



Original article

Analyzing the U.S. Post-marketing safety surveillance of COVID-19 vaccines

Omar M. Albalawi^a, Maha I. Alomran^a, Ghada M. Alsagri^a, Turki A. Althunian^a, Thamir M. Alshammari^{a,b,c,*}^a Research and Studies, Saudi Food and Drug Authority, Riyadh, Saudi Arabia^b College of Pharmacy, Riyadh Elm University, Riyadh, Saudi Arabia^c Medication Safety Research Chair, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:

Received 4 August 2021

Accepted 27 December 2021

Available online 31 December 2021

Keywords:

Adverse events following immunization

COVID-19

Vaccine safety

Pfizer-BioNTech

Moderna

Janssen Ad26.COVS.2

ABSTRACT

Introduction: Since December 2020, three COVID-19 vaccines have been authorized in the United States (U.S.) and were proceeded by large immunization programs. The aim of this study was to characterize the U.S. post-marketing safety (PMS) profiles of these vaccines with an in-depth analysis of mortality data.

Methods: This was a retrospective database analysis study. Details of the U.S. PMS reports (15 December 2020 to 19 March 2021) of the three vaccines (Pfizer-BioNTech, Moderna, and Janssen Ad26.COVS.2) were retrieved from the U.S. Vaccine Adverse Event Reporting System (VAERS). A descriptive analysis was conducted to characterize the reported adverse events (AEs). A comparative (Pfizer-BioNTech vs. Moderna) analysis of mortality was conducted. The mean count ratio of death between the two vaccines was estimated using a negative binomial regression model adjusting for the measured confounders.

Results: A total of 44,451 AE reports were retrieved (corresponding to 0.05% of the U.S. population who received at least one dose). The most commonly reported AEs were injection site reactions (30.4% of the reports), pain (reported in 26.7% of the reports), and headache (18.6% of the reports). Serious AEs were reported in only 14.6% of the reports with 4,108 hospitalizations. The total number of deaths was 1,919 with a mean count ratio of Moderna (n = 997) vs. Pfizer-BioNTech (n = 899) of 1.07 (95% confidence interval 0.86 to 1.33).

Conclusions: The vast majority of PMS AEs in the U.S. were non-serious, and the number of serious AEs is very low given the total number of vaccinated U.S. population.

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1. Introduction

The outbreak of severe acute respiratory syndrome coronavirus disease 2 (known as COVID-19) was first reported on 31 December 2019 in China (Wu et al., 2020). As of 19 March 2021, more than 29.71 million cases were identified in the United States (U.S.) with a total number of death cases of at least 540,733 (Centers for Disease Control and Prevention (CDC), 2021a). The first COVID-19

vaccine (Pfizer-BioNTech) was authorized for the use in the U.S. on 11 December 2020 (U.S. Food and Drug Administration, 2020a), which was followed by the approval of two other vaccines: Moderna (U.S. Food and Drug Administration, 2020b), and Janssen Ad26.COVS.2 (U.S. Food and Drug Administration, 2021a). All these three vaccines were authorized under the Emergency Use Authorization (EUA) framework (i.e. accompanied with a degree of pre-marketing safety uncertainty) (U.S. Food and Drug Administration, 2021b); thus necessitating an extensive post-marketing safety (PMS) assessment in the context of pharmacovigilance activities.

In Phase III clinical trials, the most commonly identified non-serious AEs related to these vaccines were pain at the injection site, fatigue, headache, myalgia, chills, arthralgia, and fever (Baden et al., 2020; Polack et al., 2020; Sadoff et al., 2021). These findings were also commonly reported after the U.S. Food and Drug Administration authorization of Pfizer-BioNTech and Moderna vaccines (in addition to dizziness and nausea) (Julianne et al., 2021). In Phase III clinical trials, the incidence of serious AEs was low, with

* Corresponding author at: College of Pharmacy, Riyadh Elm University, Riyadh, Saudi Arabia. Saudi Food and Drug Authority, Riyadh, Saudi Arabia. Medication Safety Research Chair, King Saud University, Riyadh, Saudi Arabia. Pharmacovigilance and Pharmacoepidemiology Consultant.

