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Early solicited adverse events following the BNT162b2 mRNA vaccination, a population survey from Saudi Arabia

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ABSTRACT

Post rollout safety for the coronavirus disease vaccines is crucial and recommended. To explore the early solicited adverse events (AE) following BNT162b2 mRNA vaccination in Saudi Arabia, we distributed an online survey to adults vaccinated with BNT162b2 over the first week of June 2021, to collect data on first (V1), second doses (V2), symptoms, severity, and outcome after an informed consent was obtained. We recruited 3639 BNT162b2 vaccinated individuals, of which one-third had received two doses, 63.3% were female, 77% were healthy, and 89% had 18–55 years of age, while only 9.8% had a history of allergy. Overall, 50.3% had any AEs after any dose, especially those younger than 55 years of age, female, history of comorbidity, and when adjusted for age and gender, lung or cardiovascular diseases. Overall, the most common AE were pain at the injection site (44%), tiredness (39%), or body ache (31%). Compared to V1, a higher rate of post-V2 systemic AE (36% vs. 51%). Most AEs started very early (within 3 days), and rarely delayed in recovery (>2 weeks). Anti-pyretic was the most commonly used (51.7%), a third of which was unnecessary. Only 1.7% required hospital admission. By multivariate analysis, predictors for admission were the presence of lung or immunocompromising diseases. In conclusion, common AEs after BNT162b2 in the real world were generally mild, self-limiting, higher after the second dose, and largely mimicking that reported in clinical trials. The causality of these AE and the persistence of post-vaccination symptoms needs to be investigated further.

1. Introduction

The devastating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused almost 170 million confirmed cases of coronavirus disease (COVID-19) and >3 million deaths globally (COVID-19 Map). Early on, governments around the world took drastic measures to mitigate the effects of the pandemic, leading to economic, social, and educational crises. Such efforts were introduced early during the pandemic and included lockdowns and curfew (Al-Tawfiq and Memish, 2020). Scientists and pharmaceutical manufacturers rapidly raced to develop vaccines against SARS-CoV-2 in an unprecedented time (McDonald et al., 2021). Using a variety of technologies, such efforts have led some vaccines to be granted emergency use authorization from multiple agencies, one of the very first was the BNT162b2 mRNA vaccine by Pfizer-BioNTech, which was authorized in less than a year of the virus isolation (Vasireddy et al., 2021; Barry and Bahammam, 2021).

With its 95% relative efficacy, the phase III clinical trial of the BNT162b2 mRNA vaccine has reported rare and mostly mild adverse

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events following the administration of the two-dose regimen, and the most common adverse events were injection site pain, swelling, fever, fatigue, myalgia, and lymphadenopathy (Polack et al., 2020). In the Kingdom of Saudi Arabia (KSA), the BNT162b2 mRNA vaccine was among the two approved vaccines in the country (Barry and Bahammam, 2021; Saudi Food & Drug Authority). The government has established a national vaccination campaign divided into phases, according to the individual risk assessment (Barry and Bahammam, 2021). KSA took extraordinary steps utilizing both BNT162b2 and the AstraZeneca-Oxford vaccine to accomplish 70% coverage of the population (Assiri et al., 2021). Until the end of May 2021, fourteen million doses of the two approved vaccines have been administered (More Than 3.14 Billion Shots Given, 2021). Based on the manufacturer's recommendations, the only contraindication to the BNT162b2 mRNA vaccine administration is an immediate allergic reaction (of any severity) after receipt of an mRNA COVID-19 vaccine or its components, including polyethylene glycol and polysorbate (Center for Disease Control and Prevention).

Post-vaccination adverse event (AE) is defined by United States Centers for Disease Control and Prevention (US-CDC) as temporally associated events that might be caused by a vaccine and might be coincidental and not related to the vaccination (Ronald, 2002). AE reporting and safety monitoring are recommended by multiple institutions worldwide, especially during a pandemic (Castells and Phillips, 2021; COVID-19). Recently, there have been reassuring reports on the low incidence of immediate AEs after COVID-19 vaccination. One report from the US-CDC has shown the rarity of post-vaccination anaphylaxis (Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine, 2020). A recent report from the US-CDC has warned against BNT162b2 vaccine-associated myocarditis and pericarditis (Coronavirus (COVID-19), 2021). The detection of such events requires continuous monitoring and surveillance.

There is a paucity of data on early AE after BNT162b2 vaccination in Saudi Arabia. Therefore, we aim to explore the nature and frequency of solicited early adverse events within the first two weeks following the first or second doses of the BNT162B2 mRNA vaccine and to identify outcomes and predictors to develop such adverse events, predictors for hospital admission, as well as medication consumption.

2. Method

2.1. Study design and population

This is a cross-sectional survey using an online questionnaire. The survey was distributed electronically from May 29th to June 8th, 2021 to the vaccine recipients in the general population through social media platforms (Twitter, WhatsApp, and others) and visitors of the vaccination center.

2.2. Study population

Saudi Arabia, which has a population of 32 million, rolled out vaccination against COVID-19 on December 17, 2020. We calculated the minimum required responses using the website Raosoft software to be 385 responses based on an estimate of 50% response rate and 95% confidence interval with a 5% margin of error. Eligibility criteria included being a resident of the Kingdom of Saudi Arabia at the time of enrollment, being 18 years or older, and having had received at least one dose of BNT162b2 mRNA vaccine. We excluded any incomplete responses.

