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ORIGINAL RESEARCH ARTICLE

Optimizing Safety Surveillance for COVID-19 Vaccines at the National Pharmacovigilance Centre Lareb: One Year of COVID-19 Vaccine Experience

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Abstract

Introduction Due to the COVID-19 vaccination campaign, national pharmacovigilance (PV) centres had to deal with high volumes of Individual Case Safety Reports (ICSRs) that needed to be processed and assessed in a short time span. This necessitated the development of a dedicated system to enable near real-time vaccine safety monitoring at the Dutch PV Centre Lareb.

Objectives To describe infrastructure, processes and Adverse Events Following Immunisation (AEFIs) reported for vaccine safety monitoring of COVID-19 vaccines during a large-scale vaccination campaign in the Netherlands.

Methods A COVID-19 tailored vaccine web-based reporting form collected information on the vaccine administered, AEFIs and other (medical) information. A fully automated process for ICSRs enabled the handling of the majority of common and known reported AEFIs. All other ICSRs were triaged daily and processed separately. There were daily signal detection meetings and weekly reports for batch analysis.

Results In 2021, Lareb received 184,411 ICSRs, a reporting rate of 0.67% for vaccines given in the Netherlands. 887,954 AEFIs were reported, mostly well-known, nonserious AEFIs; 2.4% were serious and 0.3% were fatal. 33.1% of all ICSRs were processed fully automatically. Based on the daily triage, 4.2% were flagged as 'high priority'; 62.7% as 'low-priority'. Twenty-seven signals and news stories about the COVID-19 vaccines were disseminated.

Conclusions Due to automatic processing of well-known AEFIs, daily triage and signal detection meetings, 99.9% of the ICSRs were processed within the compliance timeframe to Eudravigilance, and signal detection was performed during a large-scale vaccination campaign. These experiences may serve as a blueprint for future mass vaccination programs.

1 Introduction

Vaccine safety surveillance during a pandemic is challenging. In 2020, when the world was taken by surprise by the COVID-19 pandemic, there was a strong need for the development of vaccines, which were developed at a rapid pace. At the end of 2020, the first vaccine produced by BioNTech/Pfizer was recommended by the European Medicines Agency (EMA) to be granted a conditional marketing authorisation [1]. In a few months, four brands (Pfizer [2], Moderna [3], AstraZeneca [4] and Janssen [5]), based on two vaccine types (mRNA and viral vector), became available in the Netherlands, each with limited real-world safety data. More recently, in December 2021, the COVID-19 vaccine from Novavax became available as a fifth registered vaccine in our country [6].

Worldwide, a large population was vaccinated, and the administration of vaccines occurred in a short time

Key Points

Mass vaccination campaigns for COVID-19 necessitated the development of a dedicated system to enable near real-time vaccine safety monitoring.

Automatic processing of well-known adverse events following immunisation, daily triage and signal detection meetings enabled timely processing and signal detection for large numbers of incoming reports.

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frame. Although large clinical trials have been conducted [7–10], rare serious and previously unknown events may still occur. During a massive vaccination campaign with new vaccines, there are several considerations. Because these vaccines were developed at a rapid pace, risk groups for developing Adverse Events Following Immunization (AEFIs) [11] are not yet well established. In addition, for new vaccines, potential long-term effects are not entirely known. During largescale vaccination campaigns, it can be difficult to differentiate between events that occur coincidentally within a plausible time frame after vaccination and those that are 'real' effects of the vaccine given [12]. Because vaccines are biological products and often need special storage conditions, 'batch-' and 'cold chain-'related safety issues may occur and need to be traced quickly before large groups of people are vaccinated [13]. Finally, good communication is crucial because of the risk of misinformation—for instance, via social media.

The spontaneous reporting system in the Netherlands is maintained by the pharmacovigilance (PV) centre Lareb. Potential safety signals are forwarded to the Dutch Medicines Evaluation Board (MEB) who decide on the possible regulatory actions needed. In the Netherlands, the COVID-19 vaccination campaign started on 6 January 2021 [14]. As in other countries, this led to a challenge to our PV centre, since we expected a high volume of Individual Case Safety Reports (ICSRs) that needed to be processed and assessed in a short time span. This necessitated the development of a dedicated system to allow for near real-time processing of ICSRs and vaccine safety monitoring. A specific COVID-19 vaccine web-based reporting form was developed that enabled the collection of information on the vaccine administered, the experienced AEFI, and other information needed for the assessment of ICSRs.

The aim of this article is to describe the infrastructure, processes, methods developed and AEFIs experienced for vaccine safety monitoring during the COVID-19 pandemic in the first year of safety monitoring of the COVID-19 vaccines in the Netherlands. The paper focusses on the process of detection and initial enhancement of the safety signals. Regulatory actions are not covered.

