Reporting of adverse events of COVID-19 vaccines and drugs to the Food and Drug Administration Adverse Event Reporting System and EudraVigilance During the COVID-19 pandemic

Krautwurst, Yannick

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Yannick Krautwurst

REPORTING OF ADVERSE EVENTS OF COVID-19 VACCINES AND DRUGS TO THE FOOD AND DRUG ADMINISTRATION ADVERSE EVENT REPORTING SYSTEM AND EUDRAVIGILANCE DURING THE COVID-19 PANDEMIC

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Mentor:
Assist. Prof. Shelly Melissa Pranić, MSPH, PhD

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LIST OF ABBREVATIONS

Ad – adenovirus

ADRs – adverse drug reactions

AE – adverse event

AEs – adverse events

BfArM – Bundesinstitut für Arzneimittel und Medizinprodukte

CDC – United States Centers for Disease Control and Prevention

CDER – Food and Drug Administration Center for Drug Evaluation and Research

CMA – conditional marketing authorization

COVID-19 – Coronavirus disease 2019

CTL – cytotoxic T lymphocytes

CYP – cytochrome P450

DNA – deoxyribonucleic acid

ECMO – extracorporeal membrane oxygenation

EEA – European Economic Area

eGFR – estimated glomerular filtration rate

EMA – European Medicines Agency

EU – European Union

EUA – emergency use authorization

FAERS – Food and Drug Administration Adverse Event Reporting System

FDA – United States Food and Drug Administration

HALMED – Hrvatska agencija za lijekove i medicinske proizvode

HFNC – high-flow nasal cannula oxygen

HPV – human papillomavirus

ICU – intensive care unit

IM – intramuscular(ly)

IV – intravenous(ly)

mAb – monoclonal antibody

mAbs – monoclonal antibodies

MERS-CoV – Middle East respiratory syndrome coronavirus

mRNA – messenger ribonucleic acid

mTOR – mammalian target of rapamycin

NHC – beta-D-N^4-hydroxycytidine

NIH – United States National Institutes of Health

NIV – non-invasive ventilation

PHEIC – public health emergency of international concern

PO – *per os*

PRAC – European Medicines Agency Pharmacovigilance Risk Assessment Committee

PrEP – pre-exposure prophylaxis

RNA – ribonucleic acid

RCT – randomized controlled trial

SARS-CoV – severe acute respiratory syndrome coronavirus

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

TNF – tumor necrosis factor

U.S. – United States

WHO – World Health Organization

1. INTRODUCTION

1.1. Coronavirus disease 2019 (COVID-19)

1.1.1. Epidemiology

Coronavirus disease 2019, abbreviated as COVID-19, is a contagious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The first cases had been reported since December 8, 2019. On December 31, 2019, the Chinese Health Authority alerted the World Health Organization (WHO) to several cases of pneumonia of unknown etiology in Wuhan, Hubei province in central China (1).

It seems that there is an epidemiological link to the Huanan Seafood Wholesale Market where sale of live animals took place (2), and a large proportion of the initial cases in late December 2019 and early January 2020 had a direct link to this market in Wuhan City, where seafood, wild, and farmed animal species were sold. A lot of the initial patients were either stall owners, market employees, or regular visitors to this market (3), although some early cases did not show any association (1).

On January 30, 2020, the World Health Organization declared the outbreak as a Public Health Emergency of International Concern (PHEIC), as the viral etiological agent causative of COVID-19 has been confirmed and its genome sequenced (1).

While the number of cases is similar between males and females, males have a higher rate of intubation and longer hospitalization duration compared to females and have a higher mortality rate even when compared across age groups and ethnicities (4). Individuals of all ages are at risk for SARS-CoV-2 infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions (5).

As of March 15, 2022, more than 450 million cases and more than six million deaths were reported to Johns Hopkins University & Medicine (6).

The causative species of COVID-19 is SARS-CoV-2, and human coronaviruses are far from unknown, as they account for approximately 15 to 30% of common colds (7). This virus strain is the third zoonotic introduction of a highly contagious and pathogenic coronavirus into the human population, after the outbreaks of the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (8,9).

1.1.2. Prevention and treatment

The United States (U.S.) National Institutes of Health (NIH) COVID-19 Treatment Guidelines were developed by the COVID-19 Treatment Guidelines Panel, which consists of various U.S. health care organizations (10).

Vaccination is the most effective measure to prevent infection with SARS-CoV-2 and resulting COVID-19. Everyone who is eligible for vaccination should be vaccinated as soon as possible with one of the authorized vaccines (11).

Patients with acute COVID-19 are advised to isolate and to take steps to reduce the risk of SARS-CoV-2 transmission. When possible, patients with symptoms of COVID-19 should be triaged remotely via telehealth visits to determine whether they require in-person care and/or COVID-19-specific therapy. Patients with dyspnea should be referred for an in-person evaluation by a health care provider and should be followed closely during the initial days to detect early a potential deterioration of the respiratory status (12).

Management of non-hospitalized patients should generally include supportive care and consideration for the use of COVID-19-specific therapy in patients who may have a high risk for disease progression. Recommendation for the therapeutics used to treat non-hospitalized patients with mild to moderate COVID-19 with risk of clinical progression were based on the results of clinical trials for the antiviral drugs nirmatrelvir/ritonavir, remdesivir, and molnupiravir, as well as on laboratory assessments of the activity of the anti-SARS-CoV-2 monoclonal antibody bebtelovimab. Ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir (Veklury) are recommended as preferred therapy options because phase III randomized, placebo-controlled trials have reported high clinical efficacies for these agents in patients with COVID-19. Ritonavir-boosted nirmatrelvir (Paxlovid) should be preferred in most non-hospitalized patients with mild to moderate COVID-19 and high risk for progression. If not available or cannot be used because of drug-drug interactions, second-line therapy with remdesivir should be initiated. Bebtelovimab and molnupiravir are recommended only as alternative therapy options, when neither of the preferred treatment options are available, reasonable to use, or clinically appropriate (13).

For COVID-19 hospitalized adults, remdesivir is recommended for the treatment in patients without supplemental oxygen requirement and who are at high risk of progressing to severe disease. Administration should last for five days or until hospital discharge, whichever comes first. Dexamethasone or other systemic corticosteroids are not recommended in this case. For patients with COVID-19 who only require minimal conventional oxygen, remdesivir without dexamethasone is recommended, while for patients requiring conventional

oxygen, dexamethasone plus remdesivir is recommended. A second immunomodulatory drug, such as baricitinib or tocilizumab, may be added to dexamethasone in patients with rapidly increasing oxygen needs and systemic inflammation. For patients who require high-flow nasal cannula oxygen (HFNC) or noninvasive ventilation (NIV), one of the following combinations of immunomodulators should be used: dexamethasone plus oral (PO) baricitinib *or* dexamethasone plus intravenous (IV) tocilizumab. For hospitalized patients who require HFNC oxygen or NIV and have previous comorbidities, remdesivir can be added to one of the recommended immunomodulator combinations. Patients who require mechanical ventilation or extracorporeal membrane oxygenation, should receive dexamethasone plus PO baricitinib *or* dexamethasone plus IV tocilizumab if not already initiated (14).

1.2. Immunization, vaccine development and vaccine technologies

Immunization with vaccines is an effective therapeutic method to prevent millions of illnesses and mortalities every year, making it one of the most successful public health interventions, a main component of primary health care and an undeniable human right (15,16). As a result of widespread vaccine use, the smallpox virus has been completely eradicated in 1980 and the incidence of polio, measles and other childhood diseases have been enormously reduced worldwide (17). Conventional vaccine approaches, such as live attenuated, inactivated or killed pathogens and subunit vaccines, provide durable protection against a variety of severe or life-threatening diseases but for emerging virus vaccines, the main obstacle is not the effectiveness of conventional approaches but the necessity for more rapid development and substantial deployment promptly when viral diseases appear. Conventional vaccines as mentioned before may not be applicable to non-infectious diseases, such as cancer, hence there is a well-intended and urgent need for further development (18).

The COVID-19 pandemic and related disruptions in medical care have been a burden to health systems worldwide, causing 25 million children to miss out on vaccination in 2021, 5.9 million more than in 2019 and the highest number since 2009 (16).

Messenger ribonucleic acid (mRNA) vaccines show a lot of beneficial features over conventional vaccines. Regarding safety, mRNA is a non-infectious, non-integrating, genetic vector and there is no potential risk of infection or insertional mutagenesis. Degradation takes place by normal cellular processes. Various modifications make mRNA more stable and highly translatable, causing higher efficacy. Since these vaccines don't require an additional vector, anti-vector immunity is avoided, and mRNA vaccines can be administered repeatedly. They

can be rapidly and inexpensively manufactured, mainly due to the high yields of *in vitro* transcription reactions (19–23).

Current examples of mRNA vaccines used for treatment of COVID-19 are Comirnaty and Spikevax. Figure 1 portrays the components, development timeline and vaccination progress of COVID-19 mRNA vaccines.

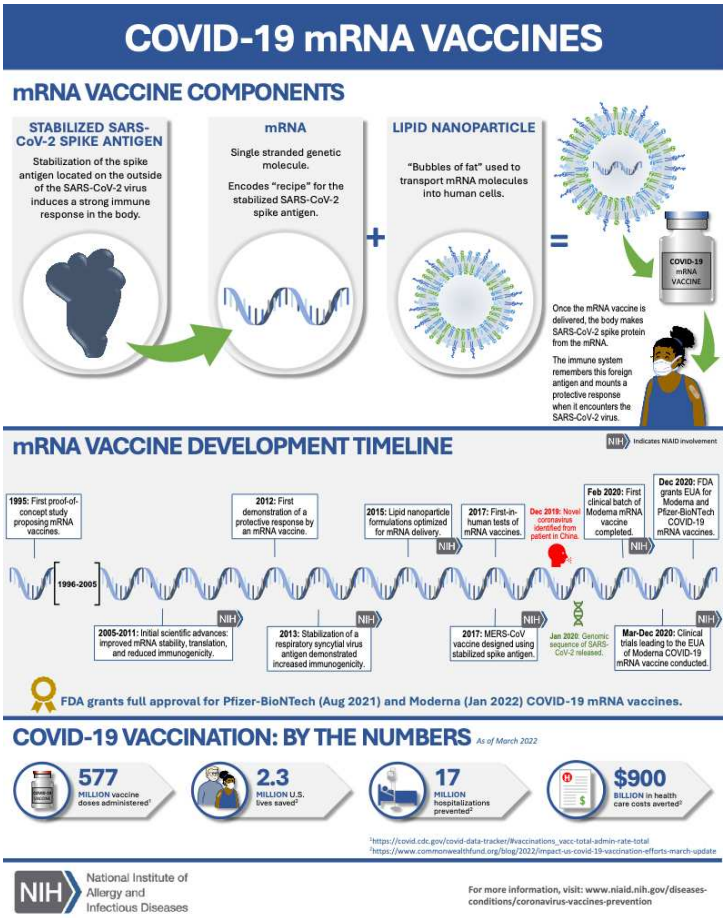

Figure 1. COVID-19 mRNA vaccines components, development timeline and vaccination progress (24)

Adenovirus (Ad) vector-based vaccines are potential candidates as vaccine vectors for emerging infectious diseases due to their high transduction efficiencies and high titer production. These vaccines possess the property of strongly inducing responses of cytotoxic T lymphocytes (CTLs) in both the systemic compartment and the mucosal compartment. This is an engaging advantage of Ad vector vaccines because pathogens tend to infect and invade the mucosa initially (25). Ad vector vaccines are in development for HIV-1, Zika virus, Influenza virus, Ebola virus and SARS-CoV-2. Four of these vaccines in use for treatment of COVID-19 are Vaxzevria (Oxford-AstraZeneca, ChAdOX1 nCoV-19), Sputnik V, and Convidecia (Ad5-

nCOV), which express the full-length spike protein of SARS-CoV-2, and Jcovden (Janssen, Ad26.COV2-S), which expresses a pre-fusion stabilized spike protein. These Ad vector vaccines efficiently elicited immune responses, including induction of anti-spike protein antibodies and $CD8^+$ T cell response, to SARS-CoV-2 following intramuscular (IM) administration (26).

