

Original Article

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Sustained COVID-19 vaccine willingness after safety concerns over the Oxford-AstraZeneca vaccine

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ABSTRACT

INTRODUCTION Prompted by reports of thromboembolic events – some with fatal outcomes – among people who had received the ChAdOx1 nCoV-19 (AZD1222) vaccine from Oxford-AstraZeneca against COVID-19, a number of European countries paused vaccination with this vaccine in early and mid-March 2021. Prior studies have suggested that vaccine willingness is highly dependent on public trust in the safety of vaccines. We therefore investigated whether vaccine willingness dropped in the wake of the reported cases of thromboembolic events in relation to the Oxford-AstraZeneca COVID-19 vaccine.

METHODS Using longitudinal survey data from Denmark, we compared vaccine willingness shortly before and after the reported cases of thromboembolic events, as well as the perceived safety of the two most widely used COVID-19 vaccines in Denmark – those from Pfizer-BioNTech and Oxford-AstraZeneca – in the wake of these events.

RESULTS We found sustained vaccine willingness after the reported cases of thromboembolic events (89% both before and after). However, the safety of the Oxford-AstraZeneca COVID-19 vaccine was perceived to be significantly and substantially lower than the safety of the vaccine from Pfizer-BioNTech, and this difference was particularly pronounced among those who were vaccine-hesitant.

CONCLUSIONS The vaccine willingness of Danes does not seem to have been affected by the reports of thromboembolic events in relation to the Oxford-AstraZeneca COVID-19 vaccine.

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TRIAL REGISTRATION not relevant.

In early and mid-March 2021, a number of European countries paused vaccination against COVID-19 with the ChAdOx1 nCoV-19 (AZD1222) vaccine from Oxford-AstraZeneca [1, 2] following reports of thromboembolic

events, some with fatal outcomes, among people who had received this vaccine [3, 4]. On 18 March 2021, after extensive scrutiny of these events, the European Medicines Agency concluded regarding the Oxford-AstraZeneca Covid-vaccine that “benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets” [5]. This led some European countries to immediately reinstate vaccination with the OxfordAstraZeneca COVID-19 vaccine, whereas other countries –

including Denmark – decided to await further examination of the potential relationship between the vaccine and the cases of thromboembolisms [6]. This train of events was covered extensively by the news media [6-8].

Prior studies have suggested that vaccine willingness is highly dependent on public trust in the safety of vaccines [9, 10].

Therefore, it seems likely that vaccine willingness may have dropped in the wake of the reported cases of thromboembolic events in relation to the Oxford-AstraZeneca COVID-19 vaccine. This would potentially threaten the success of the global COVID-19 vaccine programme, which is crucial in the management of the COVID-19 pandemic. In the present study, we examined the vaccine willingness and perceived safety of the two most widely used COVID-19 vaccines in Denmark [11]; the Oxford-AstraZeneca [1, 2] and the Pfizer-BioNTech [12] vaccine. Specifically, we addressed the following five research questions: i) Has the COVID-19 vaccine willingness dropped following the thromboembolic events reported in relation to the Oxford-AstraZeneca COVID-19 vaccine? ii) What is the perceived safety of the COVID-19 vaccines from Oxford-AstraZeneca and Pfizer-BioNTech, and does it differ between the two? iii) Do people who are vaccine-hesitant perceive the safety of the COVID-19 vaccines from

Oxford-AstraZeneca and Pfizer-BioNTech to be lower than those who are vaccine-willing? iv) Does trust in the Health Care System system differ between those who are vaccine-willing and vaccine-hesitant? and v) Is the perceived safety of the COVID-19 vaccines related to trust in the Danish healthcare system?