In addition to direct reports from healthcare professionals and patients, Lareb also receives ICSRs indirectly via Marketing Authorization Holders (MAHs). ICSRs from the Netherlands must be sent directly to the Eudravigilance database [15] of the European Medicines Agency by MAHs. Their reports are automatically forwarded from Eudravigilance to the relevant national competent authorities, in case of Dutch reports to Lareb. Because the route of handling of these reports is different from the directly received reports, we will not describe their processing in detail below. They are, however, taken into account during signal detection activities.

2 Methods

2.1 Infrastructure

2.1.1 Reporting Form and Linkage with National Vaccination Registry

A specific COVID-19 vaccine-dedicated web-based reporting form [16] was developed that enabled the collection of spontaneously reported information on the vaccine administered, AEFIs and other information needed for assessment and signal detection (Fig. 1). For other medicinal products and vaccines reporting schemes were operated as before. In the COVID-19 vaccine reporting form, patient-friendly descriptions helped in selecting the most appropriate terms, for example, the brand name of the vaccine and a patient-friendly translation of the right Medical Dictionary for Regulatory Activities (MedDRA) term [17], to collect the AEFIs. The most common well-known AEFI that were labelled in the Summary of Product Characteristics (SmPC) at the time of marketing authorization were prespecified on the reporting form to process these ICSRs rapidly. These included injection site reactions, fever, chills, headache, nausea, myalgia, arthralgia, malaise and fatigue. For injection site reactions and fever, conditional questions were asked to gather more detailed and high-quality information to distinguish between the highest body temperature measured or different types of injection site reactions, injection site inflammation and extensive limb swelling.

To process answers automatically in specific ICH-E2B(R3) fields [18] in the ICSR management system, specific COVID-19-related closed questions were asked, for example, past drug therapy on previous COVID-19 vaccines and medical history on previous COVID-19 infection(s).

Together with the prespecified AEFIs, most of the fields are filled automatically in our ICSR management system. The data structure of this system is compliant with the ICH-E2B(R3) format, which allows for standardised storage and exchange of ICSRs worldwide. All AEFIs were coded according to MedDRA (versions 23.1, 24 and 24.1) [17].

Next to the prespecified reactions, the reporter could choose an option to provide other AEFIs as free text. For all events, information was requested regarding latency time, seriousness according to international criteria, severity of the reaction according to a 5-point Likert scale (only on the consumer reporting form) [19], investigations, treatment, duration time and outcome. An event was considered to be serious if the patient died, the event led to (prolonged) hospitalisation, or a life-threatening event occurred. The patients were not asked if an event was 'serious', but only if one of the aforementioned conditions applied. Other information was asked about the batch number, previous COVID-19 vaccine(s),

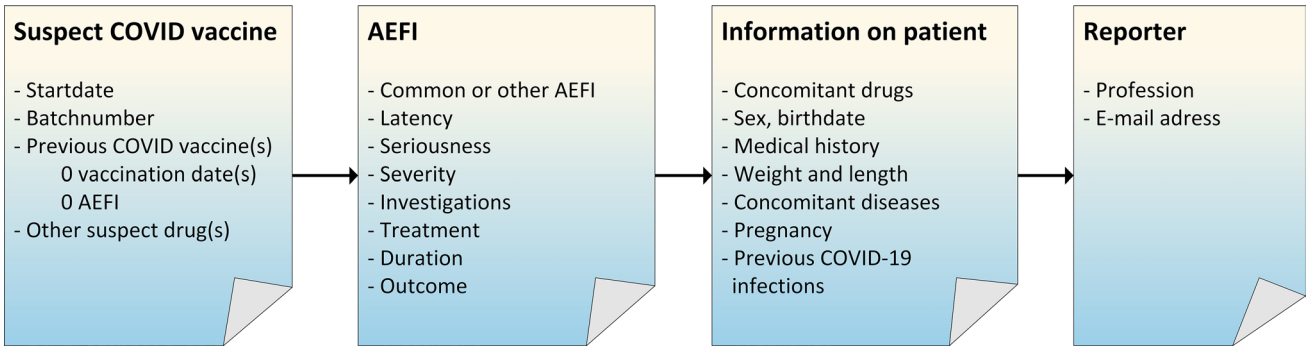

Fig. 1 Structure COVID-19 reporting form

other suspected drugs, concomitant drugs, medical history, concomitant diseases, pregnancy, previous COVID-19 infections and patient characteristics such as date of birth.

