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Regulatory Pandemic Preparedness in Pharmacovigilance

Report

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SAMENVATTING

Dit project heeft onderzoek gedaan naar de uitdagingen voor geneesmiddelbewaking tijdens de COVID-19 pandemie en lessen getrokken over hoe we ons beter kunnen voorbereiden bij een volgende pandemie. Dit onderzoek is uitgevoerd door:

1. Het in kaart brengen van de rollen van de partijen bij de geneesmiddelen bewaking van COVID-19 vaccins en geneesmiddelen voor de behandeling van COVID-19, zowel in Nederland als in de Europese context
2. Een analyse over meldingen van vermoede bijwerkingen van COVID-19 vaccins en geneesmiddelen voor de behandeling van COVID-19 in het Nederlandse meldsysteem en cohort event monitoring studie;
3. Het in kaart brengen van nieuwe kennis over bijwerkingen en bijsluiter-aanpassingen van COVID-19 vaccins;
4. Een literatuur-review en een internationaal kwalitatief onderzoek naar toekomstbestendige farmacovigilantie methoden en aanbevelingen voor een mogelijke toekomstige pandemie;
5. Onderzoek naar de beoogde maatschappelijke impact van farmacovigilantie in een pandemie en de benodigde samenwerking tussen ketenpartijen

Resultaten per deelactie:

1. Belangrijke rollen in de veiligheidsbewaking van COVID-19 vaccins in Nederland waren belegd bij het College ter Beoordeling van Geneesmiddelen (CBG), Bijwerkingencentrum Lareb, het RIVM en de fabrikanten van de verschillende vaccins. Andere stakeholders waren onder andere de Gezondheidsraad, het ministerie van Volksgezondheid, Welzijn en Sport (VWS) en de Inspectie Gezondheidszorg en Jeugd (IGJ). In Europees verband was er een belangrijke rol voor het Europees Geneesmiddel Agentschap (EMA). Echter, zonder de inspanningen van zorgverleners en gevaccineerde personen zelf, die in grote getalen meldingen gedaan hebben, zou er geen goede veiligheidsbewaking mogelijk zijn.
2. Tijdens de COVID pandemie was er sprake van een groot aantal meldingen van bijwerkingen over vaccins, doordat een groot deel van de Nederlandse bevolking tegelijkertijd werd gevaccineerd én er veel aandacht voor vaccinveiligheid was. In totaal zijn er t/m mei 2023 233,428 meldingen gedaan over COVID-19 vaccins. Daarnaast zijn er ruim 27,000 gevaccineerde personen gevolgd in een longitudinaal cohortonderzoek van 6 maanden. Het aantal meldingen over geneesmiddelen die ingezet werden om COVID-19 te behandelen was beduidend lager; in totaal 265 meldingen waaruit bleek dat een deel van de geneesmiddelen off-label is ingezet.
3. Het farmacovigilantie systeem heeft in een korte tijd veel nieuwe kennis opgeleverd over de nieuw beschikbare vaccins. Lareb verspreidde in totaal 57 kennis items over COVID-19 vaccins en 7 over geneesmiddelen voor de behandeling van COVID-19 met daarnaast nog periodieke informatie op de website en kennispagina's. In totaal werden er 49 nieuwe bijwerkingen toegevoegd aan de bijsluiters van COVID-19 vaccins, waarbij één bijwerking bij meerder vaccins opgenomen kon worden. De tijdslijnen van deze bijsluiter aanpassingen zijn verder in kaart gebracht alsmede de veiligheidssignalen die bij het Europese veiligheidscomité PRAC zijn besproken maar níet tot een bijsluiter aanpassing hebben geleid.
4. Zowel uit de literatuurreview als kwalitatieve interviews met farmacovigilantie professionals werkzaam bij buitenlandse centra, bleek dat spontane meldsystemen ook voor een toekomstige pandemie belangrijk blijven om belangrijke veiligheidssignalen te genereren. Hierbij is meer automatisering nodig om meldingen te verwerken én te analyseren. Denk aan auto-codering van bijwerkingen en tekst-mining van vrije tekst in meldingen. Ook moet een betere aansluiting gezocht worden tussen zorgsystemen en het meldsysteem om dubbelwerk voor zorg professionals te voorkomen. In een aantal landen is het mogelijk om veiligheidssignalen die gevonden zijn met spontane rapportage snel te evalueren doordat vaccinatie- en zorgdata toegankelijk zijn en met elkaar gekoppeld. Dit was ten tijde van de pandemie in Nederland niet te realiseren. Tot slot is social media

een potentieel nieuwe bron van data die in Nederland nog onderbenut is gebleven, o.a. om in kaart te brengen welke vragen rondom veiligheid er bij het publiek spelen en hoe organisaties die betrokken zijn bij veiligheidsbewaking daar antwoord op kunnen geven.

5. Tijdens de COVID-19 pandemie is de farmacovigilantieketen – zoals op dit moment ingericht met verschillende partijen met verschillende rollen – functioneel gebleken.
   Farmacovigilantie speelt een belangrijke rol bij de totstandkoming van 'onderbouwd vertrouwen' van de maatschappij in de veiligheid van geneesmiddelen en vaccins – dit vertrouwen kwam tijdens de pandemie onder druk te staan. Het bestaan van een onafhankelijk meld- en kenniscentrum voor bijwerkingen bleek tijdens de pandemie extra belangrijk voor het onderbouwd vertrouwen in medisch inhoudelijke veiligheid. Op basis van de COVID pandemie zijn lessen te trekken waarmee de medisch inhoudelijke veiligheid verder kan worden vergroot én waarmee Lareb en de keten kunnen bijdragen aan (meer) onderbouwd vertrouwen. Het nadenken in scenario's over de context van een volgende pandemie en de invloed daarvan op (de beoogde impact van) farmacovigilantie moet onderdeel worden van regulatoire pandemische paraatheid. Hiaten in het farmacovigilantie systeem waren onder andere het beperkte zicht op de veiligheid van geneesmiddelen die (off-label) werden toegepast voor de behandeling van COVID en het gebrek van een data-infrastructuur om snel vervolgonderzoek te kunnen doen na het vinden van vermoede nieuwe bijwerkingen door analyse van het meldsysteem.

Conclusie

Als we vooruitkijken naar een mogelijke toekomstige pandemie dan kunnen we lessen trekken uit een triangulatie van de deelonderzoeken van dit project. Het spontane meldsysteem blijft belangrijk voor het vroegtijdig opsporen van nieuwe bijwerkingen, maar investeren in verdere automatisering en koppeling met zorgsystemen is gewenst. Innovatieve technieken voor data-analyse moeten verder ontwikkeld en toegepast worden. Naast het spontane meldsysteem is het gebruik van andere databronnen voor het versterken en evalueren van mogelijke veiligheidssignalen essentieel. Hiervoor is investering in een data-infrastructuur nodig, waarbij data uit zorgsystemen en vaccinatiedata eenvoudiger gekoppeld kunnen worden, om sneller vervolgonderzoek te kunnen doen naar mogelijke risico's.
Tot slot is samenwerking tussen verschillende partijen en vakgebieden essentieel. Voor meer onderbouwd vertrouwen bij het publiek is een goede communicatie vanuit de verschillende partijen in Nederland die vaccinbewaking te maken hebben nodig, met inachtneming van de eigen rol van elke partij en ingespeeld om de context van de pandemie.

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SUMMARY

This project studied/investigated the challenges for pharmacovigilance during the COVID-19 pandemic and formulated learned lessons on how to better prepare for the next pandemic. This study was performed by:

1. Mapping the roles of the parties involved in the pharmacovigilance of COVID-19 vaccines and medicines for the treatment of COVID-19, both in the Netherlands and in the European context;
2. An analysis on reports of suspected adverse reactions of COVID-19 vaccines and medicines for the treatment of COVID-19 in the Dutch reporting system and cohort event monitoring study;
3. Mapping new knowledge about adverse reactions and product information (PI) adjustments of COVID-19 vaccines;
4. A literature review and an international qualitative study on future-proof pharmacovigilance methods and recommendations for a possible future pandemic;
5. Research into the intended social impact of pharmacovigilance in a pandemic and the required cooperation between regulatory stakeholders.

Results per subject:

1. Important roles in the safety monitoring of COVID-19 vaccines in the Netherlands were assigned to the Medicines Evaluation Board (MEB-CBG), The Netherlands Pharmacovigilance Centre Lareb, RIVM and the manufacturers of the various vaccines. Other stakeholders included the Health Council, the Ministry of Health, Welfare and Sport (VWS) and the Health and Youth Care Inspectorate (IGJ). In a European context, the European Medicines Agency (EMA) played an important role. However, without the efforts of health care providers and vaccinated persons themselves, who have made reports in large numbers, proper safety monitoring would not be possible.
2. During the COVID pandemic, there were a large number of reports of adverse reactions to vaccines, because a large part of the Dutch population was vaccinated at the same time and a lot of attention was paid to vaccine safety. In total, up to May 2023, 233,428 reports have been made about COVID-19 vaccines. In addition, more than 27,000 vaccinated individuals were followed in a 6-month longitudinal cohort study. The number of reports of medicines used to treat COVID-19 was significantly lower; a total of 265 reports showing that some of the medicines were used off-label.
3. The pharmacovigilance system has generated a great deal of new knowledge about the newly available vaccines in a short period of time. Lareb distributed a total of 57 knowledge items about COVID-19 vaccines and 7 about medicines for the treatment of COVID-19, along with periodic information on the website and knowledge pages on vaccines. In total, 49 new adverse effects were added to the product information (PI) of COVID-19 vaccines, whereby one adverse effect could be included in the PI for several vaccines. The timelines of these PI changes have been further mapped, as well as safety signals that have been discussed at the European Safety Committee PRAC but have not led to a PI change.
4. Both the literature review and qualitative interviews with pharmacovigilance professionals working at foreign pharmacovigilance centers showed that spontaneous reporting systems also remain important for a future pandemic in order to generate important safety signals. However, more automation is needed to process and analyze reports. Examples are the application of auto-coding of adverse effects and text-mining of free text in reports. A better connection must also be sought between electronic healthcare systems and the Lareb reporting system in order to prevent duplication of work for healthcare professionals. In a number of countries, it is possible to quickly evaluate safety signals found with spontaneous reporting because vaccination and healthcare data are accessible and linked. This was not possible in the Netherlands at the time of the pandemic. Finally, social media is a potential new source of data that has remained underused in the Netherlands, for example to gain insight in the public's questions about safety and how organizations involved in safety monitoring can answer them.
5. During the COVID-19 pandemic, the (regulatory) pharmacovigilance process– with its current set up with different parties with different roles – proved to be functional. Pharmacovigilance plays an

important role in building society's 'substantiated trust' in the safety of medicines and vaccines – this trust came under pressure during the pandemic. The existence of an independent reporting and knowledge center for adverse drug responses (ADRs) proved to be extra important during the pandemic for the substantiated trust in medical knowledge on safety. Based on the COVID pandemic, lessons can be learned regarding further improvement of medical safety and how Lareb and the pharmacovigilance chain can contribute to (more) substantiated trust. Thinking in scenarios about the context of a next pandemic and its influence on (the intended impact of) pharmacovigilance must become part of regulatory pandemic preparedness. Gaps in the pharmacovigilance system included the limited visibility of the safety of medicines used (off-label) for the treatment of COVID and the lack of a data infrastructure to quickly conduct follow-up research after finding suspected new adverse reactions through analysis of the reporting system.

Conclusion

If we look ahead to a possible future pandemic, we can draw lessons from a triangulation of the sub-studies of this project. The spontaneous reporting system remains important for the early detection of new adverse effects, but investment in further automation and linkage with healthcare systems is desirable. Innovative techniques for data analysis must be further developed and applied. In addition to the spontaneous reporting system, the use of other data sources for strengthening and evaluating possible safety signals is essential. This requires investment in a data infrastructure, in which data from healthcare systems and vaccination data can be linked more easily, so that follow-up research into possible risks can be carried out more quickly.
Finally, cooperation between different parties and disciplines is essential. More substantiated public confidence requires good communication from the various parties in the Netherlands involved in vaccine surveillance, taking into account the role of each party and responding to the context of the pandemic.

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Contents

1. INTRODUCTION

During the COVID-19 pandemic, rapid vaccine development ensured that the world population was better protected against the consequences of a COVID-19 infection. In a short time, new vaccines were developed and large clinical trials were set up (1-5). However, in trials prior to marketing authorization, the follow-up time for all included test subjects is generally relatively short. A review of larger phase III trials for COVID-19 vaccines reported a follow-up ranged from 35 to 92 days (6). In addition, the vaccines are used on an extremely wide scale, and not all different subgroups of the population were abundantly represented in the trials conducted. It is therefore extremely important to better assess the safety profile during the roll-out of new vaccines in the post-marketing phase. In addition to the vaccines, a number of medicines have also been developed for the treatment of COVID-19 patients (7) and existing medicines have been applied off-label for this new indication. Off-label use in this context is the use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine- or vaccine-related problem (8). This is necessary in order for safeguarding the health of the population using the medicine/vaccine and maintain a good overview of the risk-benefit analysis after marketing authorization.

Observations from clinical practice have proven to be indispensable for the discovery of new but also for a clearer understanding of already known adverse drug reactions (ADRs). The spontaneous reporting system (SRS) for ADRs plays an important role in this. The strength of the SRS is that the sum of suspicions, after proper analyses, can provide new insights into ADRs, such as the possible existence of an unknown ADR and insight into the circumstances under which it arises. By reporting it, clinical observations of healthcare providers and experiences of patients come together in a central place [8, 9]. A substantial part of the safety risks found for medicines and vaccines and the subsequent measures arise from spontaneous reporting systems (9-12). The Netherlands Pharmacovigilance Centre Lareb is the reporting and knowledge center in the Netherlands for ADRs of medicines, vaccines, and other health products. Lareb carries out an analysis if the nature and number of reports give reason to do so. If the analysis leads to new knowledge about (possible) ADRs, Lareb will publish about this information on its website. The center also supports the Dutch National Competent Authority, the Medicines Evaluation Board (MEB), in its task in pharmacovigilance in the Netherlands and Europe by informing the MEB about new knowledge about (possible) ADRs. These are discussed with the MEB and, in the case of vaccines, also with the national Institute for Public Health and the Environment (RIVM). The MEB then decides on regulatory follow-up actions, such as submission to the pharmacovigilance risk assessment committee (PRAC) of the European Medicines Agency (EMA). All European reporting centres, including Lareb, also forward their reports to the EMA's European database (EudraVigilance). The EMA monitors safety at European level (13).

In response to the pandemic spread of COVID-19, the following vaccines have been approved at the moment for market authorization in Europe and have been used in the Netherlands: the mRNA vaccines from Pfizer (Comirnaty®) and Moderna (Spikevax®), for which adapted vaccines for omikron subvariant have now also been approved, the viral vector vaccines from AstraZeneca (Vaxzevria®) and Janssen (Jcovden®) and the subunit protein vaccine from Novavax (Nuvaxovid®).

A rapid and large-scale vaccination program was rolled out in the Netherlands in January 2021 and included two dose vaccination with Pfizer, Moderna, AstraZeneca, or a single dose vaccination with Janssen, to complete the initial series. High-risk patients and healthcare-professionals were given priority for vaccination, followed by fixed age-groups, starting with the oldest population first. Patients with a severe immune system disorder were invited to receive an additional third vaccination with Pfizer-BioNTech or Moderna from October 2021

onwards. Within seven months, 84.4% of the Dutch population older than twelve years was vaccinated with the initial vaccination series. In November 2021, a booster campaign with existing dose Pfizer-BioNTech and Janssen and half-dose Moderna was initiated (vaccination with AstraZeneca was discontinued in the Netherlands for shelf-life reasons). Heterologous vaccination occurred on occasion. In heterologous boosting, a person is injected with a different vaccine from that was used for the primary dose. From the second half of December 2021 onwards, COVID-19 vaccination became available for children from five to eleven years of age. In February 2022 onwards, the campaign for a second booster vaccine was initiated. In the meantime, more than 81.2% of the Dutch population aged 18 and older (born in 2004 and earlier) has had the primary series of COVID-19 injections. For persons aged 12 and older this is 80.2%. From September 19 2022 to May 7, 2023, more than 4.2 million booster vaccinations against COVID-19 have been administered. For the population with an age over60 years old, the vaccination coverage for booster vaccination is currently 61% (13).

The EMA has identified several new ADRs of the COVID-19 vaccines since marketing authorization. Sharing the clinical observations amongst member states in Europe was crucial in discovering this new safety information. Serious ADRs identified through reporting included, for example: thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome, and transverse myelitis for the viral vector vaccines. For the Pfizer and Moderna mRNA vaccines, myocarditis and pericarditis are examples of newly discovered serious side ADRs (14). In the fall of 2022 it has been decided that heavy menstruation should be included as an ADR in the product information (PI) for the Pfizer and Moderna vaccines (15).

Discovering these new ADRs associated with the COVID-19 vaccines would not have been possible without the reports from healthcare providers and vaccinees themselves. In the Netherlands, the focus on COVID-19 vaccines in 2021 and 2022 has led to an unprecedented number of reports of suspected ADRs. Until May 2023 almost 250,000 reports have been received by Lareb, in which over 1 million suspected ADRs were reported. In addition, more than 27,000 vaccinees were followed in an Intensive Monitoring study (prospective longitudinal cohort study).

During the COVID-19 crisis, Lareb was a central player monitoring the safety of the COVID-19 vaccines. Lareb adjusted its processes before and during the crisis and applied new signal detection methods were automated when processing the COVID-19 reports (16). Lareb has also actively tried to map the safety of off-label use of existing medicines and new products for the treatment of COVID-19. Examples are overviews about (hydroxy)chloroquine (17), remdesivir (7), and casirivimab with imdevimab (18). In contrast to the vaccines, the number of reports was limited here. The high workload of healthcare workers in the middle of the COVID-19 pandemic has played an important role in this.

It is crucial for society's 'substantiated trust' in the safety of vaccines that their safety is being properly monitored. A good monitoring system and clear and transparent communication about ADRs of vaccines is crucial for large-scale vaccination. As a knowledge center about ADRs of COVID-19 vaccines, Lareb answers many information requests from the public, healthcare providers, media and the Dutch Ministry of Health and regulatory agencies in the Netherlands. Much up-to-date information is made available via the website.

1.1 AIM

In this (sub)project, the challenges in the field of pharmacovigilance surfaced during the past pandemic have been investigated, resulting in recommendations for improvements to be better prepared for future pandemics.

1.2 DELIVERABLES

This project has two deliverables that answer different questions.

Deliverable 2A: Retrospective (what can we learn from the COVID-19 pandemic?):

- What was the impact of the pandemic on the reporting and processing of ADRs for medicines and vaccines in general?
- How did the increase in ADR reporting for COVID-19 medicines and vaccines affect the day-to-day pharmacovigilance processes?
- To what extent was the 'pharmacovigilance system' able to detect (new) ADRs for COVID-19 medicines and vaccines?

Deliverable 2B: Prospective (What can be improved during a future pandemic?):

- How can we better deal in the future with a pandemic-induced increase in adverse event reporting?
- In which way can the analysis of data be improved to help to identify possible ADRs earlier and better (for example, by distinguishing important reports from unimportant reports)?
- And how can this contribute to more effective and efficient pharmacovigilance during a future pandemic?

This sub-project is in line with several international initiatives aimed at improving the pharmacovigilance at both European and Global level. This includes, among other things, the role of artificial intelligence (AI) and machine learning to detect ADRs earlier and to make the (international) pharmacovigilance process more efficient.

1.3 METHODS

Deliverable 2A: Retrospective (what can we learn from the COVID-19 pandemic):

1. Mapping of the pharmacovigilance activities during the COVID-19 pandemic

For this deliverable, we map how the pharmacovigilance of the COVID-19 vaccines and medicines has been performed. The roles of Lareb, MEB, RIVM, and European Medicines Agency are described herein as well as their work, activities and collaboration during the COVID-19 pandemic. We highlight the amount of data in the SRS for COVID-19 vaccines and medicines to treat COVID.

2. Overview of new safety signals and knowledge

We composed an overview of new information about COVID-19 vaccine safety that has been disseminated by Lareb in the Netherlands, and in Europe, and the timelines involved. We provide an overview of signals which were discussed at the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency. We highlight specifically the Dutch signal on menstrual disorders after COVID-19 vaccination and showcase the knowledge built-up for this signal.

3. What can we learn from the COVID-19 crisis?

The independent research agency Andersson Elffers Felix (AEF) has conducted an independent evaluation of the questions 1) *'What impact is intended with pharmacovigilance during a pandemic?*', 2) '*What does this require regarding a knowledge center for ADRs of medicines and vaccines and the cooperation with regulatory agencies',* and 3) '*what can we learn from the COVID-19 crisis?*' In 2022, AEF already carried out an evaluation of Lareb's performance during the crisis. The lessons learned from this evaluation will be taken into account. Based on a pre-defined methodology (*Input > Throughput > Output > Outcome > Impact*), pharmacovigilance during a pandemic is placed in a broader perspective. This research involves focus groups and in-depth interviews with stakeholders.

Deliverable 2B: Prospective (What can be improved during a future pandemic)

It is important to investigate how we ensure that we can properly monitor safety in the future. Lessons will be learned from the results of deliverable 2A and various opportunities for innovation will be explored, including better use of Real-World Data, artificial intelligence (AI), and machine learning. We will perform both a scoping review of the literature and a qualitative study with interviews to gain insight in the data-sources and methods used for post-market approval safety monitoring of COVID-19 vaccines and to come with a set of recommendations for pharmacovigilance during a future pandemic.

1.4 TIME SCHEDULE

Duration of project: 6 months from January 15 – June 31st

2 RETROSPECTIVE; WHAT CAN WE LEARN FROM THE COVID-19 PANDEMIC?

2.1 Pharmacovigilance during the COVID-19 pandemic

This section provided information regarding the pharmacovigilance system in place during the COVID-19 pandemic. The following chapters will provide an overview of the authorized COVID-19 vaccines and drugs and the reported signals. Before a medicine or vaccine is authorised for use, evidence of its safety and efficacy is limited to the results from clinical trials, where patients are selected carefully and followed up very closely under controlled conditions. This means that at the time of authorisation, a medicine or vaccine has been tested in a relatively small number of selected patients for a limited length of time. After authorisation such a product may be used in a large number of patients under different circumstances than during the trials and with a longer follow-up period. It is therefore essential that the safety of all medicines is monitored throughout their use in healthcare practice (19). Figure 1 gives an overview of the model of pathways and effects of pharmacovigilance activities and role of stakeholder groups (regulators, marketing authorization holders, healthcare professionals, patients, and media).

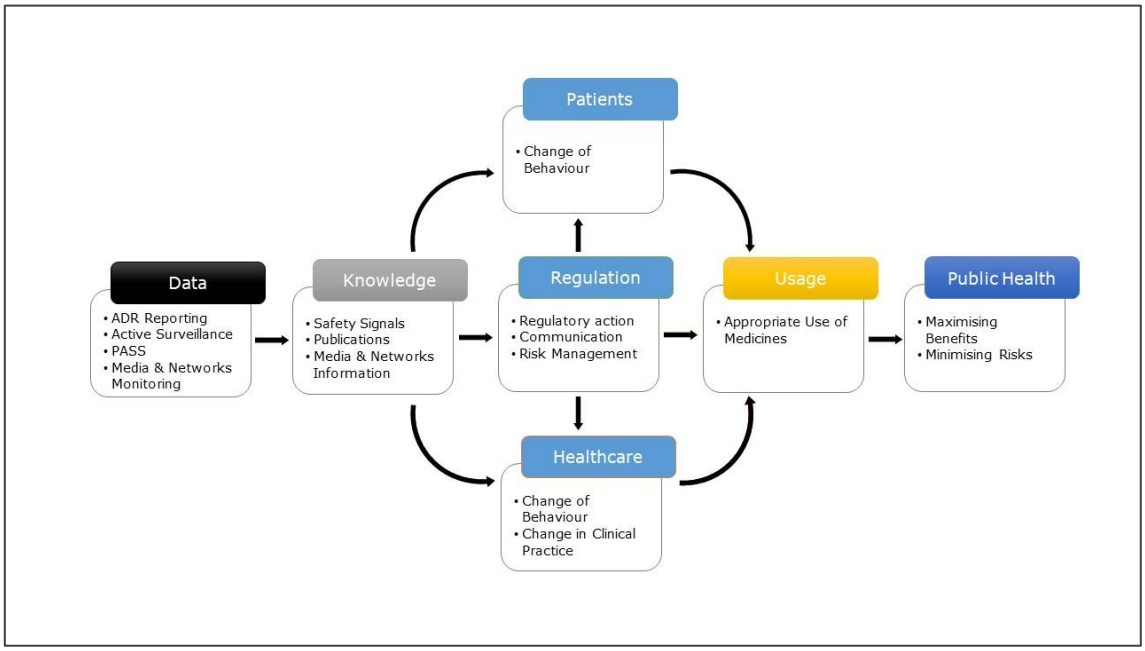

Figure 1: Model of pathways and effects of pharmacovigilance activities

European Union (EU) law requires each **marketing authorisation holder (MAH)**, **national competent authority (NCA)** and the **European Medicines Agency (EMA**) to operate a pharmacovigilance system. The overall EU pharmacovigilance system operates through cooperation between the EU Member States, EMA, and the European Commission. In some Member States, regional centres are in place under the coordination of the national competent authority.

The **European Medicines Agency (EMA)** coordinates the EU pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU. In the EU, NCAs maintain their own SRS to facilitate AE reporting and the generation of drug safety signals at national level. Spontaneous reports of all Member States are also transmitted to Eudravigilance which is a centralised database of spontaneous reports maintained by the EMA on behalf of the EU pharmacovigilance network (20).

The EMA is in the lead for signal detection of centrally authorised products (CAPs), with the **Pharmacovigilance Risk Assessment Committee (PRAC)** involved in further management steps such as validation assessment and decision making. PRAC consists of experts in medicines safety from regulatory authorities in Member States, plus scientific experts and representatives of patients and healthcare professionals nominated by the European Commission. The NCAs lead signal detection for substances authorised via the decentralised procedure or mutual recognition procedure (here referred to as nationally authorised products (NAPs) (20, 21).

During the COVID-19 pandemic, the EMA established dedicated task forces to deal with the scientific, regulatory and operational challenges it created, and initiated its business continuity plan with the aim to safeguard EMA's core activities related to the evaluation and supervision of medicines during the pandemic.

Overall, EMA initiated new and agile ways of working. The Agency has stated that their response was built on unprecedented collaboration and a united sense of purpose across regulators, developers, institutions, and citizens. It was supported by the tireless commitment and work of countless experts from the regulatory authorities – at EMA and at national level. These activities were underpinned by a fruitful collaboration between international regulators through the International Coalition of Medicines Regulatory Authorities (ICMRA) (22).

In the Netherlands, the **Medicines Evaluation Board (MEB)** is the NCA responsible for drug safety signal management. The spontaneous reporting system for AEs, however, is maintained by the **Netherlands Pharmacovigilance Centre Lareb**, a separate organisation working in close collaboration with the MEB. The **Netherlands Pharmacovigilance Centre Lareb** identifies risks associated with the use of medicines in daily practice and is the Knowledge Centre for adverse drugs reactions. Spontaneous reports are reviewed by Lareb and those with potential signal value undergo detailed analysis. In these analyses the clinical quality of the cases is reviewed, together with a study of the existing literature and possible mechanism. Safety signals are then disseminated to MEB who can take autonomous regulatory actions or forward the signal for further evaluation to the PRAC or lead member states (LMS) of NAPs when the NAP is authorised in more than one Member State (20). An overview of pharmacovigilance stakeholders is given in Figure 2.

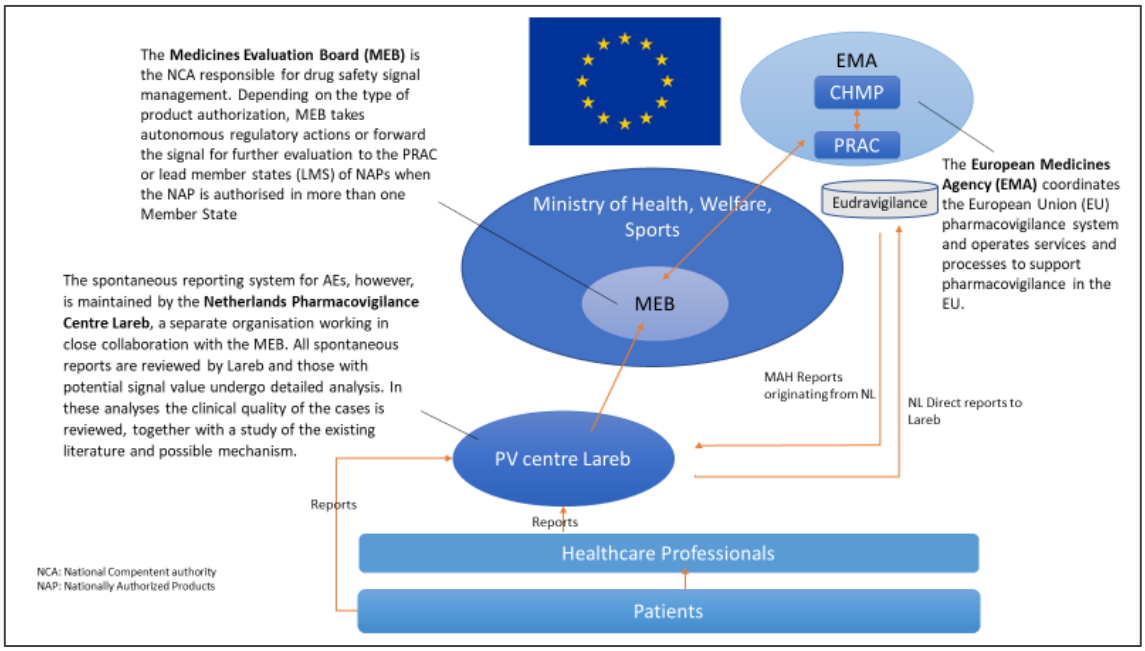

Figure 2. Pharmacovigilance stakeholders

During the pandemic, and especially in 2021, the **MEB** worked on many (conditional) marketing authorization procedures. At the end of 2021, five COVID-19 vaccines were available in Europe with a (conditional) marketing authorisation. There were also four medicines for the treatment of COVID-19 (conditionally) approved. For two medicines, which are already registered for another indication, the manufacturers have submitted data for the treatment of COVID-19. All of these drugs and vaccines have largely been reviewed by 2021. The (conditional) marketing authorizations for COVID-19 vaccines, in which the Netherlands was also involved as a (co-)rapporteur in a number of cases, involved a lot of work in various ways. Vaccines and medicines were assessed in an accelerated assessment procedure, the so-called rolling review. In this case, a company already shares information with the medicine authority, while the clinical research is still in full swing. In this way, the regulatory assessment can start earlier, saving a considerable amount of time. This is an intensive way of working with very short deadlines. The procedures demanded a great deal of effort from the MEB's assessors and Regulatory Project Leaders. In addition, numerous variations to the marketing authorizations have also been submitted and assessed. During the year, for example, the indications were expanded for Comirnaty and Spikevax, the corona vaccines from BioNTech/Pfizer and Moderna, for children and young people from the age of 12 (Comirnaty and Spikevax) and later 5 years (Comirnaty). The COVID-19 drug Veklury (remdesivir) also received a broader indication. The MEB also had their own role in pharmacovigilance; As PRAC Rapporteur for Comirnaty, the Netherlands had a pioneering role in Europe in the field of signal detection and assessment of protocols and results of post-marketing studies. There has been intensive collaboration between the MEB, RIVM and Lareb and in Europe (23).

As mentioned earlier, 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. Six months prior to the vaccination campaign in the Netherlands, **Lareb** started with internal and external working groups to prepare all technical facilities and (study)methods (Figure 3).

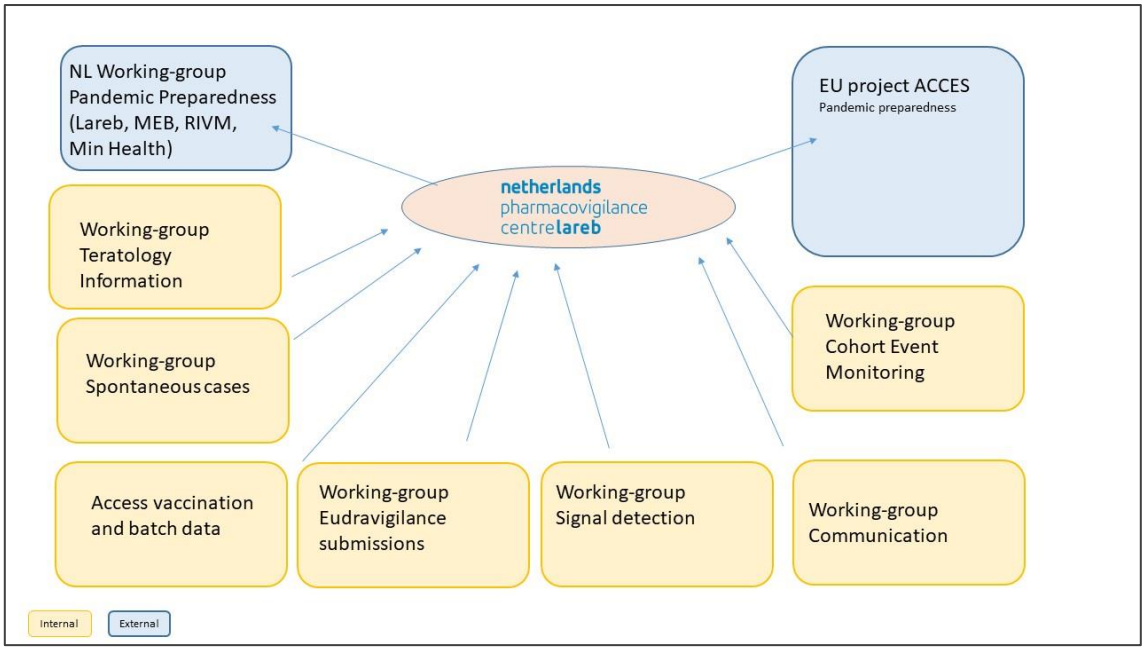

Figure 3. Working groups for Pandemic Preparation at Lareb

A COVID-19 tailored vaccine web-based reporting form collected information on the vaccine administered, adverse events following immunization (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 (24).

In 2022, independent research agency Andersson Elffers Felix (AEF) performed an evaluation of the way Lareb functioned during the COVID-19 crisis (25). Some key findings are highlighted here; During the COVID-19 pandemic, Lareb faced a double crisis. COVID-19 led to an unprecedented increase in the number of reports and a crisis, which meant that employees suddenly had to start working entirely from home and there was uncertainty about everyone's health just like with all other organizations. AEF noted that is admirable that Lareb has managed to make regular reports and to process reports about the COVID-19 vaccines in a timely manner. The AEF evaluation identified a number of success factors. At the same time there also some lessons for the future. In summary:

- Lareb has acted decisively to tackle the crisis;
- An effective crisis structure requires clear management;
- The organization has professionalized at an accelerated pace;
- Lareb was insufficiently equipped to double the number staff;
- The organization of external communication was powerful and vulnerable at the same time;
- Lareb's success is largely due to the dedication of its people.

The **RIVM** coordinated the implementation of vaccination campaigns and managed the COVID Vaccination Information and Monitoring System (CIMS) (26).

The **IGJ** considers it important that vaccination programs being offered to combat the COVID-19 pandemic are done carefully and responsibly. This is in the interest of good and safe care. The IGJ supervises this and has an eye for the entire process. Consider, for example, the storage, transport and administration of vaccines (27).

During the COVID-19 pandemic there was involvement of three additional stakeholders:

- The **Minister of Health, Welfare and Sport** made decisions on the vaccination strategy.
- The **Health Council** advised on who receives which vaccine.
- **Municipal or Common Health Service (GGDs)** carried out the vaccination, as well as general practitioners and hospitals specific target groups.

The **vaccinated persons** in the Netherlands (including caretakers) and **Healthcare professionals** have had a major role in the pharmacovigilance of COVID-19 vaccines and drugs to treat COVID-19. Without their efforts to detect potential adverse reactions and report them, pharmacovigilance with a spontaneous reporting system could not take place.

2.1.1 Drugs and vaccines authorized in the EU to treat or prevent COVID-19

A large variety of drugs to treat COVID-19 was used. Many of these drugs were used off-label. The following treatments have a marketing authorization in the EU to treat COVID-19 (28). An overview is given in table 1.

Table 1. Treatments which have a marketing authorization in the EU to treat COVID-19

Drug	Date of marketing authorization
Evusheld (tixagevimab / cilgavimab)	Marketing authorisation granted: 25/03/2022
Kineret (anakinra)	Marketing authorisation granted: 17/12/2021
Paxlovid (PF-07321332 / ritonavir)	Conditional marketing authorisation granted: 28/01/2022
Regkirona (regdanvimab)	Marketing authorisation granted: 12/11/2021
RoActemra	Marketing authorisation for COVID-19 indication granted: 07/12/2021
Ronapreve (casirivimab / imdevimab)	Marketing authorisation granted: 12/11/2021
Veklury (remdesivir)	Marketing authorisation granted: 08/08/2022 Conditional marketing authorisation granted: 03/07/2020
Xevudy (sotrovimab)	Marketing authorisation granted: 17/12/2021

The European Medicines Agency has published an overview which summarises the characteristics of the COVID-19 vaccines authorised in the EU (28).

