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Acute unsolicited adverse events following BNT162b2 vaccine in Saudi Arabia, a real-world data

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A B S T R A C T

Background: Acute adverse events and anaphylaxis were reported after the administration of coronavirus disease (COVID-19) mRNA vaccines. We aim to explore the nature and outcome of adverse events following BNT162B2 vaccine in a community vaccination center, Riyadh, Saudi Arabia.

Method: Within 30 min post vaccination, all acute adverse events (AAEs) that occurred before March 31st, 2021, and in people older than 16 years were reviewed (AAE group). We used the case definition of Brighton collaboration on vaccine safety to define anaphylaxis. Patients’ demographics, comorbidities, allergy history, and outcome at disposition were collected. Observation duration after vaccination was short (<15 min) or extended (<3 h). Statistical analysis was performed to study AAEs association with the study variables and outcomes.

Results: Out of 71,221 vaccine recipients, 144 (0.002%) had developed 345 AAEs, at a rate of 48.4 events per 10,000 dose administered. The majority of cases in AAE group were first dose recipients (93.8%) and previously healthy (59%), while the minority had a previous history of allergy (6.3%) or a laboratory-confirmed COVID-19 (4.2%). We found a significant association between female gender and the occurrence of any AAE (p-value = 0.002). Per every 10,000 doses administered, non-anaphylactic AAEs were dizziness (17.8), headache (9.7), nausea (7.1), or syncope (3.2). Only one in every ten AAEs was considered serious and resulted in an extended observation (4.8 per 10,000 doses), but only 1/144 required hospitalization for non-anaphylaxis reasons (0.1 per 10,000 doses). According to the Brighton collaboration definition of anaphylaxis, no single case of high certainty anaphylaxis was recorded. No death was documented in this cohort.

Conclusion: Acute adverse events due to BNT162b2 vaccine were rare and mostly non-serious with a tendency to occur more in women. Further prospective studies on larger vaccine recipients to evaluate the incidence of anaphylaxis in the Saudi population are warranted.

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1. Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused one of the most devastating pandemics which has affected tens of millions of people globally and resulted in millions of deaths [1]. In less than a year of the first reported case of coronavirus disease (COVID-19), several vaccines against SARS-CoV-2 have been granted emergency use authorization and have been rolled out in many countries, including Saudi Arabia [2].

BNT162B2, a lipid nanoparticle that encapsulates nucleoside modified mRNA that encodes the SARS-CoV-2 full length spike (S) protein, demonstrated 95% efficacy in preventing COVID-19 disease, seven days following a two-dose regimen [3]. However, in phase III randomized clinical trial, one in four (26.7%) vaccine recipients had at least a single adverse event within two months following any dose of BNT162B2 administration, but only 1.2% had severe or a life-threatening event [3]. Early after vaccine rollout in the real world, the United States Centers for Disease Control and Prevention (CDC) has reported that the risk of
anaphylaxis from BNT162B2 vaccine was estimated to be as low as
11.1 events per million doses administered [4], and the only con-
traindication to the vaccine is an allergic reaction (of any severity)
immediately after receipt of an mRNA COVID-19 vaccine or its
components, including polyethylene glycol; or immediate allergic
reaction (of any severity) to polysorbate [5]. The risk of such
adverse events is not known in Saudi Arabia.

The BNT162B2 vaccine was granted emergency use authoriza-
tion by the Saudi food and drug administration (SFDA) [6] on
December 10, 2020 and rolled out to the public on December
17th, 2020 [2]. Another vaccine (ChAdOx1- AstraZeneca) was also
rolled out on February 18, 2021 [7]. As of April 12, 2021, over six
million vaccine doses have been administered from both types [8].

The Saudi national protocol [9] for vaccine administration rec-
ommends that persons who receive BNT162B2 must be observed
after vaccination for 30 min for persons with a history of mild to
moderate allergies or using anticoagulants or suffering from bleed-
ing disorders, and for 10 min for all other persons.

While the mRNA vaccines have not been used outside of clinical
trials before their worldwide rollout, we aimed to explore the nat-
ure and outcome of acute unsolicited adverse events following
BNT162B2 vaccine during the observation periods in a community
vaccination center in Riyadh, Saudi Arabia.

