UNIVERSIDADE D
COIMBRA

Inês Filipa Guerra Tavares

Identification of Unknown and Serious Adverse Drug Reactions for COVID-19 Vaccines in Spontaneous Reports Received by the Pharmacovigilance Unit of Coimbra

Dissertação no âmbito do Mestrado em Biotecnologia Farmacêutica orientado pelo Professor Doutor Francisco Batel Marques e apresentada à Faculdade de Farmácia da Universidade de Coimbra.

Fevereiro de 2023

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IDENTIFICATION OF UNKNOWN AND SERIOUS ADVERSE DRUG REACTIONS FOR COVID-19 VACCINES IN SPONTANEOUS REPORTS RECEIVED BY THE PHARMACOVIGILANCE UNIT OF COIMBRA

Dissertação apresentada na Faculdade de Farmácia da Universidade de Coimbra para a obtenção do grau de Mestre em Biotecnologia Farmacêutica sob a orientação científica do Professor Doutor Francisco Batel Marques.

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Resumo

Introdução

A pandemia causada pela infeção por SARS-CoV-2, responsável pela doença COVID-19, motivou o desenvolvimento clínico acelerado das vacinas atualmente disponíveis, devido à urgência na necessidade da vacinação em massa da população. Consequentemente, o perfil de segurança das vacinas encontra-se incompletamente estabelecido. Neste sentido, foi notável a contribuição dos profissionais de saúde e utentes na notificação de suspeitas de reações adversas às vacinas contra a COVID-19. A Unidade de Farmacovigilância de Coimbra (UFC) recebeu, entre 30 de dezembro de 2020 e 31 de dezembro de 2021, 2322 notificações espontâneas. De entre a iatrogenia identificada, foram detetadas reações adversas desconhecidas à data de introdução no mercado. Assim, torna-se necessário identificar e avaliar a iatrogenia desconhecida notificada, bem como desagregar a informação quanto à gravidade e causalidade imputadas, contribuindo substantivamente para o conhecimento do perfil de segurança e posterior inclusão desta informação na avaliação das relações benefício-risco.

Objetivo

Definiu-se como objetivo primário do estudo a identificação da iatrogenia desconhecida constante das notificações espontâneas remetidas à UFC.

Definiram-se como objetivos secundários do estudo a caracterização da iatrogenia desconhecida identificada de acordo com variáveis demográficas (sexo, idade e natureza dos notificadores), gravidade e causalidade, bem como a comparação da iatrogenia desconhecida identificada entre as diversas vacinas em utilização.

Métodos

A identificação das vacinas contra a COVID-19 atualmente utilizadas em Portugal foi realizada com recurso à base de dados Infomed. A informação foi complementada com os registos disponíveis no website da Agência Europeia do Medicamento (EMA).

A identificação e caracterização das reações adversas foi realizada através da análise das notificações espontâneas remetidas à UFC durante o período de 1 ano (entre 30 de dezembro de 2020 e 31 de dezembro de 2021).

Resultados

Quatro vacinas contra a COVID-19 foram identificadas como tendo sido administradas à população portuguesa durante o ano de 2021: Comirnaty, Spikevax previously COVID-19 Vaccine Moderna, Vaxzevria previously COVID-19 Vaccine AstraZeneca and JCOVDEN (previously COVID-19 Vaccine Janssen). A UFC recebeu 2322 notificações espontâneas (NE)

contendo pelo menos uma reação adversa a medicamento (RAM) associada a pelo menos uma vacina contra a COVID-19: 1469 notificações (4382 RAM) associadas a Comirnaty, 476 notificações (1544 RAM) associadas a Vaxzevria, 195 notificações (545 RAM) associadas a Spikevax e 180 notificações (437 RAM) associadas a JCOVDEN. Das notificações espontâneas identificadas, 1016 (43,70%) foram consideradas Graves e 646 (27,78%) foram consideradas Não Descritas. As RAM mais frequentemente notificadas encontram-se categorizadas nas Classes de Sistemas e Órgãos (SOC) "Perturbações gerais e alterações no local de administração", "Afecções musculosqueléticas e dos tecidos conjuntivos" e "Doenças do sistema nervoso".

Conclusões

A notificação espontânea foi determinante na identificação de várias reações adversas previamente não descritas no Resumo das Características do Medicamento (RCM) das vacinas contra a COVID-19. Esta informação contribuiu para um melhor conhecimento do perfil benefício-risco das vacinas. A pandemia COVID-19 esteve associada a um aumento da notificação espontânea. A manutenção destes esforços permitirá minimizar as limitações conhecidas da notificação espontânea.

Palavras-chave

Vacinas contra a COVID-19; reação adversa a medicamento; notificação espontânea.

Abstract

Introduction

The pandemic caused by SARS-CoV-2 infection, responsible for the COVID-19 disease, motivated the accelerated clinical development of the vaccines currently available, due to the urgency in mass vaccination of the population. Consequently, the safety profile of these vaccines is incompletely established. Therefore, there was a notable contribution on behalf of healthcare professionals and consumers in reporting suspected Adverse Drug Reactions (ADRs) to the COVID-19 vaccines. The Pharmacovigilance Unit of Coimbra (UFC) received, between December 30th 2020 and December 31st 2021, 2322 Spontaneous Reports (SRs). Within the identified ADRs, unknown ADRs were detected. Subsequently, it is necessary to identify and evaluate the notified unknown ADRs, as well as to disaggregate the information regarding seriousness and causality, providing a substantial contribution to the knowledge of the vaccines' safety profile, and its subsequent inclusion in the evaluation of benefit-risk ratio.

Aim

The primary objective of this study was to identify unknown ADRs for COVID-19 vaccines among spontaneous reports received by the UFC.

The secondary objective of the study was to characterize unknown ADRs according to demographic variables (sex, age and reporter origin), seriousness and causality, as well as comparing unknown ADRs among the administered vaccines.

Methods

The identification of COVID-19 vaccines currently used in Portugal was performed using the Infomed database. The information was further complemented with the data available on the European Medicines Agency (EMA) website.

The identification and characterization of ADRs was performed through the analysis of spontaneous reports received by UFC in a 1-year period (from December 30th 2020 to December 31st 2021).

Results

Four COVID-19 vaccines were identified as administered to the Portuguese population during the year of 2021: Comirnaty, Spikevax previously COVID-19 Vaccine Moderna, Vaxzevria previously COVID-19 Vaccine AstraZeneca and JCOVDEN (previously COVID-19 Vaccine Janssen). The UFC received 2322 spontaneous reports containing at least one ADR associated with at least one COVID-19 vaccine: 1469 reports (4382 ADRs) associated with Comirnaty, 476 reports (1544 ADRs) associated with Vaxzevria, 195 reports (545 ADRs) associated with Spikevax and 180 reports (437 ADRs) associated with JCOVDEN. Of the identified

spontaneous reports, 1016 (43.70%) were Serious and 646 (27.78%) were Unknown. The most frequently reported ADRs are comprised in System Organ Classes (SOC) "General disorders and administration site conditions", "Musculoskeletal and connective tissue disorders" and "Nervous system disorders".

Conclusions

Spontaneous reporting allowed for the identification of many previously unknown ADRs in the Summary of Product Characteristics (SmPC) of all COVID-19 vaccines. These findings allowed for an improved knowledge of the benefit-risk ratio for these vaccines. The COVID-19 was associated with an increase of spontaneous reports. These efforts should be continuously maintained in order to minimize the known limitations of spontaneous reporting.

Keywords

COVID-19 vaccines; adverse drug reactions; spontaneous reporting.

Index

List of Abbreviations

ADR	Adverse Drug Reaction
AIBILI	Association for Innovation and Biomedical Research on Light and Image (from Portuguese, *Associação para Investigação Biomédica e Inovação em Luz e Imagem*)
COM	Comirnaty
COVID-19	Coronavirus Disease 2019
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HCP	Healthcare Professional
INE	National Institute of Statistics (from Portuguese, *Instituto Nacional de Estatística*)
JCO	JCOVDEN (previously COVID-19 Vaccine Janssen)
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
PT	Preferred Term
RNA	Ribonucleic Acid
SARS-CoV-2	Serious Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of Product Characteristics
SNF	National Pharmacovigilance System (from Portuguese, *Sistema Nacional de Farmacovigilância*)
SPI	Spikevax previously COVID-19 Vaccine Moderna
SR	Spontaneous Report
UFC	Pharmacovigilance Unit of Coimbra (from Portuguese, *Unidade de Farmacovigilância de Coimbra*)
UMC	Uppsala Monitoring Centre
URF	Regional Pharmacovigilance Unit (from Portuguese, *Unidade Regional de Farmacovigilância*)
VAX	Vaxzevria previously COVID-19 Vaccine AstraZeneca
WHO	World Health Organization

Table Index

Figure Index

I. Introduction

Introduction

COVID-19, which stands for coronavirus disease 2019, is caused by the infection with SARS-CoV-2 (serious acute respiratory syndrome coronavirus 2). Signs and symptoms include fever, dry cough, dyspnoea, fatigue, nausea/vomiting or diarrhoea, and myalgia. Olfactory and/or gustatory dysfunctions such as anosmia or ageusia have also been reported. Complications of COVID-19 may include impaired function of many organs, such as the heart, brain, lung, liver, kidney and coagulation system (1).

According to the World Health Organization's (WHO) COVID-19 dashboard, there have been near 580 million confirmed cases of COVID-19, including 6.5 million deaths. In Portugal, there have been 5.3 million confirmed cases, including 24.500 deaths (2). The rapid spread of this disease, detected in late 2019 in the province of Wuhan, China, has urged researchers worldwide to produce not only effective treatments, but also to develop vaccines.

The underlying mechanism of COVID-19 vaccines consists of coding the Spike (S) protein, composed by two sub-units (S1 and S2), which play a major role in receptor recognition and cell membrane fusion process (3). Through messenger ribonucleic acid (mRNA) (for Comirnaty® and Spikevax® vaccines) or adenoviral vectors (for Vaxzevria® and JCOVDEN® vaccines), it is possible to induce production of the Spike protein within the human organism, preparing its immune response in the event of an infection.

These vaccines were granted a conditional marketing authorisation within the scope of rolling review, a regulatory tool that allows continuous assessment of data for an upcoming application as it becomes available (4). Subsequently, a mass vaccination process began. In Portugal, risk groups such as the elderly and healthcare professionals were prioritized. After vaccine production was increased and costs were reduced, other groups were considered into the vaccination plan, eventually reaching children, with a paediatric formulation already available for Comirnaty (5-11 years old).

With limited information regarding the Adverse Drug Reactions (ADR) for COVID-19 vaccines, they were placed under additional monitoring, a pharmacovigilance activity which aims to enhance reporting of suspected ADRs.

Pharmacovigilance can be defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related

problem, such as medication errors, quality defects, and cases of abuse, misuse and occupational exposure. Pharmacovigilance activities are carried out throughout the lifecycle of all medicinal products, with a special emphasis on the post-authorisation segment. In this phase, activities such as risk management, incident management plans, medical literature monitoring, additional monitoring, periodic safety update reports, post-authorisation safety studies and signal management are crucial for the continuous safety monitoring of all medicines throughout their use in clinical practice (5).

Pharmacovigilance reporting systems are defined as systems used by an organisation (marketing authorisation holders and competent authorities) to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance (6).

In Portugal, the National Pharmacovigilance System (in Portuguese, Sistema Nacional de Farmacovigilância, hereafter designated as SNF) was created in 1992 by the Portuguese competent authority, INFARMED, I.P., and it is articulated with the European Pharmacovigilance System, coordinated by the European Medicines Agency (7). Though initially centralised, the SNF opted for decentralisation in 2000, creating four Regional Pharmacovigilance Units (in Portuguese, Unidades Regionais de Farmacovigilância, hereafter designated as URF): North, Centre, South and Azores. Over the years, this decentralisation trend evolved, in an attempt to bridge the distance between the reporters and the competent authority, as well as to combat underreporting. Currently, there are 10 active URFs: Guimarães, Braga, Porto, Beira Interior, Coimbra, Lisboa, Setúbal e Santarém, Centro e Norte Alentejano, Algarve e Baixo Alentejo, Açores e Madeira.

Physicians were the first healthcare professionals with the ability to report ADRs to the SNF, since 1992. Three years later, in 1995, pharmacists were also able to report, and another three years later, in 1998, so could nurses. It was only in 2012 that spontaneous reporting became available to consumers (8).

The Pharmacovigilance Unit of Coimbra (in Portuguese, Unidade de Farmacovigilância de Coimbra, hereafter designated as UFC) is responsible for spontaneous reports (SR) received from the districts of Aveiro, Coimbra and Leiria. These districts comprise a total population of 1.491.088 inhabitants in 9.712 km^2, according to data from the National Institute of Statistics (INE) (9) and Pordata (10). The UFC is located at AIBILI – Association for

Innovation and Biomedical Research on Light and Image, since 2008, contracted by the INFARMED, I.P.

An ADR, in turn, is vaguely defined as a noxious and unintended response to a medicine. This definition has been subject to some changes in recent years, with the understanding that these noxious effects may result not only from the authorised use of a medicinal product at normal doses, but also from medication errors and other uses outside the terms of the marketing authorisation, such as misuse and abuse (11). ADRs are further classified in six types of mechanism: A (Augmented or dose-related), B (Bizarre or non-dose-related), C (Chronic or dose-related and time-related), D (Delayed or time-related), E (End of use or withdrawal) and F (Failure) (12). It is also possible to classify ADRs regarding frequency: Very Common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000) and Very Rare (< 1/10,000) (13). Regarding seriousness, in accordance with the EMA glossary, an ADR is considered Serious when it results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect. It may also be the case that a reaction is considered Serious due to its clinical significance, for example, when clinical attention is required in order to reverse the reaction. ADRs may also be considered Unknown, when the nature or severity of the reaction is not consistent with the applicable product information such as the Summary of Product Characteristics (SmPC) (14). Regarding causality, ADRs are assessed according to the WHO-Uppsala Monitoring Centre (UMC) causality categories (15).

A SR is defined as an unsolicited communication by a healthcare professional or consumer to a competent authority or marketing authorisation holder that describes one or more suspected ADR in a patient who was given one or more medicinal products (16). Spontaneous reporting of ADRs is therefore essential for the characterization of the safety profile of approved medicines. It presents some advantages, such as its broad scope over the entire population (not excluding the elderly, children and pregnant individuals, presenting a considerable advantage over clinical trials) and the entire lifecycle of a product. It is also considered a simple, cost-effective method to identify new, rare and severe ADRs, while also not interfering with medical prescription.

Notwithstanding, spontaneous reporting presents some considerable limitations, such as delayed reporting, the difficulty in calculating incidence, the subjectivity of the reporter and most importantly, underreporting (17).

The present study attempted to contribute towards a better understanding of the safety profile of COVID-19 vaccines, through the analysis of SRs received in a Regional Pharmacovigilance Unit.

II. Aim

Aim

This project aimed primarily at identifying unknown and serious ADRs for COVID-19 vaccines among SRs received by the UFC.

As secondary objectives, this study aimed to:

- Identify and characterize approved COVID-19 vaccines;
- Characterize the identified unknown ADRs according to demographic variables, such as sex, age and reporter origin, seriousness and causality;
- Compare the unknown ADRs among the administered vaccines.

III. Materials and Methods

Materials and Methods

In order to fulfil the predefined objectives, this study was organized in two distinct sections: a theoretical background, comprising the identification and characterization of approved COVID-19 vaccines, and an analysis of the spontaneous reports received for these vaccines by the UFC.

The procedures and methods used in the elaboration of the present study are described below.

Identification of COVID-19 vaccines approved in Portugal

In order to identify all vaccines approved for the indication of COVID-19 immunisation, a search was performed in Infomed, which is a Portuguese database containing all human medicinal products available nationally.

The identified vaccines were then classified regarding their commercial denomination, active substance, pharmaceutical form, dosage and marketing authorisation holder.

To comply with the temporal scope of the study, vaccines approved after December 31st 2021 were excluded.

Characterisation of COVID-19 vaccines approved in Portugal

Previously identified vaccines were characterised according to their market introduction date and action mechanism, according to the information present in the SmPC and the European Public Assessment Reports (EPAR).

Identification of unknown adverse drug reactions for COVID-19 vaccines among spontaneous reports

The search for SRs was conducted by extraction from the national database of all cases received by the UFC associated with COVID-19 vaccines. This data belongs to the National Pharmacovigilance System (INFARMED, I.P.) and was shared with authorisation from the UFC coordination.

