Antigen rapid test screening to prevent SARS-CoV-2 transmission at mass gathering events. A protocol for a randomised trial.

THIS IS THE STUDY PROTOCOL AS OF 16. APRIL 2021. ADJUSTMENTS ARE LIKELY TO BE MADE, E.G. IN RESPONSE TO INPUT FROM THE REGIONAL ETHICS COMMITTEE, DUE TO CHANGES IN THE SARS-CoV-2 INCIDENCE, AND BASED ON AVAILABLE RESEARCH AND EVIDENCE. ALSO, SEVERAL PRACTICAL/LOGISTICAL ASPECTS OF THE TRIAL REMAIN TO BE SOLVED AND DECIDED UPON.

Antigen rapid test screening to prevent SARS-CoV-2 transmission at mass gathering events. A protocol for a randomised trial.

Atle Fretheim, Centre for Informed Health Choices, Norwegian Institute of Public Health (project lead)
Arnfinn Helleve, Centre for Evaluation of Public Health Measures, Norwegian Institute of Public Health
Martin Flatø, Centre for Fertility and Health, Norwegian Institute of Public Health
Tone Kristin Bjordal Johansen, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health
Michael Bretthauer, Clinical Effectiveness Research Group, University of Oslo
Joakim Øverbø, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health
Siri L. Feruglio, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health
Anne-Marte Bakken Kran, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health

Background

Banning of mass gatherings is among the most widely used interventions to reduce the spread of COVID-19. The rationale behind is simple: the risk of having at least one infected person in a group increases with the group size, as does the number of susceptible people who may end up infected. However, the degree to which the risk increases is not well known, and to what extent other infection control might balance off the increased risk that follows from lack of social distancing. Bans on mass gatherings pose severe restriction on individual freedoms. The right to assembly is a fundamental human right and finding means to safely allow such gatherings may be transferrable to religious institutions and schools.

Use of screening tests shortly before mass gathering events is one intervention that has been proposed as a means of allowing mass gathering events to take place safely, i.e. without an increased risk of infection compared to the risk faced if the event does not take place (1).

It is unknown if rapid testing for SARS CoV-2 virus can be used to ensure such gatherings, and rigorous scientific studies about the timing and extent of such testing are lacking. Although vaccination may make rapid testing obsolete in the medium term, rapid testing may be relevant in the event of new vaccine-resistant mutations, gatherings of children who are not yet part of vaccination programmes, and for future epidemics.

The exact performance of the available rapid SARS CoV-2 tests to identify infected individuals (sensitivity), is uncertain. The studies of test accuracy of rapid antigen tests have typically used polymerase-chain-reaction (PCR)-tests as reference standard, and the results of such studies are heterogeneous (2). Further, it is unclear what a sensitivity measure with PCR-tests as reference standard means in practice since a person that tests negative on a rapid test but positive on a PCR-test (false negative rapid testing) may be less contagious than one who test (true) positive with antigen testing.

The specificity of the tests may also be sub-optimal, but this may be less of a practical problem than the risk of false negative test. Still, false positive tests may lead to unnecessary burdens on the public health system for testing, and anxiety among those tested.
The authors of a recent Cochrane review on rapid tests for SARS-CoV-2 concluded that more research is needed on the impact of using rapid tests for mass screening: "Consideration needs to be made of the best method for evaluating mass screening. Whilst test accuracy studies help indicate which tests are likely to detect the greatest numbers of cases with the fewest false positives, assessing whether detecting asymptomatic cases leads to worthwhile reductions in disease spread will only be properly answered by studies of impact not accuracy" (2).
A trial of the impact of rapid testing in combination with mandatory use of face masks was conducted at a concert in Barcelona in December 2020 (3). The event demonstrated that the interventions were feasible to implement, and people who were randomized to attend the concert had no increased risk of COVID-19 after the concert compared to those who were randomised not to attend (0 versus 2 cases) (3). However, the total number of participants in the trial was only around 3,000, making it preliminary to draw firm conclusions due to statistical uncertainty. At the time of the concert, the 14-day incidence of COVID-19 cases in Catalonia was 220/100 000 (3).
Also, several mass gatherings with mandatory testing for SARS-CoV-2s before the events have taken place in Europe, with "encouraging results" according to media reports.[1] Scientific reports from these events are not available.
To investigate the impact of rapid SARS-CoV-2 antigen testing, we plan to conduct a large trial to assess the impact of using rapid tests to screen people before participating a mass gathering event, i.e. a music concert. Our hypothesis is that screening by means of rapid testing eliminates any increase in risk of COVID-19 from attending a mass gathering event.