Vaccine	Platform*	Strain	Use	Population ≥6 months	≥5 years	≥12 years	≥18 years
Comirnaty (BioNTech)	mRNA	Original strain	Primary vaccination	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
			Booster		✓ 5-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)	Booster			✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	Booster		✓ 5-11 years	✓	✓
Spikevax (Moderna)	mRNA	Original strain	Primary vaccination	✓ 6 months to 5 years	✓ 6-11 years	✓	✓
			Booster		✓ 6-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)	Booster		✓ 6-11 years	✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	Booster		✓ 6-11 years	✓	✓
Vaxzevria (AstraZeneca)	Adenoviral vector	Original strain	Primary vaccination				✓
			Booster				✓
Jcovden (Janssen)	Adenoviral vector	Original strain	Primary vaccination				✓
			Booster				✓
Nuvaxovid (Novavax)	Protein	Original strain	Primary vaccination			✓	✓
			Booster				✓
COVID-19 Vaccine Valneva (Valneva)	Inactivated	Original strain	Primary vaccination				✓ 18-50 years
			Booster				✓ 18-50 years
VidPrevtyn Beta (Sanofi Pasteur)	Protein	Beta variant	Booster				✓
Bimervax (HIPRA Human Health S.L.U.)	Protein	Alpha + Beta variants	Booster			✓ 16-18 years	✓

Platforms - the type of technology used to develop the vaccine.
Strains - the type of virus the vaccine targets, i.e., 'wild-type' (original), a variant or a sub-variant of the virus
Use - whether the vaccine is for primary or for booster vaccination.
Population - which age groups the vaccine is used in.

2.1.2 Data in the spontaneous reporting system and cohort event monitoring in the Netherlands

Vaccine reports

Since the Dutch COVID-19 vaccination campaign started, the Dutch Spontaneous Reporting System maintained by Lareb, received a high number of reports in a short time frame, see Figure 4. Table 2 provides demographics of the incoming reports.

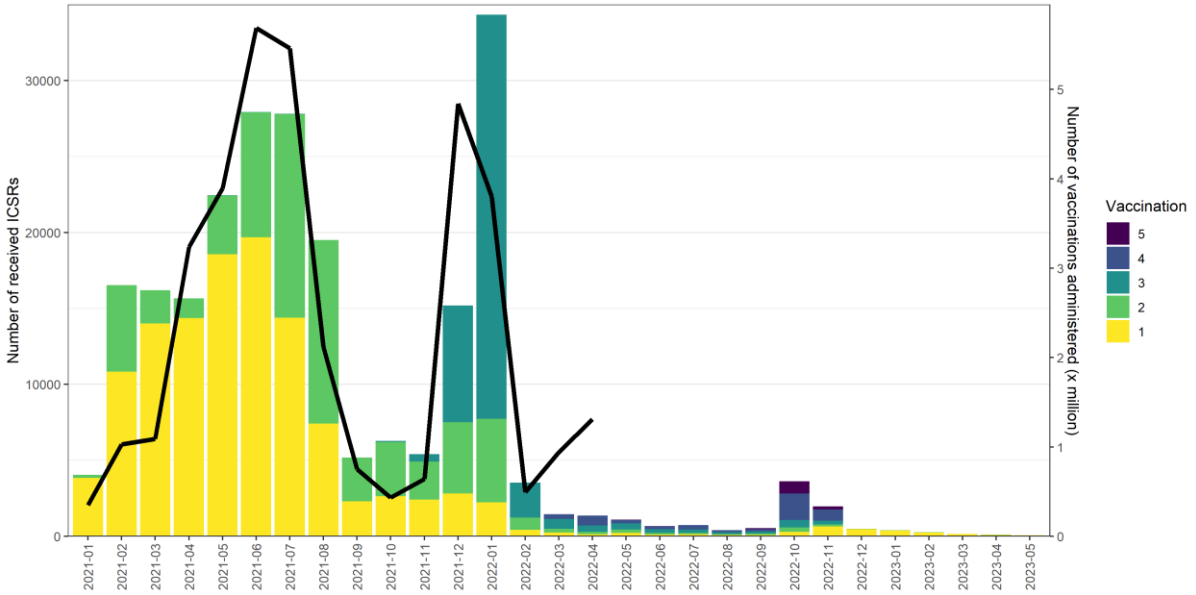

Figure 4. Number of ICSRs received per vaccination moment until May 2023. In black the cumulative number of vaccinations administered until April 2022 (end-date data-file)

Table 2. Demographics of reports on COVID-19 vaccines received until May 2023

Reporter	**Vaccination 1**	**Vaccination 2**	**Vaccination 3**	**Vaccination 4**	**Vaccination 5**
Consumer / non-health care professional	114968	66402	39574	4352	1086
Health care professional	4432	1954	538	91	31

Patient sex	Vaccination 1	Vaccination 2	Vaccination 3	Vaccination 4	Vaccination 5
Female	92725	53954	31610	3309	729
Male	26655	14398	8500	1134	388
Unknown	20	4	2		

Patient age	Vaccination 1	Vaccination 2	Vaccination 3	Vaccination 4	Vaccination 5
<5	82	28		1	
5-11	77	12	1		
12-20	5251	3015	827	22	
21-65	103273	57759	34244	3012	437
66-80	8578	6137	4550	1222	591
>80	1594	1080	372	143	63
Unknown	545	325	118	43	26

The percentage of reports with a serious outcome (seriousness defined by international criteria; adverse reactions leading to a fatal outcome, hospitalization, congenital anomaly, life-threatening, disability, other) was between 1.6-2.9% for the various vaccination moments. In Figure 5 the absolute number of serious and non-serious reports per vaccination moment is given.

Table 3. Percentage serious and non-serious reports per vaccination moment

Seriousness/ Vaccination moment	1	2	3	4	5	Total
Non serious	97,42%	97,09%	98,38%	97,16%	97,22%	97,48%
Serious	2,58%	2,91%	1,62%	2,84%	2,78%	2,52%

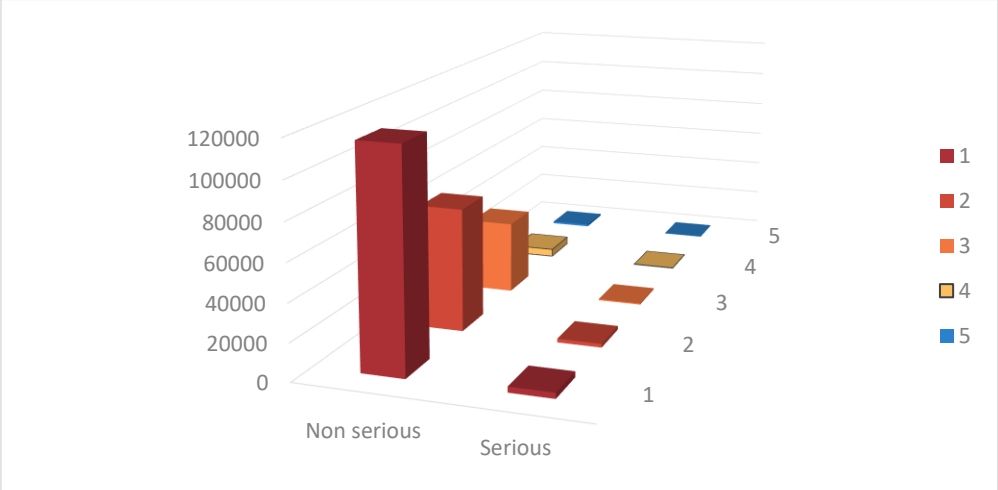

Figure 5. Reports with serious vs non-serious ADRs per vaccination moment

The percentage of reported ADRs which were labelled not labelled in the SmPC at the time of reporting are shown in Figure 6.

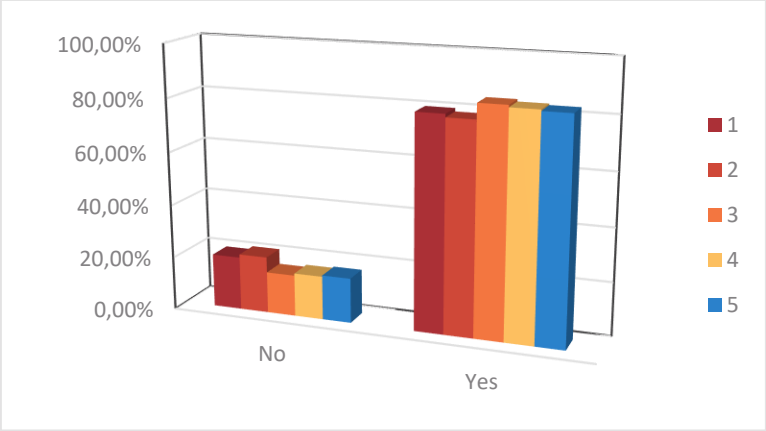

Figure 6. The percentage of reported ADRs which were labelled and not labelled in the SmPC at the time of reporting.

These results indicate that widespread use of COVID-19 medicines and particularly the COVID-19 vaccines, were accompanied with a strong increase in the reporting of suspected ADRs, with the potential to be new safety signals. In the monitoring and management of (potential) new safety issues, the SRS system played a crucial role during the COVID-pandemic.

Vaccine Cohort Event Monitoring Study

In addition to the SRS, The Netherlands Pharmacovigilance Centre Lareb conducted a patient-reported cohort event monitoring (CEM). This study using patient-reported outcomes (PROs) in the Netherlands started in February 2021 and used a prospective cohort design. The cohort was used to investigate differences in the frequencies of any and commonly reported, 'well-known', systemic AEFIs with four COVID-19 vaccines (Pfizer's Comirnaty®, Moderna's Spikevax®, AstraZeneca's Vaxzevria® and the Janssen vaccine) and to analyse the frequencies of well-known systemic adverse events after the first and, if applicable, second COVID-19 vaccinations, taking into account age, sex and prior COVID-19 infection. In addition, sex differences in the occurrence of adverse events were investigated, the incidence of menstrual disorders investigated among women and the effects of co-morbidities studied.

The cohort included 27,540 vaccinees (38.5% males). The percentage of patients reporting any AEFI was high and ranged from approximately 53% for the Pfizer vaccine to approximately 94% for the Moderna vaccine. The frequency of serious AEFIs was low, with the highest frequency found for the AstraZeneca vaccine (0.228%). AEFIs were most often experienced by participants receiving the first dose of the AstraZeneca and Janssen vaccines and the second dose of the Moderna vaccine; the Pfizer vaccine was associated with the lowest rate of AEFIs. Participants with a COVID-19 history before vaccination experienced commonly reported systemic AEFIs more frequently after the first vaccination than after the second vaccination. Women and young people experienced more AEFIs than men and older people, respectively. Females showed around two-fold higher odds of having any AEFI as compared to males with most pronounced differences after the first dose and for nausea and injection site inflammation. Age was inversely associated with AEFI incidence, whereas a prior COVID-19 infection, the use of antipyretic drugs and several comorbidities were positively associated. The perceived burden of AEFIs and time-to-recovery were slightly higher in females.

Cohort event monitoring (CEM) is considered active surveillance and allows for in-depth information on the time course of reported ADRs, with a clear denominator allowing risk quantification. It is well suited to capture reactogenic events, including those that are not medically attended, and which vaccinated persons can report themselves. The value of CEM as complement to the existing spontaneous is that is can give insight into the incidence of adverse reactions in a large group of vaccinated persons over a period of months and follow the time-to-onset, duration, treatment and burden of reported events. These data can be under-represented in published trials (29).

Publications on the COVID-19 cohort until July 1st 2023

- Duijster JW, Schoep ME, Nieboer BTE, Jajou R, Kant A, van Hunsel F. Menstrual abnormalities after COVID-19 vaccination in the Netherlands: A description of spontaneous and longitudinal patient-reported data. Br J Clin Pharmacol. 2023 May 24. doi: 10.1111/bcp.15799. Epub ahead of print. PMID: 37222170.
- Raethke M, van Hunsel F, Thurin NH, Dureau-Pournin C, Mentzer D, Kovačić B, Miroševič Skvrce N, De Clercq E, Sabbe M, Trifirò G, Luxi N, Giovanazzi A, Shakir S, Klungel OH, Schmikli S, Sturkenboom M. Cohort Event Monitoring of Adverse Reactions to COVID-19 Vaccines in Seven European Countries: Pooled Results on First Dose. Drug Saf. 2023 Apr;46(4):391-404. doi: 10.1007/s40264-023-01281-9. Epub 2023 Apr 7. PMID: 37024736; PMCID: PMC10079486.
- Duijster JW, Lieber T, Pacelli S, Van Balveren L, Ruijs LS, Raethke M, Kant A, Van Hunsel F. Sex-disaggregated outcomes of adverse events after COVID-19 vaccination: A Dutch cohort study and review of the literature. Front Immunol. 2023 Jan 30;14:1078736. doi: 10.3389/fimmu.2023.1078736. PMID: 36793715; PMCID: PMC9922710.
- Kant A, Jansen J, van Balveren L, van Hunsel F. Description of Frequencies of Reported Adverse Events Following Immunization Among Four Different COVID-19 Vaccine Brands. Drug Saf. 2022 Apr;45(4):319-331. doi: 10.1007/s40264-022-01151-w. Epub 2022 Mar 21. PMID: 35314943; PMCID: PMC8936041.
- Rolfes L, Härmark L, Kant A, van Balveren L, Hilgersom W, van Hunsel F. COVID-19 vaccine reactogenicity - A cohort event monitoring study in the Netherlands using patient reported outcomes. Vaccine. 2022 Feb 11;40(7):970-976. doi: 10.1016/j.vaccine.2022.01.013. Epub 2022 Jan 17. PMID: 35067381; PMCID: PMC8761555.

Reports on drugs to treat COVID-19

In contrast to the high number of reports on COVID-19 vaccines, the number of reports on drugs to treat COVID-19 was very low with only 265 ICSRs being reported. The majority of these (201) were reported directly to Lareb by consumers and healthcare professionals and a fraction (64) via Marketing Authorization Holders. In a report multiple reporters can be mentioned (Table 4).

Table 4. Reports of cases about drugs to treat COVID-19

Type of reporter	Number of reports (either direct or through MAH)
Consumer or other non-health professional	153
Other health professional	20
Pharmacist	31
Physician	75
Total	**279**

Patient's sex in the reports was 134 times female, 117 times male and 14 times unknown. In total, 299 times a drug was listed as suspect and/or interacting in the submitted reports. The most commonly reported drugs for the treatment of COVID-19 were remdesivir (n=36), casirivimab with imdevimab (n=21), chloroquine (n=19) and dexamethasone (n=16). All other drugs were reported as suspected/interacting in less than 10 reports.

2.2 New Knowledge and Signals

In order to answer the question *'to what extent was the 'pharmacovigilance system' able to detect (new) ADRs for COVID-19 medicines and vaccines?'* we describe the signals and knowledge items from the Dutch pharmacovigilance centre, both for vaccines and drugs to treat COVID-19. We provide a timeline of the Safety Signals leading to Product Information updates for the COVID-19 vaccines based on safety updates from the EMA. In addition, we provide an overview of signals discussed at PRAC since September 2012 for COVID-19 vaccines. As an example, we provide a comprehensive overview of the evidence collection for the signal of menstrual disorders after COVID-19 vaccination.

2.2.1 Overview of signals and knowledge items from Lareb

Since the start of the vaccination campaign in the Netherlands, in January 2023, Lareb actively disseminated safety information on the COVID-19 vaccines. Table 5 provides an overview of signals and news on adverse reactions after COVID-19 vaccination. This data is derived from analysis of the spontaneous reporting system and the cohort event monitoring system in the Netherlands or important news from the European Medicines Agency, with an explanation of the Dutch cases.

Table 5. Overview of signals and news on AEFI after COVID-19 vaccination

Date	Signals and news
08-06-2023	Overview of transverse myelitis after COVID-19 vaccination
22-03-2023	Side effects after corona vaccination in people with MS
10-03-2023	Guillain-Barré Syndrome after corona vaccination
07-02-2023	Women more often experience side effects after corona vaccination than men
25-01-2023	Pregnant woman has known and expected side effects after corona vaccination
11-01-2023	Reports of thyroid dysfunction after corona vaccination
02-12-2022	More insight needed about 'Lung COVID' complaints after corona vaccination
02-11-2023	Neuralgic amyotrophy after corona vaccination
28-10-2023	Heavy menstrual bleeding in SmPC Pfizer and Moderna corona vaccine
14-10-2022	Allergic reactions mainly reported after the first corona vaccination
28-09-2022	Skin reactions in tattoos after corona vaccination

19-09-2022	Headaches are common after corona vaccination
13-09-2022	No indications of adverse effects of corona vaccine on pregnant women
08-08-2022	Myocarditis an pericarditis possible side effect of Novavax vaccine
19-07-2022	Reports of Bell's facial palsy after corona vaccination
07-07-2022	Skin condition lichen planus reported after corona vaccination
14-06-2022	Nerve disorder neuralgic amyotrophy after vaccination
23-05-2022	More research into menstrual disorders after corona vaccination
02-05-2022	Overview of reports of deaths after corona vaccination
02-05-2022	Update reports of myocarditis and pericarditis after corona vaccinations
02-05-2022	Update reports of thromboses and embolisms after corona vaccinations
02-05-2022	Update reports of thrombosis with a low platelet count after corona vaccination
07-04-2022	Sometimes less breast milk after corona vaccination
28-03-2022	Many people experience known side effects after corona vaccination
21-03-2024	Persistent shoulder complaints after vaccination
11-03-2024	Cutaneous vasculitis after Janssen vaccination
11-03-2024	Flare capillary leak syndrome after Moderna vaccination
24-02-2024	Disturbed blood sugar level in diabetic patient after corona vaccination
04-02-2022	Enlarged lymph nodes relatively more often after corona booster vaccinations
17-01-2022	Spinal cord inflammation rare side effect AstraZeneca and Janssen vaccine
29-12-2021	Reaction on scar on old BCG-vaccination after Moderna vaccine
28-12-2021	Hypersensitivity reaction on filler after AstraZeneca vaccine
22-12-2021	Menstrual disorder possible as AEFI after COVID-19 vaccinations
20-12-2021	Less ICSRs severe allergic reactions after second COVID-19 vaccination
29-11-2021	Overview ICSRs myocarditis and pericarditis
19-11-2021	Cerebral venous sinustrombosis AEFI AstraZeneca vaccine
12-11-2021	Vasculitis reported after COVID-19 vaccination
01-10-2021	Immune thrombocytopenia (ITP) AEFI AstraZeneca and Janssen vaccine
01-10-2021	Venous thrombosis included in SmPC as AEFI with Janssen vaccine
29-09-2021	Hugh amounts of received ICSRs of menstrual disorders following COVID-19 vaccination
03-09-2021	Research on venous thrombosis after Janssen vaccination
20-08-2021	ICSRs of Bullous Pemphigoid after Pfizer/BioNTech vaccination
22-07-2021	Guillain–Barré syndrome after vaccination of AstraZeneca vaccine
15-07-2021	ICSRs thrombosis with low platelet count after COVID-19 vaccination
14-07-2021	Myelitis Transversa after vaccination with AstraZeneca vaccine
09-07-2021	Myocarditis and pericarditis AEFI with Pfizer- and Moderna vaccine
09-07-2021	Contraindication with Janssen vaccine for patients with previous systemic capillary leak syndrome
05-07-2022	Overview of ICSRs with fatal outcome after COVID-19 vaccination
11-06-2021	Research on myocarditis after COVID-19 vaccination
11-06-2021	Contraindication with AstraZeneca vaccine for patients with previous systemic capillary leak syndrome
02-06-2021	Contraindication with AstraZeneca vaccine for patient with previous thrombosis in combination with low platelet count
30-04-2021	More research needed to thrombosis and embolism after COVID-19 vaccination
08-04-2021	Thrombosis with low platelet count eight times reported after COVID-19 vaccination
07-04-2021	First overview of ICSRs with fatal outcome after COVID-19 vaccination
02-04-2021	ICSRs of thrombosis and low platelet count after vaccination with AstraZeneca vaccine
23-03-2021	Extensive limb swelling (ELS) after Pfizer/BioNTech vaccine
11-03-2021	COVID-19 vaccination and thrombosis

Drugs to treat COVID-19 were used on a much smaller scale than the vaccines, which were given to a large part of the Dutch population. In addition, a large variety of drugs was used. Due to limited amount of spontaneous reports on these drugs that Lareb received, signal detection activities were hampered.

For remdesivir, which was used in the Netherlands in 2020 on the basis of a compassionate use program (30), Lareb was in close contact with the RIVM, MAH and the MEB for the safety monitoring. On a weekly basis,

RIVM provided updates on vials of remdesivir which were distributed and Lareb reported on incoming cases. Table 6 summarized the information on safety of drugs to treat COVID-19 as disseminated by Lareb.

Table 6. Overview of signals and news on drugs for the treatment of COVID-19

Date	Signals and news
28-02-2022	Respiratory problems with treatment casirivimab / imdevimab for corona
14-09-2020	Hepatic and renal impairment with remdesivir
24-04-2020	Reports adverse drug reactions of hydroxychloroquine and chloroquine
23-04-2020	Serious adverse drug reactions of (hydroxy)chloroquine in corona patients
25-03-2020	Adverse drug reactions with drug treatment for coronavirus infection (COVID-19)
20-03-2020	Coronavirus infection (COVID-19) during pregnancy
19-03-2020	Paracetamol first choice to suppress fever in COVID-19

These overviews shows that Lareb was able to identify potential risks associated with the use of COVID-19 vaccines and medicines in daily practice and in its capacity as the Knowledge Centre for adverse drugs reactions (ADRs) disseminate information on safety issues to stakeholder groups such as regulatory agencies, healthcare professionals and the general public.

2.2.2 Safety Signals leading to Product Information updates in the EU

Since the start of the COVID-19 pandemic, regulatory authorities have been actively working on acquiring knowledge about the safety of COVID-19 vaccines, for instance based on spontaneous reporting systems and post-marketing studies. Based on the acquired knowledge, the safety profile is then further characterized, and recommendations are made for the amendment of the product information (PI). A safety signal comprises of information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation. Signals can be generated from several sources such as spontaneous reports, clinical studies, and the scientific literature (19). Mapping the knowledge build-up on the safety of COVID-19 vaccines and the time frame in which regulatory authorities have taken safety concerns into consideration is important from the viewpoint of providing timely information and transparency for different stakeholders.

Each month the PRAC analyses, prioritises, and evaluates safety signals concerning medicinal products authorised in the EU. This assessment may result in various recommendations, including an update of the product information (summary of product characteristics and package leaflet). PRAC recommendations on signals adopted each month are published after the relevant plenary meeting. When changes to the product information are recommended, the full text of the recommendation is published. Further information on each recommendation is provided in the PRAC minutes. Please note that some of the signals listed below are still under assessment by PRAC. For those, an update of the product information may be recommended at a later stage, when the PRAC has concluded the assessment (31).

Aim: To describing both the safety concerns of COVID-19 vaccines for which a PI update was recommended by the PRAC of the EMA and safety concerns that were considered by the PRAC without being labeled in the PI. Additionally, this study also had the objective to map the time frame in which the safety concerns were considered by the PRAC.

Methods: The safety concerns were extracted from the publicly available safety updates on the EMA website, published between January 1, 2021, and December 31, 2022, for the following centrally authorized COVID-19 vaccines: Comirnaty®, Spikevax®, Vaxzevria® and Jcovden®. The month of publication of the safety updates was used to map the timeframe in which the safety concerns had been considered by the PRAC. The same safety concern could be added to the summary of product characteristics (SmPC) for more than one vaccine, each

concern for each separate brand was counted independently. In addition, we consulted the EMA List of signals discussed at PRAC since September 2012 (last update 8-5-2023) (31).

Results: 49 safety concerns were recommended to be added to the PI of the COVID-19 vaccines. Examples include Thrombosis with thrombocytopenia syndrome (TTS) for the AstraZeneca and Janssen vaccine and myocarditis/pericarditis for the Pfizer and Moderna vaccines. The timelines of the knowledge build-up on the safety of the vaccines were graphically represented in Figure 7-10.

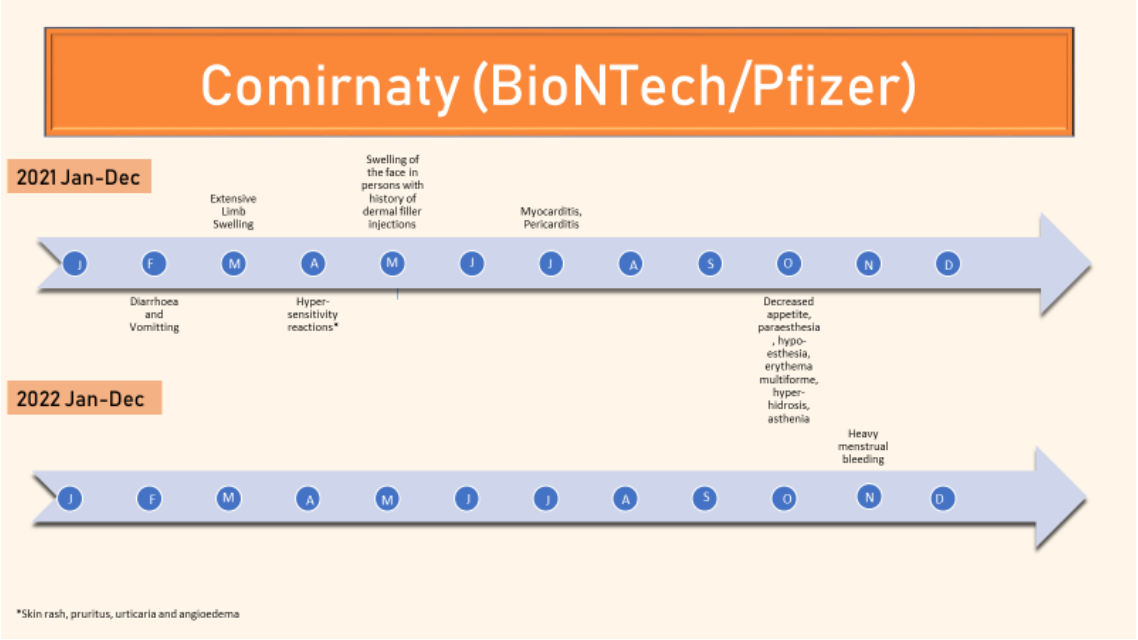

Figure 7. Timeline of safety concerns recommended to be added to the SmPC of the Pfizer vaccine

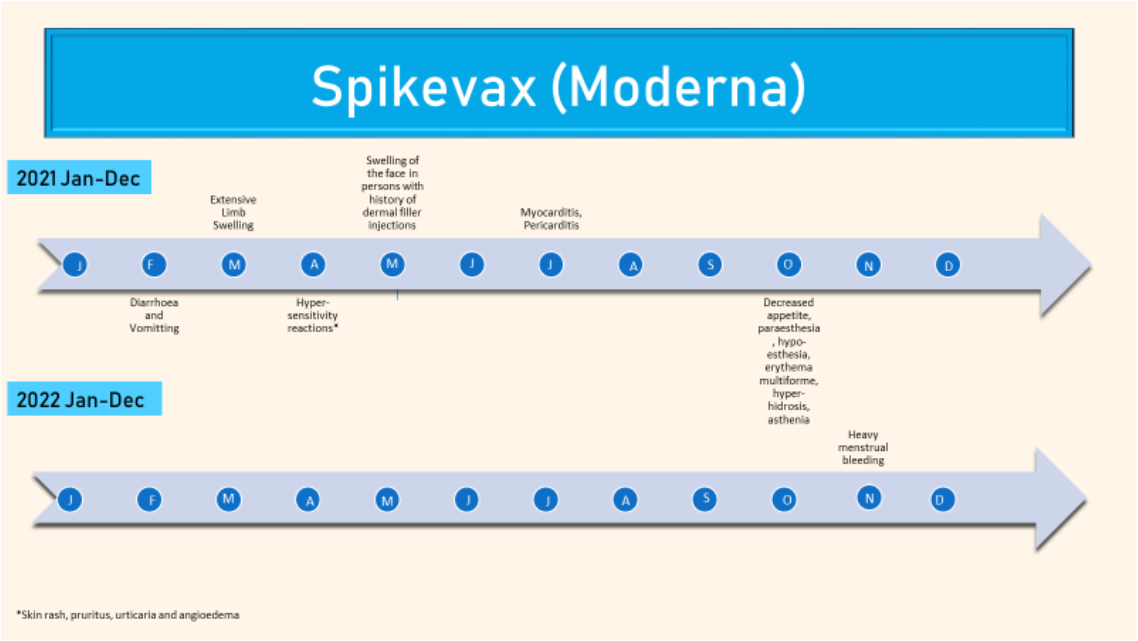

Figure 8. Timeline of safety concerns recommended to be added to the SmPC of the Moderna vaccine

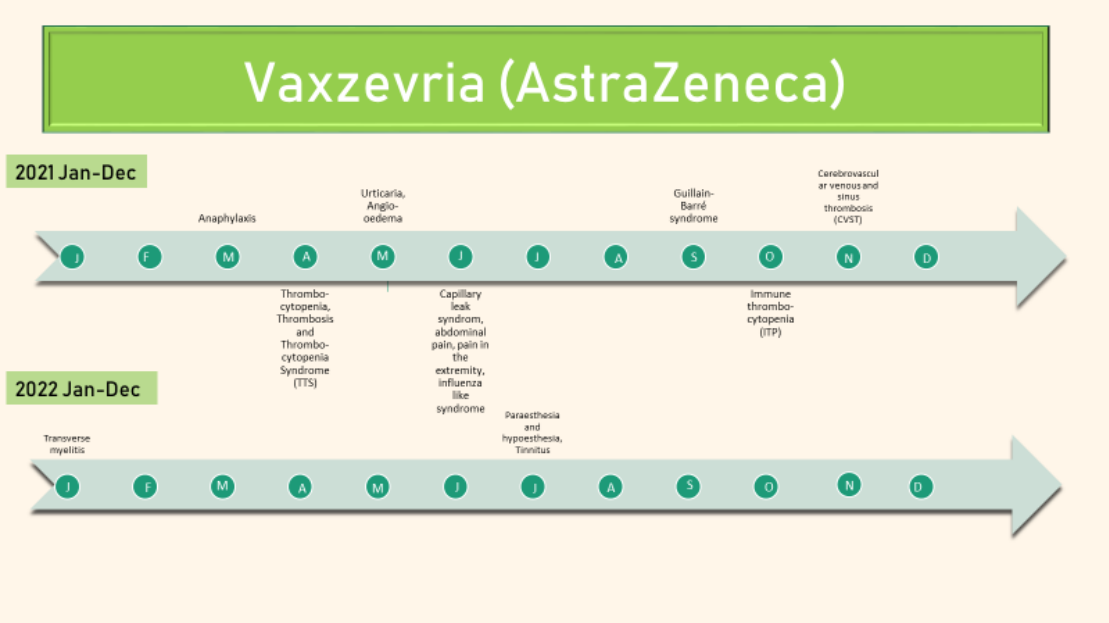

Figure 9. Timeline of safety concerns recommended to be added to the SmPC of the AstraZeneca vaccine

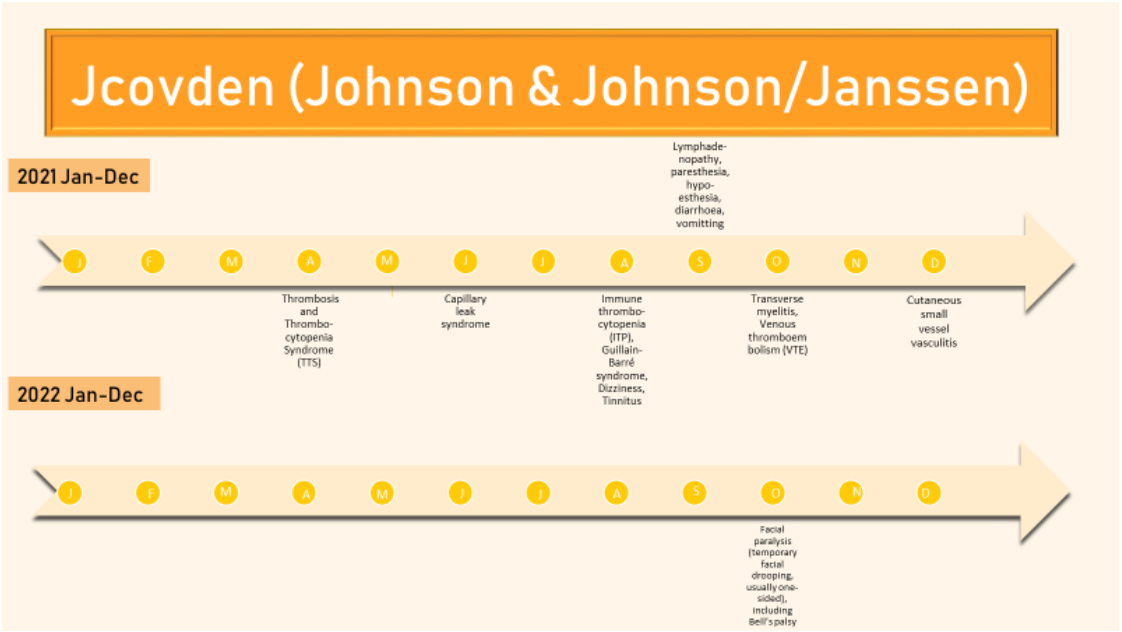

Figure 10. Timeline of safety concerns recommended to be added to the SmPC of the Janssen vaccine

The list of signals discussed at PRAC since September 2021 for COVID-19 vaccines is given in table 7. This list also includes signals that have been discussed but didn't lead to an SmPC update such as glomerulonephritis and nephrotic syndrome for the Pfizer vaccine Comirnaty® and Acute macular outer retinopathy and Corneal graft rejection for the Astrazeneca vaccine Vaxzevria®. It should be noted that this list refers only to the confirmed signals (i.e., signals discussed at PRAC under the signal management procedure), this table does not cover signal that may have been discussed in other pharmacovigilance procedures like PSURs or type II variations. Moreover, the COVID safety updates used for Figure 7-10 provided an overview of safety issues discussed in all the Pharmacovigilance procedures, not only the ones discussed under the signal assessment procedure.