The COVID-19 vaccine development also encompasses other technologies like protein subunit and virus-like particle vaccines, like in the case of Nuvaxovid (27), but will not be further discussed here.

1.3. Medicines approval processes and emergency authorizations

The U.S. and the European agencies for medicines, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively, are responsible for approving the emergency use of medicines aside from the regular approval and licensing process. The FDA is a federal agency of the Department of Health and Human Services. The EMA is an agency of the European Union (EU).

The FDA's Center for Drug Evaluation and Research (CDER) is responsible for evaluating new medicines before their introduction to the U.S. market. FDA-approval is granted when data on the drug's efficacy have been reviewed by the CDER, and the medicine has evident benefits that outweigh its known or potential risks as well as adverse effects for the intended population, i.e., the U.S. (28)

The FDA may accelerate medicine approval under certain circumstances. During public health emergencies like the COVID-19 pandemic, the FDA may grant an emergency use authorization (EUA), which is a mechanism to facilitate the prompt availability and use of medical countermeasures, including vaccines, against public health hazards. Under an EUA, the FDA may authorize the use of unapproved, newly developed medical products, or unapproved uses of previously approved medical products. For granting an EUA, certain statutory criteria must be met, including that there are currently no adequate and available alternatives, which were previously approved for the determined use. Pharmaceutical manufacturers must submit an EUA request to the FDA, and once submitted, the FDA will evaluate the request to determine whether the necessary statutory criteria are fulfilled (29).

Equivalent to the FDA's EUA mentioned above, the EMA can grant temporary pharmaceutical approval as so-called conditional marketing authorization (CMA). In the interest of the public health or in a public health emergency like the COVID-19 pandemic, less comprehensive pharmaceutical and non-clinical data may also be accepted for temporarily

approving medicines for that certain public health concern. The benefit of immediate availability of these medicines needs to outweigh the risk inherent in the fact that additional data are still required, and the medicines would fulfil an unmet medical need. Lastly, it is likely that the applicant, i.e., the pharmaceutical producer, will be able to provide comprehensive data in the post-authorization period. CMAs are valid for one year and require annual renewal unless they are converted to standard marketing authorizations (30). The EMA approval process is shown in Figure 2.

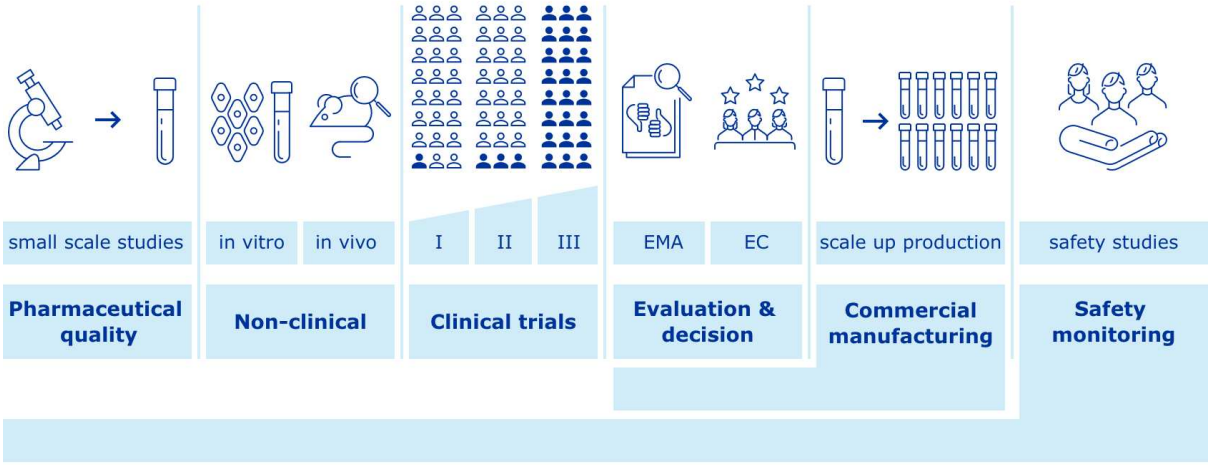

Figure 2. EMA medicine approval procedure (31)

1.4. FDA- and EMA-approved vaccines and what is (un)known about their safety and effectiveness

An overview of the FDA- and EMA-approved COVID-19 vaccines is shown in Table 1.

1.4.1. Comirnaty (Pfizer-BioNTech COVID-19 vaccine)

Comirnaty (BNT162b2), or commonly Pfizer-BioNTech COVID-19 vaccine, is an mRNA-based COVID-19 vaccine developed by BioNTech SE located in Mainz, Germany, in collaboration with U.S. pharmaceutical company Pfizer Inc. Comirnaty contains tozinameran, a single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the analogous deoxyribonucleic acid (DNA) templates, which encodes the viral spike (S) protein of SARS-CoV-2 (32).

Comirnaty is administered IM in two doses with an interval of three weeks. Adults and adolescents from the age of 12 are given 0.3 mg per dose; children aged 5 to 11 years are given 0.1 mg per dose. A third, additional dose may be given to severely immunocompromised individuals aged 5 years and older, at least 28 days after their second dose. This booster dose may be given at least 6 months after the second dose to individuals aged 12 years and older (32).

The original trial of Comirnaty that led to the EUA and CMA included 43,448 vaccinated participants which were assigned to the Comirnaty group and the placebo group in an approximate 1:1 ratio. The trial reported a 95.0% vaccine efficacy among participants without prior SARS-CoV-2 infection, and a 94.6% vaccine efficacy among participants with and those without evidence of prior SARS-CoV-2 infection, respectively. The vaccine efficacy for the interval between the first dose and the second vaccine dose was reported as 52%, indicating early protection by the vaccine, starting as soon as 12 days after receiving the first dose. During the trial period, more Comirnaty recipients than placebo recipients reported any adverse event (27% and 12%, respectively) or a related adverse event (21% and 5%). Among these adverse events, 64 vaccine recipients (0.3%) and six placebo recipients (<0.1%) reported lymphadenopathy. Four serious adverse events were reported among recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). Two recipients died (one from arteriosclerosis, one from cardiac arrest), as did four placebo recipients (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction). The investigators did not consider any deaths to be related to the vaccine or placebo (33). In a single-center study conducted between May 1 and July 15, 2021, Dionne *et al.* described a case-series of children younger than 19 years hospitalized with myocarditis within 30 days after receiving the Comirnaty vaccine. This patient group consisted of 15 patients, of which 14 were male, and had a median age of 15 years (34).

The FDA approved Comirnaty for EUA on December 11, 2020, for use in individuals 16 years of age and older, and the authorization was expanded to include those 12 through 15 years of age on May 10, 2021 (35). The vaccine received full FDA-approval on August 23, 2021, for use in individuals 16 years of age and older and was hence the first COVID-19 vaccine to be granted full FDA-approval (36). On October 29, 2021, the EUA was amended to include the use in children aged 5 through 11 years (37), and on June 17, 2022, the indication was further extended to include children aged 6 months through 4 years (38).

The EMA approved Comirnaty for CMA on December 21, 2020, initially for use in

individuals 16 years of age and older (39). On May 28, 2021, an extension of indication for use in children aged 12 to 15 was granted, with the same regimen as for adults (40). On November 25, 2021, a second extension of indication included children aged 5 to 11, with a smaller dose of 10 µg compared with 30 µg for adults (41). As of June 26, 2022, 649,000,000 doses have been administered in the EU and European Economic Area (EEA) (42).

1.4.2. Spikevax (Moderna COVID-19 vaccine)

Spikevax (mRNA-1273), also called Moderna COVID-19 vaccine, is an mRNA-based COVID-19 vaccine developed by Moderna, Inc. Spikevax contains elasomeran that is a single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the analogous DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (43).

Spikevax is given as two IM injections, 28 days apart. Adults and adolescents from the age of 12 are given 100 µg per dose; children aged 6 to 11 years are given 50 µg per dose. A booster dose may be given to people aged 6 years and older with a severely weakened immune system, at least 28 days after receiving the second dose. It is available in a multidose vial that contains 10 doses of 0.5 mL each or a maximum of 20 doses of 0.25 mL each (43).

The initial clinical trial that led to the EUA and CMA of Spikevax enrolled 30,420 volunteers, receiving two doses. It showed 94.1% efficacy at preventing COVID-19, including severe disease. Aside from transient local and systemic reactions, there were no safety concerns identified. Local reactions to the vaccine were mild. However, moderate-to-severe systemic side effects, such as fatigue, myalgia, arthralgia, and headache, were reported in about 50% of participants in the vaccine group after receiving the second dose. These adverse effects were transient, beginning about 15 hours after vaccination and resolving in most participants by the second day, without sequelae (44).

On December 18, 2020, the FDA approved Spikevax for EUA for use in individuals 18 years of age and older. On January 31, 2022, the FDA announced the approval of Spikevax for individuals 18 years of age and older, making it the second COVID-19 vaccine to get full FDA-approval (45). The EUA was amended on June 17, 2022, to include the use in individuals aged 6 months through 17 years (38).

The EMA approved Spikevax for CMA on January 6, 2021, initially for use in individuals 18 years of age and older (46). On July 23, 2021, the EMA extended the indication to include children aged 12 to 17 years (47). On February 24, 2022, children aged 6 to 11 years were also included in the extension, with a lower dose than the one used in individuals aged 12

and above (50 µg compared with 100 µg) (47). As of June 26, 2022, 155,000,000 doses have been administered in the EU/EEA (42).

1.4.3. Jcovden (Janssen COVID-19 vaccine)

Jcovden (Ad26.COV2-S), also called Janssen COVID-19 vaccine, is an adenovirus-vector COVID-19 vaccine developed by Janssen Vaccines and Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson (48). Jcovden contains an adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (49).

The original clinical trial of Jcovden included 19,630 SARS-CoV-2-negative participants who received the vaccine. The reported efficacy was 66.9% for protection against moderate to severe COVID-19 with onset at least 14 days after vaccine administration. Reported adverse effects were similar compared to previous COVID-19 vaccines. Injection-site pain was the most common local reaction (48.6%), and the most common systemic reactions were headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%) (50).

Jcovden is given as a single IM injection. A booster dose may be given at least two months after the first dose in individuals aged 18 years and older and may also be given after two doses of one of the mRNA vaccines. It is available as a multi-dose vial which contains five doses of 0.5 mL (49).

On February 27, 2021, the FDA approved Jcovden for EUA to prevent COVID-19 in individuals 18 years of age and older. On May 5, 2022, the use was restricted to individuals 18 years of age and older for whom other authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or for individuals 18 years of age and older who would otherwise choose not to be vaccinated against COVID-19 (51).

The EMA approved Jcovden for CMA for use in individuals from 18 years of age on March 11, 2021 (52). As of June 26, 2022, 19,400,000 doses have been administered in the EU/EEA (42).

1.4.4. Vaxzevria (Oxford-AstraZeneca COVID-19 vaccine)

Vaxzevria (ChAdOx1-S), also called Oxford-AstraZeneca COVID-19 vaccine, is an adenovirus-vector COVID-19 vaccine developed by Oxford University and AstraZeneca (53).

The original clinical trials of Vaxzevria included 23,848 participants and reported an overall vaccine efficacy of 70.4% after two doses. Serious adverse events occurred in 168 participants (0.7%), 79 of the Vaxzevria group and 89 of the control group (54).

Between February 17, 2021, and March 12, 2021, 54,571 adverse events were reported to EudraVigilance, of which 28 were associated with thrombotic adverse reactions. Three fatalities were related to pulmonary embolism and one fatality to thrombosis (55). Several studies reported that in very rare cases immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against platelet factor 4 (PF4) developed, which presented clinically as autoimmune heparin-induced thrombocytopenia (56). Most cases of thrombotic thrombocytopenia occurred in females under 60 years of age within two weeks of vaccination. Due to the very rare occurrence of this adverse event, the EMA confirmed that the overall benefit-risk remained positive (57).