2.3. Study tool and questionnaire development

We developed an online questionnaire based on previous studies on the safety of influenza vaccines (Pillsbury et al., 2018; Govaert et al., 1993; Allsup et al., 2001; Margolis, 1990). It was adjusted to fit the current study objectives. The English version was face validated by two experts in the field and its language was also adjusted by a Ph.D. holder in English studies. Then the questionnaire was translated to the Arabic language by the authors and was validated by a senior resident fluent in Arabic. This was followed by validation on the back translation by a Ph. D. holder in English language studies. Finally, a pilot study was carried out on 17 volunteers who provided further suggestions and feedback.

The final version of the questionnaire started with the following question: Did you ever have an adverse event following the study vaccine? (a Yes" or "No"). The answer to the following parts was based on the answer to the first question and if the answer was no, participants were allowed to answer parts one and two, and if the answer was "Yes", then they were directed to the five parts of the questionnaire. Part (1) included demographic and clinical characteristics of the vaccine recipients. Part (2) was related to vaccine dose details including the date of the first or second dose, and the interval between doses. Part (3) solicited symptoms using closed-ended questions, within two weeks following the administration and included the following vaccine side effects: local adverse events (LAE): rash, pain, swelling, itching, bleeding, pit arm swelling; systemic adverse events (SAE) which was subdivided into: flu-like AE: sore throat, runny nose, headache, tiredness, fever, body ache; allergic AE: generalized body rash, chest wheezes, lip swelling; gastrointestinal AE: diarrhea, nausea, vomiting, abdominal pain; neurological AE: dizziness, loss of consciousness, fits, other AE: anxiety, sleep disturbances, palpitation, blood pressure changes. Part (4) included the duration of symptoms, and whether medical attention was required. Level of medical intervention was based on self-reported history and was categorized into: no medical care was needed, visited primary care clinic, visited emergency room or admitted to non-critical care, or admitted to critical care unit. If the participants chose the last two items, another window will appear to further detail the emergency room visit and/or admission or critical care admission. Part (5) aimed to identify how the vaccine recipient was self-managed, whether used medications (anti-pyretic, anti-histamine, epinephrine, steroids, or others). At the end of the survey, study participants were allowed to add any other input in an open-ended question.

2.4. Ethical considerations

This study was approved by the local research and ethical committee board (meeting number 1/203), Almaarefa University, Riyadh, Saudi Arabia, on May 24th, 2021. Participants were considered consented once they agree to enroll in the study. Their anonymous data were confidentially stored in a trusted remote server with the appropriate standards of security. All participants were allowed to terminate the questionnaire at any time. There was no incentive to participants. To recruit more participants who are not familiar with the use of technology, we allowed filling the questionnaire on behalf of any relatives/friends who were unable to fill the questionnaire by themselves.

2.5. Statistical analysis

The data were collected using google forms and analyzed by the SPSS software (version-23, IBM Corp., Armonk, N.Y., USA). Descriptive statistics (range, median, and percentages) were utilized to present qualitative data. Comparison of categorical data was performed by Chi-Square test. Univariate analysis was used to identify the study end points: predictors to develop AE, the need for hospital admission, or the consumption of medications after the vaccination. Multivariate (logistic regressions) was also utilized to identify independent variables association with the study end points. Data were presented as odds ratio (OR), 95% confidence interval (95% CI, and adjusted odds ratio (aOR). The consumption of anti-pyretic, anti-histamine, and steroids was deemed unnecessary if the participant reported no history of AE.

3. Results

3.1. Respondents

Between May 29th to June 8th, 2021, after excluding 9 incomplete responses, we received complete responses from 3,639 adults aged 18 years or above from all the regions of the Kingdom of Saudi Arabia, who confirmed the receipt of the BNT162b2 mRNA vaccine at least 14 days before participation. The majority of the responses were completed by the vaccine recipients themselves (92.9%) while 7.1% were filled by someone on behalf of the vaccine recipients. One-third of the respondents (35.7%, n = 1298) had received two doses of the BNT162b2 mRNA vaccine. The interval between the two doses was less than six weeks in 58.1% (n = 727/1298), among which, only 210/727 vaccine recipients had the recommended 21-day interval. Of the participants 2302 (63.3%) were females, 3284 (90.2%) were Saudi citizens, 3271 (89.9%) were 18–55 years of age, 2801 (77%) were healthy , 2304 (63.3%) had university degree , and 2042 (56.1%) were from the central region of Saudi Arabia (Table 1). Two doses of the BNT162b2 mRNA vaccine were given to most respondents aged > 55 years (69%, n = 254/368), while the majority of the younger age group had received only one dose (68.1%, n = 2227/3271) at the time of the questionnaire. Comorbid conditions were uncommon (23%, n = 838/3639) but the frequent ones were diabetes mellitus (8.2%, n = 297) and cardiovascular diseases (5.4%, n = 197). There was a self-reported history of allergy in 9.8% (n = 358) and were mainly due to medications (n = 102) or seafood (n = 42); only a few had egg allergy (n = 21) or allergy to an unspecified type of influenza vaccine (n = 2) (Table 1).