Table 7. List of signals discussed at PRAC since September 2021 for COVID-19 vaccines

Vaccine	Signal	PRAC meeting	Update of product information recommended by PRAC
COVID-19 Vaccine Janssen	Embolic and thrombotic events	6-9 April 2021 PRAC meeting minutes	No
COVID-19 Vaccine Janssen	Embolic and thrombotic events	Signal assessement report adopted at the 20 April 2021 Extraordinary PRAC meeting	Yes
COVID-19 Vaccine Janssen	Embolic and thrombotic events	Signal assessment report adopted at the 3-6 May 2021 PRAC meeting	Yes
Comirnaty	Erythema multiforme	22 July 2021 PRAC ORGAM	No
Comirnaty	Erythema multiforme	27-30 September 2021 PRAC meeting minutes	Yes
Comirnaty	Glomerulonephritis and nephrotic syndrome	22 July 2021 PRAC ORGAM	No
Comirnaty	Glomerulonephritis and nephrotic syndrome	27-30 September 2021 PRAC meeting minutes	No
Comirnaty	Immune thrombocytopenia	8-11 March 2021 PRAC meeting minutes	No
Comirnaty	Localised swelling in persons with history of dermal filler injections	8-11 March 2021 PRAC meeting minutes	No
Comirnaty	Localised swelling in persons with history of dermal filler injections	3-6 May 2021 PRAC meeting minutes	Yes
Comirnaty	Myocarditis and pericarditis	7-10 June 2021 PRAC meeting minutes	No
Comirnaty	Myocarditis and pericarditis	5-8 July 2021 PRAC meeting minutes	Yes
Comirnaty	Myocarditis and pericarditis	Signal assessment report adopted at the 30 August-2 September 2021 PRAC meeting	No
Comirnaty	Myocarditis and pericarditis	14 October 2021 PRAC ORGAM	No
Comirnaty	Myocarditis and pericarditis	25-28 October 2021 PRAC meeting minutes	No
Vaxzevria	Acute macular outer retinopathy	20 May 2021 PRAC ORGAM	No
Vaxzevria	Acute macular outer retinopathy	5-8 July 2021 PRAC meeting minutes	No
Vaxzevria	Anaphylactic reaction	8-11 March 2021 PRAC meeting minutes	Yes

Vaxzevria	Capillary leak syndrome	6-9 April 2021 PRAC meeting minutes	No
Vaxzevria	Capillary leak syndrome	7-10 June 2021 PRAC meeting minutes	Yes
Vaxzevria	Capillary leak syndrome	30 August-2 September 2021 PRAC meeting minutes	No
Vaxzevria	Corneal graft rejection	4-7 April 2022 PRAC meeting minutes	No
Vaxzevria	Corneal graft rejection	29 August-1 September 2022 PRAC meeting minutes	No
Vaxzevria	Embolic and thrombotic events	Signal assessment report adopted at the 18 March 2021 Extraordinary PRAC meeting	Yes
Vaxzevria	Embolic and thrombotic events	Signal assessment report adopted at the 6-9 April 2021 PRAC meeting	Yes
Vaxzevria	Immune thrombocytopenia	8-11 March 2021 PRAC meeting minutes	No
Vaxzevria	Immune thrombocytopenia	3-6 May 2021 PRAC meeting minutes	No
Vaxzevria	Immune thrombocytopenia	5-8 July 2021 PRAC meeting minutes	No
Vaxzevria	Immune thrombocytopenia	27-30 September 2021 PRAC meeting minutes	Yes
Vaxzevria	Myositis	9-13 January 2023 PRAC meeting minutes	No
Vaxzevria	Pemphigus and pemphigoid	28 November-1 December 2022 PRAC meeting minutes	No
Vaxzevria	Pemphigus and pemphigoid	11-14 April 2023 PRAC meeting minutes	No
Spikevax	Amenorrhoea	7-10 February 2022 PRAC meeting minutes	No
Spikevax	Autoimmune hepatitis	29 November-2 December 2021 PRAC meeting minutes	No
Spikevax	Capillary leak syndrome	25-28 October 2021 PRAC meeting minutes	No
Spikevax, Comirnaty	Capillary leak syndrome	10-13 January 2022 PRAC meeting minutes	No
Spikevax	Erythema multiforme	22 July 2021 PRAC ORGAM	No
Spikevax	Erythema multiforme	27-30 September 2021 PRAC meeting minutes	Yes

Spikevax	Glomerulonephritis and nephrotic syndrome	22 July 2021 PRAC ORGAM	No
Spikevax	Glomerulonephritis and nephrotic syndrome	27-30 September 2021 PRAC meeting minutes	No
Spikevax	Heavy menstrual bleeding	7-10 February 2022 PRAC meeting minutes	No
Spikevax	Immune thrombocytopenia	8-11 March 2021 PRAC meeting minutes	No
Spikevax	Immune thrombocytopenia	3-6 May 2021 PRAC meeting minutes	No
Spikevax	Immune thrombocytopenia	5-8 July 2021 PRAC meeting minutes	No
Spikevax	Myocarditis and pericarditis	7-10 June 2021 PRAC meeting minutes	No
Spikevax	Myocarditis and pericarditis	5-8 July 2021 PRAC meeting minutes	Yes
Spikevax	Myocarditis and pericarditis	Signal assessment report adopted at the 30 August-2 September 2021 PRAC meeting	No
Spikevax	Myocarditis and pericarditis	14 October 2021 PRAC ORGAM	No
Spikevax	Myocarditis and pericarditis	25-28 October 2021 PRAC meeting minutes	No
Spikevax	Myocarditis and pericarditis	29 November-2 December 2021 PRAC meeting minutes	Yes
Comirnaty; Spikevax; COVID-19 Vaccine Janssen; Vaxzevria	Multisystem inflammatory syndrome	30 August-2 September 2021 PRAC meeting minutes	No
Comirnaty; Spikevax; COVID-19 Vaccine Janssen; Vaxzevria	Multisystem inflammatory syndrome	25-28 October 2021 PRAC meeting minutes	No
Spikevax	Amenorrhoea	7-10 June 2022 PRAC meeting minutes	No
Spikevax	Autoimmune hepatitis	4-7 April 2022 PRAC meeting minutes	No
Spikevax	Capillary leak syndrome	7-10 March 2022 PRAC meeting minutes	Yes
Spikevax	Corneal graft rejection	4-7 April 2022 PRAC meeting minutes	No
Spikevax	Corneal graft rejection	29 August-1 September 2022 PRAC meeting minutes	No
Spikevax	Heavy menstrual bleeding	7-10 June 2022 PRAC meeting minutes	No

Spikevax	Heavy menstrual bleeding	24-27 October 2022 PRAC meeting minutes	Yes
Spikevax	Myositis	9-13 January 2023 PRAC meeting minutes	No
Spikevax	Pemphigus and pemphigoid	28 November-1 December 2022 PRAC meeting minutes	No
Spikevax	Pemphigus and pemphigoid	11-14 April 2023 PRAC meeting minutes	No
Comirnaty	Amenorrhoea	7-10 February 2022 PRAC meeting minutes	No
Comirnaty	Amenorrhoea	7-10 June 2022 PRAC meeting minutes	No
Comirnaty	Autoimmune hepatitis	29 November-2 December 2021 PRAC meeting minutes	No
Comirnaty	Autoimmune hepatitis	4-7 April 2022 PRAC meeting minutes	No
Comirnaty	Capillary leak syndrome	7-10 March 2022 PRAC meeting minutes	No
Comirnaty	Corneal graft rejection	4-7 April 2022 PRAC meeting minutes	No
Comirnaty	Corneal graft rejection	29 August-1 September 2022 PRAC meeting minutes	No
Comirnaty	Heavy menstrual bleeding	7-10 February 2022 PRAC meeting minutes	No
Comirnaty	Heavy menstrual bleeding	7-10 June 2022 PRAC meeting minutes	No
Comirnaty	Heavy menstrual bleeding	24-27 October 2022 PRAC meeting minutes	Yes
Comirnaty	Histiocytic necrotizing lymphadenitis	29 August-1 September 2022 PRAC meeting minutes	No
Comirnaty	Myocarditis and pericarditis	29 November-2 December 2021 PRAC meeting minutes	Yes
Comirnaty	Myositis	9-13 January 2023 PRAC meeting minutes	No
Comirnaty	Pemphigus and pemphigoid	28 November-1 December 2022 PRAC meeting minutes	No
Comirnaty	Pemphigus and pemphigoid	11-14 April 2023 PRAC meeting minutes	No
Comirnaty	Vulval ulceration	29 August-1 September 2022 PRAC meeting minutes	No

Comirnaty	Vulval ulceration	9-13 January 2023 PRAC meeting minutes	No

As is shown by this overview, a large number of potential safety signals was evaluated. The time to process the various signals associated with the different COVID-19 vaccines by the involved regulatory authorities was (relatively) short seeing the unprecedented amount of data. Over 40 distinctive safety issues were discussed at PRAC in addition to those which have been discussed in other pharmacovigilance procedures like PSURs. Certain safety issues were discussed multiple times at PRAC. This resulted in update of the information in 49 instances. These findings show the time needed for regulatory decision making with keeping in mind the complexity of signal evaluation when vaccinating a large part of the population and thus having to deal with issues like background exposure of events.

2.2.3. Evidence collection for a safety signal; Menstrual disorders as an example

As an example of the evidence collection for a safety signal, a scoping review was performed with the **aim to provide an overview of events and regulatory actions taken with regards to menstrual disturbances that occurred after COVID-19 vaccination**. Literature regarding the risk of menstrual disorders after COVID-19 vaccination was systematically reviewed, and a timeline highlighting key events regarding safety signals of menstrual disorders following COVID-19 vaccines was be provided. Finally, gaps in literature were discussed, and recommendations for future research and signal assessments are provided.

Methods: This scoping review was developed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (32).

Results: The PubMed search resulted in 117 records. We found five additional eligible records through our manual search. In total, 46 studies were included in our scoping review. Of the 46 included studies, 32 were cross-sectional studies and 14 cohort studies. One study was published in 2021, the remaining in 2022 (n=42, 91%) and 2023 (n=3, 7%). A substantial number of studies was performed in Saudi Arabia (n=10, 22%). The majority of studies used self-reported (online) questionnaires to assess the presence of menstrual disorders (n=39, 85%), often spread through social media, whereas some used a menstrual cycle tracking app (n=5, 11%). Most studies excluded participants younger than 18 years. Two studies only included female adolescents aged 12-15 or 12-17 years.

Discussion: This scoping review synthesized the body of evidence on menstrual disorders following COVID-19 vaccination. We identified 46 primary studies and we summarized data on key events regarding the signal detection process. Evidence shows that COVID-19 vaccines may cause menstrual changes in women of reproductive age, and heavy menstrual bleeding was added to the product information of Pfizer and Moderna. However, there were important limitations in the study designs of many of the included studies.

Research gaps

The most important limitation of many included studies is the cross-sectional study design, which limits the possibility to investigate a causal relationship between the COVID-19-vaccines and menstrual disorders (33). Second, the majority of the included studies reported only descriptive statistics and did not use a control group. Since menstrual disorders are common in the general population, this is an important gap in previously conducted research in this area. Third, most studies excluded women younger than 18 years. Since the median age of menarche is 11.9 years (USA data) (34), it would be interesting to examine menstrual outcomes in vaccinated female adolescents as well. Fourth, most studies were performed in high-income countries with high access to healthcare access and resources to track and report menstrual disorders, which limits generalizability of the results to other countries. Due to the fact that talking openly about menstruation is a

taboo in some countries as well less reporting to spontaneous reporting systems, the number of menstrual disorders might be underestimated in several studies. The fifth limitation of the included studies is that many studies distributed the questionnaire via different social media platforms (e.g., Facebook, WhatsApp, LinkedIn, and Twitter). This may have led to selection bias with a higher inclusion of younger women and women who feel that the vaccine affected their menstruation. However, social media platforms are modern instruments to quickly reach the whole country and appropriate age groups. Moreover, several studies were performed after vaccination took place and after an increase of menstrual irregularities reported in the media, which may have led to an overestimation of actual incidence numbers. Sixth, because of the retrospective design of many includes studies, recall bias might have occurred. At last, the menstrual disorders are mainly non-serious, with short-term duration, and self-reported without confirmation of a healthcare professional. However, many women do not visit their gynecologist for minor menstrual disturbances and physicians can only confirm what the woman told him. Possibilities to medically confirm transient menstrual disturbances are limited, which means that medical confirmation does not increase the credibility of the self-reported cases.

Conclusion: This review identified a wide range of studies investigating a variety of menstrual disorders after COVID-19 vaccination. Although the menstrual changes found in this literature review after COVID-19 vaccination are short-lived and predominantly mild, it is important for women and health care professionals to be informed about these potential side effects. We identified important limitations in the study designs of many of the included studies for evaluating causality. Because of the high impact of menstrual disorders on women's quality of life, menstruation-related side effects should be investigated when developing vaccines.

Supplementary material 1 provides the entire scoping review.

2.3 What can we learn from the COVID-19 pandemic?

In this chapter we summarize the main findings from the independent research agency Andersson Elffers Felix (AEF) who conducted an independent evaluation of the questions *'What impact is intended with pharmacovigilance during a pandemic*?' and *'What does this require of a knowledge center for ADRs of medicines and vaccines and the cooperation with regulatory agencies'* and '*What can we learn from the COVID-19 crisis*? The full report in Dutch is listed as an additional Supplementary Material.

2. Pharmacovigilance also plays an important role in the establishment of 'substantiated confidence' of the society in the safety of medicines and vaccines – this confidence came under pressure during the pandemic

Pharmacovigilance also offers, by contributing to medical knowledge on safety, an important foundation for society's trust in the safety of medicines and vaccines. This substantiated trust becomes simultaneously influenced by numerous other factors, outside the sphere of influence of the (regulatory) parties involved in pharmacovigilance.

Particularly due to the context of the COVID-19 pandemic and due to numerous factors, great pressure was put on confidence in the medical knowledge on safety, and it came to be under a magnifying glass. For a long time, there was uncertainty about the nature of the virus, there was generally lower trust in government agencies and various forms of disinformation were spread. In addition, the voluntary vaccination of a group of healthy people leads to different considerations for groups of citizens about medical safety.

This specific dynamic put pressure on regulatory stakeholders of pharmacovigilance. The existence of an independent reporting and knowledge center for ADRs proved to be extra important during the pandemic for the substantiated trust in medical knowledge on safety. After all, a knowledge centre about ADRs has no direct benefits of the decision for citizens to vaccinate, whereas this benefit is there from a governate point of view.

3. Lessons can be learned from the Covid pandemic on how medical knowledge on safety can be further increased and how Lareb and regulatory stakeholders can contribute to (more) substantiated trust.
The COVID-19 pandemic teaches that substantiated confidence in the safety of medicines and vaccines is not self-evident. Clarity about role and independent position is crucial for a reporting and knowledge center for ADRs to make a credible contribution to substantiated trust. It is it is therefore important that Lareb and regulatory agencies involved strive for more transparency towards the outside world, about the different roles of parties in the pharmacovigilance process. This allows society to better understand recommendations and decisions and place information about vaccinations, medicines and ADRs into context.
To promote social confidence in medical safety it is also important Lareb and regulatory stakeholders (CBG, RIVM, Min VWS, IGJ) are aware of the content and the time of each other's communications, so that they can respond to them. For example, it should be more clear who has which role and how roles of different stakeholders relate to each other.
The medical knowledge on safety can be further increased by improvement of the input i.e., the quality and the number of reports about ADRs. Healthcare professionals in this evaluation have highlighted the need for direct reporting from electronic healthcare records to Lareb, without having to fill in separate reporting forms. In addition, by investing in the technical (data) infrastructure, such as being able to link healthcare data to vaccine data potential safety signals can be evaluated faster. This is already in place in Nordic countries such as Sweden. The medical knowledge on safety can also be improved increased by continuing to invest in Lareb's reporting system, for instance allowing for further automation so that data can be processed and evaluated (even) more quickly.

4. Thinking in scenarios about the context of the next pandemic – and its influence on (the intended impact of) pharmacovigilance – must become part of regulatory pandemic preparedness.
The intended impact of pharmacovigilance does not change during a pandemic and becomes even more important than during a non-pandemic situation given the scale of novel medicines and/or vaccines. However, the context of a next pandemic is expected to be different. Where transparency became extra important during the COVID pandemic for substantiated confidence in safety, it could be that in next pandemic other matters are (more) important. Think, for example, of speed of actions if we were to be confronted with a (much) more pathogenic virus.
Part of regulatory pandemic preparedness is thinking in scenarios about the context of a next pandemic and its impact on medical knowledge on safety and on the substantiated confidence of society in the safety of vaccines and medicines. For example, if speed is more important in the context of a future pandemic, this may have more consequences for processes and compliance with laws and regulations in general sense.

3 PROSPECTIVE; WHAT CAN WE DO BETTER DURING FUTURE PANDEMICS?

This chapter aims to answer how in case of a future pandemic we can better deal with safety surveillance. We investigated if the analysis of data can be improved to help to identify possible ADRs and how this can contribute to more effective and efficient pharmacovigilance during a future pandemic? For example, improved data analysis could assist in detecting ADRs earlier or improving the distinguishment between important and unimportant reports. We combined results from the evaluation of independent research agency Andersson Elffers Felix (AEF), a literature review on methods and data-sources for pharmacovigilance activities aimed at COVID-19 vaccines and drugs to treat COVID-19 and interviews with pharmacovigilance professionals working on COVID-19 vaccine and drug safety during the pandemic.

3.1 What can we learn from the evaluation of AEF?

From the evaluation of independent research agency AEF (see Chapter 2.3 and appendix) we highlight tangible recommendations for a future pandemic based on the qualitative interviews and focus groups with pharmacovigilance professionals working at regulatory agencies and marketing authorization holders, medical professionals and consumers. The focus of the recommendations highlighted below are on *signal detection and evaluation by* ***investing in the technical (data) infrastructure*****.**

Recommendations for investing in the technical (data) infrastructure

1. At the beginning of the pandemic, it took a lot of time in the Netherlands to set up the vaccination registry (CIMS, maintained by the RIVM). It was possible for Lareb to access these data from the RIVM. With permission from the reporter, batch numbers and vaccine brands were retrieved from the national vaccination registry (CIMS). Data from the vaccination registry were also used in signal detection, for instance in Observed vs Expected analysis were the number of vaccines given in strata of age and sex is necessary. However, it was *not* possible in the Netherlands to link vaccination data to healthcare data in a fast and efficient manner. This hampered a quick evaluation of potential signals. In contrast to the Netherlands, this was possible in many other EU member states such as Sweden and France. As a result, Lareb has had to rely on data from others on signal verification. In view of a future pandemic, it is important to invest in such a linkage. This should be done with due observance of privacy regulations in the EU. Potentially Health-RI (https://www.health-ri.nl), the organization that is working towards an integrated research infrastructure, by enabling data reuse for policy, research, and innovation could play a role. Health-RI is a national coordination center for agreements on the reuse of health data, promoting collaboration among all stakeholders, and supporting researchers.

2. Systematically registering ADRs in electronic health records (EHRs) is likely contribute to patient safety as it enables the exchange of drug safety data. ADRs registrations by healthcare professionals (HCPs) should be optimized and, in addition, making a linkage between information about ADRs directly from the system of healthcare providers to the Lareb reporting system is desirable. This has the advantage that administrative burdens can be curtailed since healthcare providers only have to register suspected adverse drug reactions once in the electronic health record (EHR) system. However, expect for some pilot studies, this linkage is currently not in place and complicated due to the variety of different healthcare systems used in the Netherlands. However, it is expected that such a linkage will lead to an increase in the number and quality of the reports received by Lareb allowing for faster signal detection.

3. Investing in the technical (data) infrastructure also includes continuing investment in the reporting system of Lareb. Based on the COVID-19 pandemic, it can be concluded that the spontaneous reporting system still functions as an efficient early warning system. However, system improvements can be made, for instance allowing for further automation so that data can be processed and evaluated (even) more quickly.

In addition to the AEF report, we highlight two recent initiatives by Lareb which connect to the recommendations for investing in the technical (data) infrastructure.

Lareb initiatives

1. In 2023 Lareb has received funding through ZonMW for a project on **Electronic healthcare records as an innovative addition to knowledge gaps in vaccine safety surveillance during pandemics**
   This is a collaboration between Lareb, the Leiden University Medical Center, and the Haga hospital in the Hague. The hospitals use EHRs to store information about the patients. This also includes information about possible ADRs that patients experienced after COVID-19 vaccination. In this study, a software tool is used to search with text-mining EHR for possible ADRs of vaccination after a potential hypothesis has been triggered by spontaneous reports. If cases are identified, they are reported to Lareb. Lareb then analyzes the reports together with spontaneously reported cases. This way of innovative safety monitoring could be a useful way of working during future pandemics. The process is shown below in Figure 11.

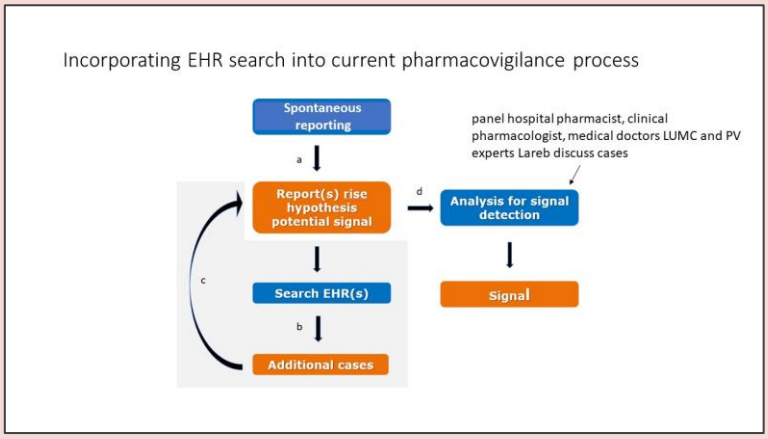

Figure 11. Process of incorporating EHR searches into the current pharmacovigilance process

2. From January 1, 2022, till December 31, 2023, pharmacovigilance centre Lareb is running **a pilot to build an infrastructure for follow-up analyses based on healthcare data**.
   Nivel and STIZON provide the necessary general practitioner (GP) data and the National Institute for RIVM provides the vaccination data. This data is first tokenized twice and then anonymized and made available for the research team via a secured Remote Access, which is disconnected from the Internet and only accessible for a few researchers via 2-factor authenticator. Data was collected for all persons aged 12 years and older that were available in the GP databases of Nivel and STIZON in the year 2021, after which these persons were linked to the vaccination data from the RIVM to include only vaccinated persons.
   This pilot project focuses on potential ADRs of the COVID-19 vaccines, such as herpes zoster, menstrual disorders, and venous thromboembolism. The research questions that are central in each analysis are:
   - Is there an increased risk of the potential side effect after COVID-19 vaccination by vaccine brand and injection moment?
   - Are there certain groups that have an increased risk of the potential side effect after COVID-19 vaccination?
   A cohort study design and a Self-Controlled Case Series/Self-Controlled Risk Interval study design will be applied in order to answer these research questions, depending on the outcome.
3. In 2022-2023 in collaboration with the LUMC and the Santeongoep, a **case-control study** is being conducted into the risk of venous thrombosis after vaccination with the BioNTtech/Pfizer, Moderna, AstraZeneca or Janssen. In addition, it is being investigated whether there are specific risk groups and risk factors that increase the risk of venous thrombosis after corona vaccination to exist.

3.2 What can we learn from literature on the COVID-19 pandemic?

In order to gain insight in the data-sources and methods used for post-market approval safety monitoring of COVID-19 vaccines, a literature review was conducted.

Research question(s);

- What methods and data-sources were used for pharmacovigilance activities aimed at COVID-19 vaccines and drugs to treat COVID-19?
- What recommendations were made in the literature that we can apply to a more effective and at the same time more efficient pharmacovigilance during a future pandemic?

Method

The study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist as the matrix for writing this study report (32). The protocol was not a priori published.

Inclusion and exclusion criteria

Types of participants: Studies describing humans only. Animal studies were not included.
Concept: Based on the review objective, both COVID-19 vaccines and medicines for the treatment of COVID were included. There was no restricting for brand of vaccines.
Context: Based on the review objective, there were no exclusion criteria regarding geographical location, cultural background, gender, or any other variant.
Type of evidence sources: Published primary data sources in English.
Types of studies: Articles on data sources used for the pharmacovigilance (for example, spontaneous report systems) were included, articles describing methods used for identifying and assessing ADRs potentially related to COVID-19 vaccination or drug treatment for COVID-19 were included. Articles on Lessons learned/recommendations for possible future pandemics were included. Case studies were excluded. Studies focusing on one specific ADR as an outcome were excluded.
Period of publishing: All articles published before March 6, 2023.

Search strategy

An electronic database search was conducted in 2 stages. The first stage consisted of a Boolean search in Pubmed using the following keywords: "COVID-19", "pharmacovigilance", "adverse drug reactions". This initial search led to the random selection of ten articles. The words in the titles and keywords of the ten selected articles were analyzed to identify the most appropriate keywords. Only articles that fit the inclusion criteria of this study were included in the initial analysis. The emerging keywords were searched in PubMed® during the second stage of the search (Full search terms in Supplementary material 2). Finally, references were checked across the articles to identify other interesting articles that could be included.

Article selection

EndNote X9® software (Clarivate, Philadelphia, PA, USA) was used to select articles and detect duplicates. During the first stage of the research, two reviewers independently screened titles and abstracts for assessment against the inclusion criteria of 10 studies. Afterward, one reviewer made the primary selection and put them in the following categories: "qualified", "maybe qualified", and "not qualified". Studies that could potentially meet the inclusion criteria were retrieved in full text. Studies that did not meet the inclusion criteria based on title or abstract were excluded, and the reason for exclusion was added in the research notes. If the reviewers had uncertainties about the relevance of a study or if the abstract was unclear, the entire article was retrieved.
Full-text studies that did not meet the inclusion criteria were excluded, and reasons for exclusion were provided in the final report. When in doubt, the inclusion of a study was decided through consensus between the researchers. The search results were fully included in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Charting

Data were extracted from the selected articles using a charting table aligned to the objectives of this review. This extraction instrument was designed based on the JBI template Source of Evidence Details, Characteristics, and Results Extraction Instrument (35). The results of the scoping review were placed in an Excel table. The following components were reported: *author, the year of publication, country, type of treatment (vaccination or medication), data source, methods, and recommendations*. Researchers independently charted the first five studies using the extraction instrument; afterward, the researchers met to discuss whether the data extraction approach was consistent with the research questions and objectives.

Results

A flow diagram of records included in the scoping review is shown in Supplementary Material 3. From the search, a total of 442 articles were obtained of which 54 articles were grouped as relevant after an initial screening of the abstract and title. After the articles were fully analyzed, 43 articles remained that were included in the study. We manually added 5 articles on the basis of a reference cross-check, bringing the total to 48 articles. The full list of articles is summarized in Supplementary Material 4.

During the COVID-19 pandemic, data derived from spontaneous reports remained a key evidence source. During a future pandemic spontaneous reporting systems will likely still play an important role in the early identification of safety signals. However, there is room for improvement of existing methods and new techniques available for automation. For example, a tool was developed for the national health authorities in France, where machine-learning natural language processing was employed to learn and predict encodings in patient reports of ADRs. In addition, an automated seriousness assessment could be performed. Different approaches for data processing and classifiers were developed and compared. Performance was evaluated using receiver operating characteristic area under the curve (AUC), F-measure, sensitivity, specificity, and positive predictive value. Both internal and external validation yielded robust results across different methods and the system has been deployed by national health authorities in France since January 2021 to facilitate pharmacovigilance of COVID-19 vaccines (36). The Swedish Medical Products Agency (MPA) used the technique of robotic process automation was used for registering and MedDRA coding certain data in the received reports, and to automatically retrieve information on batch numbers of vaccines directly from the Swedish national vaccination register. This was to unburden and speed up the handling of ADR reports (37).

In addition to more process automation, innovation in the process of signal detection can be sought; Machine learning approaches were used to investigate relationships between ADRs and person-specific factors such as sex, co-morbidities, and genetic factors (38). Unsupervised machine learning techniques can be used to cluster adverse event terms and researchers subsequently analyzed the characteristics of each symptom cluster in US VAERS data (39). Disproportionality analysis, as a more traditional signal detection tool, should take into account issues like statistical masking effects (40).

For an effective safety surveillance, other data-sources than Spontaneous Reporting Systems (SRS) should be used. There is a necessity of all types of infrastructures in safety evaluation: SRS, cohort event monitoring, as well as Electronic Healthcare Record (EHR) data as they each have their own distinct strengths and weaknesses (41). Linkage of EHR data and other data-sources such as registries can be used in the strengthening or evaluation of safety signals. The Swedish MPA, as a research project with ethical approval, set up a nationwide register-based study to detect and characterize suspected ADRs after COVID-19 vaccines (37, 42). This nationwide register-based study cohort includes all individuals 12 years or older in Sweden from2021 and is updated annually. Data, including vaccine and COVID-19 disease data, socioeconomic and demographic data, comorbidity, prescribed medicines and healthcare utilisation outcomes, are obtained from several national registers in collaboration with other Swedish Government agencies. Data from 2015 to 2019 are used as a historical comparison cohort unexposed to both the COVID-19 pandemic and to the COVID-19 vaccines (42). In

France, in the beginning of the COVID-19 vaccination campaign, the French health authority ANSM set up a specific system for a strong surveillance of the efficiency and security of COVID-19 vaccines in France. This system relies on both pharmaco-vigilance, i.e., the analysis of adverse drug reactions reported by healthcare professionals and vaccinated individuals in the national pharmacovigilance database (BNPV) and pharmaco-epidemiology that aims at measuring the efficiency of COVID-19 vaccines and to quantify their risk of adverse drug reactions at the population level. On the basis of a safety signal, they initiated a pharmaco-epidemiological study in order to evaluate the short-term risk of hospitalization for myocardial infarction, stroke, and pulmonary embolism after BNT162b2 mRNA (Pfizer-BioNTech) vaccine in people 75 years of age and older. In addition to this example, they produced numerous studies on the use and risks of health products, the risk factors for severe COVID-19 in vaccinated and unvaccinated individuals and on the epidemiological surveillance of COVID-19 vaccines (43). The Data and Connectivity COVID-19 Vaccines Pharmacovigilance (DaC-VaP) UK-wide collaboration was created to monitor vaccine uptake and effectiveness and provide pharmacovigilance using routine clinical and administrative data. Because national health services do not all use the same terminology in the UK, a working with a Common Data Model allows for pooled analysis (44). Researchers used the Observational Medical Outcomes Partnership (OMOP) common data model (CDM). Datasources included the data from the Oxford Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) for England, The EAVE II data of 5.4 million people registered in general practices in Scotland, the Secure Anonymised Information Linkage (SAIL) databank from Wales and the Business Services Organisation Honest Broker Service (HBS) from Northren Ireland. With these linked data, they could issue repeated cross-sectional reports of the incidence of the adverse events in the vaccinated population (44). Combination of data-sources was also a key strategy used by the US Food and Drug Administration. For the safety surveillance of emergency use of drug and biological products for COVID-19 the FDA conducted surveillance of adverse event and medication error data using the FDA Adverse Event Reporting System, biomedical literature, FDA-American College of Medical Toxicology COVID-19 Toxicology Investigators Consortium Pharmacovigilance Project Sub-registry, and the American Association of Poison Control Centers National Poison Data System. This meant going beyond routine pharmacovigilance practices to rapidly identify emerging safety concerns and stablishing collaborations and leveraging new data sources including near real-time data (45).

Social media platforms (such as Twitter and Facebook) could be used as an additional new data source for data collection. A method that was widely used in the studies to investigate positive, negative, and neutral tweets/posts was a sentiment analysis based on machine learning (46, 47). The purpose of the studies was to gain more insight into public perception regarding COVID-19 vaccines and cluster the most discussed topics into themes. A study looking at social media posts in the UK identified 46,762 unique Facebook posts by 14,346 users and 74,644 tweets (excluding retweets) by 36,446 users over a 4-month period and an increasing trend in the number of mentions for each AEFI on social media over the study period. The most frequent AEFI mentions were found to be symptoms related to appetite (n=79,132, 14%), allergy (n=53,924, 9%), injection site (n=56,152, 10%), and clots (n=43,907, 8%). Rare AEFI such as Bell palsy (n=11,909, 2%) and Guillain-Barre syndrome (n=9576, 2%) were being discussed as frequently as more well-known AEFI like headache (n=10,641, 2%), fever (n=12,707, 2%), and diarrhea (n=16,559, 3%) (39). These methods could be used to help identify where information gaps for the general public, which can then be addressed (47). It should be further investigated whether social media platforms can also provide a source which can be used for signal strengthening.

In Figure 12 key recommendations based on the literature review are summarized,

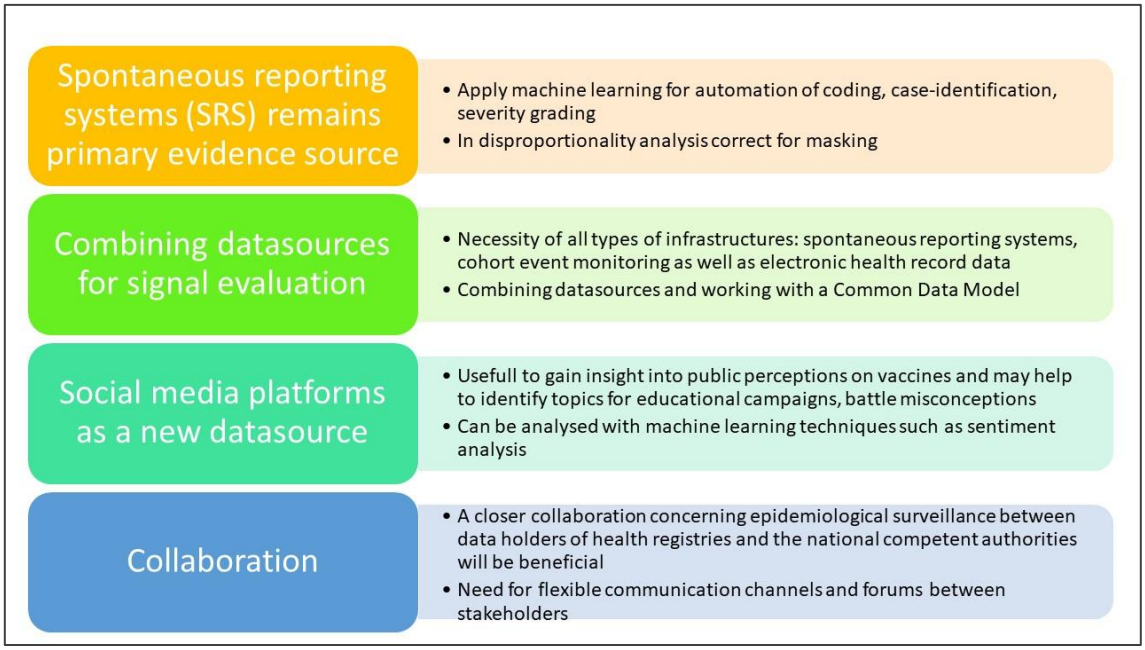

Figure 12 Key recommendations based on the literature review

Discussion and Conclusion

This literature review provides an overview of the learnings to be taken from the COVID-19 pandemic to improve pharmacovigilance. Some examples from the literature provide input for developments at the Dutch pharmacovigilance centre considering further automation; for instance, Lareb has had its own automated coding free-text to MedDRA system in place for some years for medicines, but this was not in place for coding of COVID-19 vaccine reports during the Pandemic and the plan is to develop this further. Also signal detection methods such clustering based on unsupervised machine-learning techniques have potential value and should be further developed for the Dutch SRS. Overall, it is recommended that machine learning approaches be used to enhance current pharmacovigilance surveillance systems. This includes exploring the potential of social media screening as a way of identifying what the information needs are for the general public during a Pandemic.

Signal evaluation using real-world data was possible in a very timely manner in European countries like Sweden and France (42, 43). Fast signal evaluation like this, based on Dutch data, was not possible in the Netherlands although Dutch data was used in European-wide studies, for instance in determining background rates for events (48). For an effective surveillance, combining data sources may be needed. Experiences from the FDA in the US for drugs to treat COVID-19 show that close collaboration between different stakeholders and research fields is needed to achieve this (45).

A limitation of our current study is the possibility for some selection bias in the inclusion of the articles, although the literature search and article selection were discussed by two researchers throughout the study to minimize this. We also excluded studies that focused on a specific outcome such as thrombosis as an adverse event following immunization, but could have provided insights into pharmacovigilance data-sources and methods. Also, some important articles may have been missed as the cut-off data for inclusion was set on March 2023 for publication dates.

In conclusion, The tangible recommendations deriving from this quantitative literature study will be compared and complemented by the qualitative study in the following chapter.

3.3 What can we learn from international experiences, a qualitative study of EU pharmacovigilance centres

In order to learn from experiences from other pharmacovigilance centres in Europe who dealt with the challenges of the COVID-19 pandemic, a qualitative study with interviews was performed.

Aim of this study was to learn how organizations responsible for pharmacovigilance during the COVID-19 pandemic dealt with an increase in numbers of individual case safety reports (ICSRs) and corresponding signal detection activities for these ICSRs. Based on experiences from the COVID-19 pandemic we aim to give recommendations for innovative methods that can improve signal detection in future pandemics.

Method

This study conducted qualitative research using an inductive methodology (49).

A ***semi structured interview guide*** was designed by two authors (Florence van Hunsel & Eugène van Puijenbroek). The interview guide contained 7 open-ended questions (with sub-questions) to allow the interviewees to provide in-depth answers related to their experiences with pharmacovigilance during the COVID-19 pandemic. The topics included in the interview guide were how organisations dealt with an increase in reports during the COVID-19 pandemic, what signal detection methods they used, the use of data sources other than spontaneous reports during the COVID-19 pandemic and recommendations for a future pandemic based on best practices learned from the COVID-19 pandemic. The interview guide is available in Supplementary Material 5.

Participant selection was based on purposive sample of colleagues working in pharmacovigilance, with a focus on signal detection. Recruitment was performed via the European Medicines Agency (EMA) Signal Management Review Technical (SMART) Working Group where colleagues were invited to join during the March 2023 meeting. Members of the SMART WG work at the European Medicines Agency, national competent authorities (or regional PV centres) or the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring. Through the Dutch Medicines Evaluation Board, colleagues from Swissmedic, the Swiss national agency for therapeutic products, were invited. Because Lareb colleagues are part of the SMART WG, they were included among the participants.

An email invitation with further information was sent to the potential interviewees. Participants who agreed to participate in an interview scheduled an interview appointment with the lead researcher. The interviews were conducted via Microsoft Teams® and one interview was conducted during a face-to-face meeting. An interview was estimated to last 30 minutes. All interviews were recorded and subsequently transcribed. Participants could also choose to give a written answer to the interview questions.

To maintain the confidentiality of the interviewees, pseudonymization via an alphanumeric code was employed in the presentation of the results.

Data analysis & coding process; The transcripts of the interviews were imported into QSR International Pty Ltd. NVivo® software for coding and analysis.

Data coding for thematic analysis consists of identifying data fragments in terms of their meaning and labeling them with a code (codes represent the 3rd-level hierarchy) (49, 50). As this process continues, relations or connections among these codes can be depicted, which generates high-level concepts (which represent the

2nd-level hierarchy). Groups of related high-level concepts are subsequently assembled into larger groups to create themes (which represent the 1st-level hierarchy).

To reduce the risk for interpretation bias, the first interview was coded individually by two researchers (Mina Hashimi and Florence van Hunsel), and disagreements concerning the coding were discussed to verify the credibility of the coding (32).

Ethics approval; If a study in the Netherlands is subject to the Medical Research Involving Human Subjects Act (WMO), it must undergo a review by an accredited Medical Research Ethics Committee or the central committee on research involving human subjects (CCMO). This study does not fall under the WMO act.

Results

A total of 9 interviews were conducted. Table 8 presents an overview of the participants. For two interviews, there were two participants who answered the interview questions. One participant had a dual function and worked both at the Dutch Medicines Evaluation Board and the European Medicines Agency (EMA).

Table 8. Profiles and classification of the participants

Interview identifier	Organisation	Country	Participant number, sex	Methods	Date
1	Lakemedelsverket	Sweden	2, F, M	Face-to-face meeting with recording via MS Teams	28-2-2023
2	Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	Spain	1, F	Written answers	20-04-2023
3	Uppsala Monitoring Centre (UMC)	Sweden	2, F, M	Written answers	28-4-2023
4	Paul-Ehrlich-Institut (PEI)	Germany	1, M	Written answers	2-5-2023
5	Centre de Pharmaco-épidémiologie DRUGS-SAFEr Bordeaux	France	1, M	Interview via MS Teams	27-3-2023
6	Regional Pharmacovigilance Centre of the Veneto Region	Italy	1, M	Interview via MS Teams	31-3-2023
7	Swissmedic	Switserland	1, M	Written answers	02-6-2023
8	CBG-MEB/EMA	EU	1, F	Written answers	4-4-2023
9	Netherlands Pharmacovigilance Centre Lareb	Netherlands	1, F	Written answers	21-6-2023

Interview thematic analysis

The general hierarchy chart of the coding structure from the data analysis using thematic analysis is shown in Figure 13; the size and color saturation of each section represents the number of references pertaining to that theme. The chart is divided into a two-level coding hierarchy according to which the outer box represents the themes, which is followed by high-level concepts. In subsequent figures and descriptions these concepts are further shown with an explanation of the codes. We highlight some findings with quotes from the interviews.