Each SR is associated with a single individual. Nevertheless, one SR may contain more than one ADR and more than one suspected medicinal product. In addition, each SR contains information regarding origin of the report (healthcare professional or consumer), date of reception, active substance of the suspected medicine, therapeutic indication, seriousness of the report, seriousness criteria, reactions coded according to MedDRA (Medical Dictionary for Regulatory Activities) Lowest Level Term (LLT), as well as patient demographics (sex and age).

A global analysis of all SRs was conducted using Microsoft® Excel®, followed by an analysis of SRs containing unknown ADRs. The Chi-Square test of independence was used to assess if serious ADRs were dependent of the COVID-19 vaccine administered

IV. Results

Results

1. Identification of vaccines currently approved in Portugal

The Infomed database was used to identify all vaccines currently used in Portugal for COVID-19 immunisation. The results of this search are reproduced in Table 1, according to commercial designation, active substance, pharmaceutical form, dosage and marketing authorisation holder.

Table 1 – COVID-19 vaccines approved in Portugal.

Vaccine	Active Substance	Pharmaceutical form	Dosage	Marketing Authorisation Holder
Vacina contra a COVID-19 (inativada, adjuvada) Valneva	COVID-19 vaccine (inactivated, adjuvanted, adsorbed)	Suspension for injection	33 AgU/0.5 ml	Valneva Austria GmbH
Comirnaty	COVID-19 mRNA vaccine (nucleoside modified)	Concentrate for dispersion for injection	10 mcg/0.2 ml	BioNTech Manufacturing GmbH
Comirnaty	COVID-19 mRNA vaccine (nucleoside modified)	Concentrate for dispersion for injection	30 mcg/0.3 ml	BioNTech Manufacturing GmbH
Comirnaty	COVID-19 mRNA vaccine (nucleoside modified)	Dispersion for injection	30 mcg/0.3 ml	BioNTech Manufacturing GmbH
Spikevax previously COVID-19 Vaccine Moderna	COVID-19 mRNA vaccine (nucleoside modified)	Dispersion for injection	100 mcg/0.5 ml	MODERNA BIOTECH SPAIN, S.L
Nuvaxovid	COVID-19 vaccine (recombinant, adjuvanted)	Dispersion for injection	5 mcg/0.5 ml	Novavax CZ a.s.
Vaxzevria previously COVID-19 Vaccine AstraZeneca	COVID-19 Vaccine (ChAdOx1-S [recombinant])	Suspension for injection	>= 2.5 x10e8 U.Inf./0.5 ml	AstraZeneca AB
JCOVDEN (previously COVID-19 Vaccine Janssen)	COVID-19 vaccine (Ad26.COV2-S [recombinant])	Suspension for injection	>= 8.92 log10 U.Inf./0.5 ml	Janssen-Cilag International N.V.

For the purposes of this study, only Comirnaty (hereafter designated as COM), Vaxzevria (hereafter designated as VAX), Spikevax (hereafter designated as SPI) and JCOVDEN (hereafter designated as JCO) will be considered, as these four vaccines were the only ones administered in Portugal during the year of 2021.

2. Characterisation of COVID-19 vaccines

a. Comirnaty

Comirnaty, by Pfizer and BioNTech, was the first COVID-19 vaccine to receive a conditional marketing authorisation, valid throughout the European Union, on December 21st, 2020 (18).

Regarding its action mechanism, the nucleoside-modified messenger RNA for this vaccine is formulated in lipid nanoparticles, which in turn enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 spike (S) antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the S antigen, thus contributing for protection against COVID-19 (18).

Comirnaty is given as two injections (intramuscularly, usually in the upper arm), with a recommended interval of three weeks (21 days) between administrations. Adolescents (12-17 years old) and adults are given 30 micrograms per dose, while children (5-11 years old) are given 10 micrograms per dose.

An additional dose may be administered in severely immunocompromised individuals aged 5 years or older, at least 28 days after the second dose.

A booster dose may be given at least 3 months after the second dose for individuals aged 12 years and older, or to adults who have received primary vaccination with other mRNA vaccines or adenoviral vector vaccines (19). In Portugal, a second booster dose may be administered in individuals aged 80 years or older, as well as residents in assisted living facilities (20).

b. Spikevax previously COVID-19 Vaccine Moderna

Spikevax previously COVID-19 Vaccine Moderna, by Moderna, was the second COVID-19 vaccine to receive a conditional marketing authorisation, on January 6th, 2021.

Similarly to Comirnaty, Spikevax also contains mRNA encapsulated in lipid nanoparticles, which encodes the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions and elicits both T-cell and B-cell responses to generate neutralising antibodies (21).

Spikevax is also administered in two intramuscular injections, 28 days apart. Adolescents and adults are given 100 micrograms per dose, while children aged 6 to 11 years old are given 50 micrograms per dose.

An additional dose may be administered in severely immunocompromised individuals aged 6 years or older, at least 28 days after their second dose.

A booster dose of 50 micrograms may be administered at least 3 months after the second dose to individuals aged 18 years or older (22). In Portugal, a second booster dose of this vaccine may also be administered in individuals aged 80 years or older, as well as residents in assisted living facilities (20).

c. Vaxzevria previously COVID-19 Vaccine AstraZeneca

Vaxzevria previously COVID-19 Vaccine AstraZeneca, by AstraZeneca, was the third COVID-19 vaccine to receive a conditional marketing authorisation, on January 19th, 2021.

This is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus vector, which encodes the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein is expressed locally, which stimulated neutralising antibody and cellular immune responses (23).

Vaxzevria is administered as two intramuscular injections, 4 to 12 weeks apart. This vaccine is only approved for individuals aged 18 years or older.

A booster dose may be given at least 3 months after the second dose (24). However, in Portugal, this vaccine is not recommended for booster doses.

d. JCOVDEN (previously COVID-19 Vaccine Janssen)

JCOVDEN (previously COVID-19 Vaccine Janssen), by Janssen, was the fourth COVID-19 vaccine to receive a conditional marketing authorisation, on March 11th, 2021.

This vaccine is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that, similarly to Vaxzevria, encodes SARS-CoV-2 full-length S glycoprotein which is transiently expressed following administration, stimulating both neutralising and other functional S-specific antibodies, as well as cellular immune responses directed against the S antigen, contributing for COVID-19 protection (25).

JCOVDEN is administered in a single intramuscular injection, for individuals aged 18 years or older (26).

While a booster dose may be given at least 2 months after the first dose, or after completing primary vaccination with mRNA vaccines, its use is not recommended in Portugal for these purposes.

3. Vaccine exposure in Portugal

As of September 30th 2022, more than 25 million doses of vaccines had been administered to the Portuguese population. The distribution of these vaccines (by brand), as well as an analysis of SRs received by the SNF, is further detailed in Table 2.

Table 2 – Vaccines administered and SRs per vaccine brand (27)

Vaccine	Comirnaty	Spikevax	Vaxzevria	JCOVDEN	Non-identifiable
Number of vaccines administered	18 499 496	3 696 491	2 267 487	1 137 418	N/A
Number of spontaneous reports	24 674	3 793	8 089	2 085	159
Number of spontaneous reports per 1000 vaccines administered	1.3	1.0	3.6	1.8	N/A

It should be noted that this data does not allow for the comparison of safety profiles among different vaccines, as vaccines were administered in distinct subpopulations and within different epidemiological contexts (27).

4. General overview of Spontaneous Reports received by the SNF and the UFC

The SNF has been receiving an increasing amount of Spontaneous Reports in the last decade. The evolution of SRs received by the SNF is demonstrated in Figure 1.

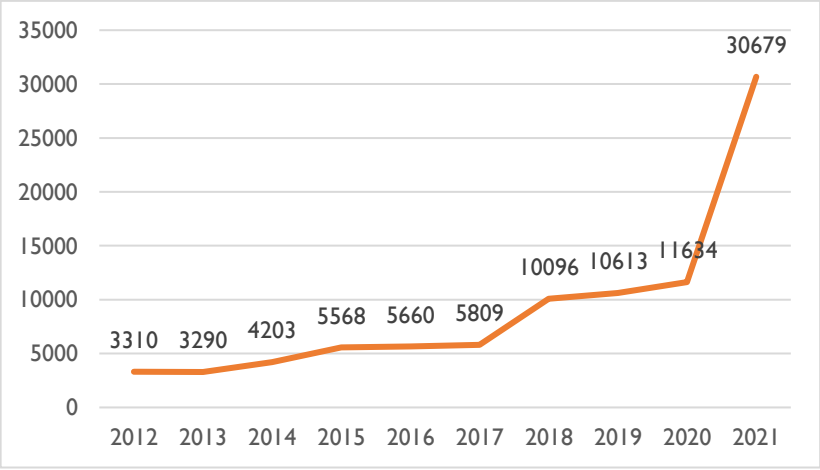

Figure 1 – SRs received by the SNF from 2012 to 2021

The UFC has also demonstrated a growing trend of Spontaneous Report reception, with a particularly large increase in the year of 2021, as shown in Figure 2.

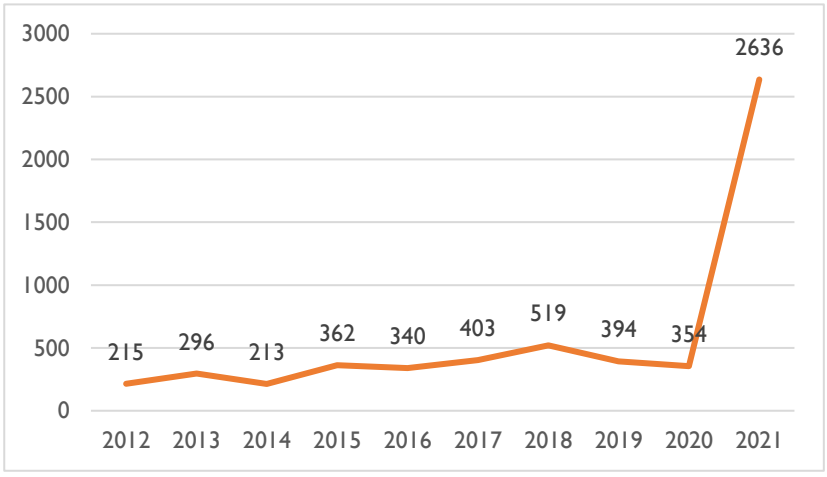

Figure 2 – SRs received by the UFC from 2012 to 2021

5. General overview of Spontaneous Reports for COVID-19 Vaccines

From December 30th, 2020 until December 31st, 2021, the UFC received 2322 SRs concerning at least one COVID-19 vaccine. Three SRs contained more than one suspected vaccine.

These SRs were validated primarily according to four minimum criteria: a description of an ADR, a suspected medicine responsible for the reaction, an identifiable patient and an identified reporter.

Afterwards, SRs were validated secondarily, according to causality, seriousness and previous knowledge.

In some cases, SRs did not contain the commercial denomination of the administered vaccine. For these purposes, this study also contains data for 1 SR concerning an mRNA vaccine (nucleoside modified), hereafter designated as MRNA, and 4 SRs concerning an unidentified COVID-19 Vaccine, hereafter designated as VAC19.

Demographic data from the 2322 reports received is further demonstrated in Tables 3 and 4.

Table 3 – Patient characteristics according to COVID-19 Vaccine, Sex and Age

Vaccine	Patient Sex						Patient Age			
	Female		Male		Unknown				Unknown	
	n	(%)	n	(%)	n	(%)	Mean	SD	n	(%)
COM	1119	(76.17)	299	(20.35)	51	(3.47)	47.7	18.7	419	(28.52)
VAX	310	(65.13)	134	(28.15)	32	(6.72)	51.4	17.0	24	(5.04)
SPI	152	(77.95)	35	(17.95)	8	(4.10)	43.3	18.1	10	(5.13)
JCO	19	(10.56)	155	(86.11)	6	(3.33)	35.2	15.2	1	(0.56)
VAC19	3	(75.00)	1	(25.00)	0	(0.00)	48.3	19.9	0	(0.00)
MRNA	1	(100.00)	0	(0.00)	0	(0.00)	31.0	-	0	(0.00)
Total	1604	(68.99)	624	(26.84)	97	(4.17)	46.9	18.5	454	(19.53)

SD: Standard Deviation

The majority of SRs received (68.99%) contained female patients. A small percentage of SRs (4.17%) contained no information regarding patient sex. Globally, patients presented a mean age of 46.9 ± 18.5 years. Age was unknown for 454 SRs (19.53%).

Table 4 – Patient characteristics according to Age Group and COVID-19 Vaccine

Age Group	COM (%)	VAX (%)	SPI (%)	JCO (%)	VAC19 (%)	MRNA (%)	Total (%)
3-11 Years	4* (0.27%)	0 (0.00%)	1*** (0,51%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (0.22%)
12-17 Years	23 (1.57%)	1** (0.21%)	4** (2.05%)	4** (2.22%)	0 (0.00%)	0 (0.00%)	32 (1.38%)
18-64 Years	1216 (82.78%)	338 (71.01%)	158 (81.03%)	168 (93.33%)	3 (75.00%)	1 (100.00%)	1884 (81.03%)
> 65 Years	194 (13.21%)	118 (24.79%)	25 (12.82%)	7 (3.89%)	1 (25.00%)	0 (0.00%)	345 (14.84%)
Unknown	32 (2.18%)	19 (3.99%)	7 (3.59%)	1 (0.56%)	0 (0.00%)	0 (0.00%)	59 (2.54%)
Total	1469 (100.00%)	476 (100.00%)	195 (100.00%)	180 (100.00%)	4 (100.00%)	1 (100.00%)	2325 (100.00%)

* Contains 1 vaccine exposure through breast milk.
** Medication errors.
*** Vaccine exposure through breast milk.

SRs were also classified according to origin of the reporter, as demonstrated in Table 5. Reports originated from physicians, nurses, pharmacists, other healthcare professionals (HCP) or consumers. In some SRs, more than one reporter was identified, which explains the discrepancy between number of SRs (2322) versus the number of reporters (2332).

Table 5 – SRs according to Origin and COVID-19 Vaccine

Origin	COM (%)	VAX (%)	SPI (%)	JCO (%)	VAC19 (%)	MRNA (%)	Total (%)
Physician	941 (63.84%)	137 (28.66%)	59 (30.26%)	75 (41.67%)	1 (25.00%)	1 (100.00%)	1214 (52.06%)
Nurse	212 (14.38%)	113 (23.64%)	36 (18.46%)	35 (19.44%)	0 (0.00%)	0 (0.00%)	396 (16.98%)
Pharmacist	36 (2.44%)	54 (11.30%)	24 (12.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	114 (4.89%)
Other HCP	17 (1.15%)	8 (1.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	25 (1.07%)
Consumer	268 (18.18%)	166 (34.73%)	76 (38.97%)	70 (38.89%)	3 (75.00%)	0 (0.00%)	583 (25.00%)
Total	1474 (100.00%)	478 (100.00%)	195 (100.00%)	180 (100.00%)	4 (100.00%)	1 (100.00%)	2332 (100.00%)

Geographically, and within the scope of the UFC, SRs were also classified according to their district of origin, which is demonstrated in Table 6.

Table 6 – Spontaneous Reports according to District and COVID-19 Vaccine

District	COM (%)	VAX (%)	SPI (%)	JCO (%)	VAC19 (%)	MRNA (%)	Total (%)
Aveiro	357 (24.30%)	156 (32.77%)	60 (30.77%)	53 (29.44%)	2 (50.00%)	1 (100.00%)	629 (27.05%)
Coimbra	751 (51.12%)	190 (39.92%)	66 (33.85%)	50 (27.78%)	2 (50.00%)	0 (0.00%)	1059 (45.55%)
Leiria	361 (24.57%)	130 (27.31%)	69 (35.38%)	77 (42.78%)	0 (0.00%)	0 (0.00%)	637 (27.40%)
Total	1469 (100.00%)	476 (100.00%)	195 (100.00%)	180 (100.00%)	4 (100.00%)	1 (100.00%)	2325 (100.00%)

SRs were further characterized according to dose of vaccine, when such data was available. Some SRs contained ADRs to more than one dose of the administered vaccine.

