Reporting Vaccine Adverse Drug Reactions

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Dedicated to my late grandmother Yvonne.

Her strength, bravery and courage which she showed me throughout her life inspires me to keep persisting. I wish she was here to see me as a pharmacist – a career she truly wished I would pursue.

Abstract

Adverse drug reaction (ADR) reporting helps identify negative effects caused by medications such as vaccines. Healthcare professionals (HCPs) and patients are encouraged to report suspected ADRs. Lack of ADR reporting negatively impacts the understanding of the safety of the product. The aims of the study were (1) to identify vaccine related ADRs and (2) to identify perception, awareness and experiences of HCPs with ADR reporting. Literature review on vaccine related ADRs of COVID-19, *Varicella zoster* and influenza vaccines was conducted on PubMed® and articles published between 2012 to 2022 were identified. A questionnaire on awareness and experience of ADR reporting was developed, validated and disseminated to HCPs. The questionnaire had 22 questions and was divided into three sections: demographics, ADR reporting awareness and experience of vaccine-related ADRs. One hundred and forty-nine articles were identified in the literature review. Commonly identified ADRs were thrombosis and thrombocytopenia (n=20) for COVID-19 vaccines, injection site reactions (n=16) for *Varicella zoster* vaccines and fatigue and myalgia (n=20) for influenza vaccines. Questionnaire respondents (N=284) included nurses (n=161), pharmacists (n=68), medical physicians (n=46) and other HCPs (n=9). HCPs were aware on the procedure of ADR reporting as they scored an overall mean score of 3.36 out of 5. Pharmacists had the highest mean score of 4.1 out of 5 from the other HCPs for awareness on ADR reporting. The level of awareness varied between HCPs (p-value= <0.001). The majority of HCPs (n=143) did not receive any training on ADR reporting. Pharmacists received more training than other HCPs (p-value = 0.035). Barriers to ADR reporting which were commonly identified were lack of awareness (n=106), lack of confidence (n=66) and time constraints (n=64). Fourteen respondents have previously reported a vaccine-related

ADR. Most commonly reported ADRs include myalgia (n=152), fever & chills (n=125) and injection site reactions (n=116). HCPs are aware on the procedure of ADR reporting, but challenges are still present which prevent HCPs from reporting more.

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ADR	Adverse drug reaction
DNA	Deoxyribonuclease acid
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
HCP	Healthcare professional
MMA	Malta Medicines Authority
MMR	Measles, mumps and rubella
mRNA	Messenger ribonucleic acid
SmPC	Summary of product characteristics
VZV	*Varicella zoster* vaccine

CHAPTER 1

Introduction

1.1. Vaccines

Vaccines trigger an immune response in the body, resulting in immunization against a pathogen. Vaccines are used to control a disease from spreading in the community. A vaccine may not eradicate a disease completely but reduces transmission rates and the severity of infection, reducing burdens on healthcare systems (Tavares Da Silvia *et al*., 2015).[1, 2]

1.2. Vaccine technology

The majority of vaccines are delivered through the parenteral route with the exception of some including polio, cholera, rotavirus and typhoid vaccines which are delivered orally. Vaccines have different modes of action, which vary in their efficacy and safety profile. To improve the immune response, adjuvants are added to vaccines (D'Amico *et al*., 2021; Facciola *et al*., 2022; Kwong *et al*., 2023). Examples of commonly used technologies include live-attenuated vaccines, inactivated vaccines, viral vector vaccines and messenger ribonucleic acid (mRNA) vaccines (Ghattas et al.,2021). [3]

[1] Centers for Disease Control and Prevention (CDC). Administer the vaccine(s) [Internet]. United States: CDC; 2021 [cited 2024 Jul 23]. Available from: https://www.cdc.gov/vaccines/hcp/admin/administer-vaccines.html

[2] World Health Organisation (WHO). WHO releases global COVID-19 vaccination strategy update to reach unprotected [Internet]. Switzerland: WHO; 2022 [cited 2024 Jul 23]. Available from: https://www.who.int/news/item/22-07-2022-who-releases-global-covid-19-vaccination-strategy-update-to-reach-unprotected

[3] Oxford Vaccine Group. Types of vaccines [Internet]. United Kingdom: University of Oxford; 2021 [cited 2024 Jul 23]. Available from: https://www.ox.ac.uk/students/welfare/health/vaccinations

1.2.1. Live-attenuated vaccines

Live-attenuated vaccines are designed using a live version of the pathogen, without its potential to replicate or cause the infection. Attenuation of the vaccine occurs by genetic modification or inactivation through chemicals. Patients with a weaker immune system may experience more ADRs with live-attenuated vaccines because the vaccine technology uses the immune system of the host as a part of its mode of action (Kamei, 2023). Examples of vaccines developed using live-attenuated technologies include the Varicella zoster vaccine (VZV) Varilix®, rotavirus and measles, mumps and rubella (MMR) vaccines (Minor, 2015; Pöyhönen *et al*, 2020). [4]

1.2.2. Inactivated vaccines

Inactivated vaccines are produced using the inactivated pathogen or toxin. The pathogen or toxin is inactivated through denaturation by either heat or using chemicals, such as formaldehyde. The immune response is not as immediate and robust as with live-attenuated vaccines and most of the times, booster doses are required. Inactivated vaccines are safer to use than live-attenuated vaccines in vulnerable patients, as less ADRs are triggered following immunisation. Examples of vaccines which use such technologies are certain brands of influenza vaccines and hepatitis A vaccines (Sanders *et al*., 2014; Bemben & Berg, 2022). [5]

[4] U.S Department of Health and Human services (HHS). Vaccine types [Internet]. United States: HHS; 2022 [cited 2024 Jul 22]. Available from: https://www.hhs.gov/immunization/basics/types/index.html

[5] News Medical. What is an inactivated vaccine? [Internet]. United Kingdom: News Medical; 2021 [cited 2024 Jul 22]. Available from: https://www.news-medical.net/health/What-is-an-Inactivated-Vaccine.aspx

1.2.3. Protein subunit vaccines

Subunit vaccines are composed of fragments of the active pathogen which is produced using biomedical technologies (Yang *et al.,* 2023). The technology used to design these vaccines is a relatively rapid process (Wijesundra *et al*., 2020). The safety of subunit vaccine technology is not a concern. The issue is that the immune response triggered within the host is weaker in comparison to the other vaccines (Bayani *et al*., 2023). Vaccines which use this technology include the COVID-19 vaccine, NovaVax®. [6]

1.2.4. Viral vector vaccines

Viral vector vaccines act as carriers with genetically modified viruses to introduce the genes which code for antigens of a specific pathogen. Cells then have the genetic code to produce antigens when exposed to pathogen in a short period of time. The COVID-19 vaccines designed by AstraZeneca® and Johnson & Johnson® both make use of the viral vector technology (Deng *et al*., 2022).

1.2.5. Messenger-ribonucleic acid vaccines

mRNA vaccines use a component from the pathogen to be able to encode the gene to produce antigens against the pathogen. mRNA vaccines, as well as the deoxyribonuclease (DNA) based vaccines are classified as nucleic acid-based vaccines. A delivery system for mRNA components is necessary to avoid damage to the component and allow for safe delivery. Examples of delivery systems include lipid nanoparticles which are used for COVID-19 vaccines and helper lipids. Such vaccines lead to a strong

[6] Mayo Clinic. Different types of COVID-19 vaccines: How they work [Internet]. United States: MFMER; 2023 [cited 2024 Aug 15]. Available from: https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465

immune response and have a lower side effect profile when compared to other vaccine technologies. Moderna® and Pfizer® COVID-19 vaccines are made using this technology (Yadav et al., 2020; Extance, 2021; Jain et al., 2021; Gote *et al*., 2023).

1.2.6. DNA vaccines

DNA vaccines deliver plasmids of the genetic component of the antigen to the host. The delivery system of this vaccine technology is more susceptible to damage. DNA vaccine technology originated in the 1990s. These vaccines have an improved temperature stability over other vaccines. DNA vaccines have a higher risk of triggering autoimmune diseases (Lee *et al*., 2018; Kozak & Hu, 2024). An approved DNA vaccine was India's COVID-19 vaccine, ZyCoV-D®. DNA vaccines have had issues in the past due to their efficacy. [7]

1.3. Clinical trials

Clinical trials evaluate the medicinal product's safety and efficacy. When conducting clinical trials on both human and animal subjects, ethical standards should be met. [8] The first three phases of clinical trials are conducted prior to marketing authorisation and the fourth phase is a continuous process occurring during the product life cycle after authorisation is granted. Patient sample size increases with every phase of the clinical

[7] Nature Biotechnology. First COVID-19 DNA vaccine approved, others in hot pursuit [Internet]. United States: Nature; 2021 [cited 2024 Aug 15]. Available from: https://www.nature.com/articles/d41587-021-00023-5

[8] World Health Organisation (WHO). International standards for clinical trials registries [Internet]. Switzerland: WHO; 2018 [cited 2024 Jul 2]. Available from: https://iris.who.int/bitstream/handle/10665/274994/9789241514743-eng.pdf?sequence=1

trial. Results of clinical trials are required for acquiring marketing authorisation, and a review of results is done by the committee for medicinal products for human use at the European Medicines Agency (EMA). [9]

All clinical trials within the European Economic Area (EEA) and European Union (EU) are registered in the clinical trial information system, a requirement listed for the EU clinical trial legislation 536/2014. The clinical trial information system provides better communication between involved authorities for clinical trials. [10 - 12]

1.3.1. Pre-clinical testing

Before advancing to clinical trials on human patients, pre-clinical testing is conducted. A hypothesis is developed and tested using statistical analysis and research (Huang & Percie du Sert, 2020). Laboratory testing is required and should be done in compliance with good laboratory practice. [8] Safety testing is done on all components of the vaccine including excipients, adjuvants and active components. In-vitro and in-vivo testing is

[9] European Medicines Agency (EMA). Obtaining an EU marketing authorisation, step-by-step [Internet]. Netherlands: EU; 2020 [cited 2024 Jul 23]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step

[10] EU Clinical trials. About this website [Internet]. Netherlands: EMA; 2023 [cited 2024 Jul 2]. Available from: https://euclinicaltrials.eu

[11] European Medicines Agency (EMA). Clinical trial regulation [Internet]. Netherlands: EMA; 2023 [cited 2024 Jul 2]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/clinical-trials-regulation

[12] European Commission. Regulation (EU) No 536/2014 of the European Parliament and of the council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [Internet]. Official Journal of the European Union. 2014; L158 [cited 2024 Jul 2]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536

carried out during the pre-clinical phase. [13] Animal models are sometimes used for in-vivo testing and the model selected by the researcher should be appropriate and relevant to receive results which are relevant to humans (Doke & Dhawale, 2015; Sasaki *et al*., 2018). [14]

1.3.2. Vaccine clinical trials

Vaccine development may be aided by human challenge trials, which take place by intentionally exposing the patient to a pathogen and investigating the effects the pathogen leaves. Human challenge trials have been useful with the development of COVID-19 vaccines, as they have reduced the time taken for the development of the vaccine (Sekhar & Kang, 2020; Manheim *et al*., 2021; Adams-Phipps *et al*., 2023). During safety testing of a vaccine, ADRs are monitored for a few days. The monitoring period may be longer for live-attenuated vaccines. [15]

[8] World Health Organisation (WHO). International standards for clinical trials registries [Internet]. Switzerland: WHO; 2018 [cited 2024 Jul 2]. Available from: https://iris.who.int/bitstream/handle/10665/274994/9789241514743-eng.pdf?sequence=1

[13] Food and drug administration (FDA). Step 2: Preclinical research [Internet]. United States: FDA; 2018 [cited 2024 Jul 2]. Available from: https://www.fda.gov/patients/drug-development-process/step-2-preclinical-research

[14] National Institutes of Health (NIH) Grants & Funding. Why animals are used in research [Internet]. United States: NIH; 2024 [cited 2024 Jul 2]. Available from: https://grants.nih.gov/grants/policy/air/why.htm

[15] European Medicines Agency (EMA). Guideline on clinical evaluation of vaccines [Internet]. Netherlands: EMA; 2023 [cited 2024 Jul 2]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-vaccines-revision-1_en.pdf

1.4. Pharmacovigilance

Pharmacovigilance involves monitoring procedures following authorisation of a medicinal product. It is the fourth phase of clinical trials which uses the largest and most diverse sample size. Pharmacovigilance ensures that the safety of the product is maintained, there are no severe long-term effects and reduces the occurrence of ADRs. One of the aspects of pharmacovigilance is ADR reporting by HCPs and patients (Petousis-Harris, 2020; Saraiva Hotel et al., 2024). Other aspects of pharmacovigilance include safety reports conducted periodically, literature monitoring and assessment of medication errors. [16]

Parties involved within pharmacovigilance in the EU, including the marketing authorisation holder and regulatory authorities, should follow good pharmacovigilance practices, as mentioned within the legislation of pharmacovigilance. The pharmacovigilance risk assessment committee is a committee within EMA which manages pharmacovigilance of products. The committee was created in accordance with the pharmacovigilance legislation. The pharmacovigilance committee works with other committees and groups including, the committee for medicinal products for

[16] European Medicines Agency (EMA). Pharmacovigilance: Overview [Internet]. Netherlands: EMA; 2024 [cited 2024 Jun 25]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/pharmacovigilance-overview

human use and coordination group for mutual recognition and decentralised procedures. [17, 18]

1.5. Adverse drug reaction reporting

Patients and healthcare professionals (HCPs) may report suspected ADRs to their local competent authority, which for Malta is the Malta Medicines Authority (MMA). Reports from countries within the European Economic Area (EEA) are published on the EudraVigilance® system, facilitating exchange of information between the national competent authority and the EMA. As mentioned in the EudraVigilance® annual report of 2023, the system has improved the rate at which ADR reports are handled. [19] The ADR reporting form is accessible online and in Malta the procedure is electronic as forms are

[17] European Medicines Agency (EMA). Good pharmacovigilance practices (GVP) [Internet]. Netherlands: EMA; 2015 [cited 2024 Jul 4]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/good-pharmacovigilance-practices-gvp#:~:text=Good%20pharmacovigilance%20practices%20(GVP)%20are,authorities%20in%20EU%20Member%20States.

[18] European Medicines Agency (EMA). Legal framework: Pharmacovigilance [Internet]. Netherlands: EMA; 2015 [cited 2024 Jul 4]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/pharmacovigilance-overview/legal-framework-pharmacovigilance

[19] European Medicines Agency (EMA). 2023 Annual Report for the European Parliament, the Council and the Commission [Internet]. Netherlands: EMA; 2024 [cited 2024 Jul 3]. Available from: https://www.ema.europa.eu/en/documents/report/2023-annual-report-eudravigilance-european-parliament-council-commission_en.pdf

completed and submitted by email. [20, 21] A public database of suspected ADRs reported to EudraVigilance® on authorised medicinal products is available and is run by EMA. [22]

1.5.1. Adverse drug reporting trends

During 2021 and 2022, EudraVigilance® received a larger volume of reports by patients and HCPs when compared to previous years. During the years 2021 and 2022, ADR reports from patients also increased and they were mostly on the COVID-19 vaccines. Possible reasons for this significant increase in ADR reports include that COVID-19 vaccines were administered to a large proportion of the global population over a relatively short period of time and the vaccines were newly authorised. Within 2023, the number of reports received were closer to pre-pandemic years. [16, 23 - 25]

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[16] European Medicines Agency (EMA). Pharmacovigilance: Overview [Internet]. Netherlands: EMA; 2024 [cited 2024 Jun 25]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/pharmacovigilance-overview

[20] European Medicines Agency (EMA). EudraVigilance [Internet]. Netherlands: EMA; 2024 [cited 2024 Jun 25]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/pharmacovigilance-research-development/eudravigilance

[21] Malta Medicines Authority (MMA). Adverse drug reaction [Internet]. Malta: MMA; 2020 [cited 2024 Jun 25]. Available from: https://medicinesauthority.gov.mt/adrportal

[22] European Medicines Agency (EMA). EudraVigilance – European database of suspected adverse drug reaction reports [Internet]. Netherlands: EMA; 2024 [cited 2024 Jun 25]. Available from: https://www.adrreports.eu/en/search.html#

[23] World Health Organisation (WHO). WHO COVID-19 Dashboard [Internet]. Switzerland: WHO; 2018 [cited 2024 Jul 3]. Available from: https://data.who.int/dashboards/covid19/vaccines

[24] Our World in Data. Coronavirus (COVID-19) vaccinations [Internet]. United Kingdom: University of Oxford; 2020 [cited 2024 Jul 3]. Available from: https://ourworldindata.org/covid-vaccinations

[25] European Medicines Agency (EMA). 2022 Annual Report for the European Parliament, the Council and the Commission [Internet]. Netherlands: EMA; 2023 [cited 2024 Jul 3]. Available from: https://www.ema.europa.eu/en/documents/report/2022-annual-report-eudravigilance-european-parliament-council-and-commission_en.pdf

1.6. Vaccine adverse drug reactions

Vaccine adverse drug reactions (ADRs) occur as a result of vaccine technology, excipients, patient factors, including age, genetics and comorbidities, or the route of administration. Vaccines given as an injection may lead to injection site reactions as a response to the physical administration of the vaccine. Other vaccines delivered orally or nasally may result in local reactions such as rhinitis in the case of nasal vaccines (Perego *et al.,* 2021).