Table 1
Basic epidemiology, past medical history, and vaccination data among a cohort of adult BNT162b2 mRNA vaccine recipients in Saudi Arabia recruited through an online questionnaire between May 29th to June 8th, 2021 (n = 3639):

Study parameter		n (%)
Age	Median, years (Interquartile range)	37.0 (28.0–48.0)
	> 55 years	368 (10.1)
	18–55 years	3271 (89.9)
Gender	Female	2302 (63.3)
	Male	1337 (36.7)
Nationality	Saudi	3284 (90.2)
	Other nationality	355 (9.8)
Residence area in the Kingdom of Saudi Arabia	Central region	2042 (56.1)
	Western region	689 (18.9)
	Eastern region	507 (13.9)
	Southern region	233 (6.4)
	Northern region	168 (4.6)
Highest education level	University Degree	2304 (63.3)
	Post-graduation Studies	463 (12.7)
	Secondary school or below	872 (24)
Job sector	Education sector	691 (19.6)
	Government sector	354 (10)
	Health sector	444 (12.6)
	Other sectors	531 (15.1)
	Unemployed	764 (21.7)
	Housewife	624 (17.7)
	Retired	118 (3.3)
Past medical history	Medically free	2801 (77)
	Diabetes Mellitus	297 (8.2)
	Cardiovascular diseases	197 (5.4)
	Obesity	166 (4.6)
	Bronchial asthma or any lung disease	164 (4.5)
	Immunocompromising conditions	84 (2.3)
	Renal or liver disease	31 (0.9)
	Other comorbid conditions	101 (2.8)
Self-reported allergy	No	3281 (90.2)
	Yes	358 (9.8)
	▪ Unspecified	124 (34.8)
	▪ Medication	102 (28.7)
	▪ Seafood	42 (11.8)
	▪ Fruits	34 (9.6)
	▪ Eggs	21 (5.9)
	▪ Nuts	12 (3.5)
	▪ Vaccine (Influenza)	2 (0.6)
	▪ Other	19 (5.3)
Doses received of the vaccine	Single-dose	**2341 (64.3)**
	Two doses	**1298 (35.7)**
The interval between the two doses, n = 1298	▪ <6 weeks	**727 (56)**
	▪ ≥6 weeks	**524 (40.4)**
	▪ No answer provided	**47 (3.6)**

3.2. Adverse events, overall

Half of the respondents (50.3%, n = 1830) experienced at least one adverse event within two weeks of any dose of BNT162b2 mRNA vaccination. Local adverse events (LAE) were reported by 46% (n = 1658) of the respondents, while systemic adverse events (SAE) were reported by 45% (n = 1633). Both LAE and SAE were reported by the same participant in 41.2% (n = 1499), but only LAE (4.4%, n = 159) or only SAE (3.7%, n = 134) were reported in a much lower proportion. The most common category was flu-like and occurred in 34% and 50% after first and second doses, respectively. The other categories were gastrointestinal, neurological, allergic, or others and were reported less commonly. Figure 1 Overall, the occurrence of any adverse event was higher following the second dose (55%, n = 714/1298) compared to the first dose (46%, n = 1950/3639). This difference was irrespective of the interval between the two doses. SAEs after the second dose (51%) were higher than that after the first dose (36%), while LAEs were reported equally after the first or the second doses (43%) Figure 2.

3.3. Adverse events types and occurrences

The most common LAEs were pain at the injection site (44%), swelling (14%), or itching (11%). The most common SAEs were tiredness (39%), body ache (31%), headache (27%), dizziness (17%), or fever (16%). In the open-ended section addressing rare adverse events, the following reactions were reported: delayed menstruation (n = 8), a flare of underlying diseases (multiple sclerosis and chronic sinusitis) (n = 2), red-eye (2), erectile dysfunction (n = 1), anemia (n = 1), and loss of appetite (n = 1). A detailed list of symptoms is presented in Figure 3. Both LAE and SAE were less common in those older than 55 years of age compared to those aged 18–55 years Figure 3.

3.4. Onset, duration, and severity

The onset of the vast majority (89.5%) of AEs occurred within the first three days following vaccination, especially the occurrence of fever, tiredness, body ache, or pain at the injection site, while delayed onset of AE has occurred in only 6.4% of the respondents. In addition, 20% of the individuals had generalized body rash, fits, or fainting occurring beyond 3 days. The median duration of AEs was two days, with the majority (70.2%) having complete recovery within three days after symptoms onset. Nevertheless, the persistence of post-vaccination symptoms for more than two weeks was reported by 79 (out of 1830, 4.3%) and had fatigue, body ache, headache, or sleep disturbance. Fortunately, 82.8% of respondents with AEs had no need for any sort of medical care (n = 1516) while 15.5% had visited primary care clinic for advice (n = 283). Thirty-one participants reported a hospital admission, with an average length of stay of 1.2 days, only two of them went to critical care unit. Longer hospital admission was reported by three respondents: acute coronary syndrome requiring coronary artery bypass graft (CABG) surgery two weeks after the 1st dose with a hospital stay of 30 days; lung fibrosis with a flare 8 days after the 1st dose with a hospital stay of 16 days; and laboratory-confirmed COVID-19 three days after the 1st dose with critical care stay of 8 days (Table 2).