Table 7 – Spontaneous Reports according to Dose and COVID-19 Vaccine

District	COM (%)	VAX (%)	SPI (%)	JCO (%)	VAC19 (%)	MRNA (%)	Total (%)
1st Dose	953 (49.64%)	413 (76.48%)	118 (51.75%)	180 (100.00%)	0 (0.00%)	0 (0.00%)	1664 (57.92%)
2nd Dose	795 (41.41%)	89 (16.48%)	63 (27.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	947 (32.96%)
Booster Dose	34 (1.77%)	0 (0.00%)	4 (1.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	38 (1.32%)
Unknown	138 (7.19%)	38 (7.04%)	43 (18.86%)	0 (0.00%)	4 (100.00%)	1 (100.00%)	224 (7.80%)
Total	1920 (100.00%)	540 (100.00%)	228 (100.00%)	180 (100.00%)	4 (100.00%)	1 (100.00%)	2873 (100.00%)

Since one SR may contain more than one ADR, Table 8 unfolds data from vaccines administered into single ADRs.

Table 8 – SRs and ADRs per COVID-19 vaccine

Vaccine	SRs (%)	ADRs (%)	Average ADR/SR
COM	1469 (63.18%)	4382 (63.37%)	2.98
VAX	476 (20.47%)	1544 (22.33%)	3.24
SPI	195 (8.39%)	545 (7.88%)	2.79
JCO	180 (7.74%)	437 (6.32%)	2.43
VAC19	4 (0.17%)	6 (0.09%)	1.5
MRNA	1 (0.04%)	1 (0.01%)	1
Total	2325 (100.00%)	6915 (100.00%)	2.97

Another variable under analysis was onset time for the first reported ADR. The minimum, maximum and average onset times (in days) for each vaccine are further described in Table 9. SRs with unknown onset time and containing unidentifiable vaccines were excluded from this analysis.

Table 9 – Onset Time for first reported ADR per COVID-19 Vaccine

Vaccine	Minimum Onset	Maximum Onset	Mode Onset	Average Onset
COM	1	270	0	11.9
VAX	1	180	0	10.1
SPI	1	240	0	15.1
JCO	1	120	0	13.7

a. Adverse Drug Reaction analysis by MedDRA PT and SOC

ADRs were coded using the MedDRA dictionary, and are classified below in Preferred Term (PT) and System Organ Class (SOC), for each vaccine.

i. Comirnaty

The UFC has received 1469 SRs for Comirnaty, comprising 4382 individual ADRs, which are described in Appendix 2. The most frequently reported ADRs for this vaccine are demonstrated in Table 10.

Table 10 – Most frequently reported ADRs for Comirnaty per PT and Primary SOC

Preferred Term / *Primary SOC*	Total (%)
Vaccination site pain *(General disorders and administration site conditions)*	668 (15.24%)
Myalgia *(Musculoskeletal and connective tissue disorders)*	396 (9.04%)
Headache *(Nervous system disorders)*	353 (8.06%)
Arthralgia *(Musculoskeletal and connective tissue disorders)*	196 (4.47%)
Pyrexia *(General disorders and administration site conditions)*	186 (4.24%)
Vaccination failure *(General disorders and administration site conditions)*	172 (3.93%)
Chills *(General disorders and administration site conditions)*	162 (3.70%)
COVID-19 *(Infections and infestations)*	147 (3.35%)
Lymphadenopathy *(Blood and lymphatic system disorders)*	135 (3.08%)
Nausea *(Gastrointestinal disorders)*	122 (2.78%)
Others	1845 (42.10%)
Total	4382 (100.00%)

The most frequently reported ADR was vaccination site pain (n=668; 15.24%), followed by myalgia (n=396; 9.04%), headache (n=353; 8.06%), arthralgia (n=196; 4.47%) and pyrexia (n=186; 4.24%). All of these are currently described in the SmPC (18).

ii. Vaxzevria previously COVID-19 Vaccine AstraZeneca

The UFC has received 476 SRs for Vaxzevria, comprising 1544 individual ADRs, which are described in Appendix 3. The most frequently reported ADRs for this vaccine are demonstrated in Table 11.

Table 11 – Most frequently reported ADRs for Vaxzevria per PT and Primary SOC

Preferred Term / *Primary SOC*	Total (%)
Pyrexia *(General disorders and administration site conditions)*	155 (10.04%)
Headache *(Nervous system disorders)*	142 (9.20%)
Myalgia *(Musculoskeletal and connective tissue disorders)*	141 (9.13%)
Vaccination site pain *(General disorders and administration site conditions)*	78 (5.05%)
Fatigue *(General disorders and administration site conditions)*	60 (3.89%)
Nausea *(Gastrointestinal disorders)*	57 (3.69%)
Arthralgia *(Musculoskeletal and connective tissue disorders)*	50 (3.24%)
Chills *(General disorders and administration site conditions)*	47 (3.04%)
COVID-19 *(Infections and infestations)*	46 (2.98%)
Vaccination failure *(General disorders and administration site conditions)*	41 (2.66%)
Others	727 (47.09%)
Total	1544 (100.00%)

The most frequently reported ADR was pyrexia (n=155; 10.04%), followed by headache (n=142; 9.20%), myalgia (n=141; 9.13%), vaccination site pain (n=78; 5.05%) and fatigue (n=60; 3.89%). All of these are currently described in the SmPC (23).

iii. Spikevax previously COVID-19 Vaccine Moderna

The UFC has received 195 SRs for Spikevax, comprising 545 individual ADRs, which are described in Appendix 4. The most frequently reported ADRs for this vaccine are demonstrated in Table 12.

Table 12 – Most frequently reported ADRs for Spikevax per PT and Primary SOC

Preferred Term / *Primary SOC*	Total (%)
Vaccination site pain *(General disorders and administration site conditions)*	45 (8.26%)
Vaccination site erythema *(General disorders and administration site conditions)*	29 (5.32%)
Pyrexia *(General disorders and administration site conditions)*	28 (5.14%)
Myalgia *(Musculoskeletal and connective tissue disorders)*	25 (4.59%)
COVID-19 *(Infections and infestations)*	24 (4.40%)
Headache *(Nervous system disorders)*	21 (3.85%)
Lymphadenopathy *(Blood and lymphatic system disorders)* Vaccination site oedema *(General disorders and administration site conditions)*	20 (3.67%)
Chills *(General disorders and administration site conditions)* Vaccination site pruritus *(General disorders and administration site conditions)*	18 (3.30%)
Nausea *(Gastrointestinal disorders)* Vaccination failure *(General disorders and administration site conditions)* Vaccination site warmth *(General disorders and administration site conditions)*	17 (3.12%)
Fatigue *(General disorders and administration site conditions)*	16 (2.94%)
Others	230 (42.20%)
Total	545 (100.00%)

Excluding inefficacy reports (COVID-19), the most frequently reported ADR was vaccination site pain (n=45; 8.26%), followed by vaccination site erythema (n=29; 5.32%), pyrexia (n=28; 5.14%), myalgia (n=25; 4.59%) and headache (n=21; 3.85%). All of these are currently described in the SmPC (21).

iv. JCOVDEN (previously COVID-19 Vaccine Janssen)

The UFC has received 180 SRs for JCOVDEN, comprising 437 individual ADRs, which are described in Appendix 5. The most frequently reported ADRs for this vaccine are demonstrated in Table 13.

Table 13 – Most Frequently Reported ADRs for JCOVDEN per PT and Primary SOC

Preferred Term / *Primary SOC*	Total (%)
COVID-19 *(Infections and infestations)*	43 (9.84%)
Pyrexia *(General disorders and administration site conditions)*	40 (9.15%)
Vaccination failure *(General disorders and administration site conditions)*	37 (8.47%)
Myalgia *(Musculoskeletal and connective tissue disorders)*	25 (5.72%)
Headache *(Nervous system disorders)*	24 (5.49%)
Presyncope *(Nervous system disorders)*	20 (4.58%)
Fatigue *(General disorders and administration site conditions)*	17 (3.89%)

Preferred Term / *Primary SOC*	Total (%)
Syncope *(Nervous system disorders)*	
Drug ineffective *(General disorders and administration site conditions)*	15 (3.43%)
Dizziness *(Nervous system disorders)*	11 (2.52%)
Arthralgia *(Musculoskeletal and connective tissue disorders)*	10 (2.29%)
Others	178 (40.73%)
Total	437 (100.00%)

Excluding inefficacy reports (COVID-19), the most frequently reported reaction was pyrexia (n=40; 9.15%), followed by myalgia (n=25; 5.72%), headache (n=24; 5.49%), presyncope (n=20; 4.58%) and fatigue (n=17; 3.89%). All of these are currently described in the SmPC (25).

v. COVID-19 Vaccine

The UFC has received 4 SRs for an unknown COVID-19 Vaccine, comprising 6 individual ADRs, which are described in Table 14.

Table 14 – ADRs for COVID-19 Vaccine per Primary SOC and PT

Preferred Term / *Primary SOC*	Total (%)
Abdominal pain (*Gastrointestinal disorders*)	1 (16.67%)
Diarrhoea (*Gastrointestinal disorders*)	1 (16.67%)
Fatigue (*General disorders and administration site conditions*)	1 (16.67%)
Headache (*Nervous system disorders*)	1 (16.67%)
Myocarditis (*Cardiac disorders*)	1 (16.67%)
Urinary tract obstruction (*Renal and urinary disorders*)	1 (16.67%)
Total	6 (100.00%)

vi. mRNA COVID-19 Vaccine (nucleoside modified)

The UFC has received 1 SR for a mRNA COVID-19 Vaccine (nucleoside modified), comprising 1 individual ADR, which is described in Table 15.

Table 15 – ADRs for mRNA COVID-19 Vaccine (nucleoside modified) per Primary SOC and PT

Preferred Term / *Primary SOC*	Total
Headache (*Nervous system disorders*)	1 (100.00%)
Total	1 (100.00%)

Headache is a frequent ADR and it is described in the SmPC for both mRNA COVID-19 vaccines identified in the present study (18) (21).

b. Seriousness

SRs received by the UFC were classified according to seriousness criteria. All SRs containing at least one serious ADR were considered serious, as a whole. One SR may contain more than one seriousness criteria.

Table 16 – SRs according to Seriousness per COVID-19 Vaccine

Seriousness	COM (%)	VAX (%)	SPI (%)	JCO (%)	VAC19 (%)	MRNA (%)	Total (%)
Serious	581 (39.55%)	244 (51.26%)	91 (46.67%)	97 (53.89%)	3 (75.00%)	0 (0.00%)	1016 (43.70%)
Non Serious	888 (60.45%)	232 (48.74%)	104 (53.33%)	83 (46.11%)	1 (25.00%)	1 (100.00%)	1309 (56.30%)
Total	1469 (100.00%)	476 (100.00%)	195 (100.00%)	180 (100.00%)	4 (100.00%)	1 (100.00%)	2325 (100.00%)

43.70% (n=1016) of all SRs received contained at least one seriousness criteria. The highest percentage of serious SRs among identifiable vaccines was attributed to JCOVDEN, with 53.89% (n=180), followed by Vaxzevria with 51.26% (n=244), Spikevax with 46.67% (n=195) and lastly, Comirnaty with 39.55% (n=581).

Table 17 illustrates the seriousness criteria associated with SRs for each vaccine.

Table 17 – SRs according to Seriousness Criteria and COVID-19 Vaccine

Seriousness Criteria	COM (%)	VAX (%)	SPI (%)	JCO (%)	VAC19 (%)	MRNA (%)	Total (%)
Death	10 (0.67%)	1 (0.20%)	2 (1.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	13 (0.55%)
Life-threatening	16 (1.08%)	10 (2.04%)	2 (1.00%)	5 (2.69%)	0 (0.00%)	0 (0.00%)	33 (1.40%)
Hospitalisation	56 (3.78%)	26 (5.32%)	7 (3.50%)	11 (5.91%)	1 (25.00%)	0 (0.00%)	101 (4.27%)
Incapacity	86 (5.80%)	67 (13.70%)	14 (7.00%)	24 (12.90%)	0 (0.00%)	0 (0.00%)	191 (8.08%)
Congenital anomaly	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Clinically important	427 (28.79%)	153 (31.29%)	71 (35.50%)	63 (33.87%)	2 (50.00%)	0 (0.00%)	716 (30.30%)
Non Serious	888 (59.88%)	232 (47.44%)	104 (52.00%)	83 (44.62%)	1 (25.00%)	1 (100.00%)	1309 (55.40%)
Total	1483 (100.00%)	489 (100.00%)	200 (100.00%)	186 (100.00%)	4 (100.00%)	1 (100.00%)	2363 (100.00%)

The Chi-Square test of independence was conducted in order to assess whether the variable Seriousness was dependent on the COVID-19 vaccine administered, within identifiable vaccines (COM, VAX, SPI, JCO), with the following result: χ^2 (3, N = 2320) =

29.63571, p=7.815. Thus, it is possible to admit that seriousness is not independent of the COVID-19 vaccine administered.

c. Causality

Causality was assessed through the global introspection (through an expert panel) method for all SRs. Since causality imputation in the national database is only required for Serious reports, Non-Serious reports were excluded from this portion of the study.

Table 18 – Serious SRs according to Causality and COVID-19 Vaccine

Causality	COM (%)	VAX (%)	SPI (%)	JCO (%)	VAC19 (%)	MRNA (%)	Total (%)
Certain	414 (71.26%)	176 (72.13%)	59 (64.84%)	74 (76.29%)	1 (33.33%)	0 (0.00%)	724 (71.26%)
Probable	73 (12.56%)	28 (11.48%)	17 (18.68%)	11 (11.34%)	1 (33.33%)	0 (0.00%)	130 (12.80%)
Possible	82 (14.11%)	35 (14.34%)	13 (14.29%)	11 (11.34%)	1 (33.33%)	0 (0.00%)	142 (13.98%)
Unlikely	10 (1.72%)	3 (1.23%)	1 (1.10%)	1 (1.03%)	0 (0.00%)	0 (0.00%)	15 (1.48%)
Conditional	1 (0.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.10%)
Unclassifiable	1 (0.17%)	2 (0.82%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (0.39%)
Total	581 (100.00%)	244 (100.00%)	91 (100.00%)	97 (100.00%)	3 (100.00%)	0 (0.00%)	1016 (100.00%)

d. Previous Knowledge

SRs received by the UFC were classified as Known or Unknown, according to the description of the reaction on the SmPC for each vaccine. All SRs containing at least one Unknown ADR were considered Unknown as a whole. The "Not Applicable" status refers to SRs that did not contain an ADR (i.e., inadvertent exposure, etc.).

Table 19 – Spontaneous Reports according to Previous Knowledge and COVID-19 Vaccine

Previous Knowledge	COM (%)	VAX (%)	SPI (%)	JCO (%)	VAC19 (%)	MRNA (%)	Total (%)
Known	1025 (69.78%)	318 (66.81%)	133 (68.21%)	133 (73.89%)	3 (75.00%)	1 (100.00%)	1613 (69.38%)
Unknown	408 (27.77%)	146 (30.67%)	50 (25.64%)	41 (22.78%)	1 (25.00%)	0 (0.00%)	646 (27.78%)
Not Applicable	36 (2.45%)	12 (2.52%)	12 (6.15%)	6 (3.33%)	0 (0.00%)	0 (0.00%)	66 (2.84%)
Total	1469 (100.00%)	476 (100.00%)	195 (100.00%)	180 (100.00%)	4 (100.00%)	1 (100.00%)	2325 (100.00%)

For all identifiable vaccines, the number of SRs containing known ADRs surpasses the number of SRs containing Unknown ADRs.

6. Identification and Characterisation of Unknown Adverse Drug Reactions

A total of 645 SRs containing at least one unknown ADR were identified. Unidentifiable vaccines were excluded from this portion of the study.

a. Demographic Characterisation

A total of 408 SRs concerning Comirnaty were identified as containing at least one unknown ADR; for Vaxzevria, 146 SRs were identified; for Spikevax, 50 SRs were identified and 41 SRs were identified for JCOVDEN. Similarly to Known SRs, a higher percentage of female patients was identified for all vaccines, except for JCOVDEN. This may be explained due to the national official recommendations for the administration of JCOVDEN (preferentially in male patients).

Demographic data from the SRs received is further demonstrated in Table 20 and Table 21.

