SARS-CoV-2 transmission in an indoor mass-gathering live music event. A randomized clinical trial.

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Abstract

The banning of mass-gathering indoor events to prevent SARS-CoV-2 spread cause an important impact on local economies. We designed a randomized-controlled open-label trial to assess the effectiveness of a comprehensive preventive intervention for a mass-gathering indoor event (a live concert) based on systematic screening of attendees with antigen-detecting rapid diagnostic tests, use of facial mask, and adequate air ventilation. According to a RT-PCR test performed on day 8 after the event, none of the 465 assistants in the experimental arm (i.e., event attendants) became infected by SARS-CoV-2 (observed incidence 0%; Bayesian estimated incidence 0.14%; 95%CI: 0% to 0.61%) versus 2 out of 495 controls (not entering into the event) (0.31%; 95%CI: 0.04% to 0.73%). No significant differences were observed between the estimated incidence in the two study arms. Our study provides evidence on the safety of indoor mass-gathering events conducted during a COVID-19 outbreak under a comprehensive preventive intervention. (ClinicalTrials.gov number, NCT04668625)

Introduction

Mass-gathering events are associated with a high risk of spreading the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1–3]. Cultural activities like a sporting event, indoor gathering parties, play, or concerts have been pointed among the riskiest activities for SARS-CoV-2 transmission[4]. Healthcare authorities have correspondingly reduced the capacity of the venues to prevent close contact between unknown attendees or have even cancelled all the events, despite the lack of scientific evidence for such increased risk in some cases[5].

Of all mass-gathering events banned during the COVID-19 pandemic, the closure of concert halls has had a remarkable impact on local economies. In 2019, music festivals had an estimated revenue of more than 5,500 million € in Spain and 2,500 million in Catalonia. The cancelation and deferment of these events in 2020 has caused substantial economic losses, and restrictions on their celebration or capacity remain in force in 2021[6].

One of the key factors that challenge the control of massive SARS-CoV-2 transmission in mass-gathering events is the difficulty in identifying individuals with infection capacity, particularly asymptomatic or pre-symptomatic individuals with a high viral load[7]. SARS-CoV-2 transmissibility begins 2 to 3 days before symptom onset, and it is estimated that nearly half of the transmissions occur from asymptomatic individuals[3,8].

The long turnaround of nucleic-acid amplification tests (NAAT)—including the gold standard real-time reverse transcriptase-polymerase chain reaction (RT-PCR)—for identifying the SARS-CoV-2 in respiratory specimens hampers implementing mass testing strategies on the same day of the event. Alternatively, antigen-detecting rapid diagnostic tests (Ag-RDTs) have been proposed as suitable tools for point-of-care screening of SARS-CoV-2 infected individuals. The main advantages of Ag-RDTs include low price, absence of need for high-tech laboratory referral, and a short turnaround time to provide a result. Despite

the overall lower sensitivity of Ag-RDTs compared with NAAT, a growing body of evidence indicates that they are suitable for identifying individuals with transmission capacity[9–11].

Current evidence on Ag-RDT performance suggests that a point-of-care screening of contagious individuals, together with containment measures like the use of adequate facial masks and optimized ventilation can create safe environments for performing mass-gathering events with a low risk of SARS-CoV-2 spread. Nevertheless, this approach has not been tested under controlled conditions. We conducted a randomized controlled trial to assess the effectiveness of a preventing strategy for a live indoor concert under the hypothesis that a same-day point-of-care screening of infected individuals and regular preventive measures would prevent an increased risk of SARS-CoV-2 transmission during the event.

Methods

Study Design and Participants.