METHODS

Survey

To investigate these research questions, we used data from the two most recent waves of a five-wave panel survey conducted by the Danish survey company Epinion (invitees sampled from Epinion's respondent pool), the first three of which are described in detail elsewhere [13-15]. In the fourth wave, which was fielded from 4 to 21 February 2021 (i.e. prior to the reports of thromboembolic events in relation to the Oxford-AstraZeneca COVID-19 vaccine), we targeted the 2,458 respondents from the first wave [13]. In addition to questions regarding psychological well-being and social and political attitudes/perceptions for other research purposes, the participants were asked: "Have you been offered vaccination against coronavirus?". The response options were: "Yes", "No" and "Do not wish to answer". Participants who answered "Yes" were then asked "Have you accepted this offer?". Participants who responded "No", were asked: "Will you accept vaccination against coronavirus, once it is offered to you?". For both of these questions, the response options were: "Yes", "No" and "Do not wish to answer". In the fifth wave, which was fielded from 15 to 25 March 2021 (i.e. after the reports of thromboembolic events in relation to the Oxford-AstraZeneca COVID-19 vaccine), we included the same questions on vaccine willingness as in wave four and added a question on COVID-19 vaccine safety, randomising the vaccine in question. Specifically, the respondents were randomly assigned one of the following two questions: "How do you consider the safety of the Pfizer vaccine against coronavirus?" and "How do you consider the safety of the AstraZeneca vaccine against coronavirus?". The response to these questions was provided on a Likert-like scale ranging from 0 – "Very low safety" to 10 – "Very high safety". The respondents could also choose a "Don't know" response. The fifth wave of the survey also included questions regarding institutional and inter-individual trust (posed in the latter part of the questionnaire). For the present study, we included the response to the question on trust in the Danish healthcare system (Danish: Sundhedsvæsenet): "On a scale of 0-10, how much do you personally trust the healthcare system?". The response was provided on a Likert-like scale ranging from 0 – "No trust at all" to 10 – "Complete trust". The respondents could also choose a "Don't know" response.

Respondents and weighting

A total of 1,654 invitees responded to the survey wave collected prior to the reports of thromboembolic events in relation to the Oxford-AstraZeneca COVID-19 vaccine, and 1,657 responded to the survey wave collected after these reports (1,491 responded to both waves). The analyses corresponding to the five research questions were based on respondents

answering both survey waves. To minimise the effect of potential sample selection bias, we weighted the responses to all questions in the survey using inverse propensity weighting [16] by sex, age, level of education, region and political party choice at last general election (5 June 2019). This weighting renders the respondents representative of the Danish population on these variables.

Statistics

We first compared willingness to accept a future COVID-19 vaccination offer across the two waves. Specifically, we compared the proportions answering in the affirmative to the question "Will you accept vaccination against coronavirus once it is offered to you?" using a logistic regression with standard errors adjusted for repeated observations and two-sided p-values. This analysis only included respondents who reported that they had not yet been offered vaccination in both waves (83.6% of the respondents). Second, we compared the mean levels of perceived safety of the two vaccines, as defined by the randomly assigned version of the question ("Pfizer" versus "AstraZeneca"), using a two-sample t-test. Third, we compared the perceived safety of the two vaccines between respondents who were vaccine-hesitant and vaccine-willing (the latter group comprised respondents who had answered in the affirmative to one of the two questions about vaccine willingness in the fifth wave of the survey, whereas the former group comprised those who answered "No" or "Do not wish to answer"), using a two-sample t-test. Fourth, the level of trust in the Danish healthcare system was compared between the vaccine-willing and vaccine-hesitant respondents using a two-sample t-test. Fifth, the relationship between the perceived safety of the COVID-19 vaccines and the level of trust in the Danish healthcare system was examined by linear regression.

Ethics

Participation in the survey was based on consent. Under Danish Law, ethical review board approval is not required for survey studies. Data were stored and handled in accordance with the General Data Protection Regulation.

Trial registration: not relevant.

RESULTS

Table 1 shows the characteristics (unweighted and weighted) of the 1,491 individuals having responded to both survey waves.

TABLE 1 Characteristics of the participants: unweighted and weighted, who responded to both survey waves.

| | Unweighted | Weighted |
|--|--------------------|--------------------|
| <i>Sex, n (%)</i> | | |
| Male | 787 (52.8) | (50.8) |
| Female | 704 (47.2) | (49.2) |
| Age (\pm SD), yrs | 52.5 (\pm 17.4) | 49.5 (\pm 17.5) |
| <i>Country of origin, n (%)</i> | | |
| Denmark | 1,366 (91.6) | (91.7) |
| Western country ^a | 41 (2.7) | (2.6) |
| Non-Western country ^b | 24 (1.6) | (1.8) |
| Missing | 60 (4.0) | (3.9) |
| <i>Level of education, n (%)</i> | | |
| Primary and lower secondary school | 212 (14.2) | (1.5) |
| Upper secondary education | 103 (6.9) | (7.5) |
| Vocational education | 611 (41.0) | (43.6) |
| Short-cycle higher education | 106 (7.1) | (6.2) |
| Medium-cycle higher education incl. bachelor | 311 (20.9) | (17.9) |
| Long-cycle higher education | 148 (9.9) | (9.4) |
| <i>Region in Denmark, n (%)</i> | | |
| North Denmark | 151 (10.1) | (10.5) |
| Central Denmark | 359 (24.1) | (22.6) |
| Southern Denmark | 308 (20.7) | (22.0) |
| Capital | 490 (32.9) | (31.0) |
| Zealand | 183 (12.3) | (13.9) |