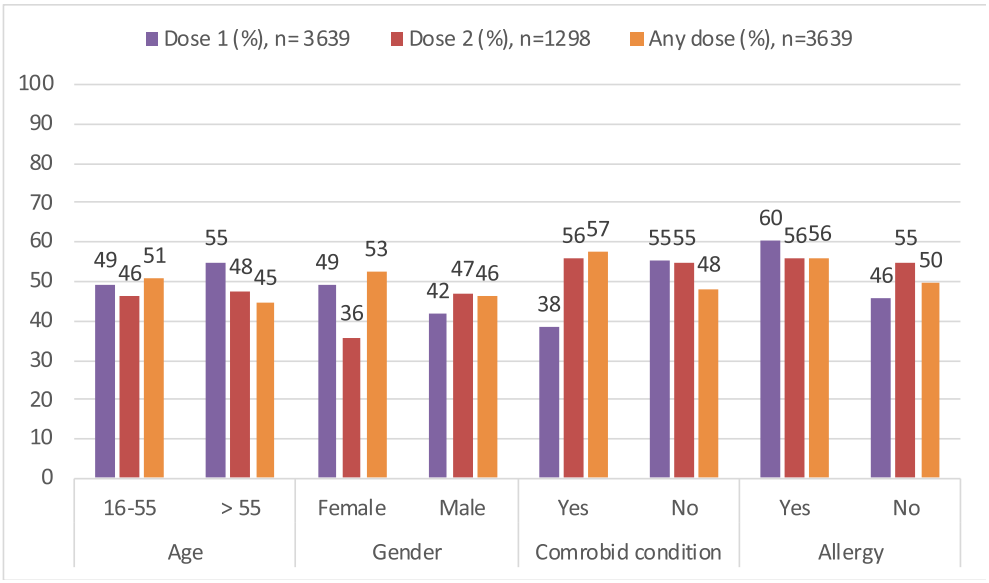

Fig. 1. The occurrence rate of any adverse events stratified by age, gender, comorbidities, or allergy, in reference to the number of doses, among a cohort of BNT162b2 mRNA vaccine recipients in Saudi Arabia recruited through an online questionnaire between May 29th to June 8th, 2021 (numbers in percentage).

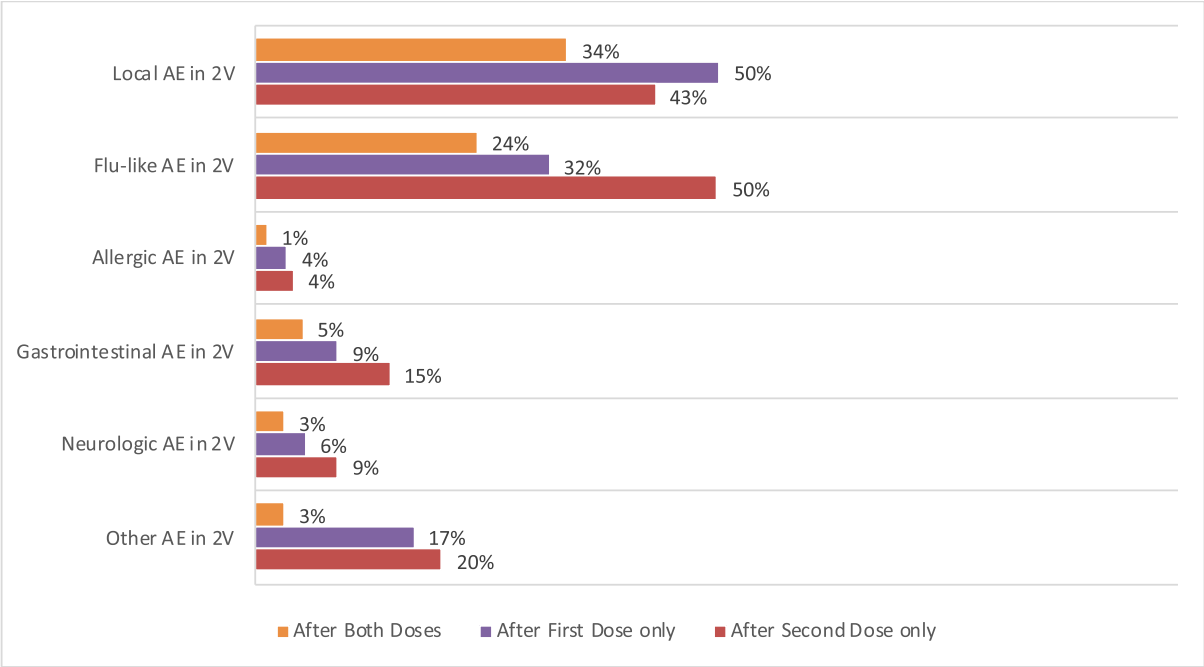

Fig. 2. Including only the two-dose vaccines recipients (2 V), a comparison between dose 1 alone, dose 2 alone, or both doses for each category of adverse events among a cohort of BNT162b2 mRNA vaccine recipients in Saudi Arabia recruited through an online questionnaire between May 29th to June 8th, 2021 (n = 1298).

3.5. *Predictors for AE and/or admission following vaccination*

We identified the age of 18–55 years (p-value $\leq$ 0.001, adjusted OR: 1.517, 95% CI: 1.206–1.909), female gender (p-value = 0.001, adjusted OR: 1.258, 95% CI: 1.099–1.442), or pre-existing comorbid condition (p-value $\leq$ 0.001, adjusted OR: 1.322, 95% CI: 1.065–1.642), and when adjusted for age and gender, history of lung diseases (p-value = 0.003, adjusted OR: 1.656, 95% CI: 1.189–2.306) or cardiovascular diseases (p-value = 0.001, adjusted OR: 1.707, 95% CI: 1.242–2.347) were independent risk factors for the development of any AE in multivariate logistic regression analysis. The need for hospital admission following vaccination was independently associated with participants who have history of lung disease (p-value = 0.002, adjusted OR: 4.336, 95% CI: 1.686–11.15) or immunocompromising conditions (p-value = 0.001, adjusted OR: 6.373, 95% CI: 2.193–18.52) when adjusted for age and gender (Table 3).