Table 20 – Patient characteristics according to COVID-19 Vaccine, Sex and Age for SRs containing Unknown ADRs

Vaccine	Patient Sex						Patient Age			
	Female		Male		Unknown				Unknown	
	n	(%)	n	(%)	n	(%)	Mean	SD	n	(%)
COM	310	(75.98)	80	(19.61)	18	(4.41)	48.2	19.0	39	(9.56)
VAX	93	(63.70)	44	(30.14)	9	(6.16)	57.0	14.7	11	(7.53)
SPI	38	(76.00)	11	(22.00)	1	(2.00)	45.5	19.8	1	(2.00)
JCO	11	(26.83)	28	(68.29)	2	(4.88)	41.9	17.5	0	(0.00)
Total	452	(70.08)	163	(25.27)	30	(4.65)	49.6	18.6	51	(7.91)

Table 21 – Patient characteristics according to Age Group and COVID-19 Vaccine for SRs containing Unknown ADRs

Age Group	COM (%)	VAX (%)	SPI (%)	JCO (%)	Total (%)
3-11 Years	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	1 (0.16%)
12-17 Years	7 (1.72%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (1.09%)
18-64 Years	288 (70.59%)	89 (60.96%)	40 (80.00%)	39 (95.12%)	456 (70.70%)

Age Group	COM (%)	VAX (%)	SPI (%)	JCO (%)	Total (%)
> 65 Years	74 (18.14%)	46 (31.51%)	8 (16.00%)	2 (4.88%)	130 (20.16%)
Unknown	39 (9.56%)	11 (7.53%)	1 (2.00%)	0 (0.00%)	51 (7.91%)
Total	408 (100.00%)	146 (100.00%)	50 (100.00%)	41 (100.00%)	645 (100.00%)

The majority of SRs containing unknown ADRs received (70.1%) contained female patients. 4.6% of SRs contained no information regarding patient sex. Globally, patients presented a mean age of 49.6 ± 18.6 years. Age was unknown for 41 SRs (7.9%).

b. Origin of the Spontaneous Report

SRs containing Unknown ADRs were also further classified according to their origin. Some SRs contain more than one reporter.

Table 22 – SRs containing Unknown ADRs according to origin of reporter and COVID-19 vaccine

Origin	COM (%)	VAX (%)	SPI (%)	JCO (%)	Total (%)
Physician	199 (48.42%)	52 (35.37%)	18 (36.00%)	17 (41.46%)	286 (44.07%)
Nurse	61 (14.84%)	15 (10.20%)	3 (6.00%)	0 (0.00%)	79 (12.17%)
Pharmacist	10 (2.43%)	11 (7.48%)	2 (4.00%)	0 (0.00%)	23 (3.54%)
Other HCP	3 (0.73%)	3 (2.04%)	0 (0.00%)	0 (0.00%)	6 (0.92%)
Consumer	138 (33.58%)	66 (44.90%)	27 (54.00%)	24 (58.54%)	255 (39.29%)
Total	411 (100.00%)	147 (100.00%)	50 (100.00%)	41 (100.00%)	649 (100.00%)

c. Most Frequently Reported Unknown Adverse Drug Reactions

Within the aforementioned 645 SRs, 1074 ADRs were identified. Their distribution is further detailed, per COVID-19 vaccine, in Table 23.

Table 23 – SRs and Unknown ADRs per COVID-19 vaccine

Vaccine	Spontaneous Reports (%)	Adverse Drug Reactions (%)
COM	408 (63.26%)	678 (63.13%)
VAX	146 (22.64%)	242 (22.53%)
SPI	50 (7.75%)	76 (7.08%)
JCO	41 (6.36%)	78 (7.26%)
Total	645 (100.00%)	1074 (100.00%)

The following section contains detailed information of unknown ADRs for each vaccine.

i. Comirnaty

The UFC has received 408 SRs, comprising 678 unknown ADRs associated with Comirnaty. The most frequently reported unknown ADRs are described in Table 24.

Table 24 – Most frequently reported unknown ADRs for Comirnaty per PT and Primary SOC

Preferred Term / *Primary SOC*	Total (%)
Dizziness *(Nervous system disorders)*	25 (3.69%)
Paraesthesia *(Nervous system disorders)* Decreased appetite *(Metabolism and nutrition disorders)*	22 (3.24%)
Cough *(Respiratory, thoracic and mediastinal disorders)*	19 (2.80%)
Asthenia *(General disorders and administration site conditions)*	16 (2.36%)
Somnolence *(Nervous system disorders)*	13 (1.92%)
Dysgeusia *(Nervous system disorders)*	12 (1.77%)
Dyspnoea *(Respiratory, thoracic and mediastinal disorders)*	11 (1.62%)
Pruritus *(Skin and subcutaneous tissue disorders)*	10 (1.47%)
Hypoaesthesia *(Nervous system disorders)* Rhinorrhoea *(Respiratory, thoracic and mediastinal disorders)*	9 (1.33%)
Others	510 (75.22%)
Total	678 (100.00%)

The most frequently reported unknown ADR was dizziness (3.69%; n=25), followed by decreased appetite and paraesthesia (3.24%; n=22), cough (2.80%; n=19) and asthenia (2.36%; n=16).

ii. Vaxzevria previously COVID-19 Vaccine AstraZeneca

The UFC has received 146 SRs, comprising 242 unknown ADR associated with Vaxzevria. The most frequently reported unknown ADRs are described in Table 25.

Table 25 – Most frequently reported unknown ADRs for Vaxzevria per PT and Primary SOC

Preferred Term / *Primary SOC*	Total (%)
Paraesthesia *(Nervous system disorders)*	9 (3.72%)
Ischaemic stroke *(Nervous system disorders)* Vertigo *(Ear and labyrinth disorders)*	7 (2.89%)
Feeling of body temperature change *(General disorders and administration site conditions)* Hypotension *(Vascular disorders)* Muscle spasms *(Musculoskeletal and connective tissue disorders)* Tremor *(Nervous system disorders)*	5 (2.07%)
Conjunctival haemorrhage *(Eye disorders)* Decreased appetite *(Metabolism and nutrition disorders)* Dyspnoea *(Respiratory, thoracic and mediastinal disorders)* Feeling cold *(General disorders and administration site conditions)* Guillain-Barre syndrome *(Nervous system disorders)* Tachycardia *(Cardiac disorders)*	4 (1.65%)
Others	175 (72.31%)
Total	242 (100.00%)

The most frequently reported unknown ADR was paraesthesia (3.72%; n=9), followed by ischaemic stroke and vertigo (2.89%; n=7), with muscle spasms, tremor, hypotension and feeling of body temperature change presenting equal percentages (2.06%; n=5).

iii. Spikevax previously COVID-19 Vaccine Moderna

The UFC has received 50 SRs, comprising 76 unknown ADRs associated with Spikevax. The most frequently reported unknown ADRs are described in Table 26.

Table 26 – Most frequently reported unknown ADRs for Spikevax per PT and Primary SOC

Preferred Term / *Primary SOC*	Total (%)
Diarrhoea *(Gastrointestinal disorders)*	4 (5.26%)
Asthenia *(General disorders and administration site conditions)* Dyspnoea *(Respiratory, thoracic and mediastinal disorders)* Haematoma *(Vascular disorders)* Tachycardia *(Cardiac disorders)*	3 (3.95%)
Axillary mass *(Musculoskeletal and connective tissue disorders)* Axillary pain *(General disorders and administration site conditions)* Cardiac discomfort *(Cardiac disorders)* Decreased appetite *(Metabolism and nutrition disorders)* Ecchymosis *(Skin and subcutaneous tissue disorders)* Herpes zoster *(Infections and infestations)* Intermenstrual bleeding *(Reproductive system and breast disorders)* Somnolence *(Nervous system disorders)* Toothache *(Gastrointestinal disorders)*	2 (2.63%)
Others	42 (55.26%)
Total	76 (100.00%)

The most frequently reported unknown ADR was diarrhoea (5.26%; n=4), followed by haematoma, dyspnoea, tachycardia and asthenia with equal frequency (3.95%; n=3).

iv. JCOVDEN (previously COVID-19 Vaccine Janssen)

The UFC has received 41 SRs, comprising 78 unknown ADRs associated with JCOVDEN. The most frequently reported unknown ADRs are described in Table 27.

Table 27 – Most frequently reported unknown ADRs for JCOVDEN per PT and Primary SOC

Preferred Term / *Primary SOC*	Total (%)
Dizziness *(Nervous system disorders)*	7 (17.07%)
Dyspnoea *(Respiratory, thoracic and mediastinal disorders)*	4 (9.76%)
Chest pain *(General disorders and administration site conditions)* Lymphadenopathy *(Blood and lymphatic system disorders)* Somnolence *(Nervous system disorders)*	3 (7.32%)
Arthritis *(Musculoskeletal and connective tissue disorders)* Guillain-Barre syndrome *(Nervous system disorders)* Hypoaesthesia *(Nervous system disorders)* Lymph node pain *(Blood and lymphatic system disorders)* Palpitations *(Cardiac disorders)* Peripheral coldness *(Vascular disorders)* Vertigo *(Ear and labyrinth disorders)*	2 (4.88%)
Others	7 (17.07%
Total	41 (100.00%)

The most frequently reported unknown ADR was dizziness (8.97%; n=7), followed by dyspnoea (5.13%; n=4), with somnolence, lymphadenopathy and chest pain sharing equal percentages (3.85%; n=3).

7. Characterisation of Unknown Adverse Drug Reactions

a. Seriousness

Each unknown ADR was classified as either Serious or Non Serious. The results are demonstrated in Table 28.

Table 28 – Unknown ADRs according to Seriousness per COVID-19 Vaccine

Seriousness	COM	VAX	SPI	JCO	Total
Serious	461 (67.99%)	190 (78.51%)	58 (76.32%)	67 (85.90%)	776 (72.25%)
Non Serious	217 (32.01%)	52 (21.49%)	18 (23.68%)	11 (14.10%)	298 (27.75%)
Total	678 (100.00%)	242 (100.00%)	76 (100.00%)	78 (100.00%)	1074 (100.00%)

b. Causality

Furthermore, each Serious and Unknown ADR was also classified according to a degree of causality, as demonstrated in Table 29.

Table 29 – Serious and Unknown ADRs according to Causality per COVID-19 Vaccine

Causality	COM (%)	VAX (%)	SPI (%)	JCO (%)	Total (%)
Certain	295 (63.99%)	127 (66.84%)	38 (65.52%)	46 (68.66%)	506 (65.21%)
Probable	61 (13.23%)	22 (11.58%)	9 (15.52%)	20 (29.85%)	112 (14.43%)
Possible	90 (19.52%)	36 (18.95%)	9 (15.52%)	0 (0.00%)	135 (17.40%)
Unlikely	13 (2.82%)	1 (0.53%)	1 (1.72%)	1 (1.49%)	16 (2.06%)
Conditional	1 (0.22%)	1 (0.53%)	0 (0.00%)	0 (0.00%)	2 (0.26%)
Unclassifiable	1 (0.22%)	3 (1.58%)	1 (1.72%)	0 (0.00%)	5 (0.64%)
Total	461 (100.00%)	190 (100.00%)	58 (100.00%)	67 (100.00%)	776 (100.00%)

V. Discussion

Discussion

The first COVID-19 vaccines were administered in Portugal at the end of 2020. Soon after, the National Pharmacovigilance System began receiving spontaneous reports for COVID-19 Vaccines.

From December 30th 2020 and until December 31st 2021, the UFC received 2325 SRs, of which 68.99% (n=1604) contained female patients, 26.84% (n=424) contained male patients and 4.17% (n=97) contained no information regarding sex. The distribution among female and male patients was similar for SRs containing unknown ADRs, with 70.08% (n=452) regarding female patients, 25.27% (n=163) regarding male patients and 4.65% (n=30) contained no information regarding sex. Globally, patients presented a mean age of 46.9 ± 18.5 years. The mean age increased slightly when accounting only SRs containing unknown ADRs, to 49.6 ± 18.6 years.

The majority of spontaneous reports (81.03%; n=1884) related to individuals between the ages of 18-64 years. 14.84% (n=345) of spontaneous reports related to individuals over 65 years of age. For SRs containing unknown ADRs, the majority (70.70%; n=456) also related to individuals between the ages of 18-64, while 20.16% (n=130) related to individuals over 65 years of age.

52.05% (n=1214) of the identified SRs originated from physicians. The second highest percentage (25.00%; n=583) of SRs was reported by consumers. This percentage may indicate that consumers are now aware of the importance of pharmacovigilance, but it also highlights potential under-reporting for some categories of healthcare professionals (28). Similarly, for SRs containing unknown ADRs, 44.07% (n=286) of SRs were reported by physicians and 39.53% (n=255) of SRs were reported by consumers.

From a geographical standpoint, and according to data from INE (9) and Pordata (10), Aveiro is the district comprising the largest population, with 708 246 inhabitants, followed by Coimbra's 420 481 inhabitants and Leiria's 362 361 inhabitants. Notwithstanding, the district of Coimbra originated 45.55% (n=1059) of SRs, with Aveiro and Leiria with lower yet similar percentages (27.05%; n=629 and 27.40%; n=637).

Three of the four identifiable vaccines were administered in a two-dose scheme. For all three, the number of SRs associated with first dose (57.92%, n=1664) is superior to the number of SRs associated with the second dose (32.96%, n=947). This characteristic is particularly evident for Vaxzevria, with 76.48% (n=413) SRs containing at least one ADR to the first dose and 16.48% (n=89) of SRs containing at least one ADR to the second dose.

Regarding Seriousness, less than half (43.70%; n=1016) of the SRs received by the UFC were considered Serious, i.e., they presented at least one seriousness criteria. Despite the fact that Comirnaty was the most frequently administered vaccine, it presented the lowest percentage (39.55%; n=581) of Serious SRs among the identifiable vaccines, while JCOVDEN, the less frequently administered vaccine, presented the highest percentage (53.89%; n=180). The Chi-Squared test of independence concluded that the variables seriousness and COVID-19 vaccine administered were not independent. It should be noted that, in the absence of exposure data, it is not possible to establish if one particular vaccine is more associated with Serious ADRs.

For the Serious SRs identified, 71.26% (n=724) were considered Certain, i.e., these spontaneous reports contained an event with plausible time relationship and could not be explained by disease or other drugs. This causality assessment enforces the necessity for intensive monitoring of ADRs, as their inclusion in the SmPC will allow for some preventability, through implementation of risk minimizing measures.

For all vaccines, the average of ADRs per SR was 2.97. Vaxzevria was the vaccine with the highest average of ADRs per SR, with 476 SRs containing 1544 ADRs.

For all identifiable vaccines, the first ADR most frequently occurred within 24 hours after vaccination.

Among the SRs received, 69.38% (n=1613) contained previously described (known) ADRs. The remainder of SRs was further analysed, in order to characterize unknown ADRs received by the UFC.

Of the 645 SRs identified as containing at least one unknown ADR, 1074 ADRs were extracted. The majority of SRs (72.25%; n=776) presented an associated seriousness criteria, and thus was considered Serious. Upon assessment of causality of these Serious ADRs, 65.21% (n=506) were imputed as Certain.

For Comirnaty and Vaxzevria, the most frequently reported ADRs were within SOCs "General disorders and administration site conditions", "Musculoskeletal and connective tissue disorders" and "Nervous system disorders", while for Spikevax the most frequently reported ADRs were within SOC "General disorders and administration site conditions". For JCOVDEN, the most frequently reported ADRs were within SOCs "Infections and infestations" and "General disorders and administration site conditions". A detailed analysis of the most frequently reported ADRs has demonstrated that these ADRs are considered Known, as they are described in the Summary of Product Characteristics. However, this was not always the case. Spontaneous reporting has contributed towards the continuous update of the product information (29), and some ADRs that were initially considered Unknown in the SNF database would now be considered Known, as their description has been included in the Summary of Product Characteristics. This is particularly evident in the most frequently reported unknown ADRs, since most of these have been posteriorly included in the product information.

For Comirnaty, a few examples are paraesthesia, hypoesthesia, erythema multiforme, myocarditis, pericarditis, diarrhoea, vomiting, extensive swelling of vaccinated limb and facial swelling (30).

For Vaxzevria, examples of these ADRs include immune thrombocytopenia and cerebrovascular venous and sinus thrombosis (31).

For Spikevax, ADRs such as myocarditis, pericarditis and extensive swelling of vaccinated limb (32).

For JCOVDEN, examples include cutaneous small vessel vasculitis, transverse myelitis and venous thromboembolism (33).