Immunocompromised patients, including patients on immunosuppressive therapy, have an increased risk of experiencing ADRs, especially immune-mediated reactions. Newly developed vaccinations are withheld from being administered to vulnerable patients due to unknown risks. The appropriate immune response may not be achieved with immunocomprised patients in comparison to healthy patients, especially when using live attenuated vaccines due to its mechanism of action (Stone *et al*., 2019; Galmiche *et al*., 2021; O'Connor *et al.*, 2021; Saini *et al.*, 2021; Zazzara *et al.,* 2021; Lamprinou *et al*., 2023).

Women of childbearing potential should be vaccinated prior to pregnancy to be protected from vaccine preventable diseases during pregnancy, and vaccination may provide passive immunity to the foetus. Vaccines which have been on the market for longer, such as tetanus and seasonal influenza vaccines, are safely administered to pregnant women as the risks associated with the disease outweigh risks associated with

vaccine administration (Swamy & Heine, 2016; Maertens *et al*., 2020). Administration of the mRNA COVID-19 vaccines pre-conception and during pregnancy is recommended. [26]

Vaccine ADRs range from mild, moderate to severe and the associated risk of occurrence varies. Mild ADRs such as fever and injection site reactions, occur in most patients and are self-limiting and resolve within a few days. There is a low risk of complications with such side effects and can generally be managed by the patient. More serious ADRs which may lead to long term complications or hospitalisation require acute care. The frequency and occurrence of serious ADRs may impact the safety of the vaccine (Dhamanti *et al.,* 2023). [27, 28]

Toxic effects exerted by vaccines may be exacerbated due to other medication being taken at the time of vaccination. An example of such a case is the use of contraceptive pills containing oestrogen, which can lead to an increased incidence of blood clotting. (Hekmat & Javanmardi, 2021; Siang Kow, 2021; Fousse et al., 2022).

[26] Centers for Disease Control and Prevention (CDC). COVID-19 vaccination for people who are pregnant or breastfeeding [Internet]. United States: CDC; 2024 [cited 2024 Aug 29]. Available from: https://www.cdc.gov/covid/vaccines/pregnant-or-breastfeeding.html

[27] Public health association of BC. Vaccine side effects [Internet]. Canada: British Columbia; 2024 [cited 2024 Jun 24]. Available from: https://immunizebc.ca/vaccine-safety/side-effects

[28] National Health System (NHS). Classification of adverse events [Internet]. United Kingdom: NHS; 2024 [cited 2024 Jun 24]. Available from: https://www.nbt.nhs.uk/research-innovation/researcher-zone/researcher-journey/study-management/safety-reporting/classification-adverse-events

1.7. Varicella zoster, influenza, and COVID-19 vaccines

The COVID-19, *Varicella zoster* and influenza vaccines are three vaccines which were first manufactured during different time periods. COVID-19 vaccines is the most modern vaccine from the three listed vaccines (Francis, 2018; Mascola & Fauci, 2020).

1.7.1. COVID-19 Vaccines

COVID-19 vaccines were developed and tested for rapidly with efforts to achieve herd immunity and control the pandemic, whilst ensuring that safety standards were still met (Cole et al., 2022). The first COVID-19 vaccine by Pfizer was granted temporary authorisation in December 2020. [29] Vaccines being used to date are Comirnaty®, Jcovden®, Spikevax®, Bimervax® and Novavax®. COVID-19 vaccines, Comirnaty ® and Spikevax ®, are licensed to be given to patients over 6 months and given in three doses. [30] Novavax® is licensed in patients over 12 years of age and is given as two doses and Bimervax® is licensed in patients over 16 years of age. [31, 32] Vaxzevria® and JCovden®

[29] European Medicines Agency (EMA). EMA recommends first COVID-19 vaccine for authorisation in the EU [Internet]. Amsterdam: EMA; 2020 [cited 2024 Jul 7]. Available from: https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu

[30] Centers for Disease Control and Prevention (CDC). Stay up to date with COVID-19 [Internet]. United States: CDC; 2024 [cited 2024 Jul 1]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html#ftnote

[31] Centers for Disease Control and Prevention (CDC). Interim clinical considerations for use of COVID-19 vaccines in the United States [Internet]. United States: CDC; 2024 [cited 2024 Jul 1]. Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

[32] European Medicines Agency (EMA). COVID-19 vaccines: authorised [Internet]. Amsterdam: EMA; 2024 [cited 2024 Jul 7]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised#authorised-covid-19-vaccines-section

vaccines were previously available but have been withdrawn from the European market by EMA due to a reduced commercial demand. [33, 34]

Viral vector technology was used for the Vaxzevria® and Jcovden® vaccine and mRNA technology was used for Comirnaty® and Spikevax® (Woo Park *et al*., 2021). Novavax® and Bimervax® are protein-based vaccines and were both authorised in 2023. [7] Strains used in COVID-19 vaccines are modified to combat variants by identifying new prevalent strains. Bivalent vaccines are sometimes preferred over monovalent vaccines The bivalent vaccines are composed of BA.4, a subvariant of COVID-19, and BA.5, the subvariant of the Omicron mutation. [35] Monovalent Omicron XBB 1.5 strain vaccines were approved by EMA in 2023 (Tamura *et al*., 2024).

The Food and Drug Administration in the United States has approved the COVID-19 vaccines administered during the end of 2024 and beginning of 2025. Developed and

[7] Nature Biotechnology. First COVID-19 DNA vaccine approved, others in hot pursuit [Internet]. United States: Nature; 2021 [cited 2024 Aug 15]. Available from: https://www.nature.com/articles/d41587-021-00023-5

[33] European Medicines Agency (EMA). Vaxzevria (COVID-19 vaccine (ChAdOx1 S [recombinant]) [Internet]. Amsterdam: EMA; 2024 [cited 2024 Jul 7]. Available from: https://www.ema.europa.eu/en/documents/public-statement/public-statement-vaxzevria-previously-covid-19-vaccine-astrazeneca-withdrawal-marketing-authorisation-european-union_en.pdf

[34] European Medicines Agency (EMA). JCovden (COVID-19 vaccine (Ad26.COV2.S) [Internet]. Amsterdam: EMA; 2024 [cited 2024 Sep 2]. Available from: https://www.ema.europa.eu/en/documents/public-statement/public-statement-jcovden-previously-covid-19-vaccine-janssen-withdrawal-marketing-authorisation-european-union_en.pdf

[35] Food and Drug Administration. Coronavirus (COVID-19) Update: FDA authorizes changes to simplify use of bivalent mRNA COVID-19 vaccines [Internet]. United States: FDA; 2023 [cited 2024 Jul 7]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-changes-simplify-use-bivalent-mrna-covid-19-vaccines

modified vaccine for the United States is monovalent and composed of JN.1 strain, which is thought to be a prevalent strain during 2024 and 2025. [36] The JN.1 strain is related to the Omicron mutation and is preferred over the XBB.1.5. strain as the JN.1 strain is prevalent in many recent COVID-19 mutations for 2024. [37]

1.7.2. *Varicella zoster* vaccines

The *Varicella zoster* virus causes *Varicella zoster* and *Herpes zoster*. VZV were designed to target immunisation against both diseases. Germany was the first European country to authorise VZV in 1984 (Warren-Gash *et al*., 2017; Marra & Lalji, 2022). VZVs which are currently authorised contain the Oka and MAV/06 *Varicella zoster* virus strains and are available with these strains as monovalent or quadrivalent (Umit et al., 2021; Shin *et al*., 2022). Different brands of VZV use different technologies. GlaxoSmithKline's VZV, Varilix®, uses recombinant technology and glycoprotein E is added as an adjuvant. Merck's VZV, Varivax®, uses the live-attenuated virus (Ilyas & Chandrasekar, 2020; Harbecke *et al.,* 2021). [38] ProQuad®, a live-attenuated combination of *Varicella zoster* and MMR, is sometimes given as part of the local vaccination programme (Lee *et al*.,

[36] Food and Drug Administration (FDA). Updated COVID-19 vaccines for use in the United States beginning in fall 2024 [Internet]. United States: FDA; 2024 [cited 2024 Aug 29]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-and-authorizes-updated-mrna-covid-19-vaccines-better-protect-against-currently

[37] European Medicines Agency (EMA). EMA confirms its recommendation to update the antigenic composition of authorised COVID-19 vaccines for 2024-2025 [Internet]. Netherlands: EMA; 2024 [cited 2024 Aug 29]. Available from: https://www.ema.europa.eu/en/documents/other/ema-confirms-its-recommendation-update-antigenic-composition-authorised-covid-19-vaccines-2024-2025_en.pdf

[38] World Health Organisation (WHO). Varicella [Internet]. Geneva, Switzerland: WHO; 2016 [cited 2024 Jul 22]. Available from: https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/vaccine-standardization/varicella

2022). [39, 40] *Varicella zoster* vaccination is not part of national immunisation programmes of some countries, including Malta. [41]

1.7.3. Influenza vaccines

The influenza virus rapidly mutates and new influenza vaccine strains are modified annually. The influenza vaccine is developed annually to work against the most prevalent strain of that season. Development of influenza vaccine started in 1930s (Barberis *et al.,* 2016). Traditional manufacturing methods of influenza vaccines include the use of chicken eggs, increasing the risk of hypersensitivity reactions occurring. Modern manufacturing methods use mammalian cells (Rockman *et al*., 2023).

Technologies used by manufacturers for the development of influenza vaccines include inactivated vaccine and live-attenuated vaccine technology. Inactivated vaccines are given through the parenteral route. Live-attenuated technologies are used in children and delivered as nasal sprays. Other technologies are used for influenza vaccines, and some examples include recombinant haemagglutin vaccines and subunit vaccines. New mutated strains are added to the vaccine. The type of technology used for development

[39]Centers for Disease Control and Prevention (CDC). MMR and MMRV vaccine composition and dosage [Internet]. United States: FDA; 2023 [cited 2024 Jul 7]. Available from: https://www.cdc.gov/vaccines/vpd/mmr/hcp/about.html#:~:text=ProQuad®%20is%20a%20combination,and%20varicella%20(MMRV)%20vaccine

[40]European Medicines Agency (EMA). ProQuad [Internet]. Amsterdam: EMA; 2020 [cited 2024 Jul 7]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/proquad

[41] Health services Government Malta. National immunisation schedule [Internet]. Malta: Goverment of Malta; 2023 [cited 2024 Jul 7]. Available from: https://healthservices.gov.mt/en/phc/pchyhi/Pages/National-Immunisation-Schedule.aspx

of the vaccine depends on the brand. Brands also vary in the number of virus strains used in the vaccine (Tregoning *et al*., 2018; Sekiya *et al.,* 2021). [42], [43]

An example of an influenza vaccine on the market is Flucelvax Tetra®, of the manufacturer Seqirus, which uses inactivated vaccine technology and was composed of four strains of the influenza virus from both type A and type B strains for 2023/2024. [44] Quadrivalent vaccines have a proven improved outcome on efficacy (Tanner *et al*, 2021). The influenza vaccine recommended for 2024/2025 was announced by the World Health Organisation and recommendations identified use of trivalent vaccines which include two type A and one type B strains. [45]

1.8. Aims

The aims of the study were: (i) to identify reported vaccine related ADRs of COVID-19, *Varicella zoster* and influenza vaccines and (ii) to identify perception, awareness and experiences of HCPs with ADR reporting.

[42] World Health Organisation (WHO). Types of seasonal influenza vaccine [Internet]. Geneva, Switzerland: WHO; 2010 [cited 2023 Mar 27]. Available from: https://www.euro.who.int/en/health-topics/communicable-diseases/influenza/vaccination/types-of-seasonal-influenza-vaccine

[43] Centers for Disease Control and Prevention (CDC). Influenza (flu): Flu shot [Internet]. United States: CDC; 2024 [cited 2023 Mar 27]. Available from: https://www.cdc.gov/flu/prevent/flushot.htm?web=1&wdLOR=cD7663CF6-5622-9545-9FD9-18CEFA9D1119

[44] European Medicines Agency (EMA). Flucelvax Tetra [Internet]. Amsterdam: EMA; 2023 [cited 2023 Mar 28]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/flucelvax-tetra

[45] World Health Organisation (WHO). Recommendation announced for influenza vaccine composition for the 2024-2025 northern hemisphere influenza season [Internet]. Geneva, Switzerland: WHO; 2024 [cited 2024 Sep 1]. Available from: https://www.who.int/news/item/23-02-2024-recommendations-announced-for-influenza-vaccine-composition-for-the-2024-2025-northern-hemisphere-influenza-season

CHAPTER 2

Methodology

2.1. Ethics Registration

This study was registered with the Faculty Research and Ethics Committee at the University of Malta with an application identification of MED-2023-00488 (Appendix 1).

2.2. Design of methodology

Methodology was split into two phases as described in Figure 2.1.

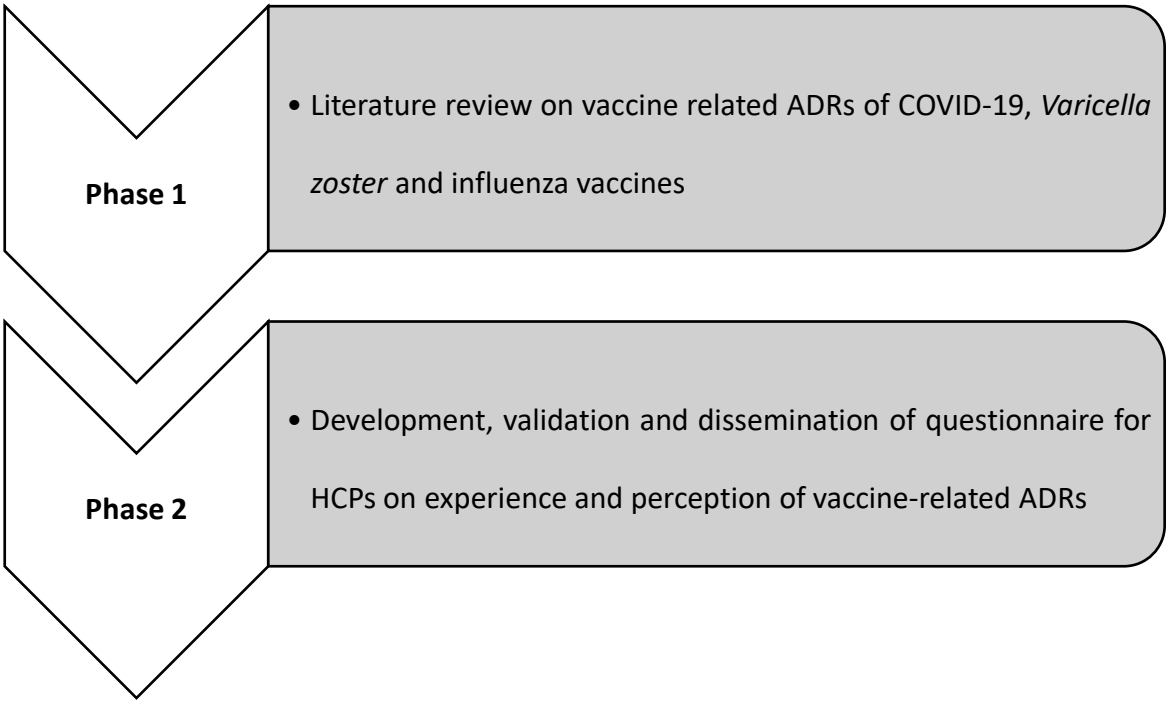

Figure 2.1. Methodology design

2.3. Phase 1: Literature review

Literature review on vaccine related ADRs was conducted. Three vaccines were selected which included COVID-19, influenza and *Varicella-zoster* vaccines. Literature included open-access, peer-reviewed journal articles from PubMed®. Keywords used included "COVID-19 vaccine adverse effects"; "*Varicella zoster* vaccine adverse effects" and "Influenza vaccine adverse effects". Early clinical studies were excluded from inclusion

criteria including pre-clinical tests, and therefore all articles included human subjects. Search parameters used for each vaccine are summarised in Table 2.1.

Table 2.1. Search parameters used

Vaccine	Time period	Article types from PubMed®	Keywords used
COVID-19 vaccine	2020-2022	Meta-analysis; Review	"COVID-19 vaccine side effects"
***Varicella-zoster* vaccine**	2012-2022	Meta-analysis; Review; Clinical trials	"*Varicella zoster* vaccine adverse effects"
Influenza vaccine	2012-2022	Meta-analysis; Review	"Influenza vaccine adverse effects"

Title of article, type of article, year of study, the vaccine technology or brand of vaccine used, the number of subjects studied on (if available) and the ADRs mentioned in the study were included in a database on Microsoft® Excel for selected vaccines. ADRs from each article were listed and grouped based on the type of ADR. ADRs were sorted and grouped based on their frequency. The same groups of ADRs were used for all three vaccines. If an ADR was mentioned with one of the vaccines, but there were no results for the other vaccines, that ADR was not included.