3.6. *Medication use*

Participants reported the use of antipyretics (n = 1880; 51.7%), antihistamine (n = 99; 2.7%), or steroids (n = 23; 0.6%). However, 31.7% of the anti-pyretic, 27.3% of the antihistamine, and 21.7% of steroids users were initiated empirically without AE (Table 2). In multivariate logistic regression, the unnecessary use of antipyretic (in the absence of

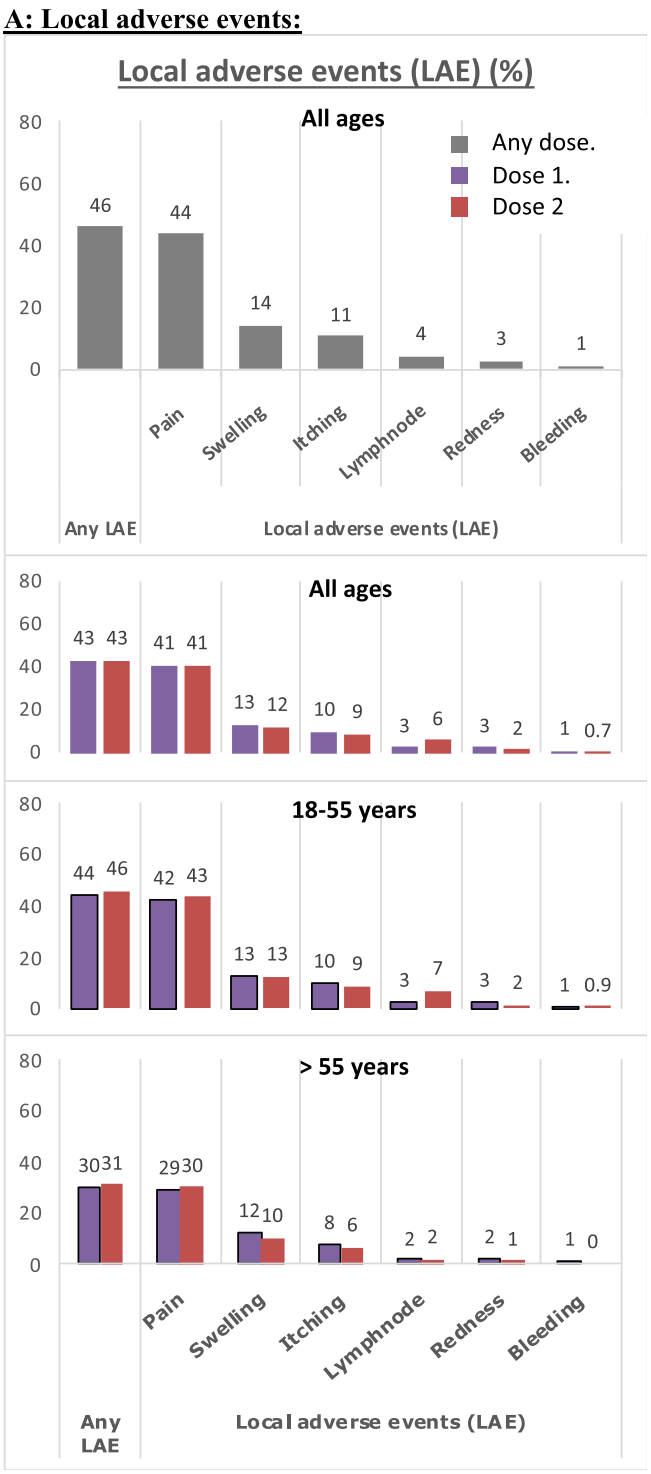

Fig. 3. A, B: Percentage of patients who developed each solicited adverse events stratified by dose and age among a cohort of BNT162b2 mRNA vaccine recipients in Saudi Arabia recruited through an online questionnaire between May 29th to June 8th, 2021 (numbers in percentage).

AEs) was independently associated with female gender (p-value= <0.001, adjusted OR: 1.444, 95% CI: 1.225–1.701), while unnecessary use of anti-histamine (in the absence of AEs) was found predictable only in participants with history of allergy (p-value= <0.001, OR: 8.510, 95% CI: 4.032–17.962). Additionally, 9.9% of unnecessary antipyretic consumption and 11.1% of unnecessary antihistamine consumption were by the workers in healthcare (HC) sector. There was no difference between HC or other job sectors in the unnecessary consumption of anti-pyretic (p-value = 0.523) or antihistamine (p-value = 0.925).

4. Discussion

In this population-based survey in KSA, we report that one in two recipients of the BNT162b2 mRNA vaccine is expected to report at least one AE within two weeks of the vaccine administration, the most common of which were local injection-site pain, tiredness, and body ache with predominately rapid onset and rapid recovery and extremely rare risk for admission. Thus far, there are no published studies on the AEs of the BNT162b2 mRNA vaccine in the region.