Nevertheless, it is important to note that ADRs must be contextualized in order to assess the previous knowledge, since some SRs contained ADRs that, while being described in the SmPC, occurred in non-described contexts. An example of well-known ADRs that were considered Unknown was fever and vomiting in a 3 year old breastfed child whose mother had been vaccinated with Comirnaty. In this case, since exposure via breast milk is not yet established (34), the ADRs were considered Unknown.

A potential limitation to the present study is related to underreporting, which is a common characteristic of pharmacovigilance systems (35). Despite the fact that all COVID-19 vaccines are subject to additional monitoring, it is possible that a large number of ADRs were not reported. This limitation reinforces the need for adequate promotion of pharmacovigilance systems and the importance of spontaneous reporting.

Another limitation is related to the difficulty of detecting late and long onset ADRs. Further studies should be conducted to follow up vaccinated individuals for a longer period of time in order to detect this type of ADRs.

A nationwide study aimed at the same objectives would be of value in validating the results of this study.

VI. Conclusions

Conclusions

The analysis of spontaneous reports received by the Pharmacovigilance Unit of Coimbra concerning ADRs associated with COVID-19 vaccines allowed for the following conclusions.

Four vaccines were administered in Portugal during the year of 2021: Comirnaty, Spikevax previously COVID-19 Vaccine Moderna, Vaxzevria previously COVID-19 Vaccine AstraZeneca and JCOVDEN (previously COVID-19 Vaccine Janssen).

The administration of COVID-19 vaccines induced an exponential growth of spontaneous reports received by the National Pharmacovigilance System, which led the national competent authority to periodically publish reports dedicated to COVID-19 vaccines, in order to promote health literacy and combat misinformation. These reports, through exposure data provided by the Ministry of Health, demonstrated that Comirnaty was the most frequently administered vaccine, followed by Spikevax, Vaxzevria and JCOVDEN. Spontaneous reports received by the UFC demonstrated a similar proportionality, with Comirnaty being the most frequently reported suspected medicine, but with more reports associated with Vaxzevria instead of Spikevax.

More than half (56.30%) of the spontaneous reports received by the UFC were considered Non Serious, and more than half (69.25%) contained known ADRs, which reinforces the hypothesis that healthcare professionals and consumers actively sought to report all ADRs, independently of their seriousness or previous knowledge. Consumers played an important role in reporting, and this new knowledge of the importance of pharmacovigilance may contribute towards the promotion of spontaneous reporting for other medicines in the future.

Furthermore, as demonstrated in the frequent revisions of the product information for COVID-19 vaccines, spontaneous reporting allowed for the inclusion of many previously unknown Adverse Drug Reactions in the SmPC of all COVID-19 vaccines. This knowledge allows for the implementation of advertences and precautions that contribute towards the well-being of the vaccinated population.

In conclusion, spontaneous reporting allowed for the identification of previously unknown ADRs for COVID-19 vaccines. The COVID-19 pandemic was associated with an increase of spontaneous reports. These efforts should be continuously maintained in order to combat previously identified limitations of spontaneous reporting.

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List of Appendices

Appendix 1 – WHO-UMC Causality Categories

Table 30. WHO-UMC Causality Categories (12)

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake; • Cannot be explained by disease or other drugs; • Response to withdrawal plausible (pharmacologically, pathologically); • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon); • Rechallenge satisfactory, if necessary.
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake; • Unlikely to be attributed to disease or other drugs; • Response to withdrawal clinically reasonable; • Rechallenge not required.
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake; • Could also be explained by disease or other drugs; • Information on drug withdrawal may be lacking or unclear.
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); • Disease or other drugs provide plausible explanations.
Conditional/Unclassified	• Event or laboratory test abnormality; • More data for proper assessment needed, or; • Additional data under examination.
Unassessable/Unclassifiable	• Report suggesting an Adverse Drug Reaction; • Cannot be judged because information is insufficient or contradictory; • Data cannot be supplemented or verified.

Appendix 2 – Adverse Drug Reactions for Comirnaty per Primary SOC and PT

Table 31 – Adverse Drug Reactions for Comirnaty per Primary SOC and PT

Primary SOC / Preferred Term	Total	%
General disorders and administration site conditions	57 (1884)	42.99%
Vaccination site pain	668	15.24%
Pyrexia	186	4.24%
Vaccination failure	172	3.93%
Chills	162	3.70%
Fatigue	114	2.60%
Vaccination site swelling	108	2.46%
Vaccination site erythema	81	1.85%
Drug ineffective	54	1.23%
Asthenia	43	0.98%
Vaccination site pruritus	43	0.98%
Malaise	40	0.91%
No adverse event	32	0.73%
Pain	18	0.41%
Injection site erythema	17	0.39%
Axillary pain	16	0.37%
Vaccination site oedema	15	0.34%
Chest pain	14	0.32%
Feeling hot	11	0.25%
Injection site pain	8	0.18%
Oedema peripheral	6	0.14%
Vaccination site warmth	6	0.14%
Chest discomfort	5	0.11%
Localised oedema	4	0.09%
Nodule	4	0.09%
Swelling	4	0.09%
Death	3	0.07%
Face oedema	3	0.07%
Feeling cold	3	0.07%
Influenza like illness	3	0.07%
Injection site swelling	3	0.07%
Peripheral swelling	3	0.07%
Vaccination site inflammation	3	0.07%
Injection site haematoma	2	0.05%
Injection site pruritus	2	0.05%
Injection site warmth	2	0.05%
Vaccination site lymphadenopathy	2	0.05%
Vaccination site movement impairment	2	0.05%
Vaccination site rash	2	0.05%
Vaccination site reaction	2	0.05%
Administration site inflammation	1	0.02%
Crying	1	0.02%
Discomfort	1	0.02%
Facial pain	1	0.02%
Feeling of body temperature change	1	0.02%
Gait disturbance	1	0.02%
Gait inability	1	0.02%
General symptom	1	0,02%

Primary SOC / Preferred Term	Total	%
Generalised oedema	1	0.02%
Injection site hypoaesthesia	1	0.02%
Injection site induration	1	0.02%
Injection site urticaria	1	0.02%
Medical device site cyst	1	0.02%
Oedema	1	0.02%
Sluggishness	1	0.02%
Vaccination site haematoma	1	0.02%
Vaccination site joint movement impairment	1	0.02%
Vaccination site paraesthesia	1	0.02%
Nervous system disorders	47 (584)	13.33%
Headache	353	8.06%
Dizziness	49	1.12%
Paraesthesia	33	0.75%
Somnolence	27	0.62%
Presyncope	18	0.41%
Dysgeusia	14	0.32%
Hypoaesthesia	13	0.30%
Syncope	7	0.16%
Ischaemic stroke	6	0.14%
Seizure	6	0.14%
Cerebrovascular accident	4	0.09%
Facial paralysis	4	0.09%
Tremor	4	0.09%
Ageusia	3	0.07%
Hemiparesis	3	0.07%
Balance disorder	2	0.05%
Burning sensation	2	0.05%
Disturbance in attention	2	0.05%
Encephalitis autoimmune	2	0.05%
Hypersomnia	2	0.05%
Loss of consciousness	2	0.05%
Memory impairment	2	0.05%
Migraine	2	0.05%
Allodynia	1	0.02%
Amnesia	1	0.02%
Anosmia	1	0.02%
Cerebral venous thrombosis	1	0.02%
Coordination abnormal	1	0.02%
Dysarthria	1	0.02%
Dyskinesia	1	0.02%
Dyslexia	1	0.02%
Encephalopathy	1	0.02%
Facial paresis	1	0.02%
Haemorrhagic stroke	1	0.02%
Head discomfort	1	0.02%
Hemianaesthesia	1	0.02%
Hypokinesia	1	0.02%
Monoplegia	1	0.02%
Multiple sclerosis relapse	1	0.02%
Muscle contractions involuntary	1	0.02%

Primary SOC / Preferred Term	Total	%
Myoclonus	1	0.02%
Neuropathy peripheral	1	0.02%
Sciatica	1	0.02%
Speech disorder	1	0.02%
Status epilepticus	1	0.02%
Taste disorder	1	0.02%
Tongue paralysis	1	0.02%
Skin and subcutaneous tissue disorders	37 (156)	3.56%
Urticaria	26	0.59%
Pruritus	23	0.52%
Rash	19	0.43%
Erythema	18	0.41%
Hyperhidrosis	7	0.16%
Rash macular	6	0.14%
Rash pruritic	6	0.14%
Angioedema	5	0.11%
Rash erythematous	5	0.11%
Rash maculo-papular	4	0.09%
Cold sweat	3	0.07%
Ecchymosis	3	0.07%
Telangiectasia	3	0.07%
Alopecia	2	0.05%
Dermatitis bullous	2	0.05%
Petechiae	2	0.05%
Purpura	2	0.05%
Acne	1	0.02%
Circumoral oedema	1	0.02%
Dermatitis	1	0.02%
Dermatitis allergic	1	0.02%
Erythema multiforme	1	0.02%
Haemorrhage subcutaneous	1	0.02%
Henoch-Schonlein purpura	1	0.02%
Nail pigmentation	1	0.02%
Night sweats	1	0.02%
Palmar-plantar erythrodysaesthesia syndrome	1	0.02%
Papule	1	0.02%
Pemphigoid	1	0.02%
Psoriasis	1	0.02%
Rash maculovesicular	1	0.02%
Rash papular	1	0.02%
Skin exfoliation	1	0.02%
Skin irritation	1	0.02%
Skin lesion	1	0.02%
Urticaria chronic	1	0.02%
Urticaria papular	1	0.02%
Gastrointestinal disorders	35 (275)	6.28%
Nausea	122	2.78%
Diarrhoea	52	1.19%
Vomiting	32	0.73%
Abdominal pain	6	0.14%
Lip oedema	6	0.14%

Primary SOC / Preferred Term	Total	%
Tongue oedema	6	0.14%
Hypoaesthesia oral	5	0.11%
Abdominal pain upper	4	0.09%
Dyspepsia	4	0.09%
Odynophagia	4	0.09%
Paraesthesia oral	4	0.09%
Abdominal discomfort	3	0.07%
Dry mouth	2	0.05%
Dysphagia	2	0.05%
Gastrooesophageal reflux disease	2	0.05%
Tongue disorder	2	0.05%
Abdominal distension	1	0.02%
Abdominal pain lower	1	0.02%
Faeces soft	1	0.02%
Flatulence	1	0.02%
Glossitis	1	0.02%
Glossodynia	1	0.02%
Lip erythema	1	0.02%
Lip swelling	1	0.02%
Lip ulceration	1	0.02%
Oedema mouth	1	0.02%
Oesophagitis	1	0.02%
Oral disorder	1	0.02%
Retroperitoneal haematoma	1	0.02%
Swollen tongue	1	0.02%
Tongue discolouration	1	0.02%
Tongue dry	1	0.02%
Tongue rough	1	0.02%
Toothache	1	0.02%
Upper gastrointestinal haemorrhage	1	0.02%
Respiratory, thoracic and mediastinal disorders	24 (95)	2.17%
Cough	20	0.46%
Dyspnoea	18	0.41%
Rhinorrhoea	10	0.23%
Pulmonary embolism	9	0.21%
Oropharyngeal discomfort	6	0.14%
Laryngeal oedema	5	0.11%
Nasal congestion	4	0.09%
Epistaxis	3	0.07%
Dysphonia	2	0.05%
Oropharyngeal pain	2	0.05%
Painful respiration	2	0.05%
Throat tightness	2	0.05%
Asthma	1	0.02%
Asthmatic crisis	1	0.02%
Hyperventilation	1	0.02%
Oropharyngeal oedema	1	0.02%
Pharyngeal swelling	1	0.02%
Pleurisy	1	0.02%
Pulmonary oedema	1	0.02%
Respiratory disorder	1	0.02%

Primary SOC / Preferred Term	Total	%
Respiratory failure	1	0.02%
Rhinitis allergic	1	0.02%
Sneezing	1	0.02%
Suffocation feeling	1	0.02%
Musculoskeletal and connective tissue disorders	21 (670)	15.29%
Myalgia	396	9.04%
Arthralgia	196	4.47%
Pain in extremity	33	0.75%
Back pain	10	0.23%
Limb discomfort	6	0.14%
Neck pain	6	0.14%
Axillary mass	3	0.07%
Muscular weakness	3	0.07%
Musculoskeletal stiffness	3	0.07%
Bursitis	2	0.05%
Muscle spasms	2	0.05%
Arthritis	1	0.02%
Groin pain	1	0.02%
Haematoma muscle	1	0.02%
Joint contracture	1	0.02%
Joint swelling	1	0.02%
Muscle tightness	1	0.02%
Musculoskeletal pain	1	0.02%
Neck mass	1	0.02%
Posture abnormal	1	0.02%
Synovial cyst	1	0.02%
Eye disorders	20 (36)	0.82%
Vision blurred	8	0.18%
Blindness transient	3	0.07%
Conjunctival haemorrhage	3	0.07%
Eye haemorrhage	2	0.05%
Eye irritation	2	0.05%
Eyelid oedema	2	0.05%
Photophobia	2	0.05%
Visual impairment	2	0.05%
Blepharospasm	1	0.02%
Ciliary body disorder	1	0.02%
Conjunctival hyperaemia	1	0.02%
Conjunctival irritation	1	0.02%
Corneal opacity	1	0.02%
Diplopia	1	0.02%
Eye pruritus	1	0.02%
Ocular hyperaemia	1	0.02%
Periorbital discomfort	1	0.02%
Retinal detachment	1	0.02%
Uveitis	1	0.02%
Vitreous floaters	1	0.02%
Vascular disorders	17 (51)	1.16%
Haematoma	8	0.18%
Pallor	8	0.18%
Hypertension	7	0.16%

Primary SOC / Preferred Term	Total	%
Hypotension	5	0.11%
Deep vein thrombosis	4	0.09%
Peripheral coldness	3	0.07%
Thrombophlebitis	3	0.07%
Vasculitis	3	0.07%
Superficial vein thrombosis	2	0.05%
Blood pressure fluctuation	1	0.02%
Cyanosis	1	0.02%
Embolism venous	1	0.02%
Flushing	1	0.02%
Giant cell arteritis	1	0.02%
Hypertensive crisis	1	0.02%
Labile blood pressure	1	0.02%
Thrombosis	1	0.02%
Infections and infestations	15 (215)	4.91%
COVID-19	147	3,35%
Asymptomatic COVID-19	54	1,23%
Herpes zoster	2	0,05%
Genital herpes	1	0,02%
Influenza	1	0,02%
Myelitis	1	0,02%
Nasopharyngitis	1	0,02%
Oral herpes	1	0,02%
Pneumonia	1	0,02%
Rash pustular	1	0,02%
Sepsis	1	0,02%
Tonsillitis	1	0,02%
Vaccination site abscess	1	0,02%
Vaccination site cellulitis	1	0,02%
Vestibular neuronitis	1	0,02%
Injury, poisoning and procedural complications	11 (44)	1.00%
Vaccination error	13	0.30%
Exposure during pregnancy	12	0.27%
Inappropriate schedule of product administration	10	0.23%
Exposure via breast milk	2	0.05%
Chillblains	1	0.02%
Contusion	1	0.02%
Foot fracture	1	0.02%
Maternal exposure during breast feeding	1	0.02%
Product preparation issue	1	0.02%
Subcutaneous haematoma	1	0.02%
Vaccination complication	1	0.02%
Investigations	10 (17)	0.39%
Blood pressure increased	3	0.07%
Heart rate increased	3	0.07%
Oxygen saturation decreased	3	0.07%
Blood pressure decreased	2	0.05%
Blood fibrinogen increased	1	0.02%
Blood pressure diastolic increased	1	0.02%
Body temperature abnormal	1	0.02%
Haemoglobin decreased	1	0.02%