The EMA approved Vaxzevria for CMA on January 29, 2021, for prevention of COVID-19 in individuals aged 18 years or older (58). As of June 26, 2022, 69,000,000 doses have been administered in the EU/EEA (42). As of June 30, 2022, Vaxzevria has not been authorized in the U.S.

1.4.5. Nuvaxovid (Novavax COVID-19 vaccine)

Nuvaxovid (NVX-CoV2373), also called Novavax COVID-19 vaccine, is recombinant nanoparticle vaccine, also described as protein subunit and virus-like particle vaccine, against SARS-CoV-2 that contains the full-length spike glycoprotein of the prototype strain plus the Matrix-M adjuvant (59). It was developed by Novavax and Coalition for Epidemic Preparedness Innovations (60).

The original clinical trial was a phase III randomized controlled trial (RCT) and included 15,187 participants. It reported a vaccine efficacy of 89.7%. Reactogenicity after receiving the vaccine was described as mild and transient, and the incidence of serious adverse events was low and similar in both the vaccine and the control group (59).

The EMA approved Nuvaxovid for CMA on December 20, 2021, for prevention of COVID-19 in individuals aged 18 years or older (61), and on June 23, 2022, extended the indication to include individuals aged 12 to 17 years (62). As of June 26, 2022, 216,000 doses have been administered in the EU/EEA (42). As of June 30, 2022, Nuvaxovid has not been authorized in the U.S.

Table 1. COVID-19 vaccines authorized by the FDA and/or EMA (63,64)

Common names	Generic names	Trade names	Pharmaceutical developers	FDA authorization status*	EMA authorization status*
Pfizer-BioNTech COVID-19 vaccine	Tozinameran	Comirnaty	BioNTech, Pfizer	A	CMA
Moderna COVID-19 vaccine	Elasomeran	Spikevax	Moderna	A	CMA
Janssen COVID-19 vaccine, Johnson & Johnson COVID-19 vaccine	Ad26.COV2-S	Jcovden	Janssen Pharmaceuticals	EUA	CMA
Oxford-AstraZeneca COVID-19 vaccine	ChAdOx1-S	Vaxzevria, Covishield	AstraZeneca	-	CMA
Novavax COVID-19 vaccine	Nuvaxovid COVID-19 vaccine (recombinant, adjuvanted)	Nuvaxovid, Covovax	Novavax	-	CMA

A = approval; CMA = conditional marketing authorization; EMA = European Medicines Agency; EUA = emergency use authorization; FDA = Food and Drug Administration; * as of June 30, 2022

1.5. FDA- and EMA-approved COVID-19 drugs and what is (un)known about their safety and effectiveness

An overview of the FDA- and EMA-approved COVID-19 drugs is shown in Table 2.

1.5.1 Remdesivir

Remdesivir is a nucleotide analog that inhibits RNA synthesis and thus viral replication. It is currently FDA-approved for use in hospitalized COVID-19 patients and in non-hospitalized patients with mild-to-moderate disease who are at high risk of disease progression. The PINETREE trial reported that three consecutive days of IV remdesivir administration resulted in an 87% relative risk reduction for hospitalization or death as outcome compared to placebo (65). Despite limited data, it is supposed to be effective against Omicron variants (66). The NIH Panel recommends using remdesivir 200 mg IV on the first day, followed by remdesivir 100 mg IV once daily on the second and third day in individuals aged ≥12 years and weighing ≥40 kg; initiation of treatment should be as soon as possible and within seven days of symptom onset. Administration should take place in a health care setting with at least one hour observation for possible anaphylactic reactions after infusion (13). In hospitalized patients who require supplemental oxygen, it is recommended to administer remdesivir or dexamethasone or the combination of both. When remdesivir is used in this setting, it is administered as a once-daily IV infusion for five continuous days (14).

The FDA initially approved remdesivir (Veklury) for EUA on May 1, 2020, later expanded it to a full approval on October 22, 2020, and approved it as first COVID-19 treatment for young children on April 25, 2020 (67,68).

The EMA approved remdesivir (Veklury) for CMA on July 3, 2020, and the grant was extended to marketing authorization on August 8, 2022 (69).

1.5.2. Nirmatrelvir/ritonavir

Nirmatrelvir is an orally bioavailable protease inhibitor that is active against the SARS-CoV-2 main protease (M^{pro}), a viral protease that is involved in viral replication (70). Antiviral activity against all human coronaviruses has been proven (71). Nirmatrelvir is packaged with ritonavir (as Paxlovid) which is a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent, necessary to raise nirmatrelvir concentrations to a target therapeutic range (70).

Nirmatrelvir/ritonavir (Paxlovid) is FDA-authorized for emergency use for the treatment of mild-to-moderate disease in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe disease, including hospitalization or death. The NIH Panel recommends using nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid) orally (PO) twice daily for five days, with initiation as soon as possible and within five days of symptom onset (13).

In the EPIC-HR trial, nirmatrelvir/ritonavir (Paxlovid) showed to reduce the risk of hospitalization or death by 88% compared to placebo in non-hospitalized adults with confirmed SARS-CoV-2 infection (72). Despite limited data, it is expected to be effective against all Omicron subvariants (66,73). In addition, it is recommended for pregnant patients because ritonavir has been safely used in HIV-pregnant women and the potential benefits, i.e., prevention of a severe clinical progression, outweigh the risks (13).

The FDA approved nirmatrelvir/ritonavir (Paxlovid) for EUA on December 22, 2021, as the first oral drug for COVID-19 treatment (74). The EMA approved nirmatrelvir/ritonavir (Paxlovid) for CMA on January 28, 2022 (69).

1.5.3. Tocilizumab

Tocilizumab is a monoclonal antibody (mAb) against the IL-6 receptor which decreases the IL-6 levels and thus leads to a decreased immune response. It has been in use for chronic autoimmune indications previously (75).

The NIH Panel recommends adding a second immunomodulatory drug, such as tocilizumab, in addition to dexamethasone in hospitalized patients who have rapidly increasing oxygen needs and systemic inflammation, as well as in patients requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) that have been in an intensive care unit (ICU) for less than 24 hours. Tocilizumab 8 mg/kg actual body weight (up to 800 mg) is administered as a single IV dose (14).

In the REMAP-CAP trial, an RCT, the use of tocilizumab combined with corticosteroids reduced mortality and improved outcomes in ICU patients with rapid respiratory decompensation (76). The RECOVERY trial reported that tocilizumab improved survival and other clinical outcomes in patients with hypoxia and systemic inflammation (77).

The FDA approved tocilizumab (Actemra) for EUA on June 24, 2021, for the treatment of COVID-19 in hospitalized adults and pediatric patients aged two years and older (74). The

EMA approved tocilizumab (RoActemra) for marketing authorization on December 7, 2021 (69).

1.5.4. Tixagevimab/cilgavimab

Tixagevimab and cilgavimab are monoclonal antibodies (mAbs) against the surface spike protein of SARS-CoV-2 and are co-packaged as Evusheld (78,79). Tixagevimab and cilgavimab bind to non-overlapping portions of the SARS-CoV-2 spike protein, hindering the virus during interaction with the human ACE2 receptor. Pharmacokinetic studies showed that these antibodies are catabolized slowly with mean half-lives of 87.9 and 82.9 days for tixagevimab and cilgavimab, respectively (80).

These anti-SARS-CoV-2 mAbs are to be used as pre-exposure prophylaxis (PrEP) for immunocompromised individuals that may have inadequate responses to COVID-19 vaccines or for individuals that are unable to be fully vaccinated due to previous severe adverse reactions to a COVID-19 vaccine. Due to prolonged half-lives, these may protect from SARS-CoV-2 infection for up to six months, depending on the variant. The NIH Panel recommends using tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld) administered as two consecutive 3-mL IM injections as SARS-CoV-2 PrEP for adults and adolescents aged ≥12 years and weighing ≥40 kg who are neither SARS-CoV-2-positive, nor have been recently exposed to a SARS-CoV-2-positive individual, and additionally are moderately to severely immunocompromised *or* unable to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions (11). Tixagevimab/cilgavimab can be administered to eligible patients every six months (80).

PROVENT is an ongoing phase III, double-blind, randomized, placebo-controlled trial evaluating the use of tixagevimab/cilgavimab for SARS-CoV-2 PrEP and reported a relative risk reduction of 76.7% for symptomatic COVID-19 infection, and at a median follow-up of six months a relative risk reduction of 82.8%. Five cases of severe or critical COVID-19 infection and two COVID-19-related deaths occurred, all among the placebo group. Adverse events were reported as 35.3% in the tixagevimab/cilgavimab group compared with 34.2% in the placebo group (81).

The FDA approved tixagevimab/cilgavimab (Evusheld) for EUA on December 8, 2021, for use as pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals 12 years of age and older weighing at least 40 kg (74). The EMA approved tixagevimab/cilgavimab (Evusheld) for marketing authorization on March 25, 2022 (69).

1.5.5. Baricitinib

Baricitinib is an orally bioavailable, selective JAK1 and JAK2 inhibitor that reduces inflammation (82).

The NIH Panel recommends adding a second immunomodulatory drug, such as baricitinib to dexamethasone in patients who have rapidly increasing oxygen needs and systemic inflammation (14).

The RECOVERY trial showed that use of baricitinib plus dexamethasone was associated with an improved survival outcome among hospitalized COVID-19 patients, reporting that JAK inhibitors, mainly baricitinib, reduce mortality by about one-fifth, and a more pronounced positive effect was demonstrated among patients receiving HFNC oxygen or NIV therapy (83). In addition, The COV-BARRIER trial demonstrated reduced mortality, which was also most pronounced in patients receiving HFNC oxygen or NIV therapy (84). Baricitinib has previously been FDA-approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) blockers (85).

The FDA authorized baricitinib (Olumiant) for EUA on November 19, 2020, for the treatment of suspected or laboratory confirmed COVID-19 in certain hospitalized patients requiring supplemental oxygen, invasive mechanical ventilation, or ECMO in combination with remdesivir (Veklury). On May 10, 2022, the FDA issued a full approval for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO (74).

Baricitinib (Olumiant) is under EMA marketing authorization evaluation since April 29, 2021, but has not been authorized in the EU (86).

1.5.6. Sotrovimab

Sotrovimab is a mAb derived from memory B cells of a patient who had recovered from SARS-CoV-2 infection, which binds to an epitope within the spike protein of sarbecoviruses (87).

The NIH Panel has previously recommended sotrovimab as a treatment option for certain non-hospitalized COVID-19 patients who are at high-risk for a severe disease progression. However, even though sotrovimab showed efficacy against the Omicron BA.1 and BA.1.1 subvariants, it showed decreased *in vitro* activity against the Omicron BA.2 subvariant (88,89).

Gupta *et al.* reported in their phase III clinical trial that out of 583 participants three patients (1%) of the sotrovimab group, as compared to 21 patients (7%) of the placebo group, had progression of disease leading to hospitalization or death. Relative risk reduction was 85%. Serious adverse events occurred less commonly with sotrovimab (2%) than with placebo (6%) (90).

The FDA approved sotrovimab for EUA on May 26, 2021, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients aged 12 years and older weighing at least 40 kilograms with SARS-CoV-2-positive and who are at high risk for progression to severe COVID-19. On March 25, 2022, the FDA limited the use of sotrovimab to treat COVID-19 due to the emerging BA.2 Omicron subvariant. On April 5, 2022, the Centers for Disease Control and Prevention (CDC) reported that the authorized dose of sotrovimab is unlikely to be effective against the BA.2 Omicron subvariant, and consequently the FDA revoked the EUA (74).

The EMA approved sotrovimab (Xevudy) for marketing authorization on December 17, 2021, for treating COVID-19 in adults and adolescents aged 12 years or older and weighing at least 40 kilograms who do not require supplemental oxygen and who are at increased risk of a severe disease progression (69).

1.5.7. Casirivimab/imdevimab

Casirivimab and imdevimab are two fully human mAbs targeting the spike protein of SARS-CoV-2 and are characterized by having virus neutralizing properties (91,92).

