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Randomised trials on non-pharmaceutical interventions for COVID-19 as of August 2021: a scoping review

Julian Hirt [1,2], Perrine Janiaud [1], Lars G. Hemkens [1,3,4]

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[1]Department of Clinical Research, University of Basel, Basel, Switzerland
[2]International Graduate Academy, Institute for Health and Nursing Science, Medical Faculty, Martin-Luther-Universitat Halle-Wittenberg, Halle (Saale), Germany
[3]Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, California, USA
[4]Meta-Research Innovation Center Berlin (METRIC-B, Berlin Institute of Health, Berlin, Germany

Correspondence to:
Dr Perrine Janiaud,
Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Basel-Stadt, Switzerland; perrinemarin echarlotte.janiaud@usb.ch

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Abstract

Objective We aimed at providing a systematic overview of randomised trials assessing non-pharmaceutical interventions (NPIs) to prevent COVID-19.

Design Scoping review.

Methods We included all randomised trials assessing NPIs to prevent COVID-19 in any country and setting registered in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform using the COVID-evidence platform (until 17 August 2021). We searched for corresponding publications in MEDLINE/PubMed, Google Scholar, the Living Overview of Evidence platform, and the Cochrane COVID-19 registry as well as for results posted in registries (until 14 November 2021). Descriptive statistics using numbers and percentages were used in the narrative synthesis of the results.

Results We identified 41 randomised trials. Of them, 12 were completed (29.3%) including 9 with published results. The 41 trials planned to recruit a median of 1700 participants (IQR 588–9500, range 30–35 256 399) with a median planned duration of 8 months (IQR 3–14, range 1–24). Most came from the USA (n=11, 26.8%). The trials mostly assessed protective equipment (n=11, 26.8%), COVID-19-related information and education programmes (n=9, 22.0%), access to mass events under specific safety measures (n=5, 12.2%), testing and screening strategies (n=5, 12.2%) and hygiene management (n=5, 12.2%).

Conclusions Worldwide, 41 randomised trials assessing NPIs have been initiated with published results available to inform policy decisions for only 9 of them. A long-term research agenda including behavioural, environmental, social and systems level interventions is urgently needed to guide policies and practices in the current and future public health emergencies.

Summary box

What is already known about this subject?

- Non-pharmaceutical interventions (NPIs) were taken worldwide to contain the COVID-19 pandemic.
- The need for randomised trials on NPIs has been highlighted.

What are the new findings?

- After 18 months of the pandemic and more than 4000 registered trials worldwide, we identified only 41 randomised trials assessing NPIs to prevent COVID-19.
- While 12 trials (29.3%) were completed with 9 of them that published results as of November 2021, most of the trials are ongoing or not yet recruiting (n=26, 63.4%).
- NPIs were diverse with approximately 1 of 4 trials assessing protective equipment.

How might it impact clinical practice in the foreseeable future?

- Recommendations on best strategies to prevent COVID-19 in schools, workplaces, nursing homes and other settings cannot be made due to a lack of randomised evidence.
- A long-term research agenda including behavioural, environmental, social and systems level interventions is urgently needed to guide policies and practices in the current and future public health emergencies.

Introduction

As of November 2021, 5 million deaths associated with SARS-CoV-2 infection and almost 250 million confirmed cases have been reported worldwide.[1] Numerous non-pharmaceutical interventions (NPIs) were taken worldwide to contain the pandemic.[2] NPIs are considered crucial to prevent infections, in particular for non-vaccinated populations and new virus variants.[3] Such interventions include drastic social distancing and lockdown measures impacting billions of people around the globe.[4] The need for randomised evidence on NPIs has been highlighted on numerous occasions.[5 6] There is a major debate on the comparative effectiveness of public health measures such as quarantine, school and workplace closures, travel restrictions and different testing regimens to prevent COVID-19.[7 8] The evidence for the benefits and harms of NPIs is mostly based on observational and modelling studies.[9] Authors of high-quality evidence syntheses have concluded that the evidence for quarantine and travel restriction measures is limited facing a lack of randomised

real-world evidence and that most of the studies use mathematical calculations based on diverging assumptions and model parameters.[10 11]