This was an open-label, randomized (1:1) clinical trial to assess the effectiveness of a comprehensive intervention to prevent SARS-CoV-2 spread during an indoor live concert. Study participants were recruited from a list of subscribers to news related to live music events; a call for enrolling in the study was performed through non-official media like WhatsApp, Telegram, or email. Eligible participants were adults aged 18 to 59 years with a negative result in an Ag-RDT performed on a nasopharyngeal swab collected immediately before entering the event. Participants with known COVID-19 diagnosis within the 14 days before the event, relevant comorbidities, or living with older people were excluded. Supplementary Appendix 2 provides a complete list of selection criteria.

SARS-CoV-2 screening and randomization

From 9 hours before starting the event, the healthcare staff collected nasopharyngeal swabs from all eligible participants. The same nasopharyngeal specimen was used to perform in situ Ag-RDT (Panbio™ COVID-19 Ag Rapid Test, Abbott) and a transcription-mediated amplification test (TMA, Procleix Panther®, Grifols). The TMA result was reported 24 to 48 hours after ending the event. All TMA-positive samples were re-tested by RT-PCR. The day after releasing the result, all TMA-positive individuals were contacted by phone for a structured interview by a physician, and their electronic medical records were screened to identify the exact date of a prior positive SARS-CoV-2 diagnostic test. All swabs with positive TMA results were assessed for viral isolation on cell culture. All study participants were visited 8 days after the event for nasopharyngeal swab collection and TMA test (follow-up day 8 test).

Study participants with a negative result on Ag-RDT were randomly assigned 1:1 to either enter the indoor live event (experimental arm) or not entering the event and returning to normal life (control arm). The computer-generated block randomization (REDCap™ module) was stratified by age, gender, and previous COVID-19 in the questionnaire.

Indoor event procedures

All participants installed two smartphone applications (apps). The “Radar Covid” (a contact tracing app) was intended to capture close contacts of subjects potentially infected during the concert. The “Test-Wallet” app was used to confidentially report the study test results (i.e., Ag-RDT, TMA, and PCR) and fill a health questionnaire before and ten days after the event, and a satisfaction questionnaire for those attending the concert (Supplementary Appendix 3). Data generated by the Test-Wallet app were encrypted using SHA-1 encryption and with 256-bit SSL security certificate. All SARS-CoV-2 positive results were reported into the public health electronic system and triggered quarantining measures and contact tracing studies.

All participants received an N95 mask at the venue entrance. Mask wearing was mandatory during the entire event. No physical distancing was required in the concert room (with a capacity of 900 persons); singing and dancing were permitted. A smoking area was set outdoors; the area had 20 people capacity and strict control of crowding and physical distancing.

Drinks—including alcoholic beverages—were served only in the bar zone, located in a supplementary room with a capacity for 1,600 people. Participants were asked to remove their face mask only when drinking. People movements inside the venue were previously defined and signaled. Securities personnel oversaw all movements and took actions—if necessary—to prevent queues in and around the venue foyer and toilets. Hydroalcoholic hand sanitizer gel was provided at multiple points in the venue.

The temperature of the dancing room and bar were maintained between 19.3 and 20.4 ºC during the event to facilitate wearing the mask and coats (the cloakroom was closed to avoid queues in front of it). Average CO_2 measurements before starting the event were 440 ppm in the dancing hall and 417 ppm in the bar room, both similar to those typically obtained on open air in the city. Public health safety guidance in force at the time of the event recommended not exceeding 1,000 ppm during the event.

The total surface of the venue was 1.024 m²: 228 m² for the dancing hall, 381 m² the bar hall, and 157 m² in the lobby. There were no outer windows in the two respective halls; however, all access and exit doors remained open during the event, allowing additional fresh air from the inner courtyard.

The event, held in the Sala Apolo (Barcelona, Spain) on December 12, 2020, lasted for five hours and included four performances: two DJ sessions and two live music acts. Besides the study participants and artists, 58 staff members (organizers, security, sound, light technicians, and bartenders) were inside the venue during the event. All of them were tested for SARS-CoV-2 using Ag-RDT at the same time points as study participants

Laboratory assessments

Nasopharyngeal specimens were collected with flocked swabs in a viral universal transport medium (Deltalab S.L, Barcelona, Spain). Samples were received at the laboratory and were processed immediately, inactivated, and analyzed by TMA. All TMA-positive results were confirmed by RT-PCR assay

to determine the cycle threshold (Ct) values (AllplexTM® SARS-CoV-2, Seegene) using the software designed by the company. Leftover positives samples were conserved at -80°C.