Weinreich *et al.* investigated casirivimab/imdevimab (REGEN-COV) in a phase III clinical trial and reported that it decreased the risk of hospitalization or death from any cause and reduced the SARS-CoV-2 viral load more rapidly than placebo. Relative risk reduction for hospitalization or death was 71.3%. The median time to symptom resolution was four days shorter with REGEN-COV than with placebo, 10 and 14 days, respectively. Serious adverse events occurred more often in the placebo group (4.0%) than in the 1200-mg REGEN-COV group (1.1%) and the 2400-mg group (1.3%) (93).

The FDA approved casirivimab/imdevimab (REGEN-COV) for EUA on November 21, 2020, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients aged 12 years and older weighing at least 40 kilograms with SARS-CoV-2-positive and who are at high risk for progression to severe COVID-19. The EUA was withdrawn on January 24, 2022, due to the predominance of the Omicron variants and its reduced efficacy (74).

The EMA approved casirivimab/imdevimab (Ronapreve) for marketing authorization on November 12, 2021, for treating COVID-19 in adults and adolescents aged 12 years or older and weighing at least 40 kilograms who do not require supplemental oxygen and who are at increased risk of a severe disease progression (69).

1.5.8. Molnupiravir

Molnupiravir is the oral prodrug of beta-D-N^4-hydroxycytidine (NHC), a ribonucleoside that has broad-spectrum antiviral activity against RNA viruses. NHC causes viral mutations and lethal mutagenesis and has potent antiviral activity against SARS-CoV-2. This mutagenic property raised concerns that molnupiravir may be metabolized by human host cells and incorporated into the host DNA, leading to undesirable mutations. In two *in vivo* rodent mutagenicity studies, one result was equivocal and the other showed no evidence for mutagenicity (94,95). The FDA concluded low risk for genotoxicity regarding the available data and the limited 5-day-administration (74).

The NIH Panel recommends using molnupiravir 800 mg PO twice daily for five days in SARS-CoV-2-positive individuals aged ≥18 years only in cases when Paxlovid and remdesivir are not available, feasible to use, or clinically appropriate (13).

Molnupiravir had lower clinical efficacy in phase III clinical trials than other, preferred treatment options. The MOVe-OUT trial showed that molnupiravir reduced the hospitalization and death rate by 30% in non-hospitalized COVID-19 patients compared to placebo (96). Molnupiravir is assumed to be active against the Omicron variants, although current data is limited (66).

The FDA approved molnupiravir (Lagevrio) for EUA on December 23, 2021, for treatment of mild-to-moderate COVID-19 in adults, who are at high-risk for progression to severe COVID-19, and for whom other treatment alternatives are not accessible or clinically appropriate. It is not recommended for use in pregnant women due to safety concerns about potential fetal toxicity observed during animal studies (74). Molnupiravir (Lagevrio) is under EMA marketing authorization evaluation since November 23, 2021, but currently not authorized (86).

1.5.9. Bebtelovimab

Bebtelovimab is a recombinant neutralizing human mAb that binds to the spike protein of SARS-CoV-2 (13). *In vitro* studies showed that bebtelovimab may have activity against the Omicron variant and its BA.1, BA.1.1, and BA.2 subvariants, as well as the previous SARS-

CoV-2 variants (88,97). The clinical trial that has been conducted was a single, phase II, randomized, placebo-controlled trial in COVID-19-positive patients who were at low risk of progressing to severe disease. No unexpected safety events were recorded, and patients in the bebtelovimab group had more rapid viral decay compared to the placebo group. No information is available on the clinical use of bebtelovimab during breastfeeding. 175 mg IV of bebtelovimab is recommended in those aged ≥12 years, only as second-line after Paxlovid and remdesivir. Treatment should be initiated as soon as possible and within seven days of symptom onset (13).

The FDA approved bebtelovimab for EUA on February 11, 2022, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients aged 12 years and older weighing at least 40 kg who are at high risk for progressing to severe COVID-19 and for whom other treatment alternatives are not accessible or clinically appropriate (74). Bebtelovimab has not been authorized in the EU (69).

1.5.10. Anakinra

Anakinra is a recombinant human interleukin 1 receptor antagonist that has been previously used for treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever and Still's disease (98,99).

The SAVE-MORE double-blind RCT included 594 participants and evaluated the efficacy and safety of anakinra and reported a decreased score on the World Health Organization Clinical Progression Scale (WHO-CPS), a decreased Sequential Organ Failure Assessment (SOFA) score, reduced 28-day mortality, and shorter hospitalization duration with the use of anakinra. The frequency of serious adverse event was 16% in the anakinra group and 21.7% in the placebo group (100).

The EMA approved anakinra (Kineret) for marketing authorization on December 17, 2021, for treatment of COVID-19 pneumonia in adults who require supplemental oxygen and who are at risk of developing severe respiratory failure (69). Anakinra (Kineret) has not been FDA-authorized for COVID-19 treatment.

1.5.11. Regdanvimab

Regdanvimab is a recombinant mAb targeting the spike protein of SARS-CoV-2 and interferes with the binding of SARS-CoV-2 to human ACE2 (101). The recommended dosage of regdanvimab is 40 mg/kg as a single IV infusion which should be initiated as soon as possible after diagnosis but not later than seven days after the symptom onset (102).

Streinu-Cercel *et al.* reported in their RCT that regdanvimab showed to accelerate clinical recovery and to reduce the hospitalization rate and need for oxygen therapy in patients with mild-to-moderate COVID-19. No serious adverse events or deaths were reported (103).

EMA approved regdanvimab (Regkirona) for marketing authorization on November 12, 2021, for treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for severe disease progression (69). Regdanvimab has not been FDA-authorized for COVID-19 treatment.

Table 2. COVID-19 drugs and non-vaccine biological products authorized by FDA and/or EMA (69,74,86)

Generic names	Trade names	Pharmaceutical developers	ROA	Repurposed (R) or newly developed (N)	FDA authorization status*	EMA authorization status*
Remdesivir	Veklury	Gilead	IV	R	A	CMA
Nirmatrelvir/ ritonavir	Paxlovid	Pfizer	PO	N	EUA	CMA
Tocilizumab	Actemra (U.S.), RoActemra (EU)	Hoffmann-La Roche	IV, SC	R	EUA	MA
Tixagevimab/ cilgavimab	Evusheld	AstraZeneca	IM	N	EUA	MA
Baricitinib	Olumiant	Eli Lilly and Company	PO	R	EUA†	UE
Sotrovimab	Sotrovimab (U.S.), Xevudy (EU)	GlaxoSmithKline	IV	N	discontinued	MA
Casirivimab/ imdevimab	REGEN-COV (U.S.), Ronapreve (EU)	Regeneron Pharmaceuticals	IV, SC	N	discontinued	MA
Molnupiravir	Lagevrio	Merck Sharp & Dohme	PO	R	EUA	UE
Bebtelovimab	Bebtelovimab	AbCellera, Eli Lilly and Company	IV	N	EUA	-
Anakinra	Kineret	Swedish Orphan Biovitrum	SC	R	-	MA
Regdanvimab	Regkirona	Celltrion	IV	N	-	MA

A = approval; CMA = conditional marketing authorization; EMA = European Medicines Agency; EUA = emergency use authorization; FDA = Food and Drug Administration; MA = marketing authorization; ROA = route of administration; UE = under evaluation; * as of June 30, 2022; † in combination with remdesivir

1.6. What is (un)known about the safety and effectiveness of the emergency use authorized vaccines and drugs in special circumstances?

Safety and effectiveness of the COVID-19 vaccines and drugs is of paramount importance and public interest.

A general safety issue may be COVID-19 vaccination in pregnant or breastfeeding women. Pregnant trial participants were excluded from the initial phase III clinical trials of COVID-19 vaccines; hence, the current data is limited regarding efficacy and safety during pregnancy. Benefits and risks of COVID-19 vaccines for pregnant women need to be individually outweighed (104). CDC recommends the vaccination of pregnant women with an mRNA-COVID-19 vaccine, since safety concerns were found neither for individuals who received an mRNA-COVID-19 vaccine late in pregnancy nor for their fetuses. There is no increased risk for miscarriage and no association with an increased risk for pregnancy complications, i.e., preterm birth, stillbirth, bacterial infection of the placenta, and excessive maternal hemorrhage perinatally. Lastly, vaccination of pregnant women prior to and during the first trimester was not associated with an increased risk of birth defects detectable on prenatal ultrasound. Breastfeeding women were not part of clinical trials in the U.S., either. Recent reports have shown that antibodies are present in breastmilk after mRNA-COVID-19 vaccination, which may be beneficial for immune protection of newborns and infants (105).
A small cohort-study showed that at six months of age 57% of infants born to pregnant women who were vaccinated during pregnancy had detectable antibodies against SARS-CoV-2, compared to 8% of infants born to pregnant individuals who suffered from COVID-19 during pregnancy (106).

Halasa *et al.* reported in a case-control study that the frequency of all medically relevant adverse events after vaccination in pregnant women was less than 1%, of which the most common events were fever, malaise or fatigue, local reactions, and lymphadenopathy or lymphadenitis. No serious, acute adverse events such as cerebral venous sinus thrombosis, Guillain-Barré syndrome, myocarditis, pericarditis, or pulmonary embolism occurred more frequently in vaccinated than in unvaccinated, pregnant individuals. In addition, they reported that 84% of babies hospitalized due to COVID-19 were born to pregnant women who were not vaccinated during their pregnancy (107).

Studies in animals receiving Comirnaty (Pfizer-BioNTech), Spikevax (Moderna) or Jcovden (Janssen) COVID-19 vaccines before or during pregnancy resulted in no safety concerns in pregnant animals or their babies (105).

To date, most clinical trials investigating COVID-19 drugs have excluded pregnant and lactating women; in cases where lactating and pregnant women have been included, only a small number did end up taking part. This limitation renders evidence-based recommendations on the use of COVID-19 drugs difficult. Safety in these vulnerable patients is crucial, hence, their COVID-19 treatment options are potentially limited. Individual options should be considered in these cases (108).

Dose adjustments may be required for COVID-19 drugs in patients with renal and hepatic impairment. For example, in the case of Paxlovid, a dose reduction is required for moderate renal impairment with an estimated glomerular filtration rate (eGFR) ≥30 to <60 mL/min) and it is contraindicated in severe renal or hepatic impairment. Hypersensitivity reactions may occur, as well as CYP interactions with other drugs (109). Based on previous data, empirical reduction or withholding of calcineurin inhibitors or mammalian target of rapamycin (mTOR) inhibitors in transplant recipients may be necessary before starting Paxlovid treatment (110). These considerations are likely to apply to other COVID-19 drugs as well.

1.7. Background and importance of adverse events surveillance systems

1.7.1. Adverse events

Adverse events (AEs) are undesirable effects associated with the use of a medical product which may be causally related. AEs can range from mild complaints such as injection site pain or abdominal discomfort to more severe effects such as cardiac arrhythmias, acute neurological disorders, or teratogenicity. AEs may be detected during clinical studies prior to release or during post-marketing-authorization surveillance (111).

1.7.2. Pharmacovigilance and adverse events surveillance in the EU

Pharmacovigilance intends to detect, assess, understand, and prevent AEs or other problems regarding medicines. The EMA oversees the coordination of the EU pharmacovigilance systems. Prior to authorization of a medicine for use, evidence of its safety and efficacy is limited to the results provided from clinical trials, in which patients are selected carefully and followed up closely under controlled conditions. After the medical product has been tested in a relatively small number of trial patients for a limited time, it can be authorized. After authorization it may be used in a large number of patients, during a long period of time

and in combination with other medicines. The appearance of side or adverse events is to be expected during that period. Hence, it is indispensable to monitor and surveil the safety of all medicines throughout their use in healthcare settings. National competent authorities, such as Hrvatska agencija za lijekove i medicinske proizvode (HALMED) in Croatia or Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Germany, are required to cooperate with the EMA in operating the EU pharmacovigilance system, as are all marketing authorization holders. On a political basis, it is a cooperation between the members of the EU, the EMA, and the European Commission. Assessing and monitoring the safety of human medicines is a task of EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which consists of experts in pharmacological safety from national authorities of the members of the EU, as well as scientific experts and organizations representing patients' and healthcare professionals' interests (112).

