Attitudinal inoculation to increase vaccination among adults with anxiety or depression
RF1MH132360
Study Protocol and Statistical Analysis Plan
May 2, 2025

Study Protocol

Trial Design

In a 3-arm, parallel-group, assessor-blinded, stratified-randomized trial, participants were enrolled based on the following eligibility criteria: aged 18 years or older, having received at least one dose of the COVID-19 vaccine but no doses since September 11, 2023, and no SARS-CoV-2 infection in the three months prior to the study start. We focused on individuals with at least one prior dose—the "moveable middle"—who show some willingness to vaccinate but remain hesitant about additional doses and may be more responsive to a brief video intervention than the unvaccinated. Our team's prior research informed the trial design, and identified safety and efficacy as their main concerns[17].

Eligible individuals were randomly allocated to one of three interventions: 1) attitudinal inoculation, 2) CBT-kernels or 3) standard public health messaging. Recruitment and randomization started on April 15, 2024 and continued on a rolling basis until May 02, 2024. Outcome assessment at 4-week follow-up started on May 13, 2024 and was completed by June 13, 2024. After consenting, enrolled participants were randomly assigned to one of three arms at a ratio of 1:1:1. Each arm was also stratified by presence or absence of moderate to severe anxiety or depression symptoms, defined by scoring ≥10 in the Patient Health Questionnaire-8[18] or GAD-7[19] at any point between December 2022 and December 2023.

Recruitment

Individuals were recruited from the CHASING COVID cohort, a well-characterized, community-based sample of geographically and socio-demographically diverse adults aged 18 years and older who reside in the US or US territories and enrolled in the cohort between March 28, 2020 and August 21, 2020. Details of recruitment and follow-up have been described elsewhere[20]. Briefly, participants in the cohort have completed, approximately quarterly, online assessments related to health and behaviors, SARS-Cov-2 infection history, COVID-19 symptoms, and COVID-19 vaccination status.

Informed Consent

The study received approval from the Institutional Review Boards of the City University Of New York (CUNY) Graduate School of Public Health and Health Policy (New York, NY, USA) (protocol NCT06119854) and followed the Consolidated Standards of Reporting Trials (CONSORT) social and psychological interventions (SPI) reporting guidelines[21,22]. Informed consent forms were completed via web browser on participants' computers or mobile devices at baseline and periodic follow-up assessments. The trial was pre-registered at: https://clinicaltrials.gov/study/NCT06119854

Participants

Participant eligibility criteria at the time of study enrollment (April-June 2024) were as follows: (1) aged 18 and older, (2) able to read in English, (3) current residence in the US, (4) completed at least one survey as part of the CHASING COVID Cohort study between December 7, 2022 and December 22, 2023, and (5) undervaccinated, defined as having received at least one dose of

the COVID-19 vaccine, but not an updated COVID-19 vaccine dose since September 11, 2023. Participants were excluded if they (1) had a SARS-CoV-2 infection in the past three months, (2) had never received *any* dose of a COVID-19 vaccine, or (3) were flagged for fraudulent behavior. Fraudulent participants were identified as showing evidence of duplicate or inconsistent contact information, suspicious response times, repeated enrolment attempts, or fraudulent flags raised from other CHASING COVID-based studies. Further details of participant characteristics can be found in Appendix A.

Intervention delivery and data collection occurred fully online. Participants completed an online survey at enrollment and at 4-weeks following enrollment.

Intervention and Control Conditions

Participants viewed one of three one-minute videos. The video content of the experimental arms was developed using formative mixed-methods research, including a pre-trial survey with CHASING COVID participants on vaccine perceptions and qualitative interviews with participants reporting anxiety or depression in earlier questionnaires. This process revealed a common concern about vaccine effectiveness as a broader "meta-narrative" across participants[17]. Additionally, those with anxiety or depressive symptoms were more likely to cite not "making time" as a reason for being behind on vaccination- a theme later incorporated into the CBT-kernels condition.

Specifically: 1) The inoculation video addressed concerns about vaccine effectiveness, focused on bolstering resistance to mis/disinformation. 2) The CBT-kernels video focused on addressing barriers to vaccination, specifically making time to get vaccinated. It focused on cognitive reframing—highlighting how individuals might selectively focus on information that reinforces vaccine-related anxiety, challenging those beliefs, and encouraging problem-solving around making time to get vaccinated. 3) The standard public health messaging arm was a brief video adapted from existing public health PSAs, with no inoculation or CBT-kernels elements.

The videos were professionally created in collaboration with Long Story Short, a production company with experience in PSA creation that has worked with local, national, and global public health organizations. Our research team worked closely with the production team throughout the process, iterating on scripts, refining takes, selecting actors, and providing detailed feedback to ensure clarity and consistency. The research team included experts in mental health disorders, COVID-19 surveillance, infection and transmission, vaccine hesitancy and uptake, public health emergency preparedness and response, and risk communication. A member of the research team was present on set during filming to oversee production and ensure fidelity to our intended messaging. By creating all videos within the same production process, we maintained control over factors such as tone, format, duration, and overall presentation, reducing the risk of unintended differences that could influence participants' responses. This approach allowed us to isolate the effects of the different messaging strategies while ensuring that all videos were aligned in terms of quality and delivery. A description and scripts of these videos can be found in Appendix D.