2. Method

2.1. Settings

2.1.1. Vaccine and vaccination center

A two-dose regimen of 30-µg of BNT162b2, a lipid
nanoparticle–formulated, nucleoside-modified RNA encoding the
SARS-CoV-2 full-length spike, were administered to each recipient
at 3–6 weeks intervals. The community vaccination center located
in a public hospital in Riyadh, Saudi Arabia is among the centers
where BNT162B2 vaccine is administered at a rate of 1500–3000
doses per day. This center is equipped with the necessary medical,
storage, and administrative support. The BNT162B2 vaccine is
stored according to the manufacturer’s recommendation.

2.1.2. Vaccination protocol

As part of the national campaign for mass vaccination against
COVID-19, the Saudi Ministry of Health (MOH) has established an
 electronic system to book vaccination appointments, through
which the vaccine recipient will choose a nearby center to receive
the COVID-19 vaccine. Upon arrival at the vaccine center, the vac-
cine recipient will be evaluated by the vaccinator for any vaccine
contraindications as per the vaccine manufacturer’s recommenda-
tions. These contraindications include pregnancy or anaphylaxis to
any of the vaccine components. If no contraindication, the vaccine is
administered and followed by a 15–30 min observation period,
according to the risk of anaphylaxis. In case the vaccine recipient is
observed to have any adverse events, the necessary medical sta-
bilization including, if needed, a transfer to critical care is provided,
and a standard reporting sheet is completed by the vaccinator. If
the patient’s status is stabilized or the vaccine recipient did not
develop any adverse events, he/she will be discharged home.

2.2. Study design and population

Between February 1st and March 31st: 2021, a retrospective
review of all recorded adverse events following BNT162B2 vaccina-
tion was performed. During our inclusion period, those younger
than 16 years of age were excluded from vaccination as per the
manufacturer’s recommendations. During the study period, the
national phased approach for vaccination included all other age
groups. The study analysis of adverse events was performed after
the exclusion of reports with insufficient data. The form included
(1) basic characteristics: demographic data, prior history of aller-
gens, any comorbid conditions, previous laboratory-confirmed
COVID-19, current regular medications, recent non-COVID-19 vac-
cination; (2) COVID-19 vaccine data: type, number of doses, date,
locations. Data on adverse events included: symptoms, administra-
tion to adverse event duration, vital signs, as well as the final dis-
position and outcome.

2.3. Definitions

According to United States Food and Drug Administration (US-
FDA) definitions, adverse events (AE) is any unwanted medical
occurrence in an individual temporally following administration
of the vaccine, either voluntarily reported by the vaccinated indi-
vidual or observed by the health care provider, while serious
adverse event (SAE) is defined as any adverse event that results
in death, life threatening event, inpatient hospitalization, signifi-
cant incapacity, or disruption to conduct normal life functions.
Other important medical events that may not result in above
states, but may require immediate intervention like allergic bron-
chospasm requiring intensive treatment, might be considered seri-
ous according to clinical judgment of physician in the scene [10].
For the purpose of this study, acute adverse event (AAE) and SAE
that occurred 10–30 min following vaccination were included.
Vaccine recipients who did not develop any adverse events were
labeled as (no-AAE).

Short observation following vaccination is defined as less than
15 minutes following vaccine administration, while extended
observation is labeled if lasted more than 15 minutes but less than
3 hours after vaccine administration.

We used Brighton Collaboration case definition criteria for an-
aphylaxis following vaccination [11]. The criteria are endorsed by
the US CDC and classify post-immunization event into 5 levels of
certainties, where the levels 1 and 2, 3 represent high, intermedi-
ate and low certainty of anaphylaxis, respectively, while level-4
and level-5 indicate unlikelihood of anaphylaxis.

2.4. Statistical analysis

Frequency, percentage, and median were used to present
numerical variables. Further statistical analysis was carried out
by using the SPSS software (version-23, IBM Corp., Armonk, N.Y.,
USA). A chi-squared test was used and all variables were subjected
to calculate the odds ratio and 95% confidence interval, as needed.