2.4. Phase 2: Development and validation of questionnaire for healthcare professionals

Questionnaire was developed using data from the literature search. Questionnaire was made up of 22 questions and was divided in three sections as the following

Demographic data including age, occupation, years of practice and area of practice;

Awareness, perception and experience related to ADR reporting;

Vaccine-related ADRs encountered during practice.

Most questions (n=13) were closed-ended and multiple choice. Likert scales were used for some questions (n=5). Likert scales used a score from 1 to 5, where 1 was the least level of agreement and 5 was the highest level of agreement. The rest of the questions (n=4) were open-ended. Questionnaire was validated for comprehensiveness and relevance by an expert panel made of four pharmacists, three in academia and one in community (Appendix 2).

2.5. Dissemination of questionnaire

Validated questionnaire was disseminated to HCPs through digital and physical platforms (Appendix 3). Dissemination was done through distribution by councils of HCPs including Council of Nurses and Midwives, Pharmacy Council and Medical Council, within a community pharmacy chosen by convenience through an intermediary and sharing through social media including Facebook groups of pharmacists and doctors. HCPs primarily targeted included pharmacists, nurses and doctors. Response rate was calculated. Responses were kept anonymous.

2.6. Data analysis of questionnaire

A 95% confidence interval was used for each test. Tests were chosen based on the type of data used. Levene's test was used to determine the distribution of data, whether it was normally or not normally distributed. If the p-value is less than 0.05, the null hypothesis of the Levene's test is accepted and data is normally distributed, therefore parametric tests are used. For p-values greater than 0.05, the null hypothesis is rejected and non-parametric tests are used.

Mean scores of questions which used a Likert scale were compared with categorical variables. The Kruskal-Wallis H was used for a comparison between numerical and categorical variables. The null hypothesis was accepted if the p-value was less than 0.05, indicating a statistically significant relationship between the categorical variable and mean score. Closed ended questions, classified as categorical variables and were not normally distributed used the Chi Square test. Null hypothesis was accepted if p-value was less than 0.05, indicating a statistically significant relationship between categorical variables.

2.7. Publication of study

Study was accepted as a poster presentation at the 82nd FIP World Congress of Pharmacy and Pharmaceutical Sciences 2024, in Cape Town (Appendix 4).

CHAPTER 3

Results

3.1. Literature Review

For COVID-19, *Varicella zoster* and influenza vaccines, a total of 149 articles were identified as relevant and matched the inclusion criteria. Ninety articles for COVID-19 vaccines were identified. The VZV resulted in 26 articles and influenza vaccines resulted in 33 articles. Thirty-three different types of ADRs were identified from literature search and are summarised in Table 3.1.

Table 3.1. Summary of adverse drug reaction groups for vaccines

ADR	COVID-19 vaccine	VZV	Influenza vaccine
Anaphylaxis, hypersensitivity and allergic reactions	•	•	•
Arrhythmia, myocardial infarction and other cardiac adverse effects	•	•	•
Arthralgia, arthritis and other ADRs affecting joints	•	•	•
Autoimmune conditions	•	•	•
Dyspnoea, wheezing and/or respiratory conditions	•	•	•
Epistaxis	•		
Erythema	•	•	•
Facial nerve palsy (incl. Bell's palsy)	•		•
Fatality	•	•	•
Fatigue and myalgia	•	•	•
Fever and chills	•	•	•
Flu-like symptoms			•
Gastrointestinal disturbances	•	•	•
Grave's disease	•		
Guillian-Barré syndrome	•	•	•
Headache and migraines	•	•	•
Hepatic adverse effects		•	
Herpes zoster and *Varicella zoster*-like skin reaction		•	
Injection site and local reactions	•	•	•
Loss of appetite			•
Lymphadenopathy/Lymph node swelling	•	•	
Multisystem inflammatory syndrome	•		
Myocarditis	•		
Neurological ADRs	•	•	•
Ocular adverse effects	•	•	•
Renal adverse effects	•	•	
Seizures	•		•
Skin reactions and/or conditions	•	•	•
Stroke	•	•	•
Syncope, vertigo and dizziness	•	•	•
Thrombosis and thrombocytopenia	•	•	
Tinnitus and hearing loss	•	•	•
Varicella zoster virus reactivation, infection or/and transmission	•	•	

3.1.1. COVID-19 Vaccines

Ninety articles were selected based on inclusion criteria out of the 673 articles resulting from the search between 2020 to 2022 (Appendix 5). Two articles were meta-analysis and the rest (n=88) were reviews. From these articles, the most commonly identified vaccine technology (n=75) was mRNA technology. The most common ADRs identified in literature were thrombosis and thrombocytopenia (n=20) and myocarditis (n=15) (Table 3.2.).

Table 3.2. Commonly identified ADRs in literature for COVID-19 vaccines (N=90)

Vaccine related adverse drug reaction	Number of articles
Thrombosis and thrombocytopenia	20
Myocarditis	15
Fatigue and myalgia	13
Headache and migraines	11
Ocular adverse effects	11
Skin reactions and/or conditions	11
Anaphylaxis, hypersensitivity and allergic reactions	10
Fever and chills	9
Injection site reactions	9
Autoimmune conditions	9
Gastrointestinal disturbances	7
Facial nerve palsy (incl. Bell's palsy)	6
Guillian-Barré syndrome	6
Lymphadenopathy/Lymph node swelling	6
Neurological ADRs	6
Arrhthymia, myocardial infarction and other cardiac adverse effects	5
Syncope, vertigo and dizziness	5
Athralgia, arthritis and other ADRs affecting joints	4
Stroke	4
Grave's disease	3
Seizures	3
Varicella zoster virus reactivation, infection or/and transmission	3
Dyspnoea, wheezing and/or respiratory conditions	2
Fatality	2
Multisystem inflammatory syndrome	2
Renal adverse effects	2
Tinnitus and hearing loss	2
Epistaxis	1
Erythema	1

3.1.2. *Varicella zoster* vaccines

Twenty-six articles were selected from a total of 78 articles resulting from the search between 2012 to 2022, with most of the articles being published in 2017 (n=5) (Appendix 6). Vaccine technology mostly identified was live-attenuated technology (n=13). The most common ADRs identified in literature were injection site reactions (n=16), fatigue and myalgia (n=14) and headaches and migraines (n=14) (Table 3.3.).

Table 3.3. Commonly identified ADRs in literature for Varicella zoster *vaccines (N=26)*

Vaccine related adverse drug reaction	Number of articles
Injection site reactions	16
Fatigue and myalgia	14
Headache and migraines	14
Skin reactions and/or conditions	13
Fever and chills	10
Gastrointestinal disturbances	9
Erythema	9
Arrhythmia, myocardial infarction and other cardiac adverse effects	6
Fatality	6
Dyspnoea, wheezing and/or respiratory conditions	5
Arthralgia, arthritis and other ADRs affecting joints	4
Thrombosis and thrombocytopenia	4
Herpes zoster-like skin reaction	4
Varicella zoster virus reactivation, infection or/and transmission	3
Neurological ADRs	3
Stroke	2
Lymphadenopathy/Lymph node swelling	2
Hepatic adverse effects	2
Ocular adverse effects	2
Guillian-Barré syndrome	1
Syncope, vertigo and dizziness	1
Anaphylaxis, hypersensitivity and allergic reactions	1
Renal adverse effects	1
Autoimmune conditions	1
Tinnitus and hearing loss	1

3.1.3. Influenza vaccines

Thirty-three articles were selected from a total 222 articles published between years 2012 to 2022 (Appendix 7). Some of the articles reported a meta-analysis (n=6). The most common vaccine technology identified in articles (n=25) included inactivated vaccine technology. The nasal spray vaccine of influenza, which is a live-attenuated vaccine (n=8) was included in some articles. Comparisons (n=2) between intramuscular and intradermal routes were also seen. An article (n=1) compared adjuvanted and unadjuvanted vaccines, and the adjuvanted form gave more ADRs. Some differences in ADRs were observed due to the differences in routes of administration. Not all articles included the number of patients (n=11). The most common ADRs identified in literature were fatigue and myalgia (n=20), fever and chills (n=18) and injection site and local reactions (n=18) (Table 3.4.).

Table 3.4. Commonly identified ADRs in literature for influenza vaccines (N=33)

Vaccine related adverse drug reaction	Number of articles
Fatigue and myalgia	20
Fever and chills	18
Injection site and local reactions	18
Headache and migraines	15
Erythema	14
Guillian-Barré syndrome	10
Dyspnoea, wheezing and/or respiratory conditions	10
Flu-like symptoms	8
Gastrointestinal disturbances	5
Allergic reactions and anaphylaxis	5
Skin reactions and/or conditions	5
Arrhthymia, myocardial infarction and other cardiac adverse effects	4
Seizures	4
Neurological ADRs	4
Autoimmune conditions	3
Loss of appetite	2
Syncope, vertigo and dizziness	2
Ocular adverse effects	2
Fatality	2
Athralgia, arthritis and other ADRs affecting joints	2
Facial nerve palsy (incl. Bell's palsy)	2
Stroke	1
Tinnitus and hearing loss	1

3.2. Dissemination of questionnaire to healthcare professionals

Questionnaire was mainly disseminated through the Council of Nurses and Midwives and the Pharmacy Council in Malta. The Council of Nurses and Midwives disseminated the questionnaire digitally to their network of registered nurses and it was disseminated to 5438 nurses. Dissemination by the council includes all registered nurses with the network including those which are retired or no longer practicing. The Pharmacy Council disseminated the questionnaire digitally to their network of registered pharmacists and

was circulated to 1322 pharmacists, which included pharmacists who are retired or no longer practicing. The Medical Council was unable to disseminate the questionnaire through their portal. Dissemination was also carried out by sharing through social media and to a community pharmacy. One response was completed physically (Table 3.5.).

Table 3.5. Dissemination of questionnaire

Source	Number of healthcare professionals targeted	Types of healthcare professionals targeted
Community pharmacy	5	Pharmacists, doctors
Social media	768	All types HCPs
Pharmacy Council	1322	Pharmacists
The council of Nurses and Midwives	5438	Nurses

3.2.1. Response rate of questionnaire

Questionnaire was completed by 284 healthcare professionals. The percentage response rates were calculated and summarized in Table 3.6. Questionnaire may have been received more than once by HCPs.

Table 3.6. Response rate of questionnaire

Healthcare professional	Dissemination	Response	Response rate
Medical physician	210	46	21.9%
Nurses	5447	161	2.96%
Pharmacists	1860	68	3.66%
Other	17	9	52.94%

3.3. Demographics of respondents

HCPs were mostly (n=102) aged between 31-40 years. Most HCPs (n=161) were nurses. HCPs who were classified as other include dentists, orthoptists, radiographers, allied HCP and pharmacy technicians. The majority of respondents (n=79) have been in practice for more than 20 years. Six of the respondents have been in practice for less than one year. Most HCPs work in hospital (n=156) and in community (n=72). The rest of the HCPs included other such as nursing homes, industry, regulatory and administration. Four of the HCPs were either not currently practicing in their field or were retired (Table 3.7.)

Table 3.7. Demographics of respondents (N=284)

	Category	Number
Age (years)	18-30	68
	31-40	102
	41-50	47
	51-59	47
	60+	20
Occupation	Medical physicians	46
	Nurse	161
	Pharmacists	68
	Other	9
Years of practice	Less than 1 year	6
	1-5 years	55
	6-10 years	58
	11-15 years	51
	16-20 years	35
	More than 20 years	79
Area of practice	Hospital	156
	Community	72
	Nursing home	16
	Regulatory, Industry & administration	27
	Currently not practicing	4
	Academia	3
	Other	6

3.4. Awareness of healthcare professionals on the procedure for adverse drug reaction reporting

Level of awareness of HCPs on the process of ADR reporting was measured as a Likert scale as a score from 1 to 5, where 1 was lowest level of awareness and 5 highest level of awareness. The overall mean score of all professions was 3.36.

Most respondents (n=143) did not receive any training on ADR reporting. From those HCPs who have received training (n=139), most of the respondents (n=70) received training from their place of practice. Other places respondents received training from was from when they were a student (n=54) and from campaigns by local authorities (n=15). One of the respondents said that they believe that they are not in a position to require training on ADR reporting.

HCPs (n=122) agree there are barriers preventing ADRs from being reported by HCPs. Forty-seven HCPs think that there are no barriers to ADR reporting and the rest of the HCPs (n=115) are not sure whether there are any barriers to ADR reporting. One hundred and forty-four of the respondents identified which barriers are mostly preventing HCPs from reporting. Lack of awareness (n=106) was identified as the most common barrier to ADR reporting (Figure 3.1.). Other (n=11) responses provided included apathy, insufficient training, bureaucracy of the process and inconvenience.

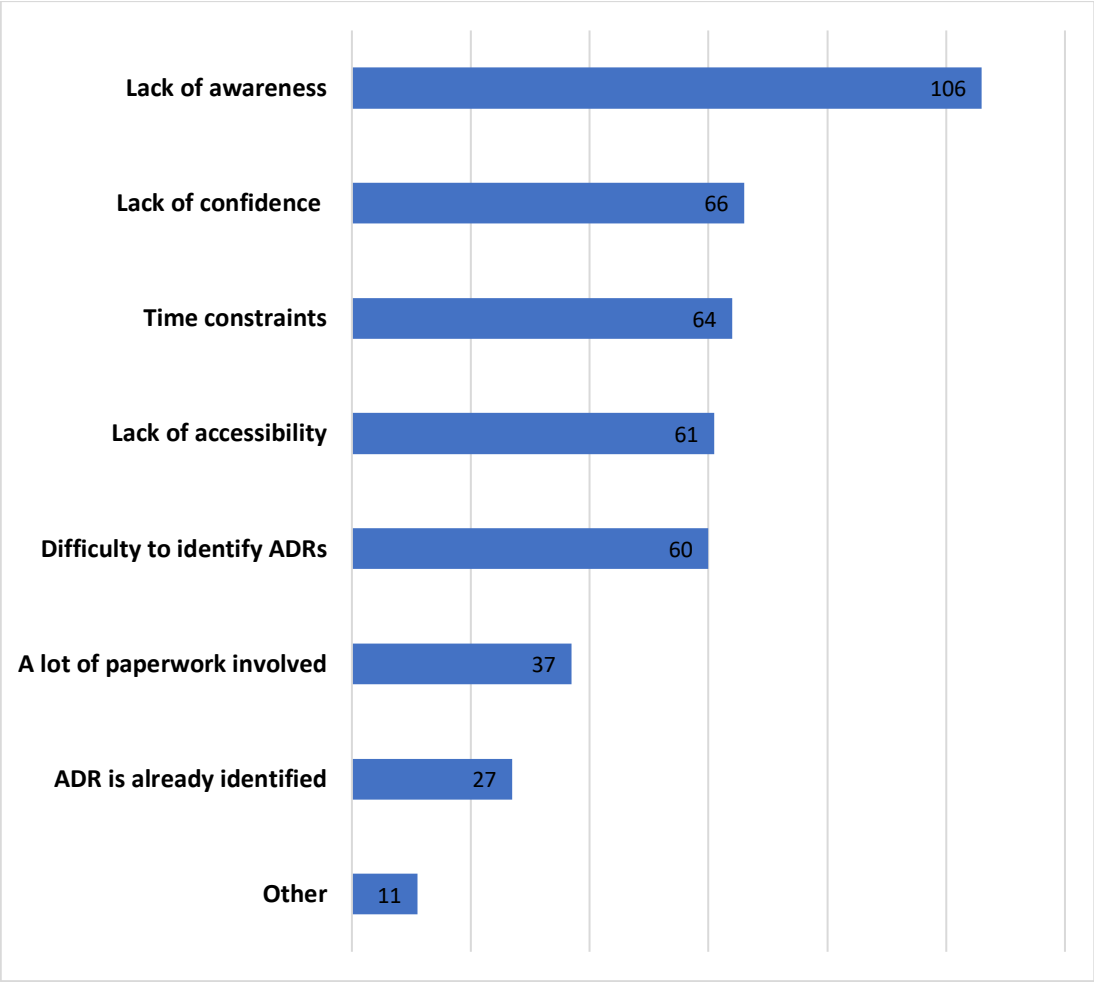

Figure 3.1. Barriers of ADR reporting identified by respondents (N=144)

3.5. Experience of healthcare professionals on the procedure for adverse drug reaction reporting

Respondents believe that they have not encountered cases of ADRs which should have been reported for medicines (n=256) and vaccines (n=229). Fourteen HCPs have encountered cases of vaccine-related ADRs which were not reported. Eighteen HCPs encountered cases of medicine ADRs which could have been reported but were not reported. Fourteen HCPs have previously reported a vaccine-related ADR. The vaccines for which a report was submitted by the respondents included COVID-19 (n=11), MMR

(n=1) and pneumococcal (n=2) vaccines. HCPs (n=36) have previously reported ADRs for medicines. The ADRs reported for medicines were not specified.

Almost all HCPs (n=204) have encountered patients who experienced vaccine related ADRs during their time of practice. Ninety-six HCPs have encountered less than 5 patients with vaccine related ADRs. Most complaints of vaccine-related ADRs were from the COVID-19 vaccines (n=200) and influenza vaccines (n=100). Other complaints were from *Varicella zoster* (n=10), pneumococcal (n=2), MMR (n=1), human papilloma virus (n=1), diphtheria, tetanus, pertussis, polio and haemophilus influenza type b (n=2) and meningococcal (n=1) vaccines. The most commonly reported ADRs from 207 responses were muscle & joint pain (n=152) and fever & chills (Figure 3.2.). Other responses (n=8) mentioned by respondents included seizures, neurological symptoms, stroke and numbness and tingling.