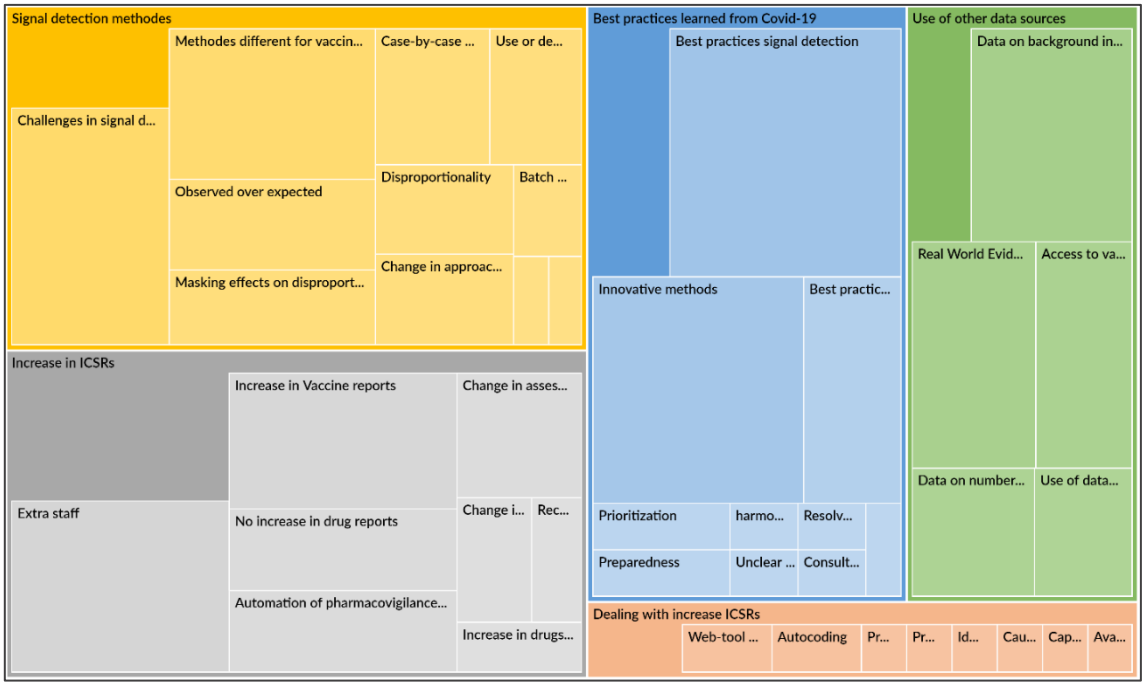

Figure 13 Overview of the coding hierarchy

Increase in reporting and handling data

All interviewed organisations had to deal with a large increase in ICSRs during the pandemic. This was almost solely due to COVID-19 vaccine reports as few organisations noticed a substantial increase in the number of cases on drugs to treat COVID-19.

Quote Interview 5: *"So there was an increase of the reports in for hydroxychloroquine, so there was an increase of the reports for ivermectin, there was an increase of the reports for some others like azithromycin. But aside of it, there was no specific increase."*

Solutions to deal with this increase in reports were found in hiring extra staff; this could be staff that dealt with coding of ICSRs or staff with pharmacovigilance/vaccine knowledge. Sometimes tasks were re-allocated from the national centre to regional centres. Also outsourcing of tasks, such as coding, to contracting agencies occurred. Especially for non-serious ICSRs, some organizations had a back-log of work in processing cases and sending them to Eudravigilance. Automation of pharmacovigilance processes played in important role; for instance, in building better web-based reporting forms, auto-coding of vaccines and/or ICSRs and duplicate detection. In Italy, there was large-scale reporting via an SMS option. Most organisations made some adjustments to the way they received or handled cases, for instance by doing a triage and only assessing selected cases in-depth by clinical assessors.

Quote interview 1: "*We introduced a quick process automation RPA (=Robotic Process Automation) technique that has helped us enormously*." "*It's basically just picking all the different boxes and filling different fields, but it's also going into the national vaccination registry and picking up batch numbers and checking that it's the correct. That, depending on the personal identification number, that in the dates right filling in the dates too and the getting the correct vaccine name too*."

Quote interview 4: "*In consideration of the huge workload of incoming ICSRs, handling was prioritized according to fatal cases, AESI-related cases and other serious case reports and the non-serious cases reports*."

And "*Adaptation of the electronic registration (online reporting portal) specifically for COVID-19 vaccines was established which also included automatic coding of known side effects. Processes of automatic MedDRA coding and Vaccine coding of ICSRs was implemented in our national database in the sense of a preselection, which however has to be checked by documentation assistants*."

Quote interview 9: "*A specific COVID-19 vaccine dedicated web-based reporting form was developed that enabled the collection of spontaneously reported information on the vaccine administered, AEFI and other information needed for assessment and signal detection. A fully automatic process for ICSRs enabled the handling of the majority of common and known reported AEFI that were prespecified on the reporting form. We decided to set up this new way of working to manage large numbers of straightforward ICSRs. All other cases were triaged and a selection of cases was assessed in depth by clinical assessors, for instance ICSRs with a fatal outcome*."

All this extra data also required additional work from EMA to keep data in EV as uniform as possible. For instance, EMA work was done to provide guidance on capturing dosing sequences in the ICSR messages sent to EV and identification of the vaccines in ICSRs sent to EV. Moreover, there was a need for more MedDRA terms to code reactions.

Quote Interview 8: *"When ICSR messages are transmitted between regulators, pharmaceutical industry and WHO, the drug information is exchanged as free text, resulting in many different ways to describe the same vaccine (e.g., Comirnaty, Pfizer/BioNTech Covid vaccine, BNT162b2, tozinameran, etc). It takes valuable resources to match/group medicinal products and active substances provided as free text in ICSRs to the different drug dictionaries that are used in pharmacovigilance databases. EMA engaged with both industry and Member States to collect information on the names used in the ICSRs to support accurate and rapid grouping."*

Quote interview 8: *"An extraordinary update of MedDRA (beyond the biannual standard releases) was released in spring 2020 to add new COVID related terms. This shows the need to be more agile in releasing new MedDRA terms, as well as the need for timely and harmonized acceptance of new MedDRA terms by all stakeholders. Cases with the new entity 'thrombosis with thrombocytopenia syndrome (TTS)' was another situation where quick availability/acceptance of a new MedDRA term became apparent."*

Furthermore, for the world-wide ICSR database (VigiBase) adjustments were made, especially for Vigilyze, which a signal detection and signal management tool.

Quote interview 3: *"VigiBase was updated twice per week compared with once per week before the pandemic. In addition, we developed tools to support national centers in better capturing and analyzing reports on Adverse Events Following Immunization, including a mobile reporting app for vaccines with offline functionality, ability to analyse individual COVID-19 vaccines separately in Vigilyze, development of Standardized Drug Groupings for different COVID-19 vaccine platforms in WHODrug Global, ability to restrict background to either drugs or vaccines when performing disproportionality analyses in VigiBase."*

Signal detection methods

Most organisations used somewhat different approaches for COVID-19 vaccine signal detection then for drugs. Case-by-case or clinical review of selected cases was mentioned as a method that is still important. Selecting relevant cases for further review was mentioned as a challenge in several interviews.
Quote interview 4: "*Managerial challenging was the handling of high volumes of reports within a short period of time including follow-up questions in regard of AESIs. Methodological challenge was to identify relevant*

reports which may trigger a safety signal in the high volume of largely non-serious reports or non-medically validated reports of consumers."

Quote interview 3: "*In view of the unseen size of the case series, we could not always review each individual report, and instead had to adopt heuristics to select reports for detailed review and develop methods to enable more efficient analyses of large case series*."

However, more statistical approaches were also widely used and became more and more important due to the enormous amount of data. Disproportionality analysis was used by many organisations, but this method has some challenges in a pandemic situation; COVID-19 vaccines were given to older population in the beginning of many vaccination campaigns and that made the choice of a comparator group for disproportionality analysis important. Also, many organisations mentioned the potential of the masking effect of the large amounts of COVID-19 vaccines (sometimes on specific associations) on disproportionality calculations.

Quote interview 3: "*We see masking as a bigger problem going forward, when the massive number of reports on COVID-19 vaccines will make it difficult to detect signals with other drugs and vaccines for certain adverse events, e.g., Bell's palsy and Myocarditis*." And as a possible solution: "*drugs and/or vaccines, or apply a more sophisticated approach, such as outlier removal*."

Disproportionality does not take into account the background rates of potential ADRs. For this reason, many organisations started using Observed vs Expected calculations. However, Observed vs Expected has its own challenges such as an unknown underreporting rate, the need for vaccination data preferably stratified for age and sex, and solid data on background incidences.

Quote interview 7: "*In terms of observed-vs-expected analyses, we considered different underreporting rates in our calculations. However, in the special situation of the broad vaccination campaign with an unusual public awareness and a high number of reported cases, it was challenging to estimate the actual underreporting rates*."

In addition, some other vaccine monitoring methods were performed, such as batch-analysis or the use of electronic reaction monitoring reports or a bespoke cluster analysis, which was developed by the UMC, and used on the COVID-19 vaccine data.

As one of the challenges for signal detection, the need for further evaluation or evaluation of signals was discussed. Although this was less of an issue in some countries, who had more access to other data sources then the spontaneous reporting system.

Use of other data sources

The most commonly used external data was on the vaccinations administered; this data could be available on population level or on individual patient level. Also, data on background incidences were used by all organisations. In the EU ACCESS (vACcine COVID-19 monitoring ReadinESS) project, background incidences had been calculated for a variety of adverse events of special interest (AESI), however some organisations also had access to databases within their country. Because in many countries the vaccination campaigns started with frail elderly, in interview 5 it was mentioned that they were able to calculate expected hospitalization and fatality rates in that population as a comparator. They were able to quickly calculate incidence rates for myocarditis by age category.
For some organisations, it was difficult to perform quick signal evaluations in real world data sources while multiple EU countries could perform these types of analysis quickly.

Quote interview 5: "*We were linking with the EPI-PHARE centre which was in charge of pharmaco-epidemiology assessment and so we could make some requests*." "*… There is an assessment for the risk of stroke with the vaccines with a high number of reports, but this is a very common event in the elderly population. However, we will never be able either to conclude positively there is a risk or either to discard it from the pharmacovigilance data, so we need Pharmacoepi to give the answer.*" "*…They ran it and so they came to a conclusion saying that no, there was no association found for a risk of stroke. They performed a self-controlled case series*."

Quote interview 1: "*We could link to the basic population register with sociodemographic data. And we could link that with data on administrations of vaccinations with date and product name batches and everything, and also with positive COVID tests.*" "*…It was possible to link with the National Patient Register. With all data on hospitalizations and all visits, outpatient visits to hospitals, that means outpatient specialist visits. And linked with the prescribed drug register, all dispense drug by prescription. Also, OTC drugs written by prescriptions are captured there. And Death register and cause of death, date of death. And then some additional; The quality register for intensive care and also cancer registration, mostly to have as a controlling factor in analysis because it is a risk factor*."

Quote interview 6: "*Yes, we have access to external data, mainly related to the denominator, for example, we have the possibility to daily check the number of doses administered. But you know that each region has a lot of information, a lot of different database registries on hospitalization, drug use and so on. So there has been, for example, a study managed by the National Institute of Health collecting information for all the regions. Just analyzing the problem for example of myocarditis. So we have the possibility to have a further validation of a potential signal by looking at the real world data*."

Quote interview 2: "*Yes, AEMPS owns BIFAP, an eHCR with more than 20.000.000 anonymized eHCR from 9 Autonomous Communities. BIFAP is one of the partners involved in the European project funded by the European Medicines Agency (EMA) with the aim to create European preparedness to monitor the benefits and safety of the new coronavirus vaccines, when they come to the market. The project called ACCESS (vACcine COVID-19 monitoring ReadinESS).*" "*…We have been also involved in international collaborations regarding the study of myocarditis and COVID 19 vaccine effectiveness.*" [Question on use of datasources] "*For signal strengthening. Better characterization and quantification of the risk*."

Best practices learned from the COVID-19 pandemic

Figure 14 shows the main themes of best practices mentioned by pharmacovigilance colleagues throughout Europe.

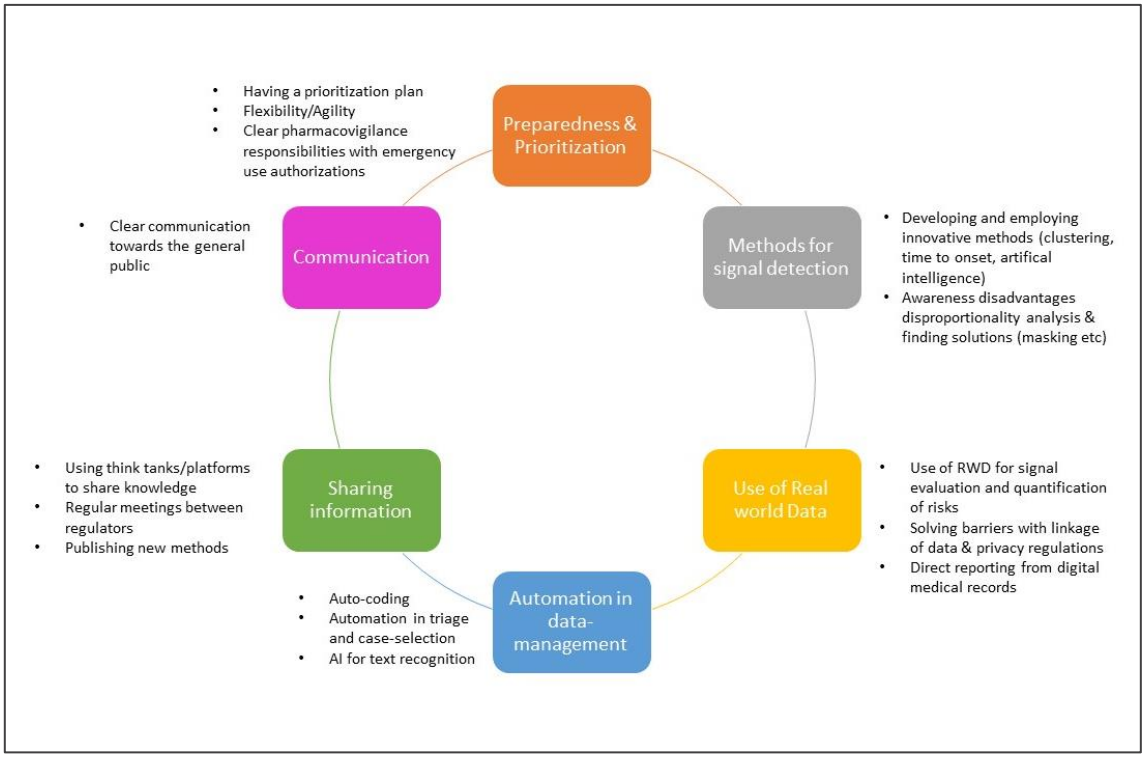

Figure 14 Recommendations for a future pandemic from qualitative interviews

Spontaneous reporting systems remain a key evidence source for finding safety signals quickly. From the interviews suggestions were made on how to manage large incoming volumes of data, the methods for signal detection, use of real-world data for signal evaluations and sharing information.

Quote interview 5: "*I don't think we ever can make a single detection tool good enough or as good as an alert clinician seeing patterns. And with that input we can evaluate and quantify the risks, no, don't identify them. But do the proper quantification like we did with the myocarditis; calculating absolute risks. How many extra cases might we see given this rate of vaccination, that is what we need, absolutely*."

Considering preparedness and prioritization flexibility and a more agile way of working were mentioned as being helpful next to having a solid preparedness plan and prioritization plan in place. It was mentioned that there have been unclear pharmacovigilance responsibilities with emergency use authorizations.

Quote interview 8: "*In EU it was noted that there is no clear legislative framework to describe pharmacovigilance obligations for non-authorised products that are made available under national emergency use authorizations. In NL we didn't use such emergency use authorization, but other countries (e.g., UK) made urgent legal changes to provide clarity on pharmacovigilance obligations for pharmaceutical industry. In order to prepare for a future pandemic, it could be considered to have legislation place that is sufficiently flexible to impose fit-for-purpose pharmacovigilance obligations on stakeholders*."

For better data-management automation of process, auto-coding for instance from text to MedDRA terminology and capturing data-elements from free-text with artificial intelligence were all mentioned. Also, direct reporting from digital medical records was something that is considered helpful for a future pandemic,

Quote interview 6: "*I think that the main problem is related on how to collect information. It means that in my view the more important problem is how you receive the information both from patient and health operators. It means that when you have the possibility to have a unique source of information, it should be easier to obtain this information. For example, when you have a drug or vaccines that are used in different systems, you have to check patient- or general practitioner- or vaccination registries and end up with few general practitioner data. So, I think that it is very important to try to have an automatic transfer of this information. This is the main problem that we have, I think, since for example all general practitioners have a software managing their patients and we actually don't have the possibility to connect this software to the spontaneous reporting database*."

For signal detection methodology it was mentioned that we need to look beyond the classical methods for statistical signal detection that we have, such as a straight-forward disproportionality analysis, and develop and employ new methods and share innovations through publications and international platforms. Since with large volumes of data, it becomes more and more difficult to find 'a needle in the haystack', better case-finding algorithms are helpful to select cases.

Once a signal has been identified, further strengthening, evaluation and assessment of the height of the risk is needed. For this purpose, data from Real World Evidence sources are needed in addition to the spontaneous reporting systems. Multiple European countries have the option to perform such analysis, however this is not the case in all countries. Issues with data-linkages and privacy regulations need to be resolved and, in some countries, work is needed to build a better data-infrastructure to be prepared for a new pandemic.

The theme 'communication' was only mentioned in one interview, but highlighted important concerns that we can do better during a future pandemic.

Quote interview 5: "*I think the other thing that needs to be worked on a lot and by a lot I really mean a lot, is the communication*." "*…It left people with more questions and more worriedness than was needed. And this contributed actually to an unnecessary burden of work for us and unnecessary anxiety for the population. So I think that we can improve the methods, we can improve the prioritisation, et cetera, et cetera, really we can improve the communication*."

Conclusion: This qualitative study investigating pharmacovigilance activities during the COVID-19 pandemic throughout Europe. The results of this section prove that various EU member states encountered comparable challenges, such as a large increase in data that had to be handled and analyzed, but all dealt with these in various manners. In line with previous chapters, 1) increased automation, 2) improvement of signal detection methodology, and 3) improved data infrastructure to facilitate the use of different data sources, are crucial factors that can improve pharmacovigilance during a future pandemic. Furthermore, 4) Intensified collaboration between organizations, 5) preparing and prioritization and 6) optimizing communication towards the public are key elements for pandemic preparedness.

4. DISCUSSION AND CONCLUSION

Pandemic preparedness means that we are well prepared for future pandemics as a consequence of outbreaks of microorganisms. This requires a good collaboration between all sectors, including the medical, economic, ecological, social and societal sectors. During a new pandemic, patients need to receive an effective treatment quickly so that the harm to both the patient and society remains limited. However, the development, testing and marketing of new treatments is a long process that is subject to many different laws and regulations: the regulatory system. During a next pandemic it might be crucial for new and effective treatments to more quickly available. However, a solid system for monitoring the safety of these treatments in the post-marketing setting is needed. The ZonMw subprogramme *Regulatory Pandemic Preparedness* aims to evaluate the current regulatory framework in the Netherlands, in relation to pandemic preparedness, on crucial themes. In addition, recommendations are made on how the regulatory framework can be strengthened (51). Attention was paid to the following themes which are all related to each other to some extend:

- Drug Rediscovery
- Pharmacovigilance
- Remote Monitoring
- Advanced Therapy Medicinal Products (ATMPs)

This current project investigated the challenges for ***pharmacovigilance*** during the COVID-19 pandemic in the Netherlands and formulated learned lessons on how to better prepare for the next pandemic. This study was performed in the first 6 months of 2023 by:

1. Mapping the roles of the parties involved in the pharmacovigilance of COVID-19 vaccines and medicines for the treatment of COVID-19, both in the Netherlands and in the European context;
2. An analysis on reports of suspected adverse reactions of COVID-19 vaccines and medicines for the treatment of COVID-19 in the Dutch reporting system and cohort event monitoring study;
3. Mapping new knowledge about adverse reactions and product information (PI) adjustments of COVID-19 vaccines;
4. A literature review and an international qualitative study on future-proof pharmacovigilance methods and recommendations for a possible future pandemic;
5. Research into the intended social impact of pharmacovigilance in a pandemic and the required cooperation between regulatory stakeholders.

If we look ahead to a possible future pandemic, we can draw lessons from a triangulation of the sub-studies of this project. The spontaneous reporting system remains important for the early detection of new adverse effects, but investment in further automation and linkage with healthcare systems is desirable. Innovative techniques for data analysis must be further developed and applied. In addition to the spontaneous reporting system, the use of other data sources for strengthening and evaluating possible safety signals is essential. This requires investment in a data infrastructure, in which data from healthcare systems and vaccination data can be linked more easily, so that follow-up research into possible risks can be carried out more quickly.

Finally, cooperation between different parties and disciplines is essential. More substantiated public confidence requires good communication from the various parties in the Netherlands involved in vaccine surveillance, taking into account the role of each party and responding to the context of the pandemic.

Although the current project had a focus on the Dutch pharmacovigilance system, it is important to learn from European initiatives as well. The European partnership for pandemic preparedness, works in the BE READY

project, to establish a consolidated research and innovation framework that provides the foundation of the expected future European partnership for pandemic preparedness (52).

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Supplementary material 1: Scoping review Menstrual disorders following COVID-19 vaccination: an overview of signal detection and scientific evidence

During the COVID-19 pandemic, vaccines development was accelerated [1]. In the meantime, more than 13 billion doses of COVID-19 vaccines have been administered worldwide [2]. Although vaccines are important to reduce the negative impact of many infectious diseases, adverse reactions after vaccination may occur [3-5]. Mild adverse reactions such as injection site reactions, fatigue, and headache are expected after vaccination and seen with a higher frequency during clinical trials, and were added to the product information of COVID-19 vaccines at the time of (conditional) marketing authorization [6, 7]. However, at that time, the safety profile of the COVID-19 vaccines was not completely known and more serious events were also included in the product information of the COVID-19 vaccines after the vaccination campaigns started, such as thrombosis for Vaxzevria (AstraZeneca) and Jcovden (Johnson&Johnson), and peri- and myocarditis for Comirnaty (BioNTech/Pfizer) and Spikevax (Moderna) [8-10], hereafter referred to as AstraZeneca, Johnson&Johnson, Pfizer, and Moderna. During the first months after the mass vaccination campaigns in 2021, first reports came in on menstrual changes. These changes were supported by anecdotal reports of menstrual disorders after COVID-19 vaccination on social media [11].

Menstrual cycles last on average 26 to 35 days, with menses lasting about five days [12]. Menstrual disorders are abnormalities in the menstrual cycle and include changes in the menstrual cycle length, changes in menses length, changes in the amount of bleeding, changes in the experience of (pre)menstrual pain, intermenstrual bleeding, and post-menopausal bleeding [13]. Although menstrual disorders are common in women, frequencies of these self-reported outcomes are difficult to estimate [14, 15]. Several factors may influence the menstrual cycle, such as lifestyle factors, biological factors, and environmental factors [16]. Even small changes in these routine bodily functions related to general health and fertility may have a large adverse impact on multiple aspects of women's quality of life, including emotional problems and worries, physical complaints, reduced participation in daily activities, and sexual functioning [17-22].

One systematic review and one meta-analysis summarized studies investigating the effect of COVID-19 vaccination on menstrual disorders [23, 24]. Nazir et al. included 14 studies in their systematic review and found that 52% of the 78,138 included women experienced a menstrual disorder after the COVID-19 vaccine [24]. This result was mainly based on cross-sectional studies and they underlined the need for prospective cohort studies. The meta-analysis by Chao et al. included four studies comparing menstrual irregularities in vaccinated vs. unvaccinated women [23]. The pooled OR was statistically significant (OR=1.91, 95%CI 1.76-2.07). They also mentioned the lack of randomized controlled trials in this field, and they recommended that future research should focus on the wide variety of menstrual disorders.

The fact that menstrual changes were reported after (newly developed COVID-19) vaccines, is an important issue, since this can contribute to vaccine hesitancy [25]. Menstrual disorders were prominently reported by women after COVID-19 vaccination. The European Medicines Agency (EMA) estimated that since June 2022 approximately 30% of reports received by women could be related to menstrual issues [26] and assessed this potential safety signal [27]**.** In October 2022, the Pharmacovigilance Risk Assessment Committee (PRAC) decided that "heavy menstrual bleeding" should be added to the product information of the COVID-19 vaccines of Pfizer and Moderna [27].

The **aim** of this scoping review is to provide an overview of events and regulatory actions taken with regards to menstrual disturbances that occurred after COVID-19 vaccination. Literature regarding the risk of menstrual disorders after COVID-19 vaccination will be systematically reviewed, and a timeline highlighting key events regarding safety signals of menstrual disorders following COVID-19 vaccines will be provided. Finally, gaps in literature will be discussed, and recommendations for future research and signal assessments will be provided.

METHODS

This scoping review was developed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [28].

Systematic review

A literature search protocol was drafted by one reviewer (V.S.) and further refined in cooperation with the project team. We performed the search in PubMed on February 28, 2023 (see Supplemental Table S1). In addition, a manual search was performed by checking references of published reviews on COVID-19 vaccines and menstrual disorders.

Eligibility criteria

Original quantitative studies that examined the association between COVID-19 vaccines and menstrual disorders were included. Articles had to be written in English or Dutch. Studies solely focusing on menstrual disorders after COVID-19 infection were excluded. No restrictions were applied for year of publication, country of publication, study design, type of COVID-19 vaccine, and type of menstrual disorder.

Screening

One reviewer (V.S.) performed the screening on titles and abstract in EndNote, based on the established criteria. A random selection of twenty included and excluded citations was screened by a second reviewer (R.J.). Any discrepancies between the two reviewers were discussed. Next, the full-text screening was performed by one reviewer (V.S.).

Data-extraction

Relevant data from included studies were extracted by one reviewer (V.S.), using a customized data-extraction form. The form was pilot-tested using five included papers and adapted in collaboration with the project team. In the final data-extraction form, the following variables were extracted: first author, year of publication, country, type of study design, type(s) of vaccine, number of analyzed people, age (mean, median, and/or range), data source/measurement methods, outcome(s), and main findings. We also listed additional notes about the study, such as important recommendations or limitations of the study. Findings from the included studies were presented using a narrative synthesis.

Signal assessment procedure

The electronic database search was supplemented by an extensive search on the EMA website including minutes of PRAC meetings, the World Health Organization (WHO) website, the Medicines and Healthcare products Regulatory Agency (MHRA) website, and the FDA website to include all relevant information with regards to the process of this signal assessment. Reports of menstrual disorders after COVID-19-vaccines were extracted from the database of Netherlands Pharmacovigilance Centre Lareb.

RESULTS

Systematic review

The PubMed search resulted in 117 records. We found five additional eligible records through our manual search. Of the 122 records screened on title/abstract, 66 were included in the full-text screening. After full-text screening, 20 studies were excluded because of a non-quantitative study design (n=14), or an irrelevant topic (n=6). In total, 46 studies were included in our scoping review [15, 29-73]. Figure 1 shows a flow chart of the selection process.

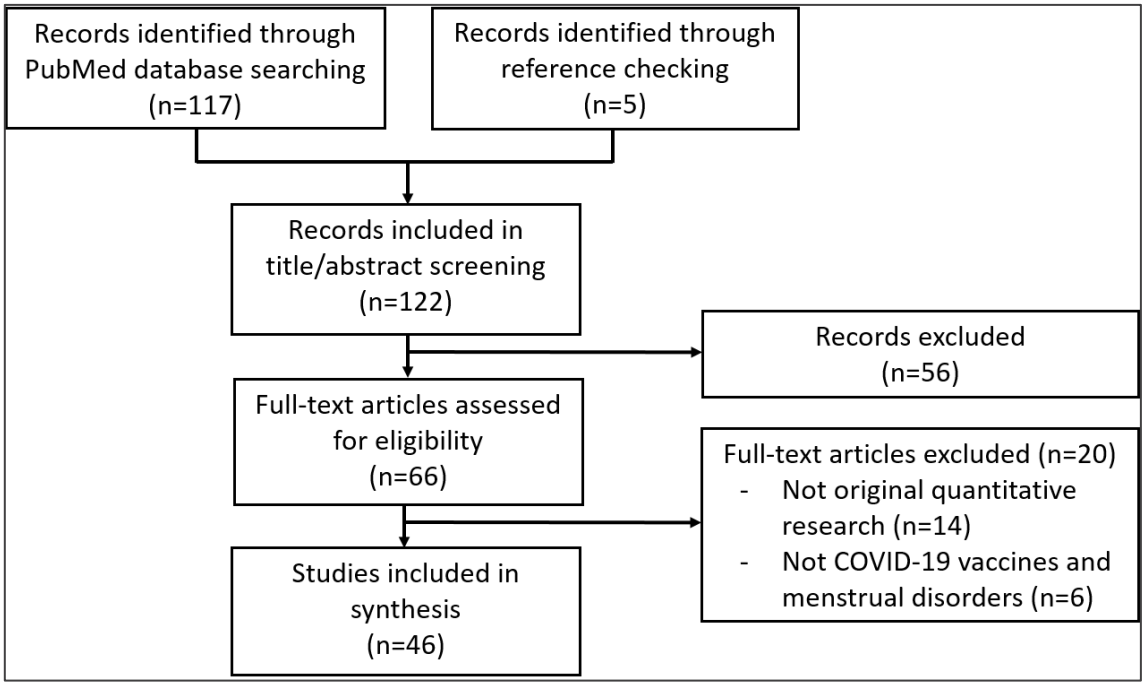

Figure 1. Flow chart of the screening process

Of the 46 included studies, 32 were cross-sectional studies and 14 cohort studies. One study was published in 2021, the remaining in 2022 (n=42, 91%) and 2023 (n=3, 7%). A substantial number of studies was performed in Saudi Arabia (n=10, 22%). The majority of studies used self-reported (online) questionnaires to assess the presence of menstrual disorders (n=39, 85%), often spread through social media, whereas some used a menstrual cycle tracking app (n=5, 11%). Most studies excluded participants younger than 18 years. Two studies only included female adolescents aged 12-15 or 12-17 years [33, 40]. The study characteristics of the 46 included studies are shown in Supplemental Table S2.

In most studies, the Pfizer vaccine was the most administered vaccine (n=29, 63%). Other administered vaccines were Moderna, Johnson&Johnson, AstraZeneca, Sinopharm, Sputnik V, Covaxin, Sinovac/Coronavac, and Turkovac. Different results were found regarding menstrual disorders after specific COVID-19 vaccine brands. Some studies did not find differences between the four brands [35, 60, 64], whereas others found that Pfizer [31, 70] or Moderna [32] resulted in a higher rate of menstrual changes compared to other COVID-19 vaccines. With regard to heavier menstrual bleeding, Trogstad et al. found slightly higher percentages after Moderna compared to Pfizer [15]. Trogstad et al. also mentioned that no differences were found between homologous and heterologous vaccination with Pfizer and Moderna.

COVID-19 vaccines and menstrual disorders

Outcomes included a wide variety of menstrual disorders, including changes in cycle length (n=40), changes in the amount of bleeding (n=32), changes in menses length (n=21), changes in the experience of (pre)menstrual pain (n=15), and breakthrough bleeding (n=10). Two studies did not specify the type of menstrual disorders [37, 43]. However, the outcomes are ambiguous. For example, “menstrual irregularities” might comprise more than only an increase or decrease in cycle length, and the terms “heavy menstrual bleeding” and “prolonged menses length” might be interpreted interchangeably or combined [49].

All included studies found a higher percentage of at least one menstrual disorder in the first cycle after different types of COVID-19 vaccination and after different doses. All included cohort studies found a positive association between COVID-19 vaccines and one or more menstrual disorders. These studies also mentioned that these disturbances were transient. Overall, menstrual disorders were predominantly mild and, in most cases, the menstrual cycle returned to normal within several months or by the time the second dose was given [15, 31, 32, 46, 49, 50, 54, 64, 67, 69, 71].

Several studies investigated factors associated with an increased risk of reporting menstrual changes after COVID-19 vaccination. One study found that heavy menstrual bleeding after vaccination was associated with a history of prolonged and heavy menses [51]. Other comorbidities including endometriosis, menorrhagia, fibroids, adenomyosis, thyroid disorders, and Polycystic Ovary Syndrome (PCOS) were also significantly related factors [55, 60]. The use of (non-)hormonal intrauterine devices was also positively correlated with menstrual changes [49, 51, 60]. Other significant associated factors that increased the risk were age [55, 59], number of children [60], marital status [59, 60], and being Hispanic of Latinx [55]. Farland et al. found that high self-reported perceived stress levels (OR=2.22, 95%CI 1.12-4.37) and greater body mass index (OR=1.04; 95%CI 1.00-1.07) were associated with greater odds of experiencing changes in the menstrual cycle after vaccination. A history of COVID-19 infection decreased the risk (OR=0.58; 95%CI 0.32-1.04) [49]. Trogstad et al. did not find significant results in their additional analyses on concurrent medical conditions and concomitant medication [15].

COVID-19 vaccination and menstrual cycle length

Changes in menstrual cycle length after COVID-19 vaccination was the outcome most assessed (n=40, 87%). The majority of studies found a statistically significant difference on this outcome between vaccinated and unvaccinated individuals. A globally conducted cohort study including 19,622 individuals (of whom 14,936 vaccinated) found an increase in cycle length of less than one day for both doses, compared to unvaccinated individuals (0.71 day increase (99.3%CI 0.47-0.96) for first dose; 0.56 day increase (99.3%CI 0.28-0.84) for second dose) [46]. Another large cohort study with a sample size of 9,652 participants (of whom 8,485 vaccinated) found similar results (first dose 0.50 days increase, 95%CI 0.22-0.78 and second dose 0.39 days increase, 95%CI 0.11-0.67) [50]. Trogstad et al. performed a self-controlled case series study, as part of a larger cohort, and found significant differences on both short and longer intervals after first and second doses (RRs ranging from 1.24-1.57) [15]. Caspersen et al. found a longer interval in girls aged 12-15 years (RR=1.15, 95%CI 1.05-1.27), and in girls aged 14-15 years (RR=1.17, 95%CI 1.05-1.31). This study also found an increased risk on shorter intervals in girls aged 12-15 years (RR=1.19, 95%CI 1.07-1.32), and girls aged 14-15 years (RR=1.18, 95%CI 1.05-1.33) [40]. Muhaidat et al. found an increase in cycle length from 27 ± 6 days prior to vaccination to 28.1 ± 10 days after being vaccinated (p<0.001) [60]. Significant changes were also reported by Velasco-Regulez et al. (increase in median cycle length of 0.5 (0.0-1.0) days (p<0.005)) [68], and Wang, who found that vaccinated women had a higher risk of an increased cycle length than unvaccinated women (OR=1.48; 95%CI 1.00-2.19) [69]. Woon et al. showed in their prospective cohort study that either dose of the COVID-19 vaccine was associated with a delay to the following period (2.3 days after dose 1 (p=0.0045); 1.3 days after dose 2, p=0.041) [71]. Alvergne et al. found a significant increase in the menstrual cycle length of 2.3 days after the first dose, and 1.3 days after the second dose [35].

COVID-19 vaccination and the amount of menstrual bleeding

The second most investigated outcome was the association between COVID-19 vaccines and alterations in the amount of bleeding (n=32, 70%). Most studies found a higher percentage of people reporting that their next period was heavier than normal after receiving the first and/or second dose of the COVID-19 vaccine. Some of these studies found that the menstrual flow returned to normal within several months [15, 54, 60], whereas another study reported that this alteration could last more than five months [58]. Caspersen et al. found in their cohort study that the risk of heavier menstrual bleeding was higher in the menstrual cycle after vaccination compared to the cycle before vaccination (RR=1.61, 95%CI 1.43-1.81) [40]. In this cohort, 99.9% received the Pfizer-vaccine. The cohort study by Trogstad et al. found a relative risk of more heavy bleeding of 1.90 (95%CI 1.69-2.13) for the first dose with Pfizer or Moderna, while the RR was 1.84 (95%CI 1.66-2.03) for the second dose [15]. Zhang et al. found a relatively low percentage of reports of menorrhagia (0.2%), compared to other menstrual outcomes after COVID-19 vaccination in their study [72]. Alvergne et al. did not find an association between COVID-19 vaccination and menstrual flow [35].

COVID-19 vaccination and menses length

Twenty-one studies (46%) investigated changes in menses length after COVID-19 vaccination. Muhaidat et al. found an increase from 6 ± 0.03 days pre-vaccine to 6.5 ± 0.1 post-vaccine (p<0.001) [60]. Caspersen et al. compared the menstrual cycle after vaccination and the cycle before vaccination in girls aged 12-15 years and found a RR for increased menses length of 1.40 (95%CI 1.23-1.60) [40]. Eight percent of the vaccinated individuals in the study of Barabas et al. suffered from prolonged bleeding lasting for more than two weeks

[39]. Lastly, Trogstad et al. found a RR of 1.46 (95%CI 1.31-1.61) after the first dose, and a RR of 1.71 (95%CI 1.55-1.89) after the second dose on prolonged bleeding [15]. Several other studies mentioned that they did not find significant results on COVID-19 vaccination and menses length [45, 46, 68].

