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Factors influencing adverse events following immunization with AZD1222 in Vietnamese adults during first half of 2021

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\textbf{A B S T R A C T}

\textbf{Background:} COVID-19 vaccines have been speedily developed and deployed. The more vaccine doses are delivered to users, the more common adverse events following immunization (AEFI) are reported. This study aimed to identify factors affecting AEFI in Vietnamese people receiving the COVID-19 vaccine AZD1222 developed by AstraZeneca and Oxford University.

\textbf{Methods:} In July 2021, an online cross-sectional survey was conducted among Vietnamese who have been vaccinated with COVID-19 vaccines. The questionnaire collected demographic characteristics, medical history, types of injected vaccines, common AEFI, and post-vaccination activities from respondents. The effects of host-related factors on AEFI including 24 specific symptoms were also explored.

\textbf{Results:} After screening, 1028 participants who were Vietnamese, over 18 years old and received at least one dose of AZD1222, were included in the study. Only 40/1028 (3.9\%) participants reported not having any AEFI, whereas 25/1028 (2.4\%) reported to have severe symptoms. The most common AEFI were moderate fever (69.4\%), muscle aches (68.6\%), followed by fatigue/sleepiness (62.5\%), body aches (59.4\%), headache (58.5\%), pain at injection site (58.3\%) and chills (45.7\%). Data analysis showed that females complained about AEFI particularly gastrointestinal symptoms more frequently than males. Age of participants and number of doses were also important factors affecting AEFI as the increase of age or number of vaccine doses was associated with the decrease of self-reported AEFI frequency.

\textbf{Conclusions:} This study provides a detailed assessment of risk factors associated with AEFI in Vietnamese people vaccinated with AZD1222. It seems that gender, age and vaccine doses are important factors affecting AEFI.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global pandemic with >180 million cases and nearly 4 million deaths reported to WHO until July 2021 \[1\].

Vaccination is the most effective way to control and diminish the pandemic, therefore a significant number of COVID-19 vaccines were developed and approved in some countries in less than a year, which is unprecedented. As updated by July 2021, eight COVID-19 vaccines including Comirnaty (BNT162b2) (Pfizer-BioNTech), AZD1222 (AstraZeneca-Oxford) with 3 versions- European (Vaxzevria), Indian (Covishield) and Korean-made version, Ad26.COV2.5 (Janssen), mRNA-1273 (Moderna), SARS-COV2 vaccine (Sinopharm) and COVID-19 vaccine (Sinovac) have been approved for human usage while 14 others are being evaluated by WHO \[2\].

By July 2021, >3 billion vaccine doses have been administered globally or roughly 24% of the world population received at least one dose of COVID-19 vaccines. However, for low-income countries, only<1% of inhabitants have been vaccinated with at least one dose \[3\], indicating a long way for these countries to obtain herd immunity. In Vietnam, COVID-19 vaccination started early March 2021. Until July 2021, nearly 4 million doses have been
administered for about 3.5% of the population and most of them were AZD1222 [3]. AZD1222, developed by Oxford university and AstraZeneca, consists of a non-replicating chimpanzee adenoviral vector ChAdOx1 which carries gene encoding for the spike protein of SARS-CoV-2 [4].

This vaccine is now widely used in many countries and its adverse effects (ADRs) have been systematically reported for inhabitants of some countries like the UK [5], South Africa [4] and Korea [6]. A post-vaccination ADR, so called adverse event following immunization (AEFI) is any untoward medical occurrence following vaccination which may not necessarily be due to the vaccine itself [7]. Most reported AEFI for AZD1222 are not severe, even though in some very rare cases, unusual blood-clots with possible link to AZD1222 could result in serious health issues [8,9].