Given the extremely complex interrelationship and parallel introduction of different interventions in a situation with strong time-dependent changes, including those of the virus itself, it is difficult and almost impossible to clearly attribute outcomes to individual interventions without parallel controls.[9] Furthermore, with no valid causal models capturing complex interrelationship between interventions and regional settings, environments, population, cultural, social and economic factors nor high-quality, high-granular data reflecting these factors and allowing for statistical adjustments, there is a substantial risk of confounding bias, even for comparisons with parallel controls.[12–14] Only a randomised trial may provide high quality evidence on comparative effects of interventions without the need to understand complex mechanisms and measure complex data.[14–16]

Randomised evaluations have been used in the past to measure causal effects of a wide range of diverse and complex behavioural, social, environmental interventions and policy strategies. For example, such randomised evaluations helped to determine how health insurance affects health outcomes,[17] assessed impact of school class sizes on academic performance and health (including mortality),[18] and explored which human papillomavirus screening strategy for cervical cancer is favourable,[19] which hygiene interventions reduce hand bacterial counts,[20] how financial incentives improve physical activity[21] or which infection control measures reduce spread of respiratory infections in children.[22]

Conversely, no randomised trials assessing any NPIs were initiated early in the COVID-19 pandemic[23] and it is likely their number have remained sparse or even lacking.[10 11 24] We aimed to provide a systematic overview of the major characteristics and results of randomised trials assessing NPIs to prevent COVID-19. Mapping the trial landscape helps to get an overview of the current trials worldwide, what evaluations on which NPIs are being conducted and what are the unmet needs.

Methods

A scoping review was performed to collect the current randomised trials on NPIs and to summarise their status and characteristics. We did not register this study or published a specific study protocol. We used the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews') framework to provide a comprehensive study report, where applicable.[25]

Eligibility criteria

This scoping review included all registered randomised trials assessing NPIs to prevent COVID-19 in any country and setting without any language restriction. NPIs were defined as any interventions to prevent COVID-19 that did not contain pharmaceutical substances or regimens. We considered any NPIs as single measures or in combination involving, for example, information and education interventions, protective equipment, disinfection, social distancing, isolation, quarantine, testing or community-wide containment strategies. We excluded interventions based on drugs, biologicals, vaccines, herbals, traditional medicine and homoeopathy. Trials assessing NPIs without any health outcome related to SARS-CoV-2-infections were excluded (eg, interventions aiming to improve vaccination rates).

Search and selection of trials

We searched the COVID-evidence platform (www.covid-evidence.org,[26]) for eligible trials as of 17 August 2021. COVID-evidence is a freely available continuously updated database that contains information about worldwide planned, ongoing, and completed randomised trials on any intervention to treat or prevent SARS-CoV-2-infections. Trials registered in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) are retrieved on a weekly basis. COVID evidence uses a multimethod approach combining peer-reviewed search strategies of study registries, continuous automated extraction of search results, automated classifications combined with manual screening and data extraction (details on the methodology are published elsewhere[27]).

For all eligible trials identified in COVID-evidence, we searched for corresponding publications (peer-reviewed and preprints) in MEDLINE/PubMed, Google Scholar, the Living Overview of Evidence platform, and the Cochrane COVID-19 registry using trial registration numbers (until 14 November 2021). We also recorded if trial results were reported in the registries. All searches were done by one researcher (JH or PJ). The selection of trials followed a three-step approach and was done by one researcher (JH or PJ). First, records within COVID-evidence were automatically screened based on keyword searches to identify randomised trials related to COVID-19. Second, we automatically screened for trials that were clearly assessing intervention containing pharmaceutical substances using the following keyword search: (drug OR biological OR vaccine) NOT (behavioral OR mask OR school OR distancing OR non-drug OR "non drug" OR non-pharma OR "non pharma"). Finally, we manually screened the remaining trials. Unclear cases were discussed and resolved within the study team (JH, PJ and LH).