An important role in the European pharmacovigilance takes EudraVigilance (EV). It is the database used for collecting, managing, and analyzing suspected adverse drug reactions (ADRs) or events to medicines authorized in the EEA. It is a digital repository for such reports seen in healthcare practice and clinical trials, and is used by member states, EMA, and industry (112). The database became operational in December 2001, on behalf of the EU medicines regulatory network (113). It is a unique tool because its relevance persists during the entire medicine's lifecycle, during research and development, marketing authorization and post-authorization (112). Data to EV can be reported by either healthcare professionals, non-healthcare professionals, i.e., lay persons, or not further specified individuals (114).

The EMA publishes data from EV accessible to the public in the European database of suspected adverse drug reaction reports, under "adrreports.eu" (112), which was launched by the EMA in 2012 to provide public access to its database (115). The electronic reporting of suspected ADRs has been mandatory in the EEA since November 5, 2005 (116).

Banovac *et al.* concluded in 2017 that among the EEA country distribution the highest number of reports originated from the Netherlands, followed by the UK, Germany, France, and Italy. These countries contributed 77% of all healthcare professional reports to EV. Especially since 2011, there has been a constant increase in the number of research publications that considered data from EV. This development likely reflects the thriving recognition of EV as an important contributor to drug safety. The easy access and usability support the early identification of safety signals, determine risks, and allow new methods for data investigation (113).

1.7.3. Pharmacovigilance and adverse events surveillance in the U.S.

The FDA Adverse Event Reporting System (FAERS) is FDA's publicly available database of adverse event reports, medication error reports and product quality complaints that resulted in AEs, i.e., the U.S. equivalent to EV. The reports submitted to FAERS are evaluated by clinical reviewers, in the CDER and the Center for Biologics Evaluation and Research, to monitor the product safety after EUA or full FDA-approval. If a potential safety concern is identified in FAERS, further evaluation is performed. Both healthcare professionals and non-healthcare professionals, i.e., consumers or lay persons, can report to FAERS. Reports are submitted electronically either via a database-to-database transmission or via the "Safety Reporting Portal", for which an FDA-created user account is necessary. Voluntary reports can be submitted via the "MedWatch Online Voluntary Reporting Form", accessible at https://www.fda.gov/Safety/MedWatch/ (117).

For the year 2014, 828,368 submitted reports were domestic, i.e., the reporter's country is the U.S., and 375,347 submitted reports were foreign, i.e., the reporter's country is outside the U.S. (118).

1.7.4. Limitations of adverse event reporting systems and peri-COVID-19 impact

In general, adverse event reporting systems have several limitations. The FDA itself describes FAERS's multiple limitations as there is no certainty that the AEs were caused by the suspected products; there is not necessarily causality between the AEs and the products; the estimated number of AEs is most likely higher, since not all events are reported to FAERS; and there may be duplicates of reports (117).

Two major limitations concern the reporting behavior and include so-called stimulated reporting and under-reporting. Stimulated reporting is the potential increase in AE reporting rates following safety warnings, publication of study findings or events in the public interest. In contrast, under-reporting refers to the fact that less than 10% of all AEs are reported, which not only affects older drugs and mild adverse events but also newly released drugs and serious AEs (119–121). Hazell and Shakir showed in their systematic review that there is evidence of significant and widespread under-reporting of AEs, including serious AEs, to adverse event reporting systems (122). Due to these circumstances, major events that could affect reporting behavior are of great interest for pharmacovigilance (119–121). The COVID-19 pandemic is such a major event that could affect the general reporting behavior.

Dörks *et al.* described the reporting behavior for FAERS before and after the COVID-19 pandemic. They reported that the daily median number of reports for methotrexate

decreased from 28 in the pre-pandemic period to 15 during and after the first wave period, without differences in other characteristics. Opposite to that, the daily median number of reports for (hydroxy)chloroquine increased slightly from one in the pre-pandemic period to three in the time span during and after the first wave. For (hydroxy)chloroquine there were also changes in the demographics of cases and a rise in the fraction of healthcare professional-reported cases. The overall daily median number of reports remained stable among the pre-pandemic and pandemic periods (123).

2. OBJECTIVES

The aims of this study were:

1. To determine whether there is a difference in the frequency of AEs (serious, non-serious or total) from COVID-19 vaccines, that have been approved or emergency use authorized by both the FDA and the EMA, compared to widely issued vaccines unrelated to COVID-19 reported to FAERS or EudraVigilance (EV) from January 2021 to March 2022;

2. To determine whether there is a difference in the frequency of AEs (serious, non-serious or total) from COVID-19 drugs, that have been approved or emergency use authorized by both the FDA and the EMA, compared to a widely prescribed drug unrelated to COVID-19 reported to FAERS or EV during three time periods: pre-pandemic (November 7, 2019 to January 29, 2020), first wave (January 30, 2020 to July 15, 2020), and subsequent waves (July 16, 2020 to March 31, 2022).

Hypotheses:

1. The numbers of AEs (serious or non-serious) from Comirnaty (Pfizer-BioNTech), Spikevax (Moderna), or Jcovden (Janssen) COVID-19 vaccines will be greater compared to tetanus and human papillomavirus (HPV) vaccines, two widely issued vaccines for other unrelated diseases, from January 2021 to March 2022 separately in FAERS and EV.
2. The numbers of reaction groups of AEs from Comirnaty (Pfizer-BioNTech), Spikevax (Moderna), or Jcovden (Janssen) COVID-19 vaccines will be greater compared to tetanus and HPV vaccines from January 2021 to March 2022 separately in FAERS and EV.
3. The numbers of AEs (serious or non-serious) from remdesivir, nirmatrelvir/ritonavir, tocilizumab, tixagevimab/cilgavimab, sotrovimab, or casirivimab/imdevimab will be greater compared to methotrexate in FAERS during three time periods: pre-pandemic (November 7, 2019, to January 29, 2020), first wave (January 30, 2020, to July 15, 2020), and subsequent waves (July 16, 2020, to March 31, 2022).
4. The numbers of reaction groups of AEs from remdesivir, nirmatrelvir/ritonavir, tocilizumab, tixagevimab/cilgavimab, sotrovimab, or casirivimab/imdevimab will be greater compared to methotrexate during three time periods: pre-pandemic (November 7, 2019, to January 29, 2020), first wave (January 30, 2020, to July 15, 2020), and subsequent waves (July 16, 2020, to March 31, 2022) in FAERS.

5. The numbers of AEs (serious or non-serious) from Comirnaty (Pfizer-BioNTech), Spikevax (Moderna), or Jcovden (Janssen) COVID-19 vaccines will be greater in FAERS compared to EV from January 2021 to March 2022.
6. The numbers of reaction groups of AEs from Comirnaty (Pfizer-BioNTech), Spikevax (Moderna), or Jcovden (Janssen) COVID-19 vaccines will be greater in FAERS compared to EV from January 2021 to March 2022.
7. The numbers of AEs (serious or non-serious) from remdesivir, nirmatrelvir/ritonavir, tocilizumab, tixagevimab/cilgavimab, sotrovimab, or casirivimab/imdevimab will be greater in FAERS compared to EV during three time periods: pre-pandemic (November 7, 2019, to January 29, 2020), first wave (January 30, 2020, to July 15, 2020), and subsequent waves (July 16, 2020, to March 31, 2022).
8. The numbers of reaction groups of AEs from remdesivir, nirmatrelvir/ritonavir, tocilizumab, tixagevimab/cilgavimab, sotrovimab, or casirivimab/imdevimab will be greater in FAERS compared to EV during three time periods: pre-pandemic (November 7, 2019, to January 29, 2020), first wave (January 30, 2020, to July 15, 2020), and subsequent waves (July 16, 2020, to March 31, 2022).

3. MATERIALS AND METHODS

3.1. Databases

The FAERS and EudraVigilance (EV) adverse event databases were searched for reports filed by health care professionals and the lay public in the U.S. and EU from November 2019 to March 2022. FAERS is accessible via https://fis.fda.gov/ and EudraVigilance via https://www.adrreports.eu. Both databases offer functions for exporting desired data in the form of listing reports, which were used for the collection of our data.

The number of reports will be shown for the different time spans. The FDA- and EMA-approved vaccines are shown as the total number of reports in the time periods from January 1, 2021, to March 31, 2022. The FDA- and EMA-approved drugs are shown in three periods of the pandemic: pre-pandemic (November 7, 2019, to January 29, 2020), the first wave (January 30, 2020, to July 15, 2020), and subsequent waves (July 16, 2020, to March 31, 2022). The WHO declared the COVID-19 pandemic a public health emergency on January 11, 2020, thus the end of this month was used as the cutoff date between the pre-pandemic and first wave periods.

In FAERS, the abbreviation "(P)" refers to the product names, i.e., the trade names, and the abbreviation "(G)" refers to the generic names of the medical products. In EV, no difference is made regarding search terms, but the search database is generally divided into reaction report sections for products, i.e., trade names, and for substances, i.e., generic names. Preferably, we tried to use generic names for the selected search terms, to reduce incomplete data collection in cases of drugs with multiple trade names.

In both FAERS and EV, all cases are classified regarding their seriousness with "serious" or "non-serious". Also, entries to the database are assigned one or more determined reactions and according to these reactions are classified into reaction groups.

Reaction groups are based on a classification of the adverse event or adverse drug reaction, using the MedDRA dictionary of adverse event terms. For example, "Cardiac Disorders" are defined as a grouping of several related reactions such as "Cardiac Arrest" or "Cyanosis". Reactions correspond to the suspected reaction reported by the reporter. The reaction is based on the MedDRA dictionary preferred term (124). Including one or more of these reported reactions does not necessarily mean that the suspected medicine was the cause of the reported reactions. For any case, there may be one or more reported reaction.

The numbers of individual reactions could be extracted for the COVID-19 vaccines and from the FAERS database only.

When searching for COVID-19 and dissimilar vaccines in FAERS we used the following search terms:

- Comirnaty (Pfizer-BioNTech COVID-19 vaccine): "COMIRNATY (P); PFIZER-BIONTECH COVID-19 VACCINE (P); TOZINAMERAN (G)"
- Spikevax (Moderna COVID-19 vaccine): "ELASOMERAN (G); MODERNA COVID-19 VACCINE (P); SPIKEVAX (P)"
- Jcovden (Janssen COVID-19 vaccine): "AD26.COV2.S (G); JANSSEN COVID-19 VACCINE (P)"
- Tetanus vaccines: "DIPHTHERIA AND TETANUS TOXOIDS (G); DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE ADSORBED (G); TETANUS TOXOID, REDUCED DIPHTHERIA TOXOID AND ACELLULAR PERTUSSIS VACCINE ADSORBED, TDAP (G); TETANUS TOXOID, REDUCED DIPHTHERIA TOXOID AND ACELLULAR PERTUSSIS VACCINE, ADSORBED ANTIGENS (G); TETANUS TOXOIDS (G)"
- HPV-vaccines: "CERVARIX (P); GARDASIL (P); GARDASIL 9 (P)"

When searching for COVID-19 and dissimilar vaccines in EV we used the following search terms:

- Comirnaty (Pfizer-BioNTech COVID-19 vaccine): "TOZINAMERAN"
- Spikevax (Moderna COVID-19 vaccine): "COVID-19 MRNA VACCINE MODERNA (CX-024414)"
- Jcovden (Janssen COVID-19 vaccine): "COVID-19 VACCINE JANSSEN (AD26.COV2.S)"
- Tetanus vaccines: "TETANUS VACCINES"
- HPV-vaccines: "HPV-16,18; HPV-6,11,16,18; HPV-6,11,16,18,31,33,45,52,58"

When searching for COVID-19 and dissimilar drugs in FAERS we used the following search terms:

- Remdesivir (Veklury): "REMDESIVIR (G); VEKLURY (P)"
- Nirmatrelvir/ritonavir (Paxlovid): "NIRMATRELVIR\RITONAVIR (G); PAXLOVID (P)"
- Tocilizumab (Actemra): "ACTEMRA (P); TOCILIZUMAB (G)"
- Tixagevimab/cilgavimab (Evusheld): "CILGAVIMAB/TIXAGEVIMAB (G); EVUSHELD (P)"
- Sotrovimab: "SOTROVIMAB (G)"

- Casirivimab/imdevimab (REGEN-COV): "CASIRIVIMAB/IMDEVIMAB (G); REGEN-COV (P)"
- Methotrexate: "METHOTREXATE (G); METHOTREXATE SODIUM (G); METHOTREXATE\METHOTREXATE SODIUM (G)"

When searching for COVID-19 and dissimilar drugs in EV we used the following search terms:

- Remdesivir (Veklury): "REMDESIVIR"
- Nirmatrelvir/ritonavir (Paxlovid): "PAXLOVID"
- Tocilizumab (RoActemra): "TOCILIZUMAB"
- Tixagevimab/cilgavimab (Evusheld): "EVUSHELD"
- Sotrovimab (Xevudy): "SOTROVIMAB"
- Casirivimab/imdevimab (Ronapreve): "CASIRIVIMAB, IMDEVIMAB"
- Methotrexate: "METHOTREXATE"

Regarding COVID-19 vaccines we excluded Vaxzevria (Oxford-AstraZeneca COVID-19 vaccine) and Nuvaxovid (Novavax COVID-19 vaccine) because at the time of research these vaccines were either not or no longer authorized by both the FDA and EMA.