This study evaluated the AEFI of AZD1222 in the Vietnamese people via a cross-sectional online survey. Importantly, it aimed to assess how AEFI of AZD1222 were influenced by host of related factors such as demographic characteristics, medical history and post-vaccination activities. This would be of significant benefit factors such as demographic characteristics, medical history and post-vaccination activities. This would be of significant benefit

2. Methods

2.1. Study design and participants

An anonymous cross-sectional online survey was set up in both Vietnamese and English using Google forms. It was released from July 3rd to July 10th, 2021, using social media platforms such as Facebook, Zalo, Viber and Whatsapp. The survey targeted mostly Vietnamese people who have been vaccinated with at least one dose of COVID-19 vaccines. The questionnaire collected data on gender, age, ethnicity, height, weight, history of allergies, habits, underlying conditions, post-vaccination activities, types of administered COVID-19 vaccine, number of administered vaccine doses, and 24 specific symptoms with their appearance and disappearance time post-vaccination. The symptoms to be reported included fever, blood pressure, body pain, edema and other respiratory and digestive symptoms. Data on the severity of symptoms was also collected using a self-rating question. Responses from adult Vietnamese (>18 years old) who received at least one dose of AZD1222 and answered appropriately to all required questions in the questionnaire were selected for data analysis.

2.2. Statistical analysis

All collected responses were filtered using Microsoft Excel (version 16.51) to select the participants who were adult Vietnamese (>18 years old) and received at least one dose of AZD1222. The effects of 9 host-related factors including: gender, age, body mass index (BMI), allergic pre-condition, habit, stimulant consumption, underlying conditions, post-vaccination action and number of AZD1222 doses on self-reported AEFI were investigated using descriptive statistics and hypothesis tests. Body mass index (BMI) was calculated as weight in kilogram divided by height in meter square (kg/m²). Participants were categorised into 4 groups: underweight (BMI < 18.5), normal (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30) and obese (BMI ≥ 30) [10]. Number of appearance of each symptom was obtained by using count tool on Microsoft Excel (version 16.51) and its proportion was calculated as number of having symptom divided by total responses in each group of a factor. The hypothesis z test was applied for factors having two groups including gender (males versus females), allergic pre-condition (with versus without), number of vaccine doses (one versus two) and the hypothesis chi-square test was applied for factors of more than two groups including age, habit, stimulant consumption, post-vaccination activity level, with p-value < 0.05 considered as significant difference (z-test) or dependence (chi-test).

3. Results

3.1. Characteristics of the study population (Participant demographic characteristics)

In the total of 1166 responses submitted from July 03rd to July 10th, 2021, 1028 responses which qualified to be from adult Vietnamese (>18 years old), received at least one dose of AZD1222 and answered appropriately to all required questions in the questionnaire, were included in the study (Table 1).

Of these 1028 participants, 899 had one AZD1222 dose and the rest (129) received 2 doses. Among them, male and female participants were 374 (36.4%) and 654 (63.6%), respectively. There were 324 (31.5%) in the age of 18–30, 546 (53.1%) of 31–45, 146 (14.2%) of 46–60 and 12 (1.2%) of 60. The height ranged from 142 to 186 cm and weight from 35 to 128 kg, resulting in a BMI range of 15.6 to 44.3 (Table 1). Data indicated that>60% of overweight/obese participants were male (Supplementary table S1). Most participants (729, 70.9 %) reported to have no underlying conditions. The left (299, 29.1%) reported to have some type of underlying conditions, among which the proportion of participants describing themselves to be allergic to something was highest (211, 20.5%). Other underlying conditions were reported in <10%.
of all participants such as hyperlipidemia (66, 6.4%), steatohepatitis (83, 8.1%), hypertension (66, 6.4%), hypotension (58, 5.6%), anemia (34, 3.3%), diabetes (16, 1.6%) and autoimmune disease (5, 0.5%) (Table 1). The most common allergens reported by participants were seafood, followed by weather, pollen, animal dust, drugs and others (data not shown).

3.2. Prevalence of self-reported AEFI

After being vaccinated, only 40/1028 (3.9%) participants reported not having any symptoms. Most participants (96.1%) had some body reaction (Fig. 1, Supplementary table S2). However, the proportion of severe cases which required hospitalization/medical care were low, only 13/1028 (1.3%). The majority of participants (>95%) just rated their AEFI as mild or moderate and none reported to have anaphylactic shock (Supplementary table S12).