After receiving the brief digital intervention, participants received two reminders to get vaccinated by text or email on the first and third days after completing the baseline assessment. Messages were tailored to each arm and included a link to a COVID-19 vaccine locator. Their content can be found in Appendix A.

Stratified Randomization Procedure and Masking

Sequence Generation
We used a two-stage procedure for randomization. First, participants eligible for recruitment were stratified into two groups based on the presence or absence of symptoms of anxiety or depression reported at any point between December 2022 and December 2023. Second, participants in both strata were randomized to one of the three intervention arms upon being enrolled. Thus, participants were randomized separately according to symptoms of anxiety or depression.

Masking
Participants and two team members involved in study operations and study implementation (AS and JN) were not blinded to study assignments. All other study team members, including investigators and the data analyst (JS), were blinded to study assignments.

Measures

Intervention Implementation (Adherence) Measure
The survey was programmed to require participants to remain on the video page for at least the duration of the video. However, time spent on the webpage doesn't necessarily reflect attentiveness, hence participants were also asked "Did this video hold your attention?" with options "Yes, it held my attention" and "No, it did not hold my attention / I did not watch the video."

Primary Outcome: Receipt of COVID-19 Vaccine Dose at 4 Weeks
At the 4-week survey, participants were asked, "Have you received a COVID-19 vaccine dose since {date of intervention}?" Participants who responded "yes" were considered vaccinated; otherwise, they were not.

Secondary Outcome: Vaccine Willingness at 4 Weeks
At the 4-week survey, participants who had not received an additional dose of the vaccine were asked, "How willing are you to receive another COVID-19 vaccine dose?" with response options: "Very willing", "Somewhat willing", "Not willing", or "Don't know". Only participants who responded 'Very willing' were defined as vaccine willing.

Pre-trial vaccine willingness. After enrollment, but before randomization into an intervention arm, participants were asked, "How willing are you to receive another COVID-19 vaccine dose?" with response options: "Very willing", "Somewhat willing", "Not willing", or "Don't know".

Post-trial vaccine willingness: Immediately after the intervention, participants were asked: "How likely are you to make time to get a vaccine in the next month?" with response options: "Very likely," "Somewhat likely," "Not likely," and "Don't know/not sure." They were also asked:
"Are you planning to make an appointment to get the COVID-19 vaccine in the next month?" with options: "Already made an appointment", "Planning", "Not planning", "Don't know/not sure". These questions were asked again in the 4-week follow-up survey, but only among participants who had not received an additional vaccine dose during that time. For participants with missing follow-up data (N=56), responses from the immediate post-intervention survey were used as imputed values.

Post-hoc Stratification Variables
Post-hoc stratification analyses were performed to assess differences in primary and secondary outcomes based on susceptibility to severe COVID-19, worry about COVID-19, and pre-trial perceptions of vaccine efficacy. Further details regarding the measurement of these stratification variables were provided in Appendix A.

Statistical Analysis Plan

All statistical analyses were performed blind to study arm allocation. We present frequencies and summaries of characteristics by treatment assignment. Standardized mean differences (SMD) were reported. For post-randomization characters, Chi-squared or Fisher's exact tests were used to compare proportions.

Primary analyses were performed under the intention-to-treat principle, including all participants who underwent randomization. Strict intention-to-treat analysis is hard to achieve for two reasons: missing outcomes for participants and protocol non-adherence. For the primary analysis, we used multiple imputation for those lost to follow-up at some point after randomization (as recommended by the CONSORT statement[23]), which has the benefit of including all randomized participants. As a sensitivity analysis, we assessed loss to follow-up assumptions under (1) multiple imputation and (2) protocol non-adherence (see Appendix).

For the primary outcome, we generated risk ratios using a robust Poisson regression model and generated risk differences. For the secondary outcome of vaccine willingness, we generated risk ratios using a Poisson regression model. The model for the overall effect estimation included the randomization arms and a term for the presence or absence of symptoms of anxiety or depression reported between December 2022 and December 2023. For an Intention to Treat (ITT) analysis of a stratified randomized trial, adjustment is recommended for the stratification variable[23,24] on the principle that the analysis should follow the design[23,25].

To assess the effect of the intervention according to symptoms of anxiety or depression, we restricted them to subsets with or without symptoms. The stratified models included only randomization arms as the independent variable. Similarly, post-hoc stratification analyses for the primary and secondary outcomes were conducted separately among subsets of participants based on the presence or absence of the post-hoc stratification factors (susceptibility to severe

COVID-19, worry about COVID-19 and pre-trial perceptions of vaccine efficacy). The model included randomization arms and accounted for the presence or absence of symptoms of anxiety or depression.

Lastly, the validity of an ITT effect estimate requires correct adjustment for selection bias due to differential loss-to-follow-up and missing outcome data[23,26,27] .We used multiple imputation for loss-to-follow-up and missing data, hence conducting stratified analyses to assess effect modification rather than relying on interaction terms, as standard interaction testing isn't directly applicable to imputed datasets[28]. Details on imputation methods are included in Appendix C. Methods for sensitivity analyses can be found in Appendix B. A series of sensitivity analyses were conducted to address assumptions related to loss to follow-up and protocol adherence, including complete case analysis, inverse probability weighting, per-protocol analysis for participants fully adhering to the intervention, and multiple imputation for missing outcomes, with consistent results observed across primary and secondary outcomes.