Nasopharyngeal specimens with positive SARS-CoV-2 TMA results despite testing negative on Ag-RDT were analyzed for viral isolation on cell culture. Vero E6 cells (ATCC CRL-1586) were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% heat inactivated fetal bovine serum (FBS), 100 U/mL penicillin and 100 µg/mL streptomycin (Invitrogen®). Two individuals with negative SARS-CoV-2 RT-PCR, and two viral stocks previously isolated were cultured in triplicates as negative controls as previously described[12]. DMEM supplemented with FBS and Pen/Strep were supplied to cells and inspected every 2 days for cytopathic effects. On day seven, cell supernatants were assayed with a high-sensitivity quantitative ELISA for SARS-CoV-2 nucleocapsid protein (ImmunoDiagnostics®).

Ethics

The study was approved by the Ethics and Clinical Research Committee of the Hospital Universitari Germans Trias in Badalona, Spain. All subjects signed electronically an informed consent (Signaturit®). The study was conducted according to the Declaration of Helsinki and local legislation and is registered at ClinicalTrials.gov: NCT04668625.

Anonymized data are fully available upon reasonable request from the corresponding author after approval by the hospital Ethics Committee.

Statistical analysis

The primary efficacy endpoint was the difference in incidence of RT-PCR-confirmed SARS-CoV-2 infection at 8 days between the control and the intervention groups. It was assessed in the full analysis set, which included all participants who were randomly assigned, attended the event (in the experimental arm), and had a valid result in the day 8 follow-up SARS-CoV-2 test.

We used a Bayesian beta-binomial model to analyze the number of infected cases in each group. This approach allows prior information to be included, which is useful when estimating the probability of rare events[13,14].

The seven days cumulative incidence observed in the city of Barcelona when the second RT-PCR was carried out was around 1.3 per thousand people, according to official data.[15] However, this value underestimates the true rates due to the difficulty in recording asymptomatic cases. On the other hand, the study population had some exclusion/inclusion criteria that could influence this value. For the control group, the prior distribution chosen was a Beta(1.1, 400), with median 0.002, and the probability of values greater than 0.01 is approximately 2%. Uncertainty about the probability of infection among the experimental group was higher, and a Beta(1, 28.4) was chosen, with a probability of obtaining values greater than 0.1 around 5% as a prior distribution. For each group the posterior median and the highest

posterior density interval were calculated. In addition, to compare the probabilities of infection between groups, the difference in their probabilities and its credible interval (CI) were calculated.

A Bayesian analysis was performed to estimate the negative predictive value of the antigen test *vs* the RT-PCR test and versus a viral cell culture[16]. For the prevalence, a Beta(1.1, 400) was chosen again as a prior distribution, and the sensitivity and specificity are given with a non-informative Beta(1 1) priors. The median and the highest posterior density CI were calculated for the negative predictive value.

All analyses were performed using R version 4.0.3.

Results

A total of 1140 participants responded to the call released through social networks and were invited to participate in the study. Of them, 1047 individuals turned out for the event and were screened for SARS-CoV-2 infection with Ag-RDT of a nasopharyngeal swab; all of them tested negative and were, therefore, randomized to either of the two arms. Of all randomized individuals, 36 lacked a follow-up assessment, and 51 did not enter the event despite being assigned to the intervention group, resulting in a full analysis set of 960 participants (Figure 1). Participants included in the full analysis set had a mean age of 33.6 years (SD 8.6); 783 (81.6%) were male. Individuals in the intervention arm spent a median of 2 hours and 40 minutes inside the concert.

