-year age group (preferred)	10-year age group	20-year age group
0–4	0–9	0–19
5–9		
10–14	10–19	
15–19		
20–24	20–29	20–39
25–29		
30–34	30–39	
35–39		
40–44	40–49	40–59
45–49		
50–54	50–59	
55–59		
60–64	60–69	60–79
65–69		
70–74	70–79	
75–79		
80+	80+	80+

3.3 Study period

The study period is from the start date of the site-specific COVID-19 vaccination programme[2] with no specified end date to provide long term active COVID-19 vaccine safety monitoring.

3.4 Study variables

3.4.1 Outcomes

The outcomes are defined in Table 2. They are the same outcomes as those in the GVDN Background rates of adverse events of special interest following COVID-19 vaccination study protocol. Each AESI was defined by harmonised ICD-10 codes. Some AESIs are defined by one ICD-10 code, others are defined by more than one, in this case any one of the ICD-10 codes listed constitutes an AESI case. The ICD-10 codes should be included/searched in primary and/or secondary diagnoses (may also be termed "associated" or "related"). Please see Table 2 for a list of the ICD-10 codes accompanied by their text.

Table 2. Study outcome measures

Category	AESI	ICD-10 Code
Neurological conditions		
	Guillain-Barré syndrome	G61.0
	Transverse myelitis	G37.3
	Facial palsy	G51.0
	Acute disseminated encephalomeningitis	G04.0
	Febrile seizures	R56.0
	Generalised seizures	G40.0–G40.9, G41.0, R56.8
Haematological conditions		
	Thrombocytopenia	D69.5, D69.6
	Idiopathic thrombocytopenia	D69.3, D69.4
	Pulmonary embolism	I26.0, I26.9
	Cerebral venous sinus thrombosis	I63.6, I67.6
	Splanchnic vein thrombosis	I81, I82.0, I82.3
Cardiovascular conditions		
	Myocarditis	I40.1, I40.8, I40.9, I51.4
	Pericarditis	I30.0, I30.8, I30.9

3.4.2 COVID-19 vaccine brand and vaccination dose profile

Each site will report on vaccination schedules relevant to that site. The brand and dose profile describes the history of vaccines received by brand and the dose number. This brand and dose profile shorthand allows for the description of homologous and heterologous schedules and revaccination schedules. Individuals who have received more than one COVID-19 vaccination will contribute data on each dose they received.

3.4.2.1 Vaccine brand

Vaccine platform and type are not consistently identified as separate entities in current literature. In this protocol, the terms platform and type are used interchangeably. The vaccine brand codes are defined in Table 3, for example, AZD = AstraZeneca COVID-19 vaccine, BNT = Pfizer/BioNTech COVID-19 vaccine, and MOD = Moderna COVID-19 vaccine. Vaccines with the same formulation and made by different manufacturers are grouped, e.g., Nuvaxoid [Novavax] and Covovax [Serum Institute of India] have the same formulation and both are coded as NVX.

3.4.2.2 Vaccination dose profile

The vaccine dose number relates to the vaccination schedule and is independent of brand. The vaccine dose is identified by a number placed immediately after the vaccine brand code, i.e., 1 = first COVID-19 vaccine dose, 2 = second COVID-19 vaccine dose (whether the brand is the same or different to that received for dose one), 3 = third COVID-19 vaccine dose, and so forth.

As examples, BNT1 = First COVID-19 vaccination was Pfizer/BioNTech vaccine, and BNT1AZD2MOD3 = First COVID-19 vaccination was the Pfizer/BioNTech vaccine, second COVID-19 vaccination was AstraZeneca vaccine, and third COVID-19 vaccine was the Moderna vaccine. In the example, BNT1AZD2MOD3, the individual would contribute data on BNT1, BNT1AZD2, and BNT1AZD2MOD3.

