COVID-19 Vaccines Safety Tracking (CoVaST): Protocol of a Multi-center Prospective Cohort Study for Active Surveillance of COVID-19 Vaccines Side Effects

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Abstract: Background: COVID-19 vaccines related side effects have a determinant role in the public decision regarding vaccination. Therefore, this study has been designed to actively monitor safety and effectiveness of COVID-19 vaccines globally; Methods: a multi-country three-phase study including a cross-sectional survey to test for the short-term side effects of COVID-19 vaccines among target population groups. In the second phase, we will monitor the booster doses side effects, while in the third phase, the long-term safety and effectiveness will be inquired. A validated self-administered questionnaire will be used to collect data from target population; Results: the study protocol has been registered at ClinicalTrials.gov with the identifier NCT04834869; Conclusions: CoVaST is the first independent study aims to monitor the side effects of COVID-19 vaccines following booster doses and the long-term safety and effectiveness of vaccines.

Keywords: cohort studies, cross-sectional studies; COVID-19; drug-related side effects and adverse reactions; health personnel; mass vaccination; prevalence

1. Introduction

COVID-19 mass vaccination has been a chief priority for health systems globally that needs to be accelerated in order to control the acute phase of the pandemic.\(^1\)\(^2\) Nevertheless, vaccine hesitancy (VH) which refers to the "delay in acceptance or refusal of vaccines despite the availability of vaccine services"; remains a serious challenge for vaccination strategies worldwide.\(^3\)\(^-\)\(^5\) In 2019, the World Health Organization (WHO) declared VH as one of the top ten global health threats which is nourished by misinformation regarding vaccines effectiveness and safety.\(^6\)

Aversion to vaccines' potential side effects is the most frequent cause for VH among various population groups.\(^7\)\(^-\)\(^8\) Therefore, a recent systematic review revealed that raising public awareness of vaccines' effectiveness and honesty regarding their side effects are vital strategies to improve vaccines uptake.\(^9\)

According to the Strategic Advisory Group of Experts on Immunization of the WHO (SAGE-WHO), distrust in pharmaceutical industry is a contextual driver of VH because vaccine manufacturers can be perceived as preferring their financial benefit over public health interest.\(^10\) In both high-income and low-income settings, distrust of pharmaceutical industry had been consistently and significantly higher among hesitant groups, and it is aggravated by lack of transparency regarding public health plans.\(^11\)\(^-\)\(^13\)
Public health systems currently experience a novel and a unique challenge due to the variety of vaccines manufacturers and the high levels of public awareness about those manufacturers and their marketing strategies. This unprecedented situation is predicted to create what we can refer to as "vaccine selectivity", where individuals can prefer a certain type or brand of vaccine over the other, this situation will increase the pressure on our weakened health systems and economies, and of course it can increase the VH levels as well.

The temporary suspension of Oxford-AstraZeneca vaccine (AZD1222) and Janssen vaccine (Ad26.COV2.S) due to reports of extremely rare side effects had triggered public debates that could have adversely affected the vaccination acceptance levels. However, the European and American drug regulators declared that the benefits of using these vaccines still outweigh their risks, very little is known about vaccine hesitancy and, probably, selectivity after these incidences.

Given the projected seasonality of COVID-19 transmission and the increasing number of its variants, vaccines manufacturers launched trials for booster doses that are predicted to be readily available by the fall of 2021. Independent (non-sponsored) studies with rigorous methods can successfully lead the unbiased pharmacovigilance efforts of COVID-19 vaccines globally. Thus, in view of their independent nature and transparent design, these studies can play a key role in suppressing VH levels by enhancing public confidence in the vaccines.

1.1. Objectives

This project aims to actively monitor the side effects and effectiveness of COVID-19 vaccines worldwide. The primary objectives of the project include:

a) to estimate the prevalence of both local and systemic side effect following each of the COVID-19 vaccines among healthcare workers (HCWs), teachers and academics (TAs), senior adults ≥ 65 years-old (SAs), and minors ≤ 18 years-old (MIs);

b) to evaluate the potential demographic and medical risk factors for side effects frequency and intensity;

c) to evaluate the long-term safety of COVID-19 vaccines.

The secondary objectives include:

a) to evaluate the relative effectiveness and safety of COVID-19 vaccines in relation to each other;

b) to evaluate the impact of palliative medications used by the vaccinated individuals for short-term side effect resolution.