Of the 960 randomized participants, all Ag-RDT negative in the baseline screening, 28 (2.9%) had a positive TMA result (13 in the experimental and 15 in the control arm); of them, two—one in each arm—had a positive RT-PCR result (Ct of 37 both) (Table 1).

According to the interview by a physician and review of their medical records, all participants with positive TMA results had been previously diagnosed with COVID-19 within a median of 50 (IQR 44 – 77) days before the event. None of the 28 specimens with a positive TMA result showed a cytopathic effect on cell cultures, as measured with a quantitative ELISA seven days post-inoculation. Conversely, control positive cultures showed evident cytopathic effect, and viral particles could be detected by ELISA.

None of the 465 assistants in the experimental arm became infected by SARS-CoV-2 (observed incidence 0%; estimated incidence 0.14%; 95% CI 0% to 0.61%) vs. 2 out of 495 controls (0.31%; 95% CI 0.04% to 0.73%), as assessed by a positive RT-PCR at day 8. The 2 subjects in the control arm with SARS-CoV-2 infection at day 8 had a positive RT-PCR and also had a positive Ag-RDT on the day 8 follow-up assessment, had mild clinical disease, and were reported to the health care system. An epidemiological questionnaire and contact tracing were performed. One of them had already been diagnosed four days after the randomization. Except for the two individuals with positive RT-PCR and Ag-RDT, all individuals with a positive TMA result at day 8 had a history of a positive nasopharyngeal specimen (assessed either with TMA or RT-PCR) within the 52 (IQR: 45-81) days before the event. The incidence difference, estimated using a Bayesian approach, did not reveal significant differences in incidence between the two

arms (Figure 2). All staff members tested negative for TMA and RT-PCR tests at both, the baseline and follow-up assessments.

The negative predictive value of the screening Ag-RDT in this cohort of asymptomatic individuals was 99.9% (95% CI 99.5% to 100%) for a positive RT-PCR, and 99.8% (95% CI 99.3% to 100%) for a positive viral culture.

The air concentration of CO_2 did not exceed the recommended threshold of 800 ppm at any measurement during the event [17]. The number of complete air exchanges per hour in the two rooms ranged from 11 to 13.

The median score of the satisfaction and enjoyment questionnaire, rated on a 10-point scale, was 8.63. Most participants who attended the event felt they could behave normally and non-constrained despite the safety measures (median score 8.08). Likewise, they expressed their willingness to attend another activity with the same safety protocol (median score 9.29). There were neither disturbances, nor interventions of security personnel aside reminders of wearing the face mask along the activity.

The staff crew inside de venue included 58 people (organizers, security, sound and light technicians and bartenders). All them were also screened before the event, were SARS-CoV-2 antigen and RT-PCR negative, and had a negative RT-PCR at D8 visit.

Discussion

To our knowledge, this is the first randomized clinical trial that assesses the risk of COVID-19 transmission in an indoor mass-gathering live concert conducted under comprehensive safety measures, including same-day SARS-CoV-2 screening with Ag-RDTs, compulsory N95 face mask wearing, and optimized air ventilation. Assistants were allowed to singing and dancing in the concert hall room and no physical distancing was recommended. None of the 465 participants became infected, compared with 2 out of 495 in the control arm.

High SARS-CoV-2 attack rates (53% of confirmed cases) following exposure at events where assistants could sing (a choir practice) without face masks have been previously documented[18]. Airborne transmission was considered as likely facilitated by close proximity (within 6 feet) during practice, augmented by the act of singing itself, and has subsequently been confirmed in other indoor events by high aerosol exposure indexes[19]. These superspreading events highlighted the importance of physical distancing, including avoiding indoor gathering in large groups, and had a role in issuing restrictions against indoor cultural activities. Our study demonstrates that the safety measures implemented can effectively diminish this risk.