The most common symptoms were moderate fever (69.4%), muscle aches (68.6%), followed by fatigue/ sleepiness (62.5%), body aches (59.4%), headache (58.5%), pain at injection site (58.3%) and chills (45.7%) (Fig. 1). High fever (>39 °C) only occurred in about 10.5 % of participants (Fig. 1, Supplementary table S2).

Furthermore, there were a few participants who reported symptoms which were not included in the questionnaire via the box “others” such as increased appetite, thirsty, toothache, swollen lymph nodes at neck and armpit, itching, hives and conjunctivitis. Most participants (>50%) reported that symptoms appeared after 3 h and lasted<12 h (Table 2). Muscle aches, body aches, rash/ bruises, loss of appetite, pain and swollen at the injection site were symptoms that significant proportion of participants reported to last for>12 h (Table 2).

Details on AEFI and their appearance and disappearance time which were reported by participants were presented in the Supplementary Table S2.

3.3. Relationship of host-related factors and self-reported AEFI

Among all investigated host-related factors including gender, age, BMI, history of allergies, underlying conditions (cardiovascular diseases, other diseases, pregnancy, menstruation), habits, post-vaccination activities (level of activity, stimulant consumption), number of vaccine doses, gender, age and number of vaccine doses showed more significant influence on self-reported AEFI in participants.

3.4. Gender, age and self-reported AEFI

For almost all symptoms (22/24), percentages of females who reported having symptoms were higher than males indicating that females complained of AEFI more frequently than males. Furthermore, the significant difference was seen in symptoms like pain (headache, dizziness, body aches), being fatigued and having rash/bruises. Interestingly, gastrointestinal symptoms (nausea/vomiting, loss of appetite and abdominal pain) also occurred significantly more common in females than males (Fig. 2A, Supplementary table S3). The only two symptoms (2/24) which appeared slightly more common in males than females were hypertension (6.7% in males and 4.1% in females) and runny/stuffy nose (11% in males and 8.8% in females); however this difference was not significant (p > 0.05) (Fig. 2A, Supplementary table S3).

We have found a decrease of self-reported AEFI for most symptoms through the increase of age from the highest proportion in the age range (18–30) to (31–45) then (46–60) and finally to the lowest proportion in the age range of>60 (Fig. 2B, Supplementary table S4). The AEFI seemed to drop markedly after 30 years old. The significant effect of age range on AEFI was observed in the symptom fever, fast heart pulse/ suspense, headache, body aches, fainting, shortness of breath and sore throat (Fig. 2B, Supplementary table S4).
3.5. Other host-related factors and self-reported AEFI

BMI did not seem to have a significant effect on AEFI in participants except for the symptom rash/bruises and dizziness. Rash/bruises was much more prevalent in groups of underweight and obese participants compared to normal and overweight participants, whereas dizziness was less likely in overweight and obese groups (Supplementary table S5).

In general, proportions of participants with allergic pre-conditions reporting AEFI were slightly higher in every symptom compared to participants with no allergic pre-conditions. Participants with history of allergies were significantly more likely to have rash/bruises, fatigue/sleepiness, pain and swelling at injection site and chills compared to those with no history of allergies (Supplementary table S6). Furthermore, our data indicated that participants with underlying conditions other than allergy also reported more frequent AEFI than participants without underlying conditions. Among the symptoms, body aches, sore throat, abdominal pain and diarrhea were reported significantly more frequently among participants with underlying conditions than among the ones without underlying conditions (Supplementary table S7).

Both good (doing exercise) or bad (smoking, drinking and staying up late) habits did not show significant effect to frequency of AEFI among participants (Supplementary table S8).

3.6. Post-vaccination activities and self-reported AEFI

Even though for many symptoms, there were more participants consuming no stimulants post-vaccination to report AEFI than participants consuming a certain stimulant such as cigarette, alcohol, tea or coffee, significant difference was only observed for two symptoms dizziness and pain/swelling at injection site (Supplementary table S9).