Regarding COVID-19 drugs we excluded baricitinib, molnupiravir, bebtelovimab, anakinra and regdanvimab because at the time of research these drugs were either not or no longer authorized by both the FDA and EMA.

3.2. Statistical analysis

Continuous variables were described with either the median and interquartile range (IQR), mean and standard deviation (SD) or 95% confidence interval (CI). Continuous variables were described using median and interquartile range (due to non-normal data distribution tested by Kolmogorov–Smirnov test). Frequencies were described with percentages and 95% CI. To assess the difference in the number of adverse events from January 2021 to March 2022 in FAERS and EV separately, we used the Mann-Whitney U test. To assess the difference in the number of adverse events at three time points (November 7, 2019, to January 29, 2020, January 30, 2020, to July 15, 2020, and after July 15, 2020) in FAERS and EV separately, we used either the Related-Samples Wilcoxon Signed Rank Test or the Related-Samples Friedman's Two-Way Analysis of Variance. We used MedCalc Statistical

Software version 17.1 (MedCalc Software bvba, Ostend, Belgium) and IBM SPSS Statistics for Windows, versions 22.0 (IBM Corp., Armonk, NY, USA). We considered a two-sided $P<0.05$ to indicate statistical significance.

4. RESULTS

4.1. COVID-19 vaccines

The numbers of serious, non-serious and total reported AEs of the COVID-19 vaccines in comparison to tetanus and HPV vaccines in the FAERS and EV databases from January 1, 2021, until March 31, 2022, are shown in Table 3 and Table 4, respectively, and the numbers of reported reaction groups of AEs of the COVID-19 vaccines in comparison to tetanus and HPV vaccines in the FAERS and EV databases from January 1, 2021, until March 31, 2022, are shown in Table 5 and Table 6, respectively.

In both the FAERS and EV databases, there was no statistical difference in the number of serious or non-serious AEs from Comirnaty (Pfizer-BioNTech COVID-19 vaccine), Spikevax (Moderna COVID-19 vaccine), or Jcovden (Janssen COVID-19 vaccine) vaccines compared to the tetanus and HPV vaccines (P=0.406 for both comparisons).

Regardless of the COVID-19 vaccine, the median number of serious AEs in the FAERS database was 94 (17-1575) while the median number of serious AEs of 11131 (120-161077) was greater in the EV database, although this comparison did not reach statistical significance (P=0.077). For non-serious AEs, the EV database reported a greater median number (17376 [IQR 209-251219]) compared to the FAERS database (59 [IQR 21-429]).

The most common reactions reported to the FAERS database varied for the respective COVID-19 vaccines. For Comirnaty, the most common were fatigue (15.46%), headache (12.54%), pyrexia (8.31%), pain in extremity (7.55%) and pain (7.35%). For Spikevax, the most common were fatigue (19.15%), pyrexia (14.36%), headache (13.77%), pain (10.97%) and nausea (10.53%). For Jcovden, the most common were fatigue (14.12%), pyrexia (12.55%), malaise (11.37%), headache (10.59%) and nausea (9.80%).

The most common reaction groups reported to the FAERS and EV databases, respectively, were almost indifferent. For Comirnaty, the most common were general disorders and administration site conditions (16.57% and 25%), nervous system disorders (11.22% and 15.95%) and musculoskeletal and connective tissue disorders (7.7% and 11.6%). For Spikevax, the most common were general disorders and administration site conditions (16.41% and 26.6%), nervous system disorders (10.21% and 16.6%) and musculoskeletal and connective tissue disorders (8.1% and 12.39%). For Jcovden, the most common were general disorders and administration site conditions (17.6% and 26.97%) and nervous system disorders (9.79% and 17.86%), while the third most common was injury, poisoning and procedural complications (8.8%) in FAERS and musculoskeletal and connective tissue disorders (17.86%) in EV, respectively.

Table 3. Adverse events of COVID-19 vaccines in comparison to tetanus and HPV vaccines in the FAERS database from January 1, 2021, until March 31, 2022

Vaccines	Serious	Non-serious	Total
Comirnaty (Pfizer-BioNTech COVID-19 vaccine)	3,183	757	3,940
Spikevax (Moderna COVID-19 vaccine)	1,039	319	1,358
Jcovden (Janssen COVID-19 vaccine)	165	90	255
Tetanus vaccines	17	27	44
HPV vaccines	22	2	24

Table 4. Adverse events of COVID-19 vaccines in comparison to tetanus and HPV vaccines in the EudraVigilance database from January 1, 2021, until March 31, 2022

Vaccines	Serious	Non-serious	Total
Comirnaty (Pfizer-BioNTech COVID-19 vaccine)	329,072	526,501	855,573
Spikevax (Moderna COVID-19 vaccine)	105,078	159,458	264,536
Jcovden (Janssen COVID-19 vaccine)	20,955	33,490	54,445
Tetanus vaccines	120	209	329
HPV vaccines	1,308	1,262	2,570

Table 5. Reaction groups of COVID-19 vaccines in comparison to tetanus and HPV vaccines in the FAERS database from January 1, 2021, to March 31, 2022

Vaccines / **Reaction groups**	Comirnaty (Pfizer-BioNTech COVID-19 vaccine)	Spikevax (Moderna COVID-19 vaccine)	Jcovden (Janssen COVID-19 vaccine)	Tetanus vaccines	HPV vaccines
Blood and Lymphatic System Disorders	290	105	17	0	2
Cardiac Disorders	553	154	9	1	6
Congenital, Familial and Genetic Disorders	42	11	2	2	0
Ear and Labyrinth Disorders	145	32	10	1	2
Endocrine Disorders	51	20	6	0	1
Eye Disorders	245	112	21	2	1
Gastrointestinal Disorders	858	371	56	6	12
General Disorders and Administration Site Conditions	2080	842	142	8	16
Hepatobiliary Disorders	155	44	7	1	1
Immune System Disorders	247	98	12	5	5
Infections and Infestations	799	313	50	6	5
Injury, Poisoning and Procedural Complications	726	414	71	29	9
Investigations	715	310	46	1	5
Metabolism and Nutrition Disorders	215	98	19	1	5
Musculoskeletal and Connective Tissue Disorders	966	416	65	5	7
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	110	58	3	0	3
Nervous System Disorders	1408	524	79	4	12
Pregnancy, Puerperium and Perinatal Conditions	39	2	0	8	0
Product Issues	38	39	4	3	1
Psychiatric Disorders	414	183	21	1	10
Renal and Urinary Disorders	191	80	20	0	5
Reproductive System and Breast Disorders	123	36	6	0	10
Respiratory, Thoracic and Mediastinal Disorders	792	257	50	4	5
Skin and Subcutaneous Tissue Disorders	656	326	45	3	4
Social Circumstances	53	26	3	1	0
Surgical and Medical Procedures	187	121	13	0	0
Vascular Disorders	452	138	30	1	4
Total	**12550**	**5130**	**807**	**93**	**131**

Table 6. Reaction groups of COVID-19 vaccines in comparison to tetanus and HPV vaccines in the EudraVigilance database from January 1, 2021, to March 31, 2022

Vaccines / **Reaction groups**	Comirnaty (Pfizer-BioNTech COVID-19 vaccine)	Spikevax (Moderna COVID-19 vaccine)	Jcovden (Janssen COVID-19 vaccine)	Tetanus vaccines	HPV vaccines
Blood and Lymphatic System Disorders	59813	17016	1387	16	122
Cardiac Disorders	67747	21846	2933	15	126
Congenital, Familial and Genetic Disorders	594	207	49	0	13
Ear and Labyrinth Disorders	25659	7470	1505	10	80
Endocrine Disorders	2372	623	119	2	33
Eye Disorders	29121	8652	1846	9	112
Gastrointestinal Disorders	147269	51911	10042	53	505
General Disorders and Administration Site Conditions	491882	172078	37569	180	1141
Hepatobiliary Disorders	2142	868	171	0	25
Immune System Disorders	21510	7204	637	29	159
Infections and Infestations	102869	27790	10227	20	227
Injury, Poisoning and Procedural Complications	37608	10366	1283	26	288
Investigations	47746	14227	6688	14	216
Metabolism and Nutrition Disorders	12642	5322	863	11	64
Musculoskeletal and Connective Tissue Disorders	228289	80139	18070	94	439
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	2008	753	106	2	75
Nervous System Disorders	313942	107353	24883	110	1054
Pregnancy, Puerperium and Perinatal Conditions	2884	984	76	2	20
Product Issues	264	110	32	1	69
Psychiatric Disorders	34720	10642	1994	27	182
Renal and Urinary Disorders	7069	3434	593	4	46
Reproductive System and Breast Disorders	84800	17086	3577	2	180
Respiratory, Thoracic and Mediastinal Disorders	82020	26578	4952	28	144
Skin and Subcutaneous Tissue Disorders	88420	33072	4220	57	358
Social Circumstances	4546	2445	447	4	13
Surgical and Medical Procedures	23028	4967	1043	3	59
Vascular Disorders	47066	13708	3982	8	143
Total	**1968030**	**646851**	**139294**	**727**	**5893**

4.2. COVID-19 drugs

The numbers of serious, non-serious and total reported AEs of the COVID-19 vaccines in comparison to methotrexate according to the time spans pre-pandemic (November 7, 2019, to January 29, 2020), first wave (January 30, 2020, to July 15, 2020), and subsequent waves (July 16, 2020, to March 31, 2022) in the FAERS and EV databases are shown in Table 7 and Table 8, respectively.

For all COVID-19 drugs in the FAERS database, there was a median 0 (0-952) AEs (both serious and non-serious AEs combined), while in the EV database there was a median 278 (0-2551) both serious and non-serious AEs, with no statistical difference between the AEs in the databases (*P*=0.111). By drug, tocilizumab had a greater median number of serious and non-serious AEs (5223 [1136-12379]) than remdesivir (972 [0-3139]), casirivimab/imdevimab (0 [0-1277]), sotrovimab (0 [0-739]), nirmatrelvir/ritonavir (0 [0-382]), and tixagevimab/cilgavimab (0 [0-110]); *P*=0.008.

There were more serious AEs recorded for methotrexate (median 14601 [IQR 8899-26493]) compared to the COVID-19 drugs (*P*=0.047) in the FAERS database, while there was no statistically significant difference in the median number of non-serious AEs (2242 [IQR 1498-3198]) for methotrexate compared to the COVID-19 drugs (*P*=0.181). There were more serious and non-serious AEs in the EV database for methotrexate (median 5370 [IQR 3868-12883]); *P*=0.026 and median 754 [IQR 672-1649]; *P*=0.043, respectively).