A key intervention to remove physical distancing in this study was screening SARS-CoV-2 infection with Ag-RDTs immediately before entering the event. Despite the lower overall sensitivity than RT-PCR, Ag-RDTs have proven the ability to detect SARS-CoV-2 infection in respiratory specimens with Ct in RT-PCR

below 25 and 30 (sensitivity of 100% and 98.6%, respectively), irrespective of the presence of symptoms and age[9,20]. While the sensitivity of these tests decreases at Ct beyond this threshold, a growing body of evidence indicates that respiratory specimens with Ct >30 have limited infection capacity[21–25]. Therefore, the systematic screening of potential attendees to an indoor event is an excellent tool for ruling out SARS-CoV-2 infectious transmitters. In our real-life experience with the screening of asymptomatic individuals, Ag-RDTs had a negative predictive value of 99.9% and 99.8% for RT-PCR and viral culture, respectively, in agreement with previous reports[26].

The use of Ag-RDT for systematic screening purposes in mass gathering events has multiple advantages over NAAT, including the lack of need for laboratory referral, and short turnaround time to report the result. However, the low analytic sensitivity of these tests and the dynamics of SARS-CoV-2 infection suggest that a negative result in Ag-RDT can only rule out infectiousness within the next few hours following test[10,27]. Another consideration regarding this screening strategy is the controversy on whether tests performed by non-trained persons (including self-testing) achieve the same accuracy as that reported for testing by healthcare workers[11].

The high sensitivity of NAAT is associated with the drawback of yielding positive results in respiratory specimens from individuals with past infection, albeit doubtful or no infectious capacity[23]. This is particularly pervasive in TMA-based tests, with a limit of detection as low as 60 copies/mL (in contrast with approximately 5000 copies/mL for RT-PCR)[28,29] that allows identifying SARS-CoV-2 RNA remains some months after the COVID-19 episode[30,31]. Despite infectious viruses have not been recovered beyond 12 days in immunocompetent subjects, intestinal biopsies obtained from asymptomatic individuals 4 months after the onset of COVID-19 have revealed persistence of SARS-CoV-2 nucleic acids by *in situ* hybridization of half of the samples.[31]

In line with these findings, various individuals (3.2% in our study) with a history of COVID-19 diagnosis (median of 50 days before the event) tested positive for TMA in our study despite a negative result in the Ag-RDT screening. Only 6% of those with positive TMA results tested positive for RT-PCR, all with Ct values ≥37, far above the Ct cutoff associated with transmission risk. All they had been diagnosed with COVID-19 a median of 50 days before and had therefore no potential for viral transmission (immunosuppressed subjects were excluded). Quite unexpectedly, some TMA tests in our participants were positive in subjects with previous confirmed COVID-19 up to 5.5 months before. Remarkably, none of the TMA-positive samples from subjects with a prior SARS-CoV-2 infection was associated with a positive cell culture.

Taken together, our findings suggest that high-sensitive techniques like TMA are not suitable as screening tools for creating safe environments in indoor events.

Our intervention included other containment measures aside from the baseline screening that might have contributed to event safety. N95 mask-wearing was mandatory during the event, except when drinking (alcoholic beverages were allowed) or smoking. The lack of facial mask-wearing during indoor activities

without physical distancing measures had been pointed to as a high-risk scenario for superspreading events[18]. Although our study design precludes from drawing strong conclusions regarding the relative contribution of face masks, our findings regarding cell culture of TMA-positive individuals with a negative result in an Ag-RDT suggest that a point-of-care Ag-RDT screening might remove the need for face masks in a short time window. Nevertheless, this is to be proven yet.