E-mail address: thamer.alshammari@riyadh.edu.sa (T.M. Alshammari).

Peer review under responsibility of King Saud University.



Production and hosting by Elsevier

no differences between the vaccines and placebo groups (0.4 to 0.6%) (Baden et al., 2020; Polack et al., 2020; Sadoff et al., 2021). The number of death cases was lower in the three vaccine groups compared with placebo groups (2 to 6 vs. 4 to 16; respectively) (Baden et al., 2020; Polack et al., 2020; Sadoff et al., 2021). In the first US PMS report, serious AEs were reported in 640 reports (113 deathcases) after COVID-19 vaccinations (Julianne et al., 2021). Given the degree of uncertainty associated with the safety profile of these vaccines due to their approved under EUA, we aimed at evaluating the PMS of the current COVID-19 vaccines authorized for use in the U.S. in the context of spontaneous reporting with an in-depth analysis of mortality data.

2. Methods

2.1. Data source

This retrospective analysis was conducted using the publically available database of the U.S. Vaccine Adverse Event Reporting System (VAERS). VAERS is a critical component of the national passive surveillance (spontaneous reporting) system of the approved vaccines in the U.S. (CDC, 2021a). VAERS was established in 1990 under the joint administration of CDC and the U.S. FDA (Shimabukuro et al., 2015). The purposes of VAERS have been to detect early warning safety signals and to generate hypotheses about possible new unexpected AEs or changes in the frequency of the known ones (CDC, 2021b). Reports in VAERS are sent from manufacturers, healthcare professionals and the public (CDC, 2021b). It has been a source of data for many published studies (DiMiceli et al., 2006; Shimabukuro et al., 2021; Welsh et al., 2021).

Data were extracted from 15 December 2020 to 19 March 2021. Data (available in tables) were assessed and cleaned by of the research team. Demographics (e.g., person, place, and time), onset intervals, and potential confounders in the mortality assessments (cardiovascular diseases [CVD], respiratory diseases, diabetes, renal diseases, and to the history of allergies or allergic were identified. AEs were classified as serious AEs defined by the federal regulatory (U.S. Food and Drug Administration, 2021c).

2.2. Statistical analysis

Distributions of non-serious and serious AEs per state, gender, vaccine, age group, and time of AE were summarized. These findings were provided using a population-level estimate (i.e. based on the number of people who received at least one dose of the study vaccine in the U.S up to 19 March 2021 as a denominator), and using the reporting rate (i.e. using the number of reports per 100,000 doses as a denominator). From 14 December 2020 to 19 March 2021, 85,778,745 persons received at least 1 dose of COVID-19 with a total of 118,313,818 doses in the U.S. (CDC, 2021c). Of these, 59.21 million doses were for Pfizer-BioNTech COVID-19 vaccine, 56.94 million doses were for Moderna vaccine, and 2.03 million doses for Janssen Ad26.COV2.S vaccine (Our World in Data, 2021).

An in-depth, comparative analysis of mortality between Pfizer-BioNTech vs. Moderna was conducted with the mean count ratio as a primary effect estimate (Janssen Ad26.COV2.S was excluded from the analysis given its recent approval). The mean count ratio of death between the two vaccines was estimated using a negative binomial regression model adjusting for the measured confounders (age, gender, history of allergy, onset intervals after the first dose, and the presence of several chronic diseases [Cardiovascular disease, diabetes, a respiratory disease, and renal disease]). The negative binomial model was used instead of a poisson model due to

the presence of overdispersion. All analyses were completed using RStudio Version 1.4.1103.

3. Results

By 19 March 2021, 44,451 AE reports (0.05% of the total 85,778,745 vaccinated U.S. population) were extracted from VAERS. The median age in the identified reports was 49 years (range 13–115 years), and most symptoms occurred within two days of the vaccination (range 0–64 days). More than two-third of patients were female, and less than one-third have a type of allergy (Table 1). The most frequently reported AEs (per total number of AE reports) were injection site reactions (13,480 [30.3%]), pain (11,897 [26.7%] ;), headache (8,271 [18.6%]), chills (6,347 [14.0%]), fatigue (5,972 [13.0%]), and pyrexia and dizziness (4,611 [10.3%] and 4,537 [10.0%], respectively) (Table 1). Of the 44,451 AE reports, 23,890 (53.7%) were reported after the vaccination with Pfizer-BioNTech., 19,424(43.7%) after the vaccination with Moderna, and 1,107 (2.5%) after the vaccination with Janssen Ad26.COV2.S (Table 2).