Data items and charting process

One researcher (JH) extracted data on trial status, start to end date, country, number of enrolled individuals and clusters, if applicable, population and setting, intervention and comparison, health-related COVID-19 outcome(s), and design features (randomisation unit, number of arms and outcome measurement type). Data extraction was based on trial registry information and, if available, published trial results. Extractions from registries took place in August 2021. Last update of trial and publication status was conducted on 14 November 2021. Extractions were tabulated and verified by two other researchers (PJ and LH).

Synthesis of results

Descriptive statistics using numbers and percentages were used in the narrative synthesis of the results. For calculations, we used R (V.4.1).

Patient and public involvement

We did not involve patients or members of the public in selecting the research question, designing the study, interpreting the results or writing the manuscript.

Results

We identified 41 eligible randomised trials (figure 1, table 1).

As of August 2021, 12 trials were completed (29.3%) including 9 with published results, 17 ongoing (41.5%), 9 not yet recruiting (22.0%) and 3 terminated early or withdrawn (7.3%). Most came from the USA (n=11, 26.8%), UK (n=4, 9.8%) and France (n=4, 9.8%). Of note, none of the completed and terminated trials had made their results available on the registries.

The types of NPIs were diverse. Of the 41 trials, 11 trials (26.8%) assessed protective equipment such as various masks, face shields or goggles; 9 trials (22.0%) assessed diverse COVID-19-related

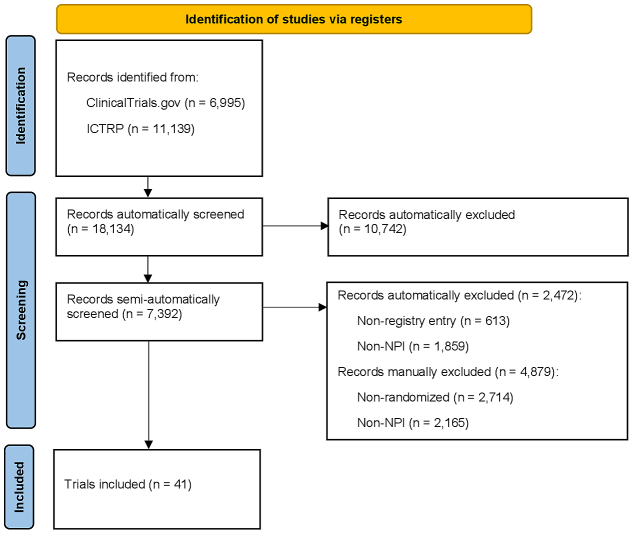

Figure 1 Retrieval and trial selection process. Abbreviations: ICTRP, International Clinical Trials Registry Platform; NPI, non-pharmaceutical interventions.

information and education programmes (eg, text messages, newsfeeds, personalised health education, Facebook advertisements, nurse-led home visits); 5 trials (12.2%) assessed the impact of attending a musical mass event/concert under specific safety measures; 5 trials (12.2%) assessed diverse testing and screening strategies in nursing homes, schools, universities and the emergency department; 5 trials (12.2%) assessed multicomponent behavioural interventions on hygiene management in the community. The other six trials assessed access to fitness centres, school opening, special housing of homeless individuals, direct income support for individuals with COVID-19-related financial disruptions, yoga sessions for healthcare professionals and COVID-19-related symptom tracking in outpatients with cancer.

The trials planned to recruit a median of 1700 participants (IQR 588–9500, range 30–35 256 399) with a median planned duration of 8 months (IQR 3–14, range 1–24). The largest trial assessed the impact of Facebook advertisements to prevent travelling and family reunions during Thanksgiving and Christmas with >35 million participants,[28] the shortest trial assessed the audience infection rate 8 days after an indoor music event.[29] A typical randomised trial on NPIs randomly allocated individuals (n=23, 56.1%), rather than clusters (n=18, 43.9%), to two comparison groups (n=38, 92.7%) and assessed a COVID-19-related primary outcome (n=33, 80.5%) that was laboratory confirmed (n=30, 73.2%).