Table 3. Vaccine brand codes

Vaccine platform/type	Code	Vaccine brand(s) [Manufacturer(s)]
Inactivated	BIBP	Covilo or SARS-CoV-2 Vaccine (Vero Cell) [Sinopharm (Beijing)]
	BBV	Covaxin [Bharat Biotech]
	SINO	CoronaVac or Sinovac [Sinovac Biotech]
	VAL	COVID-19 Vaccine Valneva [Valneva]
	WIBP	Inactivated (Vero cell) [Sinopharm (Wuhan)]
Nucleic acid-based	CADI	ZyCoV-D [Zydus Cadila]
	BIBNT	Comirnaty or Riltozinameran or Pfizer/BioNTech COVID-19 Vaccine Bivalent [Pfizer/BioNTech]
	BNT	Comirnaty or Tozinameran [Pfizer/BioNTech or Fosun-BioNTech]
	PBNT	Comirnaty or Tozinameran Paediatric [Pfizer/BioNTech or Fosun-BioNTech]
	BIMODO	Elasomeran or Spikevax Bivalent Original/Omicron [Moderna]
	HMOD	Elasomeran or Spikevax or TAK-919 Half Dose [Moderna or Takeda]
	MOD	Elasomeran or Spikevax or TAK-919 [Moderna or Takeda]
Protein-based	BIOE	Corbevax [Biological E Limited]
	CVF	Covifenz [Medicago]
	MVC	MVC-COV1901 [Medigen]
	NVX	Covovax or Nuvaxoid [Novavax or Serum Institute of India]
	SCB	Clover [Clover Biopharmaceuticals]
Non-replicating viral vector	ADN	Convidecia or Convidence [CanSino]
	AZD	Covishield or Vaxzevria [AstraZeneca or Serum Institute of India]
	LGM	Sputnik Light or Gam-COVID-Vac [Gamaleya Research Institute]
	MGM	Sputnik M [Gamaleya Research Institute]
	VGM	Sputnik V [Gamaleya Research Institute]
	JJJ	Janssen or Jcovden [Janssen/Johnson & Johnson]

Note: This table was current at the time of publication, new vaccines may have been authorised for use since publication.

3.4.3 Adverse events of special interest (AESI) codes

Table 4 provides the code to identify each AESI in the dataset.

Table 4. AESI codes

Code	AESI
	Neurological conditions
NE_GBS	Guillain-Barré syndrome
NE_TRM	Transverse myelitis
NE_BP	Facial palsy
NE_ADM	Acute disseminated encephalomeningitis
NE_FSZ	Febrile seizures
NE_GSZ	Generalised seizures
	Haematological conditions
HM_THR	Thrombocytopenia
HM_ITC	Idiopathic thrombocytopenia
HM_PEM	Pulmonary embolism
HM_CER	Cerebral venous sinus thrombosis
HM_SVT	Splanchnic vein thrombosis
	Cardiovascular conditions
CV_MYO	Myocarditis
CV_PER	Pericarditis

3.5 Data preparation

3.5.1 Post-vaccination periods

Periods following the vaccine brand/vaccination dose profile of interest (see above) where the observed rates are ascertained. The following risk intervals will be used after each dose: 0–7 days, 8–21 days, and 22–42 days, illustrated in Figure 1. For each vaccination dose, Day 0 is the day of vaccine receipt.

Figure 1. Post-vaccination risk windows following a single vaccination

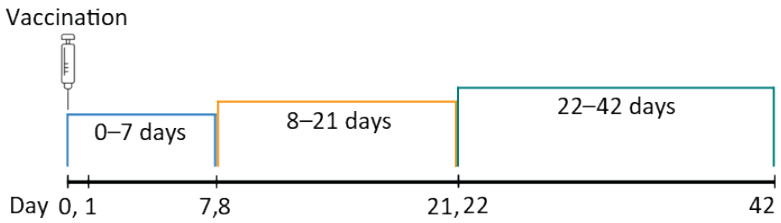
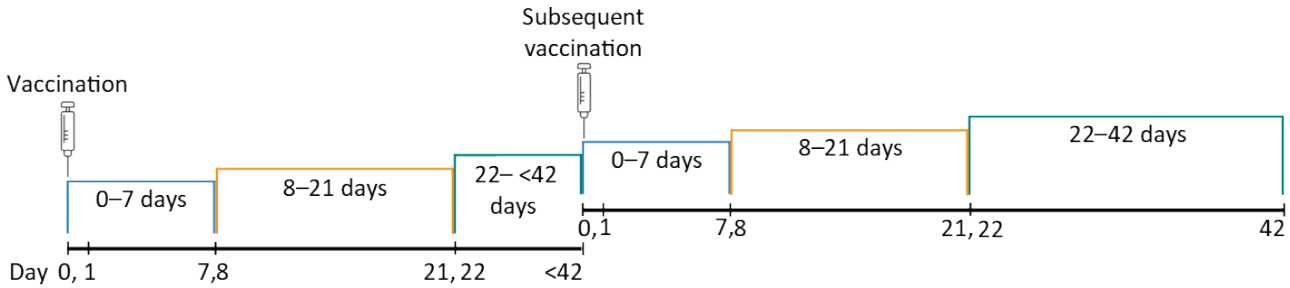


Figure 2 illustrates determination of risk windows when a second COVID-19 vaccination is administered within a risk window following a prior COVID-19 vaccination. When this occurs, the previous dose risk window ends, and the day of the subsequent vaccination is reset to Day 0 and the intervals of 0–7 days, 8–21 days, and 22–42 days observed.