Since vaccines are produced in batches, quality defects related to the production may have affected a specific batch. This would have necessitated the identification of specific batches. For this reason, when not known and with permission from the reporter, batch numbers were retrieved from the national vaccination registry (CIMS) [20] maintained by the National Institute for Public Health and the Environment (RIVM). In the reporting form, the citizen service number (BSN) is asked. This number is stored in a dedicated database and is not visible in the ICSR management system for privacy reasons. Once a week, a list of ICSRs with unknown batch numbers was sent to CIMS, and provided with batch numbers (if known in CIMS). This list was automatically imported to the specific ICSR in the ICSR management system and exported to Eudravigilance, the system for managing and analysing information on suspected adverse reactions to medicines that have been authorised or are being studied in clinical trials in the European Economic Area (EEA) [15]. If no batch number was found in CIMS, a second attempt was made. When the batch number retrieval was successful or failed after the second attempt, the citizen service number (BSN) was set to 'privacy' in the dedicated database.

With the linkage between adverse events and batch numbers of the vaccine administered, and the availability of data on background incidences of AEFI, we enabled the development of dedicated signal detection tools, including the analysis of batch-specific ICSRs [21].

2.2 Process

2.2.1 Processing and Assessment of Individual Case Safety Reports (ICSRs)

A fully automatic process for ICSRs enabled the handling of the majority of common and known reported AEFIs that were prespecified on the reporting form. We decided to set up this new way of working to manage large numbers of straightforward ICSRs. The criteria for the automatic handling of ICSRs were as follows: the only suspected drug was a selected COVID-19 vaccination, concomitant drugs were coded automatically by selecting these from a list on the reporting form, AEFIs were reported as non-serious according to international criteria, and all selected AEFIs for automation had corresponding MedDRA LLT codes [17], which were mapped automatically on the pre-specified AEFIs in the reporting form. This automation process ran several times a day and made these ICSRs available for further processes such as signal detection within a day.

All other ICSRs were triaged daily by team PV assessors with expertise in vaccine AEFIs and signal detection (Fig. 2). A report was selected as high priority when it was marked as serious according to CIOMS criteria [22], concerned an Adverse Event of Special Interest (AESI) [23], or was deemed to have high signal value. This team (13.7 full-time equivalents (FTEs)) was also responsible for the signal detection and communication and included FTEs for coordination of tasks.

We arranged a 'low-priority' team (16.4 FTE) that handled ICSRs in a brief timespan on the most common AEFIs and reports we selected as 'low-priority' and a 'high-priority team', consisting of dedicated vaccines experts at Lareb, for assessing ICSRs that needed further clinical review and serious ICSRs. The total FTEs of this 'COVID-19-team' is 30.1 FTEs. For comparison, the vaccine team for the pharmacovigilance before COVID-19 consisted of 3.75 FTEs.

2.2.2 Signal Detection and Signal Management

A possible safety signal in this context is defined as 'information about a new or known adverse reaction that may be caused by a COVID-19 vaccine and that warrants further investigation' [24]. Signal detection generally relies on both the analysis of the clinical information and disproportionality analysis. In the latter approach a Reporting

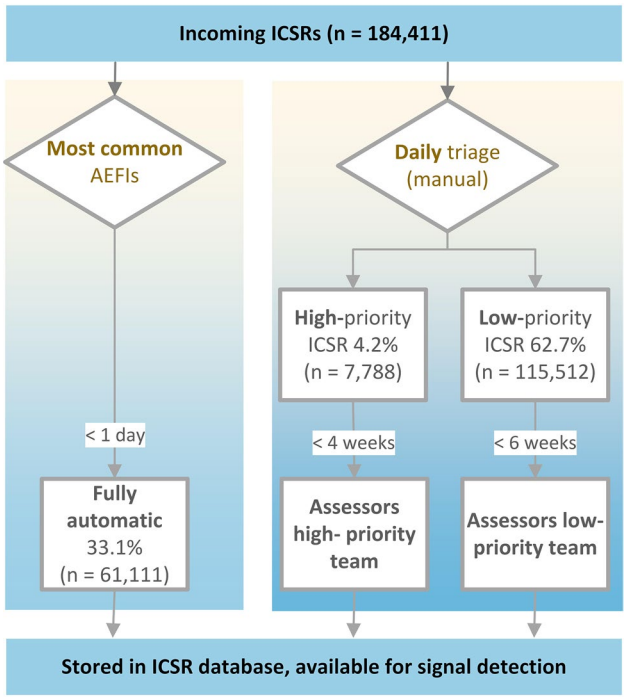

Fig. 2 ICSRs routes of handling

Odds Ratio (ROR) is calculated to see if the proportion of reported events for specified COVID-19 vaccines is compared to other drugs in the database. Although the disproportionality analysis offers the possibility to analyse large amounts of data, it is possible that results may be biased and may depend on the composition of the dataset. Interpretation should be carried out with caution and detailed knowledge of the underlying data should be taken into account. The influence of large amounts of data related to COVID-19 vaccines on disproportionality analysis was not known. To avoid any potential bias in the signal detection process, a first selection was based on the clinical content of reported cases. The ROR, stratified for vaccines, was one of the features in both weekly line-listings and the batch analysis, both described below.