Discussion

Worldwide, 41 randomised trials assessing NPIs have been initiated with published results available to inform policy decisions for only 9 of them. The number of trials assessing NPIs to prevent COVID-19 is a tiny fraction of more than 4000 randomised trials on COVID-19 registered globally as of August 2021.[27] Given the unprecedented public health impact worldwide and the wide debates about benefits and harms of NPIs, this number seems disproportionate in light of other interventions that have been the focus of much more randomised trials.[8] For example, over 300 randomised trials included the highly debated hydroxychloroquine in their intervention arm[30] which has been found to be associated with increased mortality in COVID-19 patients.[31] The reasons for such an imbalance remain speculative and require urgent investigation. However, trials assessing NPIs face some challenges. One hurdle is the need for large sample sizes to detect an effect of public health measures in populations with low event rates. For example, it was shown that about 1000 schools in Norway would have been needed to participate in a trial assessing school closures to demonstrate a meaningful risk reduction in a situation with low incidences.[32] However, this number is put into perspective when one considers that there are more than 80 000 primary schools in France, Germany, UK alone and more than 1.5 billion students were deprived of schooling worldwide in the early days of the pandemic.[33–36] The fact that 117 million students are still affected by full school closure as of September 2021 underlines the continuous need to determine best strategies.[37] A randomised assessment would have helped to find optimal ways for schools to safely teach millions of students globally. One other potential hurdle is costs. However, worldwide, governments have made astronomical funds available for preventive measures. For example, it has been reported that Germany made available 700 million Euro for mobile air filters.[38] Such implementation could have been directly assessed through randomised roll-outs providing access to the preventive measures all the while providing robust evidence on their effectiveness.[39] Another barrier may be that as vaccines become more available and accessible, the need for randomised evaluations of NPIs may be perceived to be decreasing.[32] The fatal course of the disease, with the dramatic increase in deaths in the early days of the pandemic has probably also shifted the research focus from prevention to treatments for COVID-19 to the detriment of evaluating NPIs.[9 30] Overall, the specific role and relevance of these factors is not clear and requires an evidence-based assessment with sound meta-research.

The list of available treatments for COVID-19 remains limited,[40–42] with vaccination rates plateauing in many countries[43] and increasing numbers of confirmed cases during the summer and autumn 2021,[1] NPIs and their effectiveness will remain a central debate.[9] Our analysis clearly indicates that randomised trials are generally feasible to assess the benefits and harms of NPIs during a pandemic situation, in a very short time using the most reliable method to provide reliable evidence for optimal health policy decision making. WHO is committed to improve the evidence base on effectiveness of public health and social measures,[44] and this overview may inform further developments in this important area of evidence generation.[9]

This study is limited as our sample relies on accurate trial registration and reporting. We cannot exclude that some NPI randomised trials might have been missed because they were not registered, and outcomes related to SARS-CoV-2-infections were incorrectly or not reported in the registries. Searching the grey literature (eg, via web search engine or institutional searches) or contacting key informants outside academia could have retrieved eligible trials that were not registered nor published in an academic format. In particular, NPI trials with inconclusive results or not supporting their use may be at risk of not being published potentially causing a publication bias.[45] Non-published results can be expected since some trials should have been completed according to their completion date given in the registry. Furthermore, we could have missed eligible trials because of our single-reviewer screening approach. However, it is unlikely that we have been unaware of pertinent major results of further NPI trials, given their substantial impact on current debates and scarcity of the evidence.[46]

To provide continuous guidance for policy and practice, we will continuously track randomised trials assessing NPIs and provide all information on their key design characteristics and their status, freely accessible via covid-evidence.org.[26]