2. Materials and Methods

2.1. Design

This project is composed of three main phases; a) a cross-sectional survey for the short-term side effects of COVID-19 vaccines; b) a prospective cohort study for the safety of COVID-19 vaccines following booster doses; c) a prospective cohort study for the long-term safety and effectiveness of COVID-19 vaccines.
2.1. Phase A

A validated self-administered questionnaire will be developed and delivered online to the target population groups (HCWs, Tas, SAs & MIs). In certain circumstances, telephone interviews and paper questionnaires will be used instead of the online questionnaire in order to adapt to the local setting. The questionnaire will be inquiring about the short-term side effects following either the first dose, the second dose, or both doses of the COVID-19 vaccine. The side effects will be classified as local or systemic, and their onset, duration, and intensity will be self-assessed and self-reported by the participating subjects. This phase is planned to take place until December 31, 2021.

2.1.2. Phase B

A validated self-administered questionnaire will be developed and delivered online to the volunteers who participated in Phase A and expressed their interest to report on their long-term outcomes. The short-term side effects following booster doses will be investigated in this phase. This phase is tentatively planned to take place from October 2021 until April 2022.

2.1.2. Phase C

A validated self-administered questionnaire will be developed and delivered online to the volunteers who participated in Phase A and expressed their interest to self-report their long-term outcomes. The vaccine's effectiveness and safety will be monitored, and this phase will last for five consecutive years starting from January 2022.

2.2. Population

In Phase A, a pragmatic approach will be used by tracking each target population group according to the individual governments’ distributional plans, which in most countries went from HCWs, SAs, TAs to MIs. The sample of Phases B and C will be pre-identified based on the outcomes of Phase A.

If more than 25% of Phase A participants show their interest to join Phase B, no additional recruitment will be required. If less than 25% of Phase A participants show their interest in participating in Phase B, additional recruitments will be carried out targeting HCWs who will receive booster doses. In case of the emergence of special side effects after booster doses, additional recruitments of a sample of HCWs will be required.

2.2.1. Inclusion Criteria

- HCWs, TAs, SAs, and MIs who received COVID-19 vaccine in the post-authorization phase.
- The recently vaccinated individuals who received their vaccine dose within the previous 30 days will be prioritized to be invited for the study; even though, the study will not be limited to the recently vaccinated individuals.
- Participating subjects should be at least 18-year-old and able to give their informed consent independently.

2.2.2. Exclusion Criteria
• HCWs, TAs, SAs, and MI s who received the COVID-19 vaccines as part of phase III clinical trials.

2.2.3. Sample Size

The pragmatic sample size for each target group in each country will be calculated using Epi Info™ version 7.2.4 (CDC. Atlanta, GA. 2020). The formula of population survey studies will be used to achieve 5% of error margin and 95% - 99% confidence level. The expected frequency (outcome probability) is assumed to be 60% as the prevalence of side effects following COVID-19 vaccines ranged between 62% to 93% in our previous studies.[21],[22] (Figure 1)

Population size: total number of healthcare workers in the Czech Republic in 2017.[30]

Expected frequency: the overall prevalence of side effects following COVID-19 vaccines ranged between 62% and 93%; therefore, 60% was assumed as a threshold.

Acceptable Margin of Error: 5% will be the permissible level for all CoVaST groups.

Design effect: 1 – per the recommendation of the CDC for simple sampling.[29]

Clusters: 1 – per the recommendation of the CDC for simple sampling.[29]

The pragmatic sample size is 368 – 635 (CI 95% - 99%).

Figure 1: Sample size of healthcare workers (HCWs) in the Czech Republic – Epi-Info™ version 7.2.4

2.3. Instrument

The questionnaire will be based on the growing evidence of COVID-19 vaccines side effects and adverse reactions and will be updated and validated accordingly. The questionnaire consists of four categories a) demographic data (age, gender, height, weight, profession, and geographic region); b) medical anamneses (chronic illnesses, medications, smoking and alcohol consumption); c) COVID-19-related anamneses (type of vaccine, number of vaccine doses, dates of vaccine doses, previous infection, and diagnosis date); d) vaccine side effects (local side effects, systemic side effects, onset, and duration). Appendix 1

The multi-linguistic versions of the instrument will be produced through a pragmatic workflow for translation and cultural adaptation.[31] The current instrument is designed and validated for the HCWs group. The instrument will be validated for the other two populations of interest (OAs, TAs) by a validation process using an expert panel with four experts from the targeted population and four experts with a background in public health, epidemiology, infectious disease, and vaccination.

Two native speakers of the target language with a high level of English proficiency will translate the instrument independently. An expert panel composed of three members (the two forward translators and a third native speaker with a biomedical background and advanced level of English language) will review the
two translated versions and will resolve discrepancies between them aiming to generate a harmonized final version. The working version will undergo reliability testing through test-re-test. In the test-re-test, a minimum of 10 volunteers should fill-in the questionnaire twice with at least two weeks apart.