The main driver of signal detection at our centre remains the clinical assessment of cases by the 'high priority team'. On a daily basis, cases with 'high signal values', including AESIs and serious ICSRs, were discussed in a daily signal detection meeting. This team is supported by an external Clinical Advisory Board consisting of medical specialists in various fields of expertise, such as immunology, haematology, vascular medicine and internal medicine. In addition to the case-by-case analysis, a custom-made electronic reaction monitoring report was used to monitor all incoming ICSRs and to serve as an additional signal detection method in addition to case-by-case analysis. Available data elements in the electronic reaction monitoring report are provided in the Electronic Supplemental Material (ESM), Resource 1. Reporting rates per 100,000 per association for specific brands were incorporated into the report. When needed, further analyses of the AEFIs were conducted. If possible, background incidences of the condition in question were also included in the analyses. In the European project ACCESS [25], the background incidences of a large number of potential AEFIs have already been mapped out. For Observed/Expected analysis [26], stratification of background incidences by age groups and sex was performed. Data on the exposed population were provided by the RIVM based on the vaccination registry CIMS [20]. Background incidences specific to the Dutch population were provided on request by the PHARMO Institute. The PHARMO Database Network has detailed information of more than 4 million (≈ 25%) residents of a well-defined population in the Netherlands for an average of 10 years and makes it possible to use tailor-made and disease-specific cohorts [27]. Standardised Morbidity Rates (SMR) were used to compare the number of spontaneously reported cases of the association of interest (Observed) in the COVID-19 vaccinated population with the Expected number based on Dutch background incidence rates within a risk window following immunisation, stratified per vaccine, dose, sex and age.

SMR = O/E [28, 29]

$E = (N_{\text{events in PHARMO}}/N_{\text{person years in PHARMO}}) * (\text{risk period (days)}/365) * N_{\text{vaccine exposure}}$.

95% confidence intervals: $\sqrt{((\sum (O - / + 1)^2)/\sum E}$; using Poisson distribution tables for low numbers of O (< 10)

The batch analysis compared the number of reports of one batch with the number of reports of the other batches of the same brand of vaccine. Batches with an LLROR > 1 (lower-level reporting odds ratio) were considered positive batches. The reports of these batches were investigated further to determine whether there were indications of a batch-related problem. The batch analysis was performed for fever and for injection-site infection. All positive batches were compared with the other batches of the same brand of vaccine in order to detect suspicious patterns. Among other things, the number of reports and the number of associated AEFIs, the number of serious reports and the number of serious AEFIs are examined. The reported serious PTs of the suspect batch were compared with the serious PTs of the other batches; this was also carried out with the non-serious PTs. The latency period and outcome were also considered. The age and gender distribution of the suspect batch were compared with the other batches of the same brand. Finally, a heat map was made of all reported PTs from all batches of

a trademark and it was checked to see if there were noticeable patterns in the positive batches compared to the other batches.

For COVID-19 vaccine signal detection, Lareb worked in close collaboration with the Dutch Medicines Evaluation Board (CBG-MEB) and the National Institute for Public Health and the Environment (RIVM). These organizations provided input on signal detection activities and signal management. A weekly report was disseminated and discussed during a biweekly meeting with the MEB and RIVM. Safety signals were disseminated to MEB, who can take autonomous regulatory actions or forward the signal for further evaluation to the Pharmacovigilance Risk Assessment Committee (PRAC) or lead member states. The PRAC is the European Medicines Agency's (EMA) committee responsible for assessing and monitoring the safety of human medicines [30]. ICSRs on fatal outcomes were assessed within a 24-h timeframe and shared with the regulatory framework on a daily basis. Reports with a fatal outcome were each independently reassessed by two members of the Clinical Advisory Board. Potential safety signals were discussed within the regulatory framework to allow for regulatory action or additional studies.

3 Results

3.1 Processing and Assessment of ICSRs

Between 6 January and 31 December 2021, more than 27.5 million vaccines were administered in the Netherlands [20]. In this period, the Netherlands PV centre Lareb received 184,411 ICSRs after COVID-19 vaccination, of which 96.7% concerned consumer reports. With regard to the brand of vaccine, 54.2% were about the Pfizer vaccine, 20.5% about the AstraZeneca vaccine, 17.3% the Moderna vaccine, 7.9% the Janssen vaccine and 0.1% other. The reporting rate was 0.67% in general. The reporting rate was the highest (0.93%) after the first vaccination (Table 1). Most ICSRs were received between May and August 2021 (Fig. 3), which reflects the amount of vaccinations given in that period [14].

Fully automatic processing was possible for 33.1% (n = 61,111) of all ICSRs received on a daily basis. After daily triage of all remaining incoming ICSRs, 4.2% (n = 7788) were flagged as 'high-priority' ICSRs, and the remaining 62.7% (n = 115,512) were flagged as 'low-priority' ICSRs. The compliance for forwarding reports to Eudravigilance for the 15- or 90-day timeframe was 99.9%. Batch numbers were added from CIMS in 73.1% of the requests after permission of the reporter. This results in a known batch number in 81.1% of the ICSRs.