Primary SOC / Preferred Term	Total	%
Heart rate abnormal	1	0.02%
Heart rate irregular	1	0.02%
Psychiatric disorders	10 (78)	1.78%
Insomnia	60	1.37%
Anxiety	4	0.09%
Sleep disorder	4	0.09%
Confusional state	3	0.07%
Disorientation	2	0.05%
Agitation	1	0.02%
Impaired reasoning	1	0.02%
Mental disorder	1	0.02%
Morbid thoughts	1	0.02%
Tachyphrenia	1	0.02%
Cardiac disorders	9 (37)	0.84%
Tachycardia	14	0.32%
Myocarditis	9	0.21%
Palpitations	5	0.11%
Bradycardia	3	0.07%
Arrhythmia	2	0.05%
Cardiac discomfort	1	0.02%
Cardio-respiratory arrest	1	0.02%
Sinus tachycardia	1	0.02%
Ventricular extrasystoles	1	0.02%
Reproductive system and breast disorders	9 (15)	0.34%
Menstruation irregular	4	0.09%
Menstrual disorder	3	0.07%
Dysmenorrhoea	2	0.05%
Amenorrhoea	1	0.02%
Breast oedema	1	0.02%
Breast pain	1	0.02%
Intermenstrual bleeding	1	0.02%
Vaginal haemorrhage	1	0.02%
Vulvovaginal burning sensation	1	0.02%
Metabolism and nutrition disorders	7 (32)	0.73%
Decreased appetite	24	0.55%
Hypoglycaemia	2	0.05%
Polydipsia	2	0.05%
Diabetes mellitus	1	0.02%
Food refusal	1	0.02%
Hyperglycaemia	1	0.02%
Hypertriglyceridaemia	1	0.02%
Renal and urinary disorders	6 (9)	0.21%
Acute kidney injury	2	0.05%
Haematuria	2	0.05%
Pollakiuria	2	0.05%
Micturition urgency	1	0.02%
Renal failure	1	0.02%
Tubulointerstitial nephritis	1	0.02%
Blood and lymphatic system disorders	5 (145)	3.31%
Lymphadenopathy	135	3.08%
Lymphadenitis	7	0.16%

Primary SOC / Preferred Term	Total	%
Leukaemoid reaction	1	0.02%
Spontaneous haematoma	1	0.02%
Thrombocytopenia	1	0.02%
Ear and labyrinth disorders	5 (15)	0.34%
Tinnitus	6	0.14%
Vertigo	5	0.11%
Hypoacusis	2	0.05%
Ear discomfort	1	0.02%
Vestibular ataxia	1	0.02%
Hepatobiliary disorders	4 (5)	0.11%
Hepatitis toxic	2	0.05%
Hepatic failure	1	0.02%
Hepatitis acute	1	0.02%
Portal vein thrombosis	1	0.02%
Immune system disorders	3 (12)	0.27%
Anaphylactic reaction	10	0.23%
Anaphylactic shock	1	0.02%
Hypersensitivity	1	0.02%
Endocrine disorders	2 (2)	0.04%
Thyroid mass	1	0.02%
Thyroiditis	1	0.02%
Pregnancy, puerperium and perinatal conditions	2 (2)	0.04%
Abortion spontaneous	1	0.02%
High risk pregnancy	1	0.02%
Surgical and medical procedures	1 (3)	0.07%
COVID-19 immunisation*	3	0.07%
Total	357 (4382)	100.00%

*3 spontaneous reports contained more than one suspected vaccine. In these cases, it is recommended to code LLT "revaccination with different COVID-19 vaccine", which corresponds to PT "COVID-19 immunisation".

Appendix 3 – Adverse Drug Reactions for Vaxzevria per Primary SOC and PT

Table 32 – Adverse Drug Reactions for Vaxzevria per Primary SOC and PT

Primary SOC / Preferred Term	Total	%
General disorders and administration site conditions	47 (588)	38.08%
Pyrexia	155	10.04%
Vaccination site pain	78	5.05%
Fatigue	60	3.89%
Chills	47	3.04%
Vaccination failure	41	2.66%
Malaise	30	1.94%
Pain	16	1.04%
Drug ineffective	14	0.91%
Feeling cold	13	0.84%
Vaccination site swelling	12	0.78%
Asthenia	11	0.71%
Vaccination site erythema	10	0.65%
No adverse event	9	0.58%
Chest pain	8	0.52%
Discomfort	7	0.45%
Vaccination site oedema	7	0.45%
Feeling of body temperature change	6	0.39%
Vaccination site pruritus	6	0.39%
Feeling hot	5	0.32%
Oedema peripheral	5	0.32%
Vaccination site warmth	5	0.32%
Hyperthermia	4	0.26%
Vaccination site haematoma	4	0.26%
Influenza like illness	3	0.19%
Face oedema	2	0.13%
Injection site erythema	2	0.13%
Nodule	2	0.13%
Swelling	2	0.13%
Thirst	2	0.13%
Vaccination site discomfort	2	0.13%
Vaccination site inflammation	2	0.13%
Vaccination site movement impairment	2	0.13%
Vaccination site rash	2	0.13%
Administration site macule	1	0.06%
Death	1	0.06%
Effusion	1	0.06%
Facial pain	1	0.06%
Feeling abnormal	1	0.06%
Hangover	1	0.06%
Hypothermia	1	0.06%
Injection site haemorrhage	1	0.06%
Localised oedema	1	0.06%
Peripheral swelling	1	0.06%
Vaccination site induration	1	0.06%
Vaccination site mass	1	0.06%
Vaccination site reaction	1	0.06%
Vaccination site urticaria	1	0.06%

Primary SOC / Preferred Term	Total	%
Nervous system disorders	32 (265)	17.16%
Headache	142	9.20%
Dizziness	33	2.14%
Somnolence	19	1.23%
Paraesthesia	11	0.71%
Ischaemic stroke	7	0.45%
Tremor	7	0.45%
Guillain-Barre syndrome	5	0.32%
Syncope	5	0.32%
Ageusia	3	0.19%
Balance disorder	3	0.19%
Dysgeusia	3	0.19%
Anosmia	2	0.13%
Cerebrovascular accident	2	0.13%
Diplegia	2	0.13%
Hypoaesthesia	2	0.13%
Migraine	2	0.13%
Parosmia	2	0.13%
Altered state of consciousness	1	0.06%
Bell's palsy	1	0.06%
Cerebral venous sinus thrombosis	1	0.06%
Coordination abnormal	1	0.06%
Dysarthria	1	0.06%
Electric shock sensation	1	0.06%
Febrile convulsion	1	0.06%
Head discomfort	1	0.06%
Memory impairment	1	0.06%
Monoplegia	1	0.06%
Neurological symptom	1	0.06%
Presyncope	1	0.06%
Speech disorder	1	0.06%
Taste disorder	1	0.06%
Transient ischaemic attack	1	0.06%
Skin and subcutaneous tissue disorders	26 (83)	5.38%
Rash	12	0.78%
Urticaria	10	0.65%
Pruritus	9	0.58%
Hyperhidrosis	7	0.45%
Rash pruritic	7	0.45%
Erythema	6	0.39%
Ecchymosis	3	0.19%
Petechiae	3	0.19%
Rash erythematous	3	0.19%
Rash macular	3	0.19%
Cold sweat	2	0.13%
Livedo reticularis	2	0.13%
Pain of skin	2	0.13%
Skin sensitisation	2	0.13%
Alopecia	1	0.06%
Dermatitis allergic	1	0.06%
Macule	1	0.06%

Primary SOC / Preferred Term	Total	%
Palmar erythema	1	0.06%
Photosensitivity reaction	1	0.06%
Pityriasis rosea	1	0.06%
Plantar erythema	1	0.06%
Purpura	1	0.06%
Skin burning sensation	1	0.06%
Skin haemorrhage	1	0.06%
Skin irritation	1	0.06%
Skin reaction	1	0.06%
Gastrointestinal disorders	22 (155)	10.04%
Nausea	57	3.69%
Vomiting	39	2.53%
Diarrhoea	26	1.68%
Abdominal pain	6	0.39%
Abdominal pain upper	3	0.19%
Anal spasm	2	0.13%
Aphthous ulcer	2	0.13%
Dyspepsia	2	0.13%
Gastrointestinal disorder	2	0.13%
Lip oedema	2	0.13%
Odynophagia	2	0.13%
Paraesthesia oral	2	0.13%
Abdominal distension	1	0.06%
Eructation	1	0.06%
Glossitis	1	0.06%
Hypoaesthesia oral	1	0.06%
Mesenteric vein thrombosis	1	0.06%
Mesenteric venous occlusion	1	0.06%
Oral discomfort	1	0.06%
Stomatitis	1	0.06%
Tongue oedema	1	0.06%
Truncus coeliacus thrombosis	1	0.06%
Vascular disorders	14 (32)	2.07%
Hypotension	6	0.39%
Thrombophlebitis	6	0.39%
Deep vein thrombosis	3	0.19%
Haematoma	3	0.19%
Hypertension	2	0.13%
Peripheral coldness	2	0.13%
Superficial vein thrombosis	2	0.13%
Vasculitis	2	0.13%
Capillary leak syndrome	1	0.06%
Embolism	1	0.06%
Hypertensive crisis	1	0.06%
Poor peripheral circulation	1	0.06%
Venous thrombosis	1	0.06%
Venous thrombosis limb	1	0.06%
Musculoskeletal and connective tissue disorders	11 (228)	14.77%
Myalgia	141	9.13%
Arthralgia	50	3.24%
Pain in extremity	12	0.78%

Primary SOC / Preferred Term	Total	%
Back pain	10	0.65%
Muscle spasms	5	0.32%
Muscular weakness	3	0.19%
Limb discomfort	2	0.13%
Neck pain	2	0.13%
Mastication disorder	1	0.06%
Muscle contracture	1	0.06%
Muscle fatigue	1	0.06%
Respiratory, thoracic and mediastinal disorders	11 (22)	1.42%
Dyspnoea	6	0.39%
Cough	3	0.19%
Pulmonary embolism	3	0.19%
Epistaxis	2	0.13%
Throat tightness	2	0.13%
Nasal congestion	1	0.06%
Nasal discomfort	1	0.06%
Oropharyngeal discomfort	1	0.06%
Respiratory failure	1	0.06%
Throat irritation	1	0.06%
Wheezing	1	0.06%
Cardiac disorders	10 (17)	1.10%
Tachycardia	5	0.32%
Acute myocardial infarction	2	0.13%
Arrhythmia	2	0.13%
Palpitations	2	0.13%
Angina pectoris	1	0.06%
Atrial fibrillation	1	0.06%
Cardiac discomfort	1	0.06%
Extrasystoles	1	0.06%
Intracardiac thrombus	1	0.06%
Pericarditis	1	0.06%
Investigations	10 (18)	1.17%
Body temperature increased	4	0.26%
Body temperature abnormal	3	0.19%
Blood pressure abnormal	2	0.13%
Blood pressure increased	2	0.13%
Heart rate increased	2	0.13%
Blood pressure decreased	1	0.06%
Body temperature fluctuation	1	0.06%
Heart rate irregular	1	0.06%
Plateletcrit decreased	1	0.06%
Weight decreased	1	0.06%
Eye disorders	9 (15)	0.97%
Conjunctival haemorrhage	4	0.26%
Vision blurred	3	0.19%
Retinal vein occlusion	2	0.13%
Eye opacity	1	0.06%
Eye pruritus	1	0.06%
Lacrimation increased	1	0.06%
Swelling of eyelid	1	0.06%
Visual acuity reduced	1	0.06%

Primary SOC / Preferred Term	Total	%
Visual impairment	1	0.06%
Infections and infestations	7 (59)	3.82%
COVID-19	46	2.98%
Asymptomatic COVID-19	8	0.52%
Cytomegalovirus hepatitis	1	0.06%
Herpes simplex reactivation	1	0.06%
Herpes zoster	1	0.06%
Urinary tract infection	1	0.06%
Vaccination site cellulitis	1	0.06%
Metabolism and nutrition disorders	5 (18)	1.17%
Appetite disorder	7	0,45%
Decreased appetite	7	0,45%
Hyperglycaemia	2	0,13%
Ketosis	1	0,06%
Polydipsia	1	0,06%
Blood and lymphatic system disorders	4 (6)	0.39%
Lymphadenopathy	3	0.19%
Lymphadenitis	1	0.06%
Thrombocytopenia	1	0.06%
Thrombocytopenic purpura	1	0.06%
Ear and labyrinth disorders	4 (14)	0.91%
Vertigo	10	0.65%
Ear pain	2	0.13%
Ear congestion	1	0.06%
Tinnitus	1	0.06%
Psychiatric disorders	4 (6)	0.39%
Insomnia	3	0.19%
Emotional distress	1	0.06%
Impaired reasoning	1	0.06%
Nightmare	1	0.06%
Injury, poisoning and procedural complications	3 (12)	0.78%
Vaccination error	8	0.52%
Maternal exposure during breast feeding	3	0.19%
Exposure during pregnancy	1	0.06%
Immune system disorders	1 (3)	0.19%
Anaphylactic reaction	3	0.19%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1)	0.06%
High-grade B-cell lymphoma	1	0.06%
Renal and urinary disorders	1 (1)	0.06%
Dysuria	1	0.06%
Reproductive system and breast disorders	1 (1)	0.06%
Balanoposthitis	1	0.06%
Total	223 (1544)	100.00%

Appendix 4 – Adverse Drug Reactions for Spikevax per Primary SOC and PT

Table 33 – Adverse Drug Reactions for Spikevax per Primary SOC and PT

Primary SOC / Preferred Term	Total	%
General disorders and administration site conditions	38 (298)	54.68%
Vaccination site pain	45	8.26%
Vaccination site erythema	29	5.32%
Pyrexia	28	5.14%
Vaccination site oedema	20	3.67%
Chills	18	3.30%
Vaccination site pruritus	18	3.30%
Vaccination failure	17	3.12%
Vaccination site warmth	17	3.12%
Fatigue	16	2.94%
Vaccination site swelling	13	2.39%
No adverse event	12	2.20%
Drug ineffective	8	1.47%
Injection site erythema	7	1.28%
Malaise	7	1.28%
Asthenia	4	0.73%
Axillary pain	4	0.73%
Injection site pain	4	0.73%
Vaccination site rash	4	0.73%
Vaccination site urticaria	4	0.73%
Face oedema	2	0.37%
Injection site swelling	2	0.37%
Vaccination site induration	2	0.37%
Vaccination site inflammation	2	0.37%
Administration site erythema	1	0.18%
Death	1	0.18%
Feeling hot	1	0.18%
Influenza like illness	1	0.18%
Injection site hypersensitivity	1	0.18%
Injection site pruritus	1	0.18%
Oedema peripheral	1	0.18%
Pain	1	0.18%
Swelling face	1	0.18%
Vaccination site exfoliation	1	0.18%
Vaccination site irritation	1	0.18%
Vaccination site movement impairment	1	0.18%
Vaccination site nodule	1	0.18%
Vaccination site papule	1	0.18%
Vaccination site reaction	1	0.18%
Skin and subcutaneous tissue disorders	13 (30)	5.50%
Rash	11	2.02%
Erythema	3	0.55%
Pruritus	3	0.55%
Rash macular	3	0.55%
Ecchymosis	2	0.37%
Acne	1	0.18%
Angioedema	1	0.18%
Dermatitis allergic	1	0.18%

Primary SOC / Preferred Term	Total	%
Rash erythematous	1	0.18%
Rash papular	1	0.18%
Rash pruritic	1	0.18%
Skin reaction	1	0.18%
Urticaria	1	0.18%
Gastrointestinal disorders	11 (44)	8.07%
Nausea	17	3.12%
Vomiting	11	2.02%
Diarrhoea	6	1.10%
Lip oedema	2	0.37%
Toothache	2	0.37%
Abdominal discomfort	1	0.18%
Abdominal pain	1	0.18%
Duodenogastric reflux	1	0.18%
Oral disorder	1	0.18%
Paraesthesia oral	1	0.18%
Tongue oedema	1	0.18%
Nervous system disorders	11 (38)	6.97%
Headache	21	3.85%
Dizziness	4	0.73%
Presyncope	3	0.55%
Somnolence	3	0.55%
Bell's palsy	1	0.18%
Cerebrovascular accident	1	0.18%
Guillain-Barre syndrome	1	0.18%
Head discomfort	1	0.18%
Ischaemic stroke	1	0.18%
Paraesthesia	1	0.18%
Syncope	1	0.18%
Respiratory, thoracic and mediastinal disorders	6 (8)	1.47%
Dyspnoea	3	0.55%
Aphonia	1	0.18%
Choking sensation	1	0.18%
Dysphonia	1	0.18%
Laryngeal oedema	1	0.18%
Oropharyngeal discomfort	1	0.18%
Infections and infestations	5 (29)	5.32%
COVID-19	24	4.40%
Herpes zoster	2	0.37%
Asymptomatic COVID-19	1	0.18%
Otitis externa	1	0.18%
Vaccination site pustule	1	0.18%
Injury, poisoning and procedural complications	5 (13)	2.39%
Wrong product administered	5	0.92%
Vaccination error	4	0.73%
Inappropriate schedule of product administration	2	0.37%
Exposure during pregnancy	1	0.18%
Exposure via breast milk	1	0.18%
Musculoskeletal and connective tissue disorders	5 (37)	6.79%
Myalgia	25	4.59%
Arthralgia	6	1.10%

Primary SOC / Preferred Term	Total	%
Pain in extremity	3	0.55%
Axillary mass	2	0.37%
Arthritis reactive	1	0.18%
Reproductive system and breast disorders	5 (6)	1.10%
Intermenstrual bleeding	2	0.37%
Abnormal withdrawal bleeding	1	0.18%
Breast mass	1	0.18%
Menstrual disorder	1	0.18%
Menstruation irregular	1	0.18%
Cardiac disorders	4 (7)	1.28%
Tachycardia	3	0.55%
Cardiac discomfort	2	0.37%
Myocarditis	1	0.18%
Pericarditis	1	0.18%
Eye disorders	2 (2)	0.36%
Conjunctival haemorrhage	1	0.18%
Retinal artery occlusion	1	0.18%
Vascular disorders	2 (4)	0.73%
Haematoma	3	0.55%
Deep vein thrombosis	1	0.18%
Renal and urinary disorders	2 (2)	0.36%
Haemorrhage urinary tract	1	0,18%
Renal pain	1	0,18%
Blood and lymphatic system disorders	1 (20)	3.67%
Lymphadenopathy	20	3.67%
Ear and labyrinth disorders	1 (1)	0.18%
Tinnitus	1	0.18%
Immune system disorders	1 (1)	0.18%
Drug hypersensitivity	1	0.18%
Investigations	1 (1)	0.18%
Blood pressure increased	1	0.18%
Metabolism and nutrition disorders	1 (2)	0.37%
Decreased appetite	2	0.37%
Psychiatric disorders	1 (1)	0.18%
Agitation	1	0.18%
Surgical and medical procedures	1 (1)	0.18%
COVID-19 immunisation*	1	0.18%
Total	116 (545)	100.00%

*1 spontaneous report contained more than one suspected vaccine. In these cases, it is recommended to code LLT "revaccination with different COVID-19 vaccine", which corresponds to PT "COVID-19 immunisation".

