

## ORIGINAL RESEARCH

# Safety and Adverse Events Related to COVID-19 mRNA Vaccines; a Systematic Review

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**Abstract:** **Introduction:** Knowledge of vaccine-related adverse events is crucial as they are among the most important factors that cause hesitation in receiving vaccines. Therefore, we aimed to systematically review the adverse events related to the mRNA vaccines reported in the literature. **Methods:** A systematic literature search was carried out in the databases of Scopus, PubMed, Cochrane, and Web of Science. We selected original studies that explored the side effects of mRNA COVID-19 vaccines using a two-phase (title/abstract and full-text) screening process. **Results:** Cardiac complications were the most commonly reported severe adverse events. It appeared that systemic adverse reactions are more common after the second dose of vaccines. The number of adverse effects reported after the Pfizer vaccine was higher than other vaccines, mostly due to its earlier approval and more widespread use throughout the world. Cardiac adverse events had a higher prevalence but no significant association has been found between COVID-19 mRNA vaccines and cardiac adverse events except for myopericarditis. **Conclusion:** Vaccines play a crucial role in controlling the COVID-19 pandemic and decreasing mortalities and the results of the present review acknowledge the fact that the benefits outweigh the adverse events of these vaccines.

**Keywords:** Adverse effects; COVID-19 vaccines; 2019-nCoV Vaccine mRNA-1273; mRNA vaccines; BNT162 Vaccine

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## 1. Introduction

The COVID-19 pandemic is a global health crisis that demands enormous measures in order to be controlled. Mass vaccination of the population is critical for containing it; thus, countries all over the world are attempting to vaccinate their people against this disease (1-4). Vaccines operate by stimulating the body's natural immunological response. Immediately after the genetic sequence of the novel coronavirus



was uncovered, vaccine manufacturers all around the world jumped into action to develop a vaccine (5). Currently available SARS-CoV-2 vaccines are produced using one of the following technologies: mRNA-based vaccines, whole virus or inactivated virus vaccines, protein subunit vaccines, and viral vector-based vaccines (6).

Pfizer-BioNTech BNT162b2 and Moderna mRNA1273 are the first and only mRNA-based vaccines approved by the World Health Organization so far and have been used in several countries. These vaccines encode a stable full-length SARS-CoV-2 spike ectodomain, derived from the Wuhan-Hu-1 genetic sequence (7, 8). They are a novel-nucleic acid type of vaccine that employs genomic information such as messenger RNA (mRNA), a method that introduces a portion of the genetic code into human cells (9, 10). Furthermore, the high level of reactogenicity of the SARS-CoV-2 mRNA vaccines is one of their distinguishing features, provoking both local and systemic reactions observed by the majority of patients in Phase 1-3 trials. Additionally, the levels of systemic reactogenicity associated with SARS-CoV-2 mRNA vaccines have generated concerns about a more serious adverse event profile in patients with underlying immunological dysregulation as these patients, who often consume immunosuppressive and biologic medications for immune-mediated inflammatory illnesses such as inflammatory bowel disease (IBD), were mostly exempted from the vaccine trials. Activation of the innate immune system through pattern-recognition receptor ligation, followed by the production of inflammatory cytokines such as tumor necrosis factor, interleukin-6, and interleukin-1 is often responsible for the vaccine's reactogenicity (11, 12).

Adverse drug reactions (ADRs) and medication-related incidents could be fatal, likewise, the side effect of vaccines could be catastrophic. If clinical trials are not powered enough to detect the very rare events, these rare but important adverse events may go undetected. Due to variances in age, race, and underlying conditions, the reported rates of adverse effects have been inconsistent across different studies. Even though their safety has been established, concerns of immune-mediated disease flare-ups or new-onset inflammatory diseases following their administration have recently emerged (13-16). The Vaccine Adverse Event Reporting System (VAERS), co-developed and maintained by the Centers for Disease Control and Prevention (CDC) and the United States Food and Drug Administration (FDA), serves as a national passive surveillance system for continuous monitoring of vaccine safety once it has been distributed in the market (17). The data from VAERS show that the most commonly reported side effects are injection site pain, fever, headache, neck pain, nausea, vomiting, drowsiness, diarrhea, dizziness, enlarged lymph nodes, decreased alcohol tolerance, dyspnea, cough, stuffy nose, fainting, thirst, excessive sweating,

sore throat, loss of appetite, insomnia, irritability, stupor, photosensitivity, eye pain, numbness in the extremities, and malaise (18-20).

Vaccine safety is important to the success of any vaccination effort, particularly during a pandemic. Hence, with the increase in vaccination rates, it is crucial to monitor their adverse events post-vaccination. Raising awareness of associated adverse events (AEs) is crucial for reducing vaccine hesitancy as well as improving the safety of vaccines if necessary (21). Therefore, in this study, we aimed to systematically review the adverse events related to the mRNA vaccines reported in the literature. The findings could present and enhance scientific literacy across the many stakeholders and provide concise and evidence-based solutions to the COVID-19 vaccine safety concerns.

## 2. Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of relevant records was carried out in the online databases using selected keywords on September 15th, 2021.

### 2.1. Data sources

We carried out a systematic search using the keywords and search queries in online databases including Scopus, PubMed, Cochrane, and Web of Science.

### 2.2. Search strategy

Search strategies were constructed by two authors of the research team. Search terms were connected in a highly-sensitive syntax via the Boolean operator OR. The search strategy that was used to retrieve the records in each online database is as follows:

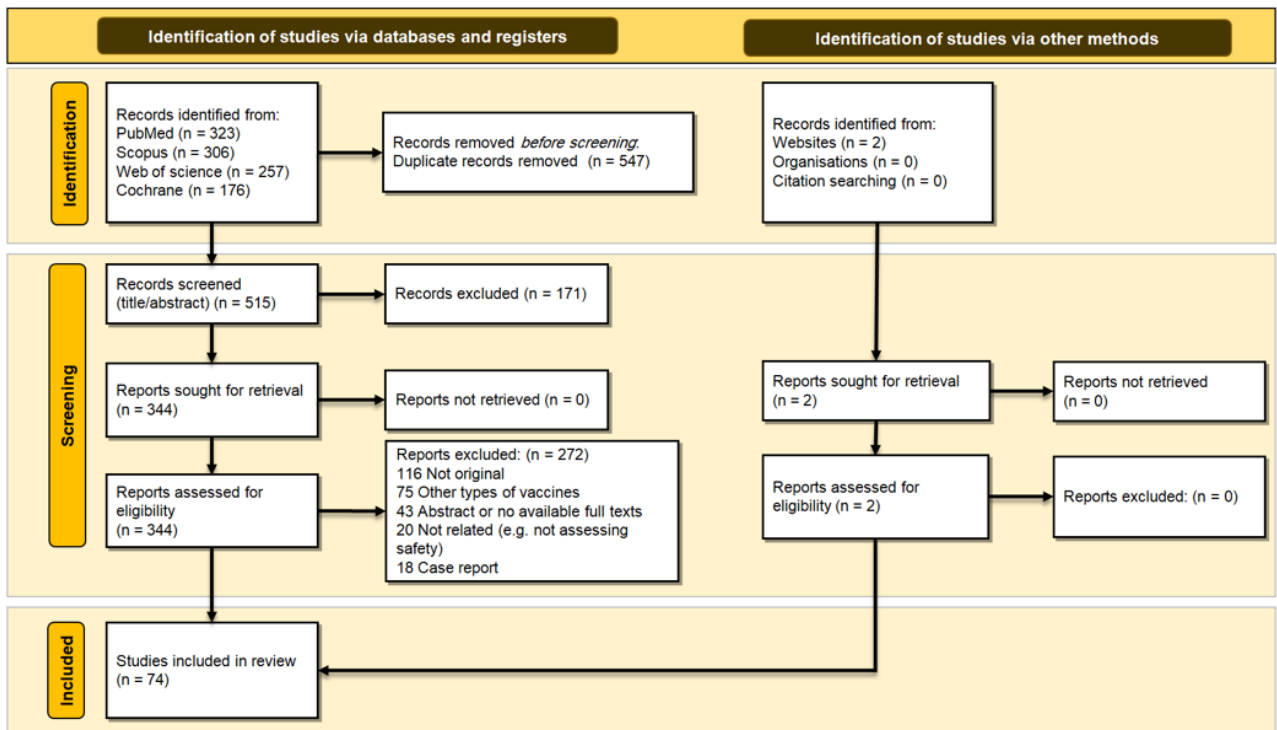
```
((((((COVID-19[Title]) OR (SARS-CoV-2[Title])) OR (SARS-CoV2[Title])) OR (2019-nCoV[Title])) OR (Novel Coronavirus[Title])) AND (((Vaccine*[Title]) OR (Vaccination[Title]) OR (Vaccinated[Title])) OR (Immunization[Title])) AND (((Safety[Title]) OR (Side effect*[Title])) OR (Adverse event*[Title])) OR (Adverse effect*[Title])) OR (Adverse reaction*[Title]))
```

### 2.3. Eligibility criteria

Original English articles that reported the adverse events of mRNA COVID-19 vaccine were included, applying the following exclusion criteria:

- 1) Abstracts/conference abstracts or unavailability of full texts
- 2) Ongoing clinical trials with unpublished results
- 3) Non-original studies, including review articles, meta-analyses, protocols, and editorials





**Figure 1:** PRISMA flow diagram of the systematic review.

- 4) Studies on other types of vaccines rather than mRNA vaccines, or those only reporting efficacy of mRNA vaccines without reporting their adverse events
- 5) Protocols of randomized clinical trials (RCTs) and other original studies

**2.4. Selection of studies and Data Screening**

The EndNote X9 software was used to organize the retrieved articles. Search results from different databases were combined in a single EndNote library and duplicates were removed. Two authors independently screened the retrieved articles in two steps. First, the title and abstract of the retrieved records were screened and the ineligible articles were removed. The full texts of the remaining articles were reviewed based on the inclusion and exclusion criteria and the eligible studies were included in the final qualitative analysis of the results.

**2.5. Data Extraction**

The following data were independently extracted by four researchers: first author, type of study, country of research, manufacturer of the mRNA vaccine, sample population, age, gender, severe adverse events, time from the injection to the appearance of adverse events, and local and systemic adverse events. These findings were organized into a table and were used for qualitative synthesis. Another author reviewed

the extracted data and addressed any inconsistencies that existed between authors.

**2.6. Quality assessment**

The Newcastle-Ottawa scale (NOS) was used to assess the quality of included studies. This criteria yields a maximum score of nine for questions regarding selection, comparability, and exposure (22). Studies with poor quality assessment scores of four or less were excluded from this systematic review.

**3. Results**

Our search yielded a total of 1062 studies, and two more records were identified through manual searching. After removing the 547 duplicates, 515 records remained. A total of 171 records were excluded in the title/abstract screenings, and 346 full-text reports were assessed for eligibility (344 from database search, two via manual searching). Finally, 74 studies were found to be eligible for this systematic review (Figure 1).

The mean NOS quality assessment score of the studies was 6.5. No study had a score of four or less and therefore, no study was excluded from this systematic review due to low quality score.

The purpose of this study was to review and describe the



findings of articles that reported safety and adverse events related to COVID-19 mRNA vaccines. We included articles that investigated the adverse effects of COVID-19 mRNA vaccines (Pfizer-BioNTech, Moderna, BNT, and BNT162b1) in the 1st, 2nd, and 3rd-phase RCTs, cross-sectional, and cohort studies.

### 3.1. Adverse reactions

In both Pfizer and Moderna vaccines mild to moderate local and systemic adverse reactions were reported. The findings have shown that the incidence of systemic adverse reactions could increase following the second dose. Also, the prevalence of systemic adverse reactions in younger adults (age group of 18-55) was higher in comparison with older adults. Injection site pain and muscle pain were the most common local adverse reactions reported in studies. Also, headache was the most prevalent systemic adverse reaction, followed by fatigue, myalgia, chills, and fever. Other local adverse reactions included tenderness, redness, urticaria, rash and swelling, neck pain, hand numbness, erythema, induration, itching, local loss of hair, and edema. Some other less common systemic adverse reactions were as follows: body aches, gastrointestinal symptoms, arthralgia, nausea, vomiting, diarrhea, dizziness, vertigo, weakness, and visual symptoms (Table 1). It should be noted that adverse reactions and severe adverse events could affect all healthy, pregnant, and immunocompromised vaccine recipients.

### 3.2. Severe adverse events (SAE)

In this review, severe adverse events were reported and classified into five categories including cardiac, allergic, neurologic adverse events, and adverse events that may occur in pregnant and immunocompromised patients who received COVID-19 mRNA vaccines. The time interval between inoculation and onset of severe adverse events varied from one hour to 84 days after the injection of the first or second dose. Severe adverse events are reported as follows:

#### -Cardiac

Most of the reported severe adverse events were related to cardiac events. A cross-sectional study among 700 participants who received Pfizer-BioNTech reported severe chest pain (0.4%) and acute hypertension (0.3%) after the first vaccine shot (6). A retrospective study among 113 allogeneic hematopoietic stem cell transplant recipients, who received Pfizer and Moderna vaccines, reported tachycardia and increased blood pressure (0.8%) (23). In a 3rd phase RCT among 14134 participants who received mRNA-1273 (Moderna), the authors reported one case of cardiopulmonary arrest (0.007%) (24). Another study on 884,828 participants who received Pfizer vaccine reported myocarditis (risk ratio, 3.24 and risk difference 2.7 events per 100,000 persons) (25). A cross-sectional study on 8275 participants reported one

case of acute myocardial infarction (26). Another cross-sectional study on 432 participants who received the Moderna vaccine reported chest pain (1.85%) and syncope (0.93%) (27). Likewise, in another cross-sectional study on 803 participants who had received Pfizer vaccine, chest pain (1.12%) and Syncope (0.12%) were reported as serious adverse events (20). Another cross-sectional study on 190 patients who had received the Pfizer vaccine reported one case of supraventricular tachycardia (1%) and one case of decompensated heart failure (1%) (28). In a 2nd phase RCT on 43,448 participants, 21720 of whom received BNT162b2 vaccine, one case of paroxysmal ventricular tachycardia (0.004%) was reported (29).