3.2 Adverse Events Following Immunisation (AEFIs) and Signal Detection

An overview of coded and assessed ICSRs per vaccine brand and vaccination dose is shown in Tables 2 and 3. The majority of AEFIs were well-known, nonserious AEFIs. Serious AEFIs that were described in the signals and overviews considered reports on thrombosis combined with thrombocytopenia (TTS) for AstraZeneca and Janssen[31], transverse myelitis after vaccination with AstraZeneca [32], and Guillain Barré Syndrome after vaccination with AstraZeneca [33], among others. Lareb also published an overview of received myocarditis and pericarditis cases. In part, the Dutch reports and Observed/Expected analysis were consistent with the literature, with a known risk of myocarditis and pericarditis with mRNA vaccines, mainly following the second dose and in younger men [34–37]. However, this overview showed that myocarditis and pericarditis had also been reported in the Netherlands in other age groups, in women as well, and also with AstraZeneca and Janssen [38]. A total of 27 signals and news stories among the COVID-19 vaccines were disseminated in 2021 and are shown in ESM Resource 2.

With respect to the various batches used, no signals of possible batch-related problems have been detected for the various brands of COVID-19 vaccines.

4 Discussion

The ability to respond adequately and quickly to potential safety signals related to COVID-19 vaccines is essential for safety surveillance. Good safety surveillance is crucial for confidence in the vaccines/vaccination campaign and in combating and managing the current pandemic. During the COVID-19 pandemic, the challenges and complexities of safety monitoring in pharmacovigilance have been amplified as a result of the novelty of the disease and the novelty of vaccines, the high amount of data to be handled and processed in a short time-span due to the large part of the population being vaccinated, and increased public attention [39]. Signal detection of spontaneously reported adverse drug reactions (ADRs; or in the case of vaccines,

Table 1 Reporting rates per vaccination moment

Vaccination moment	Number of vaccinations given	Number of reports received	Reporting rate (%)
1	12,403,566	114,925	0.93
2	10,825,369	61,218	0.57
3	4,314,695	8268	0.19
Total	27,543,630	184,411	0.67