B: Systemic Adverse events:

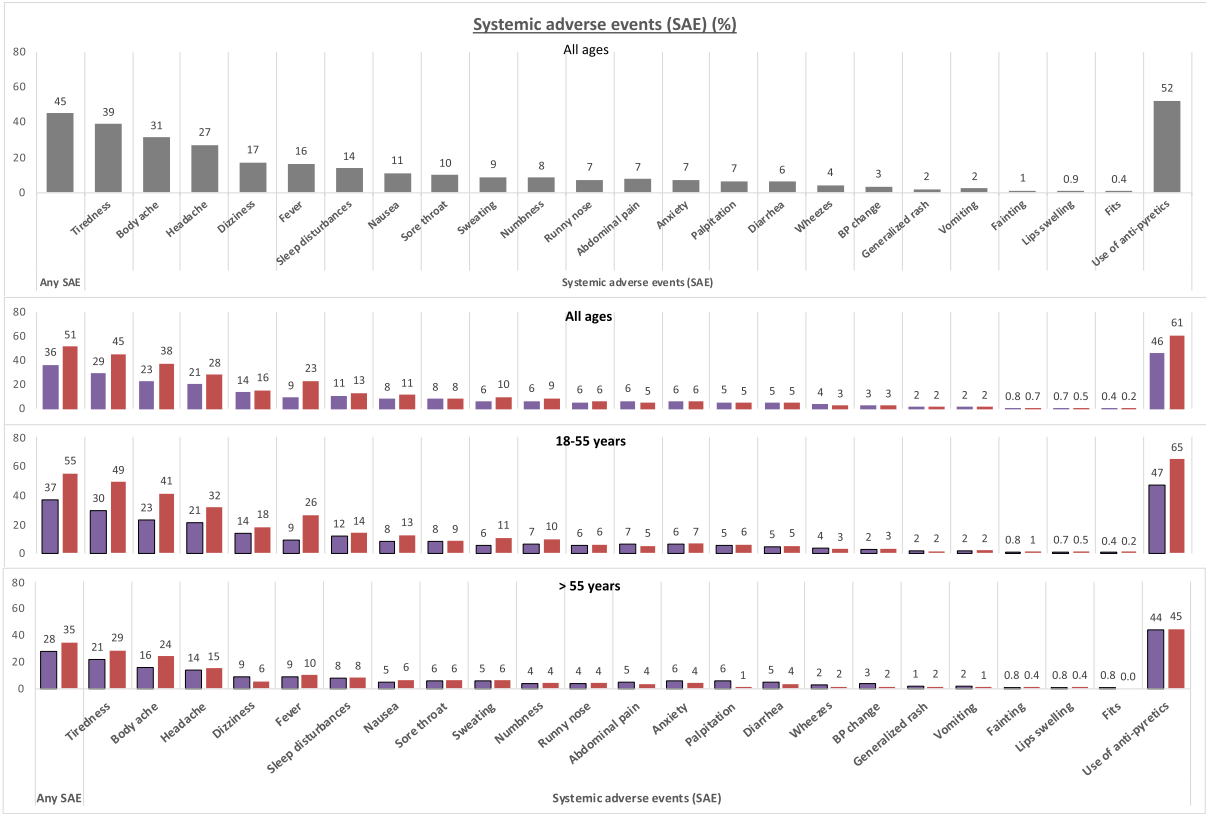

Fig. 3. (*continued*).

After the 1st dose of BNT162b2 mRNA vaccine in our cohort, tiredness was the most common systemic AE (29% of the first dose recipients) and this rate is lower than that reported in the literature (34–47% in clinical trial (Polack et al., 2020) and 49% among health care workers (Kadali et al., 2021); but higher than that reported from the United Kingdom (UK) (Menni et al., 2021) (8.4%). Potential reasons for such differences were the differences in the population surveyed, patients and language perception of the terms used, as well as the nature of data collection. In addition, an overestimation of the effect of the vaccine in clinical trials as related to the reported tiredness is possible, given that at least 23% of placebo recipients reported fatigue as well (Polack et al., 2020). In contrast, the most common local AE following the first dose in our cohort was pain at the injection site (41%) and is consistent with the reported rates of 29% in the UK study (Menni et al., 2021) and 71–83% in clinical trial (Polack et al., 2020). Unlike tiredness, individualized differences in pain perception due to genetic, sociological, and psychological factors are well known in the literature (Coghill, 2010) and could have played a role in this difference.

The second dose in this study was associated with 41% more systemic AEs compared to the first, irrespective of the interval between the two doses. This is similar to what was reported in the clinical trial (25–50% higher) and by the UK prospective study (88% higher) (Menni et al., 2021). Such higher reactogenicity following the second dose is believed to be related to post 1st dose immunogenicity. Recently, higher reactogenicity among COVID-19 convalescent individuals who received the SARS-CoV-2 vaccine was reported (Menni et al., 2021), likely because of a higher antibody titer compared to the vaccine recipients who never had COVID-19 natural infection (Krammer et al., 2021). Although seven participants reported palpitations, six of them were after the first dose and only one was after the second dose, however, none of them have reported myocarditis or pericarditis, and due to the nature of our study design, electro cardiac or cardiac imaging data were unavailable. Recently acute myocarditis was reported few hours after the second dose (Montgomery et al., 2021).

As expected from clinical trials and previous mRNA vaccine studies (Menni et al., 2021), we found a higher proportion of AEs among those younger than 55 years of age, women, those with comorbid illnesses, and among those with a history of allergy, compared to older individuals, males, and those with no history of allergy. Age and gender were found, by multivariate logistic regression analysis, to be independent risk factors for the development of an AE. It was not clear if age and gender differences are specific to the vaccine, its immunogenicity, or other unrelated factors. Although it has been reported that the female gender is more likely to report AEs after medications in general due to many factors (Tran et al., 1998), but further investigation is needed to assess if vaccine immunogenicity in younger age groups or women could explain their risk for AEs development.