Serious AEs were present in 6,514 (14.0%) total AE reports (corresponding to 0.007 % people vaccinated) (Table 3). Most patients with serious AEs were elderly (median: 70 years [range 16–106]). The majority of these serious AEs (4,018 [9.0%]) led to hospitalization (0.004 % of people vaccinated). Life-threatening complications were reported in 431 (0.9%), corresponding to 0.0005% people vaccinated. Anaphylaxis was reported in 326 AE reports (0.73% of AE reports, 0.00038 % people vaccinated), and 130 of 326 (39.8%) of these cases occurred among patients with a documented history of allergy. Thromboembolism was identified in 173 reports (0.3% of AE reports, 0.00002 percent of people vaccinated). Of the 173 cases, 94 (54%) occurred after the vaccination with Moderna, 78 (45%) after Pfizer-BioNTech. Pregnancy-related AEs (spontaneous abortion) were identified in only 64 reports.

Death was identified in 1,919 reports (4.3% of 44,451 AE reports, corresponding to 0.002 % people vaccinated). The median age at death was 80 years (range 18–106 years), and more than one-third (38.4 %) of patients had a history of a CVD. The most commonly reported cause of death was death due to a cardiovascular disease (including cardiac arrest) in 273 of 1,919 (6.0%) of death cases. Of 1,919 death cases, 119 (6.2%) cases were attributed to COVID-19 infection. Of the total death reports, 997 (52.0%) were

Table 1
Characteristics of reported cases of AEs after receipt of COVID-19 vaccines.

| Characteristics | Number of AEs reports (n = 44,451) | |
|-------------------------------------------|---------------------------------------|---------------|
| Gender | Male | 10,637 (23.9) |
| | Female | 32,806 (73.8) |
| | Unspecified | 1,008 (2.2) |
| | December | 10,640 (24.1) |
| VAERS reported by date (Month) | January | 19,968 (45.2) |
| | February | 8,498 (19.3) |
| History of chronic disease | March | 5,035 (11.4) |
| | Cardiovascular disease (CVD) | 4,599 (10.3) |
| | Respiratory disease | 3,592 (8.1) |
| | Diabetes | 2,564 (5.7) |
| | Renal disease | 6,85 (1.5) |
| Allergies | No | 30,652 (69.0) |
| | Yes | 13,799 (31.0) |
| Most common AEs (mild-to-moderate) | Injection site reactions | 13,480 (30.3) |
| | Pain | 11,897 (26.7) |
| | Headache | 8,271 (18.6) |
| | Chills | 6,347 (14.0) |
| | Fatigue | 5,972 (13.0) |

Table 2

Number and report rate (per 100,000 doses administered) of AES reports per vaccine.

| Vaccine brand name | Non-serious AEs reports (n = 37,910) | Serious AEs reports (n = 6,541) | Number of total reports (n = 44,451) | Total number of doses administered | Total non-serious reporting rate* | Total serious reporting rate* | Total reporting rate* |
|----------------------------|--------------------------------------|---------------------------------|--------------------------------------|------------------------------------|-----------------------------------|-------------------------------|-----------------------|
| Pfizer-BioNTech | 20,640 | 3,248 | 23,890 | 59,210,000 | 34.8 | 5.4 | 40.3 |
| Moderna | 16,227 | 3,197 | 19,424 | 56,940,000 | 28.4 | 5.6 | 34.1 |
| Janssen Ad26.COV2.S | 1,051 | 56 | 1,107 | 2,030,000 | 51.7 | 2.7 | 54.5 |
| Unspecified | 17 | 13 | 30 | N/A | N/A | N/A | N/A |