COVID-19 vaccination and the experience of (pre)menstrual pain
Heavier or less menstrual pain or cramps during the next period after COVID-19 vaccination was assessed by 15 (33%) studies. Trogstad et al. found a significant increase in the percentage of people experiencing more pain between the last cycle before vaccination and the first cycle after vaccination (first dose: 11.4% vs. 14.6%, RR=1.24 (95%CI 1.24-1.47), second dose: 9.8% vs. 16%, RR=1.62 (95%CI 1.49-1.77)) [15]. Caspersen et al. also found a significant increase on stronger period pains (RR=1.14, 95%CI 1.04-1.26 for girls aged 12-15 years), and RR=1.14 (95%CI 1.02-1.27) for girls aged 14-15 years [40]. Four other studies also found increased percentages on menstrual cramps after vaccination [32, 49, 59, 62]. On the other hand, Morsi et al. also found that 11% reported a decrease in the severity of pain [59]. However, Velasco-Regulez et al. observed no significant changes in the percentages of pain intensity [68].

COVID-19 vaccination and breakthrough bleeding
Ten studies (22%) investigated the association between COVID-19 vaccination and breakthrough bleeding, spot bleeding, and/or postmenopausal bleeding. Lee et al. reported that 66% of postmenopausal women experienced a breakthrough bleeding. This outcome was significantly associated with age, systemic vaccine side effects (fever and/or fatigue), history of pregnancy or birth, and ethnicity [55]. Other studies reported 2.4% [67] and 16% [72] of women experiencing intermenstrual bleeding after vaccination. Trogstad et al. found a RR of 1.09 (95%CI 1.01-1.17) after the first dose, and a RR of 1.49 (95%CI 1.37-1.62) after the second dose [15]. Caspersen et al did not find an association between COVID-19 vaccination and spot bleeding [40].

Timing of vaccination
Discrepancies exist between studies with regard to the influence of timing of vaccination on menstrual disorders. Some studies did not find an effect of timing on the flow or the next period [35, 71], whereas others stated that the risk of menstrual disturbances was higher in specific phases of the menstrual cycle [40, 50, 68]. One study stated that COVID-19 vaccination has a larger impact on menstrual regularity when both doses are given within the same menstrual cycle, with a mean delay of 2.32 days (95%CI 1.59-3.04) to their next period [45].

Signal assessment procedure
Figure 2 shows a timeline highlighting key events regarding the update of the Summary of Product Characteristics (SmPCs) of Moderna and Pfizer. In August 2021, EMA's PRAC assessed scientific literature on reported cases of menstrual disorders occurring after COVID-19 vaccination. Based on the assessment of all data by the Danish Medicines Agency (DMA), i.e., literature, approximately 2,800 reported cases in Denmark, and detailed analyses on characteristics of these cases, the PRAC concluded that there was no evidence for a causal relationship between the vaccines and menstrual disorders [74]. Menstrual disorders were considered common in the general population and were in the reported cases most likely caused by other events, such as stress or underlying medical conditions. Moreover, no potential mechanism could be identified. The Norwegian Medicines Agency (NoMA) also raised awareness for prioritization of this signal, based on the reports they received (over 50 reports of various types of menstrual disorders by June 2021) [26, 75-77]. The Medicines Agencies continued to monitor the potential safety issue.

So far, the MHRA received over 30,000 reports of menstrual changes following COVID-19 vaccination in the British Yellow Card surveillance system and they also evaluated these reports [78, 79]. Similar to the PRAC, they concluded that there is no link since the number of reports is low relative to the general prevalence of menstrual disorders and the number of people who received COVID-19 vaccines. They also noticed that menstrual changes were mostly transient. They continued to review the reports of the Yellow Card scheme [78]. However, the need to perform research to explore the link between COVID-19 vaccines and menstrual changes increased. Researchers stated that comparisons between vaccinated and unvaccinated people should be investigated, and cases of menstrual problems were probably underreported in the pharmacovigilance systems since women might be ashamed of their events, might not have thought the events were related to the COVID-19 vaccine, or might not have been encouraged by their healthcare professional to report their adverse event in the reporting system [79, 80]. The National Institutes of Health (NIH) has awarded

supplemental grants to five American institutions to explore potential links and to investigate potential mechanisms [81].

One month later, the first study on menstrual disorders after COVID-19 vaccination was published [34]. This cross-sectional study, conducted in Saudi Arabia, analyzed more than 4,000 people vaccinated with Pfizer or AstraZeneca. In total, 0.98% of the female participants reported a delay in their menstrual cycle or an increase in bleeding or pain after the first and second dose of the Pfizer COVID-19-vaccine, compared to 0.68% after the first dose of the AstraZeneca-vaccine.

In December 2021, The Netherlands Pharmacovigilance Centre Lareb published a signal covering menstrual disorder reports [82, 83]. From January 6, 2021 (start of the National COVID-19 immunization campaign) until December 1, 2021, Lareb received a total of 17,735 individual case reports of menstrual disorders and postmenopausal blood loss after AstraZeneca, Johnson&Johnson, Moderna and Pfizer (see Figure 3). With regard to heavy menstrual blood loss, this number was 4,537 (2,481 after the first dose, 2,056 after the second dose). Of these, 26 (0.6%) were serious reports. At the time of reporting, 26% were recovered/resolved with a mean duration of 13 days. The highest reporting rates were after Johnson&Johnson in the age category 20-45 years (134.5 per 100,000 vaccinations), followed by 90.1 reports per 100,000 vaccinations after the first dose of Pfizer in the same age category. Overall, the highest reporting rates were after Johnson&Johnson (98.3 reports per 100,000 vaccinations), followed by Moderna (51.4 reports per 100,000 first dose vaccinations, 62.5 reports after second dose vaccinations), Pfizer (36.8 reports per 100,000 first dose vaccinations, 37.0 reports after second dose vaccinations), and AstraZeneca (9.1 reports per 100,000 first dose vaccinations, 9.5 reports after second dose vaccinations). Lareb stated that it is plausible that the COVID-19 vaccines caused the menstrual disorders.

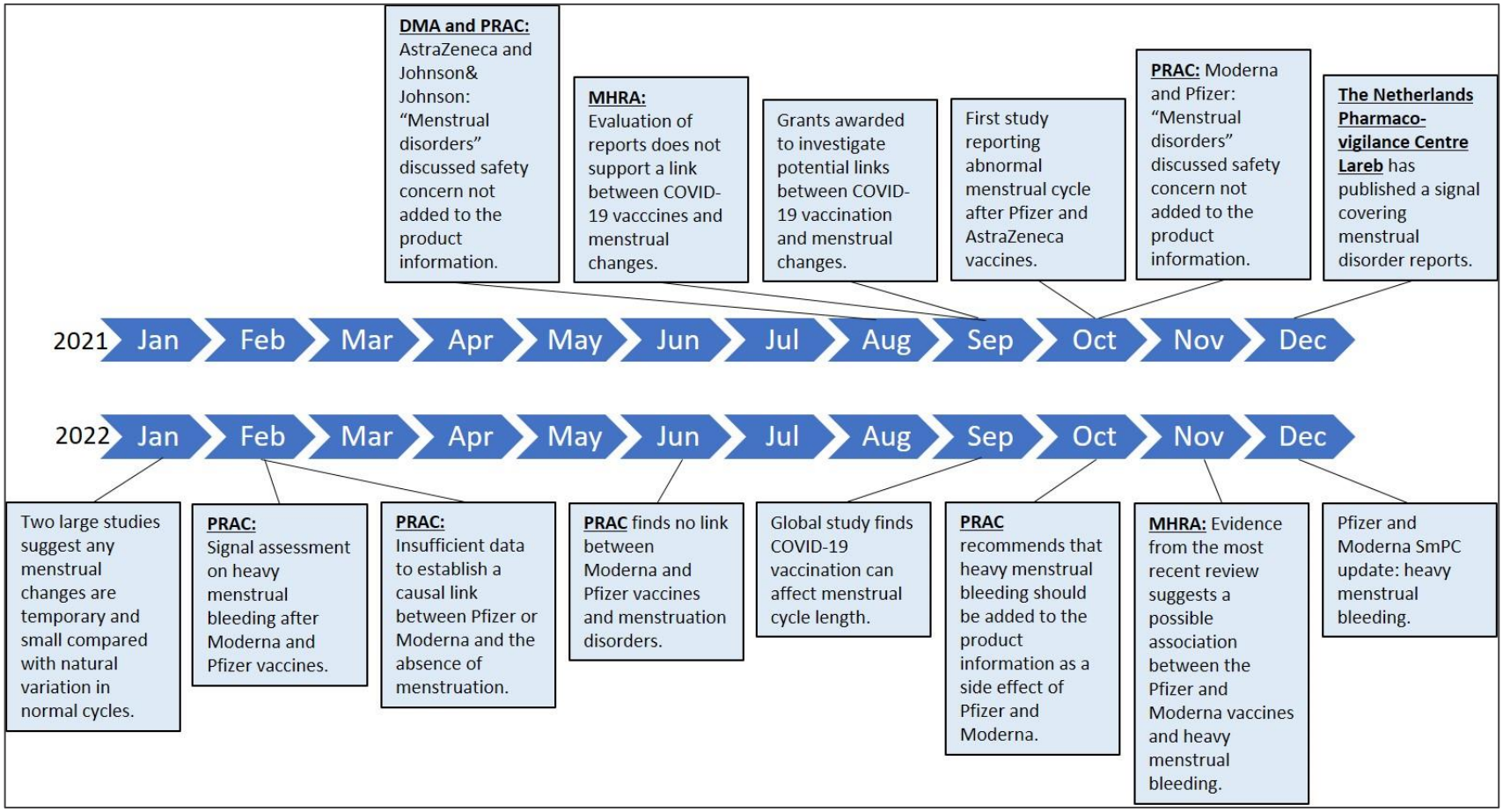

Figure 2. Timeline of key events regarding menstrual disorders after the COVID-19 vaccines of Moderna, Pfizer, AstraZeneca, and Johnson&Johnson. DMA, Danish Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; PRAC, Pharmacovigilance Risk Assessment Committee

In January 2022, two large studies on menstrual disorders after COVID-19 vaccination were published [15, 45]. The cohort study by Edelman et al. did not include heavy menstrual bleeding as an outcome, but solely focused on menstrual cycle length and menses length. In 3,959 Americans between 18 and 45 years, of whom 2,403 vaccinated, a less than 1-day change difference in cycle length between vaccinated and unvaccinated people was found (first dose 0.64 days, 98.75%CI 0.27-1.01; second dose 0.79 days, 98.75%CI 0.40-1.18) [45]. The self-controlled case series study by Trogstad et al. included a broad spectrum of menstrual disorders, including more heavy bleeding than usual. They analyzed 5,688 Norwegian women between 18 and 30 years and found a relative risk of 1.90 (95%CI 1.69-2.13) of more heavy bleeding than usual for vaccinated women (first dose Pfizer or Moderna) compared to unvaccinated women. For the second dose, the RR was 1.84 (95%CI 1.66-2.03). Menstrual disturbances returned to normal within approximately two months [15].

The findings from the literature and the increased number of spontaneous reports led to further assessment of heavy periods or amenorrhea following COVID-19 vaccination by the PRAC in February 2022. At this point, it was still not clear whether there is a causal association between the COVID-19 vaccines (Moderna and Pfizer) and the reports of heavy menstrual bleeding or amenorrhea. The PRAC decided to request an in-depth evaluation of available data from spontaneous reporting systems (EudraVigilance), cases reported during clinical trials, and data from the literature [84]. Four months later, the committee continued the assessment of the safety signal and requested from the marketing authorization holders an updated cumulative review of the cases of heavy periods. With regards to amenorrhea, the PRAC concluded that there was insufficient data to establish a causal link between Pfizer or Moderna and the absence of menstruation [85].

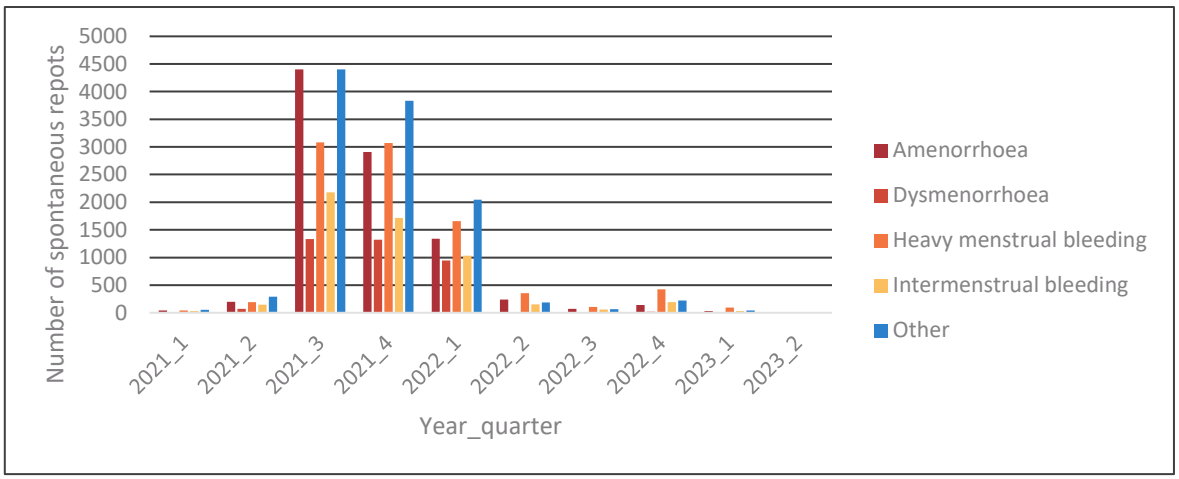

Figure 3. Number of spontaneous reports of menstrual disorders after the COVID-19 vaccines of Moderna, Pfizer, AstraZeneca, and Johnson&Johnson over time, as received by The Netherlands Pharmacovigilance Centre Lareb.

Until March 2022, The WHO global database VigiBase received 186,962 reports of menstrual disorders, of which 47,486 of heavy menstrual bleeding. Of these, 4,508 were serious reports. Most of the menstrual reports were associated with the Pfizer vaccine [83]. In the meantime, Lareb received over 27,000 cases of various menstrual disorders. The Johnson&Johnson vaccine had the highest reporting rates compared to the other vaccines (523 reports per 100,000 vaccinations) [14]. Amenorrhea/oligomenorrhea was the most reported menstrual disorder (33%), followed by heavy menstrual bleeding (29%) and irregular bleeding (23%). No large differences between vaccine brands were found. An overview of menstrual disorders after COVID-19 vaccinations reported to Lareb and possibly related factors are described in the study of Duijster et al. [14].

In October 2022, the PRAC has finalized the assessment of heavy menstrual bleeding and recommended that this side effect should be added to the product information of the COVID-19 vaccines Pfizer and Moderna. Based on worldwide reports of heavy menstrual bleeding after first, second and booster doses, the PRAC concluded that there is at least a reasonable possibility that the occurrence of heavy menstrual bleeding is casually associated with these vaccines [86]. 'A reasonable possibility of a causal association' is a criterion for SmPC update. Most of the reviewed cases had transient and non-serious complaints. The frequency category

assigned to the adverse event is 'not known', since frequencies from spontaneous reports of suspected side effects are difficult to estimate. At this point, cases of heavy menstrual bleeding were still monitored and healthcare professionals and patients were encouraged to continue to report these side effects to the national authorities. A pathophysiological mechanism was not yet understood [27, 86]. The MHRA has also continued to review reports of menstrual disorders following COVID-19 vaccination in the UK. At the end of November 2022, a total of 51,695 suspected reactions relating to a variety of menstrual disorders has been reported in 40,327 individual Yellow Card reports. Their review did not support a link between COVID-19 vaccines and other menstrual disorders [87].

On November 25, 2022, the product information of Pfizer and Moderna was amended by adding the following text: 'Reproductive system and breast disorders: Heavy menstrual bleeding. Frequency: not known (cannot be estimated from the available data)' [26, 75, 88, 89]. A footnote stating that 'most cases appeared to be non-serious and temporary in nature' was added.

DISCUSSION

Summary of evidence

This scoping review synthesized the body of evidence on menstrual disorders following COVID-19 vaccination. We identified 46 primary studies and we summarized data on key events regarding the signal detection process. Evidence shows that COVID-19 vaccines may cause menstrual changes in women of reproductive age, and heavy menstrual bleeding was added to the product information of Pfizer and Moderna. Although the menstrual changes are short-lived and predominantly mild, it is important for women and health care professionals to be informed about these potential side effects.

Research gaps

The most important limitation of many included studies is the cross-sectional study design, which limits the possibility to investigate a causal relationship between the COVID-19-vaccines and menstrual disorders [90]. Second, the majority of the included studies reported only descriptive statistics, and did not use a control group. Since menstrual disorders are common in the general population, this is an important gap in previously conducted research in this area [26]. Third, most studies excluded women younger than 18 years. Since the median age of menarche is 11.9 years [91], it would be interesting to examine menstrual outcomes in vaccinated female adolescents as well. Fourth, most studies were performed in high-income countries with high access to healthcare access and resources to track and report menstrual disorders, which limits generalizability of the results to other countries [24]. Due to the fact that talking openly about menstruation is a taboo in some lower-developed countries, the number of menstrual disorders might be underestimated in several studies [65]. The fifth limitation of the included studies is that many studies distributed the questionnaire via different social media platforms (e.g., Facebook, WhatsApp, LinkedIn, and Twitter). This may have led to selection bias with a higher inclusion of younger women and women who feel that the vaccine affected their menstruation [51]. However, social media platforms are modern instruments to quickly reach the whole country and appropriate age groups [26]. Moreover, several studies were performed after vaccination took place and after an increase of menstrual irregularities reported in the media, which may have led to an overestimation of actual incidence numbers [90]. Lareb found clear peaks of received reports when menstrual disorders were discussed in the media [83]. However, start dates of the menstrual disorders seem to correlate with the Dutch vaccination program. Ideally, studies should ask for menstrual disorders before and after vaccination [15]. Sixth, because of the retrospective design of many includes studies, recall bias might have occurred. At last, the menstrual disorders are mainly non-serious, with short-term duration, and self-reported without confirmation of a healthcare professional [90]. However, many women do not visit their gynecologist for minor menstrual disturbances and physicians can only confirm what the woman told him. Possibilities to medically confirm transient menstrual disturbances are limited, which means that medical confirmation does not increase the credibility of the self-reported cases [26, 75].

Implications for further research

In addition to the aforementioned research gaps and implications for further research to cover these limitations, we would recommend performing an extensive systematic review on menstrual disorders after COVID-19 vaccination. In this review, differences between vaccine types and number of doses should be investigated. We also recommend examining differences between groups who might be more vulnerable to

develop menstrual disorders, including older women, women with a higher body mass index (BMI), women with gynecological disorders, and women using hormonal contraceptives. In addition, it would be interesting to investigate the long-term effects of COVID-19 vaccines on the menstrual cycle, and to examine the biological mechanism of COVID-19 vaccines and menstrual disorders, since the pathological pathway is yet not completely understood.

Recommendations for future signal assessment procedures

Although menstrual disorders after the first COVID-19 vaccination did not influence the willingness of these women to get vaccinated a second time [15], it is important to investigate these side effects when developing vaccines [66, 79]. In this way, women can make well-informed decisions about taking a vaccine [79]. However, different signaling approaches may lead to different results, and it is still discussable which methodology is best used [92]. Nevertheless, it is important that clinicians and patients have the knowledge and possibility to report adverse events after vaccination, and that possible signals are rapidly discussed [93]. Piché-Renaud et al. compared different vaccine pharmacovigilance approaches used in their review and stated that early collaboration and communication between the public, researchers, and specialists at local, (sub)national, and global level is of high importance to identify possible signals [93].

Study limitations

This scoping review has some limitations. First, we did not perform a risk of bias assessment of the included studies. However, we extracted relevant data including additional notes such as flaws in the study design or other limitations of the study. Second, literature screening and data-extraction was performed by one person. Third, we only searched in one database. However, we reference-checked published studies and added four studies. Fourth, with regards to the signal assessment procedure, we mainly used the EMA signal assessment reports on heavy menstrual bleeding after COVID-19 vaccination. Although we searched for gray literature on many other websites, we could not find more relevant information on the signal detection procedure. Moreover, we only used information that was publicly available.

Conclusions

This review identified a wide range of studies investigating a variety of menstrual disorders after COVID-19 vaccination. Although the menstrual changes found in this literature review after COVID-19 vaccination are short-lived and predominantly mild, it is important for women and health care professionals to be informed about these potential side effects. We identified important limitations in the study designs of many of the included studies for evaluating causality. Because of the high impact of menstrual disorders on women's quality of life, menstruation-related side effects should be investigated when developing vaccines.

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Supplemental Table S1. Literature search in PubMed

COVID-19	"COVID-19" [MeSH] OR "COVID-19" OR "COVID19" OR "COVID2019" OR "COVID 2019" OR "coronavirus" OR "SARS-CoV-2" [MeSH] OR SARS-CoV-2 OR "SARSCoV2" OR "SARS-CoV2" OR "2019nCoV" OR "2019-nCoV" OR "nCoV-2019" OR "2019 coronavirus" OR "2019 corona virus" OR "coronavirus disease 2019"
	AND
Vaccines	"COVID-19 vaccines" [MeSH] OR "COVID-19 vaccine" OR "COVID-19 vaccines" OR "mRNA vaccines" [MeSH] OR mRNA vaccin OR "Vaccination" [MeSH] OR vaccination OR "mRNA-1273 vaccine" OR "mRNA vaccine" OR "mRNA COVID-19 vaccines" OR "BNT162 vaccine" OR "BNT162b2" OR "BNT162" OR "Spikevax" OR "Comirnaty" OR "ChAdOx1 nCoV-19" [MesH] OR "ChAdOx1 nCoV-19" OR "Immunization" [MeSH] OR immun* OR "Immunization Programs"[Mesh] OR "immunization program" OR "immunization programs" OR "Injections"[Mesh] OR inject* OR vaccin*
	AND
Menstruation disorders	"Menstruation Disturbances" [MeSH] OR "menstruation disturbance" OR "Menstrual Cycle" [MeSH] OR "menstrual cycle" OR "irregular menstrual cycle" OR "menstrual" OR "Menorrhagia" [MeSH] OR "menorrhagia" OR "Metrorrhagia" [MeSH] OR "metrorrhagia" OR "Menarche" [MeSH] OR "menarche" OR "Menstruation" [MeSH] OR "menstruation"

Supplementary material 2. Search strategies and keywords

MESH terms: COVID-19 Vaccines, COVID-19 vaccines/adverse effects, COVID-19 Drug Treatment, adverse drug reaction reporting systems, pharmacovigilance, machine learning, artificial intelligence

Vaccines

1. (COVID-19 Vaccines[MeSH Terms]) OR (COVID-19 Vaccines[Text Word]) AND ((adverse effects[Text Word]) OR (adverse events[Text word]) AND (adverse drug reaction reporting systems[MeSH Terms]) OR (adverse drug reaction reporting systems[Text Word]) AND (pharmacovigilance[MeSH Terms]) OR (pharmacovigilance[Text Word)) → 178 hits
2. (COVID-19 Vaccines[MeSH Terms]) OR (COVID-19 Vaccines[Text Word]) AND ((adverse effects[Text Word]) OR (adverse events[Text word]) AND (adverse drug reaction reporting systems[MeSH Terms]) OR (adverse drug reaction reporting systems[Text Word]) AND (pharmacovigilance[MeSH Terms]) OR (pharmacovigilance[Text Word]) AND (Machine Learning[MeSH Terms]) OR (Machine Learning[Text Word]) AND (Artificial Intelligence[MeSH Terms]) OR (Artificial Intelligence[Text Word])) → 104 hits
3. (COVID-19 Vaccines[MeSH Terms]) OR (COVID-19 Vaccines[Text Word]) AND ((adverse effects[Text Word]) OR (adverse events[Text word]) AND (adverse drug reaction reporting systems[MeSH Terms]) OR (adverse drug reaction reporting systems[Text Word]) AND (pharmacovigilance[MeSH Terms]) OR (pharmacovigilance[Text Word]) AND (United States Food and Drug Administration[Mesh]) OR (United States Food and Drug Administration[Text Word])) → 108 hits

Drug treatment

1. (COVID-19 Drug Treatment [MeSH Terms]) OR (COVID-19 Drug Treatment [Text Word]) AND ((adverse effects [Text Word]) OR (adverse events[Text word]) AND (adverse drug reaction reporting systems[MeSH Terms]) OR (adverse drug reaction reporting systems[Text Word]) AND (pharmacovigilance[MeSH Terms]) OR (pharmacovigilance[Text Word])) → 52 hits

Supplementary material 3. Flow diagram of records included in the scoping review

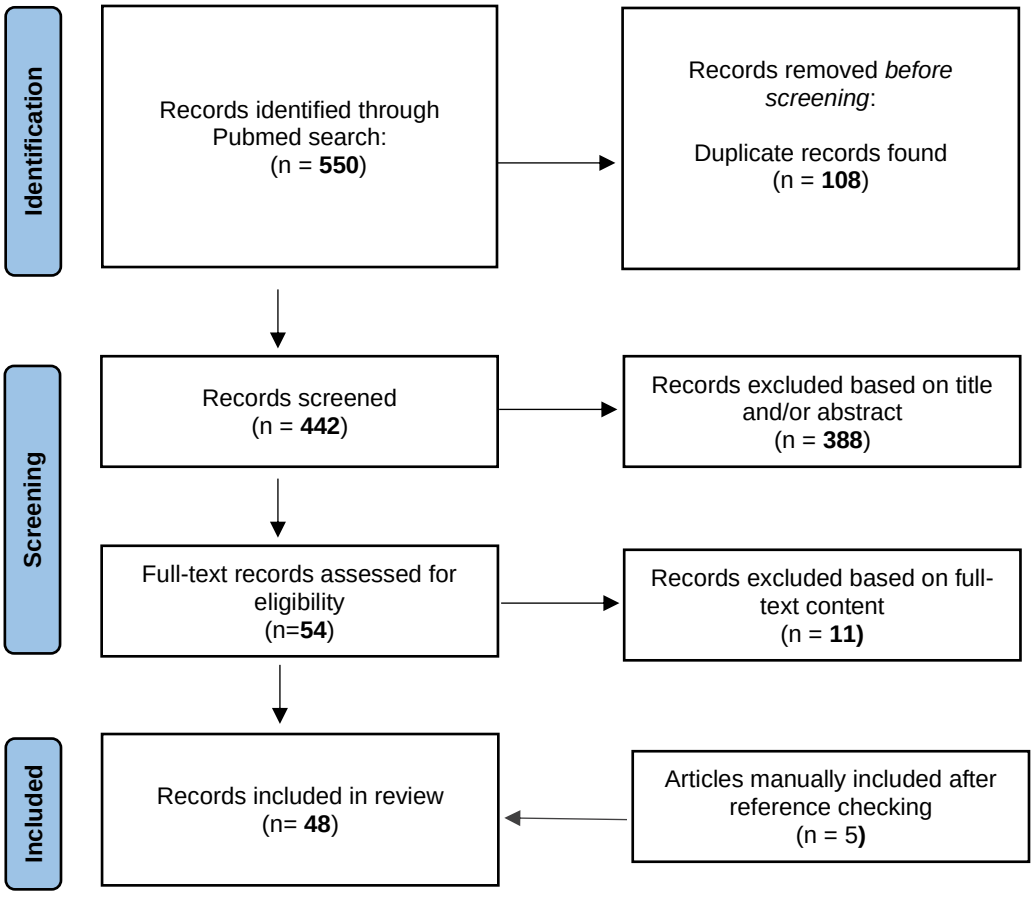

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of PubMed databases only. *Adapted from:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Supplemental Material 5: Articles included for the PRISMA scoping review

Ref No.	Name author	Year	Country	Medicines or vaccines	Data source	Method	Recommendations
1	Tuccori, M et al.	2020	-	Medical therapies utilized for COVID-19 prevention/treatment	Literature (review)	The article initially conducted an analysis that looked at information dissemination relative to certain drugs used during the COVID-19 pandemic. In addition, the evidence for the usage of these medicines as well as the communication about the effect on COVID-19 disease and how people responded to it was examined. Next, the approach of regulatory agencies to ensure the minimization of the possible risks of this behavior by the people was also examined. In addition, the role of stakeholders in pharmacovigilance in managing emergencies and possible strategies to be prepared for similar pandemics in the future were also discussed.	An "infodemic," or massive spread of information, often sensational and distorted, represented a novel challenge for health authorities. In this scenario, pharmacovigilance must face different challenges, such as promoting clinical and observational studies, implementing spontaneous adverse drug reaction reporting systems and signal detection, and implementing and supporting risk communication strategies. We should use the lessons learned during the COVID-19 pandemic to adapt our pharmacovigilance systems accordingly to be prepared for similar situations in the future.
2	Ferreira-da-Silva, R et al.	2021	-	COVID-19 vaccinations (in general)	-	Work plan proposal that consists of six coherent multidimensional guidelines aimed at controlled drug surveillance during the COVID-19 pandemic by pharmacovigilance centers. The following key terms were included: active drug monitoring programs, intensive monitoring in special populations, electronic reporting, integrative ADRs systems, awareness campaigns, and, effective communication.	Digital technologies (e.g telemedicine and mobile health applications) could strengthen pharmacovigilance during pandemics. Real-world data could provide useful information for the identification and surveillance of ADRs associated with COVID-19 vaccines. Proactive pharmacovigilance approaches should be applied including risk management plans and signal detection systems to enable early identification and management of safety concerns. A good mutual collaboration between pharmacovigilance centers, regulatory authorities, healthcare professionals, and patients to facilitate the knowledge transfer of safety information associated with COVID-19 vaccines is crucial. Transparency in the sharing and reporting of safety information related to COVID-19 vaccines will help to combat misconceptions regarding COVID-19 vaccines and enhance public confidence in drug safety surveillance.
3	Al-Taie, A et al.	2022	-	Medical therapies utilized for COVID-19 prevention/treatment	Literature (review)	Systematic literature review	Clinical studies investigating COVID-19 drugs should also consider pharmacogenomics and aspects of personalized medicine. ADRs due to

							COVID-19 medication could be minimized by further evaluating pharmacogenetic biomarkers.
4	Cocoros, N.M et al.	2021	USA	Medical therapies utilized for COVID-19 prevention/treatment	FDA Sentinel System that utilizes electronic health data.	To support the FDA during the COVID-19 pandemic, Sentinel implemented a multi-pronged approach to manage the increased data and analysis needs during the pandemic. This approach allowed for the inclusion of new data sources, faster database refreshes, and the development of protocols to assess the course of COVID-19. In addition, it allowed the validation of a diagnosis code-based algorithm that was deployed to identify patients with COVID-19 in administrative claims data as well as coordinating with other national and international efforts. The Sentinel system is also being used to investigate the use, safety, and efficacy of treatments for COVID-19.	It is essential that clinical information is available at the nationwide level. To achieve an optimal dataset, Electronic Health Record (EHR) data should be linked. This requires comprehension of root source data, workflows, and documentation practices so that medication and other details can be identified. This requires continued investments in health surveillance systems. For example, consider insights on coding and storage, proper use of data, etc.
5	Martin, G et al.	2022	France	COVID-19 vaccinations (in general)	Development of autocoding method	Development of an artificial intelligence model identifying adverse drug reactions and assessing seriousness in patients reports from the French national pharmacovigilance web portal. The artificial intelligence models showed promising performance to automatically code patient ADR report and the system has been deployed by national health authorities in France since January 2021 to facilitate pharmacovigilance of COVID-19 vaccines.	AI models should be trained and validated to enable ADRs to be identified and even the severity of ADRs to be assessed from nationwide patient reports. In addition, it also recommends that the performance of pharmacovigilance systems does need to be validated in real-world situations. The best-obtained model can then be further identified to serve as evidence for the use of AI systems in the automated precoding of pharmacovigilance reports.
6	Flora, J et al	2022	USA	Pfizer, Moderna, and Janssen COVID-19 vaccinations	Vaccine data for Pfizer, Moderna, and Janssen from the Vaccine Adverse Event Reporting System (VAERS). Online surveys were also used to obtain additional data.	For this study, two individual data sets were compiled with the information obtained from the VAERS and online surveys. The top 20 most common AEs were used to examine for associations with machine learning (ML) techniques. Interrelationships between AEs and reported allergies and other person-specific factors (such as age group and gender).	Recommendations in using VAERS data involve careful preprocessing of data, the flexibility of model features, robust model development pipelines, ML model verification, and model stability and efficiency. Evaluation of model efficiency should be done using robust tests to ensure accurate prediction and reasonable use of computational resources. This would be key to improving the applicability and reproducibility of models and safeguarding vaccine safety and efficacy.
7	Dang, Q et al	2022	China	COVID-19 vaccinations (in general)	The data source used during the study is China's Sina Weibo	Data collection from China's Sina Weibo platform using Python self-compiled code. The key words used were "COVID-19 vaccination", "new coronavirus	Machine learning methods can be used to extract information from social media related to COVID-19 vaccination. It could provide valuable and

					platform, a Chinese microblogging website.	vaccination", "COVID-19 vaccine", "new coronavirus vaccine", and "COVID-19 vaccine inoculation". Sentiment analysis was conducted using the Chinese Emotional Vocabulary Ontology Database from Dalian University of Technology in order to analyze the sentiments expressed in microblog texts related to COVID-19 vaccination. Calculation of the number of positive and Clustering of topics was conducted.	useful information for public health departments, governments, policymakers, and health communication researchers. In addition, it is also recommended that public health departments should come up with appropriate strategies and engage more in effective communication to address hesitation about vaccines. Moreover, the study also suggests that policymakers should opt for a national surveillance system to monitor more closely what is being discussed on the internet (mainly social media) and censor where necessary to reduce the negative effect of vaccinations. It is also discussed that public health campaigns should focus on topics that are much discussed in microblog discussions. According to the study, machine learning is an important tool to better understand public health and epidemiological issues because it allows for the rapid processing of multivariate data and the extraction of hidden relationships in large data sets.
8	Cheon, S et al	2023	USA	COVID-19 vaccinations (in general)	US VAERS data	Machine learning approach to study people who experienced adverse events with the COVID-19 vaccine by gender, age, vaccine manufacturer, and dose of vaccinations by using a language model and symptom clustering with unsupervised machine learning. To discover any association rules among adverse events, a data mining approach was used	The study emphasizes that pre-processing of data when analyzing the VAERS dataset before each analysis is essential. It also recommends that health professionals and recipients be more aware of the underlying diseases, medications, and allergies of the person receiving the vaccine to better anticipate and be prepared for adverse events. It is also recommended that more research should continue, using machine-learning techniques with additional data sets and VAERS data sourced from other countries.
9	Hussain, Z et al.	2022	UK	COVID-19 vaccinations (in general)	Facebook and Twitter	First, the Facebook posts and tweets were filtered thematically using a 2-step approach. Predefined COVID-19 keywords were used to perform the first filter and vaccine-related keywords were used for the second filter. The search strategy for the AEFIs was based on reports from the Yellow Card Scheme and the Vaccine Adverse Event Reporting System. The AEFIs were grouped and the frequency per group was	More research should be done regarding social media to better understand public perceptions surrounding specific adverse effects. This could add value to complement existing surveys and perhaps help inform their design. Social media analysis could also provide support for pharmacovigilance in the future.