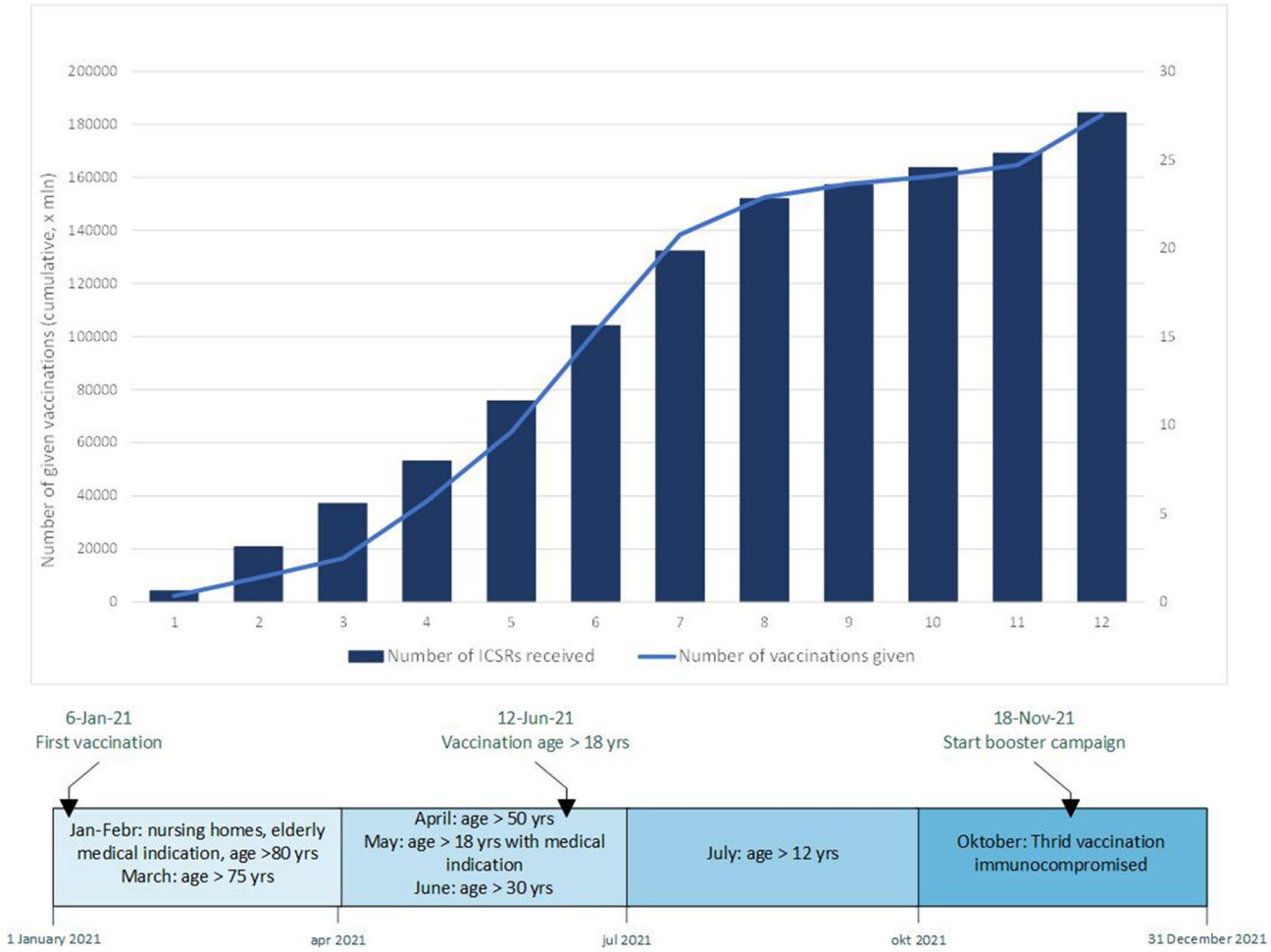

Fig. 3 ICSR numbers and number of vaccinations given

AEFIs) has its origin in case-by-case analysis where all case reports containing one or more ADRs are assessed by clinically qualified assessors. For a proper assessment of causality, there are four domains of importance: the AEFI, the chronology of the AEFI, the vaccine, and patient characteristics [40]. Key in the assessment of a potential signal between the vaccine and the reported AEFI is the clinical information provided by the reporter, among which are information on timing and course of the reaction and other characteristics. With the COVID-19 vaccination, case-by-case analysis was highly important in finding signals, such as thrombosis with thrombocytopenia syndrome (TTS) linked the use of viral vector vaccines from AstraZeneca and Janssen [41]. The use of the AstraZeneca vaccine was suspended in multiple European countries after reports of TTS [42]. Vaccination campaigns in the Netherlands were not halted due to the signal for myocarditis and pericarditis for the mRNA vaccines, although the potential risk was taken into account in the considerations to vaccinate adolescents [43].

4.1 Number of ICSRs Received

Lareb has vaccine monitoring procedures in place for the yearly influenza campaign [44] and has past experience with the monitoring of vaccines during the H1N1 influenza pandemic during 2009/2010 [45]. Regarding COVID-19 vaccination, the Netherlands was one of the countries with the most ICSRs in Europe; as of 19 March 2022, the Pfizer vaccine had the highest number of reports in the Eudravigilance database compared to the other vaccines. Germany had 153,218 ICSRs, the Netherlands had 111,816 ICSRs and France had 97,553 ICSRs [15]. With adjustment for the number of ICSRs per million residents of these countries, the Netherlands received 6.4 ICSRs per million residents, followed by Germany (1.8) and France (1.4). The high number of ICSRs could possibly be explained by the attention given to the AEFIs after COVID-19 vaccination in the media and the transparency of our PV centre. This leads to an upwards spiral of even more media attention, resulting in even more ICSRs being received. In the beginning of

Table 2 Key figures of ICSRs

	COVID-19 vaccine brand name						
	Pfizer	Moderna	AstraZeneca	Janssen	Other/UNK*	Total	Percentage
ICSRs (n)							
Total	100,006	31,871	37,761	14,451	322	184,411	
After vaccination dose 1	53,118	12,836	34,297	14,446	228	114,925	62.3[1]
After vaccination dose 2	43,264	14,423	3460	5	66	61,218	33.2
After vaccination dose 3	3624	4612	4	0	28	8268	4.5
Fatal outcome	440	58	76	14	18	606	0.3[2]
Qualification reporter (n)							
HealthCare Professional	3908	770	1186	228	62	6154	3.3[3]
Consumer	96,098	31,101	36,575	14,223	260	178,257	96.7
Patient (n)							
Male	21,167	6931	7863	3965	90	40,016	21.7
Female	78,825	24,939	29,896	10,486	231	144,377	78.3
Sex unknown	14	1	2	0	1	18	0.001
Age < 12 years	83	25	6	4	0	118	0.1
Age 12–20 years	3893	378	605	616	8	5500	3.0
Age 20–65 years	80,383	28,700	35,132	13,776	207	158,198	85.8
Age 65–80 years	12,759	2537	1933	46	44	17,319	9.4
Age > 80 years	2824	218	72	2	58	3174	1.7
Age unknown	64	13	13	7	5	102	0.1
AEFI							
Total	405,667	187,222	221,505	75,403	1190	890,987	
Serious ICSRs (n)							
Total	2855	464	882	192	48	4441	2.4[4]
After vaccination dose 1	1590	208	666	192	29	2685	60.5[5]
After vaccination dose 2	1206	206	216	0	15	1643	37.0
After vaccination dose 3	59	50	0	0	4	113	2.5