3. Results

During the study period, a total of 71,363 individuals arrived for
COVID-19 vaccination in our center. Out of those, 142 persons
were not given the vaccine for variable reasons. [Fig. 1] Hence,
the total number of vaccine recipients (VRs) were 71,221 individu-
als, ninety percent (91.17%) were younger than 55 years of age
(n = 64,934) with a median age of 32 years (range: 16–109 years),
56% were male (n = 39,884), and 91% were Saudi nationals
(64,811). Regarding adverse events, we found 144 (0.002%) vaccine
recipients who had developed 345 acute adverse events (AAE
group), while the remaining 71,077 vaccine recipients did not
develop any adverse events (No-AAE group). A significantly larger
percentage of female individuals were observed in the AE group
compared to the no-AAE group (56.9% versus 44%) (p-
value = 0.002) [Table 1].

The majority of cases in the AAE group had adverse events after
the first dose of the two-dose regimen (93.8%). There were only
nine VRs (6.3%) who reported a previous history of allergy to food (n = 4), drug (n = 2), or non-specific (n = 3). Past medical history was non-revealing in 59% of the VRs, while the more frequently reported comorbidity condition were cardiac disease (hypertension or ischemic heart disease, 11.8%) and/or diabetes mellitus (9%). Only six cases had a history of laboratory-confirmed COVID-19 [Table 2].

One in every ten (9.9%) adverse events reported was considered serious adverse events (SAE). The most common of which was the acute transient loss of consciousness (n = 23), resembling in most instances a vasovagal response, which occurred at a rate of 3.2 per 10,000 doses administered, most of which required <15 min of observation. However, the rate of extended observation (being number of adverse events in any single patient increased the likelihood for extended observation and/or hospitalization (p-value = 0.001), there was no statistical association between demographic, past medical history, and/or history of allergy with the data on the vital signs were not analyzed due to the lack of data in the majority of this study cohort [Table 3].

Following any type of adverse events, three-quarters (75.7%) of vaccine recipients were observed for < 15 min and discharged in stable condition. However, the rate of extended observation (beyond 15 min) or hospitalization due to an SAE was estimated to be 4.9 per 10,000 doses administered [Table 3]. While an increasing number of adverse events in any single patient increased the likelihood of extended observation and/or hospitalization (p-value < 0.001), there was no statistical association between demographic, past medical history, and/or history of allergy with increased likelihood for extended observation and/or hospitalization [Table 4].

4. Discussion

In this real-world study from Saudi Arabia, acute adverse events within 30 min following administration of the BNT162b2 vaccine was found to be extremely low, at a rate of 48.4 events in every 10,000-dose administered, most of which required<15 min of observation.

### Table 1
Demographic data among BNT162b2 vaccine recipients (VR) in a community vaccination center, Riyadh, Saudi Arabia between February 18th - March 31st 2021 (n = 71,221), stratified by the number of those who developed acute adverse events (AAE) and those who did not (No-AAE).

| Parameters          | Total n = 71,221 (%) | AE group n = 144 (%) | No-AAE group n = 71,077 (%) | p-value | Odds ratio (OR) (95% CI) |
|---------------------|----------------------|----------------------|-----------------------------|---------|-------------------------|
| Age                 |                      |                      |                             |         |                         |
| Median (range)      | 32 (16–109)          | 29 (17–70)           | 32 (16–109)                 | 0.17    | 1.69 (1.21–2.34)        |
| 16–55 years         | 64,934 (91.17)       | 136 (94.4)           | 64,798 (91.2)               |         |                         |
| > 55 years          | 6,287 (8.83)         | 8 (5.6)              | 6,279 (8.8)                 |         |                         |
| Sex                 |                      |                      |                             |         |                         |
| Female              | 31,337 (44)          | 82 (56.9)            | 31,255 (44)                 | 0.002   | 1.69 (1.21–2.34)        |
| Male                | 39,884 (56)          | 62 (43.1)            | 39,822 (56)                 |         |                         |
| Nationality         |                      |                      |                             |         |                         |
| Saudi               | 64,811 (91)          | 136 (94.4)           | 64,675 (91)                 | 0.15    |                         |
| Other               | 6,410 (9)            | 8 (56)               | 6,402 (9)                   |         |                         |

AE (adverse events) or no-AE, vaccine recipients who developed or did not develop adverse events.
observation. Moreover, the rate of SAE that required extended observation and/or hospitalization was 4.8 events in every 10,000-dose administered. There was no single case of anaphylaxis nor death observed within the study. Compared to the fatality risk of COVID-19 in Saudi Arabia (1.24%, 124 deaths per 10,000 infected person) [12], such high safety profile during the immediate period post-vaccination is largely reassuring.