2.4. Recruitment

Data will be collected in two phases by an on-line validated self-administered questionnaire. Although the data collection strategies may differ across the globe, the target groups are recommended to be approached by governmental, professional and university networks.

2.4.1. Phase A

A.1. HCWs will be approached by medical and healthcare chambers and/or healthcare professional organizations, and the snowballing technique will be applied;

A.2. Senior adults (≥ 65) will be approached by the "university of the third age", by the professional medical association of "young general practitioners" and professional organizations for older adults, and the snowballing technique will be applied;

A.3. School teachers will be approached by the networks of educational institutions, while university teachers will be approached via all main universities, and the snowballing technique will be applied.

A.4. Minors (≤ 18) will be principally approached through their schools where the parents (guardians) will be invited to fill-in the questionnaire on behalf of their children.

Data collection of A.1, A.2, A.3, and A.4. population groups will be adjusted according to each participating country’s local setting.

2.4.2. Phase B and C

Volunteers who will participate in Phase A and express their interest to self-report their long-term side effects will be approached again. The vaccine effectiveness and side effects following booster doses will be investigated in Phase B. Phase C will take place for five consecutive years starting from 2022.

2.5. Timeline

As the local timelines are dependent on the setting of each participating country including governments’ distribution plans, vaccines availability, and administrative processes, the proposed timeline is deemed to guide the overall Co-VaST progress. (Table 1)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Stage</th>
<th>Population</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1</td>
<td>HCWs</td>
<td>May – Aug 2021</td>
<td></td>
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<tr>
<td>A.2</td>
<td>SAs</td>
<td>Jun – Dec 2021</td>
<td></td>
</tr>
<tr>
<td>A.3</td>
<td>TAs</td>
<td>Jun – Dec 2021</td>
<td></td>
</tr>
<tr>
<td>A.4</td>
<td>MI</td>
<td>Jun – Dec 2021</td>
<td></td>
</tr>
<tr>
<td>B.1</td>
<td>HCWs</td>
<td>Oct 2021 – Feb 2021</td>
<td></td>
</tr>
<tr>
<td>B.2</td>
<td>SAs</td>
<td>Nov 2021 – Apr 2022</td>
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<tr>
<td>Stage B.3.</td>
<td>TAs</td>
<td>Nov 2021 – Apr 2022</td>
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<tr>
<td>Stage B.4.</td>
<td>MIs</td>
<td>Nov 2021 – Apr 2022</td>
<td></td>
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<tr>
<td>Stage C</td>
<td>Stage C.1.</td>
<td>HCWs, SAs, TAs, MIs</td>
<td>Jan – Dec 2022</td>
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<td>Stage C.2.</td>
<td>HCWs, SAs, TAs, MIs</td>
<td>Jan – Dec 2023</td>
<td></td>
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<tr>
<td>Stage C.3.</td>
<td>HCWs, SAs, TAs, MIs</td>
<td>Jan – Dec 2024</td>
<td></td>
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<tr>
<td>Stage C.4.</td>
<td>HCWs, SAs, TAs, MIs</td>
<td>Jan – Dec 2025</td>
<td></td>
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<tr>
<td>Stage C.5.</td>
<td>HCWs, SAs, TAs, MIs</td>
<td>Jan – Dec 2026</td>
<td></td>
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</tbody>
</table>

2.6. Ethics

The study was reviewed and approved by the Ethics Committee of the Faculty of Medicine at Masaryk University on May 19, 2021 (Ref. 26/2021). Ethical clearance will be secured from a designated institutional review board in each participating country before study commencement.

Digital informed consent will be obtained from each participant prior to participation. The participants will be allowed to withdraw from the study at any moment without justification, and no data will be saved before the participant submit their answers completely.

2.7. Analysis

Descriptive statistics will be performed to check the normality of data distribution, and to present the frequencies and percentages of dependent variables (side effects) and independent variables (demographic data, medical anamneses, and COVID-19-related anamneses). Inferential statistics will be performed to evaluate the potential association of each side effect and the suggested demographic and medical risk factors. All tests will be performed using SPSS 27 and the significance level cut-off will be set at $p \leq 0.05$.\(^{[32]}\)

3. Registration

The study protocol had been registered the US National Library of Medicine registry (ClinicalTrials.gov) with the identifier NCT04834869.\(^{[33]}\) The ClinicalTrials.gov record will be regularly updated by the project principal investigators, and any deviations from the protocol will be mentioned and justified \textit{a priori} in the electronic record and the manuscript of the final study.