ICSR Individual Case Safety Report, *AEFI* adverse event following immunization

*Concerns COVID-19 vaccine brand name unknown, and a few CureVac and Novavax given in clinical trials

[1]Percentage of ICSRs for vaccination moment 1 (total); 114,925/184,411

[2]Total number of ICSRs with a fatal outcome as a percentage of the total number of ICSRs; 606/184,411

[3]Percentage of total reports by Healthcare professionals; 6154/184,411

[4]Percentage serious ICSRs (total); 4441/184,411

[5]Percentage serious ICSRs for vaccination moment 1 compared to total serious ICSRs; 2685/4441. This is also calculated for vaccination moment 2 and 3

August, media attention was given to menstruation cycle changes by women after COVID-19 vaccination. This led to more than 18.000 ICSRs on menstrual disorders in 2021, of which most were reported after media attention. In general, media attention seemed to be a good predictor for receiving high numbers of reports [46].

In general, the reporting rate followed the number of vaccines given (Fig. 3), with the exception of the first months of 2021. Here, relatively more ICSRs were received, possibly due to the Weber effect, a type of reporting bias characterized by the increased reporting of ADRs shortly after marketing authorization of a drug [47].

Due to automatic processing of the majority of common and known reported AEFIs, daily triage and daily signal detection meetings, we managed to process almost all ICSRs within a 15- or 90-day compliance timeframe. Due to daily triage, we tracked the high-priority ICSRs and paid sufficient attention to serious ICSRs and AESIs.

To process large numbers of ICSRs, data cleaning could not be completed on a daily basis for all reports received. We therefore checked the minimal ICH-E2b(R3) data elements required for the 'low-priority' ICSRs upon data entry. In case specific associations were analysed in more detail for signal detection purposes, this was combined with cleaning process for the underlying ICSRs.

Table 3 Twenty-five most reported serious Adverse Events of Special Interest (AESI) and Adverse Events Following Immunisation (AEFIs)

No.	AEFI total (PT)	ICSRs (n)	AESI (PT)	ICSRs (n)	Serious (PT)	ICSRs (n)
1	Fatigue	89358	Pulmonary embolism	486	Pulmonary embolism	432
2	Headache	88573	Deep vein thrombosis	327	Dyspnoea	315
3	Malaise	87751	Hypersensitivity	264	Cerebral infarction	267
4	Myalgia	81781	Pericarditis	224	Malaise	225
5	Chills	65800	Epilepsy	206	Abortion spontaneous	221
6	Injection site pain	56427	Thrombocytopenia	144	Deep vein thrombosis	159
7	Pyrexia	48401	Myocardial infarction	140	Pyrexia	150
8	Nausea	46862	Thrombosis	117	Fatigue	138
9	Arthralgia	45004	Bell's palsy	104	Myocardial infarction	136
10	Injection site inflammation	27829	Facial paralysis	93	Transient ischaemic attack	128
11	Injection site swelling	22792	Facial paresis	86	Headache	108
12	Injection site warmth	22225	Myocarditis	85	Nausea	100
13	Injection site erythema	17182	Cerebrovascular accident	80	Thrombocytopenia	99
14	Body temperature increased	10555	Cerebral haemorrhage	74	Chest pain	96
15	Injection site pruritus	7258	Anaphylactic reaction	70	Pneumonia	94
16	Dizziness	6891	Death	64	Pericarditis	92
17	Heavy menstrual bleeding	6671	Seizure	52	Ischaemic cerebral infarction	92
18	Lymphadenopathy	6281	Sudden hearing loss	50	Cardiac arrest	88
19	Injection site haematoma	5862	Sudden death	49	Hypersensitivity	88
20	Dyspnoea	4267	Guillain–Barre syndrome	48	Dizziness	80
21	Diarrhoea	4117	Vasculitis	38	Cerebrovascular accident	77
22	Intermenstrual bleeding	4017	Immune thrombocytopenia	37	Epilepsy	75
23	Extensive swelling of vaccinated limb	3998	Hypersomnia	35	Cerebral haemorrhage	74
24	Amenorrhoea	3809	Acute myocardial infarction	33	Condition aggravated	72
25	Menstruation delayed	3047	Febrile convulsion	32	Myocarditis	68

This way of working enabled us to ensure maintaining the high-quality standard for our signal detection process data cleaning.

4.2 Signal Detection

High-quality clinical observations were crucial, for instance in the detection of thrombosis and thrombocytopenia syndrome linked to the AstraZeneca and Janssen vaccines.