The risk of anaphylaxis following vaccine administration is repeatedly reported to be low with various types of vaccines [13]. The current vaccine, BNT162b2, was expected to cause vacci-
nation hesitancy given its extraordinary rapid development and relatively new manufacturing technology. Phase III clinical trial of BNT162b2 vaccine did not show a significant risk of acute adverse events including anaphylaxis [3]. However, the United States centers for disease control and prevention (US CDC) reported a risk of anaphylaxis in 11.1 cases per million doses administered [4], especially among those with a history of documented allergy. This could suggest that the anaphylaxis incidence following BNT162b is 8.5 times the incidence reported in 2016 following other vaccines (1.31 per million doses) [14], though this is still considered extremely low. Among the current study participants, the absence of anaphylaxis can be explained by few factors. First, in our 71,221-dose cohort, the rate of occurrence of anaphylaxis as per the US CDC rate is expected to occur in less than one case (0.7 case), which lead to the absence of anaphylaxis in our cohort. Second, the exclusion of those with a known history of severe anaphylaxis (n = 32) might have prevented the occurrence of anaphylaxis.

The nature of post-vaccination syncope is not clearly understood. Recently, the World Health Organization (WHO) has proposed a new term, immunization stress-related response (ISRR), which is described as a spectrum of anxiety-related symptoms and signs that may develop before or after immunization. The symptoms may vary from mild feelings of worry to tachycardia, palpitations, dyspnea, syncope, or hyperventilation [15]. Such a term can apply to most of the symptoms reported in our cases. Post-vaccination syncope occurrence in our cases was as low as 3.2 per 10,000 vaccines administered. Reassuringly, such a rate falls within the range reported in the medical literature for other vaccines, 1.4 per 10,000 doses [16] – 8.8 per 10,000 doses [17]. However, in its phase III clinical trial, post-vaccination syncope was less observed in the BNT162b2 vaccine recipients compared to placebo. These altogether might hint toward that the observed syncope in our cohort was part of ISRR rather than other medical causes of syncope, especially that all of the study cohort spontaneously recovered.

Compared to males, female vaccine recipients were 69% more likely to experience acute adverse events, including allergic and/or non-allergic types of events. This has been previously documented in multiple reports that showed gender difference (more to females) in the hypersensitivity reactions following exposure to different allergens [18], including H1N1 vaccines [19] and BNT162b2 [4,20]. It is unclear whether this association is due to reporting bias or due to specific biological reasons, further studies are needed to explore this association. There was no significant association between age and the likelihood to develop AAEs. This is in contrast to the reported findings in the BNT162b2 phase III trial on acute and non-acute adverse events, in which those older than 55 years were less likely to develop any adverse events.

Overall, non-anaphylaxis adverse events in this cohort were mostly systemic and were considered non-serious, i.e., dizziness, headache, nausea, vomiting, fatigue. These events were all documented in the phase III trial of the BNT162b2 vaccine but with a higher frequency, mostly due to longer follow-up in the trial.

The medical management of post-vaccination adverse events is largely based on symptomatic treatment, as per the current recommendation by the US CDC as well as the Saudi MOH. No single patient within the cohort needed an epinephrine injection or invasive ventilation, and/or resulted in an immediate complication that led to death. This might be due to the exclusion of patients with any history of significant anaphylaxis from receiving the vaccine.

Although this study included a large number of vaccination doses, the current study has few limitations. Being retrospective, especially with the lack of control subjects could limit the generalization of its conclusion. Besides, lack of objective evaluation of these adverse events (i.e., laboratory and other diagnostics) might limit underlying cause identifications.

5. Conclusion

Acute adverse events due to BNT162b2 vaccine were rare and mostly non-serious with a tendency to occur more commonly in women. Further prospective studies on larger vaccine recipients to evaluate the incidence of anaphylaxis in the Saudi population are warranted.

Disclosure

All authors have read and agreed on the final version of this article. All authors have contributed to this research work.

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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Ethical approval

Approved by the institutional review board with an IRB log number: KFMC-21-146E.

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