4. Discussion

Post-marketing evaluation of vaccines safety has typically relied on voluntary reporting of side effects by the health care professionals, vaccinated individuals, and caregivers. While there is a surging demand for rigorous pharmacovigilance systems with active surveillance designs rather than the traditional passive surveillance, a very limited number of high-income countries managed to develop such systems so far.\(^{[34]}\)

The United Kingdom (UK) is one the leading countries in this field due to its early efforts in developing active surveillance systems of diphtheria/tetanus/pertussis (DTP) and measles/mumps/rubella (MMR) vaccines safety since early 1990s.\(^{[35]}\) In terms of COVID-19 vaccines safety, the Medicines & Healthcare products Regulatory Agency (MHRA) of the UK had adopted an innovatively hybrid system that includes: a) enhanced passive surveillance through the Yellow Card
scheme where members of the public and healthcare professionals voluntarily report suspected side effects, b) targeted active monitoring using the Yellow Card scheme, c) formal epidemiological studies like the OpenSAFELY17 Collaborative and COVID Symptom Study app.\cite{25,36,37}

The results of post-marketing studies may differ to various degrees from the outcomes of phase III trials where apparently healthy volunteers are usually recruited following strict criteria. Riad et al. 2021 found that the overall prevalence of Pfizer-BioNTech COVID-19 vaccine side effects among recently vaccinated HCWs in the Czech Republic was relatively higher than those reported by the manufacturer.\cite{21} Similarly, the side effects of Moderna COVID-19 vaccine and CoronaVac vaccine were more prevalent among HCWs in the US and Turkey, respectively, than the manufacturers’ reports.\cite{22,27} On the other hand, Menni et al. 2021 found that the side effects of Pfizer-BioNTech and Oxford-AstraZeneca COVID-19 vaccines occurred less frequently among a large cohort in the UK than those reported by the phase III trials.\cite{25}

The demographic and medical risk factors for side effects frequency and intensity are not usually reported by phase III trials as they are not necessarily outcomes of interest during this stage. Therefore, post-marketing studies are in an ideal position to confirm or refute suggested risk factors using large datasets of self-reported outcomes. For example, all post-marketing studies of mRNA vaccines found that the frequency of side effects following the second dose is higher than the first dose.\cite{21,23,25} The phase III trials displayed the same pattern; therefore, the post-marketing studies only came to confirm such preliminary finding.\cite{23,38,39} Female gender was consistently associated with an increased risk of side effects following different types of COVID-19 vaccines; interestingly, the gender-based differences were reported by manufacturers.\cite{21,23,25,28}

As more COVID-19 vaccines are currently in the pipeline of clinical trials and authorization, readily available instruments for active surveillance will be much needed to shorten the time period of post-marketing investigation by academic institutions. Moreover, the prospective booster doses safety should be evaluated in relatively shorter periods of time to relieve our weakened healthcare systems. Therefore, the CoVaST project aims to provide an international infrastructure for active surveillance of booster doses side effects and long-term safety and effectiveness of COVID-19 vaccines.

### 4.1. Strengths and Limitations

To the best of the authors’ knowledge, this is the first multinational study aiming to monitor the safety of various COVID-19 vaccines especially following booster doses. Another strong point of this study is its unified evaluation instrument, target groups and methods that will be used in all participating countries which should maximize the results internal validity. Recruiting HCWs is supposed to limit the reporting bias that is naturally predicted in this survey-based study due to the fact that HCWs retain high levels of health literacy and scientific interest. This study is one of the early registered studies that are concerned with long-term safety of COVID-19 vaccines and their effectiveness.
In general, this study is limited by the heterogeneous time span between vaccination and survey commencement across the participating countries; therefore, sub-group analysis according to the time span will be carried out during data analysis. One more limitation is recall bias, as in various countries, vaccination covered the majority of the population who tended to be vaccinated. Due to the recruitment of participants who received the vaccine in the first half of the 2021, there is a possibility of recall bias when filling out the questionnaire. Since the COVID vaccination is worldwide a hot topic, we assume that participants could remember well all experienced side effects.

5. Conclusions

The side effects of COVID-19 vaccines require active surveillance in the post-authorization phase, as the side effects can potentially impact the decision regarding vaccination. CoVaST as a multi-national study aims to evaluate the short-term and long-term side effects and effectiveness of various COVID-19 vaccines.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: CoVaST Instrument.docx


Funding: This study protocol preparation was funded by Masaryk University, grant numbers MUNI/IGA/1543/2020 and MUNI/A/1608/2020.

Institutional Review Board Statement: The study will be conducted according to the guidelines of the Declaration of Helsinki and it was approved by the Ethics Committee of the Faculty of Medicine, Masaryk University Ref. 26/2021 on 19 May 2021.

Informed Consent Statement: Digital informed consent will be obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments: This work is dedicated to the more than three million worldwide fatalities and their families who have fallen victim to COVID-19.

Conflicts of Interest: The authors declare no conflict of interest.

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