#### -Pregnancy

Among studies included in our review, two studies were conducted on pregnant women who had received mRNA vaccine during their pregnancy, and one study on 35691 pregnant women reported possible serious adverse effects as follows: spontaneous abortion (46 cases; 37 in the first trimester, 2 in the second trimester, and 7 in which the trimester was unknown or not reported), stillbirth, premature rupture of membrane, and vaginal bleeding with 3 reports for each, and no congenital anomalies were documented (30). In another study on pregnant women, the rates of adverse pregnancy outcomes among 133 women who received at least 1 dose of the COVID-19 vaccine in pregnancy were similar to that of unvaccinated pregnant women regarding stillbirth (0.0% vs 0.2%), fetal abnormalities (2.2% vs 2.5%), postpartum hemorrhage (9.8% vs 9.0%), cesarean delivery (30.8% vs 34.1%), small for gestational age (12.0% vs 12.8%), maternal high-dependency unit or intensive care admission (6.0% vs 4.0%), and neonatal intensive care unit admission (5.3% vs 5.0%). In addition, three fetal abnormalities, including spina bifida, ventriculomegaly, and hydronephrosis, were reported. The spina bifida case was diagnosed before the pregnant woman received the first dose of the vaccine. The ventriculomegaly case was diagnosed at 37 weeks gestation and was isolated, with no associated brain abnormalities, as confirmed by fetal brain magnetic resonance imaging. The hydronephrosis was mild, with no associated abnormality at birth (31).

#### -Allergic

Some studies reported rare allergic adverse events such as swelling of eyelids, severe allergic reaction of eyelids, anaphylactoid reactions, and Angioedema (9, 24, 27, 32, 33). In a cross-sectional study conducted on 700 participants who received Pfizer vaccine, two cases with swelling and severe allergic reaction of eyelids were reported (1). In a similar cross-sectional study on 432 participants who received Moderna vaccine, swelling in the mouth or throat (0.46), asthma exacerbation (0.46%), swelling of lips (0.23%), and anaphylaxis (0.23%) were observed (27). Also, in the 3rd phase RCT among 14,134 white and black USA residents who received



Moderna, hypersensitivity reactions were reported in 1.5% of participants (24, 27). Two cross-sectional studies reported allergic reactions in 2.2% (15 out of 688) of participants and two cases of Angioedema (0.4%) (2 out of 474) within 48 hours of vaccine injection, respectively (34, 35).

Between December 14, 2020, and January 18, 2021, based on CDC reports, after vaccination with 9,943,247 Pfizer-BioNTech doses and 7,581,429 Moderna doses in the US (CDC unpublished data, February 2021), the risk of anaphylaxis was 4.7 cases/per-million-dose for Pfizer-BioNTech, and 2.5 cases/per-million-dose for Moderna vaccine. Overall, since late January 2021, CDC reported 66 cases of anaphylaxis, including 47 cases after the Pfizer-BioNTech vaccine and 19 cases after the Moderna vaccine. All these 66 persons were treated in health care settings. The median time to event was 6 minutes (range, <1-45 minutes). Almost all cases recovered in the follow-up and no deaths from anaphylaxis after vaccination with either product were reported (36).

In another cross-sectional study, the authors investigated the adverse effects of 578,835 doses of the mRNA-based vaccines in the Japanese population, 733 Adverse Event Following Immunizations or AEFIs (85 males [12%], 647 females [88%], 1 unknown [<1%]) were reported. Among these, there were 181 (first dose: 177; second dose: 3; unknown: 1) suspected anaphylaxis reports, resulting in a reporting rate of 31.3/100,000 doses. In 171 of 181 cases, women developed suspected anaphylaxis and anaphylactoid symptoms within ≤5min or >30 min of injection (33).

#### - Neurologic

In total, 10 studies reported adverse neurologic events among healthy patients and patients with prior neurologic diseases. These adverse events were Bell's palsy, herpes zoster, ischemic stroke, new or worsening neurological symptoms (muscle weakness, walking difficulty, gait instability, visual problems, pain, sensory disturbances, and sphincteric problems) among patients with underlying neurological diseases, Guillain-Barre syndrome, seizure, loss of consciousness, fainting, syncope, leg paresthesia, functional syndromes, acute transverse myelitis, and lumbar radiculopathy exacerbation (20, 24-27, 29, 37-40).

A 3rd-phase RCT on 14134 who received Moderna reported three cases of Bell's palsy in both the vaccine group (<0.1%) and placebo group (<0.1%) (24). In addition, one case of Bell's palsy was reported 11 days after the 1st dose of Pfizer vaccine in a cross-sectional study. The unadjusted 15-day rate of adverse events per 100,000 residents following the first dose of vaccine was the same in both vaccinated and unvaccinated groups for Bell's palsy (26). Herpes zoster was observed at the rate of 15.8 events per 100,000 persons among 884,828 who received the Pfizer vaccine (25). Other neurological symptoms were as follows: 73 participants (16.7%) who had a history of rare neuro-immunological disorders reported new or

worsening neurological symptoms following Pfizer and Moderna vaccination (37), 36 participants (15.1%) with Multiple Sclerosis who received Pfizer COVID-19 vaccine reported new or worsening neurological symptoms (muscle weakness, walking difficulty, gait instability, visual problems, pain, sensory disturbances and sphincteric problems) (41), Guillain-Barre syndrome (GBS) was seen in a healthy male 4 days after the second dose of Moderna (39), there was one case of the seizure (0.23%) after receiving Moderna vaccine (27), food intolerance (0.25%), loss of consciousness or fainting (0.25%), seizures (0.12%), and syncope (0.12%) among 803 participants who had received Pfizer (20), and one case of leg paresthesia in a 2nd-phase RCT of Pfizer vaccine (29).

In addition, a cohort study on 704,003 participants who received Pfizer vaccine reported 33 (0.005%) serious adverse events, 17 of which (51.5%) were neurologic (2.4/100,000 doses) in the first 30 days after vaccination, however, no death was reported due to the complications. Among those 17 patients, seven cases had seizures (0.99/100,000 doses); four mentioned functional syndromes (0.56/100,000 doses); three had GBS (0.43/100,000 doses); two were diagnosed with acute transverse myelitis (0.28/100,000 doses); and one case was consistent with lumbar radiculopathy exacerbation (0.14/100,000 doses) (40).