* Per 100,000 doses administered. N/A: not available

Table 3

Summary of serious adverse events after receipt of COVID-19 vaccines.

| Characteristics | Number of reports (n = 6,514 [%]) | Percentage of the total AEs reports |
|---------------------------------------------------------------------|-----------------------------------|-------------------------------------|
| Gender | | |
| Male | 2,881 (44.2) | 6.4 |
| Female | 3,534 (54.32) | 7.9 |
| Unspecified | 99 (1.5) | 0.2 |
| Serious AEs | | |
| Hospitalization (excluding death) | 4,018 (61.6) | 9.0 |
| Death | 1,919 (29.4) | 4.3 |
| Life-Threatening (un-hospitalized) | 431 (6.6) | 0.9 |
| Other Serious (i.e., thromboembolism, anaphylaxis and miscarriage)* | 56 (2.3) | 0.3 |
| Vaccine brand name | | |
| Pfizer-BioNTech | 3,248 (49.8) | 7.3 |
| Moderna | 3,197 (49.0) | 7.1 |
| Janssen Ad26.COV2.S | 56 (0.8) | 0.1 |
| Unspecified | 13 (0.19) | 0.02 |

*Other Serious Medical events is the cases that are not classified in either death or hospitalization or life threatening.

Table 4

Characteristics of the death cases after receipt of COVID-19 vaccines.

| Characteristics | Number of reports (n = 1,919 [%]) | Percentage of the total AEs reports |
|-----------------------------------|-----------------------------------|-------------------------------------|
| Gender | | |
| Male | 1,039 (54.1) | 2.3 |
| Female | 840 (43.7) | 1.8 |
| Unspecified | 40 (2.1) | 0.08 |
| History (Allergies) | | |
| No | 1,444 (75.2) | 3.2 |
| Yes | 475 (24.7) | 1.0 |
| History of chronic disease | | |
| Cardiovascular disease (CVD) | 737 (38.4) | 1.6 |
| Respiratory disease | 251 (13.0) | 0.56 |
| Diabetes | 312 (16.2) | 0.7 |
| Renal disease | 187 (9.7) | 0.4 |
| Vaccine brand name | | |
| Pfizer-BioNTech | 899 (46.8) | 2.0 |
| Moderna | 997 (50.9) | 2.2 |
| Janssen Ad26.COV2.S | 16 (0.8) | 0.03 |
| Unspecified | 7 (0.4) | 0.01 |

reported after the vaccination with Moderna, 899 (46.8%) after Pfizer-BioNTech, 16 (0.8%) after Janssen Ad26.COV2.S (Table 4). The numbers of death cases between Moderna vs. Pfizer-BioNTech were comparable (1.07; 95% confidence interval 0.86 to 1.33).

4. Discussion

Our study showed that most of the reported AEs among those who received the three approved COVID-19 vaccines in the US were non-serious. The study also showed no emerging trends in unknown serious AEs (the most commonly reported serious AEs were reported were hospitalization, followed by death and life threatening). Finally, our study showed that both vaccines (Moderna vs. Pfizer-BioNTechCOVID) have a similar probability of death.

The proportion/report rate of AEs observed in our study are consistent with the findings of the previous studies (from a population-level and rate perspectives) that used a spontaneous-

reporting database (both in the U.S. and internationally (Julianne et al., 2021)). For example, the percentage of the total reported AEs among the vaccinated population (0.05%) was similar to the observed one in previous VAERS-based PMS assessment of the first month post-authorization (0.05%) (Julianne et al., 2021). Additionally, the reporting rate in our study (37.5 cases per 100,000 doses administered) was similar to that reported in a Canadian analysis (31.0 reports per 100,000 doses of all administered up to 21 May 2021) (Public Health Agency of Canada, 2021). The higher reporting percentage among the females in our study was also observed in previous studies (Julianne et al., 2021; Venkatakrishnan et al., 2021). This difference has been attributed to several potential risk factors such as (e.g. genetic differences and the higher tendency to report AEs among the female group) (Kleina et al., 2014; Public Health Agency of Canada, 2021).