Other measures with potential contribution to creating a safe environment included a limited movement of participants inside the venue, the avoidance of queues in toilettes and at entry/exit of the concert, the presence of dispensing points of hydroalcoholic sanitizer gel, and the controlled environment conditions. Limited air exchange in closed spaces is associated with an increased risk of SARS-CoV-2 transmission[32]. In fact, multiple infection events that prompted the banning of massive gathering events[33,34] had been associated with inadequate ventilation[35]. In our study, all air flows and room ventilation were optimized in the indoor rooms, and air exchange was monitored along the entire event. CO_2 measurements were maintained below or around 800 ppm in the two crowded zones (dancing and bar areas). Of note, after the event, local authorities intensified the recommendations for air quality beyond European recommendations[17,36]; according to the updated thresholds, air quality during our event would have been qualified as median/good, but not optimal[36]. Therefore, in future activities in our area, leveraging the air ventilation would be set to maintain a maximum of 500 ppm (good quality) or 350 ppm (optimum quality).

The deployment of screening strategies like the one used in our experiment is challenged by the need to test thousands of people within the few hours preceding the massive gathering event[32]. Therefore, organizational difficulties and costs should be considered. In this regard, mHealth solutions like the smartphone app Test-Wallet®, designed to manage Ag-RDT results promptly while maintaining privacy, can help significantly to manage screening procedures and result delivery. When balancing the costs and benefits of the intervention, it should additionally be considered the public health implications of identifying and isolating asymptomatic SARS-CoV-2 infected individuals of age groups that often remain undetected.

The SARS-CoV-2 transmission results from our study must be placed in the context of the existing epidemiological situation at that time. The 4^{TH} round of the National longitudinal sero-epidemiological ENE-COVID study was performed in Spain during 16-29 November 2020 (the closest to the concert) with 51.409 participants. According to the IgG results, the accumulative prevalence of subjects with a positive result in the province of Barcelona was 12.4%, with 9.8% having a positive result during the 4^{TH} round. The day before the indoor event, 256 new COVID-19 cases were reported in the city of Barcelona (1.6 million people); the 14-day attack rate in Catalonia was 220,7 cases/10^5 inhabitants, and the number of active cases (during the last 14 days) was 16,696, with 309,388 cumulative cases and an Effective Growth Potential (EGP) of 210 (worrying when >150).[15] The week after the concert (before the day 8 follow-up RT-PCR was done), the EGP increased to 371. Owing to the low number of COVID-19 cases

expected given the epidemiological scenario, we considered the Bayesian estimate of the infection rate an appropriate approach to the primary endpoint.

Our study has some limitations. First, participants could have modified their behavior during the event due to their awareness of being observed, having signed an informed consent, and participating in a clinical trial. This phenomenon, known as the Hawthorne effect, is intrinsic to clinical trials, and may limit the applicability of the results to the real-life scenario. Nevertheless, in the post-event questionnaire, all participants manifested normal behavior during the event, without feeling under the scrutiny of security controls. Second, the planned number of participants (1,000 per study arm) had to be halved due to restrictions dictated by local health care authorities. Our results encourage future studies with 100% of the estimated capacity of the venues. Finally, 16 participants did not enter the event because the result of the randomization was communicated too close to the event, and at that time they had already returned home. This delay was not due to the pace in the performance of screening tests but to a computer center failure involving the block randomization. Therefore, it should not impact antigen mass screening in future events

In conclusion, our study provides evidence on the safety of indoor mass gathering events conducted during a COVID-19 outbreak under a comprehensive preventive intervention based on same-day screening with Ag-RDT, compulsory facial mask-wearing, and adequate ventilation. Ag-RDT screening had a high performance in identifying infectious individuals compared to RT-PCR and particularly TMA. The results regarding virological assessment suggest that a baseline screening might allow easing some of the additional preventive measures, particularly in indoor events with preassigned seats (i.e., theaters), associated with lower transmission risk. Our findings, which pave the way to reactivate cultural activities halted during the COVID-19, may have important sociocultural and economic implications.

Declarations

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Declaration of Interests: The authors declare no conflicts of interest.