Appendix 5 – Adverse Drug Reactions for JCOVDEN per Primary SOC and PT

Table 34 – Adverse Drug Reactions for JCOVDEN per Primary SOC and PT

Primary SOC / Preferred Term	Total	%
Nervous system disorders	21 (97)	22.20%
Headache	24	5.49%
Presyncope	20	4.58%
Syncope	17	3.89%
Dizziness	11	2.52%
Somnolence	4	0.92%
Guillain-Barre syndrome	3	0.69%
Tremor	3	0.69%
Hypoaesthesia	2	0.46%
Cerebrovascular accident	1	0.23%
Cognitive disorder	1	0.23%
Dysgeusia	1	0.23%
Facial paralysis	1	0.23%
Generalised tonic-clonic seizure	1	0.23%
Migraine	1	0.23%
Monoplegia	1	0.23%
Muscle spasticity	1	0.23%
Myoclonus	1	0.23%
Paraesthesia	1	0.23%
Paraesthesia mucosal	1	0.23%
Parosmia	1	0.23%
Radiculopathy	1	0.23%
General disorders and administration site conditions	19 (148)	33.87%
Pyrexia	40	9.15%
Vaccination failure	37	8.47%
Fatigue	17	3.89%
Drug ineffective	15	3.43%
Vaccination site pain	7	1.60%
No adverse event	6	1.37%
Pain	6	1.37%
Chest pain	4	0.92%
Asthenia	3	0.69%
Chills	3	0.69%
Malaise	2	0.46%
Discomfort	1	0.23%
Inflammation	1	0.23%
Oedema peripheral	1	0.23%
Vaccination site discomfort	1	0.23%
Vaccination site erythema	1	0.23%
Vaccination site oedema	1	0.23%
Vaccination site pruritus	1	0.23%
Vaccination site swelling	1	0.23%
Gastrointestinal disorders	12 (21)	4.81%
Nausea	6	1.37%
Diarrhoea	3	0.69%
Vomiting	3	0.69%
Abdominal discomfort	1	0.23%
Abdominal pain	1	0.23%

Primary SOC / Preferred Term	Total	%
Burning mouth syndrome	1	0.23%
Eructation	1	0.23%
Lip oedema	1	0.23%
Oral discomfort	1	0.23%
Paraesthesia oral	1	0.23%
Thrombosis mesenteric vessel	1	0.23%
Tongue oedema	1	0.23%
Musculoskeletal and connective tissue disorders	10 (51)	11.67%
Myalgia	25	5.72%
Arthralgia	10	2.29%
Pain in extremity	5	1.14%
Back pain	3	0.69%
Arthritis	2	0.46%
Feeling hot	2	0.46%
Muscle fatigue	1	0.23%
Muscle spasms	1	0.23%
Muscular weakness	1	0.23%
Torticollis	1	0.23%
Respiratory, thoracic and mediastinal disorders	8 (15)	3.43%
Dyspnoea	5	1.14%
Cough	3	0.69%
Sneezing	2	0.46%
Dry throat	1	0.23%
Oropharyngeal discomfort	1	0.23%
Oropharyngeal pain	1	0.23%
Pulmonary embolism	1	0.23%
Rhinorrhoea	1	0.23%
Skin and subcutaneous tissue disorders	8 (13)	2.97%
Hyperhidrosis	4	0.92%
Rash	2	0.46%
Urticaria	2	0.46%
Alopecia	1	0.23%
Night sweats	1	0.23%
Petechiae	1	0.23%
Rash erythematous	1	0.23%
Rash pruritic	1	0.23%
Eye disorders	4 (4)	0.92%
Eye pain	1	0.23%
Eye swelling	1	0.23%
Photophobia	1	0.23%
Visual impairment	1	0.23%
Injury, poisoning and procedural complications	4 (7)	1.60%
Vaccination error	4	0.92%
Head injury	1	0.23%
Medication error	1	0.23%
Wrong product administered	1	0.23%
Investigations	4 (4)	0.92%
Blood glucose decreased	1	0.23%
Blood pressure decreased	1	0.23%
Blood pressure increased	1	0.23%
Heart rate irregular	1	0.23%

Primary SOC / Preferred Term	Total	%
Ear and labyrinth disorders	3 (5)	1.15%
Tinnitus	2	0.46%
Vertigo	2	0.46%
Hyperacusis	1	0.23%
Psychiatric disorders	3 (3)	0.69%
Confusional state	1	0.23%
Nervousness	1	0.23%
Restlessness	1	0.23%
Vascular disorders	3 (5)	1.14%
Pallor	2	0.46%
Peripheral coldness	2	0.46%
Hypotension	1	0.23%
Blood and lymphatic system disorders	2 (5)	1.15%
Lymphadenopathy	3	0.69%
Lymph node pain	2	0.46%
Cardiac disorders	2 (3)	0.69%
Palpitations	2	0.46%
Arrhythmia	1	0.23%
Infections and infestations	2 (52)	11.90%
COVID-19	43	9.84%
Asymptomatic COVID-19	9	2.06%
Metabolism and nutrition disorders	2 (2)	0.46%
Decreased appetite	1	0.23%
Fluid retention	1	0.23%
Endocrine disorders	1 (1)	0.23%
Cushing's syndrome	1	0.23%
Reproductive system and breast disorders	1 (1)	0.23%
Dysmenorrhoea	1	0.23%
Total	109 (437)	100.00%

Appendix 6 – Unknown Adverse Drug Reactions for Comirnaty per Primary SOC and PT

Table 35 – Unknown Adverse Drug Reactions for Comirnaty per Primary SOC and PT

Primary SOC / Preferred Term	Total	%
Nervous system disorders	43 (153)	22.57%
Dizziness	25	3.69%
Paraesthesia	22	3.24%
Somnolence	13	1.92%
Dysgeusia	12	1.77%
Hypoaesthesia	9	1.33%
Presyncope	7	1.03%
Ischaemic stroke	6	0.88%
Seizure	6	0.88%
Cerebrovascular accident	4	0.59%
Tremor	4	0.59%
Ageusia	3	0.44%
Hemiparesis	3	0.44%
Syncope	3	0.44%
Balance disorder	2	0.29%
Burning sensation	2	0.29%
Disturbance in attention	2	0.29%
Encephalitis autoimmune	2	0.29%
Loss of consciousness	2	0.29%
Memory impairment	2	0.29%
Amnesia	1	0.15%
Anosmia	1	0.15%
Cerebral venous thrombosis	1	0.15%
Coordination abnormal	1	0.15%
Dysarthria	1	0.15%
Dyskinesia	1	0.15%
Dyslexia	1	0.15%
Encephalopathy	1	0.15%
Haemorrhagic stroke	1	0.15%
Hemianaesthesia	1	0.15%
Hypersomnia	1	0.15%
Hypokinesia	1	0.15%
Migraine	1	0.15%
Monoplegia	1	0.15%
Multiple sclerosis relapse	1	0.15%
Muscle contractions involuntary	1	0.15%
Myoclonus	1	0.15%
Neuropathy peripheral	1	0.15%
Sciatica	1	0.15%
Speech disorder	1	0.15%
Status epilepticus	1	0.15%
Taste disorder	1	0.15%
Tongue paralysis	1	0.15%
Trigeminal neuralgia	1	0.15%
Gastrointestinal disorders	34 (70)	10.32%
Diarrhoea	8	1.18%
Tongue oedema	5	0.74%

Primary SOC / Preferred Term	Total	%
Vomiting	5	0.74%
Dyspepsia	4	0.59%
Lip oedema	4	0.59%
Odynophagia	4	0.59%
Paraesthesia oral	4	0.59%
Abdominal discomfort	3	0.44%
Abdominal pain upper	3	0.44%
Hypoaesthesia oral	3	0.44%
Dry mouth	2	0.29%
Dysphagia	2	0.29%
Gastrooesophageal reflux disease	2	0.29%
Abdominal distension	1	0.15%
Abdominal pain	1	0.15%
Abdominal pain lower	1	0.15%
Faeces soft	1	0.15%
Flatulence	1	0.15%
Glossitis	1	0.15%
Glossodynia	1	0.15%
Lip erythema	1	0.15%
Lip swelling	1	0.15%
Lip ulceration	1	0.15%
Oedema mouth	1	0.15%
Oesophagitis	1	0.15%
Oral disorder	1	0.15%
Retroperitoneal haematoma	1	0.15%
Swollen tongue	1	0.15%
Tongue discolouration	1	0.15%
Tongue disorder	1	0.15%
Tongue dry	1	0.15%
Tongue rough	1	0.15%
Toothache	1	0.15%
Upper gastrointestinal haemorrhage	1	0.15%
Skin and subcutaneous tissue disorders	28 (64)	9.44%
Pruritus	10	1.47%
Erythema	8	1.18%
Rash	4	0.59%
Rash macular	4	0.59%
Ecchymosis	3	0.44%
Hyperhidrosis	3	0.44%
Telangiectasia	3	0.44%
Urticaria	3	0.44%
Alopecia	2	0.29%
Angioedema	2	0.29%
Cold sweat	2	0.29%
Dermatitis bullous	2	0.29%
Petechiae	2	0.29%
Rash erythematous	2	0.29%
Acne	1	0.15%
Circumoral oedema	1	0.15%
Dermatitis	1	0.15%
Haemorrhage subcutaneous	1	0.15%

Primary SOC / Preferred Term	Total	%
Henoch-Schonlein purpura	1	0.15%
Nail pigmentation	1	0.15%
Palmar-plantar erythrodysaesthesia syndrome	1	0.15%
Pemphigoid	1	0.15%
Psoriasis	1	0.15%
Purpura	1	0.15%
Rash papular	1	0.15%
Rash pruritic	1	0.15%
Skin exfoliation	1	0.15%
Skin lesion	1	0.15%
General disorders and administration site conditions	26 (77)	11.36%
Asthenia	16	2.36%
Chest pain	8	1.18%
Feeling hot	7	1.03%
Oedema peripheral	6	0.88%
Chest discomfort	5	0.74%
Fatigue	5	0.74%
Axillary pain	3	0.44%
Death	3	0.44%
Nodule	3	0.44%
Face oedema	2	0.29%
Localised oedema	2	0.29%
Pain	2	0.29%
Pyrexia	2	0.29%
Chills	1	0.15%
Facial pain	1	0.15%
Feeling cold	1	0.15%
Feeling of body temperature change	1	0.15%
Gait disturbance	1	0.15%
Gait inability	1	0.15%
Influenza like illness	1	0.15%
Injection site hypoaesthesia	1	0.15%
Medical device site cyst	1	0.15%
Peripheral swelling	1	0.15%
Sluggishness	1	0.15%
Swelling	1	0.15%
Vaccination site paraesthesia	1	0.15%
Eye disorders	20 (36)	5.31%
Vision blurred	8	1.18%
Blindness transient	3	0.44%
Conjunctival haemorrhage	3	0.44%
Eye haemorrhage	2	0.29%
Eye irritation	2	0.29%
Eyelid oedema	2	0.29%
Photophobia	2	0.29%
Visual impairment	2	0.29%
Blepharospasm	1	0.15%
Ciliary body disorder	1	0.15%
Conjunctival hyperaemia	1	0.15%
Conjunctival irritation	1	0.15%
Corneal opacity	1	0.15%

Primary SOC / Preferred Term	Total	%
Diplopia	1	0.15%
Eye pruritus	1	0.15%
Ocular hyperaemia	1	0.15%
Periorbital discomfort	1	0.15%
Retinal detachment	1	0.15%
Uveitis	1	0.15%
Vitreous floaters	1	0.15%
Respiratory, thoracic and mediastinal disorders	18 (72)	10.62%
Cough	19	2.80%
Dyspnoea	11	1.62%
Rhinorrhoea	9	1.33%
Pulmonary embolism	8	1.18%
Oropharyngeal discomfort	6	0.88%
Epistaxis	3	0.44%
Nasal congestion	3	0.44%
Dysphonia	2	0.29%
Oropharyngeal pain	2	0.29%
Asthma	1	0.15%
Asthmatic crisis	1	0.15%
Laryngeal oedema	1	0.15%
Painful respiration	1	0.15%
Pleurisy	1	0.15%
Pulmonary oedema	1	0.15%
Rhinitis allergic	1	0.15%
Sneezing	1	0.15%
Suffocation feeling	1	0.15%
Vascular disorders	17 (39)	5.75%
Hypertension	7	1.03%
Haematoma	5	0.74%
Pallor	4	0.59%
Deep vein thrombosis	3	0.44%
Hypotension	3	0.44%
Thrombophlebitis	3	0.44%
Vasculitis	3	0.44%
Peripheral coldness	2	0.29%
Blood pressure fluctuation	1	0.15%
Cyanosis	1	0.15%
Embolism venous	1	0.15%
Flushing	1	0.15%
Giant cell arteritis	1	0.15%
Hypertensive crisis	1	0.15%
Labile blood pressure	1	0.15%
Superficial vein thrombosis	1	0.15%
Thrombosis	1	0.15%
Musculoskeletal and connective tissue disorders	14 (22)	3.24%
Limb discomfort	3	0.44%
Muscular weakness	3	0.44%
Muscle spasms	2	0.29%
Back pain	2	0.29%
Bursitis	2	0.29%
Musculoskeletal stiffness	2	0.29%