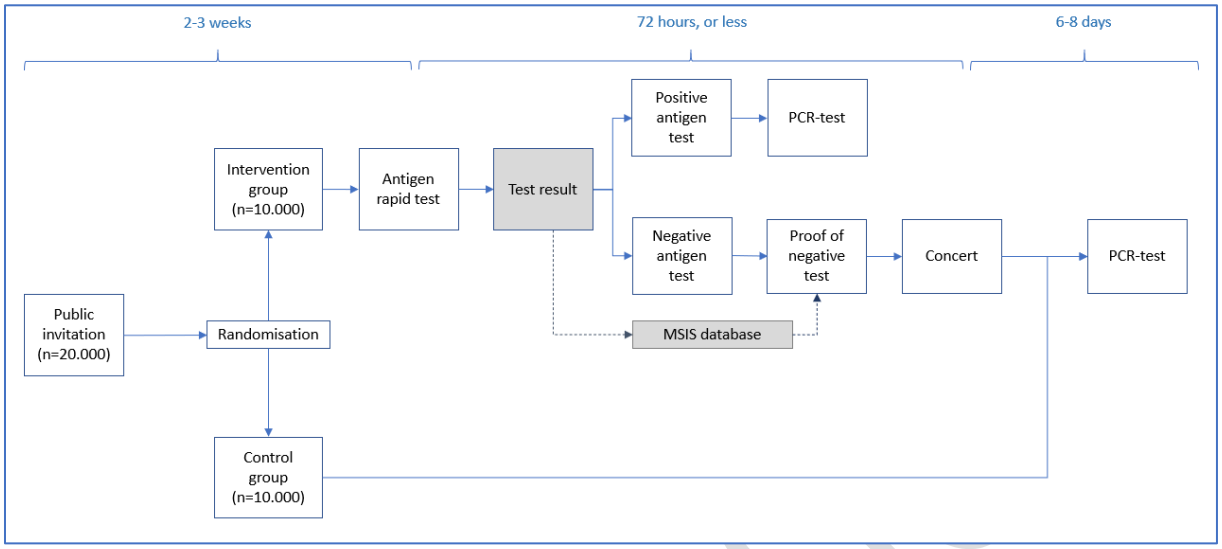
Methods

We will recruit individuals aged 18-45 years who will be randomised to be given access to a music concert (concert group), or not (no-concert group). Those who are randomised to the concert group will be tested for SARS-CoV-2 using a rapid antigen test, shortly before the concert, either by self-testing or at testing facilities (to be decided). Those who test positive will be excluded from attending the concert and will immediately be offered a PCR-test (see figure).
All participants will be instructed to stay at home if they have symptoms of COVID-19 or are in quarantine. Participants who have symptoms or are quarantined at the time of the follow-up test will be offered a test through home visit by a mobile clinic.
Those who are allocated to the concert group may be randomised a second time, to different forms of infection control measures, e.g. to wearing a face mask, or not (to be decided).
Infection control measures will be applied to all concert participants in line with standards established by the sector, e.g. hand hygiene measures and a logistical system that seeks to minimise the risk of transmission during entry to the arena and exit after the concert (4).
All participants (both concert and no-concert groups) will sign a consent form where they commit to using a contact tracing app, and to allowing the research group to use their data in the Norwegian Emergency Preparedness Register (Beredt C19). They will also consent to having a COVID-test (PCR) conducted 6-8 days after the concert date.
To ensure fidelity to follow up testing, we will consider hosting a concert for the members of the no-concert group, at a later stage (e.g. receiving tickets for the "control group concert" might be dependent on showing up for PCR-test), or some other form of encouragement. Also, those who tested positive on the rapid test therefore excluded from participating in the trial, would be offered tickets to such an event. Alternatively, the refund for the ticket payment for those allocated to the

[1] https://www.dw.com/en/dutch-researchers-test-ways-to-party-during-the-pandemic/a-56953021; https://www.theguardian.com/world/2021/mar/28/5000-attend-rock-concert-in-barcelona-after-covid-19-screening; https://www.nytimes.com/2020/11/03/world/europe/coronavirus-concert-study-germany.html

no-concert group could be made dependent on having conducted a follow-up test 6-8 days after the concert date. The terms will be made clear at the recruitment stage and included in the informed consent statement.