#### - Immunocompromised patients

A retrospective study on 113 allogeneic hematopoietic stem cell transplant recipients who received Pfizer-BioNTech and Moderna vaccine reported one case of axillary lymphadenopathy, one case of increased blood pressure, and tachycardia. In addition, neutropenia, thrombocytopenia, lymphopenia, and eosinophilia were observed in 13.3%, 11.5%, 8.8%, 4.4% of vaccine recipients 20.5, 34, 19.5, and 28 days after vaccination. In addition, they reported new chronic Graft-versus-host disease (GVHD) (9.7%) or worsening chronic GVHD (3.5%) 3 to 48 days after vaccination. Also, two patients experienced both new and worsening GVHD symptoms. One patient with a previous history of chronic GVHD was hospitalized (23). Another study on 80 allogeneic hematopoietic cell transplantation recipients or CD19-based chimeric antigen receptor T-cell (CART) therapy patients who received Pfizer vaccine reported cytopenia (12% of the patients after the 1st dose and 10% of the patients after the 2nd dose), graft-versus-host disease exacerbation (4.5%), and a single case of impending graft rejection as possible vaccination adverse effects within 1st week of injection (42). One cohort study on 741 solid organ transplant recipients who received Pfizer or Moderna vaccines, reported one case of acute rejection after the 2nd dose, and infection (3% after 1st dose and <0.01% after 2nd dose) within 7 days post-vaccination. Lao, in a cohort study that was conducted on 151 cancer patients and 54 healthy patients who received Pfizer or Moderna vaccines, reported only one case





of deranged liver function test 3 weeks after the 1st dose in the control group (43). In a study of 373 cancer patients who received Pfizer-BioNTech or Moderna vaccine, eight patients reported severe adverse events as follows: chest pain (0.3%), dyspnea (1.1%), urosepsis(0.3%), febrile neutropenia (0.3%), and lymphadenopathy (0.5%) within seven days after injection, and venous thromboembolism (VTE) (0.3%) within seven days after vaccination (44).

## 4. Discussion

In this review, we synthesized the safety data and side effects of COVID-19 vaccines from 74 published articles. It appeared that the adverse reactions were often mild to moderate with few serious adverse events. At least one case of serious adverse events was reported in 30 articles. Most studies had investigated the adverse events after the Pfizer-BioNTech vaccine, while few studies had studied Moderna (mRNA-1273) or both mRNA vaccines' adverse effects. The number of adverse effects reported after the Pfizer vaccine was higher, but this was mostly due to its earlier approval and more widespread uptake across the world. The reported severe adverse events associated with the COVID-19 vaccines were more frequently related to allergic events, neurological events, and cardiovascular implications including chest pain, myocardial infarction, acute hypertension, tachycardia, myocarditis, syncope, supraventricular tachycardia, decompensated heart failure, and paroxysmal ventricular tachycardia.

The majority of vaccine recipients reported at least one local or systematic side effect after inoculation with the mRNA COVID-19 vaccine. Albeit, all reported side effects were minor and had a short duration. Local and systemic adverse reactions were found to be more prevalent after the second dose. Common adverse reactions were injection site pain, headache, muscle pain, myalgia, chills, and fever. The systemic adverse reactions had moderate intensity in the young age group in comparison with those who were 65 years old or older. The majority of adverse reactions like fatigue, joint pain, muscle pain, and headache were reported by the younger age group (18-55 years) and obviously, less reported by the older adults. These findings are in line with findings of a similar study that assessed 11 clinical trials of COVID-19 vaccines (45).

Ten studies in this review reported possible cardiac adverse effects. In those who received Pfizer vaccine, severe chest pain, acute hypertension, tachycardia, myocarditis, syncope, supraventricular tachycardia, decompensated heart failure, and paroxysmal ventricular tachycardia were reported. On the other hand, increased blood pressure, tachycardia, cardiopulmonary arrest, chest pain, and syncope were reported in Moderna receivers. In addition, acute myocardial infarction was documented after mRNA vaccine inoculation.

No significant association has been found between COVID-19 mRNA vaccines and cardiac adverse events mentioned above, except for myopericarditis. The findings of a systematic review conducted to investigate the safety and adverse events of COVID-19 vaccines among children and adolescents were in line with our findings; 27 cases of approved myocarditis or pericarditis were found in 7 assessed studies (including one RCT, two case series, and four case reports), all of which occurred after the 2nd dose of Pfizer vaccine. This systematic study's findings show an incidence rate of 0.008% for myopericarditis in adolescents aged 16 to 17 years old and also 0.01% in adolescents aged 12 through 15 years following the second dose (25, 46).

In another study, 16 cases of myocarditis, pericarditis, and myopericarditis were reported after injection of both types of mRNA vaccines. These severe cardiac adverse effects occurred after the first vaccine dose in six cases (35%), after the second dose in ten cases (59%), and after both doses in one case (6%). The median time to event was 14 days (range 1–28) after the first vaccination and 3 days (range 1–17) after the second shot (47). Similar findings were reported in a systematic review that investigated the cardiac adverse outcomes after COVID-19 vaccine injection. In total, 42 acute myocardial infarction (AMI) and 35 myocarditis cases were reported after COVID-19 vaccination and 41 (98%) and 31 (89%) of these cases had been vaccinated by mRNA vaccines, respectively. The majority were men, and myocarditis cases were younger than AMI patients. Myocarditis was observed after an average of 3 days after vaccination, while AMI mostly occurred after an average of 1 day. Thirty-five (83%) myocarditis and six (33%) AMI patients developed symptoms after their second dose. The majority of the myocarditis (83%) and AMI patients (86%) had received the Pfizer BioNTech vaccine. The remaining patients with myocarditis received the Moderna (14%) and Janssen vaccine (2%) vaccines, while AMI patients had received the Oxford-AstraZeneca vaccine (11%) and Moderna vaccine (3%) (48). These findings were consistent with our study indicating a strong possibility of myocarditis (risk ratio, 3.24; [CI95% 1.55-12.44]) after BNT162b vaccination; however, this risk was significantly lower in comparison with myocarditis after SARS-COV-2 infection, which is 18.28 (95% confidence interval [CI95% 3.95-25.12]) (25). In addition, some included studies in our review had reported cases of severe chest pain and acute myocardial infarction.

It seems that the rate of adverse pregnancy outcomes is no different between vaccinated and unvaccinated pregnant women and no association between mRNA vaccines and pregnancy outcomes was found. This finding was consistent with the findings of other systematic reviews, which were conducted on pregnant women who received either of the mRNA vaccines. No increased risk of adverse obstetrical or neonatal outcomes was reported and the proportion of in-

fant outcomes reported, including spontaneous abortions, stillbirth, induced abortion ectopic pregnancy, and spontaneous abortions, were similar to non-vaccinated pregnant women. Also, safety data indicated that pregnant and lactating populations experienced vaccine-related reactions at similar rates to the general population (49, 50).