						calculated and then plotted. The study used a so-called hybrid ensemble model; a combination lexicon rule-based (VADER and TextBlob) and deep machine learning-based (BERT) approaches to analyze sentiment trends around vaccines in the UK.	
10	Weeks, R et al.	2022	USA	COVID-19 vaccinations (in general)	Semi-structured focus group discussions (FGDs) were conducted to assess the appropriateness of different styles of responses to common COVID-19 vaccine questions.	The two groups recruited were residents aged 18-28 years and health professionals. Participants were required to complete a demographic questionnaire using Qualtrics software. As for the FGDs, these were held via Zoom®. During the FDGs, participants were introduced to VIRA (a chatbot). A grounded theory approach was used to develop a conceptual framework of responses to different styles of COVID-19 messages.	More studies should be performed to determine if a chatbot can convince users to change their perception of safety and vaccine effectiveness and allow themselves to get vaccinated.
11	Umair, A. et al.	2023	Global	COVID-19 vaccinations (in general)	Twitter tweets	A sentiment analysis was performed; For categorization and to determine the polarity of the tweets, the TextBlob() function was used. In addition, the BERT model was used to classify the sentiments. Geospatial methods were used for the geo-coding and visualization of the key points.	Twitter-based sentiment analyses are valuable and convenient methods to be implemented for the identification of vaccine sentiments among the population of people. By combining this method with geocoded data, the rationale for different views surrounding COVID-19 vaccinations can be easily identified. The BERT model is a good tool to classify vaccine sentiments. In addition, the study solidifies that analyzing hidden sentiments in tweets using this advanced method is effective to get a better picture of public perception among people.
12	Sv,P et al.	2021	India	COVID-19 vaccinations (in general)	Social media posts on side effects of COVID-19 vaccinations in India.	First, Python was used to collect social media posts regarding adverse reactions to COVID-19 vaccines within the Indian population. Next, sentiment analysis was conducted using machine learning to better understand the population's perception around this topic. Lastly, topic modeling was performed to purposefully analyze the side effects most frequently mentioned in the posts.	More efforts should be made by the government and NGOs to reassure the population regarding the side effects of COVID-19 vaccinations. In addition, governments should speed up vaccination programs to suppress the COVID-19 crisis and prevent future pandemics.
13	Roe, C et al.	2021	UK	COVID-19 vaccinations (in general)	English tweets from Twitter and questionnaires.	A sentiment analysis model (lexicon-based) was used for data analysis. Participants who were fully vaccinated were required to complete a questionnaire to analyze their sentiments.	For the assessment of vaccinations regarding the safety and efficacy of COVID-19 vaccinations, more use should be made of sentiment analysis. This will provide a better picture of the public's

							perception of COVID-19 vaccinations and identify any misconceptions surrounding the issue, which can then be addressed. By gaining more knowledge about this, educational campaigns, for example, can be used for this purpose to ultimately gain more trust from the public and convince more people to vaccinate themselves.
14	Liu, S et al.	2021	Global	COVID-19 vaccinations (in general)	Tweets all over the world regarding COVID-19 vaccines	Machine learning and transfer learning models were used to classify tweets regarding COVID-19 vaccines. In addition, to analyze the perceptions surrounding COVID-19 vaccines over time, temporal analysis was used. To evaluate the changes around perceptions, statistical values and P-values from the Augmented Dickey-Fuller test were employed. Next, key topics had been extracted using top modeling (Dirichlet assignment analysis). The prevalence of tweets with sentiments was also examined and analyzed over time. The tweets were categorized into positive, negative, positive behavioral intentions, and negative behavioral intentions. This allowed the identification of the 10 main themes for each category.	This study suggests that social media is a beneficial source to analyze perceptions of the public. In addition, based on these analyses, effective interventions could also be designed and implemented to gain greater acceptance regarding COVID-19 vaccines.
15	Kwok, S	2021	AUS	COVID-19 vaccination (in general)	Tweets among Australian Twitter users.	First, data collection was done by collecting tweets regarding COVID-19 vaccination among Australian Twitter users. For data analysis, high frequencies word clouds and correlations between word tokens were visualized. By constructing a latent Dirichlet allocation model (LDA), frequently commented topics were identified in the tweets. Finally, sentiment analysis was conducted to better understand the public perception regarding this topic within the Australian population.	More research should be conducted by the government on public perceptions surrounding COVID-19 vaccinations. The results can be used to effectively develop vaccine promotion campaigns. According to this study, social media is a valuable resource to accomplish this. This article recommends applying machine learning approaches such as LDA on social media to extract public perceptions about certain topics. In addition, actions should be taken against misinformation about COVID-19 vaccinations to encourage people to vaccinate themselves.
16	Khan, I.U et al.	2022	Saudi Arabia	COVID-19 vaccination (in general)	Dataset of Arabic tweets on Twitter.	To predict the level of acceptability and awareness around COVID-19 vaccines in Saudi Arabia, machine learning models were used. The models used were Support Vector Machine (SVM), Naïve Bayes (NB) and Logistic Regression (LR). In addition, N-gram and Term Frequency-Inverse Document Frequency (TF-IDF) techniques for feature extraction were also used in	This article suggests that the study can be improved by analyzing specific aspects of the vaccine (e.g., safety, efficacy, and side effects) to better understand public perceptions regarding COVID-19 vaccines. In addition, it is also recommended that other social media platforms be explored to better understand awareness and

						this study. For comparing the performance between machine learning and deep learning, Long Short-Term Memory model (LSTM) with word embedding was used.	acceptability of COVID-19 vaccines. It is also recommended that a multilingual sentiment analysis tool must be developed to create more awareness and ensure a minimal spread of the virus around the world.
17	Jamshidi, E et al.	2023	Switzerland /Iran	Six vaccines were examined: The AZD1222, Sputnik V, BBIBP-CorV, COVAXIN, BNT162b2, and the mRNA-1273 vaccine.	Prospective data from 19943 participants from Iran and Switzerland (online surveys from 90 hospitals in Iran and Switzerland)	A novel machine learning (ML) approach was designed to generate personalized predictions of the most common adverse side effects following injection of six different COVID-19 vaccines based on personal and health-related characteristics. Predictors included 46 parameters, which included age, sex, blood type, smoking history, substance abuse, alcohol dependence, BMI, comorbidities, use of specific medications, and previous COVID-19 infection status.	Artificial intelligence (AI) programs could be instrumental in establishing rapid and cost-effective strategies to inform COVID-19 vaccine selection and generate personalized factsheets to curb concerns about adverse side effects.
18	Zeitoun, A et al.	2023	Lebanon	The vaccines that were examined: Pfizer-BioNTech, AstraZeneca, Sputnik, and Sinopharm	Data sources consisted of the Vaccine Hotline Call Center, the IMPACT Platform, the Kobo-toolbox and case reports to PV Program	A retrospective study of case reports received to the Lebanese Pharmacovigilance (PV) Program in one year.	The surveillance system for the safety of COVID-19 vaccines should be strengthened through continuous monitoring of AEFIs and appropriate awareness programs must be implemented to educate people about the safety and efficacy of COVID-19 vaccines. In addition, it is essential to inform people about the importance of reporting AEFIs after being vaccinated. It is also important to consider long-term effects and conduct additional research on this as well.
19	Yamaguchi, T et al.	2022	Japan	COVID-19 vaccinations (in general)	Japanese spontaneous reporting system.	In Japan, a joint council in the Ministry of Health, Labour and Welfare was held every two to three weeks to summarise information on the adverse events following COVID-19 vaccination, with assessment of individual case safety reports and comparison with background incidence rates.	Information regarding monitoring the safety of COVID-19 vaccines should be shared at an international level. This information can be used during international discussions to ultimately achieve better safety monitoring of COVID-19 vaccines.
20	Shresta, S et al.	2021	-	COVID-19 vaccinations (in general)	Literature review	This article describes the essentials of having an adverse event monitoring system.	Post-marketing surveillance of adverse reaction data needs to be strengthened with more active safety monitoring because there is insufficient information available on the long-term effects of COVID-19 vaccines.
21	Rudolph, A et al.	2022	Global	COVID-19 vaccinations (in general)	VigiBase (global case safety database)	Statistical methods were used to screen unknown ADRs from Vigibase and identify patterns. These were then manually reviewed by experts in the field.	Pharmacovigilance systems and tools should be strengthened to identify, assess and analyze the

						Possible safety signals were prioritized during weekly multidisciplinary discussions. Several tools were developed and applied such as report-specific de-duplication tool and prioritization strategies for ICRs. For the validation of AEFIs, the Brighton Collaboration criteria were used. Causality assessed by applying a combined methodology that included association over time, individual risk factors, alternative causes, and the integration of results from different epidemiologic methods.	increased volume of reports in a timely manner with a focus on detecting emerging safety signals. In addition, the study recommends evaluating the use of mobile apps for pharmacovigilance during the COVID-19 pandemic. It also recommends increased collaboration with pharmacovigilance stakeholders to better understand the global perspective. In addition, transparent reporting of safety information by vaccine manufacturers and regulators should continue to be shared. Furthermore, background rates and incidence rates of AEFIs when possible, should be calculated to confirm safety signals.
22	Rolfes, L et al.	2022	Netherlands	COVID-19 vaccination (Pfizer, Moderna, Janssen and AstraZeneca)	Cohort event monitoring study	Online questionnaires were distributed among participants using the LIM system. Descriptive statistics were then used to gain further insight into the study population. Multivariable logistic regression was used to analyze potential factors associated with the occurrence of reactogenicity.	The impacts of potential risk factors and the occurrence and characteristics of an AEFI should be further investigated. Also, more research should be done on AEFIs after the first and second moments of vaccination and expectations at the individual level.
23	Portelli, B et al.	2022	Global	COVID-19 vaccination (in general)	English tweets on Twitter regarding COVID-19 vaccines.	The following methods/analyses were performed during the study to process the data: localization module, hashtag analysis and analysis of the news sources mentioned in the most recent tweets, factuality analysis, and lastly sentiment analysis. Machine learning-based models (RoBERTa model) were also used for model validation.	Tools should be developed to monitor public perceptions toward COVID-19 vaccines. Social media can be a valuable source for obtaining information to ultimately support pharmacovigilance and counter wrong perceptions. Also, opinions on social media about COVID-19 should be graphically displayed and accessible to users to get an overview of shared perceptions on social media. In addition, there should be better tools for extracting AEFIs from tweets in different languages. Also, all codes, tweet IDs, and calculated statistics of previously collected tweets should be made available on GitHub.
24	Phillips, A et al.	2021	AUS	COVID-19 vaccination (in general)	Semi-structured interviews with Australian experts with expertise in vaccine safety and	The research was conducted with a qualitative approach and used thematic analysis to examine the interviews conducted with experts and government representatives.	The article makes four recommendations: First, it recommends that there should be better integration of the entirety of pharmacovigilance resources in Australia. With this, a multifaceted and adaptive system can be developed. In addition, vaccine pharmacovigilance should be

					major government officials.		more targeted and supported by the government which should also strive for innovation. Also, more attention should be paid to developing nationally coordinated and systemic approaches for active population-level monitoring so that challenges in the future regarding pharmacovigilance can be made easy. Finally, greater capacity for monitoring the safety of COVID-19 vaccines should be pursued. This could include expanding current systems and developing new approaches to pharmacovigilance and communication.
25	Oosterhuis, I et al.	2023	Netherlands	COVID-19 vaccinations (in general)	Dutch Spontaneous Reporting System (SRS)	Description of the 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.	The study recommends developing a technical process that provides support for the following: rapid assessment of AEFIs and early detection of signals. Application of new signal detection methods taking into account background rates is necessary. It is also recommended to be able to accommodate unplanned changes in vaccination strategies and media attention. There should also be an appreciation for the involvement of clinical experts within their expertise in the clinical assessment of ICSRs. The article also encourages collaboration with other partners to optimize signal detection and a transparent communication strategy.
26	Ljung, R et al.	2021	Sweden	COVID-19 vaccinations (in general)	National registers (CoVacSafe-SE register) from different government agencies.	The Swedish Medical Products Agency has launched a project platform for epidemiological surveillance to detect and characterize suspected adverse effects of COVID-19 vaccines in Sweden. The study used different national registers from different government agencies. The participants included people who were 12 years or older from Sweden in 2021. The data were finally compared to cohorts from the past (from 2015 to 2019). These cohorts were not involved in the COVID-19 pandemic and associated vaccines. The following data were examined: COVID-19 vaccines, COVID-19 morbidity, socioeconomic and demographic data, comorbidities, drugs prescribed, and healthcare use outcomes.	The study recommends the need for new registry-based regulatory tools for follow-up studies regarding the efficacy and safety of COVID-19 vaccines. This would facilitate non-interventional studies. In addition, signals regarding potential adverse events related to COVID-19 vaccines should be regularly advanced. In addition, government decision-making should be supported. It is also important to focus on both short-term and long-term effects of COVID-19 vaccines, vaccination coverage and vaccine effectiveness with CoVacSafe-SE studies. Moreover, the article mentions that longitudinal design of the CoVacSafe-SE registry can be applied

							to achieve all types of product-specific studies. In addition, to support health inequalities, it is also important to combine health data with sociodemographic and socioeconomic factors. Data from the CoVacSafe-SE registry could also be used in combination with other sources of information to investigate specific medical conditions. Countries that have registries of high completeness and validity at their disposal are able to answer many important research questions through population-based research.
27	Lian, A et al.	2022	USA	COVID-19 vaccinations (in general)	Twitter	An approach based on machine learning and natural language processing was used to identify adverse events related to COVID-19 vaccines from the twitter dataset. A pipeline was developed for the study that extracted the experiences regarding COVID-19 vaccines in which characterizations of the vaccines such as brand, dose and adverse events were extracted from the tweets. For data analysis, the location, time and frequency of the extracted tweets were examined.	Data from social media platforms can be supportive of existing systems related to vaccine pharmacovigilance.
28	Laemmle-ruff, I et al.	2022	AUS	COVID-19 vaccinations (in general)	Surveillance system operated by the Victorian Department of Health in Australia. The system includes a combination of enhanced spontaneous surveillance, active surveillance, and syndromic surveillance from multiple alternate data sources, as well as vaccine safety data-linkage.	In this study, spontaneous, active surveillance, syndromic surveillance were used from different alternative data sources for the data collection. In addition, vaccine safety data linkage was also used. For spontaneous surveillance, health care providers, family and or patients could make reports online or with their mobile. These were then examined by immunization nurses. For the active surveillance, the patients vaccinated were asked to complete questionnaires at different times after receiving a covid-19 vaccination through the AusVaxSafety system. Because there was a huge increase in AEFI reports, this resulted in several changes within the workflow and management. For example, a priority triage list was created, and adjustments were made to the procedures for coding reports, In addition, new staff was required and innovations were made for automating, filtering and triaging the AEFI reports for	The study suggests that post-market surveillance of vaccines on safety using spontaneous and active mechanism is fundamental and an important aspect of the vaccination program. Further investment in long-term systems is needed to ensure vaccine safety. The detection and understanding of less common AEFIs from COVID-19 vaccines, for example, may be beneficial in establishing eventual vaccine policy and gaining public confidence regarding COVID-19 vaccines. Extra resources are required to increase the capacity and to provide support for vaccine safety systems. A solution for providing more capacity, flexibility and increase the ability to interact with additional datasets would be a new e-health database infrastructure. Quick adjustment, adequate prioritization and informatics innovation, and involvement with the

						follow-up with priority, Also the processes for signal detection needed to be expanded. In collaboration with the Ministry of Health, a vast network has been established called (Victorian Specialist Immunization Services (VicSIS). Staffing clinics with various subspecialists were used for the clinical assessment of AEFIs. To improve triage, coordinate appointments and link with SAEFVIC, a central electronic referral hub was developed. In addition, meetings between VicSIS clinicians, SAEFVIC and the Department of Health were regularly scheduled to develop key issues such as the development of clinical guidelines related to COVID-19 vaccines and knowledge transfer. Weekly public reports were also written by SAEFVIC regarding the safety of COVID-19 vaccines. The SAEFVIC also had short lines of communication with local and state governments and regulatory agencies. Information sharing was done at both national and international levels with the goal of obtaining more information on underlying (biological) mechanism and risk factors. The study also used a centralized database system. This was in collaboration with Western Australia (Western Australian Vaccine Safety Surveillance). This enabled joint innovations and collaborations. In addition, they also believed it was important to facilitate internal communication and collaborations via weekly SAEFVIC "huddles"	public's perspective are necessary to sustain the COVID-19 vaccine program.
29	Lacroix, C et al.	2021	France	COVID-19 vaccinations (in general)	French Pharmacovigilance network (Spontaneous Reporting System)	This article reports that the French pharmacovigilance network and ANSM have been optimizing a mutually beneficial approach and interaction to achieve intensive pharmacovigilance and surveillance of vaccines with the goal to ensure the safety of these vaccines. Information from the French pharmacovigilance network regarding the safety of COVID-19 vaccines information was collected weekly by two regional centers. All reported ADRS were then investigated on an immediate basis in a direct loop	Safety, transparency, and efficacy of COVID-19 vaccines must be a part of vaccination campaigns. In order to refer a complete analysis in real time, it is necessary to adopt a multiple approach in line with a strong collaboration between all authorities involved and the optimization of existing pharmacovigilance organizations. It is important to be able to adapt as a pharmacovigilance system to identify new patient profiles with ADRs and adapt to complex vaccination strategies According to the study, it is

						that included the ANSM and weekly safety reports were created and also ultimately published online.	also essential to carefully and acutely monitor new COVID-19 vaccines to preserve or regain the public trust.
30	Kein, K et al.	2022	Europe	COVID-19 vaccinations (in general)	The study used a two-part survey: Survey A (development-based pharmaceutical companies) and survey B (limited to EFPIA member companies that have developed or are in the process of developing a COVID-19 therapeutic and companies that have already been licensed for a COVID-19 therapeutic.)	Survey A gathered information regarding the opinions and experience and lessons learned from research and development-based pharmaceutical companies regarding the applied flexibilities made in regulations to counteract challenges resulting from the COVID-19 pandemic and ensure continued development and delivery of drugs. Questions in Survey B included the value of regulatory flexibilities regarding supporting/accelerating developments around COVID-19 therapies from EFPIA member companies that have developed or are in the process of developing a COVID-19 therapeutic and companies that have already been licensed for a COVID-19 therapeutic. For the consolidation and analysis of the data obtained (from the surveys), Microsoft Excel was used.	The European Regulatory Systems can be made more efficient and improved with important flexibilities mentioned by pharmaceutical companies being introducing dynamic regulatory and supply arrangements, virtual and digitally supported working and collaboration across jurisdictions to support development and supply. In addition, with these insights, EU pandemic preparedness can be enhanced.
31	Kant, A et al.	2022	Netherlands	COVID-19 vaccination (in general)	Spontaneous reporting system (Lareb)	Description of methods which can be used for the analysis of vaccine data in a spontaneous reporting system (SRS).	Analysis methods for vaccines in a pandemic situation should take into account background incidence. However, it also mentions that a thorough analysis of the underlying clinical data and the pharmacological mechanism are a requirement before a conclusion can be made. The study also suggests that underreporting must be taken into account and that reporting rates only give an impression of the occurrence of an AEFI. Moreover, it also mentions that quantification of incidence rates requires epidemiological follow-up studies.
32	Kant, A et al.	2022	Netherlands	COVID-19 vaccination (in general)	Cohort Event Monitoring	A web-based prospective cohort design was used for data collection. The extent to which common (systemic) AEFI's occur after COVID-19 vaccine was examined. The study used descriptive statistics and Heatmaps to describe the characteristics of the cohort. Furthermore, a sensitivity analysis was also	Collecting real-world data is important to make the safety profile of COVID-19 vaccines as complete as possible and to understand it, as there is much diversity within the vaccinated population. Also, the study recommends using patient-reported data to better understand the

						performed in which participants who had enrolled on the day of vaccination were compared with those who enrolled later.	occurrence of AEFIs after vaccination with COVID-19 vaccines.
33	Harpaz, R et al.	2022	USA	COVID-19 vaccinations (in general)	VAERS database	Analysis of all available VAERS reports from the period 1990 to Oct. 1, 2021, representing a total of 1,599,958 reports, which included 39 weeks of COVID-19 vaccine reports. The study focused on seven adverse events of interest, which were identified using a hidden association detection and ranking approach. The article describes four signal detection methods that were used to evaluate disproportionality statistics, which include Multi-item Gamma Poisson Shrinker (MGPS), Bayesian Confidence Propagation Neural Network (BCPNN), proportional reporting ratio (PRR), and RGPS (a signal detection method that uses logistic regression). The signal scores had been compared according to various concepts and conditions, which included signal threshold, signal present/absent, statistically significant difference in signal score, candidate masking association, and extent of masking effect.	The employment of more advanced statistical methods, as these enable detection of masked potentially safety problems related to COVID-19 vaccines is recommended and assessing masked associations needs to be done continuously, as statistical signal detection methods are time sensitive. Masked associations could have negative impact on safety surveillance of COVID-19 vaccines and should be addressed for that reason. Methodology in which masking effects are automatically identified and corrected for should be used.
34	Duszynski K.M. et al.	2021	The Asia-Pacific region.	COVID-19 vaccinations (in general)	Survey	This study used data sources to map pharmacoepidemiologic research on vaccines in the Asia-Pacific region. Nineteen countries targeted for database reporting were identified using published country lists and review articles. Surveillance capacity was assessed using two surveys.	An essential requirement for a surveillance system is the availability of comprehensive vaccine exposure data. A Common Data Model (CDM) designed to standardize the structure of coding systems and observational data can be a good tool for performing combined analyses in different databases with a standardized analytical code.
35	J.W Duijster et al.	2023	The Netherlands	Vaccines: AstraZeneca Johnson&Johnson Moderna Pfizer	Cohort Event Monitoring Study and literature review	A web-based prospective cohort design was used for data collection. The incidence and course of reported AEFIs was compared between males and females for multiple outcomes for separating first and second vaccination doses. A literature review of the key findings of the study was also performed.	The recommendation is to include representative sex distribution in clinical trials and analyze gender stratified data on safety and efficacy.
36	G. Delanerolle et al.	2022	United Kindom	COVID-19 vaccinations (in general)	Data and Connectivity COVID-19 Vaccines Pharmacovigilance	Exposures and outcomes of interest to DaC-VaP for pharmacovigilance studies were selected. Mappings of these variables to different terminologies used across the United Kingdom's devolved nations' health	The study revealed that the OMOP Common Data Model (CDM) is a good system to identify linkages for the monitoring of adverse reactions to COVID-19 vaccines.

					(DaC-VaP) UK-wide collaboration	services were identified from the Observational Health Data Sciences and Informatics (OHDSI) Automated Terminology Harmonization, Extraction, and Normalization for Analytics (ATHENA) online browser.	This study concludes that concept mapping to a wide variety of terminologies, such as that used within OMOP and the ATHENA online browser, is both useful and valid for performing pooled analyses of heterogeneous data. The local curation of clinical variables at the database level would be beneficial to address granularity issues. This would enable local expert adaptation of mappings that can be utilized by others for restricted merged analysis of a limited number of clinical concepts. The interlinking of the merged analysis might also provide support for the MHRA's Spontaneous Report System used to improve patient safety.
37	S. Crommelynck et al.	2022	France	COVID-19 vaccinations (in general)	ANSM database (Spontaneous Reporting System)	In France, the ANSM system is involved in the pharmacovigilance of COVID-19 vaccines. This is an enhanced system that provides routine and specific reports of each of the four authorized vaccines. This system also has the capability to include international signals in the French data and scientific literature for monthly reports and periodic safety updates. For pharmacovigilance, the ANSM system is used by 31 regional centers.	The use of enhanced pharmacovigilance paired with pharmaco-epidemiology and international cooperation can be instrumental in identifying potential safety risks and taking necessary action.
38	S.M. Büyüker et al.	2023	Turkey	COVID-19 vaccinations (in general)	Online questionnaire spread through social and electronic media.	An online study on adverse events following immunization (AEFIs) of the COVID-19 vaccines with a a retrospective and cross-sectional design.	The factors influencing the reluctance to vaccinate among pregnant and lactating women should be further investigated to promote vaccination to reduce the risk of serious diseases due to COVID-19. Regional differences should also be studied. Evaluation of the safety of COVID-19 vaccines requires long-term monitoring of side effects. Health authorities have an important role in communicating and informing about the benefits of COVID-19 vaccines.
39	M. Benkebil et al.	2021	France	COVID-19 vaccinations (in general)	ANSM database (Spontaneous Reporting System)	Description of the drug monitoring system deployed by the French government to continuously monitor and evaluate adverse reactions to COVID-190 vaccines in France.	
40	D. Araja et al.	2022	Europe	COVID-19 vaccinations (in general)	EudraVigilance European Database	Analysis of ADRs related to COVID-19 vaccines reported by health professionals and patients to the	The application of modern methods, such as machine learning and big-data analysis may

					for Suspected Adverse Drug Reaction Reports (EDSADRR).	EudraVigilance European Database for Suspected Adverse Drug Reaction Reports (EDSADRR).	complement the usual passive surveillance methods.
41	A.I. Alzarea et al	2022	Saudi Arabia	COVID-19 vaccinations (in general)	Survey	Cross-sectional quantitative study performed in Saudi Arabia on the side effects of COVID-19 vaccines among the general population.	Continuous safety monitoring is important, especially for serious events including those with a fatal outcome. The public should be informed about safety of COVID-19 vaccines to address misconceptions. It is important to consider the high nocebo effect reported in the placebo groups.
42	Y. Albogami et al.	2021	Saudi Arabia	COVID-19 vaccinations (in general)	Overview	An overview of the available systems that can be utilized to monitor the COVID-19 vaccines' safety and discussion of opportunities for data integration to improve data quality and generate real-world evidence on COVID-19 vaccine safety.	The following recommendations can be pointed out: 1. Strengthen data integration of government agencies to respond quickly to avoid risks. Therefore, actions should be taken to increase data sharing and its integration among health institutions. Adopting a Common Data Model (CDM) can help streamline and integrate data. 2. Improving data management to ensure privacy, security, and ethical use of data. 3. Developing research protocols to ensure the quality of collected data so that it can be used as reliable evidence. 4. Ensuring transparency and communication for public trust for the use of real-world data for pharmacovigilance.
43	N.A. Rahman et al.	2022	Malaysia	COVID-19 vaccinations (in general)	A long-term observational, retrospective study on active safety monitoring with a case-based monitoring approach, also called the SAFECOVAC study.	A long-term observational, retrospective study on active safety monitoring with a case-based monitoring approach, also called the SAFECOVAC study. This includes the research linking various administrative databases and monitoring hospitalization data to identify adverse effects of particular relevance after COVID-19 vaccines in Malaysia. The population who received at least one dose of the COVID-19 vaccine were included in the study. The study used a self-controlled and covered vaccination design to identify and assess risk of adverse effects following COVID-19 vaccine.	To detect adverse events, routine data from administrative databases can be valuable addition to systems already in place for drug safety surveillance

44	M. Zureik et al.	2023	France	COVID-19 vaccinations (in general)	Overview	During the COVID-19 pandemic, EPI-PHARE, a scientific group in pharmaco-epidemiology created by the French National Agency for the Safety of Medicines and Health Products (ANSM) and the French National Health Insurance (Cnam), analysed data of the French Health Data System (SNDS) from the beginning of the first lockdown in France in March 2020, we were able to publish numerous results on the use, benefits and risks of medicines, on the risk factors of COVID-19 before and after vaccination, and on the benefits and risks of COVID-19 vaccines.	Analysis of a National Health Data system allows regulators to take informed decision in this pandemic situation in order to ensure the health of the population
45	K.M. Kälkner	2023	Sweden	COVID-19 vaccinations (in general)	Overview	Observed to expected analyses of safety concerns identified in the national signal detection work were evaluated using the aforementioned nationwide registers on hospitalizations and specialized out-patient care visits linked to the vaccination register.	To improve the efficacy of the present daily pharmacovigilance activity, a robotic process automation technique and additional measures to facilitate the submitting of ADRs is recommended. A closer collaboration concerning epidemiological surveillance between data holders of health registries and the national competent authorities will be beneficial.
46	I.L, Diak, IL	2023	US	COVID-19 drugs	Overview	Overview describing the FDA's approach to monitoring the safety of drugs to treat or prevent COVID-19 across multiple data sources and the subsequent actions taken by the FDA to protect public health.	Establishing collaborations and leveraging new data sources including near real-time data were essential in the Food and Drug Administration's response to the pandemic.
47	V. Bauchau,	2023		COVID-19 vaccinations (in general)	Overview	An Industry Expert View on the Successes, Challenges, and Future Opportunities in Real-World Monitoring of COVID-19 Vaccines.	Co-operation among coronavirus disease 2019 (COVID-19) vaccine manufacturers in the area of pharmacovigilance was critical to the development and timely deployment of COVID-19 vaccines. Several innovations were implemented, from regulatory processes to the creation of new data platforms. Near real-time access to high-quality, comprehensive, and relevant data, as well as more rapid and flexible communication channels and forums between stakeholders, are points for future improvements.
48	R. Chandler	2023		COVID-19 vaccinations (in general)	Overview	Review of the various tools and their strengths and limitations and discuss what functioned well in high income settings and the limitations that unequal	The Covid-19 pandemic showed the need for all types of infrastructures: passive surveillance systems, cohort event monitoring as well as

						vaccine safety pharmacovigilance capacity imposed upon middle- and low-income countries.	electronic health record data. The time prior to issuance of the EUA emergency use licensure was well used; template protocols were created; background rates were determined and lists of AESI and their definitions were compiled. Availability of existing networks that could leverage vaccine experts, public health infrastructure data, and pre-existing relationships are critical to a rapid response during a pandemic.

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Supplementary material 6. Interview guide Pandemic Preparedness in Pharmacovigilance

This interview will focus on how organizations responsible for pharmacovigilance during the COVID-19 pandemic dealt with an increase in numbers of individual case safety reports (ICSRs) and corresponding signal detection activities for these ICSRs. The interview will also address innovative methods that may be helpful in future pandemics.
The interview will be recorded if you have no objections.

General Information

1. Could you please state your name?
2. Could you please state the date this questionnaire was taken?
3. For which organization do you work?
4. Where is your organization located?
5. Could you describe the function of your organization in one sentence?
6. Could you shortly describe your job and responsibilities within the organization?

Pharmacovigilance during the COVID-19 pandemic

1. Could you give an estimation of the increase in ICRS reports (number, percentage) during the COVID-19 pandemic at your organization?
    a. Were there any changes in the number of reports on other drugs of vaccines? (That may have influences the total workload for your organization?)
    b. Was this increased caused by reports on ICSRs for COVID-19 vaccines or by drugs for the treatment of COVID-19 vaccines or both.
2. How did your organization deal with an increase in ICSRs during the COVID-19 pandemic? (Both for COVID vaccines and other type of ICSRs)
    a. Did you hire more staff, e.g. pharmacovigilance assessors?
        i. With/without special knowledge on vaccine safety (if so, specify)
    b. Did you change the way you handle ICSRs?
    c. Did you change the way you assess ICSRs?
    d. Did you focus on automation of your pharmacovigilance processes?
        i. If so, could you explain which areas automation played a role e.g., coding, literature searches, signal detection?
3. What signal detection methods did you use during the COVID-19 pandemic? (e.g., case-by-case assessment, disproportionality, Observed/Expected analysis etc)
    a. Which methods were key in your signal detection process?
        i. Were these methods different for vaccines and drugs to treat COVID-19?
    b. Did you change the way you approach signal detection during the COVID-19 pandemic as compared to the situation before the pandemic?
    c. Did you use or develop new methods for Signal detection during the COVID-19 pandemic? If so, please specify.
    d. What challenges did you encounter in your signal detection work? (These could be Managerial challenges and methodological ones or both)
        i. Are there possible solutions for these challenges?
    e. How did you deal with the possibility of masking effects of the Covid-19 vaccines in your database?
        i. What do you see as possible solutions to deal with masking effects?
4. Did you use data sources other than spontaneous reports during the COVID-19 pandemic?
    a. Did you have access to data on number of vaccinations given?
        i. Was this on a patient level or on a population level?
    b. Did you have access to data on background incidences? If so, which did you use?
    c. Did you have access to Real World Evidence sources?
    d. How did you use these data sources in relation to your daily work? E.g., signal strengthening, verification etc.
5. If we look towards a future pandemic, what best practices learned from the COVID-19 pandemic would you recommend?
    a. What best practices from a methodological or signal detection point of view
    b. What best practices considering (data) management?
6. What innovative methods, meaning new and original methods, for pharmacovigilance would be useful during a new pandemic?
    a. Has your organization been active in developing these methods?
        i. If not, how would you apply these methods?
    b. What would be platforms/ways to share information on these innovations?
7. Do you have anything you would like to add?

6. AEF REPORT FARMACOVIGILANTIE IN EEN PANDEMIE

Andersson Elffers Felix

Farmacovigilantie in een pandemie

Eindrapportage

17-5-2023

Hoofdboodschap impact van farmacovigilantie tijdens een pandemie [1/2]

1

Farmacovigilantie beoogt in eerste instantie bij te dragen aan medisch inhoudelijke veiligheid – ook tijdens de covidpandemie

Farmacovigilantie moet bijdragen aan het veilig gebruik van een veilig product (geneesmiddelen en vaccins). Dit noemen we de ”medisch inhoudelijke veiligheid”.

Tijdens de Covid-19 pandemie stond de beoogde impact van farmacovigilantie als het gaat om medisch inhoudelijke veiligheid niet ter discussie. De betrokken partijen binnen de farmacovigilantieketen voerden het farmacovigilantieproces evenwel – ondanks onzekerheden rondom het Covid-19 virus en de hogere input – uit conform (Europese) wet- en regelgeving.

Tijdens de Covid-19 pandemie moesten processen sneller en soms parallel worden uitgevoerd. Volgens geïnterviewde partijen kon het farmacovigilantieproces desalniettemin zorgvuldig worden doorlopen en is de farmacovigilantieketen – zoals op dit moment ingericht met verschillende partijen met verschillende rollen – functioneel gebleken.

2

Farmacovigilantie speelt ook een belangrijke rol bij de totstandkoming van ‘onderbouwd vertrouwen’ van de maatschappij in de veiligheid van geneesmiddelen en vaccins – dit vertrouwen kwam tijdens de pandemie onder druk te staan

Farmacovigilantie biedt, met het bijdragen aan medisch inhoudelijke veiligheid, ook een belangrijke onderbouwing voor het vertrouwen van de maatschappij in de veiligheid van geneesmiddelen en vaccins. Dit onderbouwd vertrouwen wordt tegelijkertijd beïnvloed door tal van andere factoren, buiten de invloedssfeer van de keten van geneesmiddelenbewaking.

Met name door de context van de Covid-19 pandemie ontstond grote druk op het vertrouwen in de medisch inhoudelijke veiligheid door tal van factoren, en kwam het onder een vergrootglas te liggen. Zo was er lange tijd onzekerheid over de aard van het virus, was er in het algemeen een lager vertrouwen in overheidsinstanties en werden verschillende vormen van desinformatie verspreid. Bovendien leidde de vrijwillige vaccinatie van een groep gezonde mensen tot andere afwegingen bij groepen burgers over medisch inhoudelijke veiligheid.

In deze specifieke dynamiek kwam druk te liggen op de keten van geneesmiddelenbewaking. Het bestaan van een onafhankelijk meld- en kenniscentrum voor bijwerkingen bleek tijdens de pandemie extra belangrijk voor het onderbouwd vertrouwen in medisch inhoudelijke veiligheid. Immers, een meld- en kenniscentrum over bijwerkingen heeft er geen direct belang bij of burgers zich wel of niet laten vaccineren, waar de overheid dit belang wel heeft.

Hoofdboodschap impact van farmacovigilantie tijdens een pandemie [2/2]

3

Op basis van de covidpandemie zijn lessen te trekken waarmee de medisch inhoudelijke veiligheid verder kan worden vergroot én waarmee Lareb en de keten kunnen bijdragen aan (meer) onderbouwd vertrouwen.

De Covid-19 pandemie leert dat onderbouwd vertrouwen in de veiligheid van geneesmiddelen en vaccins niet vanzelfsprekend is. Duidelijkheid over rol en onafhankelijke positie is cruciaal voor een meld- en kenniscentrum voor bijwerkingen om een geloofwaardige bijdrage te leveren aan onderbouwd vertrouwen. Het is daarom belangrijk dat Lareb en de keten streven naar meer transparantie naar de buitenwereld, over de verschillende rollen van partijen in het farmacovigilantieproces. Hierdoor kan de maatschappij adviezen en besluiten rondom vaccinaties, geneesmiddelen en bijwerkingen beter begrijpen en plaatsen.

Om maatschappelijk vertrouwen in medisch inhoudelijke veiligheid te bevorderen is het ook belangrijk dat partijen in de farmacovigilantieketen op de hoogte zijn van de inhoud en het moment van elkaars communicatie-uitingen, zodat zij hierop kunnen inspelen. Zo moet beter duidelijk zijn wie welke rol heeft en hoe rollen zich tot elkaar verhouden.

De medisch inhoudelijke veiligheid kan verder worden vergroot door het verbeteren van de input c.q. de kwaliteit en het aantal meldingen over bijwerkingen. En door te investeren in de technische (data)infrastructuur, zoals het kunnen koppelen van zorgdata aan vaccindata. Ook kan de medisch inhoudelijke veiligheid verder worden vergroot door blijvend te investeren in het meldsysteem van Lareb.

4

Het nadenken in scenario's over de context van een volgende pandemie – en de invloed daarvan op (de beoogde impact van) farmacovigilantie – moet onderdeel worden van regulatoire pandemische paraatheid.

De beoogde impact van farmacovigilantie verandert niet tijdens een volgende pandemie. De context van een volgende pandemie is naar verwachting wél anders. Daar waar tijdens de covidpandemie transparantie extra belangrijk werd voor het onderbouwd vertrouwen in de veiligheid, kan het zijn dat in een volgende pandemie andere zaken belangrijk(er) zijn. Denk bijvoorbeeld aan snelheid mochten we geconfronteerd worden met een (veel) ziekmakender virus.

Onderdeel van regulatoire pandemische paraatheid is het nadenken in scenario's over de context van een volgende pandemie en de invloed daarvan op de medisch inhoudelijke veiligheid én op het onderbouwd vertrouwen van de maatschappij in de veiligheid van vaccins en geneesmiddelen. Als bijvoorbeeld snelheid belangrijker wordt door de context van een volgende pandemie, dan kan dit meer consequenties hebben voor de processen en het naleven van de wet- en regelgeving in algemene zin.

Inhoud

1. Aanleiding en onderzoeksvraag

Een versterkte pandemische paraatheid van de zorg en infectieziektebestrijding

De covidcrisis onderstreept het belang van sterke regulatoire pandemische paraatheid

De uitbraak van het coronavirus heeft geleid tot een ongekende pandemie die niet alleen Nederland, maar de hele wereld heeft getroffen. De covidcrisis toonde aan dat de structuren en systemen in de zorg kwetsbaar zijn voor grootschalige noodsituaties. De pandemie onderstreept het belang van een goede voorbereiding op de mogelijkheid van een nieuwe pandemie. Om deze uitdaging aan te gaan, heeft de minister van Volksgezondheid, Welzijn en Sport (VWS) een beleidsagenda[1] opgesteld waarin de eerste contouren voor een versterkte pandemische paraatheid van de zorg en infectieziektebestrijding zijn geschetst. Daarmee streeft het ministerie van VWS naar een beter kennis- en innovatieklimaat in Nederland om de bestrijding van infectieziekten en pandemieën te verbeteren.

ZonMw laat onderzoek doen naar regulatoire pandemische paraatheid

Tijdens een nieuwe pandemie is het belangrijk dat patiënten snel een effectieve behandeling kunnen krijgen. Zo blijft de schade op zowel patiënt als samenleving beperkt. Maar het ontwikkelen, testen en op de markt brengen van nieuwe therapieën is een langdurig proces dat is verbonden aan allerlei wetten en regels: het regulatoire systeem.