Figure. Flow chart



Outcomes

The main outcome will be SARS-CoV-2 infection, as diagnosed by PCR test.

Secondary outcomes:

- Clinical COVID-19 disease
- Hospital admissions
- Clinical Covid-19 disease in close contacts
- False positive rapid test
- Number of quarantined persons

We will also assess the relationship between the number of close contacts (based on data from contact tracing app) and COVID-19 risk.

Managing person data

Consent will be provided using the MinID-identifier. The results from the rapid test will be transferred digitally to the participants' mobile phones, and to the national registry for COVID-19 test results (MSIS Lab-database). An app which confirms a negative test result will have to be installed on all participants' mobile phones and will be needed to access the concert.

Person identifiable data from the mobile phone app on movements etc. will be collected and stored, in a secure manner (the exact technological solution is yet to be decided upon). These data will be linked to test result data, to enable analyses of the association between COVID-19 risk and movement patterns, number of close contacts etc. As soon as this information is linked, we will create a fully anonymised datafile.

No person data or biological material will be transferred outside the EEC.

Ethical dilemmas

The main ethical concern is that the participants may be exposed to increased risk of COVID-19 by attending the concert. This possibility will be clearly communicated. All participants will have to be over 18 years old and declare that they have no underlying condition which puts them at particular risk of severe COVID-19 disease, should they be infected. We will have an upper age limit of 45 years, because the risk of severe COVID-19 is very small in healthy individuals under 45 years old (5).

Before implementing the trial concert, we will seek approval from the health authorities (Norwegian Directorate of Health) and the local authorities in the municipality where the event would take place.

Conflicts of interest

The practical implementation of the experiment will be done in collaboration with representatives from the sector, who have a strong interest in finding ways of hosting large events in a corona-safe manner. They will offer in kind contributions by hosting and executing the event, and they may also co-sponsor the trial financially (this is yet to be decided and is to be discussed with the leadership at the Norwegian Institute of Public Health). The main investigator, the Norwegian Institute of Public Health, has no financial interest and will be solely responsible for the scientific aspects of the study.

Dissemination of findings

We plan to make the findings from the study publicly available shortly after the conduct of the trial, e.g. by posting a brief report on our institute's web site and/or a manuscript on a pre-print server.

Sample size calculations

Currently, the 14-day incidence of COVID-19 (i.e. positive tests) is around 700/100 000 among young adults in Oslo. Assuming that this reflects the expected PCR-test positivity rate in the control group at 6-8 days after the concert, we estimate a need for a total of 23 000 participants to detect a statistically significant difference of 0.35 percentage points to the experimental group, i.e. a 50% increase (significance level 5%, power 80%).

1. Sommerens store utendørsarrangementer. Innspill fra arbeidsgruppe nedsatt av Kultur- og likestillingsminister Abid Q. Raja.
2. Dinnes J, Deeks JJ, Berhane S, Taylor M, Adriano A, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Domen J, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Taylor-Phillips S, Hooft L, Leeflang MMG, McInnes MDF, Spijker R, Van den Bruel A. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database of Systematic Reviews 2021, Issue 3. Art. No.: CD013705. DOI: 10.1002/14651858.CD013705.pub2. Accessed 07 April 2021.
3. Josep M Llibre, Boris Revollo, Ignacio Blanco et al. SARS-CoV-2 transmission in an indoor mass-gathering live music event. A randomized clinical trial., 01 March 2021, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-244584/v1]. Accessed 07 April 2021.
4. COVID-19. Smittevern på konserter og arrangementer Rev.1. NHS C19002:2021ns
5. Himmels JPW, Borge TC, Brurberg KG, Gravningen KM, Feruglio SL, Berild JD. COVID-19: COVID-19 and risk factors for hospital admission, severe disease and death [Covid-19 og risikofaktorer for sykehusinnleggelse, alvorlig sykdom og død - en hurtigoversikt, tredje oppdatering. Hurtigoversikt 2020] Oslo: Norwegian Institute of Public Health, 2020.