Author Contributions: B.R., S.V., B.C. and J.M.L. conceived the project and designed the study. P.S. recruited participants and organized the venue framework. J.P. screened virological tests to all participants. J.T. managed the database. X.P. and V.N. performed statistical analyses. I.B. and C.C. performed laboratory analyses on clinical samples. N.I. and D.P-Z. performed SARS-CoV-2 cell cultures. BR and J.M.L. wrote the paper. All authors had the opportunity to discuss the results and comment on the manuscript.

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Table

Table 1. Results of the virological assessment for SARS-CoV-2 at baseline and day 8 after the event.

	Control (n=495)	**Experimental** (n=465)
Baseline screening		
Ag-RDT positive	0	0
TMA positive[1]	15 (3.0%)	13 (2.8%)
Cell culture positive	0	0
RT-PCR positive	1 (0.2%)	1 (0.2%)
Follow-up assessment		
Ag-RDT positive	2 (4.0%)	0
TMA positive[2]	15 (3.0%)	12 (2.6%)
TMA positive at baseline	4	3
TMA negative at baseline	11	9
RT-PCR positive	2 (4.0%)	0
SARS-CoV-2 Infected	2 (4.0%)	0

Ag-RDT: Antigen-detecting rapid diagnostic tests; TMA: transcription-mediated amplification test; RT-PCR: real-time reverse transcriptase-polymerase chain reaction.

[1] Three TMA results in the control arm were inconclusive (n=492).

[2] One TMA result in the experimental arm was inconclusive (n=464).