Om nieuwe en effectieve behandelingen tijdens een volgende pandemie sneller beschikbaar te maken, start ZonMw binnen het programma *Pandemische Paraatheid* met het deelprogramma *Regulatoire Pandemische Paraatheid*. Het bijbehorende ZonMw deelprogramma *Regulatoire Pandemische Paraatheid* sluit aan op verschillende beleidsopgaven van de beleidsagenda van VWS. Het doel van het ZonMw deelprogramma is om het huidige regulatoire systeem in Nederland te evalueren, aanbevelingen te doen voor verbetering en om concrete handvatten te bieden. De uitkomsten van het onderzoek worden gebruikt om toe te werken naar een adaptief regulatoir systeem, dat snel en passend kan reageren bij een pandemie.

Lareb onderzoekt het thema farmacovigilantie

Het ZonMw deelprogramma richt zich op vier onderzoeksthema's: 1) Drug rediscovery; 2) Farmacovigilantie; 3) Remote monitoring; en 4) Geavanceerde therapeutische producten.

ZonMw heeft Lareb gevraagd om het onderzoek over het thema farmacovigilantie (geneesmiddelenbewaking) op zich te nemen, met als doel antwoord te krijgen op twee onderzoeksvragen:

- wat kunnen we leren van de covidpandemie (retrospectief); en
- wat kan beter in toekomstige pandemieën (prospectief)?

[1] Kamerbrief over beleidsagenda pandemische paraatheid (overheid.nl)

U vraagt om een onderzoek naar de beoogde impact van farmacovigilantie in een pandemie

AEF draagt bij aan het onderzoek farmacovigilantie van Lareb
Lareb wil farmacovigilantie niet alleen vanuit een medisch perspectief bekijken, maar vanuit een breder kader waarin ook de beoogde maatschappelijke impact van farmacovigilantie in ogenschouw wordt genomen. Op deze manier is het mogelijk om meer fundamentele aanbevelingen te doen voor een toekomstig goed functionerend meldsysteem voor bijwerkingen. Om deze reden heeft Lareb onderzoeks- en adviesbureau Andersson Elffers Felix (AEF) gevraagd bij te dragen aan het onderzoek. Specifiek heeft Lareb AEF gevraagd onderzoek te doen naar de beoogde maatschappelijke impact van farmacovigilantie in een pandemie, naar de benodigde samenwerking tussen ketenpartijen én naar wat geleerd kan worden van de covidpandemie.

AEF heeft onderzoek gedaan naar de hoofdvraag:
Hoe moet geneesmiddelenbewaking worden ingericht tijdens een pandemie?

Voor de beantwoording hiervan zijn **twee deelvragen** geformuleerd:
1. Welke impact wordt beoogd met geneesmiddelenbewaking tijdens een pandemie?
2. Wat vraagt dit van een meld- en kenniscentrum voor bijwerkingen van geneesmiddelen en vaccins in samenwerking met de keten en wat kunnen we leren van de covidcrisis?

We nemen in ons onderzoek de farmacovigilantieketen onder de loep, vanuit het perspectief van Lareb

Het onderzoek behandelt de vraagt hoe geneesmiddelenbewaking moet worden ingericht tijdens een pandemie. Enerzijds kijken we hiervoor naar de impact van geneesmiddelenbewaking tijdens een pandemie; anderzijds kijken we naar wat dit vraagt van een meld- en kenniscentrum in relatie tot de farmacovigilantieketen.

We kijken voor dit onderzoek deels terug naar de covidpandemie en halen geleerde lessen op; ook kijken we vooruit en doen we aanbevelingen voor een mogelijke pandemie in de toekomst.

- ✓ De **inrichting van de farmacovigilantieketen** en de rol die Lareb heeft ten opzichte van de betrokken partijen in de keten.
- ✓ De **input, throughput, output, outcome en impact van farmacovigilantie**, en het verschil in een pandemie (beschreven vanuit Lareb in relatie tot de keten).

- X De **inhoudelijke en wetenschappelijke kwaliteit** van het meldsysteem van Lareb.
- X Het **functioneren van de organisatie** van Lareb tijdens de Covid-19 pandemie. Het functioneren van de Lareb organisatie is eerder onderzocht door AEF.

2. Onderzoeksaanpak

Met de doelenboom hebben we richting gegeven aan dit onderzoek

Als basis voor onze aanpak hebben we een onderzoekskader gehanteerd. Om uitspraken te doen over de inrichting van geneesmiddelenbewaking tijdens een pandemie, hebben we in het onderzoek eerst de beoogde maatschappelijke impact van farmacovigilantie in kaart gebracht. Om een vertaling te maken tussen de inrichtingsvraag en de beoogde impact, hebben we gebruikgemaakt van een doelenboom.

We hebben in kaart gebracht welke verwachtingen er zijn bij verschillende stakeholders ten aanzien van de impact van geneesmiddelenbewaking tijdens een pandemie. Het beeld dat daarmee ontstond, hebben we benut als ijkpunt om lessen te trekken en aanbevelingen te doen over de inrichting van geneesmiddelenbewaking tijdens een pandemie. We hebben deze lessen en aanbevelingen geordend in termen van *input*, *throughput*, *output* en *outcome.*

Doelenboom

Input	Throughput	Output	Outcome	Impact
Wat is de input van farmacovigilantie? Hoe zag de input eruit tijdens de covidcrisis?	Welke activiteiten worden uitgevoerd bij genees-middelenbewaking? Welke organisaties zijn er in de keten, welke andere stakeholders? Welke rol spelen zij? Hoe zag dit eruit tijdens de covidcrisis?	Met welke producten krijgt geneesmiddelenbewaking vorm (signalen, adviezen, rapporten, kennis, beantwoording vragen media)? Welke output was er tijdens de covidcrisis?	Welke effecten heeft de output? Wat levert de output (direct) op? Wordt deze herkend, leidt deze tot actie, bv in concrete maatregelen? Welke effecten had de output tijdens de covidcrisis?	Aan welk meer langdurig maatschappelijk effect draagt geneesmiddelen-bewaking (en daarbinnen een meld- en kenniscentrum voor bijwerkingen) bij (tijdens een pandemie)?

We hebben op drie manieren informatie verzameld om de onderzoeksvragen te beantwoorden [1/2]

Onze aanpak bestond uit drie kernactiviteiten: een **documentenstudie, focusgroepen** en semigestructureerde **interviews**.

We startten met een documentenstudie

In de documentstudie legden we de basis voor het onderzoek. Als startpunt hebben we een analyse van voornamelijk openbare bronnen gemaakt. Daarnaast hebben we interne rapportages gebruikt. Ook hebben we op hoofdlijnen de regelgeving met betrekking tot farmacovigilantie bestudeerd. Hiernaast is een lijst met bronnen opgenomen.

Na de documentenstudie hebben we ter voorbereiding op de focusgroepen en interviews een voorbereidend gesprek gevoerd met een expert op het gebied van farmacovigilantie. Op basis van de bevindingen uit de documentenstudie en dit gesprek hebben we de gespreksleidraad voor de focusgroepen en de interviews opgesteld.

Bestudeerde documenten [1]

- Jaarverslag Bijwerkingencentrum Lareb 2021
- Naamsbekendheidsonderzoek Bijwerkingencentrum Lareb
- Poject Voorstel Regulatoire Pandemische Paraatheid – Pharmacovigilance – Bijwerkingencentrum Lareb
- Artikel Overview Pharmacovigilance EMA
- Artikel EMA's governance during COVID-19 pandemic
- Artikel Effects of the COVID pandemic on Pharmacovigilance strategy, systems, and processes of large, medium and small companie
- Artikel Coronavaccins, bijwerkingen en veiligheid
- Artikel Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events
- Artikel Optimizing Safety Surveillance for COVID-19 vaccines at the national pharmacovigilance centre Lareb: one year of covid-19 vaccine experience
- Artikel Global safety monitoring of COVID-19 vaccines: how pharmacovigilance rose to the challenge
- Artikel Monitoring the Safety of Medicines and Vaccines in Times of Pandemic: Practical, Conceptual, and Ethical Challenges in Pharmacovigilance
- Diverse nieuwsberichten in de media over Lareb en bijwerkingen

[1] In bijlage 1 vindt u de volledige referenties van de genoemde artikelen

We hebben op drie manieren informatie verzameld om de onderzoeksvragen te beantwoorden [2/2]

We voerden drie focusgroepen uit met verschillende stakeholders

Verschillende partijen en burgers hebben op verschillende manieren belang bij farmacovigilantie, en spelen verschillende rollen bij de uitvoering ervan. Middels de focusgroepen konden we op een efficiënte wijze verschillende perspectieven op het vraagstuk ophalen. In de focusgroepen nodigden we de gesprekspartners uit om hoofdzakelijk met ons en elkaar in gesprek te gaan over de beoogde impact van geneesmiddelenbewaking tijdens een toekomstige pandemie.

De drie focusgroepen bestonden uit:

- Eén groep met patiënten/burgers (10 deelnemers);
- Eén groep met professionals van fabrikanten (6 deelnemers);
- Eén groep met overheid/ketenpartners (10 deelnemers).

Initieel stond er ook een focusgroep met zorgprofessionals gepland, maar vanwege beperkte beschikbaarheid hebben we in plaats van één focusgroep drie semigestructureerde interviews gevoerd met zorgprofessionals.

We voerden 15 semigestructureerde interviews

Ook zijn we met verschillende stakeholders individueel in gesprek gegaan. We voerden semigestructureerde interviews aan de hand van een gespreksleidraad. Tijdens de interviews spraken we over drie onderwerpen:

1) geneesmiddelenbewaking in het algemeen
2) inrichting van geneesmiddelenbewaking tijdens een pandemie
3) de rol van Lareb tijdens een pandemie.

In totaal spraken we met 15 stakeholders. In **bijlage 2** vindt u een overzicht van alle gesprekspartners.

Farmacovigilantie of geneesmiddelenbewaking omvat zowel geneesmiddelen als vaccins. Tijdens de gesprekken is door gesprekspartners vooral gesproken over covid-19 vaccins en bleek dat er in algemene zin minder bekendheid was en/of aandacht uitging naar covid-19 geneesmiddelen.

3. Bevindingen

Onderdeel I. Een feitelijke beschrijving van farmacovigilantie op hoofdlijnen

Farmacovigilantie beslaat het opsporen, analyseren en voorkomen van bijwerkingen

Opsporen, evalueren, begrijpen en voorkomen van bijwerkingen

Geneesmiddelenbewaking of farmacovigilantie beslaat het opsporen, analyseren en voorkomen van bijwerkingen en andere aan geneesmiddelen gerelateerde problemen na het op de markt komen van een geneesmiddel of vaccin[2]. Door farmacovigilantie is het mogelijk om zicht te houden op de balans tussen de positieve effecten van geneesmiddelen en vaccins en de nadelige neveneffecten (bijwerkingen), zodat steeds de afweging kan worden gemaakt tussen *risks en benefits*. Formeel gezien start het farmacovigilantieproces na markttoelating van een geneesmiddel of vaccin; maar al voor markttoelating worden bijwerkingen geregistreerd door betrokken fabrikanten die input bieden voor het farmacovigilantieproces. Farmacovigilantie gaat over alle geneesmiddelen/vaccins die gebruikt worden, zowel officieel geregistreerd als niet-geregistreerd voor een bepaalde indicatie (off label gebruik). Vroeger was farmacovigilantie voornamelijk productgericht. Inmiddels is goed gebruik van geneesmiddelen/vaccins ook onderdeel van farmacovigilantie.

Farmacovigilantie is streng gereguleerd in Europese wetgeving

De regels rond farmacovigilantie staan in Europese wetgeving. Deze wetgeving vereist dat fabrikanten van geneesmiddelen en vaccins (handelvergunninghouders), nationaal bevoegde autoriteiten (zoals het CBG en Lareb in Nederland) en de European Medicines Agency (EMA) een aantal geneesmiddelenbewakingsprocessen volgen nadat een geneesmiddel of vaccin op de markt is toegelaten. Deze processen zijn uitgewerkt in de Good Pharmacovigilance Practices-documenten.

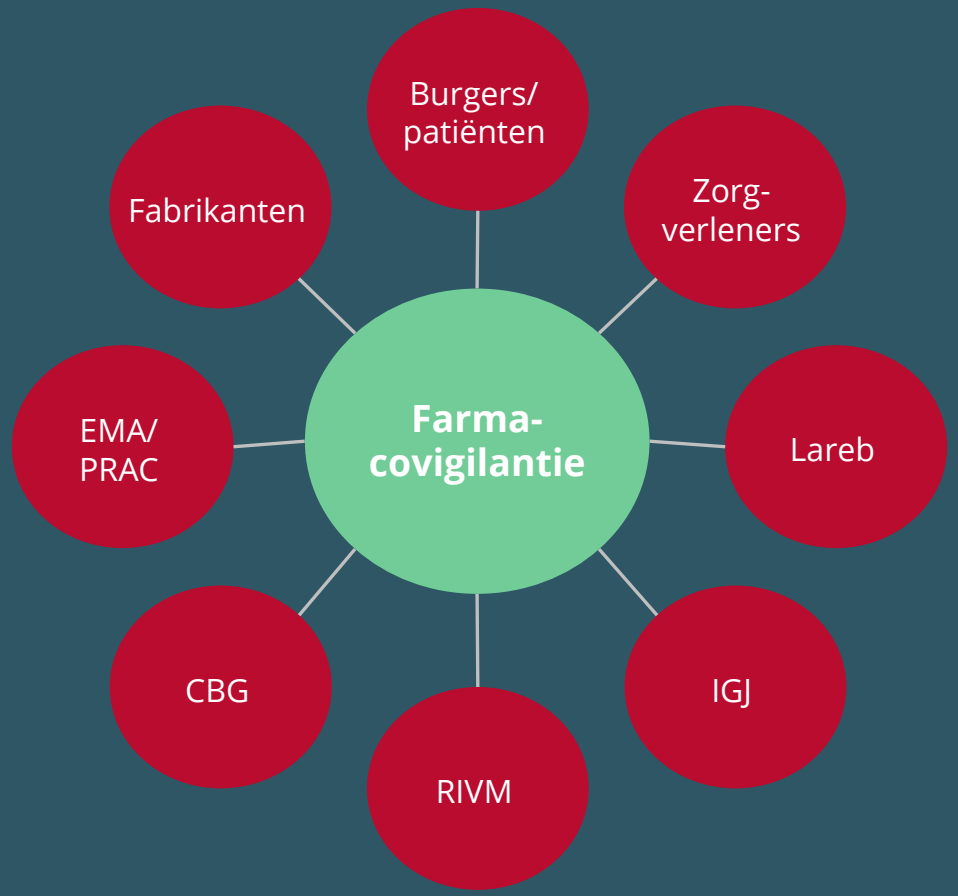
Op de volgende pagina's leest u:
- Een overzicht van de betrokken partijen bij farmacovigilantie
- Over de rol en werkzaamheden van Lareb
- Een schematische weergave van het farmacovigilantieproces

[2] European Medicines Agency. Pharmacovigilance: Overview. 2022.

Verschillende stakeholders zijn betrokken bij farmacovigilantie

Er zijn diverse stakeholders betrokken bij farmacovigilantie met ieder een eigen rol. Hieronder leest u op hoofdlijnen welke stakeholders betrokken zijn bij farmacovigilantie.

- **Fabrikanten:** c.q. handelsvergunninghouders zijn verantwoordelijk voor de kwaliteit en veiligheid van hun geneesmiddelen en vaccins. Ook na markttoelating registreren zij bijwerkingen en zijn zij verplicht deze te melden bij de autoriteiten.
- **EMA/PRAC:** de European Medicines Agency (EMA) is het Europese agentschap voor geneesmiddelenbeoordeling. De PRAC – het beoordelingscomité van de EMA – besluit over toelating van geneesmiddelen en vaccins op de Europese Markt. De EMA bewaakt ook na markttoelating de veiligheid van geneesmiddelen/vaccins.
- **CBG:** het College ter Beoordeling van Geneesmiddelen (CBG) is in Nederland verantwoordelijk voor geneesmiddelenbeoordeling. Het CBG besluit over toelating van geneesmiddelen/vaccins op de Nederlandse markt. Het CBG beoordeelt ook na markttoelating de risico-baten verhouding van geneesmiddelen/vaccins.
- **Burgers/patiënten:** burgers c.q. patiënten zijn gebruikers van geneesmiddelen en vaccins en kunnen zelf (of via hun zorgverlener) een melding doen van een bijwerking.
- **Zorgverleners:** zorgverleners kunnen een melding doen over een bijwerking van een geneesmiddel of vaccin (bij een ernstige bijwerking zijn ze dit verplicht).
- **Lareb:** Lareb is het meld- en kenniscentrum voor bijwerkingen van geneesmiddelen, vaccins en andere gezondheidsproducten. Op de volgende pagina leest u meer over de rol van Lareb.
- **IGJ:** de Inspectie Gezondheidszorg en Jeugd (IGJ) controleert of handelsvergunningshouders zich houden aan de wet- en regelgeving rondom farmacovigilantie. Zo voeren ze o.a. inspecties uit en kunnen ze maatregelen opleggen.
- **RIVM:** het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) coördineert de uitvoering van vaccinaties en beheert het landelijk registratiesysteem van vaccinaties*.



Tijdens de covidpandemie was er betrokkenheid van drie extra stakeholders:

- De **minister van VWS** neemt besluiten wie wanneer welk Covid-19 vaccin krijgt.
- De **Gezondheidsraad** adviseert over wie welk vaccin krijgt.
- **GGD'en** voeren de vaccinatie uit; evenals huisartsen en ziekenhuizen voor specifieke doelgroepen.

*Het RIVM beheerde het COVID-vaccinatie Informatie- en Monitoringsysteem (CIMS). In CIMS worden gegevens over de COVID-19-vaccinatie bijgehouden.

Lareb beheert in opdracht van het CBG het landelijke meldsysteem

Lareb is het onafhankelijk meld- en kenniscentrum voor bijwerkingen

Bijwerkingencentrum Lareb is het onafhankelijk meld- en kenniscentrum voor bijwerkingen van geneesmiddelen, vaccins en andere gezondheidsproducten. Iedereen kan vermoedens van bijwerkingen bij Lareb melden via een online meldformulier. Een team van deskundigen van Lareb bekijkt deze meldingen. Als de aard of het aantal van de meldingen daar aanleiding toe geeft, dan voeren de experts van Lareb een analyse uit. Hiervoor gebruikt Lareb alles wat er al bekend is over het geneesmiddel of vaccin. Bijvoorbeeld informatie uit andere meldingen en wetenschappelijk onderzoek. Zo ontdekt Lareb nieuwe kennis over bijwerkingen. Lareb verspreidt deze kennis vervolgens via nieuwsberichten en kennispagina's op de website, wetenschappelijke publicaties, artikelen voor zorgverleners, patiënten en algemeen publiek, de nieuwsbrief, social media en de media. Daarnaast doet Lareb ook eigen vragenlijstonderzoek.

Lareb ondersteunt het CBG bij diens taak in de geneesmiddelenbewaking

Lareb ondersteunt het CBG bij diens taak in de geneesmiddelenbewaking in Nederland en Europa door hen te informeren over nieuwe kennis over (mogelijke) bijwerkingen. Nieuwe kennis over (mogelijke) bijwerkingen worden besproken met het CBG (en als het vaccins betreft ook met het RIVM). Het CBG beslist vervolgens over de vervolgacties. Zo kan het CBG bijvoorbeeld de bijsluiter bij een geneesmiddel aanpassen of zorgverleners waarschuwen voor risico's. Ook kan het CBG een signaal over een mogelijk veiligheidsissue inbrengen bij het beoordelingscomité (PRAC) van het EMA.

Lareb beheert het spontaan meldsysteem voor bijwerkingen

Voor het ontdekken van nieuwe bijwerkingen en voor het beter in kaart brengen van reeds bekende bijwerkingen, zijn observaties uit de praktijk onmisbaar gebleken. Het spontaan meldsysteem voor bijwerkingen van Lareb speelt hierin een rol. De kracht van het meldsysteem is dat een optelsom van vermoedens (meldingen van voornamelijk zorgverleners, patiënten en handelsvergunninghouders), na goede analyses, nieuwe inzichten in bijwerkingen kan geven zoals het mogelijk bestaan van een nog onbekende bijwerking én inzicht in de omstandigheden waaronder deze ontstaat. Door het melden ervan komen klinische observaties van zorgverleners en ervaringen van patiënten op een centrale plek bij elkaar[3] [4] . Een substantieel deel van de gevonden veiligheidsrisico's voor geneesmiddelen en vaccins en daaruit volgende maatregelen komt voort uit spontane meldsystemen[5] [6].

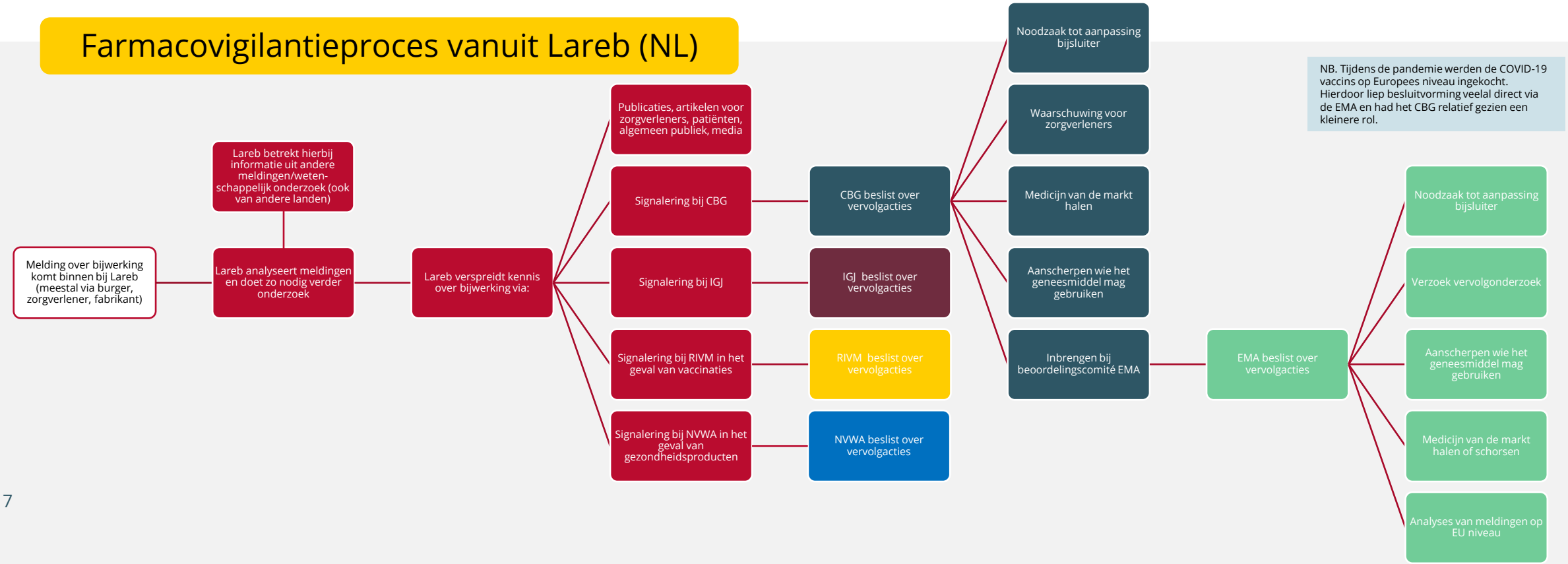
Tijdens de covidpandemie was Lareb een centrale speler in het bijhouden (en monitoren) van bijwerkingen van de COVID-19-vaccins en geneesmiddelen. Er werd door meerdere partijen (waaronder het CBG, de overheid en Lareb zelf) opgeroepen om bijwerkingen zo veel mogelijk te melden bij Lareb. Lareb heeft voor en tijdens de crisis zijn processen aangepast en waar mogelijk geautomatiseerd en nieuwe signaaldetectie methoden toegepast bij het verwerken van de COVID-19 meldingen. Ook heeft Lareb geprobeerd de veiligheid van off-label gebruik van bestaande geneesmiddelen en nieuwe producten voor de behandeling van COVID-19 in kaart te brengen.

[3] Kant A, van Hunsel,F., Somar,P. (2022). Coronavaccins, bijwerkingen en veiligheid. Medisch Contact
[4] van Puijenbroek E. (2017). Geneesmiddelen en bijwerkingen. Geneesmiddelenbulletin.
[5] Voysey M et al. (2021). Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials;
[6] Ramasamy MN et al, (2021). Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial.

Een schematische weergave van het farmacovigilantie-proces

De onderstaande figuur geeft een schematische weergave van de EU/nationale procedure rondom farmacovigilantie bezien vanuit Lareb. Hierin zijn de belangrijkste stappen en stakeholders bij het proces opgenomen. Het farmacovigilantieproces begint wanneer een patiënt een geneesmiddel of vaccin gebruikt. Als deze patiënt bijwerkingen ervaart, kunnen deze bijwerkingen worden gerapporteerd aan zorgverleners of direct bij Lareb. Alle Europese meldcentra, en dus ook Lareb, sturen hun meldingen ook door naar de **Europese databank (EudraVigilance)** van het EMA. Het EMA bewaakt de veiligheid op Europees niveau.

Farmacovigilantieproces vanuit Lareb (NL)



3. Bevindingen

Onderdeel II. Farmacovigilantie tijdens de pandemie

Farmacovigilantie in de pandemie | De bevindingen aan de hand van de doelenboom

In dit hoofdstuk zijn de bevindingen van het onderzoek weergegeven aan de hand van de doelenboom en geordend in termen van *input, throughput, output, outcome* en *impact.*

Op de volgende pagina geven we de kernbevindingen uit het onderzoek weer in één overzicht. Belangrijk hierbij is dat dit geen weergave is van het volledige farmacovigilantieproces, maar inzoomt op Lareb in relatie tot de keten. In de daaropvolgende pagina's worden de bevindingen per onderdeel van de doelenboom uitgebreid toegelicht.

Farmacovigilantie in de pandemie | De kernbevindingen in één overzicht

Input	Throughput	Output	Outcome	Impact
▹ Meldingen over bijwerkingen van vaccins/geneesmiddelen ▹ Achtergrondinformatie (o.a. aantallen mensen gevaccineerd) ▹ Inzichten uit (vragenlijst)onderzoek	▹ Registreren, analyseren van meldingen van bijwerkingen en vragenlijstonderzoeken t.b.v. het signaleren en delen van kennis over risico's	▹ Informatie over bijwerkingen (accuraat beeld van benefit/risk ratio) ▹ Communicatie-uitingen over bijwerkingen	▹ Besluitvorming overheid over gebruik vaccin/ geneesmiddel ▹ Uitleg over werking van farmacovigilantie-systeem ▹ Goede informatiepositie burgers/zorgverleners	▹ Veilig(e) medicatie/ vaccin(gebruik) ▹ Onderbouwd vertrouwen van de maatschappij in de veiligheid
Belangrijkste delta pandemie				
▹ Toename aantal meldingen na oproep ▹ Meer samenwerking nodig voor verkrijgen achtergrondinformatie ▹ Cruciale koppeling van gezondheidsdata niet mogelijk	▹ Processen moesten sneller (en soms parallel) doorlopen worden ▹ Vanwege beperkte capaciteit was niet al het onderzoek mogelijk ▹ Partijen werkten intensiever samen	▹ Meer (media) aandacht ▹ Rapporten/kennisdeling tussen stakeholders sneller/meer gedeeld ▹ Meer communicatie-uitingen op hetzelfde moment door verschillende partijen	▹ Grotere maatschappelijke behoefte aan transparantie, duidelijkheid	▹ De aard van de impact blijft gelijk, maar door de context van de pandemie is er meer twijfel over en aandacht voor en wordt er zwaarder getild aan veiligheid en vertrouwen

Input | Het aantal meldingen nam tijdens de pandemie substantieel toe; gelijktijdig zijn er verbetermogelijkheden

De input voor geneesmiddelenbewaking bestaat grofweg uit drie categorieën: meldingen over bijwerkingen van vaccins/geneesmiddelen door zorgprofessionals, farmaceutische industrie en/of burgers, achtergrondinformatie (o.a. aantal gevaccineerde mensen, achtergrondincidentie) en inzichten uit wetenschappelijk onderzoek door fabrikanten, academici en vragenlijstonderzoek van Lareb zelf.

Lareb ontving een enorme hoeveelheid meldingen van burgers

Tijdens de covidcrisis was er sprake van een enorme toename van het aantal meldingen van bijwerkingen, afkomstig van het grote aantal mensen dat tegelijkertijd werd gevaccineerd (zie p. 21). De oproep van Lareb om zoveel mogelijk te melden heeft er – volgens de ketenpartners en fabrikanten – mede toe geleid dat Nederland Europees gezien behoorde tot de landen met de meeste meldingen van burgers. Een groot deel van de ketenpartners en fabrikanten is van mening dat Lareb de mogelijkheid tot melden op verschillende manieren zichtbaar heeft gemaakt.

Niet alle burgers weten Lareb even goed te vinden

Tegelijkertijd geven enkele zorgprofessionals en burgers zelf aan dat ze Lareb in de praktijk niet altijd (voldoende) zichtbaar vonden. Zorgprofessionals merken dat burgers de weg naar Lareb niet altijd wisten te vinden en uitten zorgen over de toegankelijkheid van het melden voor burgers met beperkte gezondheidsvaardigheden of laaggeletterdheid. Tijdens de focusgroep met burgers kwam naar voren dat ze niet goed wisten dat ze zelf een melding konden doen bij Lareb. Geen van hen had ervaring met het doen van een melding. Burgers (uit de focusgroep) gaven aan enige terughoudendheid te voelen, omdat het moeilijk is om in te schatten ”of iets al dan niet een bijwerking is”. Volgens hen kunnen zorgverleners deze inschatting beter maken en zijn zij daarom geschikter om bijwerkingen door te geven aan Lareb. Bovendien hebben zorgverleners meer informatie over de patiënt, zoals eventueel ander medicatiegebruik, en kunnen zij de patiënt direct adviseren om te stoppen of over te stappen naar een ander geneesmiddel. Burgers vermeldden in de focusgroep dat ze deze informatie niet van Lareb kunnen krijgen en daarom niet direct de eigen/individuele meerwaarde zien in het maken van een melding.

Voor het melden door zorgverleners is verbetering mogelijk

Zorgverleners benoemden dat ze zich focussen op de behandeling van de bijwerking en geven aan dat het melden ervan geen prioriteit kent, met name bij patiënten met ernstige bijwerkingen. Zorgverleners benoemen dat het maken van een melding bij Lareb een extra administratieve handeling is die vanwege tijdsdruk te veel tijd vraagt. Hierdoor werden ernstige bijwerkingen tijdens de pandemie veelal op individueel niveau en onsystematische wijze bijgehouden door artsen, waardoor een van de zorgverleners zich afvraagt of belangrijke informatie wel altijd bij Lareb terecht is gekomen. Zorgverleners gaven aan dat het bijvoorbeeld zou helpen als gegevens over bijwerkingen uit het elektronisch patiëntendossier op een bepaalde manier gekoppeld kunnen worden met het systeem van Lareb, zodat bijwerkingen automatisch worden doorgegeven.

Input | Partijen werkten goed samen om tot de benodigde input te komen

Cruciale koppeling van zorgdata was in Nederland niet mogelijk tijdens de pandemie
Aan het begin van de pandemie kostte het in Nederland veel tijd om een vaccinatieregister op te zetten met gegevens over wie welk vaccin ontvangen heeft en kostte het Lareb extra inspanning om toegang te krijgen tot deze gegevens van het RIVM. Met deze vaccinatiegegevens kon Lareb na toestemming van de melder een koppeling maken tussen de gemelde bijwerking en het vaccin. Het was in Nederland echter niet mogelijk om vaccinatiegegevens te koppelen aan zorgdata. Hierdoor werd het uitvoeren van vervolgonderzoek en analyses om hypothesen over mogelijke bijwerkingen te toetsen bemoeilijkt. In veel andere EU-lidstaten was dit wel mogelijk. Nederland heeft hierdoor moeten varen op data van andere landen.

Samenwerking is nodig voor een goed beeld van de achtergrondincidentie
Daarnaast is het om de risico's van een bijwerking goed in kaart te kunnen brengen noodzakelijk het aantal meldingen over een bepaalde bijwerking af te zetten tegen hoe vaak de bijwerking naar verwachting voorkomt in een normale situatie, ofwel de achtergrondincidentie. Deze informatie was niet direct voorhanden tijdens de pandemie en vroeg om samenwerking met (internationale) stakeholders waaronder universiteiten/onderzoekscentra. Het merendeel van de stakeholders geeft aan dat dit tijdens de pandemie volop gebeurde, al kijken enkele ketenpartners hier wat kritischer naar en benoemen ze dat op dit vlak de samenwerking met universiteiten en onderzoekscentra verbeterd kan worden.

Tijdens de pandemie werden inzichten uit onderzoek goed gedeeld
Naast meldingen en achtergrondinformatie dienen inzichten uit wetenschappelijk onderzoek als input voor geneesmiddelenbewaking. Deze (vragenlijst)onderzoeken worden uitgevoerd door Lareb zelf, maar ook door fabrikanten, academici en andere onderzoeksinstellingen. Doordat de rol van Lareb pas begint als een vaccin of geneesmiddel is toegelaten tot de markt, beschikt Lareb niet over alle dossiers en inzichten over de veiligheid van vaccins of geneesmiddelen uit de eerste klinische studies. Tijdens de pandemie werden volgens fabrikanten en ketenpartners kennis en inzichten uit onderzoek internationaal goed verspreid.

Aantal bij Lareb ontvangen meldingen naar meldgroep [7]	2021	2020	Verschil in %
Patiënten	**190.714**	**8.495**	**2145**
Meldingen van geneesmiddelen en overige vaccins	14.289	8.495	68
Meldingen van COVID vaccins	178.569	n.v.t.	
Zorgverleners	**9.595**	**4.824**	**99**
Meldingen van geneesmiddelen en overige vaccins	3.532	4.824	-27
Meldingen van COVID vaccins	6.255	n.v.t.	

[7] Jaarverslag Bijwerkingencentrum Lareb 2021

Throughput | Stakeholders voerden dezelfde activiteiten sneller uit en werkten intensiever samen

Activiteiten (throughput) met betrekking tot farmacovigilantie bestaan uit het registreren, analyseren en monitoren van meldingen van bijwerkingen en het uitvoeren van vragenlijstonderzoeken ten behoeve van het signaleren en delen van kennis over risico's.

Tijdens de pandemie werden dezelfde activiteiten sneller uitgevoerd

Tijdens de pandemie werden grotendeels dezelfde activiteiten voor farmacovigilantie uitgevoerd. Het grote verschil zat in de snelheid waarmee processen doorlopen werden. Zo werd er afgeweken van de tijdslijnen die de EMA normaliter hanteert voor markttoelating en werden bepaalde processen parallel doorlopen in plaats van achter elkaar, zodat de vaccins sneller beschikbaar waren. Hierop werden in korte tijd grote groepen burgers gevaccineerd. Tegelijkertijd moest Lareb zo snel mogelijk alle bijwerkingen analyseren om eventuele ernstige bijwerkingen eruit te kunnen filteren. Het was tijdens de pandemie dus van belang dat betrokken organisaties tijdig konden opschalen naar de benodigde capaciteit.

De zorgvuldigheid is niet ten koste gegaan van de snelheid

Ketenpartners en fabrikanten benadrukken dat de zorgvuldigheid niet ten koste ging van de snelheid tijdens farmacovigilantie. Zo werd de veiligheid van vaccins bijvoorbeeld extra vaak gemonitord. Tegelijkertijd was niet alle gewenste informatie real-time beschikbaar en lukte het Lareb niet altijd om signalen sneller te kunnen bevestigen en tot meer informatie te komen. Hierdoor moest Lareb werken met een grote mate van onzekerheid. Hoewel Lareb snel en goed heeft geprobeerd op te schalen in personeel en automatisering van systemen, was er door de enorme drukte niet altijd voldoende capaciteit om bijvoorbeeld follow-up onderzoek uit te voeren. Ook bij fabrikanten speelde dit probleem. Enkele geïnterviewden zien overbelasting als een risico van de oproep van Lareb om alles zoveel mogelijk te melden.

De grote hoeveelheid aan reeds bekende bijwerkingen die nu ook gemeld werden kan er volgens hen voor zorgen dat weinig vóórkomende, nog onbekende bijwerkingen gemist zijn. Lareb geeft aan dat dit een bewuste afweging is geweest en middels goede triage bijwerkingen uit de meldingen kon filteren. Ook het merendeel van de stakeholders geeft aan dat Lareb snel en goed gewerkt heeft en het systeem in staat was om ernstige bijwerkingen uit de massale hoeveelheid meldingen te halen. Een PRAC-lid benoemt dat Lareb het ook internationaal gezien goed deed en nauwelijks achter liep met het verwerken van meldingen in vergelijking tot andere EU lidstaten.

Er werd intensiever samengewerkt tijdens de pandemie

Tijdens de pandemie werkten partijen intensiever samen en zochten ze elkaar eerder op. Zo werkte de EMA intensiever samen met fabrikanten, kwam het PRAC vaker bij elkaar en was er meer informele schakeling en informatie-uitwisseling tussen partijen als het RIVM, CBG en Lareb. Geïnterviewden geven aan dat de pandemie het belang van samenwerking en korte lijnen extra heeft benadrukt, zowel op nationaal als Europees niveau, om tot de benodigde informatie te komen.