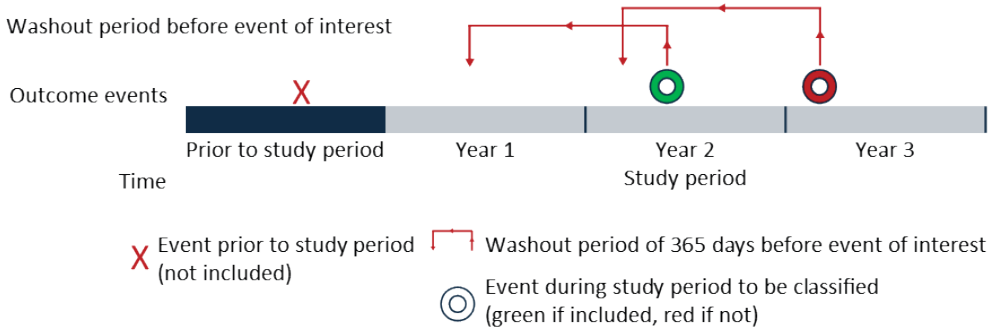
Figure 2. Post-vaccination risk windows when a second COVID-19 vaccination is administered within a risk window following a prior COVID-19 vaccination



3.5.2 Washout period

Outcome events that occur outside the study period or within a washout period of **365 days**, see Figure 3, are not included. An individual may contribute several outcome events on the condition they are separated in time by at least the washout period, see Figure 3.

Figure 3. Example of inclusion, or not, of events during study period and washout period



3.6 Reporting AESI rates

3.6.1 Observed number of cases

The observed rates for a given post-vaccination period and for a given vaccine brand/vaccination dose profile comprise the number of cases observed in the period with the requisite vaccine brand/vaccination dose profile divided by an estimate of the corresponding duration of follow-up in this period obtained from the underlying population with the requisite vaccine brand/vaccination dose profile.

The number of observed cases for each combination of AESI, vaccine brand/vaccination dose profile, and post-vaccination period will have to be reported. Case definitions should follow those given in the GVDN Background rates of adverse events of special interest following COVID-19 vaccination study protocol, i.e., if a site has reported background rates for myocarditis cases using inpatient hospital records, the observed rates should be based on myocarditis cases using inpatient hospital records. Similarly, the identification of incident cases from outcome events (or episodes) using a wash-out period of one year should adhere to the approach laid out in the GVDN Background rates of adverse events of special interest following COVID-19 vaccination study protocol.

Event date, number of doses, vaccine brand(s) and date of each vaccination must be available at the individual-level to allocate cases correctly to vaccine brand/vaccination dose profile and post-vaccination periods.

PATIENT_TYPE
1 = emergency department, 2 = hospital inpatient, 3 = hospital outpatient, 4 = primary care, 5 = all of hospital inpatient, outpatient, emergency department, primary care, 99 = missing.

V_PROFILE
The vaccine brand and dose profile describe the history of vaccines received by brand and the dose number. Refer to Section 3.4.2 for detailed information.

V_PERIOD
Post-vaccination risk period after each dose: 0–7 days, 8–21 days, 22–42 days.

COUNT
The number of observed outcome incident cases in the patient type, vaccine profile, and post-vaccination period group specified by the other columns.

3.6.2 Duration of follow-up

The duration of follow-up will have to be reported for all relevant vaccination schedules and post-vaccination periods according to the same site-specific age and sex stratification used in the calculation of background rates. However, since each site could report background rates in AESI-specific strata which supported local guidelines for data privacy, it is likely that several age group stratifications, both within and across sites, have been used. In this case, the post-vaccination follow-up should be reported according to the age stratification with the largest number of groups possible, ideally the 5-year grouping.

3.6.2.1 Scenario I: Immunisation register with individual-level data available.

The immunisation register must cover the same underlying population as the outcome and population data sets used in the calculation of background rates.

For each vaccination schedule and post-vaccination period, it will be easy to calculate the exact duration of follow-up and stratify it according to age and sex. Immunisation register data will typically be in long-format with rows containing recordings of vaccination events:

Rows: Unique vaccination events
Columns: ID, SEX, DOB, V_BRAND_DOSE, V_DATE

ID
Individual-level identifier, often pseudo-anonymised. String, e.g., ID0014984.

SEX
M, F, O where M=male, F=female, O= other gender or missing.

DOB
Date of birth, two-digit day, three-letter abbreviation of the month, four-digit year, e.g., 15AUG2002.

V_BRAND_DOSE
Vaccine brand and dose, e.g., BNT1.

V_DATE
Date of vaccination, two-digit day, three-letter abbreviation of the month, four-digit year, e.g., 04JUL2022.

V_PROFILE
The vaccine brand and dose profile describe the history of vaccines received by brand and the dose number. Refer to Section 3.4.2 for detailed information.

V_PERIOD
Post-vaccination risk period after each dose: 0–7 days, 8–21 days, 22–42 days.