Post-vaccination working level had some influence on AEFI of participants. For most cases, groups of people who described themselves as having gentle work or usual work reported significantly less symptoms. All participants who worked hard reported to have dizziness, body aches, muscle aches but none of them had body edema. (Supplementary table S10).

3.7. Number of AZD1222 doses and self-reported AEFI

The proportion of participants receiving 2 doses of AZD1222 to report AEFI was mostly smaller than participants receiving only one dose for most AEFI except for muscle aches (Fig. 3. Supplementary table S11, S12). The marked difference between participants receiving one dose and two doses were seen in symptoms moderate fever, headache, dizziness, muscle aches, chills, sweating and cough. Participants receiving two doses also rated the severity of AEFI after the second dose much less than the first dose (Supplementary table S12).

4. Discussion

As the survey was generated using a free online form, Google forms, so the question design options were limited. In addition, it was released using social media thus the study population was biased to people who use social media, have internet access and are willing to participate. Furthermore, controlling number of questions and simplifying them to have more respondents to the survey would result in loss of some detailed information and the data on symptoms were self-reported and might not be fully exact if the person was vaccinated long before filling the survey. However, in spite of these limitation in data collection, this study has applied a simple, economical, and contact-free approach and importantly can generate significant results in a short time.

In this study, even though the number of respondents was not high, their characteristics were quite close to the expected characteristics of the whole population such as BMI distribution in Vietnamese adults [11]. As AZD1222 has been used as the principal COVID-19 vaccine due to its availability in Vietnam and the vaccination campaign is now focusing on people more exposed to the virus such as the ones at the frontline of COVID-19 and the working force, we observed mainly responses from AZD1222-vaccinated people and people from 18 to 60 years old.

AEFI data of AZD1222 have been reported and updated regularly on government websites in developed countries like UK [12], Australia [13,14], Canada [14] and in several scientific publications [5,6,15].
These data were somehow in agreement with the data of our study that the most frequently reported AEFI (>10%) were fever, muscle aches, followed by fatigue/sleepiness, body aches, headache, pain at injection site, chills, dizziness, sweating and fast heart pulse/suspense. However, our proportions were generally higher for these symptoms [5,6,15]. Furthermore, previous studies showed that most AEFI was not severe and resolved within few days post-vaccination, our data presented similar findings with the majority of mild and moderate AEFI, but we showed more clearly that AEFI generally appeared after 3 h and lasted <12 h post-vaccination [5,6,15]. The proportion of severe cases in our study was relatively higher as we included cases which required medical care while other studies included really serious cases which required intensive care unit admissions, experienced life-

[Fig. 2. Influence of gender and age on self-reported AEFI. A) Influence of gender; B) Influence of age. * Indicated significant influence of either gender or age on a certain symptom (p < 0.05).]
threatening events, and suffered permanent disability/sequelae [16].

Among all assessed host-related factors in this study, age, gender and number of vaccine doses showed most significant effect on self-reported AEFI which were also in agreement with previous studies [5,17]. In general, our data not only indicated that AEFI of AZD1222 were reported more common in females than males, in younger adults than older ones, in the first dose than in the second dose like other published data, but also presented a clearer report on the types of significantly more common symptoms in females, in this case gastrointestinal symptoms, the proportional decrease in symptoms over 4 age ranges and over 2 doses. Other factors like BMI, history of allergies, underlying conditions, habits, post-vaccination working level or stimulant consumption had some influence on AEFI but not as much as the ones mentioned above. However, it is interesting to note down that hard-work post vaccination had positive effect on body edema but generally caused much dizziness and aches.

CRediT authorship contribution statement

Tran Van Nhi: Investigation, Formal analysis. Nguyen Hoang An: Investigation, Formal analysis. Le Thi Thanh An: Supervision. Truong Thanh Tung: Data curation, Conceptualization. Nguyen Phuong Thao: Supervision. Nguyen Thi Thu Hoai: Supervision, Writing – review & editing.

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.09.060.

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