De rolverdeling werd voor betrokken partijen duidelijker, voor externen niet

Ketenpartners en fabrikanten geven aan dat de rolverdeling tijdens de pandemie niet is veranderd, maar vooral verduidelijkt. Hierbij plaatsen ze de kanttekening dat dit voor de buitenwereld wellicht minder gold. Dit wordt bevestigd in de focusgroep met burgers. Ze geven aan dat de rol van Lareb en overheidspartijen voor hen onduidelijk is. Dit terwijl door meerdere stakeholders wordt benadrukt hoe belangrijk een duidelijke rolverdeling is voor het vertrouwen in het systeem van farmacovigilantie tijdens een pandemie.

Output | Communicatie over bijwerkingen was versnipperd en niet altijd afgestemd tussen partijen

Input voor farmacovigilantie levert middels throughput informatie en communicatie over bijwerkingen op. Deze communicatie en informatie worden door verschillende partijen in Nederland geuit, waaronder Lareb, het CBG en het RIVM.

Informatie over bijwerkingen lag onder een vergrootglas
Uit de interviews blijkt dat Lareb volgens de stakeholders goed in staat was om causale verbanden te leggen tussen vaccins en bijwerkingen en goed kon aangeven in welke mate ernstige bijwerkingen speelden in Nederland. Mede dankzij goede internationale samenwerking zijn ernstige bijwerkingen zoals TTS en myocarditis snel gesignaleerd. Tegelijkertijd was het vanwege de snelheid niet mogelijk om altijd direct tot 100% accurate informatie over de *risk-benefit* ratio te komen, wat laat zien in hoeverre de positieve effecten van een geneesmiddel opwegen tegen de negatieve effecten. Vanuit de maatschappij was er een grote behoefte aan deze informatie en dankzij de massale media-aandacht werd de beschikbare informatie onder een vergrootglas gelegd. Het grote aantal meldingen over bijwerkingen en de aandacht hiervoor kon volgens sommige ketenpartners bij burgers onterecht de indruk wekken dat er een groot individueel risico op bijwerkingen is. Mensen kunnen over het algemeen risico's moeilijk inschatten en duiden, waar Lareb volgens enkele zorgprofessionals een grotere rol had kunnen pakken door meer uitleg te geven over de risico's.

Lareb deelde informatie over bijwerking op verschillende manieren
Normaliter deelt Lareb informatie over bijwerkingen via officiële rapporten. Tijdens de pandemie werd informatie omwille van de snelheid op informele wijze gedeeld met relevante stakeholders. Daarnaast verspreidt Lareb kennis over bijwerkingen voor het algemene publiek via de website en de media. Lareb beantwoordde tijdens de pandemie ook vragen vanuit de media en was zichtbaar in interviews. Als onafhankelijke partij treedt Lareb naar buiten met informatie op het moment dat Lareb het maatschappelijk relevant vindt.

Communicatie-uitingen door verschillende partijen werden niet altijd afgestemd
Daartegenover staat dat Lareb soms informatie naar buiten bracht waar andere partijen nog niet van op de hoogte waren, waardoor zij zich op hun beurt niet goed konden voorbereiden op vragen vanuit de media. Een ander voorbeeld dat genoemd wordt in de interviews is dat Lareb al informatie publiceerde over een bijwerking waarvan het PRAC enkele dagen later zou bekijken of er wel of geen sprake is van een causaal verband met het vaccin. Vanuit de onafhankelijke positie van Lareb is er bij ketenpartners en fabrikanten begrip voor om eerder naar buiten te treden, maar tegelijkertijd wordt benoemd dat dit ook kan zorgen voor ruis. Naast Lareb communiceren fabrikanten, het CBG en het RIVM op hun beurt ook over bijwerkingen en de veiligheid van vaccins. Partijen proberen elkaar vooraf wel te informeren, maar dit gebeurt niet altijd. Hierdoor was er tijdens de pandemie sprake van verschillende en versnipperde informatie over bijwerkingen via verschillende organisaties.

Outcome | Duidelijkheid en transparantie waren onvoldoende aanwezig tijdens de pandemie

De hiervoor benoemde output dient onder andere voor besluitvorming door de overheid over het gebruik van vaccins en geneesmiddelen, uitleg over hoe bepaalde besluiten tot stand zijn gekomen, en om een goede informatiepositie voor burgers te bewerkstelligen. De beschreven outcome wordt slechts deels bepaald door output van Lareb, externe omstandigheden en activiteiten dragen hier ook aan bij.

Burgers waren in verwarring door versnipperde informatie

Tijdens de pandemie had de maatschappij vooral behoefte aan duidelijkheid. Wat kan je verwachten aan bijwerkingen wanneer je gevaccineerd wordt? Wat zijn de risico's hiervan? Hoe worden deze in kaart gebracht? Doordat deze informatie zo versnipperd en verschillend naar buiten werd gebracht tijdens de pandemie en de diverse rollen van betrokken partijen onvoldoende helder waren voor de buitenwereld, zorgde dit voor onduidelijkheid en verwarring onder burgers. Partijen spraken elkaar soms tegen en het was moeilijk om uit de brij van informatie te halen wat er precies aan de hand was. Een risico van onduidelijkheid over de verschillende rollen is volgens diverse stakeholders dat het farmacovigilantiesysteem "als één wordt gezien", terwijl door nagenoeg alle stakeholders wordt aangegeven dat het hebben van verschillende rollen zo belangrijk is voor het vertrouwen.

Transparantie over onzekerheden was helpend geweest

Daarnaast geven fabrikanten, zorgprofessionals, burgers en enkele ketenpartners aan dat het helpend zou zijn geweest als de overheid en andere partijen transparant zijn over onzekerheden, bijvoorbeeld dat sommige informatie over risico's van bijwerkingen nog niet compleet is en er meer tijd nodig is om dit uit te zoeken. Een ander voorbeeld hiervan is dat de besluitvorming tussen EU landen verschilde over het gebruik van vaccinaties. Het ene land stopte volledig met het gebruik van AstraZeneca vaccins, terwijl andere landen doorgingen. Dit zorgde voor verwarring en onrust onder de bevolking. Transparantie (en meer duidelijke communicatie) over dat, en waarom, Nederland soms andere afwegingen en keuzes maakt dan andere EU lidstaten was wenselijk geweest.

De balans tussen informeren en onrust voorkomen is gevoelig

Verschillende geïnterviewden benoemen dat het tijdens de pandemie moeilijk was om een goede balans te creëren tussen informeren en het voorkomen van onrust. Enerzijds is een bepaalde mate van wantrouwen van belang, veel effecten en risico's zijn nog onduidelijk en het is daarom goed om erop alert te zijn dat er van alles kan gebeuren. Anderzijds is dat niet de boodschap die de overheid wil uitdragen, het is maatschappelijk gezien belangrijk dat zoveel mogelijk mensen zich laten vaccineren en er is daardoor de neiging om burgers gerust te stellen. Een van de geïnterviewden geeft aan dat er vanuit deze laatste redenering onvoldoende aandacht is geweest voor de groep patiënten die onduidelijke of ernstige klachten heeft overgehouden na vaccinatie.

De onafhankelijke rol van Lareb ten opzichte van de overheid is belangrijk

Enkele fabrikanten en ketenpartners benoemen dat de objectieve communicatie vanuit Lareb over bijwerkingen rust heeft gebracht in het verhitte debat. Volgens hen is het grote aantal mensen dat zich heeft laten vaccineren mede hieraan te danken. Tegelijkertijd wordt genoemd dat dit niet direct een taak of doel van Lareb is. Lareb signaleert risico's, maar hierop volgende maatregelen of adviezen over de vaccinatiecampagne zijn niet aan hen.

Impact | Veiligheid en vertrouwen zijn tijdens een pandemie extra belangrijk (1/2)

Bij impact gaat het om de vraag aan welk (langdurig) maatschappelijk effect farmacovigilantie (en daarbinnen een meld- en kenniscentrum voor bijwerkingen) bijdraagt.

Verschillende stakeholders noemen dezelfde impact, maar benadrukken andere onderdelen
In de focusgroepen met diverse stakeholders worden dezelfde begrippen genoemd als het gaat om het maatschappelijke effect van farmacovigilantie: veiligheid, transparantie, vertrouwen en betrouwbaarheid. De verschillende stakeholders benadrukken echter elk andere aspecten. Burgers benoemen met name het belang van veiligheid en duidelijkheid, terwijl ketenpartners en fabrikanten zich eerder richten op het aspect van vertrouwen. Uit de interviews komen veiligheid en vertrouwen beide naar voren als voornaamste maatschappelijke effecten van farmacovigilantie.

Veiligheid bestaat uit product- en procesveiligheid
Met veiligheid worden zowel product- als procesveiligheid bedoeld. De veiligheid van een geneesmiddel of vaccin betekent veilig volgens de hieraan gestelde eisen in wet- en regelgeving. Dit komt er op neer dat de positieve effecten van een geneesmiddel opwegen tegen de negatieve effecten van een geneesmiddel, de zogenaamde *risk-benefit ratio*. Behalve dat het product veilig dient te zijn, is het ook belangrijk dat deze geneesmiddelen veilig gebruikt worden. Volgens sommige geïnterviewden is hier momenteel onvoldoende aandacht voor tijdens farmacovigilantie.

De maatschappij moet vertrouwen hebben in de veiligheid en het systeem
Naast veilig(e) medicatie(gebruik) is het belangrijk dat de maatschappij ook vertrouwen heeft in de veiligheid van geneesmiddelen en in de werking van het systeem dat zich hiermee bezig houdt. De maatschappij moet er op kunnen vertrouwen dat de risico's die er zijn zorgvuldig in kaart worden gebracht, en dat hierop geacteerd wordt om te zorgen dat een geneesmiddel een goede balans kent tussen veiligheid en effectiviteit.

De beoogde impact blijft gelijk, maar weegt zwaarder tijdens een pandemie
De impact van farmacovigilantie is volgens nagenoeg alle geïnterviewden niet anders tijdens een pandemie, maar door de veranderde context in de pandemie liggen veiligheid en vertrouwen onder een vergrootglas. Met name in de beginfase van de pandemie heerste er angst en onzekerheid onder de bevolking over het Covid-19 virus. In een stroomversnelling werd er onderzoek gedaan naar potentiële geneesmiddelen en vaccins. Vanuit de overheid werd een pakket aan maatregelen uitgedragen, waar op den duur een vaccinatiecampagne onderdeel van uitmaakte. Om het Covid-19 virus tegen te gaan werd de hele Nederlandse bevolking gevraagd zich (vrijwillig) te laten vaccineren, waardoor gezonde mensen massaal gevaccineerd werden. Mensen die ziek zijn kijken anders naar de veiligheid van een geneesmiddel en accepteren mogelijk meer en andere risico's dan gezonde mensen die preventief een vaccin nemen. De maatschappij stelde hierdoor hogere veiligheidseisen aan vaccins.

Impact | Veiligheid en vertrouwen zijn tijdens een pandemie extra belangrijk (2/2)

Zorgen voor onderbouwd vertrouwen is een uitdaging tijdens een pandemie
Gelijktijdig was er veel aandacht in de (sociale) media en vanuit de politiek voor de Covid-19 pandemie, geneesmiddelen en vaccinaties(fabrikanten) en eventuele bijwerkingen. Het creëren van vertrouwen tijdens een pandemie is hierom extra belangrijk. Ketenpartners en fabrikanten geven aan dat dit niet altijd gemakkelijk was tijdens de pandemie. Vertrouwen beslaat volgens hen niet alleen vertrouwen in het geneesmiddel, maar ook in het farmacovigilantiesysteem, in de overheid en alle betrokken instanties zoals de industrie. Er was een grote groep mensen die zich massaal verzette tegen het pakket aan maatregelen wegens gevoelens van wantrouwen richting autoriteiten. In combinatie met massale media-aandacht en desinformatie die verspreid werd via social media was het volgens geïnterviewden een uitdaging om te zorgen voor onderbouwd vertrouwen van de maatschappij.

4. Conclusies en aanbevelingen

De beoogde impact van farmacovigilantie gaat over veiligheid én onderbouwd vertrouwen

Farmacovigilantie beoogt in eerste instantie bij te dragen aan medisch inhoudelijke veiligheid – ook tijdens de covidpandemie

Farmacovigilantie moet bijdragen aan het veilig gebruik van een veilig product (geneesmiddelen en vaccins). Dit noemen we de "medisch inhoudelijke veiligheid". Een geneesmiddel of vaccin wordt als 'veilig' bestempeld als de positieve effecten van het geneesmiddel/vaccin in algemene zin opwegen tegen de nadelige neveneffecten (bijwerkingen). De veiligheid is niet beperkt tot 'productveiligheid', maar gaat ook over veilige toediening en veilig gebruik van een geneesmiddel of vaccin. Ook als het product wordt gebruikt voor een indicatie waar het product officieel niet voor is geregistreerd (*off-label* gebruik).

Farmacovigilantie speelt een belangrijke rol bij het tot stand komen van 'onderbouwd vertrouwen' van de maatschappij in de veiligheid van geneesmiddelen en vaccins

Farmacovigilantie biedt, met het bijdragen aan medisch inhoudelijke veiligheid, ook een belangrijke onderbouwing voor het vertrouwen van de maatschappij in de veiligheid van geneesmiddelen en vaccins. Dit omvat ook dat de maatschappij erop kan vertrouwen dat het farmacovigilantiesysteem dusdanig functioneert dat neveneffecten c.q. bijwerkingen van geneesmiddelen en vaccins tijdig worden opgespoord door de betrokken partijen, waardoor zij een juiste afweging kunnen maken tussen *risks* en *benefits*. Ook omvat dit dat de maatschappij erop vertrouwt dat er door de betrokken partijen/autoriteiten direct wordt ingegrepen als er nieuwe kennis wordt opgedaan over bijwerkingen en de risico's daarmee niet (meer) opwegen tegen de voordelen van het geneesmiddel of vaccin.

Met onderbouwd vertrouwen is het voor zorgverleners en burgers mogelijk om zelf een afweging te maken tussen *risks* en *benefits* van een geneesmiddel of vaccin en een weloverwogen beslissing te maken om een geneesmiddel of vaccin wel of niet te gebruiken.

In hoeverre er in de maatschappij sprake is van onderbouwd vertrouwen in geneesmiddelen en vaccins wordt beïnvloed door tal van andere factoren, waarvan een groot deel buiten de invloedsfeer van de keten van geneesmiddelenbewaking.

De beoogde impact blijft hetzelfde in een pandemie, maar de context maakt dat de veiligheid onder een vergrootglas ligt

De beoogde impact van farmacovigilantie - als het gaat om de medisch inhoudelijke veiligheid - stond niet ter discussie tijdens de Covid-19 pandemie

Tijdens de Covid-19 pandemie stond de beoogde impact van farmacovigilantie - als het gaat om medisch inhoudelijke veiligheid - niet ter discussie. De betrokken partijen binnen de farmacovigilantieketen voerden het farmacovigilantieproces evenwel, ondanks onzekerheden rondom het Covid-19 virus en de hogere input, uit conform (Europese) wet- en regelgeving.

Tijdens de Covid-19 pandemie moesten processen sneller en soms parallel worden uitgevoerd. Volgens geïnterviewde partijen kon het farmacovigilantieproces desalniettemin zorgvuldig worden doorlopen en is de farmacovigilantieketen – zoals op dit moment ingericht met verschillende partijen met verschillende rollen – functioneel gebleken.

De context van de Covid-19 pandemie maakte dat onderbouwd vertrouwen onder druk kwam te staan

Met name door de context van de Covid-19 pandemie ontstond druk op het vertrouwen in de medische inhoudelijke veiligheid door tal van factoren, en kwam het onder een vergrootglas te liggen. Zo was er lange tijd onzekerheid over de aard van het virus, was er in het algemeen een lager vertrouwen in overheidsinstanties en werden verschillende vormen van desinformatie verspreid. Bovendien leidde de vrijwillige vaccinatie van een groep gezonde mensen tot andere afwegingen bij groepen burgers over medisch inhoudelijke veiligheid.

Dit zorgde ervoor dat de betrokken partijen binnen het farmacovigilantiesysteem hun werk moesten doen onder toenemende druk. In algemene zin nam de hoeveelheid werk en daarmee onderlinge communicatie significant toe tijdens de Covid-19 pandemie. Niet alleen omdat de *input* hoger was, maar vooral omdat betrokken partijen, waaronder Lareb, moesten inspelen op de context om te streven naar onderbouwd vertrouwen van de maatschappij. Dit uitte zich concreet in een flinke toename van het aantal communicatieuitingen. Voor Lareb gold dat – omdat een groot deel van de bevolking zich liet vaccineren – de consequenties vele malen groter zouden zijn als een (ernstige) bijwerking niet zou worden gevonden.

Aanbevelingen

- Tijdens een pandemie verandert de context dusdanig dat er nog meer en andere invloeden van buitenaf spelen. Tijdens een pandemie wordt het daarom voor Lareb (in samenwerking met de keten) nóg belangrijker om oog te hebben voor- en flexibel in te kunnen spelen op ontwikkelingen van buitenaf, om zo te streven naar onderbouwd vertrouwen in de maatschappij.

De beoogde impact kan worden vergroot door te leren van de covidpandemie [1/4]

Op basis van de covidpandemie zijn lessen te trekken waarmee de medisch inhoudelijke veiligheid en het onderbouwd vertrouwen in geneesmiddelen en vaccins kan worden vergroot. Op deze en de volgende slides leest u concrete aanbevelingen die wij doen aan Lareb en de keten. We clusteren deze aan de hand van de doelenboom.

Meer transparantie over de verschillende rollen van partijen draagt bij aan meer onderbouwd vertrouwen

Op basis van ons onderzoek concluderen wij dat de meeste winst te behalen is met meer transparantie over de verschillende rollen van de verschillende partijen in het farmcovigilantieproces. Dit draagt eraan bij dat de maatschappij adviezen en besluiten rondom vaccinaties en bijwerkingen beter kan begrijpen. Tijdens de Covid-19 pandemie was het namelijk voor het brede publiek onvoldoende duidelijk welke partij welke rol vervult bij het bewaken van de veiligheid van covidvaccins. En waarom er op een bepaalde manier en op een bepaald moment werd gecommuniceerd over bijwerkingen van vaccins. Hierdoor werden sommige communicatie-uitingen, besluiten en adviezen soms onvoldoende begrepen en in enkele gevallen zelfs als tegenstrijdig ervaren. Daarnaast – als onvoldoende helder is welke partij welke rol vervult in de keten – wordt de farmacovigilantieketen al snel ”als één gezien”. Bij een laag vertrouwen in de overheid en/of fabrikanten, leidt dit direct ook tot minder vertrouwen in het systeem als geheel.

Voor onderbouwd vertrouwen is het extra belangrijk dat een meld- en kenniscentrum voor bijwerkingen onafhankelijk is gepositioneerd

Een onafhankelijk meld- en kenniscentrum voor bijwerkingen draagt bij aan onafhankelijk onderzoek en onafhankelijke communicatie over bijwerkingen. Op basis van ons onderzoek concluderen wij dat dit met name in een pandemie belangrijk is. Immers, een meld- en kenniscentrum voor bijwerkingen heeft er geen direct belang bij dat burgers zich wel of niet laten vaccineren, daar waar de overheid hier wel een belang bij heeft. Gelijktijdig is het wel belangrijk voor het onderbouwd vertrouwen van de maatschappij dat ‘het brede publiek’ de inhoud van communicatie-uitingen van partijen begrijpt en kan plaatsen (zie volgende pagina voor een toelichting op wat hiervoor nodig is).

Aanbevelingen *(outcome)*

- Draag zorg voor (meer) transparantie over de verschillende rollen van de verschillende partijen in de farmacovigilantieketen
  - Er is in algemene zin relatief weinig (voor het brede publiek) toegankelijke informatie te vinden over geneesmiddelenbewaking en de verschillende rollen van betrokken partijen bij farmacovigilantie. Wij adviseren om de informatievoorziening over rollen van partijen bij farmacovigilantie te verbeteren.
- Lareb kan de eigen onafhankelijke positie ten opzichte van het ministerie van VWS en CBG nog nadrukkelijker uitdragen.

De beoogde impact kan worden vergroot door te leren van de covidpandemie [2/4]

Voor meer onderbouwd vertrouwen is het nodig om te kunnen inspelen op elkaars communicatie-uitingen

Door de context van de Covid-19 pandemie was het nodig als farmacovigilantieketen om de hoeveelheid communicatie en daarmee de zichtbaarheid in de media (flink) te verhogen ten behoeve van het onderbouwd vertrouwen. Op basis van de beoogde outcome van farmacovigilantie doen wij allereerst de aanbeveling om de verschillende rollen van betrokken partijen te expliciteren in communicatie-uitingen (zie pagina hiervoor). Dit draagt eraan bij dat 'het brede publiek' begrijpt waar een bepaalde communicatie-uiting vandaan komt. Ten tweede doen wij de aanbeveling om waar mogelijk in te spelen op elkaars communicatie-uitingen. Voor het onderbouwd vertrouwen is het belangrijk dat partijen vanuit een eigen rol communiceren, gelijktijdig is het ook belangrijk dat 'het brede publiek' de inhoud van verschillende communicatie-uitingen goed kan begrijpen. Daarom is het wenselijk dat partijen elkaar op de hoogte brengen van de boodschap en het tijdstip van communiceren. Zo kunnen partijen hier in de eigen communicatie beter op inspelen zodat beter duidelijk is wie welke rol heeft en hoe de rollen zich tot elkaar verhouden. In algemene zin blijkt uit ons onderzoek dat Lareb met de optredens in de media heeft bijgedragen aan het vertrouwen dat er is geweest in de covidvaccins.

Aanbevelingen (*output*)

- Benadruk in communicatie-uitingen de eigen rol binnen de farmacovigilantieketen
- Pas communicatie-uitingen continu aan op de context van de pandemie, met inachtneming van de eigen rol. Breng elkaar zoveel mogelijk op de hoogte van het tijdstip en de inhoud van communicatie-uitingen.

De beoogde impact kan worden vergroot door te leren van de covidpandemie [3/4]

Een crisisstructuur met de keten draagt bij aan het kunnen inspelen op elkaars communicatie-uitingen

Meer en sneller werk van betrokken partijen vraagt ook automatisch om meer en snellere communicatie onderling. Tijdens de covid-19 pandemie bleek de overlegstructuur tussen VWS, RIVM, CBG en Lareb redelijk goed te werken; al werden organisaties onderling toch soms verrast door (de inhoud van) elkaars uitingen in de pers. We adviseren daarom om op dit moment al na te denken over een crisis/overlegstructuur met de belangrijkste partijen in het farmacovigilantieproces. Ook in communicatie en samenwerking internationaal is winst te behalen; met name tussen de partijen die vanuit de lidstaten adviseren over de vaccinaties. Immers, het draagt niet bij aan 'onderbouwd vertrouwen' als Nederland een bepaald vaccin adviseert voor een bepaalde doelgroep en een van onze buurlanden dat niet doet.

Betrokken organisaties moeten tijdig kunnen opschalen naar voldoende absorptievermogen

Tijdens de covidcrisis bleek dat (substantieel) verhoogde input vraagt om meer en sneller werk van alle betrokken partijen. Tijdens een volgende pandemie is – met het oog op de beoogde impact - het snel kunnen opschalen naar de benodigde capaciteit/organisatieomvang op basis van de verhoogde input cruciaal. Als het niet lukt om tijdig op te schalen naar de benodigde capaciteit/organisatieomvang loopt men het risico dat het farmacovigilantieproces vastloopt. We adviseren daarom betrokken partijen het absorptievermogen van de eigen organisatie onder de loep te nemen en lessen te trekken uit de covid-19 pandemie.

In 2022 heeft Andersson Elffers Felix in opdracht van Lareb onderzoek gedaan naar het functioneren van de Lareb organisatie tijdens de covidpandemie. Op basis van dit onderzoek hebben we geconcludeerd dat Lareb daadkrachtig heeft gehandeld om de crisis het hoofd te bieden. Gelijktijdig hebben we geconcludeerd dat Lareb onvoldoende toegerust was op een verdubbeling van het aantal medewerkers – de capaciteit die nodig was om het extra werk te verzetten. In bijlage 3 leest u de volledige hoofdboodschap van dit onderzoek.

Aanbevelingen (*throughput*)

- Draag zorg met de keten voor een crisisstructuur/overlegstructuur tijdens een pandemie om te kunnen inspelen op elkaars communicatie-uitingen.
- Zorg ervoor dat het absorptievermogen van de organisaties van betrokken partijen in het farmacovigilantiesysteem.
- Uit ons onderzoek blijkt dat sommige processen sneller/parallel konden worden uitgevoerd en dat dit in algemene zin niet heeft afgedaan aan de zorgvuldigheid. We doen de aanbeveling om (eventueel in Europees verband) nader te onderzoeken welke processen aangepast kunnen worden ter voorbereiding op een volgende pandemie.

De beoogde impact kan worden vergroot door te leren van de covidpandemie [4/4]

Om de input te verbeteren is het nodig om te investeren in de technische (data)infrastrucuur

Aan het begin van de pandemie kostte het in Nederland veel tijd om een vaccinatieregister op te zetten met gegevens over wie welk vaccin ontvangen heeft en kostte het Lareb extra inspanning om toegang te krijgen tot deze gegevens van het RIVM. Met deze vaccinatiegegevens kon Lareb na toestemming van de melder een koppeling maken tussen de gemelde bijwerking en het vaccin. Het was in Nederland echter niet mogelijk om vaccinatiegegevens te koppelen aan zorgdata. Hierdoor werd het uitvoeren van vervolgonderzoek en analyses om hypothesen over mogelijke bijwerkingen te toetsen bemoeilijkt. Met het oog op een volgende pandemie is het investeren in zo'n koppeling nodig.

Daarnaast is het wenselijk dat informatie over bijwerkingen direct uit het systeem van zorgverleners in het meldsysteem van Lareb kan worden geïmporteerd. Dit heeft als voordeel dat met name huisartsen bijwerkingen maar één keer hoeven te registreren (aan de bron, in het huisartsensysteem) waardoor administratieve lasten ingeperkt worden en naar verwachting het aantal (en de kwaliteit van de) meldingen bij Lareb zal toenemen.

Ook omvat het investeren in de technische (data)infrastructuur het blijvend investeren in het meldsysteem van Lareb. Op basis van de Covid-19 pandemie kan geconcludeerd worden dat de waarschuwingssystemen in het systeem werken; gelijktijdig ontbrak het aan een systeem om signalen sneller te kunnen bevestigen om zo tot meer informatie over bijwerkingen te kunnen komen. Bij een volgende pandemie is het wenselijk dat er bij een vermoeden van een ernstige bijwerking Lareb beschikking heeft over snellere technische mogelijkheden om deze vermoeden te verifiëren.

De (naams)bekendheid van Lareb kan beter richting doelgroepen met minder gezondheidsvaardigheden

In vergelijking met Europa is Lareb als meldcentrum voor bijwerkingen vrij bekend bij zowel burgers als zorgaanbieders; maar de (naams)bekendheid van Lareb en het belang van melden vraagt blijvend aandacht. Met name doelgroepen met minder gezondheidsvaardigheden wisten de weg tijdens de Covid-19 pandemie onvoldoende naar Lareb te vinden. Dat geldt zowel voor het doen van een melding als voor het verkrijgen van informatie over bijwerkingen.

Aanbevelingen (*input*)

- Investeer in de technische (data)infrastructuur (met inachtneming van de privacyregels)
  - Maak het mogelijk om vaccindata te koppelen aan zorgdata
  - Maak het mogelijk voor zorgprofessionals om via het eigen systeem een melding van een bijwerking te doen
  - Blijf investeren in het meldsysteem van Lareb
- Investeer in de (naams)bekendheid van Lareb als meld- en kenniscentrum, met name richting doelgroepen met minder gezondheidsvaardigheden

Regulatoire pandemische paraatheid vraagt om het denken in scenario's over de context van een volgende pandemie

Maak scenario denken onderdeel van regulatoire pandemische paraatheid

De beoogde impact van farmacovigilantie verandert niet tijdens een volgende pandemie. De context van een volgende pandemie is naar verwachting wél anders. Daar waar tijdens de covidpandemie transparantie extra belangrijk werd voor het onderbouwd vertrouwen in de veiligheid, kan het zijn dat in een volgende pandemie andere zaken belangrijk(er) zijn. Denk bijvoorbeeld aan snelheid mochten we geconfronteerd worden met een (veel) ziekmakender virus.

Onderdeel van regulatoire pandemische paraatheid is het nadenken in scenario's over de context van een volgende pandemie en de invloed daarvan op de medisch inhoudelijke veiligheid én op het onderbouwd vertrouwen van de maatschappij in de veiligheid van vaccins en geneesmiddelen. Als bijvoorbeeld snelheid belangrijker wordt door de context van een volgende pandemie, dan kan dit meer consequenties hebben voor de processen en het naleven van de wet- en regelgeving in algemene zin.

Aanbeveling

- We adviseren – als onderdeel van regulatoire pandemische paraatheid – om te denken in scenario's over de context van een volgende pandemie en de invloed daarvan op de medisch inhoudelijke veiligheid én het onderbouwd vertrouwen van de maatschappij in de veiligheid van vaccins en geneesmiddelen.

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Bijlage 2. Gesprekspartners

Interviews

- Instituut Verantwoord Medicijngebruik (IVM) – Ruud Coolen van Brakel – Directeur
- European Medicines Agency (EMA) – Menno van der Elst – lid Pharmacovigilance Risk Assessment Committee (PRAC) EMA
- Ministerie van Volksgezondheid, Welzijn en Sport – Ilja van Bergen en Gwen Soete – Beleidsmedewerker team vaccinaties / MT-lid COVID vaccinaties
- Lareb – Eugene van Puijenbroek, Florence van Hunsel en Agnes Kant – Hoofd wetenschap & onderzoek / Hoofd Veiligheidsinnovatie / directeur
- Pfizer – Barbara de Bernardi, Nicola Machella, Lisette Swanenburg – QPPV / Country Safety Officer NL / Senior Safety Officer
- College ter Beoordeling van Geneesmiddelen (CBG) – Ton de Boer – Voorzitter
- Rijksinstituut voor Volksgezondheid en Milieu (RIVM) – Hans van Vliet – Programmamanager COVID-19 vaccinatieprogramma
- Universitair Medisch Centrum Utrecht (UMCU) – prof. dr. Miriam Sturkenboom – Hoogleraar Datascience & Biostatistics
- Marleen Kraaij-Dirkzwager – Arts Maatschappij en Gezondheid
- Erasmus Medisch Centrum (Erasmus MC) – Maurits van Maaren – Internist, allergoloog, immunoloog
- Amsterdam Universitair Medische Centra (UMC) – Michiel Agtmael - Internist infectieziekten en hoogleraar klinische farmacologie
- Bureau Wibaut – Jop de Vrieze – Wetenschapsjournalist
- Patiëntenfederatie Nederland – Jan Benedictus - Programmamanager
- Vereniging Innovatieve Geneesmiddelen (VIG) – Peter Bertens – Manager Innovatie & Business Climate
- Landelijke Huisartsen Vereniging (LHV) – Iddo de Ruiter – Huisarts en beleidsmedewerker LHV

Focusgroep overheid/ketenpartners

- College ter Beoordeling van Geneesmiddelen (CBG)
- Centrale Commissie Mensgebonden Onderzoek (CCMO)
- Inspectie Gezondheidszorg en Jeugd (IGJ)
- Ministerie van Volksgezondheid, Welzijn en Sport (VWS)
- Rijksinstituut voor Volksgezondheid en Milieu (RIVM)

Focusgroep professionals vanuit de farmaceutische industrie

- Pfizer
- Nederlandse Vereniging voor Farmaceutische Geneeskunde (NVFG)
- Gilead
- Merck
- Janssen

Bijlage 3. Hoofdboodschap onderzoeksrapport over het functioneren van Lareb in de covid-19 pandemie [1/2]

In de covidperiode kreeg Lareb een dubbele crisis te verwerken. Covid leidde tot een ongekende toename van het aantal meldingen én tot een crisis net als bij alle andere organisaties, waardoor medewerkers plotseling moesten thuiswerken en er onzekerheid bestond over ieders gezondheid.

Het is bewonderenswaardig dat het Lareb gelukt is om de reguliere meldingen én de meldingen over de covidvaccins tijdig te verwerken. We hebben hiervoor in onze evaluatie een aantal succesfactoren geïdentificeerd. Gelijktijdig zien we ook een aantal lessen voor de toekomst.

Lareb heeft daadkrachtig gehandeld om de crisis het hoofd te bieden

Lareb was niet voorbereid op een crisis van deze omvang. Ondanks dat werd bij aanvang van de crisis door de directie een stevig besluit genomen: naast het covid gerelateerde werk moest ook het reguliere proces doorgaan. Dat dit besluit snel werd genomen, zorgde ervoor dat Lareb daadkrachtig kon handelen in de voorbereiding. Maar toen bleek dat het aantal meldingen een stuk hoger lag dan was ingeschat, heeft dat niet direct tot bewuste herijking geleid van het genomen besluit en/of tot het stellen van prioriteiten. Dit past bij een organisatie die gaat voor het hoogst haalbare. Hiermee heeft de organisatie echter ook een risico genomen met betrekking tot welzijn van medewerkers en kwaliteit van het werk. We bevelen aan om bij een toekomstige crisis meer structureel de effecten in de organisatie te monitoren, en te reflecteren of er aanleiding is voor nadere prioritering of bijsturing op gemaakte keuzes.

Een effectieve crisisstructuur vraagt om heldere aansturing

Intern is een crisisstructuur opgezet: een kernteam voor besluitvorming én een covidteam voor het (operationele) covid gerelateerde werk. Door het covidwerk los te knippen van het reguliere werk kon Lareb effectief optreden. Een medewerker uit elk kernproces werd naar het covidteam overgeheveld, waardoor de '*braindrain*' in de reguliere kernprocessen beperkt bleef. Op het niveau van de hoofden werd geen expliciet besluit genomen wie het covidproces moest aansturen. Dat leidde ertoe dat er onduidelijkheid bestond over de aansturing van het covidwerk. We bevelen aan om in een toekomstige crisissituatie een expliciet besluit te nemen over de aansturing van het crisisteam en dit helder te communiceren in de organisatie.

De organisatie is versneld geprofessionaliseerd

Lareb is een platte organisatie. Alleen de twee directieleden zijn formeel leidinggevenden. De hoofden stuurden de kernprocessen aan, geen mensen. In de covidperiode werd zichtbaarder dat dit model niet werkte. De hoofden voelden zich ook verantwoordelijk voor de mensen, maar waren dit formeel niet. Ook beschikten zij niet over de tijd om de ontwikkeling van mensen te ondersteunen. Lareb heeft de geleerde les op dit onderdeel al opgepakt: er zijn teams en (mensgerichte) teamleiders geïntroduceerd. Het is knap dat dit tijdens de covidperiode is gelukt. Ook in de automatisering zijn flinke slagen gemaakt. In algemene zin concluderen wij dat de covidperiode ervoor heeft gezorgd dat Lareb een versnelde professionalisering van de organisatie heeft doorgemaakt.

Bijlage 2. Hoofdboodschap onderzoeksrapport over het functioneren van Lareb in de covid-19 pandemie [2/2]

Lareb was onvoldoende toegerust op een verdubbeling van het aantal medewerkers

Lareb handelde proactief in de opschaling. Extra financiële middelen werden tijdig aangevraagd, waardoor Lareb snel kon opschalen in mensen en in automatisering. Echter, bij de opschaling in mensen bleek dat de organisatie onvoldoende was toegerust op een verdubbeling van het aantal medewerkers. De werving vroeg veel van de medewerker die belast was met het HR-proces en het proces was niet toegerust op grote aantallen. Lareb beschikte bovendien over te weinig gekwalificeerde medewerkers die gelijktijdig de werkprocessen konden uitvoeren én mensen konden inwerken. We bevelen aan om te zorgen voor een basis van voldoende gekwalificeerde medewerkers die het inwerken van collega's voor hun rekening kunnen nemen. Daarnaast bevelen we aan om het wervings- en inwerkproces te optimaliseren.

De organisatie van externe communicatie was krachtig én kwetsbaar

In de praktijk lag de externe communicatie, waaronder de woordvoering over meldingen gerelateerd aan covidvaccins, hoofdzakelijk bij de directeur. Hierdoor heeft Lareb naar buiten één lijn uitgedragen, die er volgens stakeholders aan heeft bijgedragen dat Lareb een belangrijke rol heeft gespeeld in het vertrouwen dat er is geweest in de covidvaccins. De keuze om de externe communicatie hoofdzakelijk te beleggen bij één persoon is dus krachtig gebleken, maar is tegelijk ook kwetsbaar. In een volgende crisis kan de uitvoering van de communicatiestrategie breder (in een team) binnen de organisatie worden belegd. Zo is bij uitval overname mogelijk en kan het woordvoerderschap stevig inhoudelijk en procesmatig worden ondersteund.

Het succes van Lareb is grotendeels te danken aan de toewijding van mensen

In algemene zin concluderen wij dat zowel directie als medewerkers zich in de covidperiode met enorme toewijding en een groot verantwoordelijkheidsgevoel hebben ingezet. Hierdoor zijn bergen werk verzet. Dit heeft ook een keerzijde: de werkdruk bij individuele medewerkers was hoog. Hier is aandacht voor geweest, maar dit is niet door iedereen als voldoende gevoeld. Een geleerde les voor de toekomst is om explicieter aandacht te besteden aan de impact van een crisis op het werk en op de mensen. Het is daarom aan te raden om reflectie en debriefing structureel en organisatiebreed onderdeel te maken van de crisisstrategie. Eventueel kan het zinvol zijn om een crisismanager aan te stellen, die reflectie inbouwt en de directie wijst op eventuele bottlenecks in de crisisstrategie.

Meer weten?

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