Primary SOC / Preferred Term	Total	%
Pain in extremity	1	0.15%
Groin pain	1	0.15%
Muscle tightness	1	0.15%
Haematoma muscle	1	0.15%
Neck mass	1	0.15%
Joint contracture	1	0.15%
Arthritis	1	0.15%
Joint swelling	1	0.15%
Infections and infestations	11 (12)	1.77%
Herpes zoster	2	0.29%
Genital herpes	1	0.15%
Myelitis	1	0.15%
Nasopharyngitis	1	0.15%
Oral herpes	1	0.15%
Pneumonia	1	0.15%
Sepsis	1	0.15%
Tonsillitis	1	0.15%
Vaccination site abscess	1	0.15%
Vaccination site cellulitis	1	0.15%
Vestibular neuronitis	1	0.15%
Psychiatric disorders	10 (15)	2.21%
Confusional state	3	0.44%
Disorientation	2	0.29%
Insomnia	2	0.29%
Sleep disorder	2	0.29%
Agitation	1	0.15%
Anxiety	1	0.15%
Impaired reasoning	1	0.15%
Mental disorder	1	0.15%
Morbid thoughts	1	0.15%
Tachyphrenia	1	0.15%
Investigations	9 (14)	2.06%
Oxygen saturation decreased	3	0.44%
Blood pressure decreased	2	0.29%
Blood pressure increased	2	0.29%
Heart rate increased	2	0.29%
Blood fibrinogen increased	1	0.15%
Blood pressure diastolic increased	1	0.15%
Haemoglobin decreased	1	0.15%
Heart rate abnormal	1	0.15%
Heart rate irregular	1	0.15%
Cardiac disorders	8 (22)	3.24%
Tachycardia	8	1.18%
Palpitations	5	0.74%
Bradycardia	3	0.44%
Arrhythmia	2	0.29%
Cardiac discomfort	1	0.15%
Cardio-respiratory arrest	1	0.15%
Sinus tachycardia	1	0.15%
Ventricular extrasystoles	1	0.15%
Reproductive system and breast disorders	8 (14)	2.06%

Primary SOC / Preferred Term	Total	%
Menstruation irregular	4	0.59%
Menstrual disorder	3	0.44%
Dysmenorrhoea	2	0.29%
Amenorrhoea	1	0.15%
Breast oedema	1	0.15%
Breast pain	1	0.15%
Intermenstrual bleeding	1	0.15%
Vaginal haemorrhage	1	0.15%
Metabolism and nutrition disorders	7 (30)	4.42%
Decreased appetite	22	3.24%
Hypoglycaemia	2	0.29%
Polydipsia	2	0.29%
Diabetes mellitus	1	0.15%
Food refusal	1	0.15%
Hyperglycaemia	1	0.15%
Hypertriglyceridaemia	1	0.15%
Renal and urinary disorders	6 (9)	1.33%
Acute kidney injury	2	0.29%
Haematuria	2	0.29%
Pollakiuria	2	0.29%
Micturition urgency	1	0.15%
Renal failure	1	0.15%
Tubulointerstitial nephritis	1	0.15%
Ear and labyrinth disorders	5 (14)	2.06%
Tinnitus	6	0.88%
Vertigo	4	0.59%
Hypoacusis	2	0.29%
Ear discomfort	1	0.15%
Vestibular ataxia	1	0.15%
Injury, poisoning and procedural complications	4 (4)	0.60%
Chillblains	1	0.15%
Contusion	1	0.15%
Foot fracture	1	0.15%
Subcutaneous haematoma	1	0.15%
Blood and lymphatic system disorders	3 (3)	0.45%
Leukaemoid reaction	1	0.15%
Lymphadenopathy	1	0.15%
Spontaneous haematoma	1	0.15%
Hepatobiliary disorders	3 (4)	0.59%
Hepatitis toxic	2	0.29%
Hepatic failure	1	0.15%
Hepatitis acute	1	0.15%
Endocrine disorders	2 (2)	0.30%
Thyroid mass	1	0.15%
Thyroiditis	1	0.15%
Pregnancy, puerperium and perinatal conditions	2 (2)	0.30%
Abortion spontaneous	1	0.15%
High risk pregnancy	1	0.15%
Total	279 (678)	100.00%

Appendix 7 – Unknown Adverse Drug Reactions for Vaxzevria per Primary SOC and PT

Table 36 – Unknown Adverse Drug Reactions for Vaxzevria per Primary SOC and PT

Primary SOC / Preferred Term	Total	%
Nervous system disorders	27 (58)	23.97%
Paraesthesia	9	3.72%
Ischaemic stroke	7	2.89%
Tremor	5	2.07%
Guillain-Barre syndrome	4	1.65%
Ageusia	3	1.24%
Dysgeusia	3	1.24%
Syncope	3	1.24%
Anosmia	2	0.83%
Cerebrovascular accident	2	0.83%
Diplegia	2	0.83%
Parosmia	2	0.83%
Altered state of consciousness	1	0.41%
Balance disorder	1	0.41%
Bell's palsy	1	0.41%
Coordination abnormal	1	0.41%
Dizziness	1	0.41%
Dysarthria	1	0.41%
Electric shock sensation	1	0.41%
Febrile convulsion	1	0.41%
Memory impairment	1	0.41%
Migraine	1	0.41%
Monoplegia	1	0.41%
Neurological symptom	1	0.41%
Presyncope	1	0.41%
Speech disorder	1	0.41%
Taste disorder	1	0.41%
Transient ischaemic attack	1	0.41%
General disorders and administration site conditions	17 (29)	11.98%
Feeling of body temperature change	5	2.07%
Feeling cold	4	1.65%
Chest pain	3	1.24%
Oedema peripheral	3	1.24%
Swelling	2	0.83%
Death	1	0.41%
Effusion	1	0.41%
Face oedema	1	0.41%
Facial pain	1	0.41%
Feeling hot	1	0.41%
Hangover	1	0.41%
Hypothermia	1	0.41%
Injection site haemorrhage	1	0.41%
Localised oedema	1	0.41%
Nodule	1	0.41%
Pain	1	0.41%
Thirst	1	0.41%
Gastrointestinal disorders	15 (19)	7.85%

Primary SOC / Preferred Term	Total	%
Abdominal pain upper	2	0.83%
Anal spasm	2	0.83%
Aphthous ulcer	2	0.83%
Odynophagia	2	0.83%
Abdominal pain	1	0.41%
Dyspepsia	1	0.41%
Glossitis	1	0.41%
Hypoaesthesia oral	1	0.41%
Lip oedema	1	0.41%
Mesenteric vein thrombosis	1	0.41%
Mesenteric venous occlusion	1	0.41%
Oral discomfort	1	0.41%
Paraesthesia oral	1	0.41%
Stomatitis	1	0.41%
Truncus coeliacus thrombosis	1	0.41%
Skin and subcutaneous tissue disorders	12 (19)	7.85%
Ecchymosis	3	1.24%
Petechiae	3	1.24%
Cold sweat	2	0.83%
Livedo reticularis	2	0.83%
Pain of skin	2	0.83%
Alopecia	1	0.41%
Photosensitivity reaction	1	0.41%
Pityriasis rosea	1	0.41%
Rash macular	1	0.41%
Rash pruritic	1	0.41%
Skin burning sensation	1	0.41%
Skin haemorrhage	1	0.41%
Respiratory, thoracic and mediastinal disorders	11 (18)	7.44%
Dyspnoea	4	1.65%
Cough	3	1.24%
Epistaxis	2	0.83%
Pulmonary embolism	2	0.83%
Nasal congestion	1	0.41%
Nasal discomfort	1	0.41%
Oropharyngeal discomfort	1	0.41%
Respiratory failure	1	0.41%
Throat irritation	1	0.41%
Throat tightness	1	0.41%
Wheezing	1	0.41%
Cardiac disorders	10 (16)	6.61%
Tachycardia	4	1.65%
Acute myocardial infarction	2	0.83%
Arrhythmia	2	0.83%
Palpitations	2	0.83%
Angina pectoris	1	0.41%
Atrial fibrillation	1	0.41%
Cardiac discomfort	1	0.41%
Extrasystoles	1	0.41%
Intracardiac thrombus	1	0.41%
Pericarditis	1	0.41%

Primary SOC / Preferred Term	Total	%
Eye disorders	9 (15)	6.20%
Conjunctival haemorrhage	4	1.65%
Vision blurred	3	1.24%
Retinal vein occlusion	2	0.83%
Eye opacity	1	0.41%
Eye pruritus	1	0.41%
Lacrimation increased	1	0.41%
Swelling of eyelid	1	0.41%
Visual acuity reduced	1	0.41%
Visual impairment	1	0.41%
Vascular disorders	8 (17)	7.02%
Hypotension	5	2.07%
Haematoma	3	1.24%
Hypertension	2	0.83%
Peripheral coldness	2	0.83%
Vasculitis	2	0.83%
Hypertensive crisis	1	0.41%
Poor peripheral circulation	1	0.41%
Thrombophlebitis	1	0.41%
Investigations	6 (8)	3.31%
Blood pressure abnormal	2	0.83%
Blood pressure increased	2	0.83%
Blood pressure decreased	1	0.41%
Heart rate increased	1	0.41%
Heart rate irregular	1	0.41%
Weight decreased	1	0.41%
Infections and infestations	5 (5)	2.07%
Cytomegalovirus hepatitis	1	0.41%
Herpes simplex reactivation	1	0.41%
Herpes zoster	1	0.41%
Urinary tract infection	1	0.41%
Vaccination site cellulitis	1	0.41%
Ear and labyrinth disorders	4 (11)	4.55%
Vertigo	7	2.89%
Ear pain	2	0.83%
Ear congestion	1	0.41%
Tinnitus	1	0.41%
Metabolism and nutrition disorders	4 (8)	3.31%
Decreased appetite	4	1.65%
Hyperglycaemia	2	0.83%
Ketosis	1	0.41%
Polydipsia	1	0.41%
Musculoskeletal and connective tissue disorders	4 (10)	4.13%
Muscle spasms	5	2.07%
Pain in extremity	2	0.83%
Muscular weakness	2	0.83%
Mastication disorder	1	0.41%
Psychiatric disorders	4 (5)	2.07%
Insomnia	2	0.83%
Emotional distress	1	0.41%
Impaired reasoning	1	0.41%

Primary SOC / Preferred Term	Total	%
Nightmare	1	0.41%
Blood and lymphatic system disorders	1 (1)	0.41%
Thrombocytopenic purpura	1	0.41%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1)	0.41%
High-grade B-cell lymphoma	1	0.41%
Renal and urinary disorders	1 (1)	0.41%
Dysuria	1	0.41%
Reproductive system and breast disorders	1 (1)	0.41%
Balanoposthitis	1	0.41%
Total	141 (242)	23,97%

Appendix 8 – Unknown Adverse Drug Reactions for Spikevax per Primary SOC and PT

Table 37 – Unknown Adverse Drug Reactions for Spikevax per Primary SOC and PT

Primary SOC / Preferred Term	Total	%
General disorders and administration site conditions	11 (14)	18.42%
Asthenia	3	3.95%
Axillary pain	2	2.63%
Death	1	1.32%
Injection site erythema	1	1.32%
Malaise	1	1.32%
Oedema peripheral	1	1.32%
Pyrexia	1	1.32%
Swelling face	1	1.32%
Vaccination site exfoliation	1	1.32%
Vaccination site nodule	1	1.32%
Vaccination site warmth	1	1.32%
Nervous system disorders	8 (9)	11.84%
Somnolence	2	2.63%
Cerebrovascular accident	1	1.32%
Dizziness	1	1.32%
Guillain-Barre syndrome	1	1.32%
Headache	1	1.32%
Ischaemic stroke	1	1.32%
Paraesthesia	1	1.32%
Presyncope	1	1.32%
Skin and subcutaneous tissue disorders	7 (8)	10.53%
Ecchymosis	2	2.63%
Acne	1	1.32%
Erythema	1	1.32%
Rash	1	1.32%
Rash erythematous	1	1.32%
Rash macular	1	1.32%
Rash pruritic	1	1.32%
Gastrointestinal disorders	5 (9)	11.84%
Diarrhoea	4	5.26%
Toothache	2	2.63%
Abdominal pain	1	1.32%
Duodenogastric reflux	1	1.32%
Oral disorder	1	1.32%
Reproductive system and breast disorders	4 (5)	6.58%
Intermenstrual bleeding	2	2.63%
Abnormal withdrawal bleeding	1	1.32%
Menstrual disorder	1	1.32%
Menstruation irregular	1	1.32%
Respiratory, thoracic and mediastinal disorders	4 (6)	7.89%
Dyspnoea	3	3.95%
Aphonia	1	1.32%
Dysphonia	1	1.32%
Oropharyngeal discomfort	1	1.32%
Cardiac disorders	3 (6)	7.89%
Tachycardia	3	3.95%

Primary SOC / Preferred Term	Total	%
Cardiac discomfort	2	2.63%
Pericarditis	1	1.32%
Eye disorders	2 (2)	2.63%
Conjunctival haemorrhage	1	1.32%
Retinal artery occlusion	1	1.32%
Infections and infestations	2 (3)	3.95%
Herpes zoster	2	2.63%
Otitis externa	1	1.32%
Musculoskeletal and connective tissue disorders	2 (3)	3.95%
Axillary mass	2	2.63%
Arthritis reactive	1	1.32%
Renal and urinary disorders	2 (2)	2.63%
Renal pain	1	1.32%
Haemorrhage urinary tract	1	1.32%
Vascular disorders	2 (4)	5.26%
Haematoma	3	3.95%
Deep vein thrombosis	1	1.32%
Ear and labyrinth disorders	1 (1)	1.32%
Tinnitus	1	1.32%
Investigations	1 (1)	1.32%
Blood pressure increased	1	1.32%
Metabolism and nutrition disorders	1 (2)	2.63%
Decreased appetite	2	2.63%
Psychiatric disorders	1 (1)	1.32%
Agitation	1	1.32%
Total	57 (76)	100.00%

Appendix 9 – Unknown Adverse Drug Reactions for JCOVDEN per Primary SOC and PT

Table 38 – Unknown Adverse Drug Reactions for JCOVDEN per Primary SOC and PT

Primary SOC / Preferred Term	Total	
Nervous system disorders	15 (25)	32.05%
Dizziness	7	8.97%
Somnolence	3	3.85%
Guillain-Barre syndrome	2	2.56%
Hypoaesthesia	2	2.56%
Cerebrovascular accident	1	1.28%
Cognitive disorder	1	1.28%
Dysgeusia	1	1.28%
Facial paralysis	1	1.28%
Generalised tonic-clonic seizure	1	1.28%
Myoclonus	1	1.28%
Paraesthesia mucosal	1	1.28%
Parosmia	1	1.28%
Presyncope	1	1.28%
Radiculopathy	1	1.28%
Syncope	1	1.28%
Gastrointestinal disorders	8 (8)	10.26%
Abdominal discomfort	1	1.28%
Abdominal pain	1	1.28%
Burning mouth syndrome	1	1.28%
Diarrhoea	1	1.28%
Eructation	1	1.28%
Oral discomfort	1	1.28%
Paraesthesia oral	1	1.28%
Vomiting	1	1.28%
Investigations	4 (4)	5.13%
Blood glucose decreased	1	1.28%
Blood pressure decreased	1	1.28%
Blood pressure increased	1	1.28%
Heart rate irregular	1	1.28%
Ear and labyrinth disorders	3 (4)	5.13%
Vertigo	2	2.56%
Hyperacusis	1	1.28%
Tinnitus	1	1.28%
Eye disorders	3 (3)	3.85%
Eye pain	1	1.28%
Eye swelling	1	1.28%
Photophobia	1	1.28%
General disorders and administration site conditions	3 (5)	6.41%
Chest pain	3	3.85%
Feeling hot	1	1.28%
Oedema peripheral	1	1.28%
Psychiatric disorders	3 (3)	3.85%
Confusional state	1	1.28%
Nervousness	1	1.28%
Restlessness	1	1.28%
Respiratory, thoracic and mediastinal disorders	3 (6)	7.69%

Primary SOC / Preferred Term	Total	
Dyspnoea	4	5.13%
Dry throat	1	1.28%
Rhinorrhoea	1	1.28%
Skin and subcutaneous tissue disorders	3 (3)	3.85%
Alopecia	1	1.28%
Petechiae	1	1.28%
Rash pruritic	1	1.28%
Blood and lymphatic system disorders	2 (5)	6.41%
Lymphadenopathy	3	3.85%
Lymph node pain	2	2.56%
Cardiac disorders	2 (3)	3.85%
Palpitations	2	2.56%
Arrhythmia	1	1.28%
Musculoskeletal and connective tissue disorders	2 (3)	3.85%
Arthritis	2	2.56%
Torticollis	1	1.28%
Endocrine disorders	1 (1)	1.28%
Cushing's syndrome	1	1.28%
Injury, poisoning and procedural complications	1 (1)	1.28%
Head injury	1	1.28%
Metabolism and nutrition disorders	1 (1)	1.28%
Fluid retention	1	1.28%
Reproductive system and breast disorders	1 (1)	1.28%
Dysmenorrhoea	1	1.28%
Vascular disorders	1 (2)	2.56%
Peripheral coldness	2	2.56%
Total	57 (78)	100,00%