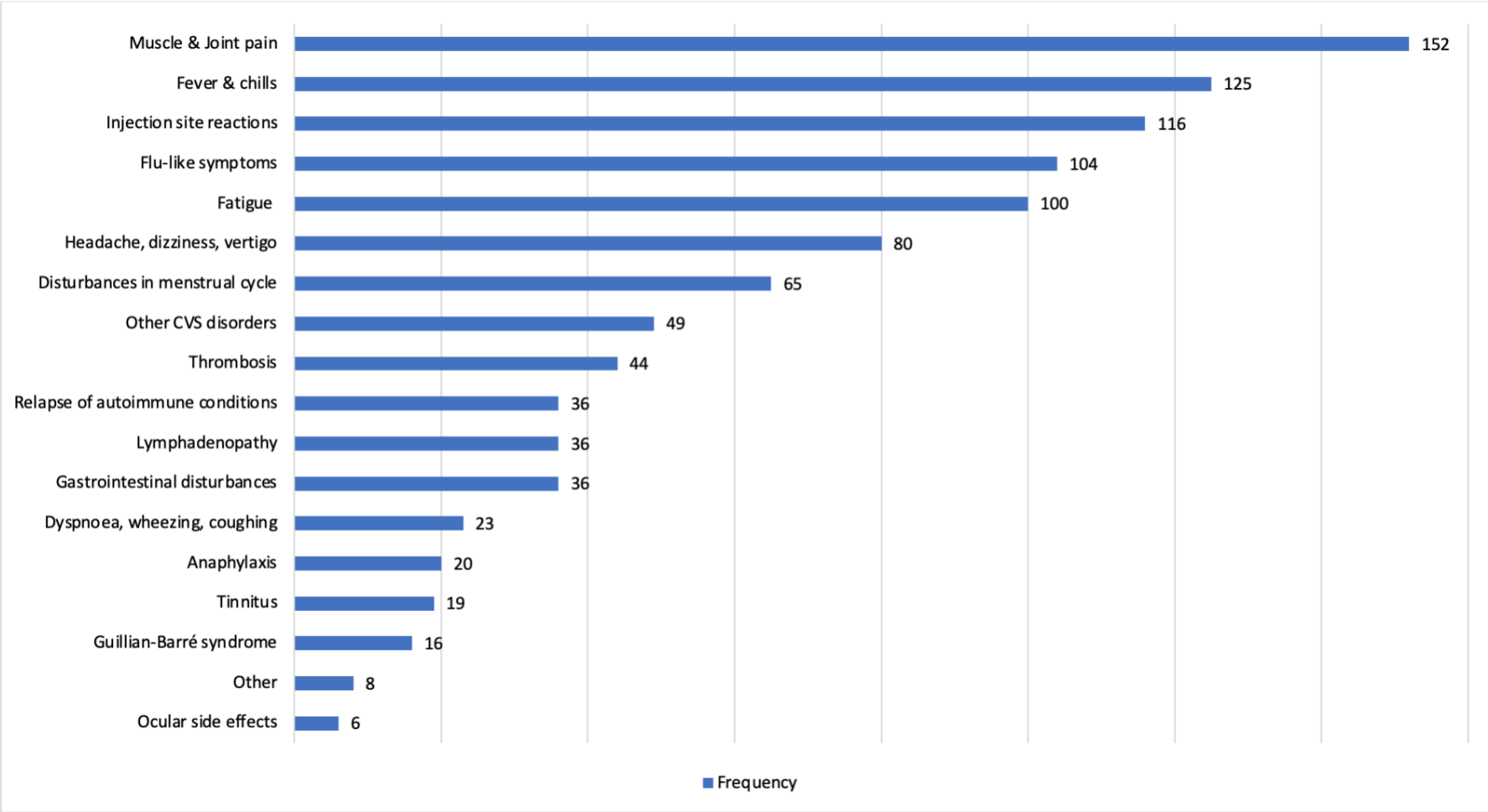

Figure 3.2. Commonly identified ADRs by respondents (N=207)

3.6. Healthcare professionals' perceptions on vaccines

Likert scales with a score from 1 to 5 to evaluate the perceptions of vaccines, where 1 was strongly disagree and 5 was strongly agree, were used. Table 3.8. summarises the statements and the overall mean scores. The first statement had the highest agreement (mean score=3.79 out of 5) between HCPs when comparing to the other statements. The statement of more ADRs experienced when taking two vaccines had the lowest agreement (mean score=2.81 out of 5) among respondents.

Table 3.8. Statements and mean scores

Statement	Overall mean score
1. I received more complaints on ADRs related to the COVID-19 vaccine than other vaccines.	**3.79**
2. Patients who received the influenza and COVID-19 vaccines together complained more of vaccine related ADRs than those patients who were vaccinated by the two vaccines on two different occasions.	2.81
3. I have seen more cases of ADRs caused by the COVID-19 vaccine than other vaccines (e.g. disturbances in menstrual cycle, tinnitus, ocular effects, etc).	3.35
4. I have seen more cases of ADRs which led to hospitalisation from the COVID-19 vaccine than other vaccines (e.g. thrombosis, lymphadenopathy, myocarditis, etc.)	2.82

3.7. Other remarks from respondents

Twenty-three of the respondents gave further remarks and opinions on the subject. Respondents (n=2) highlighted the importance of providing more training to HCPs on ADR reporting procedures for better awareness and on handling ADRs received from patients. Comments (n=12) mentioned the quality of ADR reports received and whether

the ADR is genuinely related to the vaccine and not as a coincidence. Other comments (n=8) dealt with COVID-19 vaccination and the misinformation surrounding these vaccines. One comment highlighted the importance of improving accessibility of ADR reporting form as for example making it an online form.

3.8. Statistical analysis

Comparisons between different variables was conducted to test if any significant relationship between variables can be observed. Results from Levene's test showed that data was not normally distributed (p-value=0.003), and non-parametric tests were used.

3.8.1. Awareness of different healthcare professionals

Pharmacists had the highest level of awareness on ADR reporting as they achieved the highest mean score of 4.1 out of 5 from all other HCPs. Medical physicians had the lowest of level of awareness as they attained a mean score of 2.48 out of 5. Between the different occupations, a significant difference in the level of awareness was observed (p-value= <0.001). Therefore, pharmacists have a significantly greater level of awareness on the process of ADR reporting when compared to other occupations (Table 3.9.).

Table 3.9. Mean scores for awareness and occupation (N=284)

Occupation	Count	Mean score (out of 5)	Standard deviation of mean score	p-value
Medical physician	46	2.48	± 0.196	**<0.001**
Nurse	161	3.31	± 0.11	
Pharmacist	68	**4.1**	± 1.07	
Other	9	3.33	± 1.5	
Total	284	3.37	± 1.42	

3.8.2. Level of training provided to HCPs

In comparison to other HCPs, pharmacists (60.3%) received more training on ADR reporting and other HCPs (33.3%) received the least amount of training. The occupation of the HCP has no overall influence on whether training was received (p-value=0.101). However, if the level of significance between the individual occupations and training received was identified, a significant relationship (p-value=0.035) for the occupation of pharmacists was observed. Therefore, pharmacists received a significantly greater amount of training in comparison to other HCPs (Table 3.10).

Table 3.10. Occupations and training received (N=284)

Occupation	Count	Received training	Did not receive training	Percentage of HCPs who received training	Individual p-value	Overall p-value
Medical physician	46	18	28	39.1%	0.131	0.101
Nurse	161	77	84	47.8%	0.312	
Pharmacist	68	41	27	**60.3%**	**0.035**	
Other	9	3	6	33.3%	0.814	

A comparison between the years in practice and training received was conducted. HCPs in practice for less than 1 year (66.7%) received the most training. The sample size for those in practice for less than 1 year made up 2.1% of the total population, which is a small proportion of the population and may not be significantly important. HCPs in practice for 6-10 years (39.7%) received the least amount of training. The number of years in practice had no influence on whether training was received by the HCP (p-value=0.272). (Table 3.11).

Table 3.11. Years in practice and training received (N=284)

Years in practice	Count	Received training	Did not receive training	Percentage of HCPs who received training	p-value
Less than 1 year	6	4	2	**66.7%**	0.272
1-5 years	55	27	28	49.1%	
6-10 years	58	23	35	39.7%	
11-15 years	51	30	21	58.8%	
16-20 years	35	20	15	57.1%	
More than 20 years	79	35	44	44.3%	

3.8.3. ADR reporting experience

A comparison between the reporting experiences for vaccines and medicines and the area of practice was conducted. Most HCPs who have previously submitted an ADR report for medicines (25.9%) were in regulatory, industry and administration. HCPs in academia have not previously reported any ADRs for medicines (0%). No significant difference between reporting experience of medicines and the area of practice of the HCP (p-value=0.173) was observed (Table 3.12.).

Table 3.12. Area of practice and ADR reporting experience for medicines

Area of practice	Count	Have reported	Had the opportunity, but did not report	Have not reported	Percentage reported	p-value
Academia	3	0	0	3	0%	0.173
Community	72	8	3	61	11.1%	
Currently not practising	4	1	1	2	25%	
Hospital	156	17	11	128	10.9%	
Nursing home	16	1	1	14	6.3%	
Regulatory, Industry, Administration	27	7	2	18	25.9%	
Other	6	1	0	5	16.7%	

The category “Other” was the area of practice with the highest number of HCPs who have previously reported a vaccine related ADRs (16.7%). Academia, those not currently practising and nursing homes did not report any vaccine related ADRs (0%). A statistically significant difference between the area of practice and vaccine-related ADR experience was observed (p-value=0.001) (Table 3.13).

Table 3.13. Area of practice and ADR reporting experience for vaccines

Area of practice	Count	Have reported	Had the opportunity, but did not report	Have not reported	Percentage reported	p-value
Academia	3	0	0	3	0%	**0.001**
Community	72	4	2	66	5.6%	
Currently not practising	4	0	2	2	0%	
Hospital	156	6	8	142	3.8%	
Nursing home	16	0	0	16	0%	
Regulatory, Industry, Administration	27	2	2	23	7.4%	
Other	6	1	0	5	16.7%	

3.8.4. Vaccine perceptions and experiences

Mean scores given from 1 to 5 depending on the level of agreement with four statements for each occupation were determined. The lowest variability in scores was given for statement 3. Statement 3 had the lowest variability in the scores given (standard deviation= ± 0.433). The agreement between statements 2 and 4 was similar between the different occupations. No statistical significance was observed for statements 2 (p-value=0.525) and 4 (p-value= 0.271), meaning there is no difference in the degree of agreement between occupations. HCPs scored higher mean scores for statements 1 and 3, showing a higher level of agreement. Statistical significance was observed for statements 1 (p-value=<0.001) and 3 (p-value=0.05). Therefore, a significant difference between the mean scores given and the occupation is observed (Table 3.14.).

Table 3.14. Scores for each statement sorted by occupation

Statement	Medical Physician	Nurse	Pharmacist	Other	Overall Mean score	Standard deviation of score	p-value
1. I received more complaints on ADRs related to the COVID-19 vaccine than other vaccines.	4.5	3.4	4.2	3.8	**3.79**	± 1.494	**<0.001**
2. Patients who received the influenza and COVID-19 vaccines together complained more of vaccine related ADRs than those patients who were vaccinated by the two vaccines on two different occasions.	2.9	2.7	2.9	3.1	2.81	± 1.31	0.525
3. I have seen more cases of ADRs caused by the COVID-19 vaccine than other vaccines (e.g. disturbances in menstrual cycle, tinnitus, ocular effects, etc).	3.6	3.1	3.7	3.1	**3.35**	± 0.433	**0.05**
4. I have seen more cases of ADRs which led to hospitalisation from the COVID-19 vaccine than other vaccines (e.g. thrombosis, lymphadenopathy, myocarditis, etc.)	2.9	2.8	2.8	2.8	2.82	± 1.495	0.271

CHAPTER 4

Discussion

4.1. Vaccine-related ADRs in literature

The highest number of articles identified in literature were related to ADRs caused by COVID-19 vaccines. fever & chills and fatigue & myalgia were common ADRs reported for all three vaccines. These types of ADRs are common responses to vaccines and are generally self-managed with over-the-counter remedies. [46]

The most common ADRs identified in the literature review for COVID-19 vaccines were thrombosis and thrombocytopenia. Within the SmPCs of Vaxzevria® and JCovden®, thrombosis and thrombocytopenia were included as an ADR. Thrombosis and thrombocytopenia were noted more commonly among patients with comorbidities, as mentioned within the SmPCs of Vaxzevria® and JCovden®. [47, 48] Thrombosis was noted to occur more often with Vaxzevria® and JCovden® vaccination; vaccines which use viral vector technology (Sharifian-Dorche et al., 2021). A relationship between COVID-19 vaccination and occurrence of thrombosis has been identified. [49] Iba & Levy (2022) reported that most cases of thrombosis and thrombocytopenia were associated with

[46] Centers for Disease Control and Prevention (CDC). Understanding adverse events and side effects [Internet]. US: CDC; 2021 [cited 2024 Jul 13]. Available from: https://www.cdc.gov/vaccinesafety/ensuringsafety/sideeffects/index.html#:~:text=Types%20of%20adverse%20events%20that%20may%20occur%20after%20vaccination&text=Injections%20site%20pain%2C%20redness%20or,can%20last%20for%20several%20days.

[47] AstraZeneca. Vaxzevria suspension for injection SmPC. 2023 [cited 2024 Jul 15] Available from: https://www.ema.europa.eu/en/documents/product-information/vaxzevria-epar-product-information_en.pdf

[48] Johnson&Johnson. JCovden suspension for injection SmPC. 2024 [cited 2024 Jul 15]. Available from: https://www.ema.europa.eu/en/documents/product-information/jcovden-epar-product-information_en.pdf

[49] UK Research and Innovation (UKRI). Studying the link between COVID-19 vaccines and rare blood clots [Internet]. United Kingdom: UKRI; 2024 [cited 2024 Aug 14]. Available from: https://www.ukri.org/who-we-are/how-we-are-doing/research-outcomes-and-impact/mrc/studying-the-link-between-covid-19-vaccines-and-rare-blood-clots/

viral-vector vaccination. The literature search conducted identified most cases of thrombosis and thrombocytopenia to be caused by viral vector vaccines. However, mRNA vaccinations also have the risk of causing thrombosis and thrombocytopenia (Iba & Levy, 2022; Cocco et al., 2023).

Myocarditis was the second most commonly identified ADR in the literature review. Vaccine-related myocarditis is often linked with mRNA vaccines. Proposed mechanisms for causing vaccine-related myocarditis show that mechanism of action may be linked to the release of leukocytes (Ciabatti *et al*., 2023; Fairweather *et al*., 2023). Most articles identified in literature review reporting myocarditis were using mRNA technology. Occurrence of vaccine-related myocarditis is not a unique ADR to mRNA vaccines and has occurred with other COVID-19 vaccine technologies at a reduced frequency, including inactivated and subunit vaccine technologies. Vaccine-related myocarditis was also reported with other vaccines including influenza and smallpox vaccines. COVID-19 infection has also caused myocarditis (Altman *et al*., 2023).

Less severe ADRs identified in the literature review for COVID-19 vaccines included fatigue and myalgia. During clinical trials of mRNA vaccines as mentioned in the SmPCs, common ADRs including injection site reactions, fatigue and headaches were experienced. [50, 51] A comparative study of three COVID-19 vaccines by Patel *et al*. (2022)

[50] Pfizer-BioNTech. Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection COVID-19 mRNA Vaccine SmPC. 2024 [cited 2024 Jul 15]. Available from: https://www.medicines.org.uk/emc/product/15044/smpc#gref

[51] Moderna. Spikevax XBB.1.5 0.1 mg/mL dispersion for injection (MDV) SmPC. 2024 [cited 2024 Jul 15]. Available from: https://www.medicines.org.uk/emc/product/14632/smpc

discovered that fatigue was a common complaint, especially among geriatric patients. Myalgia was noted with mRNA vaccines, being more common in younger patients (Patel *et al*., 2022).

Guillian-Barre syndrome was another ADR identified in literature for COVID-19 vaccines. Guillain-Barré syndrome has also been identified with VZV and influenza vaccines. Patel *et al.* (2022) reported Guillain-Barré syndrome following JCovden® vaccination. A case of Guillain-Barré syndrome following COVID-19 infection was also identified in literature (Noon *et al*., 2022; Patel *et al*., 2022). Neurological conditions for COVID-19 vaccines including facial nerve palsy and seizures were identified in the literature review. Occurrence of neurological ADRs are severe and rare ADRs of COVID-19 vaccines as listed within the SmPCs of COVID-19 vaccines. Afshar et al. (2023) also identifies neurological ADRs similar to the literature review conducted (Afshar *et al*., 2023). COVID-19 infection may also cause neurological ADRs and therefore a relationship between the occurrence of neurological ADRs with vaccines and infection may be present (Ghasemiyeh *et al*., 2020).