Delayed onset of AEs beyond three days was reported by the minority of our participants (n = 117/1830), and this was similar to previous studies (Menni et al., 2021; Reactions and Adverse Events of the Pfizer-BioNTech COVID-19 Vaccine). Although this does not rule out delayed onset AEs beyond the window of our study, most of the reports in the literature on the AEs following vaccines, in general, have indicated an onset of AE within few weeks following their administration. This applies even to AEs that their causality with the vaccine was not confirmed, including Guillain-Barré syndrome or narcolepsy following the Influenza vaccine which has a typical onset within a few weeks (Juurlink, 2006; Duffy et al., 2014). Reassuringly, the chance of post-vaccination severe events that required a hospital admission was extremely rare (n = 31/3639, 1.7%) with an average hospital stay of 1.2 days. The few incidents of persistence of symptoms reported by our respondents, which increases by the presence of the history of admission, need further

Table 2
The nature, the duration, and the medications used among a cohort of adult BNT162b2 mRNA vaccine recipients in Saudi Arabia recruited through an online questionnaire between May 29th to June 8th, 2021:

Study parameter		n (%)
The onset of adverse events,n = 1830	First 3 days following vaccination	1637 (89.5)
	After 4–7 days of vaccination	69 (3.8)
	After 1 week of vaccination	48 (2.6)
	Not answered	76 (4.2)
Adverse events durationn = 1830	Median	2 days
	Resolved within 3 days	1284 (70.2)
	Resolved after 3 days	467 (25.5)
	Still suffering	79 (4.3)
	▪ Local pain	66
	▪ Fatigue	60
	▪ Body ache	51
	▪ Headache	49
	▪ Sleep disturbance	44
Self-reported medical intervention, n = 1830	No medical care was needed.	1,516 (82.8)
	Visited primary care clinic.	283 (15.5)
	Admitted to non-critical care.	29 (1.6)
	Admitted to critical care unit.	2 (0.1)
Medications consumption,n = 3639	Anti-pyretic	1880 (51.7)
	▪ With local adverse event (LAE)	1172/1880 (62.3)
	▪ With systemic adverse event (SAE)	1194/1880 (63.5)
	▪ With both LAE and SAE	1099/1880 (58.5)
	▪ Without adverse event	596/1880 (31.7)
	Antihistamine	99 (2.7%)
	▪ With local adverse event (LAE)	1/99 (1)
	▪ With systemic adverse event (SAE)	4/99 (4)
	▪ With both LAE and SAE	66/99 (66.7)
	▪ Without adverse event	27/99 (27.3)
	Steroids	23 (0.6)
	▪ With local adverse event (LAE)	0 (0)
	▪ With systemic adverse event (SAE)	2/23 (8.7)
	▪ With both LAE and SAE	16/23 (69.6)
	▪ Without adverse event	5/23 (21.7)
	Other medications*	25 (0.7)

* Other treatment reported: vitamin C supplements (n = 10), cold compression (n = 8), intravenous fluids (n = 4), antibiotics (n = 2), or topical ointment (n = 1).

investigations to determine the underlying etiology.

The use of prophylactic antipyretic, anti-histamine, or steroids following vaccination is not currently recommended. Nevertheless, half of the respondents in this cohort reported using at least one of these medications, especially antipyretic medications of which 32.6% (612/1888) was without AE. Such unnecessary use is discouraged due to the potential direct or indirect suppression of vaccine effectiveness by antipyretics through various mechanisms (Ezzeldin and Emmanuel, 2016), in addition to unnecessary medication side effects. Further awareness of the public, including health care workers, against such unnecessary use, is warranted.

The other aim of this study was to identify the predictors to develop AEs, and the outcome thereafter. The history of any comorbid condition is one of the predictors for AEs that may lead to admission. Additionally, admission was more common among those who had delayed onset of symptoms. Most of the reported admissions in this cohort were very short in duration and were only for intravenous fluids and/or analgesia.

We noted that the median age of the vaccine recipients in this study (37 years) was much lower than the studies on the BNT162b2 mRNA AEs in the literature (64 years (Menni et al., 2021), including phase III clinical trial (55 years) (Polack et al., 2020). Although elderly population was prioritized in the Saudi vaccination rollout plan (Barry and Bahammam, 2021), the domination of the young population in this study is expected due to the fact that older individuals might not be so familiar to use the electronic method we used for data collection, in addition to the known younger population in KSA compared to other nations (Worldometer - real time world statistics).

Several limitations were encountered in this study. First, the retrospective nature of data collection could be affected by recall bias, future prospective studies are recommended to minimize such bias. Additionally, despite that we allowed on-behalf participation, and an English version of the questionnaire, we were unable to enroll a sufficient number of older population and ethnicity other than Arabs. As expected in any self-administered questionnaire, non-response bias might overestimate the rate of AEs. Furthermore, a prior history of COVID-19 infection was not collected which could influence or reduce the likelihood of adverse drug reaction following the vaccine. Lastly, patients with severe immunocompromising conditions were under-represented and further studies addressing the safety in such population are warranted.