The percentage of serious AEs (14.6%) in our study is higher than that of a previous VAERS-based study (9.2%) (Julianne et al., 2021). The reporting rate of anaphylactic cases was lower in comparison with a previous study (2.7 vs. 4.5 reported cases per mil-

lion doses administered) (Julianne Gee et al., 2021). The number of spontaneous abortion cases we observed in our study (64 reports) is slightly higher than the 46 cases observed in a previous analysis of COVID-19 vaccine PMS data among the pregnant U.S. population, which covered the period up to 28 February 2021 (14). The percentage of the overall of death cases (4.3%) in our study (1,919 of 44,451) was higher than that of a previous VAERS-based study (1.3%, 113 of 6,994) (Julianne Gee et al., 2021). The discrepancy in the proportion of serious AEs, including death cases, between our study and the one, reported to the FDA could be because we covered or analyzed a period of up to three months of COVID-19 vaccine PMS data among the U.S. population with 118,313,818 doses administered. In contrast, FDA's previous study covered only the first month (only 13,794,904 vaccine doses were administered) (Julianne Gee et al., 2021). The median age at death was 80 years (most with co-morbidities), and a similar finding was reported in other countries (Dutta et al., 2021). We could not find any differences in the number of death cases between the most commonly used COVID-19 vaccines in the U.S. (i.e. Pfizer vs. Moderna). A similar result was reported in other other countries using the WHO database (VigiBase[®]) (Dutta et al., 2021) and sources of COVID-19 data such as in Canada where dominated by mRNA technology vaccine (Pfizer and Moderna) (Public Health Agency of Canada, 2021).

The number of the retrieved AE reports allowed us to extend the PMS assessment to diverse US populations and to populations that were not covered in the pre-marketing clinical development programs of the three approved vaccines. However, our analyses were conducted in the context of the spontaneous (unsolicited) AE reporting passive framework of VAERS. This precluded us from running all typical risk-, rate- or hazard-based analyses (i.e. having the actual population of the study as a denominator). It also precluded us from running several comparative analyses among the three vaccines adjusting for the relevant measured confounders. Our study has several limitations. First limitation to this study is that the data source we used (i.e., VAERS) cannot and does not determine whether a vaccine caused these AEs. Furthermore, our data was from December 2020 to March 2021, which was at the beginning of the rolling out COVID-19 vaccines, and more data are added to VAERS, which might not have the same patterns that our data did. Future real-world studies using electronic health records (EHRs) would be more informative in the post-marketing safety assessment of these vaccines.

5. Conclusions

Our study showed that the vast majority of the PMS AEs in the U.S. were non-serious and comparable to the findings of the Phase III trials. The study also showed no emerging trends in unknown serious AEs. Finally, we did not find any differences in the number of reported death cases between Moderna vs. Pfizer-BioNTech COVID-19 vaccines. Future large-scale, real-world studies are needed to confirm the findings of this study.

6. Statement of Proprietary Data:

Data used in this study are available and accessible through VAERS public domain (<http://vaers.hhs.gov/index>).

7. Funding/Support:

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Role of Sponsor: No funding was allocated for this study.

The study was design and co-supervised by Thamir Alshammari and Turki Althunian. Omar Albalawi and Maha Alomran contributed to the conception and design of the study. Maha Alomran, Omar Albalaw and Ghada Alsagry completed the data extraction, linkage and coding. Omar Albalaw, Maha Alomran conducted the descriptive statistical analyses. Turki Althunian conducted the regression analysis of mortality data. Omar Albalawi drafted the manuscript, and Turki Althunian supervised the writing process and made a substantial contribution to editing the manuscript. The final version was reviewed by Thamir Alshammari. All authors were reviewed approved the final version of the manuscript.

8. Ethics approval

This study was conducted retrospectively from de-identified data obtained for pharmacovigilance and clinical purposes (publicly available). Thus, no ethical approval was needed.

9. Consent to participate

Not applicable.

10. Consent for publication

Not applicable.

11. Disclaimer:

The views expressed in this paper are those of the author(s) and not do not necessarily reflect those of the SFDA or its stakeholders. Guaranteeing the accuracy and the validity of the data is a sole responsibility of the research team".

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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