Reactivation of viruses, especially of the *Varicella zoster* virus, was identified in literature review and is a rare ADR, more commonly occurring among patients with other comorbidities. The association and mechanism of action between *Varicella zoster* virus reactivation and COVID-19 was investigated by Shafiee *et al*. (2023). Two of the three cases identified in this literature review were caused by mRNA vaccines, which as mentioned in the study by Shafiee *et al*. (2023) is the vaccine technology most likely to cause reactivation of the *Varicella zoster* virus (Shafiee *et al.*, 2023).

The safety of VZVs has been well established for many years compared to COVID-19 vaccines. VZV is not administered to the entire population as of yet, as it is not a part of some local vaccination programmes, meaning the number of patients who have received the vaccine is less in comparison to COVID-19 vaccines (Lee *et al.,* 2022).

Non-serious ADRs for VZVs were commonly identified in literature review. Injection site reactions was the most commonly identified ADR in the literature review. Studies by Parikh *et al*. (2023) and Mwakingwe-Omari *et al*. (2023) identified injection site reactions as being the most common ADR. Injection site reactions are not related to the mechanism of action of the vaccine but to the method of administration. (Mwakingwe-Omari *et al*., 2023; Parikh *et al*., 2023).

Skin reactions were identified in literature review, especially erythema and *Herpes zoster*-like rashes. Parikh *et al.* (2023) discusses the safety of recombinant VZVs and refers to reports on different skin reactions experienced by patients. Older patients and patients with underlying skin disorders had a higher risk of experiencing skin reactions as an ADR (Parikh *et al*., 2023).

Strains of influenza vaccines are changed annually. Manufacturing processes of influenza vaccines may also change, including the introduction of manufacturing procedures which do not use eggs as a medium and reduce the risk of hypersensitivity

reactions.[52, 53] Non-serious ADRs, fatigue and myalgia, fever and chills and local reactions, were the three most common ADRs for influenza vaccines identified in the literature review. The SmPC of the quadrivalent inactivated influenza vaccine states myalgia as a very common ADR and fatigue as an uncommon ADR. Fever and chills and injection site reactions were listed as common ADRs. [54]

SmPCs report nasal congestion and rhinorrhoea as common ADRs for live attenuated influenza vaccines. The live attenuated vaccine is delivered as a nasal spray to paediatric patients.[55] Local ADRs for the nasal spray vaccine were identified within literature review.

Cardiovascular ADRs were identified in the literature review for influenza vaccines. Cardiovascular risks due to influenza vaccination are unlikely to occur and benefits of vaccination outweigh risks. Cardiovascular risks of influenza infection are higher than

[52] Department of Health and Aged Care. 2024 seasonal influenza vaccines [Internet]. Austrailia: Government of Australia; 2024 [cited 2024 Sep 1]. Available from: https://www.tga.gov.au/resources/publication/publications/2024-seasonal-influenza-vaccines

[53] Centers for Disease Control and Prevention (CDC). Cell based flu vaccines [Internet]. United States: CDC; 2023 [cited 2024 Sep 2]. Available from: https://www.cdc.gov/flu/prevent/cell-based.htm#:~:text=The%20cell%2Dbased%20vaccine%20manufacturing%20process%20uses%20mammalian%20cells%20(Madin,derived%20rather%20than%20egg%2Dderived.

[54] Sanofi Pasteur. Quadrivalent influenza Vvccine (split virion, inactivated), suspension for injection in pre-filled syringe SmPC. 2024 [cited 2024 Jul 17]. Available from: https://www.medicines.org.uk/emc/product/666/smpc

[55] AstraZeneca UK Ltd. Fluenz Tetra nasal spray suspension Influenza vaccine (live attenuated, nasal) SmPC. 2023 [cited 2024 Jul 17]. Available from: https://www.medicines.org.uk/emc/product/3296/smpc#gref

vaccination rates as highlighted in study by Yeldapati *et al.* (2021), promoting the safety and benefits of influenza vaccination (Yeldapati *et al*., 2021).

4.2. Questionnaire for healthcare professionals on vaccine adverse drug reporting

The Council of Nurses and Midwives disseminated the questionnaire to the largest number of HCPs A small proportion of the sample (16.5%) were medical physicians. The Medical Council were unable to disseminate the questionnaire to medical physicians, which has limited the amount of responses received from medical physicians as they were reached only through social media.

Response rates for medical physicians and other occupations were at 21.9% and 52.94% respectively. Other occupations such as orthoptists and dentists have been reached through social media. Response rates for pharmacists and nurses were 3.66% and 2.96%. A factor which may have contributed to the lower response rate for nurses and pharmacists was that some of the respondents may have received the questionnaire more than once from both social media and from the council.

Most HCPs practiced at hospital and in community. Community and hospital are areas of practice where HCPs encounter a diverse number of patients and are more likely to encounter cases of ADRs which should be reported. Whilst HCPs working in the regulatory field were expected to be more knowledgeable on the ADR reporting procedure, during their practice, they encounter less patients when compared to other fields which reduces the likelihood of encountering patients with ADRs.

4.3. Awareness, perception and experience related to adverse drug reaction reporting

HCPs who have participated in the study were aware of the procedure for ADR reporting since the mean score for awareness was 3.36 out of 5. From all participating occupations, pharmacists had the highest level of awareness with a mean score of 4.1 out of 5. A statistically significant difference between occupations and the level of awareness was noted, confirming that pharmacists were more knowledgeable on the procedure than other occupations. The higher level of awareness may be linked to the training received by pharmacists as 60.3% have received training on ADR reporting. Khardali (2024) reported that pharmacists had a good level of knowledge and awareness on pharmacovigilance in their study (Khardali, 2024). Study by Albayrak & Karahalil (2022) was conducted to evaluate perceptions and knowledge of pharmacists on ADR reporting and has also identified pharmacists as being knowledgeable (Albayrak & Karahalil, 2022).

Medical physicians (mean score=2.48) and nurses (mean score=3.31) had lower mean scores than pharmacists. Most medical physicians and nurses did not receive training on ADR reporting, which had an impact on the level of awareness. The majority of participants in study by Shah *et al*. (2021) which included nurses and doctors, also did not receive training. The study took place in Nepal, showing that a lack of training on ADR reporting is an issue for other countries as well. For HCPs in this study and in the study by Shah *et al.* (2021), a lack of training on ADR reporting has impacted awareness and confidence of HCPs on ADR reporting (Shah *et al.*, 2021).

Despite having more than half the HCPs did not receive training on ADR reporting, different training programmes on the process of ADR reporting are offered by authorities. Locally, the MMA offers training programmes on ADR reporting and pharmacovigilance to all HCPs.[56] The government of United Kingdom offers short online training modules on ADR reporting. Modules are streamed to pharmacists, nurses and medical physicians.[57].

A statistical difference between occupations and training received was noted. However no statistical difference between the number of years in practice was observed. No major changes in educational curricula and training requirements on ADR reporting may have been implemented since no differences were noted between the training received and number of years in practice.

Only 12.6% of the HCPs within the study have previously reported an ADR for medicines. Percentage is lower for vaccine-related ADRs, as only 4.9% of the HCPs have previously reported. The low percentage shows that HCPs in this study were not experienced at reporting ADRs. Results from this study compare with a study done by Kassa Alemu & Biru (2019), who also found that 29.8% have encountered and reported an ADR (Kassa Alemu & Biru, 2019).

[56] Malta Medicines Authority (MMA). MMA academy for patient centred excellence and innovation in regulatory sciences [Internet]. Malta; MMA: 2024 [cited 2024 Jul 22]. Available from: https://medicinesauthority.gov.mt/academyforregulatorysciences

[57] Yellow Card. E-Learning modules [Internet]. UK; Medicines & Healthcare products regulatory agency: (undated) [cited 2024 Jul 22]. Available from: https://yellowcard.mhra.gov.uk/resources/elearning

Only a small proportion of ADRs that occur are reported. Underreporting of ADRs is an issue as it may impact the safety of the product (Shafei *et al.*, 2023). Maltese pharmacovigilance legislation specifies the requirement and duty to report ADRs. Barriers should be minimised and overcome to encourage more HCPs to report ADRs (Borg *et al.,* 2018; Al Meslamani, 2023). The barriers which are contributing towards underreporting were explored among the respondents.

Lack of awareness was identified as the most common barrier to prevent HCPs from reporting. Nduka *et al.* (2024), conducted a study among pharmacists and found that the main barrier of ADR reporting was also lack of awareness. Islam *et al.* (2020) reported similar barriers within their study including lack of awareness (Islam *et al.,* 2020; Nduka *et al.,* 2024). Time constraints was also a common barrier chosen by HCPs in this study and similarly in a study by Li *et al.* (2018) (Li *et al*., 2018).

The challenge in identifying an ADR was also identified as a barrier to ADR reporting in this study. In a dissertation by Curtolo and in a study by Srisuriyachanchai *et al*. (2022) difficulty in identifying an ADR was a barrier to ADR reporting (Curtolo *et al.,* 2022; Srisuriyachanchai *et al*., 2022). [58]. Difficulty in determining a confirmatory cause of an ADR due to different comorbidities and drugs is a challenge. O'Donovan *et al.* (2022), explored the issue of identifying ADRs by evaluating the completeness of submitted ADR reporting forms and investigating the approaches taken by HCPs. O'Donovan *et al*. (2022) concluded on the importance of including as much data as possible in ADR

[58] Curtolo E. An innovative approach to pharmacovigilance [dissertation]. Msida (Malta): Department of Pharmacy, University of Malta; 2021.

reporting forms and taking a narrative approach to further investigate the cause of ADRs (Curtolo *et al*., 2022; O'Donovan *et al*., 2022; Srisuriyachanchai *et al*., 2022).

The most common ADRs reported in the questionnaire were muscle & joint pain (74.5%), fever & chills (60.1%) and injection site reactions (55.8%). Non-severe ADRs were reported as the most common in the questionnaire. Severe ADRs such as and relapse or occurrence of autoimmune conditions (17.6%) and Guillian-Barré syndrome (7.8%) were also reported. Reports of thrombosis (21.6%) may be accounted for due to majority of respondents (n=154) working in hospital, where most cases of thrombosis and thrombocytopenia would be expected to occur.

HCPs agreed (mean score=3.79 out of 5) that the COVID-19 vaccines were associated with more complaints from patients on ADRs. The rapid dissemination of COVID-19 vaccines may have influenced the number of ADRs complaints received by HCPs. A significant difference between occupations and agreement was observed with this statement, with medical physicians having the highest mean score.

HCPs did not strongly agree (mean score=2.81 out of 5) with the statement that COVID-19 and influenza vaccines given together increases the number of ADRs experienced. HCPs may have had no experience with administering or encountering patients who have received COVID-19 and influenza vaccines together and do not agree with the statement. In 2024, a combined vaccine of COVID-19 booster and seasonal influenza for the winter season is issued to the market for the first time and more patients taking

both vaccines at once will occur.[59] A study by Wu *et al.* (2024), found that the combination of COVID-19 and influenza vaccines reduced the risk of developing long COVID-19. The association between taking both vaccines together and the risk is not clear (Wu *et al*., 2024).

HCPs agreed (mean score=3.35 out of 5) when asked about the cases of ADRs observed with the COVID-19 vaccine. The examples given with this statement were specific to COVID-19 vaccine ADRs observed in literature including disturbances in menstrual cycle and tinnitus. A statistically significant difference between the different HCP occupations and the mean scores was present.

HCPs did not strongly agree (mean score=2.82) with the statement on cases of hospitalisation observed with the COVID-19 vaccines. Disagreement with this statement was expected because these ADRs are severe and rare and were less likely to be encountered in practice.

Respondents commented on the quality of the ADR reports received and the differences between the ADRs submitted by patients and those submitted by HCPs. Toki & Ono (2020) compared ADR reports received from both patients and HCPs and no major differences were noted in the completeness of the report (Toki & Ono, 2020). A respondent mentioned how ADR reporting forms should be made more accessible by

[59] Centers for Disease Control and Prevention (CDC). CDC recommends updated 2024-2025 COVID-19 and flu vaccines for fall/winter virus season [Internet]. United States: CDC; 2024 [cited 2024 Aug 14]. Available from: https://www.cdc.gov/media/releases/2024/s-t0627-vaccine-recommendations.html

being completed through online forms, as currently the form is available as a printable format. Accessibility and creating more awareness on ADR reporting by using information systems improved ADR reporting rates as mentioned within a study by Ribeiro-Vaz *et al.* (2016) (Ribeiro-Vaz *et al.*, 2016).

4.4. Limitations of the study

The small sample size of HCPs limits the local significance of the results. COVID-19 vaccines were discussed more than the influenza vaccines and VZVs due to the novelty and widespread administration of this vaccine to the market

4.5. Further recommendations

As further study, questionnaire may continue to be disseminated, especially to medical physicians. The questionnaire may be eventually modified to be disseminated to patients and compare perceptions and experiences of vaccines of patients with of HCPs.

4.6. Conclusion

Vaccine related ADRs reported in literature are similar to the ones reported by the HCPs in the study. Introduction of the COVID-19 vaccines on the market might have influenced ADR reporting rates and attitudes towards ADR reporting. HCPs are aware on the procedure of ADR reporting. However, barriers and challenges are still recognised, which limits confidence and reduces reporting rates.

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APPENDIX 1

Ethics registration

Kristina Filletti <kristina.filletti.19@um.edu.mt>

The status of your REDP form (MED-2023-00488) has been updated to Acknowledged

1 message

form.urec@um.edu.mt <form.urec@um.edu.mt> 18 January 2024 at 07:39
To: kristina.filletti.19@um.edu.mt

Dear Kristina Filletti,

Please note that the status of your REDP form (MED-2023-00488) has been set to *Acknowledged*.

This status change was accompanied by the following explanation/justification: *Dear applicant, Your research ethics application has been received. This does not mean that your application has FREC ethical approval and may be subject to an audit review. The FREC number generated by submission for records only cannot be used as proof of ethical approval. As indicated in the Research Ethics Review Procedures, submissions which have no self-assessment issues are kept for record and audit purposes only, so research may commence. Kindly note that FREC will not issue any form of approval as the responsibility for the self-assessment part lies exclusively with the researcher. Please note that SCPD generally requires review. If you have any questions or doubts or require any further clarification you can contact the MED FREC secretary. Regards, MED FREC*

You can keep track of your applications by visiting: https://www.um.edu.mt/research/ethics/redp-form/frontEnd/.

This email has been automatically generated by URECA. Please do not reply. If you wish to communicate with your F/REC please use the respective email address.*

APPENDIX 2

Questionnaire validation tool for expert panel

REPORTING VACCINE ADVERSE DRUG REACTIONS

TOOL FOR VALIDATION

Date: _____

Part 1: Demographic Data

1. Age (years)
    - 20-30
    - 31-40
    - 41-50
    - 51-60
    - 65+

	1 (strongly disagree)	**2 (disagree)**	**3 (neutral)**	**4 (agree)**	**5 (strongly agree)**
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

2. Occupation
    - Pharmacist
    - Doctor
    - Nurse
    - Other: _____ *(please specify)*

	1 (strongly disagree)	**2 (disagree)**	**3 (neutral)**	**4 (agree)**	**5 (strongly agree)**
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

3. Years of practice

- Less than 1 year
- 1-2 years
- 3-5 years
- 6-10 years
- 11-15 years
- 16-20 years
- More than 20 years

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

4. Current area of practice
    - Community
    - Hospital
    - Industry
    - Academia
    - Other (please specify): _____

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

Part 2: Adverse drug reporting awareness

5. Are you aware of the procedure for reporting adverse drug reactions (ADR)?
    - Yes, I am aware of procedure
    - I have an idea about the procedure, but I am not very confident
    - No, I am not aware of the procedure to report an ADR.

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					

Relevance					

Suggested changes/comments:

_____
_____
_____

6. Have you ever received any training on ADR reporting?
    - Yes, from my place of practice
    - Yes, as a student
    - Yes, from online campaigns by local authorities
    - No, I was never given any training.

	1 (strongly disagree)	**2 (disagree)**	**3 (neutral)**	**4 (agree)**	**5 (strongly agree)**
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

7.

a) Have you had the opportunity to report an ADR for a medicinal product?
    - Yes, I have had the opportunity and have reported before.
    - Yes, I had the opportunity but I did not report it.
    - No, I have never had the opportunity or encountered any cases which I believe should have been reported.

	1 (strongly disagree)	**2 (disagree)**	**3 (neutral)**	**4 (agree)**	**5 (strongly agree)**
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

b) If you answered "Yes" in question 7(a), how many ADR reports have you submitted for active ingredients within the past:
    - year: _____
    - 2 years: _____
    - 5 years: _____

- 10 years: _____
- 20 years or more: _____

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

8.

a) Have you had the opportunity to report an ADR for a vaccine?
   - Yes, I have had the opportunity and have reported before.
   - No, I have never had the opportunity or encountered any cases which I believe should have been reported.

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

b) If you answered "Yes" in question 8(a), how many ADR reports have you submitted for vaccines within the past:
   - year: _____
   - 2 years: _____
   - 5 years: _____
   - 10 years: _____
   - 20 years or more: _____

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					

Relevance					

Suggested changes/comments:

_____
_____
_____

c) If you answered "Yes" in question 8(a), for which vaccine(s) did you submit an ADR report for?