This immunisation dataset is then converted into an aggregated dataset.

Columns: V_PROFILE, V_PERIOD, SEX, AGE, PYRS.

AGE
The pre-defined age group intervals (5-year, 10-year, or 20-year). Where possible, the narrowest age intervals should be used.

SEX
M, F, O (other genders or missing).

PYRS (person-years)
The cumulative amount of follow-up (in years) in the vaccinated population in the age-, sex-, vaccine profile, and post-vaccination period group specified by the other columns. Individuals who receive two, three or more doses, contribute follow-up after each dose. If the inter-dose interval is less than 42 days, the follow-up should be counted towards the most recent dose received.

As an example, if an individual is vaccinated with a second dose of BNT, 26 days after a first dose of BNT, this individual's contribution to the PYRS for BNT1 will be 26 days with 8, 14 and 4 days in the 0–7, 8–21 and 22–42 days periods, respectively. After that, further follow-up is counted after the second dose of BNT with 8, 14, and 21 days in the 0–7, 8–21, and 22–42 days periods, respectively.

3.6.2.2 Scenario II: Population-level vaccination uptake.

In many countries, daily updated vaccination uptake dashboards exist. To the extent that the number of individuals vaccinated according to a specific schedule is given in age and sex strata, these numbers can be converted into PYRS by multiplying with the number of days in the relevant PERIOD.

As an example, if the number of males aged 60–79 years at site A that have received the first dose of BNT is 1,421,775, the corresponding rows in the aggregated data set to be reported to the GVDN is:

AGE=60–79, SEX=M, V_PROFILE=BNT1, V_PERIOD=0–7 days, PYRS=1421775*(8/365)
AGE= 60–79, SEX=M, V_PROFILE=BNT1, V_PERIOD=8–21 days, PYRS=1421775*(14/365)
AGE= 60–79, SEX=M, V_PROFILE=BNT1, V_PERIOD=22–42 days, PYRS=1421775*(21/365)

A limitation of this approach is that the age and sex strata used may not match the ones used in the background rates calculations.

3.7 Data analysis

3.7.1 Calculation of observed vs. expected measures

For each site we will calculate the observed number of cases and compare this with the expected number of cases using the age- and sex-stratified background rates.

a) The observed follow-up period (PYRS) for a given vaccination profile and post-vaccination period is stratified according to age group and sex. As an example, we may observe 7 cases per 7345 person-year of follow-up which when stratified (by females/males and 20–39 year/40+) corresponds to, 1267 PYRS among males aged 20–39 years, 1345 PYRS among females aged 20–39 years, 2150 PYRS among males aged 40+ years, and 2583 PYRS among females aged 40+ years.
b) Each of the age-sex-stratified PYRS are multiplied by the corresponding age-sex-stratified background rate (2015–2019). This will result in the expected number of cases in each stratum, which can then be summed to give the expected number of cases that we would expect in the observed follow-up period. In our example, we may calculate that we would expect 9.34 cases in the 7345 person-years of follow-up.

c) We now have our observed vs. expected results, e.g., 7 vs. 9.34 and 7/7345 vs. 9.34/7345 resulting in an O/E ratio of 0.75.

d) 95% confidence intervals can be calculated based on the Poisson distribution of the observed counts.

3.7.2 Combining results across sites

Ideally, the observed number of cases per AESI and age-sex stratified PYRS for a given vaccination profile and post-vaccination period, are aggregated across available sites, and the combined observed vs. expected numbers of cases and the O/E ratio is calculated with 95% confidence interval. The expected number of cases in the vaccinated population is estimated by multiplying the age, sex, and site-specific background rates with the age-sex-site stratified PYRS, and then summed across sites.[1]

For sites that cannot provide the data, site-specific O/E ratios for each AESI, vaccination-profile and post-vaccination period of interest can be combined in meta-analysis using the random effects model accounting for heterogeneity between study sites. Outliers will be investigated.

3.7.3 Analysis schedule

After the initial conduct of the observed vs. expected analyses using all available data at the time of analysis, it is planned to update the results ideally each six months. Date availability/updates will vary across sites.

4. COMPLIANCE

4.1 Ethics approval and local authorisations

The study will be conducted in full conformance with local authority requirements.
Ethical approval will be sought from the local Human Research Ethics Committee (HREC)/Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required.

4.2 Changes to the protocol

Written protocol amendments will be documented as changes to the protocol, which will be summarised in the table of protocol amendments at the beginning of this publication. Major changes will almost always need to be approved by the appropriate HREC/IRB/IEC if such review is required at the site. In such circumstances, the adjustment will not be enacted until it has received approval. The investigator will file minor protocol adjustments, such as administrative changes, at each participating site and submit them to the appropriate local HREC/IRB/IEC as required.

5. REFERENCES

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