Figures

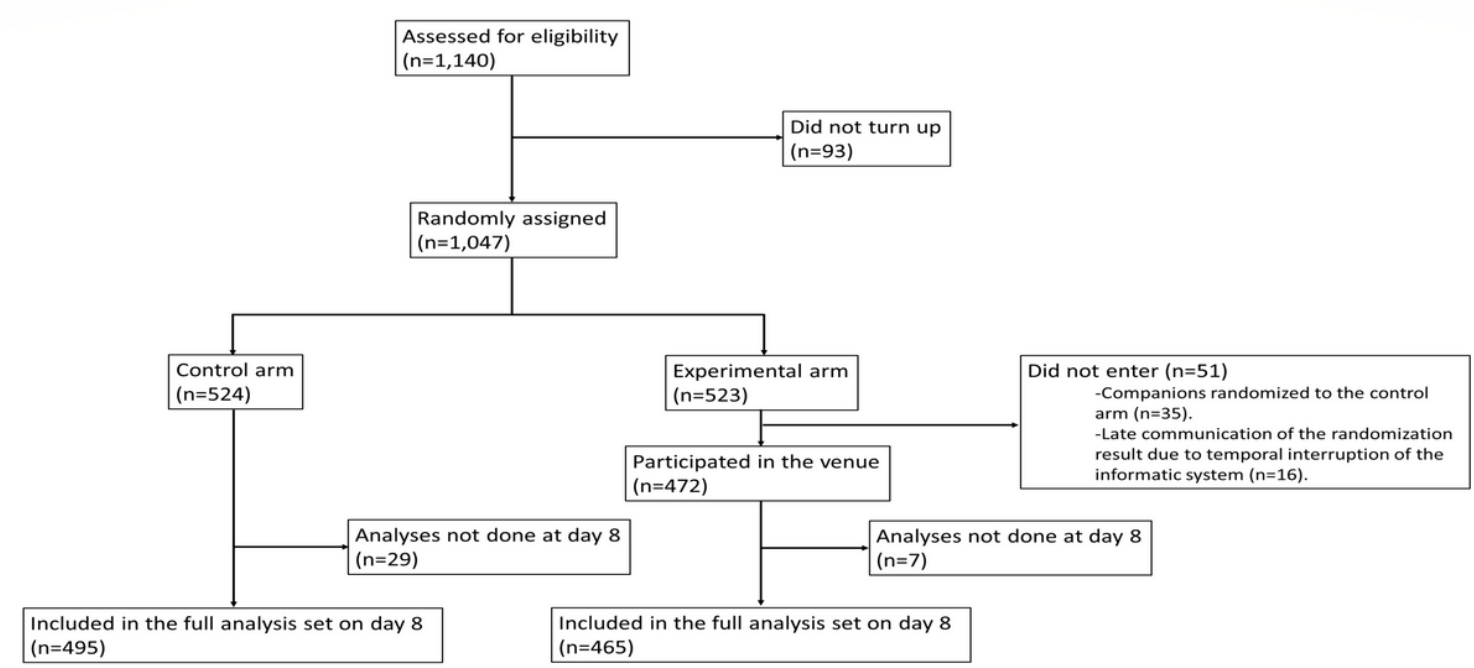

Figure 1

Trial profile.

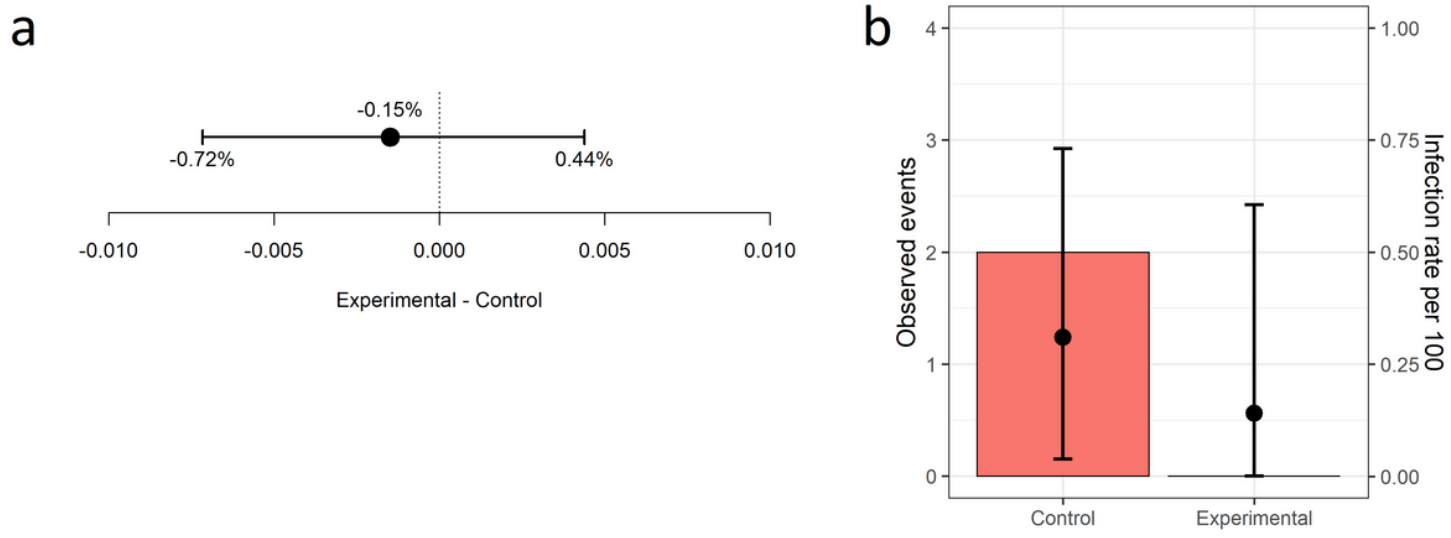

Figure 2

Incidence of SARS-CoV-2 infection in the two study arms (control arm N=495; intervention arm N=465). A: Bayesian estimate of the incidence difference between the experimental and control arms. B: observed events (bars) and estimated (Bayesian approach) infection rate per 100 people (dots) with the 95% credible interval (error bars).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplAppendix1.docx
- SupplAppendix2.docx
- SupplAppendix3.docx