_____

	1 (strongly disagree)	**2 (disagree)**	**3 (neutral)**	**4 (agree)**	**5 (strongly agree)**
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

9.

a) Do you feel that there are any obstacles which are preventing healthcare practitioners from reporting ADRs?
   - Yes
   - No
   - Not sure

	1 (strongly disagree)	**2 (disagree)**	**3 (neutral)**	**4 (agree)**	**5 (strongly agree)**
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

b) If you answered yes in question 9(a), select the reasons that you believe are preventing healthcare practitioners from reporting. *You may select more than one reason*.
   - Time constraints
   - Lack of accessibility to ADR reporting form
   - Lack of awareness on ADR reporting

- Lack of confidence on ADR reporting
- Difficulty to identify ADRs being caused by a medicinal product
- ADR is already identified and well known
- Other: _____

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

Part 3: Vaccine Adverse Drug reactions

10.

a) Did you ever experience patients complaining of a vaccine related ADR?
   - Yes
   - No
   - Not sure

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments:

_____
_____
_____

b) If you answered "Yes" in question 10(a), how many patients have complained of vaccine related ADRs per year?
   - Less than 5 patients
   - 10-20 patients
   - 20-25 patients
   - More than 25 patients

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments:

_____

_____

c) If you answered "Yes" in question 10(a), to which vaccines were these complaints related to? *(You may select more than one)*
   - o COVID-19 Vaccine (Comirnaty®; Spikevax®, Vaxzevria®, Janssen, etc)
   - o *Varicella zoster* vaccines (Varilix®; Zostavax®)
   - o Seasonal Influenza vaccine
   - o Other vaccines: _____

	1 (strongly disagree)	**2 (disagree)**	**3 (neutral)**	**4 (agree)**	**5 (strongly agree)**
Clarity					
Relevance					

Suggested changes/comments:

_____

_____

d) If you answered "Yes" in question 10(a), which ADRs were experienced by these patients? *(You may select more than one)*
   - o Fever and chills
   - o Injection site reactions (rash, pain, swelling)
   - o Anaphylaxis
   - o Fatigue
   - o Muscle and Joint pain
   - o Headache, dizziness and/or vertigo
   - o Vomiting, nausea and/or diarrhoea
   - o Lymphadenopathy/Lymph node swelling
   - o Flu-like symptoms
   - o Thrombosis
   - o Dyspnoea, wheezing and/or coughing
   - o Disturbances in menstrual cycle
   - o Tinnitus
   - o Ocular side effects (e.g. retinal detachment)
   - o Myocarditis or other cardiac side effects
   - o Relapse or worsening of autoimmune conditions
   - o *Guillain-Barre* Syndrome
   - o Other: _____

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments:

_____

_____

11. Rate the following statements with 1 being ***strongly disagree*** and 5 being ***strongly agree***.

		1	2	3	4	5
a)	I received more complaints about ADRs related to the COVID-19 vaccine than other vaccines.					

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments: _____

_____

_____

b)	When a patient received both the influenza and COVID-19 vaccine together, they complained of ADRs.					

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments: _____

_____

_____

c)	I have seen more cases of ADRs caused by the COVID-19 vaccine than other vaccines (e.g. disturbances in menstrual cycle, tinnitus, ocular effects, etc).					

	1 (strongly disagree)	2 (disagree)	3 (neutral)	4 (agree)	5 (strongly agree)
Clarity					
Relevance					

Suggested changes/comments: _____
_____
_____

d)	I have seen more cases of serious ADRs caused by the COVID-19 vaccine than other vaccines (e.g. thrombosis, lymphadenopathy, myocarditis, etc.)					

	1 (strongly disagree)	**2 (disagree)**	**3 (neutral)**	**4 (agree)**	**5 (strongly agree)**
Clarity					
Relevance					

Suggested changes/comments: _____
_____
_____

12. Would you like to add any other comments or remarks?

_____

THANK YOU

APPENDIX 3

Questionnaire submitted for dissemination

REPORTING VACCINE ADVERSE DRUG REACTIONS

Dear Healthcare Professional,
As part of my Master of Pharmacy dissertation "Reporting Vaccine Adverse Drug Reactions" under the supervision of Dr Janis Vella Szijj, I am disseminating a questionnaire to help understand reporting of adverse drug reactions (ADRs). The questionnaire focuses primarily on vaccine-related ADRs and on the awareness and knowledge and tendencies to reporting ADRs. Your identity will be kept anonymous. By completing this questionnaire, you are consenting to participating in this study.
I would like to thank you for taking the time to participate in this study.

Kristina Filletti
(kristina.filletti.19@um.edu.mt)

Date: _____

Part 1: Demographic Data

1. Age (years)
    - 18-30
    - 31-40
    - 41-50
    - 51-59
    - 60+

2. Occupation
    - Pharmacist
    - Medical physician
    - Nurse
    - Other: _____ *(please specify)*

3. Years of practice
    - Less than 1 year
    - 1-5 years
    - 6-10 years
    - 11-15 years
    - 16-20 years
    - More than 20 years

4. Current area of practice

- Community
- Hospital
- Industry
- Academia
- Other (please specify): _____

Part 2: Adverse drug reporting awareness

5. Are you aware of the procedure for reporting adverse drug reactions (ADR)? *(Choose 1)*

1 – Not at all aware	2 - Not aware	3 – Neutral	4 - Aware	5 – Very well aware

6. Have you ever received any training on ADR reporting?
   - Yes, from my place of practice
   - Yes, as a student
   - Yes, from online campaigns by local authorities
   - No, I was never given any training.
   - Other: _____

7.
   a) Have you had the opportunity to report an ADR for a medicinal product (excl. vaccines)?
      - Yes, I had the opportunity and have reported before.
      - Yes, I had the opportunity but I did not report it.
      - No, I never had the opportunity or encountered any cases which I believe should have been reported.

   b) If you answered "Yes" in question 7(a), kindly indicate the number of ADR reports you have submitted for a medicinal product (excl. vaccines) and in which years you have made your submissions.

      _____

8.
   a) Have you had the opportunity to report an ADR for a vaccine?
      - Yes, I had the opportunity and have reported before.
      - Yes, I had the opportunity but I did not report it.
      - No, I never had the opportunity or encountered any cases which I believe should have been reported.

b) If you answered “Yes” in question 8(a), kindly indicate the number of ADR reports you have submitted for vaccines and in which years you have made your submissions.

_____

c) If you answered “Yes” in question 8(a), for which vaccine(s) did you submit an ADR report for?

_____

9.

a) Do you feel that there are any obstacles which are preventing healthcare practitioners from reporting ADRs?
   - Yes
   - No
   - Not sure

b) If you answered yes in question 9(a), select the reasons that you believe are preventing healthcare practitioners from reporting. *You may select more than one reason*.
   - Time constraints
   - Lack of accessibility to ADR reporting form
   - Lack of awareness on ADR reporting
   - Lack of confidence on ADR reporting
   - Difficulty to identify ADRs being caused by a medicinal product
   - ADR is already identified and well known
   - A lot of paperwork is involved with the process
   - Other: _____

Part 3: Vaccine Adverse Drug reactions

10.

a) Did you ever experience patients complaining of a vaccine related ADR?
   - Yes
   - No
   - Not sure

b) If you answered “Yes” in question 10(a), approximately how many patients have you encountered which complained of vaccine related ADRs per year?
   - Less than 5 patients
   - 10-20 patients
   - 20-25 patients
   - More than 25 patients
   - Other: _____

c) If you answered "Yes" in question 10(a), to which vaccines were these complaints related to? *(You may select more than one)*
   - COVID-19 Vaccine (Comirnaty®; Spikevax®, Vaxzevria®, Janssen, etc)
   - *Varicella zoster* vaccines (Varilrix®; Zostavax®)
   - Seasonal Influenza vaccine
   - Other vaccines: _____

d) If you answered "Yes" in question 10(a), which ADRs were experienced by these patients? *(You may select more than one)*
   - Fever and chills
   - Injection site reactions (rash, pain, swelling)
   - Anaphylaxis
   - Fatigue
   - Muscle and Joint pain
   - Headache, dizziness and/or vertigo
   - Vomiting, nausea and/or diarrhoea
   - Lymphadenopathy/Lymph node swelling
   - Flu-like symptoms
   - Thrombosis
   - Dyspnoea, wheezing and/or coughing
   - Disturbances in menstrual cycle
   - Tinnitus
   - Ocular side effects (e.g. retinal detachment)
   - Myocarditis or other cardiac side effects
   - Relapse or worsening of autoimmune conditions
   - *Guillain-Barre* Syndrome
   - Other: _____

11. Rate the following statements with 1 being ***strongly disagree*** and 5 being ***strongly agree***.

		1	2	3	4	5
a)	I received more complaints on ADRs related to the COVID-19 vaccine than other vaccines.					
b)	Patients who received the influenza and COVID-19 vaccines together complained more of vaccine related ADRs than those patients who were vaccinated by the two vaccines on two different occasions.					
c)	I have seen more cases of ADRs caused by the COVID-19 vaccine than other vaccines (e.g. disturbances in menstrual cycle, tinnitus, ocular effects, etc).					

d)	I have seen more cases of ADRs which led to hospitalisation from the COVID-19 vaccine than other vaccines (e.g. thrombosis, lymphadenopathy, myocarditis, etc.)					

12. Would you like to add any other comments or remarks?

_____

Thank you!

APPENDIX 4

Poster presentation for the 82nd FIP World Congress of Pharmacy and Pharmaceutical Sciences 2024, in Cape Town.

L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

REPORTING VACCINE ADVERSE DRUG REACTIONS

Kristina Filletti, Janis Vella Sziji, Lilian M Azzopardi

Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

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INTRODUCTION

Vaccines may induce adverse drug reactions (ADRs) to different extents of severity and frequency. The reporting of ADRs is a critical component of pharmacovigilance, aiding in the identification of negative effects triggered by medications, including vaccines. Insufficient ADR reporting hinders a comprehensive understanding of a medicinal product's safety profile.

AIMS

- To identify vaccine-related ADRs of COVID-19, *Varicella zoster* and influenza vaccines
- To identify perception, awareness and experiences of healthcare professionals (HCPs) with ADR reporting

METHOD

PHASE 1

- Literature review on ADRs caused by COVID-19, *Varicella zoster* and influenza vaccines was conducted.
- Open-access, peer-reviewed journal articles from PubMed published between 2012-2022 were identified.

PHASE 2

- Questionnaire on perception, awareness and experiences with vaccine-related ADR reporting was developed and validated.
- The scored questionnaire consisted of 22 questions related to ADR reporting awareness and vaccine related ADRs.
- Questionnaire was disseminated to nurses, pharmacists and medical physicians

RESULTS

Vaccine-related ADRs identified from literature search included thrombosis (n=20) for COVID-19 vaccines, injection site reactions (n=16) for *Varicella zoster* vaccines and fatigue and myalgia (n=20) for influenza vaccines. Questionnaire was completed by 284 HCPs, including nurses (n=161), doctors (n=46), pharmacists (n=68), and other HCPs (n=9). Respondents (mean score=3.37 out of 5) were aware and confident with the process of ADR reporting. Pharmacists scored the highest mean score of 4.1 out of 5. The level of awareness varied between HCPs (p-value = <0.001). Pharmacists received more training on ADR reporting than other HCPs (p-value = 0.035). Most respondents (n=122) believe that there are barriers to ADR reporting. Lack of awareness on the procedure (n=106), lack of confidence (n=66) and time constraints (n=64) were barriers (Figure 1). Respondents identified muscle and joint pain (n=145), fever and chills (n=125) and injection site reactions (n=116) as the most common vaccine-related ADRs .

Figure 1: Barriers to ADR reporting (N=144)

CONCLUSION

HCPs are knowledgeable on the process of ADR reporting but still identify and recognise challenges which are preventing HCPs from reporting. Awareness on the process is a major barrier, highlighting the need of training on ADR reporting.

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APPENDIX 5

Literature review results for COVID-19 vaccines (N=90)

Title of article	Year of publication	Authors	Type of study	Vaccine technology/brand	Number of subjects	ADRs identified within study
mRNA Vaccines to Prevent Covid-19 Disease and reported allergic reactions: current evidence and suggested approach	2020	Banjeri *et al*.	Review	mRNA (Pfizer)	N/A	Skin reactions and/or conditions Dyspnoea Syncope Gastrointestinal disturbances
Maintaining Safety with SARS-CoV-2 Vaccines	2020	Castells & Philips	Review	mRNA (Pfizer, Moderna)	N/A	Fever Fatigue & Myalgia Headache Injection site reactions
Vaccine and natural infection-induced mechanisms that could modulate vaccine safety	2020	Kostoff *et al.*	Meta-analysis	mRNA	N/A	Autoimmune conditions Hypersensitivity
Covid-19 Vaccine and myocarditis	2021	Salah & Mehta	Review	mRNA (Pfizer, Moderna); Viral vector (Johnson&Johnson)	15	Myocarditis
Covid-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of	2021	Meo *et al*	Review	mRNA (Pfizer, Moderna)	N/A	Injection site reactions Fever & chills Fatigue & Myalgia Headache Gastrointestinal disturbances

Pfizer/BioNTech and Moderna vaccines						Lymphadenopathy/Lymph node swelling
						Arrythmia
						Syncope
						Skin reactions and/or conditions
Covid-19 vaccine-associated immune thrombosis and thrombocytopenia: Diagnostic and therapeutic recommendations for a new syndrome	2021	Franchini *et al*.	Review	Viral vector (AstraZeneca)	40	Thrombosis and thrombocytopenia
Vaccine-induced immune thrombotic thrombocytopenia (VITT) and cerebral venous sinus thrombosis post Covid-19 vaccination; a systematic review	2021	Sharifian-Dorche et al.	Review	Viral vector (AstraZeneca, Johnson&Johnson)	N/A	Thrombosis and thrombocytopenia
Myocarditis with Covid-19 mRNA vaccines	2021	Bozkurt *et al*.	Review	mRNA	N/A	Myocarditis
Covid-19 vaccines and the skin	2021	Sun *et al.*	Review	mRNA	N/A	Skin reactions and/or conditions
						Varicella zoster virus reactivation, infection or/and transmission
						Injection site reactions

Covid-19 vaccine induced myocarditis: case report with literature review	2021	Nassar *et al.*	Review	Viral vector (Johnson&Johnson)	1	Myocarditis
Spectrum of neurological complications following Covid-19 vaccination	2021	Garg & Paliwal	Review	mRNA	N/A	Fever
						Fatigue & Myalgia
						Guillian-Barré syndrome
						Syncope, vertigo and dizziness
						Headache
						Seizure
						Anaphylaxis
						Facial nerve palsy (incl. Bell's palsy)
						Thrombosis and thrombocytopenia
						Arthralgia
						Stroke
						Autoimmune conditions
AstraZeneca Covid-19 vaccine and Guillian-Barre syndrome in Tasmaina: A casual link?	2021	Oo *et al.*	Review	Viral vector (AstraZeneca)	15	Guillian-Barré syndrome
Ocular adverse events after Covid-19 vaccination	2021	Ng *et al*	Review	mRNA, Protein subunit, Viral vector, Whole virus	N/A	Grave's disease
						Ocular adverse effects
						Facial nerve palsy (incl. Bell's palsy)

Efficacy, immunogenicity and safety of Covid-19 vaccines: a systematic	2021	Sharif *et al*	Meta-analysis	mRNA, Viral vector	N/A	Injection site reactions
						Fever & chills
						Fatigue
						Arthralgia
						Gastrointestinal disturbances
Review the safety of Covid-19 mRNA vaccines: a review	2021	Anand & Stahel	Review	mRNA (Pfizer, Moderna)	N/A	Injection site reactions
						Fever
						Headache
						Fatigue
						Anaphylaxis
						Facial nerve palsy (incl. Bell's palsy)
Temporal association between COVID-19 Ad26.COV2.S vaccine and acute myocarditis: a case report and literature review	2021	Sulemankhil *et al.*	Review	mRNA	81	Myocarditis
Efficacy and safety of COVID-19 vaccines: a systematic review and meta analysis of randomised clinical trials	2021	Pormohammad *et al.*	Review	mRNA	N/A	Injection site reactions
						Fever & chills
						Skin reactions and/or conditions
						Myalgia
						Arthralgia
						Gastrointestinal disturbances
	2021	Gambichler *et al.*	Review	mRNA, Viral vector	N/A	Injection site reactions

Cutaneous findings following COVID-19 vaccination: review of world literature and own experience						Hypersensitivity Erythema Autoimmune conditions Skin reactions and/or conditions *Varicella zoster* virus reactivation, infection or/and transmission
Allergy to COVID-19 vaccines: a current update	2021	Cabanillas & Novak	Review	mRNA	N/A	Anaphylaxis
Thrombotic events and COVID-19 vaccines	2021	Brazete *et al*.	Review	mRNA, Viral vector	N/A	Thrombosis & thrombocytopenia
Lymphadenopathy following COVID-19 vaccination: imaging findings review	2021	Keshavaraz *et al.*	Review	mRNA	68	Lymphadenopathy/Lymph node swelling
Autopsy findings and casuality relationship between death and COVID-19 vaccination: a systematic review	2021	Sessa *et al.*	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson)	38	Fatality
A focused review on technologies, mechanisms, safety and efficacy of available COVID-19 vaccines	2021	Ghasemiyeh *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson); Other brands not authorised in the EU	N/A	Injection site reactions Fatigue & Myalgia Headache Fever & chills Gastrointestinal disturbances Arthralgia