5. Conclusion

Common AEs following the BNT162b2 mRNA vaccination in the real world were generally mild, self-limiting, and largely mimicking that reported in clinical trials. The most common of which were local pain, tiredness, or body ache. The second dose was found to cause higher AEs compared to the first. Several predictors for the development of an AE after any dose were identified, including younger age, female gender, or history of any allergy. Public education against the widespread prophylactic use of over-the-counter antipyretic after vaccination is strongly needed. The causality of these AEs and the persistence of post-vaccination symptoms needs to be investigated further.

6. Disclosure

All authors have read and agreed on the final version of this article. All authors have contributed to this research work. A copy of the utilized questionnaire is available upon reasonable request from corresponding author.

CRediT authorship contribution statement

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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.

Table 3
Predictors to develop any adverse events or hospital admission among a cohort of BNT162b2 mRNA vaccine recipients in Saudi Arabia recruited through an online questionnaire between May 29th to June 8th, 2021 (n = 3639).

Predictors	Univariate analysis		Multivariate analysis (Logistic regression)			
			Model (1)Any comorbidity adjust for age and gender		Model (2)Comorbidity classes adjusted for age and gender	
	p-value	OR(95% CI)	*p*-value	Adjusted ORFor ageand gender (95% CI)	*p*-value	Adjusted ORFor age and gender (95% CI)
Predictor to develop any adverse event after any dose						
Age 18–55 years (vs. > 55 years)	0.027	1.276 (1.027–1.584)	<0.001	1.517 (1.206–1.909)	0.001	1.255 (1.193–1.948)
Female gender (vs. male)	<0.001	1.275(1.114–1.460)	0.001	1.258 (1.099–1.442)	0.001	1.524 (1.193–1.948)
Any comorbid condition	<0.001	1.441 (1.233–1.684)	<0.001	1.322 (1.065–1.642)		
History of Lung disease,	<0.001	1.805 (1.304–2.501)			0.003	1.656 (1.189–2.306)
History of Cardiovascular disease	0.013	1.444 (1.079–1.933)			0.001	1.707 (1.242–2.347)
History of Diabetes mellitus	0.659	0.948 (0.748–1.202)			0.445	1.107 (0.853–1.437)
History of Immunocompromising conditions	0.053	0.648 (0.416–1.009)			0.151	1.390 (0.887–2.178)
History of Obesity	0.021	1.449 (1.056–1.988)			0.056	1.371 (0.991–1.895
History of Allergy, (vs. none)	0.020	1.298 (1.042–1.617)			0.149	1.180 (0.943–1.476)
Predictors for unnecessary anti-pyretic use*						
Age 18–55 years (vs. > 55 years)	0.127	0.785 (0.574–1.072)	0.54	1.107 (0.799–1.535)	0.854	1.033 (0.734–1.453)
Female gender (vs. male)	< 0.001	1.444 (1.225–1.701)	< 0.001	1.541 (1.271–1.868)	<0.001	1.520 (1.253–1.845)
Any comorbid condition	0.013	0.790 (0.654–0.955)	0.027	0.771 (0.613–0.971)		
History of Lung disease,	0.090	1.519 (0.934–2.472)			0.075	0.639 (0.390–1.046)
History of Cardiovascular disease	0.026	0.638 (0.423–0.963)			0.149	0.698 (0.428–1.137)
History of Diabetes mellitus	0.017	0.681 (0.492–0.942)			0.106	0.723 (0.487–1.072)
History of Immunocompromising conditions	0.411	1.307 (0.689–2.479)			0.290	0.706 (0.370–1.346)
History of Obesity	0.968	1.009 (0.662–1.538)			0.668	1.099 (0.715–1.689)
History of Allergy, (vs. none)	0.338	0.870 (0.655–1.157)			0.418	1.127 (0.844–1.506)
Predictors for hospital admission after vaccination						
Age 18–55 years (vs. > 55 years)	0.201	0.537 (0.204–1.415)	0.947	0.966 (0.349–2.673)	0.567	0.719 (0.232–2.226)
Female gender (vs. male)	0.800	1.104 (0.512–2.382)	0.804	1.103 (0.509–2.391)	0.819	0.911 (0.412–2.018)
Any comorbid condition	<0.001	3.546 (1.693–7.429)	< 0.001	4.143 (1.922–8.929)		
History of Lung disease,	<0.001	5.529 (2.306–13.253)			0.002	4.336 (1.686–11.15)
History of Cardiovascular disease	0.045	2.833 (0.976–8.221)			0.148	2.445 (0.729–8.207)
History of Diabetes mellitus	0.666	1.301 (0.392–4.325)			0.733	0.791 (0.206–3.042)
History of Immunocompromising conditions	<0.001	7.948 (2.904–21.758)			0.001	6.373 (2.193–18.52)
History of Obesity	0.017	3.405 (1.171–9.900)			0.187	2.191 (0.684–7.018)
History of Allergy, (vs. none)	0.001	3.548 (1.560–8.070)			0.081	2.234 (0.907–5.501)

OR: odds ratio. CI: confidence interval.
* Defined as the consumption of medication without history of adverse event.
Note: History of allergy, among all the study variables, was the only predictor for an unnecessary use of anti-histamine (p-value $\leq$ 0.001, OR = 8.510, 95% CI: 4.032–17.962).

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Ethical approval

This study was approved by the local research and ethical committee board (meeting number 1/203), Almaarefa University, Riyadh, KSA, on May 24th, 2021.

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