As shown in Table 9, there was a median of 1755 (IQR 297-7980) serious and 1191 (IQR 370-1821) non-serious AEs for COVID-19 drugs in the FAERS database (*P*=0.018 and *P*=0.002, respectively) in the subsequent waves of COVID-19 than in the pre-pandemic and first wave. Similarly, there was a median of 234 (IQR 145-3576) serious and 97 (IQR 45-476) non-serious AEs for COVID-19 drugs in the EV database (both *P*=0.002) respectively) in the subsequent waves of COVID-19 than in the pre-pandemic and first wave (Table 10).

Table 7. Adverse events of COVID-19 drugs in comparison to methotrexate in the FAERS database according to the time periods of the COVID-19 pandemic from November 7, 2019, until March 31, 2022

Drugs	Pre-pandemic*			First wave†			Subsequent waves‡		
	Serious	Non-serious	Total	Serious	Non-serious	Total	Serious	Non-serious	Total
Remdesivir (Veklury)	-	-	-	1299	341	1640	4452	1350	5802
Nirmatrelvir/ritonavir (Paxlovid)	-	-	-	-	-	-	322	465	787
Tocilizumab (Actemra)	1180	48	1228	6683	1320	8003	18565	2583	21148
Tixagevimab/cilgavimab (Evusheld)	-	-	-	-	-	-	222	84	306
Sotrovimab	-	-	-	-	-	-	640	1567	2207
Casirivimab/imdevimab (REGEN-COV)§	-	-	-	-	-	-	2869	1032	3901
Methotrexate	3197	754	3951	14601	2242	16843	38385	4154	42539

* November 7, 2019 – January 29, 2020
† January 30, 2020 – July 15, 2020
‡ July 16, 2020 – March 31, 2022
§ Cut-off date for subsequent waves on January 24, 2022, due to revision by the FDA

Table 8. Adverse events of COVID-19 drugs in comparison to methotrexate in the EudraVigilance database according to the time periods of the COVID-19 pandemic from November 7, 2019, until March 31, 2022

Drugs	Pre-pandemic*			First wave†			Subsequent waves‡		
	Serious	Non-serious	Total	Serious	Non-serious	Total	Serious	Non-serious	Total
Remdesivir (Veklury)	-	-	-	294	9	303	1856	395	2251
Nirmatrelvir/ritonavir (Paxlovid)	-	-	-	-	-	-	180	67	247
Tocilizumab (RoActemra)	743	117	860	2173	275	2448	8737	719	9456
Tixagevimab/cilgavimab (Evusheld)	-	-	-	-	-	-	40	5	45
Sotrovimab (Xevudy)	-	-	-	-	-	-	192	58	250
Casirivimab/imdevimab (Ronapreve)§	-	-	-	-	-	-	276	126	402
Methotrexate	2366	590	2956	5370	754	6124	20396	2543	22939

* November 7, 2019 – January 29, 2020
† January 30, 2020 – July 15, 2020
‡ July 16, 2020 – March 31, 2022
§ Cut-off date for subsequent waves on January 24, 2022, due to revision by the FDA

Table 9. Adverse events of COVID-19 drugs in the FAERS database according to the time periods of the COVID-19 pandemic

Drugs	Serious			Non-serious		
	Pre-pandemic*	First wave†	Subsequent waves‡	Pre-pandemic*	First wave†	Subsequent waves‡
	Median (IQR)					
Remdesivir (Veklury)	0 (0-295)	0 (0-2645)	1755 (297-7980)	0 (0-12)	0 (0-586)	1191 (370-1821)
Nirmatrelvir/ritonavir (Paxlovid)						
Tocilizumab (Actemra)						
Tixagevimab/cilgavimab (Evusheld)						
Sotrovimab						
Casirivimab/imdevimab (REGEN-COV)						
P-value	0.018			0.002		

* November 7, 2019 – January 29, 2020
† January 30, 2020 – July 15, 2020
‡ July 16, 2020 – March 31, 2022

Table 10. Adverse events of COVID-19 drugs in the EudraVigilance database according to the time spans of the COVID-19 pandemic

Drugs	Serious			Non-serious		
	Pre-pandemic*	First wave†	Subsequent waves‡	Pre-pandemic*	First wave†	Subsequent waves‡
	Median (IQR)					
Remdesivir (Veklury)	0 (0-186)	0 (0-764)	234 (145-3576)	0 (0-29)	0 (0-76)	97 (45-476)
Nirmatrelvir/ritonavir (Paxlovid)						
Tocilizumab (RoActemra)						
Tixagevimab/cilgavimab (Evusheld)						
Sotrovimab (Xevudy)						
Casirivimab/imdevimab (Ronapreve)						
P-value	0.002			0.002		

* November 7, 2019 – January 29, 2020
† January 30, 2020 – July 15, 2020
‡ July 16, 2020 – March 31, 2022

Table 11. Reported reaction groups of COVID-19 drugs in comparison to methotrexate in the FAERS database from January 1, 2021, to March 31, 2022

Drugs / **Reaction groups**	Remdesivir (Veklury)	Nirmatrelvir/ritonavir (Paxlovid)*	Tocilizumab (Actemra)	Tixagevimab/cilgavimab (Evusheld)*	Sotrovimab	Casirivimab/imdevimab (REGEN-COV)†	Methotrexate
Blood and Lymphatic System Disorders	99	11	812	11	24	62	4380
Cardiac Disorders	450	20	2936	43	95	345	3606
Congenital, Familial and Genetic Disorders	3	0	37	0	1	3	287
Ear and Labyrinth Disorders	5	12	685	6	10	30	784
Endocrine Disorders	4	0	291	1	0	4	455
Eye Disorders	13	16	1006	15	20	107	1482
Gastrointestinal Disorders	150	289	7246	42	204	768	11949
General Disorders and Administration Site Conditions	803	260	12744	110	493	1582	21380
Hepatobiliary Disorders	245	6	1210	2	17	7	2702
Immune System Disorders	57	17	4533	12	67	229	6860
Infections and Infestations	529	54	7515	31	139	370	11342
Injury, Poisoning and Procedural Complications	747	182	11093	82	1291	1553	12652
Investigations	575	122	6797	39	243	933	10144
Metabolism and Nutrition Disorders	88	49	1851	4	50	145	2811
Musculoskeletal and Connective Tissue Disorders	47	73	9424	29	94	378	14500
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	4	1	1100	3	2	5	3329
Nervous System Disorders	160	322	3795	74	247	1058	6676
Pregnancy, Puerperium and Perinatal Conditions	80	0	368	0	11	21	409
Product Issues	30	40	306	7	10	24	166
Psychiatric Disorders	50	59	2827	11	55	244	4234
Renal and Urinary Disorders	226	29	879	7	21	74	2091
Reproductive System and Breast Disorders	3	5	167	0	2	11	441
Respiratory, Thoracic and Mediastinal Disorders	352	96	4287	49	235	1320	6619
Skin and Subcutaneous Tissue Disorders	119	63	6603	42	196	762	9516
Social Circumstances	5	2	1221	1	2	23	1655
Surgical and Medical Procedures	86	9	1117	5	56	92	1440
Vascular Disorders	147	40	2115	28	118	630	3224
Total	**5077**	**1777**	**92965**	**654**	**3703**	**10780**	**145134**

* No entries before January 1, 2022

† Revision by the FDA on January 24, 2022

Table 12. Reported reaction groups of COVID-19 drugs in comparison to methotrexate in the EudraVigilance database from January 1, 2021, to March 31, 2022

Drugs / **Reaction groups**	Remdesivir (Veklury)	Nirmatrelvir/ritonavir (Paxlovid)*	Tocilizumab (Actemra)	Tixagevimab/cilgavimab (Evusheld)*	Sotrovimab (Xevudy)	Casirivimab/imdevimab (Ronapreve)	Methotrexate
Blood and Lymphatic System Disorders	32	8	345	1	6	9	2238
Cardiac Disorders	236	5	1049	6	38	65	1432
Congenital, Familial and Genetic Disorders	3	0	16	0	1	0	118
Ear and Labyrinth Disorders	4	1	301	2	2	7	398
Endocrine Disorders	2	0	95	0	0	0	160
Eye Disorders	8	12	250	1	3	4	552
Gastrointestinal Disorders	72	124	3058	7	49	77	5787
General Disorders and Administration Site Conditions	260	73	4914	19	101	226	9664
Hepatobiliary Disorders	162	2	378	0	11	4	1366
Immune System Disorders	33	8	2057	5	23	33	2705
Infections and Infestations	187	25	2802	6	40	56	4349
Injury, Poisoning and Procedural Complications	129	26	3759	1	48	44	5576
Investigations	279	55	2831	5	49	100	4660
Metabolism and Nutrition Disorders	26	21	666	0	14	9	1057
Musculoskeletal and Connective Tissue Disorders	11	17	3950	3	18	12	6366
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	2	0	391	1	1	8	1417
Nervous System Disorders	61	113	1389	11	47	70	2690
Pregnancy, Puerperium and Perinatal Conditions	28	0	116	0	3	1	126
Product Issues	16	5	42	0	0	0	157
Psychiatric Disorders	23	18	1320	1	10	6	1917
Renal and Urinary Disorders	96	4	237	2	8	11	821
Reproductive System and Breast Disorders	1	4	49	0	0	2	159
Respiratory, Thoracic and Mediastinal Disorders	153	38	1725	7	62	150	2886
Skin and Subcutaneous Tissue Disorders	83	26	2941	4	41	80	4362
Social Circumstances	1	1	450	0	0	0	691
Surgical and Medical Procedures	15	0	354	0	10	3	534
Vascular Disorders	59	28	668	7	29	52	1202
Total	**1982**	**614**	**36153**	**89**	**614**	**1029**	**63390**

* No entries before January 1, 2022

5. DISCUSSION

5.1. COVID-19 vaccines

The numbers of reported AEs (serious, non-serious and total) of Comirnaty (Pfizer-BioNTech), Spikevax (Moderna), or Jcovden (Janssen) COVID-19 vaccines are greater compared to tetanus and HPV vaccines in both the FAERS and EV databases from January 2021 to March 2022, which may indicate a rise in safety issues and concomitant AEs or a change in reporting behavior or both. Additionally, the numbers of reported reaction groups of AEs of all three COVID-19 vaccines are in total greater in contrast to tetanus and HPV vaccines in both the FAERS and EV databases from January 2021 to March 2022. Also, most individual reaction groups of the COVID-19 vaccines exceed the equivalent ones of the control vaccines greatly.

The numbers of reported AEs (serious, non-serious and total) from all three COVID-19 vaccines are lower in the FAERS database in comparison to the EV database from January 2021 to March 2022, which indicates that AE reporting of COVID-19 vaccines is higher in the EU than in the U.S. In addition, the numbers of reported reaction groups of AEs from all three COVID-19 vaccines are almost always lower in the FAERS database compared to the EV database from January 2021 to March 2022.

The most common reported reaction group of the COVID-19 vaccines was general disorders and administration site conditions, which includes among others fatigue, pyrexia, malaise, and pain. These were mostly also the common reported reactions reported. These are common and usually mild and uncomplicated adverse events following vaccinations (125). As widely reported, the benefits of COVID-19 vaccines outweigh the potential safety risks.

5.2. COVID-19 drugs

The numbers of reported AEs (serious, non-serious and total) of remdesivir, nirmatrelvir/ritonavir, tocilizumab, tixagevimab/cilgavimab, sotrovimab, or casirivimab/imdevimab compared to methotrexate are lower in both the FAERS database and the EV database during all time spans. Also, the numbers of reported reaction groups of AEs of the COVID-19 drugs in contrast to methotrexate are lower in both the FAERS database and the EV database during all time periods. These results may indicate that the safety profile of the COVID-19 drugs is sufficient, that the overall use of these drugs is rather low or at least lower than methotrexate, or that reporting behavior is insufficient.

The numbers of reported AEs of the COVID-19 drugs are greater in the FAERS database in comparison to the EV database during all time spans. Also, the numbers of reported

reaction groups of AEs of the COVID-19 drugs are greater in FAERS than in EudraVigilance during all time periods.