The findings of included studies showed that those who have received the Pfizer vaccine are more likely to have allergic reactions than those who received Moderna vaccine. A systematic review including 26 articles, involving 26,337,421 mRNA SARS-CoV-2 vaccine recipients (14,505,399 doses of Pfizer-BioNTech and 11,831,488 doses of Moderna) reported similar results. This study reported that vaccination with Pfizer-BioNTech vaccine resulted in higher rate of anaphylactic reactions compared to Moderna vaccine (9.31/per-million-dose and 3.42/per-million-dose). This study also reports a lower incidence of non-anaphylactic reactions with Pfizer compared to Moderna (75.27/per-million-doses, versus 99.01/per-million-doses administered) (51). In another systematic review and meta-analysis, which investigated the risk of allergic and severe adverse events, the incidence rate of anaphylaxis was reported as 7.91/per-million-cases (among 41,000,000 patients) (52).

The post-COVID-19 vaccination neurological adverse events are relatively rare and the causal association between neurological symptoms and vaccination is uncertain. Bell's palsy was reported as one of the neurological adverse events in two assessed studies (26, 53). However, no significant differences in Bell's palsy incidence were reported between vaccinated and unvaccinated individuals. A review has also acknowledged that most Bell's palsy cases were associated with mRNA vaccines. No difference was found between clinical features of vaccine-associated Bell's palsy and conventional types and the pathogenesis remains unclear (54). In addition, some neurological adverse events including Guillain-Barre syndrome, herpes zoster, seizure, loss of consciousness or fainting, syncope, leg paresthesia, and acute transverse were reported; the causal association of adverse events and vaccination or coincidence of them must be carefully assessed.

Most of the COVID-19 vaccine randomized trials have excluded those with immunocompromised conditions, so there is limited data available about adverse events in individuals with autoimmune disease and cancer. However, in transplant recipients, graft-versus-host disease exacerbation, and impeding graft rejection were reported as possible vaccination adverse events. No significant difference was reported between severe complications in cancer patients and healthy patients, as the control group, who received Pfizer or Moderna vaccines (43, 44).

The adverse events of vaccination should continuously be monitored to identify any new issues in the safety of vaccines, which require investigations. In other words, while

assessing the safety of vaccines, any unexpected or unusual patterns in vaccinated individuals, which have a higher rate than the general population should be considered. In this study, the most commonly reported serious adverse events were cardiac events, additional studies are recommended to investigate the association between vaccination and cardiac complications. Also, in order to collect data on the clinical, cardiological, neurological, and immunological profile of the COVID-19 vaccinated population, cohort studies could further assess the frequency of adverse events in the general population.

## 5. Conclusion

Some severe adverse events were observed among the recipients of mRNA vaccines, but a direct relationship between the vaccines and adverse events has not been clearly established for the adverse events, except for myopericarditis. The rate of severe adverse effects is low and obviously, the benefits of receiving vaccines in preventing severe COVID-19 and death outweigh the possible rare adverse events of the COVID-19 vaccines. Therefore, healthcare officials should enlighten people on the safety of the vaccines, in this case mRNA vaccines, to avoid further hesitations in COVID-19 vaccination, which may endanger the lives of people and pose a huge burden on the healthcare system.

## 6. Declarations

### 6.1. Acknowledgments

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### 6.2. Data availability

The data is at the disposal of the corresponding author of the article and it can be made available to the researchers upon request.

### 6.3. Authors' contributions

- (1) The conception and design of the study: Esmail Mehraeen, SeyedAhmad SeyedAlinaghi
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- (6) Final approval of the version to be submitted: all authors



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#### 6.5. Competing interests

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

#### 6.6. Availability of data and material

The authors stated that all information provided in this article could be shared.

#### 6.7. Consent to publication

Not applicable

#### 6.8. Ethics approval and consent to participate

The present study was approved by Tehran University of Medical Sciences with the ethics code: IR.TUMS.IKHC.REC.1400.510.

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**Table 1:** Severe adverse events, local and systemic side effects of mRNA COVID-19 vaccination

First Author Country	Study type	Manuf- acturer*	Sample	Age	Gender (%)	Severe adverse event	Time to appearance	Side effects (%)	
								Local	Systemic
Tom T. Shimabukuro. (55) USA/White	Cross-sectional	PB, M	35,691	16 to 54 years	Female (100)	Spontaneous abortion, Preterm birth, small size for gestational age	N/A	Injection-site pain	Headache, Myalgia, Chills, and fever
Abu-Halaweh, S. (56) USA	Observational cohort	PB	491	>70 years	Male (67) Female (33)	N/A	N/A	Injection site pain, Muscle pain	Fatigue, Headache, Arthralgia, Fever
Abu-Hammad, O. (57) USA	Cross-sectional	PB	409	N/A	N/A	No severe adverse reaction	1.39 ± 1.12 days	Injection site pain or arm numbness	Fatigue, Myalgia, Headache
Al Ghafri, T. S. (58) Oman	Cross-sectional	PB	753	62	Males (54.1), Female (45.9)	No severe adverse reaction	2 days	Pain and tenderness	Fever and body aches
Al Khames Aga, Q. A. (9) USA	Cross-sectional	PB	700	18 and above	Male (51.6), Female (48.4)	Tenderness or swollen lymph nodes, severe allergic reaction of eyelids, severe chest pain, acute hypertension, acute hyperglycemia	1.903±2.128 days	Pain, Redness, Urticarial, and swelling at the site of the injection	Fatigue, body Pain, Headache, Muscle Pain, Fever, and gastrointestinal effects
Alhazmi, A. (10) Saudi Arabia	Cross-sectional	PB	533	18 to 70 years	Male (43), Female (57)	Hospitalization due to side effect	1-5 days	Pain, and redness at the site of injection	Fatigue, Fever, Chills, and headache
Ali, H. (23) USA	Retrospective study	PB	113	66.5	Male (69), Female (31)	Axillary lymphadenopathy, Increased blood pressure, and tachycardia	26 days	Injection site pain, Injection-site rash, and swelling	Myalgia, Arthralgia, Fatigue, Nausea, Vomiting, Diarrhea, and headache
Anderson, E. J. (59) USA	RCT First phase	M	40	56-70	Male (48), Female (52)	Paronychia	2 days	Injection-site pain	Headache, Fatigue, Fever, Myalgia, and chills,
Andrzejczak-Grządko, S. (18) Poland	Cross-sectional	PB	196	20-84	Male (15), Female (85)	Enlarged lymph nodes, decreased alcohol tolerance	N/A	Injection site pain, Shoulder pain, Muscle aches, Neck pain, and hand numbness	Headache, Fever, Chills, Nausea, Vomiting, Drowsiness, Diarrhea, and dizziness
Baden, L. R. (24) USA/White and black	RCT Third phase	M	14134	51.4	Male (52.7), Female (47.3)	Cardiopulmonary arrest, Bell's palsy	N/A	Injection site pain, Erythema, Induration, and tenderness	N/A
Barda, N. (25) USA	RCT	PB	884828	36	Male (52), Female (48)	Myocarditis, Lymphadenopathy, Appendicitis, Arrhythmia, Deep-vein thrombosis, Myocardial infarction, Myocardial Infarction, intracranial hemorrhage, pulmonary embolism, herpes zoster	N/A	N/A	Vertigo