						Arrythmia
						syncope
						Allergic reactions
						Skin reactions and/or conditions
						Multisystem inflammatory syndrome
						Facial nerve palsy (incl. Bell's palsy)
						Guillian-Barré syndrome
						Thrombosis & thrombocytopenia
Cutaneous adverse reactions associated with SARS-CoV-2 vaccines	2021	Bellinato *et al*.	Review	mRNA, Viral vector	805	Skin reactions and/or conditions
						Injection site reactions
Adverse reactions to COVID-19 vaccines: a practical approach	2021	Rutkowski *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca)	N/A	Anaphylaxis
New-onset nephrotic syndrome after Janssen COVID-19 vaccination: a case report and literature review	2021	Lim *et al*.	Review	Viral vector (Johnson&Johnson)	1	Renal adverse effects
Development of Graves' disease after SARS-CoV-2 mRNA vaccination: a case report and literature review	2021	Wai Lui *et al*	Review	mRNA (Pfizer)	1	Grave's disease

Clinical review of cerebral venous thrombosis in the context of COVID-19 vaccinations: evaluation, management and scientific questions	2021	Thakur *et al*.	Review	Viral vector (AstraZeneca, Johnson&Johnson)	381	Thrombosis & thrombocytopenia
Adverse rare events to vaccines for COVID-19: from hypersensitivity reactions to thrombosis and thrombocytopenia	2021	Novak *et al*.	Review	mRNA, DNA	N/A	Thrombosis & thrombocytopenia Anaphylaxis, hypersensitivty and allergic reactions
Allergic reactions against Covid-19 vaccines	2021	Unsal *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson)	N/A	Anaphylaxis, hypersensitivty and allergic reactions Injection site reactions
Multisystem inflammatory syndrome in an adult after Covid-19 vaccination: a case report and literature review	2021	Park *et al*.	Review	Viral vector (AstraZeneca)	1	Multisystem inflammatory syndrome
Vaccine-associated thrombocytopenia and thrombosis: venous endotheliopathy leading to venous combined micro-macrothrombosis	2021	Chang & Hawley	Review	Not disclosed	N/A	Thrombosis & thrombocytopenia

Hypersensitivity reactions to vaccines: current evidence and standards for SARS-CoV-2 vaccines	2021	Carvalho *et al*	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson); Other brands not authorised in the EU	N/A	Anaphylaxis, hypersensitivty and allergic reactions
Post-vaccination COVID-19 deaths: a review of available evidence and recommendations for the global population	2021	Lamptey	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson)	N/A	Fatality
Possible risk of thrombotic events following Oxford-AstraZeneca COVID-19 vaccination in women receiving estrogen	2021	Hekmat & Javanmardi	Review	Viral vector (AstraZeneca)	N/A	Thrombosis & thrombocytopenia
Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine-United States, December 21, 2020 - January 10, 2021	2021	Shimabukuro	Review	mRNA (Moderna)	10	Anaphylaxis
The clinical correlates of vaccine-induced immune thrombotic thrombocytopenia after immunisation with	2021	Gaunt & Mabbott	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson); Other brands not authorised in the EU	N/A	Anaphylaxis, hypersensitivty and allergic reactions Thrombosis & thrombocytopenia Myocarditis

adenovirus vector-based SARS-CoV-2 vaccines						Cardiac adverse events
						Seizure
						Stroke
Pfizer-BioNTech COVID-19 vaccine (BNT162b2) side effects: a systematic review	2022	Dighriri *et al*	Review	mRNA (Pfizer)	10632	Injection site reactions
						Fatigue & Myalgia
						Headache
						Arthralgia
						Fever & chills
						Lymphadenopathy/Lymph node swelling
						Gastrointestinal disturbances
						Dyspnoea
Cardiovascular complications of SARS-CoV-2 vaccines: an overview	2022	Shiravi *et al*	Review	mRNA	N/A	Thrombosis & thrombocytopenia
						Myocarditis
						Arrhthymia, myocardial infarction and other cardiac adverse effects
The eye of the storm: COVID-19 vaccination and the eye	2022	Le Ng *et al*	Review	mRNA, Protein subunit, Whole virus	N/A	Facial nerve palsy (incl. Bell's palsy)
						Ocular adverse effects
						Grave's disease
SARS-CoV-2 vaccine-associated-tinnitus: a review	2022	Ahmed *et al*	Review	mRNA (Pfizer); Viral vector (AstraZeneca)	4	Tinnitus

Renal side effects of COVID-19 vaccination	2022	Zhang *et al*	Review	All types of vaccines	128	Autoimmune conditions
Short-term side effects of COVID-19 vaccines: a cross-sectional study in Jordan	2022	Nassar *et al*.	Review	mRNA (Pfizer); Viral vector (AstraZeneca); Other brands not authorised in the EU	1044	Injection site reactions
						Fatigue & Myalgia
						Neurological ADRs
						Arthralgia
						Headache
COVID-19 vaccine-associated ocular adverse effects: an overview	2022	Ichhpujani *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson)	N/A	Facial nerve palsy (incl. Bell's palsy)
						Ocular adverse effects
COVID-19 vaccine-related myocarditis: a descriptive study of 40 case reports	2022	Hong Chen *et al*.	Review	mRNA (Pfizer, Moderna)	40	Myocarditis
COVID-19 vaccination and neurological manifestations: a review of case reports and case series	2022	Sriwastava *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca)	51	Facial nerve palsy (incl. Bell's palsy)
						Thrombosis & thrombocytopenia
						Guillian-Barré syndrome
						Neurological ADRs
						Autoimmune conditions
						Seizure
COVID-19 vaccine associated axillary lymphadenopathy-a systematic review	2022	Co *et al*.	Review	mRNA (Pfizer, Moderna)	31	Lymphadenopathy/Lymph node swelling

Ocular adverse effects of COVID-19 vaccines: a systematic review	2022	Kumari *et al*.	Review	All types of vaccines	145	Ocular adverse effects
COVID-19 vaccine-related arthritis: a descriptive study of case reports on a rare complication	2022	Dawoud *et al*.	Review	mRNA (Moderna); Viral vector (AstraZeneca); Other brands not authorised in the EU	16	Athralgia, arthritis and other ADRs affecting joints
Thrombosis patterns and clinical outcome of COVID-19 vaccine-induced immune thrombotic thrombocytopenia. A systematic review and meta-analysis	2022	Kim *et al*.	Review	Viral vector (AstraZeneca, Johnson&Johnson)	664	Thrombosis & thrombocytopenia
Otolaryngology adverse events following COVID-19 vaccines	2022	Colizza *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca)	N/A	Tinnitus and hearing loss
						Syncope, vertigo and dizziness
						Facial nerve palsy (incl. Bell's palsy)
						Epistaxis
COVID-19 mRNA vaccine-associated uveitis leading to diagnosis of sarcoidosis: case report and review of literature	2022	Matsuo *et al*.	Review	mRNA (Pfizer)	1	Ocular adverse effects

Myocarditis after COVID-19 mRNA vaccination: a systematic review of case reports and case series	2022	Yong Park *et al*.	Review	mRNA	275	Myocarditis
Case report of COVID-19 mRNA vaccine-associated myocarditis	2022	Licata & Clements	Review	mRNA (Pfizer, Moderna)	1	Myocarditis
Headache onset after vaccination against SARS-CoV-2: a systematic literature review and meta-analysis	2022	Castaldo *et al*.	Review	mRNA (Pfizer); Viral vector (AstraZeneca)	1.57 million	Headache and migraines
New-onset systemic lupus eythematosus following BNT162b2 mRNA COVID-19 vaccine: a case series and literature review	2022	Sagy *et al*.	Review	mRNA (Pfizer)	6	Autoimmune conditions
Multiple sclerosis relapse after COVID-19 vaccination: a case report-based systematic review	2022	Nabizadeh *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca); Other brands not authorised in the EU	29	Autoimmune conditions
Autoimmune hepatitis after COVID-19 vaccination	2022	Zheng *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca); Other brands not authorised in the EU	27	Autoimmune conditions

Cardiovascular complications of COVID-19 vaccines	2022	Liu *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson)	N/A	Thrombosis & thrombocytopenia
						Myocarditis
Safety of COVID-19 vaccines: spotlight on neurological complications	2022	Tondo *et al*.	Review	All types of vaccines	N/A	Headache
						Thrombosis & thrombocytopenia
						Stroke
						Autoimmune conditions
						Ocular adverse effects
						Facial nerve palsy (incl. Bell's palsy)
						Guillian-Barré syndrome
						Varicella zoster virus reactivation, infection or/and transmission
						Neurological ADRs
Development of IgA vasculitis with severe glomerulonephritis after COVID-19 vaccination: a case report and literature review	2022	Sugita *et al*.	Review	mRNA (Pfizer)	1	Autoimmune conditions
Longitudinally extensive transverse myelitis after COVID-19 vaccination: case report and review of literature	2022	Farzad Maroufi *et al*.	Review	Viral vector (AstraZeneca)	1	Neurological ADRs

Subacute thyroiditis after receiving the mRNA COVID-19 vaccine (Moderna): the first case report and literature review in Korea	2022	Jhon *et al*.	Review	mRNA (Moderna)	1	ADRs affecting thyroid
The flare of rheumatic disease after SARS-CoV-2 vaccination: a review	2022	Xie *et al*.	Review	All types of vaccines	N/A	Athralgia, arthritis and other ADRs affecting joints
Cutaneous leukocytoclastic vasculitis following COVID-19 vaccination with Ad26.COV2.S vaccine: a case report and literature review	2022	Betetto *et al*.	Review	Viral vector (Johnson&Johnson)	1	Cardiac adverse events
Ocular vascular events following COVID-19 vaccines: a systematic review	2022	Serhan *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson); Other brands not authorised in the EU	129	Ocular adverse effects
Epidemiology, clinical ramifications and cellular pathogenesis of COVID-19 mRNA-vaccination induced adverse cardiovascular outcomes:	2022	Almas *et al*.	Review	mRNA (Pfizer, Moderna)	153	Myocarditis Cardiac adverse events Thrombosis & thrombocytopenia

a state-of-the-heart review						
Myocarditis following COVID-19 vaccination: cardiac imaging findings in 118 studies	2022	Keshavarz *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson); Other brands not authorised in the EU	532	Myocarditis
SARS-CoV-2 vaccination and chilblain-like lesions: what do we know so far?	2022	Shaikh *et al*.	Review	mRNA (Pfizer, Moderna); Other brands not authorised in the EU	12	Skin reactions and/or conditions
COVID-19 vaccination and the rate of immune and autoimmune adverse events following immunization: insights from a narrative literature review	2022	Mahroum *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca)	N/A	Guillian-Barré syndrome
						Facial nerve palsy (incl. Bell's palsy)
						Myocarditis
						Thrombosis & thrombocytopenia
						Autoimmune conditions
						Renal adverse effects
Cerebral venous sinus thrombosis following COVID-19 vaccination: analysis of 552 worldwide cases	2022	de Gregorio *et al*.	Review	All types of vaccines	N/A	Thrombosis & thrombocytopenia
Myocarditis following COVID-19 vaccination: a	2022	Behers *et al*.	Review	mRNA (Pfizer, Moderna)	53	Myocarditis

systematic review of case reports						
Pilot findings on SARS-CoV-2 vaccine-induced pituitary diseases: a mini review from diagnosis to pathophysiology	2022	Taieb & Mounira	Review	mRNA (Pfizer); Viral vector (AstraZeneca)	8	ADRs affecting pituitary gland
Reactogenic sleepiness after COVID-19 vaccination. A hypothesis involving orexinergic system linked to inflammatory signals	2022	Garrido-Suarez *et al*.	Review	mRNA (Pfizer)	N/A	ADRs affecting nerves
Rare heterogenous adverse events associated with mRNA-based COVID-19 vaccines: a systematic review	2022	Oueijan *et al*.	Review	mRNA (Pfizer, Moderna)	N/A	Myocarditis
						Cardiac adverse events
						Thrombocytopenia
						Allergic reactions
						Skin reactions and/or conditions
Axillary lymph node swelling after COVID-19 booster vaccination: Japanese case report and literature review	2022	Yoshimoto *et al*.	Review	mRNA (Pfizer, Moderna)	1	Lymphadenopathy/Lymph node swelling
Prolonged diarrhoea following COVID-19	2022	Akaishi *et al*.	Review	mRNA (Pfizer)	1	Gastrointestinal disturbances

vaccination: a case report and literature review						
Oral lesions following anti-SARS-CoV-2 vaccination: a systematic review	2022	Di Spirito *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca, Johnson&Johnson); Other brands not authorised in the EU	16	Skin reactions and/or conditions
Pituitary apoplexy and COVID-19 vaccination: a case report and literature review	2022	Aliberti *et al*.	Review	mRNA (Pfizer, Moderna)	1	ADRs affecting pituitary gland
COVID-19 vaccination and late-onset myasthenia gravis: a new case report and review of the literature	2022	Virgilio *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca)	26	Autoimmune conditions
Severe immune thrombocytopenia after COVID-19 vaccination: two case reports and a literature review	2022	Shonai *et al*.	Review	mRNA (Pfizer, Moderna)	2	Thrombosis & thrombocytopenia
Subacute thyroiditis with liver dysfunction following COVID-19 vaccination: report of two cases and a literature	2022	Kishimoto *et al*.	Review	mRNA (Pfizer, Moderna)	2	ADRs affecting thyroid

Two flares of Still's disease after two doses of the ChAdOx1 vaccine	2022	Roongta *et al*.	Review	Viral vector (AstraZeneca)	1	Autoimmune conditions
Acute encephalitis after COVID-19 vaccination: a case report and literature review	2022	Gao *et al*.	Review	mRNA (Moderna)	1	Neurological ADRs
Pityriasis Rosea-like eruptions following COVID-19 mRNA-1273 vaccination: A case report and literature review	2022	Wang *et al*.	Review	mRNA (Moderna)	1	Skin reactions and/or conditions
A novel development of sarcoidosis following COVID-19 vaccination and a literature review	2022	Numakura *et al*.	Review	mRNA (Pfizer)	1	Ocular adverse effects
Herpes simplex encephalitis following ChAdOx1 nCoV-19 vaccination: a case report and review of the literature	2022	Moslemi *et al*.	Review	Viral vector (AstraZeneca)	1	Neurological ADRs
Axillary lymph node swelling mimicking breast cancer metastasis after COVID-19 vaccination: a Japanese case report and literature review	2022	Yoshimoto *et al*.	Review	mRNA	1	Lymphadenopathy/Lymph node swelling

Retinal venous occlusion following COVID-19 vaccination: report of a case after third dose and review of the literature	2022	Dutta Majumder & Prakash	Review	Viral vector (AstraZeneca)	1	Ocular adverse effects
Stroke associated with COVID-19 vaccines	2022	Kakovan *et al*.	Review	mRNA (Pfizer, Moderna); Viral vector (AstraZeneca)	546	Stroke

APPENDIX 6

Literature review results for* Varicella zoster *vaccines* (*N=26)

Title of article	Year of publication	Authors	Type of study	Vaccine technology/brand	Number of subjects	ADRs identified within study
Prevention of Herpes Zoster: a focus on the effectiveness and safety of Herpes Zoster vaccines	2022	Marra & Lalji	Review	Live attenuated (Zostavax), Adjuvanted recombinant (Shingrix)	N/A	Fever Injection site reactions Headache Skin reactions Stroke Myocardial infarction Guillian-Barré syndrome Fatigue and myalgia
Efficacy, effectiveness and safety of herpes zoster vaccine in the immunocompetent and immunocompromised subjects: a systematic review and network meta-analysis	2022	Xia *et al*.	Review	Live attenuated (Zostavax), Adjuvanted recombinant (Shingrix)	N/A	Fatigue and myalgia Headache Gastrointestinal disturbances
An analysis of spontaneously reported data of vesicular and bullous cutaneous eruptions occurring following vaccination with the adjuvanted	2021	Pirrotta *et al*.	Review	Adjuvanted recombinant (Shingrix)	2423	Skin reactions and/or conditions

recombinant zoster vaccine						
Varicella virus vaccination in the United States	2018	Shaw & Gershon	Review	Live attenuated	N/A	Skin reactions and/or conditions
						Injection site reactions
						Thrombocytopenia
						Dyspnoea, wheezing and/or respiratory conditions
						Hepatic adverse effects
						Erythema
						Stroke
						Varicella zoster virus reactivation, infection or/and transmission
						Fatality
						Neurological ADRs
Varicella and herpes zoster vaccine development: lessons learned	2017	Warren-Gash *et al.*	Review	Live attenuated	N/A	Injection site reactions
						Erythema
						Skin reactions and/or conditions
Safety of live vaccinations on	2017	Croce *et al.*	Review	Live attenuated	21,082	Injection site reactions
						Headache

immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation-a systematic review of randomised trials, observational studies and case reports						Gastrointestinal disturbances Fatigue and myalgia Arthralgia Fever
Vaccines for preventing herpes zoster in older adults	2016	Gagliardi *et al.*	Review	Live attenuated, Adjuvanted recombinant	N/A	Fatigue Injection site reactions Fatality Headache
Pathogenesis and current approaches to control of Varicella-zoster virus infections	2013	Gershon & Gershon	Review	All technologies	211	Skin reactions and/or conditions Dyspnoea, wheezing and/or respiratory conditions Autoimmune conditions Neurological ADRs *Varicella zoster* virus reactivation, infection or/and transmission