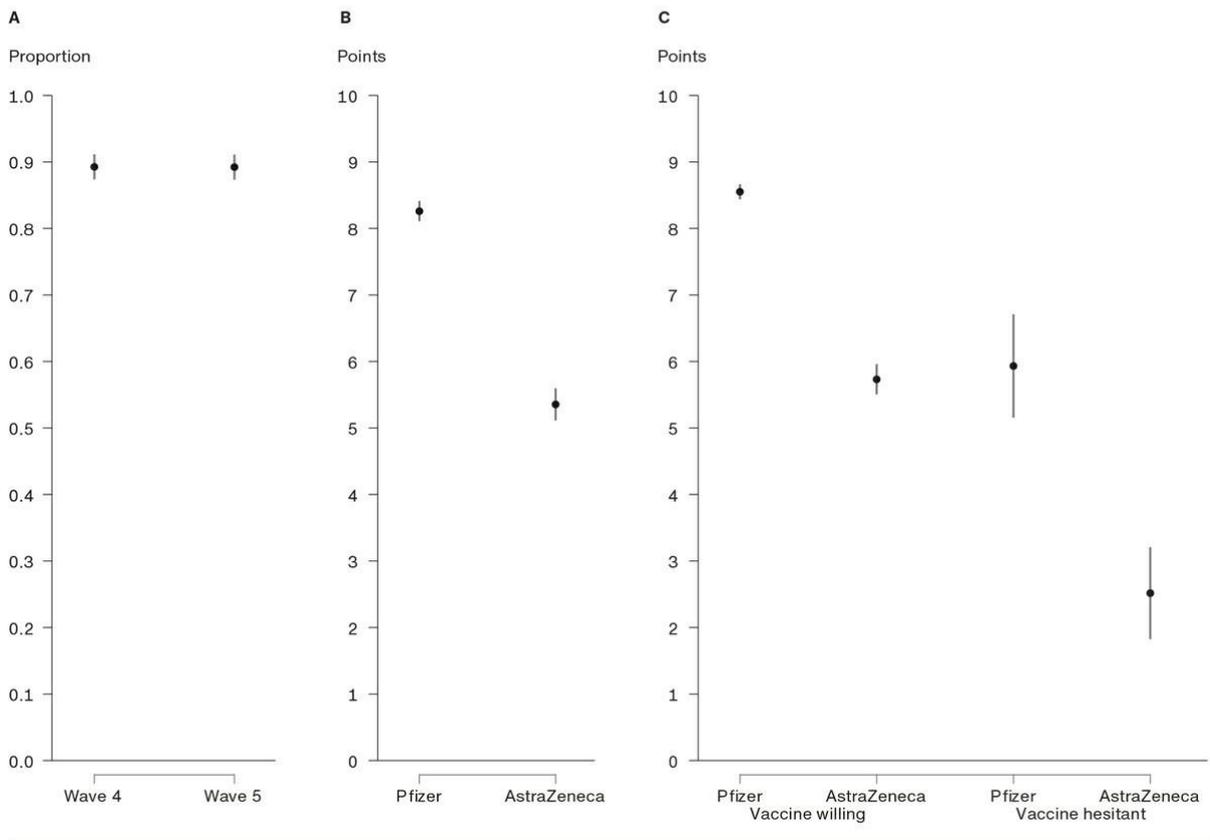
SD = standard deviation.

a) Western Europe and remaining European Union, North America, Australia and New Zealand.

b) Other countries than those mentioned in point a.