**Table 1:** Severe adverse events, local and systemic side effects of mRNA COVID-19 vaccination

First Author Country	Study type	Manuf- acturer*	Sample	Age	Gender (%)	Severe adverse event	Time to appearance	Side effects (%)	
								Local	Systemic
Bardenheier, B. H. (26) USA/white, black	Cross-sectional	PB	8275	18 and above	Male (38.1), Female (61.9)	Acute Myocardial Infarction, Bell's Palsy, Stroke, ischemic, Venous thromboembolism, and Pulmonary Embolism	15-day	N/A	N/A
Benda, M. (60) Austria	Cross-sectional	PB	259	65.1	Male (57.5), Female (42.5)	No severe adverse reaction	7-day	Injection site pain	Fatigue, Severe headache, Severe general muscle pain, and fever
Blakeway, H. (31) UK/ Afro-Caribbean, Asian ethnicity, and White	Retrospective cohort study	PB, M	1328	18-40	Female (100)	Spina bifida, Ventriculomegaly, hydronephrosis, fetal abnormalities, postpartum hemorrhage	N/A	N/A	N/A
Caminati, M. (61) Italy	Cross-sectional	N/A	253	N/A	N/A	No severe adverse reaction	N/A	N/A	N/A
Levy I. (62) Israel	Prospective study	PB	143	49.8±11.5 years	Male and female	N/A	21 days	Local pain	Fatigue, headache, fever,
Li J. (63) UK	RCT	PB	463	57.8±4.7	Male (54) Female (46)	N/A	28 days and 84 days	Mild to moderate pain at the injection site, injection-site redness, or swelling.	Fever, fatigue, headache, and muscle and joint pain
Li J. (32) China	Prospective study	N/A	N/A	N/A	N/A	Anaphylactic reaction (1/100000)	N/A	Pain at the injection site, injection-site redness or swelling	Fever, fatigue, headache, and muscle and joint pain
Li X. (64) UK	Cohort study	N/A	126661070	N/A	Male (49.5) Female (50.5)	Hemorrhagic and non-hemorrhagic stroke, pulmonary embolism, Bell's palsy, immune thrombocytopenia, Guillain-Barre syndrome, and disseminated intravascular coagulation	N/A	N/A	N/A
Ligumsky H. (65) Israel	Retrospective cohort study	PB	326	66	Male (37.7) Female (62.3)	N/A	40 days	Local pain (n = 64, 19.6%)	Weakness (17.5) Myalgia (12.6) Headache (6.4)
Liu X. (66) China	RCT	First phase	PB	296	51	Male (16.4) Female (83.6)	N/A	7 days after the 1st or 2nd dose Pain, Redness, Swelling, Induration	Headache, Fatigue, Joint pain, Muscle pain, Chills, Nausea, Anorexia, Diarrhea, Vomiting

**Table 1:** Severe adverse events, local and systemic side effects of mRNA COVID-19 vaccination

First Author Country	Study type	Manuf- acturer*	Sample	Age	Gender (%)	Severe adverse event	Time to appear- ance	Side effects (%)	
								Local	Systemic
Lotan I. (37) USA	Cross- sectional	PB, M	438	51	Male (16.4) Female (83.6)	New or worsening neurological symptoms	N/A	Local reactions, including pain, redness, swelling at the injection site	Muscle weakness, Visual symptoms, Gait instability, Increased pain, Sensory disturbances, Sphincteric problems
Lotan I. (41) Israel	Cross- sectional	PB	N/A	42	Male (24) Female (76)	New or worsening neurological symptoms (Muscle weakness, Walking difficulty, Gait instability, Visual problems, Pain, Sensory disturbances, Sphincteric problems)	N/A	Pain/redness/ swelling at the injection site	Generalized muscle pain, headache, dizziness, fever, chills, fatigue,
Maeda K. (67) Japan	Present prospective observa- tional study	PB	225	41.8	Male (30.2) Female (69.8)	N/A	28 days	Site pain	Systemic fever, headache, and fatigue
Mascellino MT. (68) Brazil	N/A	PB, M	9000	N/A	Male (55) Female (45)	N/A	28 days	A small pinched pain at the injection site, a little bit of redness	Fatigue, headache, muscle, and joint pain, and fever
Massoud F. (69) Kuwait	Cross- sectional	N/A	111	N/A	N/A	N/A	N/A	Pain at the injection site (43.8)	Fatigue (46.9), Headache (34.4), Myalgia (50)
Matarneh AS. (39) Qatar	Cross- sectional	PB, M	N/A	N/A	N/A	Guillain-Barre syndrome	4 days	N/A	Upper extremity weakness and numbness four days following the vaccine.
Mathioudakis AG. (70) UK	Cross- sectional	PB, M	532	45	N/A	N/A	N/A	Pain, swelling, tenderness, redness, itching, or other	Fever, skin rash, shortness of breath, tingling in the mouth, face, body/extremities, swelling in the face or mouth, generalized swelling, anaphylaxis, tiredness or fatigue, flu-like illness
McMurry R. (71) USA	Cohort study	PB, M	31029	N/A	N/A	N/A	Within 7,14,21 days	Local pain and swelling	Fatigue, fever, chills, myalgia, arthralgia, headache, lym- phadenopathy, erythema, diarrhea, vomiting, Facial paralysis,



**Table 1:** Severe adverse events, local and systemic side effects of mRNA COVID-19 vaccination

First Author Country	Study type	Manuf-acturer*	Sample	Age	Gender (%)	Severe adverse event	Time to appearance	Side effects (%)	
								Local	Systemic
Menni C. (72) USA	Prospective observational study	PB	1607620	50-6	Male (38-4) Females (61-6)	N/A	Within 8 days	Pain, Swelling, Tenderness, Itch, Swollen armpit glands, Redness, Warmth, Bruising, rash, skin burning,	Headache, Fatigue, Chills and shiver, Diarrhea, Fever, Arthralgia, Myalgia, Nausea, red welts on face and lips
Modenese A. (73) Italy	Observational study	PB	76	48.4	Males (19) Females (81)	N/A	4 weeks	Pain sensation at the injection site 73.6% redness in the injection site	Asthenia and sleepiness, chills, 32%, myalgia and arthralgia, 31% for headache/ migraine, and 18% for fever, diarrhea, erythema, abdominal pain, itch, and vertigo
Hall VG (74) Toronto, Canada	Prospective study	M	127	66.2	Male (69.3) Female (30.7)	Varicella-Zoster Virus reactivation (0.78%), Fever and pruritic rash (0.78%), hospitalization (0.78%)	Within 7 days	Pain, erythema, swelling	Fever, headache, fatigue, myalgia, arthralgia, chills,
Hatmal MM (75) Jordan	Cross-sectional	PB, M	612	18 and above	N/A	N/A	Within 4h to three days	Pain, swelling	Fatigue, headache, sleepiness, laziness, chills, myalgia, joints pain, fever, dizziness, decreased sleep quality, numbness in limbs, tingling in limbs, dry or sore throat, nausea, sweating, abdominal pain, irregular heartbeats, clogged nose, runny nose, haziness, chest pain, dyspnea, cough, diarrhea, abnormal blood pressure, allergic reactions, itchy, swollen ankles and feet, vomiting.
Kadali RAK. (27) USA	Cross-sectional	M	432	18-80 years old	Male (10.4) Female (89.6)	Seizures (0.23%), chest pain (1.85%), syncope (0.93%), swelling in the mouth/throat (0.46%), asthma exacerbation (0.46%), swelling of lips(0.23%), anaphylaxis (0.23%)	N/A	Pain, swelling, itching, rash, lym-phadenopathy, skin discoloration, bleeding,	Weakness, headache, chills, fever, sweating, dizziness, flushing, Myalgia, arthritis, muscle stiffness/spasm, Nausea, decreased appetite, diarrhea, abdominal pain, heartburn, vomiting, constipation, swallowing, decreased sleep quality, anxiety, decrease in memory, depression, manic mood changes, psychological stress, brain fogging or confusion, incoordination, extremity weakness, fainting, seizures, herpes or shingle-like lesions, eye pain, runny nose, ringing sensation in the ears, ear pain, blurred vision, flashing lights, changes in hearing, double vision, nose bleed, bleeding gums, hoarseness, Palpitations heart, blood pressure changes, chest pain,