Vaccination against herpes zoster in developed countries	2021	Drolet *et al.*	Review	Live attenuated	19,270	*Varicella zoster*-like skin reaction
Evaluation of recombinant herpes zoster vaccine for primary immunization of Varicella-seronegative transplant recipients	2021	L'Huillier *et al.*	Clinical trial	Adjuvanted recombinant (Shingrix)	23	Injection site reactions
						Myalgia
						Fever
						Cardiac adverse effects
						Gastrointestinal disturbances
						Hepatic adverse effects
						Cardiac adverse effects
						Ocular adverse effects
						Thrombosis and thrombocytopenia
						Renal adverse effects
Safey of the adjuvanted recombinant zoster vaccine in adults aged 50 years or older. A phase IIIB, non-randomised, multinational, open-label study in previous ZOE-50 and ZOE-70 placebo recipients	2020	Ocran-Appiah *et al*.	Clinical trial	Adjuvanted recombinant	8687	Injection site reactions
						Erythema
						Athralgia, arthritis and other ADRs affecting joints
						Arrhthymia, myocardial infarction and other cardiac adverse effects
						Fever
						Headache

						Dyspnoea, wheezing and/or respiratory conditions
Immunogenicity and safety of the adjuvanted recombinant Zoster vaccine in chronically immunosuppressed adults following renal transplant: a phase 3, randomised clinical trial	2019	Vink *et al.*	Clinical trial	Adjuvanted recombinant	264	Injection site reactions
						Fatigue and myalgia
						Thrombosis and thrombocytopenia
						Fever and chills
						Headache
						Neurological ADRs
						Myocardial infarction
						Gastrointestinal disturbances
Safety of live attenuated varicella-zoster vaccine in patient with underlying illnesses compared with healthy adults: a prospective cohort study	2019	Ohfuji *et al.*	Clinical trial	Live attenuated	1491	Skin reactions and/or conditions
						Injection site reactions
						Erythema
						Headache
						Fever
						Fatigue
safety profile of the adjuvanted recombinant zoster vaccine: pooled analysis of two large	2019	Lopez-Fauqued *et al.*	Clinical trial	Adjuvanted recombinant	29305	Injection site reactions
						Skin reactions
						Fever and chills
						Fatigue and myalgia

randomised phase 3 trials						Dyspnoea, wheezing and/or respiratory conditions
						Ocular adverse effects
						Arthralgia
						Gastrointestinal disturbances
						Erythema
						Cardiac adverse effects
Safety and seropositivity after live attenuated vaccine in adult patients receiving hematopoietic stem cell transplantation	2019	Aoki *et al.*	Clinical trial	Live attenuated	37	Lymphadenopathy/Lymph node swelling
						Dyspnoea, wheezing and/or respiratory conditions
						Skin reactions and/or conditions
						Fever
Immunogenicity, reactogenicity and safety of 2 doses of an adjuvanted herpes zoster subunit vaccine administered 2, 6 or 12 months apart in older adults: results of a phase	2018	Lal *et al.*	Clinical trial	Adjuvanted recombinant	342	Fatigue and myalgia
						Injection site reactions
						Cardiac adverse effects
						Fatality
						Arthralgia
						Skin reactions and/or conditions
						Erythema

III, randomised, open-label, multicenter study						Headache
Immunogenicity and safety of the HZ/su adjuvanted herpes zoster subunit vaccine in adults previously vaccinated with a live attenuated herpes zoster vaccine	2017	Grupping *et al.*	Clinical trial	Adjuvanted recombinant	430	Fatigue and myalgia Injection site reactions Gastrointestinal disturbances Headache Fever and chills
A randomised lot-to-lot immunogenicity consistency study of the candidate zoster vaccine HZ/su	2017	Strezova *et al.*	Clinical trial	Adjuvanted recombinant	634	Injection site reactions *Varicella zoster* virus reactivation, infection or/and transmission Myalgia Ocular adverse effects Fever
Safety and immunogenicity of a hepres zoster subunit vaccine in Japanese population aged ≥50 years when administered	2017	Vink *et al.*	Clinical trial	Subunit	60	Injection site reactions Gastrointestinal disturbances Headache Fever and chills Renal adverse effects

subcutaneously vs intramuscularly						Fatigue and myalgia
Immunogenicity and safety of an adjuvanted herpes zoster subunit candidate vaccine in adult ≥50 years of age with a prior history of herpes zoster: A phase III, non-randomised, open-label clinical trial	2017	Godeaux *et al.*	Clinical trial	Subunit	93	Fatigue and myalgia
						Injection site reactions
						Headache
						Fever and chills
						Gastrointestinal disturbances
Efficay of the herpes zoster subunit vaccine in adults 70 years of age or older	2016	Cunningham *et al.*	Clinical trial	Subunit	13900	Injection site reactions
						Headache
						Gastrointestinal disturbances
						Fatigue and myalgia
						Fever and chills
Immunogenicity and safety of a live attenuated zoster vaccine (ZostaVax™) in Korean adults	2015	Suk Choi *et al.*	Clinical trial	Live attenuated	180	Skin reactions and/or conditions
						Erythema
						Headache
						Gastrointestinal disturbances

						Neurological ADRs
						Ocular adverse effects
						Dyspnoea, wheezing and/or respiratory conditions
						Fatigue and myalgia
						Fever and chills
Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults	2015	Lal *et al.*	Clinical trial	Adjuvanted recombinant	15411	Injection site reactions
						Headache
						Gastrointestinal disturbances
						Neurological ADRs
						Tinnitus and hearing loss
						Fatality
						Arrhthymia, myocardial infarction and other cardiac adverse effects
						Fatigue and myalgia
Comparison of intramuscular and subcutaneous administration of herpes zoster live-attenuated	2015	Diez-Domingo *et al*.	Clinical trial	Live attenuated	354	Skin reactions and/or conditions
						Injection site reactions
						Herpes zoster-like skin reaction

vaccine in adults aged ≥50 years: a randomised non-inferiority clinical trial						Erythema
						Thrombosis and thrombocytopenia
Immunogenicity and safety of a live attenuated shingles vaccine (Zostavax®) in individuals aged ≥70 years: a randomised study of a single dose vs two different two-dose schedules	2013	Vesikari *et al.*	Clinical trial	Live attenuated	757	Injection site reactions
						Headache
						Erythema
						Herpes zoster-like skin reaction
						Skin reactions
Efficacy, safety and tolerability of herpes zoster vaccine in persons aged 50-59 years	2012	Schmader *et al.*	Clinical trial	Live attenuated	21105	Injection site reactions
						Headache
						Herpes zoster-like skin reaction
						Anaphylaxis, hypersensitivty and allergic reactions
						Fatality
						Skin reactions and/or conditions

APPENDIX 7

Literature review results for influenza vaccines (N=33)

Title of article	Year of publication	Authors	Type of study	Vaccine technology/brand	Number of subjects	ADRs identified within study
Association of influenza vaccination with cardiovascular risk	2022	Behrouzi *et al.*	Meta-analysis	Live attenuated vaccine	2890	Cardiac adverse events
						Fatality
Headache after vaccination: an update on recent clinical trials and real-world reporting	2022	Garces *et al.*	Review	Live attenuated vaccine; Inactivated vaccine	N/A	Headache
						Fatigue & myalgia
						Fever & chills
						Loss of appetite
						Injection site reactions
Immunogenicity of H5N1 influenza vaccines in elderly adults: a systematic review and meta-analysis	2021	Zhang *et al.*	Meta-analysis	Inactivated vaccines	3951	Injection site reactions
						Skin reactions and/or conditions
						Erythema
						Fever
						Headache
						Myalgia
Inclusion of safety-related issues in economic evaluations for seasonal influenza vaccines: a systematic review	2021	Fens *et al.*	Review	Live attenuated vaccine; Inactivated vaccine	N/A	Guillian-Barré syndrome
						Anaphylaxis, hypersensitivty and allergic reactions
						Local site reactions
						Seizures
						Syncope

						Erythema
						Skin reactions and/or conditions
						Flu-like symptoms
						Fever & chills
						Headache
						Fatigue & myalgia
Immunogenicity and safety of reduced-dose intradermal vs intramuscular influenza vaccines	2021	Egunsola *et al.*	Meta-analysis	Not specified	177780	Erythema
						Injection site reactions
						Headache
						Arthralgia
						Gastrointestinal disturbances
						Fever
						Myalgia
Laryngeal myasthenia gravis following influenza vaccination: a case report and literature review	2021	Wang *et al.*	Review	Trivalent inactivated influenza vaccine	1	Flu-like symptoms
						Autoimmune conditions
						Neurological ADRs
						Fatigue & myalgia
						Headache
						Guillian-Barré syndrome
						Gastrointestinal disturbances
						Ocular adverse effects

Immunogenicity and safety levels of inactivated quadrivalent influenza vaccine in healthy adults via meta-analysis	2021	Liang *et al.*	Meta-analysis	Trivalent inactivated influenza vaccine	N/A	Injection site reactions Fatigue & myalgia Headache Fever
Effects of influenza vaccination on the risk of cardiovascular and respiratory diseases and all-cause mortality	2020	Cheng *et al.*	Review	Not specified	N/A	Stroke Arrhthymia, myocardial infarction and other cardiac adverse effects Dyspnoea, wheezing and/or respiratory conditions Fatality
Antigenic variability a potential factor in assessing relationship between Guillain Barre Syndrome and influenza vaccine-up to date literature review	2020	Soni *et al.*	Review	Seasonal influenza vaccine, Pandemic influenza vaccine	N/A	Guillian-Barré syndrome
Adjuvanted-influenza vaccination in patients infected with HIV: a systematic review and meta-analysis of immunogenicity and safety	2020	Chen *et al.*	Meta-analysis	Unadjuvanted influenza vaccine, Adjuvanted influenza vaccine	N/A	Injection site reactions Fatigue & myalgia Arthralgia Headache
	2019	Cohet *et al.*	Review		N/A	Guillian-Barré syndrome

Safety of AS03-adjuvanted influenza vaccines: a review of evidence				Adjuvanted live attenuated vaccine		Neurological ADRs Seizures Autoimmune conditions Anaphylaxis
Challenges in implementing yearly enhanced safety surveillance of influenza vaccination in Europe: lessons learned and future perspectives	2019	Dos Santos	Review	Not specified	N/A	Injection site reactions Headache Myalgia Skin reactions and/or conditions Flu-like symptoms Decreased appetite Dyspnoea, wheezing and/or respiratory conditions Fever Erythema
Cell-based quadrivalent inactivated influenza virus vaccine (Flucelvax® Tetra/Flucelvax Quadrivalent®): a review in the prevention of influenza	2019	Lamb	Review	Inactivated vaccine	N/A	Injection site reactions Headache Fatigue and myalgia Erythema
Bilateral deafness two days following influenza vaccination: a case report	2019	Kolarov *et al.*	Review	Not specified	N/A	Tinnitus and hearing loss

Vaccines for preventing influenza in healthy adults	2018	Demicheli *et al.*	Review	Not specified	N/A	Autoimmune conditions
						Neurological ADRs
						Fatigue & myalgia
						Injection site reactions
						Gastrointestinal disturbances
						Erythema
						Dyspnoea, wheezing and/or respiratory conditions
						Facial nerve palsy (incl. Bell's palsy)
						Arrhthymia, myocardial infarction and other cardiac adverse effects
						Skin reactions and/or conditions
Influenza vaccines: evaluation of the safety profile	2018	Trombetta *et al.*	Review	Parenteral inactivated influenza vaccines, Intranasal live attentuated vaccines	N/A	Injection site reactions
						Headache
						Myalgia
						Guillian-Barré syndrome
						Seizures
						Erythema
						Anaphylaxis, hypersensitivty and allergic reactions

						Flu-like symptoms
Influenza vaccine for chronic obstructive pulmonary disease (COPD)	2018	Kopsaftis *et al.*	Review	Live attenuated vaccine; Inactivated vaccine	N/A	Fatigue and myalgia
						Headache
						Fever
						Flu-like symptoms
						Injection site reactions
						Guillian-Barré syndrome
Immunogenicity, safety and tolerability of intradermal influenza vaccines	2018	Hung & Yuen	Review	Not specified	N/A	Injection site reactions
						Fever
						Fatigue
Recurrence of pericarditis after influenza vaccination: a case report and review of the literature	2018	Mei *et al.*	Review	Inactivated vaccines	1	Cardiac adverse effects
Post-licensure surveillance of quadrivalent inactivated influenza (IIV4) vaccine in the United States, vaccine adverse event reporting system (VAERS), July 1, 2013-May 31,2015	2016	Haber *et al.*	Review	Inactivated vaccines	1838	Injection site reactions
						Fatality
						Erythema
						Guillian-Barré syndrome
						Seizures
						Anaphylaxis
						Cardiac adverse effects
						Ocular adverse effects

						Skin reactions and/or conditions
						Renal adverse effects
						Gastrointestinal disturbances
Immunogenicity and safety of pandeic influenza H5N1 vaccines in healthy adults through meta-analysis	2016	Guo *et a*l.	Meta-analysis	Inactivated vaccines	N/A	Fever and chills
						Erythema
						Skin reactions and/or conditions
						Fatigue
						Injection site reactions
						Headache
Acute disseminated encephalomyelitis after infliuenza vaccination: a case report	2016	Chen *et al.*	Review	Inactivated vaccine	1	Neurological ADR
Immunogenicity and safety of inactivated quadrivalent influenza vaccine in adults: a systematic review and meta-analysis of randomised controlled trials	2016	Moa *et al*	Review	Inactivated vaccines	8934	Injection site reactions
						Fatigue and myalgia
						Headache
						Fever
						Flu-like symptoms
						Gastrointestinal disturbances
Sex-based biology and the rational design of	2014	Klein & Pekosz	Review	Live attenuated vaccine; Inactivated vaccine	N/A	Fatigue
						Headache
						Erythema

influenza vaccination strategies						Injection site reactions
						Gastrointestinal disturbances
						Facial nerve palsy (incl. Bell's palsy)
						Guillian-Barré syndrome
						Flu-like symptoms
						Anaphylaxis, hypersensitivty and allergic reactions
Review of 10 years of clinical experience with Chinese domestic trivalent influenza vaccine Anflu®	2014	Liu *et al.*	Review	Trivalent inactivated influenza vaccine	N/A	Skin reactions and/or conditions
						Headache
						Injection site reactions
						Gastrointestinal disturbances
						Fatigue & myalgia
						Arthralgia
						Flu-like symptoms
						Dizziness
A meta-analysis of intradermal versus intramuscular influenza vaccines: immunogenicity and adverse events	2013	Marra *et al.*	Review	Live attenuated vaccine; Inactivated vaccine	N/A	Local site reactions
						Fever & chills
						Erythema
						Skin reactions and/or conditions
						Myalgia

						Gastrointestinal disturbances
						Arthralgia
Vaccines for preventing influenza in people with asthma	2013	Cates e*t al.*	Review	Live attenuated vaccine; Inactivated vaccine	2303	Flu-like symptoms
						Injection site reactions
						Skin reactions and/or conditions
						Dyspnoea, wheezing and/or respiratory conditions
Influenza vaccination in HIV-postive subjects: latest evidence and future perspective	2013	Ceravolo *et al.*	Review	Trivalent inactivated influenza vaccine	N/A	Fatigue & myalgia
						Fever & chills
						Erythema
						Skin reactions and/or conditions
						Injection site reactions
Influenza vaccine-induced interstitial lung disease	2013	Watanabe *et al.*	Review	Not specified	7	Respiratory conditions
Intanz® 9ug intradermal seasonal influenza vaccine for adults 18 to 59 years of age	2013	Leroux-Roels & Weber	Review	Intradermal trivalent inactivated influenza vaccine	N/A	Erythema
						Fever & chills
						Headache
						Arthralgia
						Skin reactions and/or conditions
						Injection site reactions

Current evidence on intradermal influenza vaccines administerr by Soluvia (TM) licensed microinjection system	2012	Icardi *et al.*	Review	Intradermal trivalent inactivated influenza vaccine	645	Erythema
						Fever
						Headache
						Skin reactions and/or conditions
						Injection site reactions
Effectiveness and harms of seasonal and pandemic influenza vaccines in children, adults and elderly	2012	Manzoli *et al.*	Review	live attentuated, parenteral inactivated vaccines, aerosol inactivated vaccines	N/A	Guillian-Barré syndrome
						Fever
						Injection site reactions
Egg-allergic patients can be safely vaccinated against influenza	2012	Roches *et al.*	Review	Trivalent inactivated influenza vaccine	N/A	Anaphylaxis, hypersensitivty and allergic reactions
						Skin reactions and/or conditions
						Gastrointestinal disturbances