However, with large numbers of ICSRs received, it is no longer possible to solely rely on case-by-case analysis. Manual review of all ICSRs is no longer feasible, and patterns in data that may reveal risk factors or other characteristics of AEFIs are not always easily detectable [41]. Observed-to-Expected analysis became an important additional tool in analysing our potential safety signals for COVID-19 vaccines. However, in the beginning of 2021, observed-to-expected analyses were affected by uncertainties regarding the numbers of vaccinated persons to a backlog of data to the national vaccination registration and lack of age-specific background incidence rates for the Dutch population. Other limitations and obstacles of the Observed-to-Expected analysis with spontaneous reporting include (varying degrees of) under-reporting in a spontaneous reporting system, the choice of the right risk window, effect the ongoing COVID-19 pandemic can have on background incidences, among others.

4.3 Collaboration

For Signal management close collaboration with the regulatory framework in the Netherlands (Dutch Medicines Evaluation Board, National Institute for Public Health and the Environment and the Ministry of Health, Welfare and Sport (VWS)) was important because it allowed us to discuss relevant signals quickly and to take appropriate measures if needed. Lareb also closely followed the information provided by the EMA. The collaboration with the National Institute for Public Health with their national vaccination registry was also very important because we were able to perform a batch analysis to detect possible problems with batches or cold chains.

4.4 Lessons from the H1/N1 Pandemic

In an evaluation of the European Medicines Agency's activities during the 2009 (H1N1) flu pandemic, the EMA concluded that the European PV system was effective for monitoring the safety of A/H1N1 vaccines and antivirals. The system coped with a sudden increase in the number of ICSRs received by the National Spontaneous Reporting Systems (SRS), and rapidly provided information to support the detection and evaluation of potential safety issues. In addition to the spontaneous reporting system, appropriate post authorization safety (PASS) studies were also agreed upon [48]. At Lareb, experience with this past pandemic showed that automated processes may help to provide efficient ways of processing ICSRs in the event of a pandemic [45]. The dissemination of information and transparency is seen as highly important, and since the beginning of the COVID-19 vaccination campaign, the Lareb website http://www.lareb.nl has dedicated pages where new findings are summarized, frequently asked questions are answered, and listings are shown of reported AEFIs per vaccine brand.

4.5 Limitations

This article provides an overview of the work performed at Lareb to handle, assess and analyse data on COVID-19 vaccines in the spontaneous reporting system. To describe individual analysis and signals in detail is beyond the scope of this article. We have also not described work based on a large cohort-event monitoring (CEM) study for COVID-19 vaccines [49, 50]. Data from this CEM study were analysed in parallel with the ICSRs.

4.6 Lessons Learned

- After the approval of the COVID-19 vaccinations, there was a high need to monitor them closely. A quick processing time of assessing AEFIs and signal detection was necessary. We managed to cope with all ICSRs within the compliance time frame due to a highly technically supported process.
- Changing the vaccination strategy from the government and unforeseen media attention led to unpredictable and more ICSRs than expected. This requires a flexible and proactive attitude.
- Clinical assessment of ICSRs remained a high value in signal detection, and the input from clinical experts working in the field was invaluable. Signal detection methods that take into account the background incidence have become more important.
- Collaboration with other partners, such as MEB and RIVM, is of high importance to manage the process, and achieve good signal detection.
- In a situation in which less is known about the safety of drugs or vaccines, it is highly important to have transparent and frequent communication with the public.

5 Conclusion

During the national COVID-19 vaccination campaign, a large number of AEFIs were reported that required the development of a variety of methods for our PV centre to allow for timely signal detection.

Due to automatic processing of the majority of common and known reported AEFIs, daily triage and daily signal detection meetings, we were able to process 99.9% of the 184,411 received ICSRs within the 15- or 90-day compliance timeframe for submitting reports to Eudravigilance. Due to daily triage, we tracked the high-priority ICSRs and paid sufficient attention to serious ICSRs and AESIs.

Signal detection methods were used to deal with high numbers of ICSRs and background incidence of reactions. Clinical assessment of ICSRs remains at the heart of signal detection. The experiences for assessing ICSRs and performing signal detection may serve as a blueprint for future mass vaccination programs during a pandemic.

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Declarations

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Consent to participate No approval or consent was needed for this study.

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Availability of data and material The datasets for this article are not publicly available because of the data protection policy of pharmacovigilance centre Lareb. Requests to access the datasets should be directed to the first author and will be granted on reasonable request.

Code availability The SQL statements for the data used in this article are not publicly available because of the data protection policy of Lareb. Requests to access the datasets should be directed to the first author and will be granted on reasonable request.

Authors' contributions The original study protocol was designed by IO and FH. The query and dataset were established by JS. Data analysis was performed by IO and FH. The design of the article was determined by all authors. All authors contributed to the final data analysis and to manuscript drafting and revision. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

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