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								Local	Systemic
									syncope, Shortness of breath, and cough, hives, atopic eczema, fever, swelling in the mouth/throat, asthma exacerbation, anaphylaxis, burning with urination, frequent urination, blood in urine, urinary incontinence
Renuka A.K. Kadali. (20) USA	Cross-sectional	PB	803	18-90 years old	Male (13.4) Female (86.6)	Food intolerance (0.25%), Loss of consciousness /fainting (0.25%), Seizures (0.12%), Chest pain (1.12%), Syncope (0.12%)	N/A	Sore arm/pain, swelling at the injection site, Itching, Lymphadenopathy Rash, skin discoloration, Bleeding, Loss of hair locally	Soreness, fatigue, myalgia, headache, chills, fever, joint pain, nausea, muscle spasm, sweating, dizziness, flushing, feelings of relief, brain fogging, anorexia, localized swelling, decreased sleep quality, itching, tingling, diarrhea, nasal stuffiness, palpitations
Kim T. (76) Republic of Korea	Cross-sectional		2574	20 to ≥60	Male (24.7) Female (75.2)	none	<3 hour-≥48 hour	Local tenderness/erythema/heating sensation, edema	General myalgia, febrile sensations, chills, fatigue, rash, headache, Arthralgia, Dizziness, Nausea, vomit, pruritus, dyspnea
MiloslavKluger. (35) Czech Republic	Cross-sectional	PB, M	474	N/A	Male (25.7) Female (73.6) Unknown (0.6)	Severe side effects (0.4%), Angioedema (0.4%)	N/A	injection site pain, injection site swelling, injection site redness, ulcers, vesicles, blisters, angular cheilitis, white/red plaque, oral paresthesia, taste disturbance, halitosis, bleeding gingiva, swollen mucosa, rash, Urticarial, angioedema	Fever, chills, headache/fatigue, muscle pain, joint pain, nausea, lymphadenopathy
Iguchi, T. (33) Japan	Cross-sectional	PB	578,835 doses and 733 adverse events	22-56 years old	Male (12) Female (88)	181 cases of Anaphylaxis and anaphylactoid symptom	≤5min ->30,min	N/A	Anaphylaxis and anaphylactic symptoms



**Table 1:** Severe adverse events, local and systemic side effects of mRNA COVID-19 vaccination

First Author Country	Study type	Manuf- acturer*	Sample	Age	Gender (%)	Severe adverse event	Time to appearance	Side effects (%)	
								Local	Systemic
A. Riad. (77) Czech Republic/South Moravian	Cross-sectional	PB	877	43	Male (11.6) Female (88.4)	N/A	1-3 days	Injection site pain and redness, labial blisters, plaque, bleeding gingiva, halitosis, lymphadenopathy	Fatigue, headache, muscle and joint pain, chills, rash, nausea, fever
A. Riad. (78) Slovakia/Slovak	Cross-sectional	PB	522	37.77±11	Male (23) Female (77)	N/A	1-3	Injection site pain, swelling, and redness, oral side effects, lymphadenopathy	Fatigue, chills, muscle, and joint pain, headache, malaise, fever, nausea, rash
Y. Rechavi. (79) Israel/Arabs	Cohort study	PB	136	40.09	Male (34) Female (66)	N/A	N/A	Injection site pain, swelling, and redness	About 23 patients in 1st dose and 71 in the 2nd one
R. Ram. (42) Israel/Arabs	Cohort study	PB	80	65	Male (55) Female: (45)	GVHD exacerbation (4.5%)	1st week	Vasculitis rash on the leg after allogeneic HCT, arthralgia,	Cytopenia, fasciitis, humoral or cellular response
B. Quiroga. (80) Spain/European	Cohort study	PB	708	44±11	Male (35) Female (65)	N/A	N/A	A local reaction followed by Myalgia	Tiredness, headache
K. Polewska. (28) Poland/Jewish	Cross-sectional	PB	190	68	Male (64.7) Female (35.3)	Supraventricular arrhythmia (n=2), COVID after 1st dose (n=2), COVID after 2nd dose (n=3), Pneumonia (n=1), dialysis peritonitis (n=1), catheter infection (n=1), deterioration of glycemic control (n=2), decompensated heart failure (n=1)	7 days for local 1-3 days systemic 30days for severe adverse effects	Local site reaction, pain, shoulder pain, sinusitis	Fatigue, muscle pain, joint pain, headache, chills, increased sweating, change in smell and taste, deterioration of glycemic control, dizziness
F. Polack. (29) 152 sites worldwide/ White, Black or African American, Hispanic or Latinx	RCT Second phase	PB	43,448	52 all >16	Male (51) Female (49)	Shoulder injury, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, right leg paresthesia	7days for local	Injection site pain (1 severe), redness, swelling, lymphadenopathy	Fatigue, headache, fever, chills
F. Pimpinelli. (81) Italy/European	Cohort study	PB	92	N/A	Male (53.3) Female (46.7)	N/A	N/A	Pain, tenderness	Fever, headache, malaise, myalgia, chills
M. I. Parvej. (34) Bangladesh/ Indo-Aryan	Cross-sectional	N/A	1529	18 and above	Male (66) Female (34)	Thrombosis (0.15%) Allergy (2.2%)	2 days	Pain in the injection site	Fever, Muscle Pain, headache, allergy, itching, diarrhea