5.3. Limitations

There are several limitations that should be noted. The COVID-19 drugs were developed, released, and authorized at different times during the periods of data collection. Some of the COVID-19 were previously used for different indications and repurposed for the treatment of COVID-19. These circumstances cause that during the pre-pandemic period only tocilizumab and methotrexate had available data, while during the first wave period additionally data of remdesivir was available, and finally, during the subsequent waves period data from all listed COVID-19 drugs became available. Although data for all COVID-19 drugs was reported during the subsequent waves period, the investigated drugs did not become available at the exact same points in time, which may cause distortion.

Another limitation is the inequivalent duration of the time spans, with the subsequent waves period being the longest (20.5 months) in contrast to the pre-pandemic period (2.67 months) and first wave period (5.5 months).

Methotrexate, which has been used as control drug, is as an antifolate a very potent drug mainly used for the treatment of rheumatoid arthritis and a range of adult and childhood cancers. The toxicity and the resulting AEs for both high-dose and low-dose methotrexate are due to it pharmacological properties enormous (126,127). Due to its toxic nature, it may be that AEs are generally, significantly higher for methotrexate than for COVID-19 drugs, which mainly belong to the groups of antivirals or biologicals.

The AEs of the COVID-19 vaccines reported to FAERS may also be significantly lower than the ones reported to EV due to the existence of a second adverse event reporting system in the U.S., the Vaccine Adverse Event Reporting System (VAERS), which is a reporting system and database specifically for vaccine AEs run by the CDC (128) but it is less transparent to the public and was not part of our research, thus, it would need further investigation.

6. CONCLUSIONS

Adverse event reporting systems embody a low-cost data source that allows the early identification of safety concerns of medical products, including long-term and newly authorized products, and thus are important and beneficial tools for pharmacovigilance.

Reporting of AEs from COVID-19 vaccines compared to the control vaccines has been significantly high for the investigated period, while reporting of AEs from COVID-19 drugs in contrast to the control drug has been low. Reporting of AEs from COVID-19 vaccines has been higher in the EV database than in the FAERS database for the investigated period. In contrast, reporting of AEs from COVID-19 drugs has been higher in the FAERS database than in the EV database for the investigated period.

Generally, reporting of AEs has not relevantly changed during the COVID-19 pandemic, although the introduction of COVID-19 vaccines and mass-vaccinations worldwide likely led to stimulated reporting of vaccine AEs, while general under-reporting likely still prevails. Our results may indicate a deficit in the U.S. reporting behavior of AEs following vaccine administration, but this requires further investigation.

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8. SUMMARY

Objectives: The aims of this study were to determine whether there are differences in the frequency of adverse events (AEs) from COVID-19 vaccines compared to widely issued vaccines and from COVID-19 drugs in contrast to a widely prescribed drug reported to the FDA Adverse Event Reporting System (FAERS) or EudraVigilance (EV) during the COVID-19 pandemic.

Materials and methods: The FAERS and EV adverse event databases were searched for adverse event reports filed in the U.S. and EU from November 2019 to March 2022. We included all COVID-19 vaccines and drugs which have been approved or emergency use authorized by both the FDA and EMA as of March 31, 2022. The numbers of AEs (serious or non-serious) and the numbers of reaction groups of AEs from Comirnaty (Pfizer-BioNTech), Spikevax (Moderna), or Jcovden (Janssen) COVID-19 vaccines were compared to tetanus and human papillomavirus (HPV) vaccines from January 2021 to March 2022 separately in FAERS and EV. The numbers of AEs (serious or non-serious) and the numbers of reaction groups of AEs from remdesivir, nirmatrelvir/ritonavir, tocilizumab, tixagevimab/cilgavimab, sotrovimab, or casirivimab/imdevimab were compared to methotrexate during three time periods: pre-pandemic (November 7, 2019, to January 29, 2020), first wave (January 30, 2020, to July 15, 2020), and subsequent waves (July 16, 2020, to March 31, 2022).

Results: In both the FAERS and EV databases, there was no statistical difference in the number of serious or non-serious AEs from the COVID-19 vaccines compared to the tetanus and HPV vaccines (*P*=0.406 for both comparisons), although numbers of reported AEs from COVID-19 vaccines are higher in both databases. The median number of serious AEs from COVID-19 vaccines was greater in the FAERS database than in the EV database (94 ([IQR 17-1575]) vs. 11131 ([IQR 120-161077]) although this comparison did not reach statistical significance (*P*=0.077). For non-serious AEs from COVID-19 vaccines, the EV database reported a greater median number (17376 [IQR 209-251219]) compared to the FAERS database (59 [IQR 21-429]). There were more serious AEs recorded for methotrexate (median 14601 [IQR 8899-26493]) compared to the COVID-19 drugs (*P*=0.047) in the FAERS database, while in the EV database there were more both serious and non-serious AEs for methotrexate (median 5370 [IQR 3868-12883]); *P*=0.026 and median 754 [IQR 672-1649]; *P*=0.043, respectively). There was a median of 1755 (IQR 297-7980) serious and 1191 (IQR 370-1821) non-serious AEs from COVID-19 drugs in the FAERS database (*P*=0.018 and *P*=0.002, respectively) in the subsequent waves of COVID-19 than in the pre-pandemic and first wave. Similarly, there was

a median of 234 (IQR 145-3576) serious and 97 (IQR 45-476) non-serious AEs for COVID-19 drugs in the EV database (both P=0.002) respectively) in the subsequent waves of COVID-19 than in the pre-pandemic and first wave.

Conclusions: Adverse event reporting systems are important and beneficial tools for pharmacovigilance. Reporting of AEs from COVID-19 vaccines has been significantly high, which may indicate a rise in safety issues and concomitant AEs or a change in reporting behavior or both, while reporting of AEs from COVID-19 drugs has been low, which may indicate that the safety profile of the COVID-19 drugs is sufficient, that the overall use of these drugs is rather low or at least lower than methotrexate, or that reporting behavior is insufficient. Among the two databases, reporting of AEs from COVID-19 vaccines has been higher in the EV database than in the FAERS database, and, in contrast, reporting of AEs of COVID-19 drugs has been higher in the FAERS database than in the EV database for the investigated period. Generally, reporting of AEs has not relevantly changed during the COVID-19 pandemic, although the introduction of COVID-19 vaccines and mass-vaccinations worldwide likely led to stimulated reporting of vaccine AEs, while general under-reporting likely still prevails. Our results may indicate a deficit in the U.S. reporting behavior of AEs following vaccine administration, but this requires further investigation.

9. CROATIAN SUMMARY

Naslov: Prijava nuspojava cjepiva i lijekova protiv COVID-19 iz Food and Drug Administration Adverse Event Reporting System i EudraVigilance tijekom pandemije COVID-19

Ciljevi: Ciljevi ove studije bili su utvrditi postoje li razlike u učestalosti nuspojava od cjepiva protiv COVID-19 u usporedbi na obično korištena cjepiva i od lijekova za COVID-19 u usporedbi na obično propisani lijek koji je prijavljen FDA Adverse Event Reporting System (FAERS) ili EudraVigilance (EV) tijekom pandemije COVID-19.

Materijali i metode: U bazama podataka o štetnim događajima FAERS i EV pretražene su prijave štetnih događaja podnesenih u SAD-u i EU od studenog 2019. do ožujka 2022. Uključili smo sva cjepiva protiv COVID-19 i lijekove koje su FDA i EMA odobrili ili odobrili za hitne slučajeve od 31. ožujka 2022. Broj nuspojava (ozbiljnih ili neozbiljnih) i brojevi reakcijskih skupina nuspojava iz Comirnaty (Pfizer-BioNTech), Spikevax (Moderna) ili Jcovden (Janssen) cjepiva protiv COVID-19 uspoređeni su s cjepivima protiv tetanusa i humanog papiloma virusa (HPV) od siječnja 2021. do ožujka 2022. zasebno u FAERS-u i EV. Broj nuspojava (ozbiljnih ili neozbiljnih) i broj reakcijskih skupina nuspojava remdesivira, nirmatrelvira/ritonavira, tocilizumaba, tixagevimaba/cilgavimaba, sotrovimaba ili casirivimaba/imdevimaba uspoređen je s metotreksatom tijekom tri vremenska razdoblja: prije pandemije (7. studenog 2019. do 29. siječnja 2020.), prvi val (30. siječnja 2020. do 15. srpnja 2020.) i sljedeći valovi (16. srpnja 2020. do 31. ožujka 2022.).

Rezultati: U bazama podataka FAERS i EV, nije bilo statističke razlike u broju ozbiljnih ili neozbiljnih nuspojava od cjepiva protiv COVID-19 u usporedbi s cjepivima protiv tetanusa i HPV-a (*P*=0,406 za obje usporedbe), iako je broj prijavljenih nuspojava od cjepiva protiv COVID-19 viši u obje baze podataka. Medijan broja ozbiljnih nuspojava od cjepiva protiv COVID-19 bio je veći u bazi podataka FAERS nego u bazi podataka EV (94 ([IQR 17-1575]) naspram 11131 ([IQR 120-161077]) iako ova usporedba nije dosegla statističku značajnost (*P*=0,077). Za neozbiljne nuspojave od cjepiva protiv COVID-19, baza podataka EV prijavila je veći srednji broj (17376 [IQR 209-251219]) u usporedbi s bazom podataka FAERS (59 [IQR 21-429]). Bilo je više ozbiljnih nuspojava zabilježenih za metotreksat (medijan 14601 [IQR 8899-26493]) u usporedbi s lijekovima protiv COVID-19 (*P*=0,047) u bazi podataka FAERS, dok je u bazi podataka EV bilo više i ozbiljnih i neozbiljnih nuspojava za metotreksat (medijan 5370 [IQR 3868-12883]); *P*=0,026 i medijan 754 [IQR 672-1649]; *P*=0,043, redom). Postojao

je medijan od 1755 (IQR 297-7980) ozbiljnih i 1191 (IQR 370-1821) neozbiljnih nuspojava uzrokovanih lijekovima protiv COVID-19 u bazi podataka FAERS (*P*=0,018 odnosno *P*=0,002) u narednim COVID-19 valovima nego u razdoblju prije pandemije i prvom valu. Slično tome, postojao je medijan od 234 (IQR 145-3576) ozbiljnih i 97 (IQR 45-476) neozbiljnih nuspojava za lijekove protiv COVID-19 u EV bazi podataka (oba *P*=0,002) u narednim COVID-19 valovima nego u razdoblju prije pandemije i prvom valu.

Zaključci: Sustavi za prijavu nuspojava važni su i korisni alati za farmakovigilanciju. Prijavljivanje nuspojava od cjepiva protiv COVID-19 bilo je značajno visoko, što može ukazivati na porast sigurnosnih problema i pratećih nuspojava ili promjenu ponašanja pri prijavljivanju ili oboje, dok je prijavljivanje nuspojava od lijekova protiv COVID-19 bilo nisko, što može ukazivati na to da sigurnosni profil lijekova za COVID-19 je dovoljan, da je ukupna upotreba ovih lijekova prilično niska ili barem niža od metotreksata, ili da je ponašanje prijavljivanja nedovoljno. Među dvjema bazama podataka, prijava nuspojava od cjepiva protiv COVID-19 bila je veća u bazi podataka EV nego u bazi podataka FAERS, a, nasuprot tome, prijava nuspojava lijekova protiv COVID-19 bila je veća u bazi podataka FAERS nego u bazi podataka EV za istraživano razdoblje. Općenito, prijavljivanje štetnih događaja nije se značajno promijenilo tijekom pandemije COVID-19, iako je uvođenje cjepiva protiv COVID-19 i masovnih cijepljenja u cijelom svijetu vjerojatno dovelo do poticanog prijavljivanja štetnih događaja cjepiva, dok općenito nedovoljno prijavljivanje vjerojatno i dalje prevladava. Naši rezultati mogu ukazivati na deficit u izvještavanju o ponašanju štetnih događaja nakon primjene cjepiva u SAD-u, ali to zahtijeva daljnje istraživanje.