The results of the analyses corresponding to the three first research questions are shown in Figure 1. Figure 1A shows that vaccine willingness in Denmark was very high both before (89.3%) and after (89.2%) the thromboembolic events reported in relation to the Oxford-AstraZeneca COVID-19 vaccine ($p = 0.961$). Figure 1B shows that the perceived safety of the Oxford-AstraZeneca COVID-19 vaccine was substantially lower than that of Pfizer-BioNTech (mean safety perception on the scale of 0-10 of 5.35 versus 8.26, $p < 0.001$). Figure 1C shows that it was particularly those who were vaccine-hesitant who perceived the safety of the vaccines to be low – especially the Oxford-AstraZeneca COVID-19 vaccine (mean safety perception of 2.55 compared with 5.86 for Pfizer-BioNTech, $p < 0.001$).

FIGURE 1 A. Proportion expressing vaccine willingness, point estimates with 95% confidence intervals (CI), 2,494 observations/ 1,247 individuals. **B + C.** Perceived safety (0-10 scale) of the Covid-19 vaccines from Oxford-AstraZeneca and Pfizer-BioNTech (B), differentiated in willing and hesitant individuals (C), point estimates with 95% CI, 1,300 individuals/observations.



As regards the fourth and the fifth research question, the mean level of trust in the Danish healthcare system on the scale of 0-10 was 6.30 among the vaccine-hesitant and 8.09 among the vaccine-willing ($p < 0.001$).

Furthermore, a positive correlation was observed between the level of trust in Danish healthcare system and the perceived safety of the Oxford-AstraZeneca COVID-19 vaccine (standardised linear regression coefficient: 0.36, $p < 0.001$) and the Pfizer-BioNTech COVID-19 vaccine (standardised linear regression coefficient: 0.38, $p < 0.001$).

DISCUSSION

The results of this study are reassuring with regard to COVID-19 vaccine uptake in Denmark following the thromboembolic events reported in relation to the Oxford-AstraZeneca COVID-19 vaccine. However, the perceived safety of the Oxford-AstraZeneca COVID-19 vaccine is substantially lower than that of Pfizer-BioNTech, especially among those who are vaccine-hesitant. These results are compatible with – although not proof of – perceived safety being associated with vaccine willingness, which is in line with the literature on this topic [9, 10]. Furthermore, the present study replicated the finding of a positive association between trust in healthcare systems and vaccine willingness [17, 18], and reported that trust in the Danish healthcare system is also positively associated with perceived safety of the COVID-19 vaccines. Taken together, these findings suggest that maintenance of vaccine uptake will likely benefit from health authorities investing in increasing trust in the safety of the Oxford-AstraZeneca COVID-19 vaccine.

Some limitations need to be considered when interpreting the results of this study. First and foremost, the assessment of vaccine willingness is based on a survey questionnaire. Whereas this method is widely used [9, 10, 19], data on actual vaccine uptake (and rejection) would be superior as they will not be affected by social desirability bias (reporting vaccine willingness without eventually accepting the vaccine). Such studies should be pursued as data on vaccine uptake become available. Second and relatedly, although the results of this study are weighted on key sociodemographic variables, we cannot rule out that non-response bias may have resulted in overestimation of vaccine willingness. Third, we did not collect data on the perceived safety of the COVID-19 vaccines from Oxford-AstraZeneca and Pfizer-BioNTech in the survey wave fielded prior to the reports of thromboembolic events in relation to the Oxford-AstraZeneca COVID-19 vaccine. Therefore, we cannot know whether the low level of perceived safety of the Oxford-AstraZeneca COVID-19 vaccine observed after these events would also have been found prior to them, had these questions been asked then. Given the severity of the thromboembolic events [3, 4], the paused use of the vaccine [3, 4, 6], and the associated media coverage [6, 7, 8], this, however, seems unlikely. Fourth and finally, vaccine willingness in Denmark is among the highest worldwide [19], and the results regarding sustained vaccine willingness may therefore not necessarily generalize to countries with a lower “baseline” vaccine willingness. Specifically, in countries with lower institutional trust than Denmark – where institutional trust is among the highest in the world [20] – it may prove challenging for the health authorities to uphold support for COVID-19 vaccination, given the recent events.

CONCLUSIONS

The (high) vaccine willingness of Danes does not seem to have been affected by the reports of thromboembolic events in relation to the Oxford-AstraZeneca COVID-19 vaccine. However, the perceived safety of the OxfordAstraZeneca COVID-19 vaccine is low – especially among vaccine-hesitant individuals. Consequently, maintenance of vaccine uptake will likely benefit from health authorities investing in increasing trust in the safety of the Oxford-AstraZeneca COVID-19 vaccine.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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