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A. Park. (16) Korea/Asian	Cross- sectional	PB	27368	20 and above	Male (10) Female (90)	Dyspnea (0.025)	24 hrs	Pfizer(first dose): Local pain Pfizer(second dose): Local pain	Pfizer(first dose): Fever, Chills, Myalgia, Headache, Nausea, Vomiting Pfizer(second dose): Fever, Chills, Myalgia, Headache, Nausea, Vomiting
D. S. Panda. (82) India/Indo- Aryan	Cross- sectional	N/A	29	18 and above	Male (68.8) Female (31.2)	N/A	N/A	N/A	Fever, Headache
M. T. Ou. (83) USA	Prospective cohort	M	741	60	Male (43) Female (57)	acute rejection of graft after 2nd dose (0.1%) Infection (after 1st dose (0.4%) and after 2nd dose (0.1%))	<7 days	pain in injection site	fatigue, headache
Oh HK. (84) Korea/Asian	Retrospective study	PB	3586814	N/A	N/A	N/A	N/A	N/A	Myalgia, fever, headache
J. Morales- Nunez. (85) Mex- ico/Hispanic	Cohort study	PB	303	45±12	Male (40.9) Female (59.1)	N/A	N/A	Rhinorrhea, dysgeusia, chest pain	Myalgia, shivers, arthralgia, fever, irritability, odynophagia, cough, headache, diarrhea
L. Monin. (43) UK/White and Black	Cohort study	PB	205	73 cancer 40.5 healthy	Male (52) Female (48)	Deranged liver function test grade 4 (0.5%)	3 weeks after 1st dose	Injection site pain, erythema, swelling, lym- phadenopathy	Flue like symptoms, fatigue, headache, chills, arthralgia, nausea or vomiting, fever, diarrhea
NoémieTissot. (86) France	Prospective cohort	PB	311	55.4 ± 6.4	Male (40) Female (60)	N/A	Between 21 and 28 days	Injection site symptoms pain and erythema	Fever chills joint pain Fatigue muscle pain headache
Emanuel Zitt. (87) Austria	Cohort study	PB	50	67.6 ± 14	Male (68) Female (32)	N/A	7 days	Pain	Fever chills joint pain Fatigue muscle pain headache
XiaomoXiong. (88) USA	Cohort study	PB, M	8,976	18–64 years	Male (21.4) Female (78.6)	Death (2.7%), Life-threatening illness (2.7%), Permanent Disability (1%), Hospitalizations (7.1%)	7 days	Injection site pain	Pyrexia chills Dizziness Fatigue Nausea Headache Pyrexia, pain in extremity, Dyspnea
Wi YM. (89) Korea	Cohort study	PB	80	35.83 ± 10.99	Male (31) Female (69)	N/A	After the first and second week	Pain, redness/swelling Lymphadenopa- thy	Vomiting, nausea, fatigue, chills, fever, myalgia, arthralgia
Werbel WA. (90) USA	Cohort study	PB, M	12	57	Male (55) Female: (45)	N/A	14 days	Pain, redness/swelling	Fatigue, chills, fever, myalgia, diarrhea, headache
Edward E. Walsh. (91) USA	RCT First phase	PB	195	35	Male (42) Female (58)	N/A	7 days	Pain, redness/swelling	Fever, fatigue, chills



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Alfred Chung Pui So. (44) UK	Retrospective cohort	PB, M	373	56	Male (37.5) Female (62.5)	chest pain(0.3%), Dyspnea(1.1%), Urosepsis(0.3%), VTE(0.3%)	7 days	Pain at injection site/Sore arm, Erythema	Vomiting, nausea, fatigue, chills, fever, myalgia, arthralgia, diarrhea, dizziness, lym- phadenopathy, anorexia, paresthesia, abdominal pain
Novena Skroza. (92) USA	Cohort study	PB	436	57.26	Male (60) Female (40)	N/A	10 days	N/A	N/A
Tom T. Shimabukuro. (30) USA	Cohort study	PB, M	35,691	27.43 Female 100	N/A	14 days After	Pain, red- ness/swelling	Vomiting, Nausea, Fatigue, Chills, Fever, Myalgia, Arthralgia, Diarrhea, Rash	
Cinzia Ro- tondo. (93) Italy	Cohort study	PB, M	325	60.2 ± 14.2	Male (42) Female (58)	N/A	4 days after vaccination	Pain, redness/swelling	Chills, Fever, Myalgia, diarrhea, headache fever
Yu-Wei Chen. (94) USA	Cohort study	PB, M	81	70	Male (60) Female (40)	Respiratory distress, acute hemolytic anemia, Shock requiring pressure support, Myositis, Cardiogenic shock, Pancreatitis/rash	1, 5, 7 days	N/A	N/A
Patrice Chevallier. (95) France	Prospective study	PB	112	57	Male (50.7) Female (62.2)	N/A	7 days	Pain, redness, Swelling	Fever, Chills, Fatigue, Myalgia, Headache, Nausea
Laurence Chu. (96) USA White, African Ameri- can, Asian, American Indian, Na- tive Hawai- ian	RCT Second phase	M	600	18-87	Male (35) Female (65)	N/A	7 days	Pain, Erythema, swelling, Lym- phadenopathy	Headache, fatigue, myalgia, arthralgia, nau- sea/vomiting, chills
Coggins. (11) USA White, Black, Asian, Hawaiian	Cohort study	PB	206	42.4	Male (30.6) Female (69.4)	N/A	N/A	Soreness, pain	Fatigue, headache, myalgia, arthralgia, fever, chills, Lym- phadenopathy



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Efrati. (97) Israel	Cohort study	PB	333	46	Male (51) Female (49)	N/A	At least 7 days	Pain, redness, and swelling	Fever, chills, Fatigue, Headache, Nausea, Vomiting, Diarrhea, Muscle aches, joint aches, Allergic reaction
Nagla A El- Shitany. (98) Saudi Arabia Retrospec- tive	Cross- sectional	PB	455	N/A	Male (35.8) Female (64.2)	N/A	N/A	Arm pain, injection site pain, swelling, and redness	Whole-body pain, muscle ache, joint ache, hypersensitivity, burning sensation in the eye
Robert W. French. (99) Multi- national African American, American Indian or Alaska, Asian, Latin	RCT Third phase	PB	2260	12-25	Male (51) Female (49)	N/A	7 days	Pain at the injection site, Swelling, Redness	Fatigue, Headache, Chills, Muscle pain, joint pain, fever, diarrhea, vomiting
Miguel García- Grimshaw. (40) Mexico	Prospective observa- tional cohort	PB	704,003	36	Male (74.2) Female (26.8)	0.005 with no observed deaths	3 to 5 hours	Injection site pain	Headache, Fatigue, Muscle pain, joint pain, chills, Nausea, Fever, Tachycardia, Rhinorrhea, Diarrhea, vomiting, irritability
Yarden Golan. (100) USA African American, white, Asian	Cohort study	PB, M	50	35	Female (100)	none	80 days	Pain, redness, swelling, itching, rash around the injection site	Fever, Chills, Headache, Joint pain, Muscle/body aches, fatigue, Nausea, Diarrhea

Time to appearance: Time from injection to the appearance of adverse events; \*PB, Pfizer BioNTech; M, Moderna.  
RCT: randomized controlled trial