Table 1 Characteristics of all 41 randomised trials on non-pharmaceutical interventions to prevent COVID-19 as of August 2021

Trial ID	Start to end date	Country	Intervention topic	N individuals (clusters*)	Description (population, intervention and comparison, and outcomes related to SARS-CoV-2 infections) Results (we report information on published results for primary outcomes related to SARS-CoV-2 infections where available, and for secondary outcomes only where the primary outcome was not related to SARS-CoV-2 infections; of note, outcomes reported in published results might differ from the registry information)
Completed (n=12)					
Completed with published results (n=9)					
ChiCTR2000030317	2020–02 to 2020–04	China	Masks	320	Fully closed negative-pressure gastroscope isolation mask vs no mask for patients (18–79 years) during hospital-based gastroscopy on COVID-19 cases (secondary outcome). Results: No COVID-19 cases were recorded during follow-up.
NCT04337541	2020–04 to 2020–06	Denmark	Masks	6024	Surgical face mask recommendation vs no such recommendation in community-living adults (≥18 years) on confirmed and/or diagnosed SARS-CoV-2 infection and/or COVID-19 (combined primary outcome), confirmed SARS-CoV-2 infections (secondary outcome), and self-reported symptoms of COVID-19, healthcare confirmed or diagnosed SARS-CoV-2 infections, and mortality associated with COVID-19 (tertiary outcomes). Results: No statistically significant differences in SARS-CoV-2 infections/COVID-19 (OR, 0.82 (95% CI 0.54 to 1.23))
NCT04406909†	2020–05 to 2020–06	Norway	Fitness centre	3764	Access to indoor fitness centres applying physical distancing and enhanced hand and surface hygiene vs no access for community-living adults (18–64 years) on confirmed SARS-CoV-2 infections or hospital admissions for COVID-19 (co-primary outcomes), individuals with COVID-19 antibodies, need of ventilator treatment after hospital admissions for COVID-19, intensive care unit admissions for COVID-19, cause-specific mortality and confirmed SARS-CoV-2 infections in employees at training centres (secondary outcomes). Results: No transmission of SARS-CoV-2 at training facilities (only one participant allocated to the intervention tested positive but did not use the training facilities). No outpatient visits or hospital admissions due to COVID-19 in either group. None of the employees were tested positive.
CTRI/2020/07/026667†	2020–09 to 2020–11	India	Yoga	280	Morning and evening Pranayama yoga sessions vs general fitness practices (eg, walking, jogging, running) for hospital-based healthcare professionals (18–65 years) with COVID-19 duties on confirmed SARS-CoV-2 infections (primary outcome) and its severity (secondary outcome). Results: Statistically significant difference of SARS-CoV-2 infections between the intervention and control group favouring yoga sessions (1 vs 9 participants, p=0.01).
NCT04644328‡	2020–11 to 2021–01	USA	Facebook ads	11 954 109; 23 302 290 (820; 767)	Facebook ads for community-living adults (≥18 years) containing a short video on the importance of staying safe during Thanksgiving and Christmas by considering not travelling, social distancing, and using a mask when appropriate vs no Facebook ads on confirmed SARS-CoV-2 infections (analysis on a zip-code level) (secondary outcome). Results: Statistically significant differences of SARS-CoV-2 infections between the intervention and control group (zip-code area) favouring the Facebook ads (recorded infections declined by 3.5% (adjusted 95% CI −6.2% to −0.7%)).

Continued

Table 1 Continued

Trial ID	Start to end date	Country	Intervention topic	N individuals (clusters*)	Description (population, intervention and comparison, and outcomes related to SARS-CoV-2 infections) Results (we report information on published results for primary outcomes related to SARS-CoV-2 infections where available, and for secondary outcomes only where the primary outcome was not related to SARS-CoV-2 infections; of note, outcomes reported in published results might differ from the registry information)
NCT04630054†	2020–11 to 2021–04	Bangladesh	Masks and behaviour change	342 126 (600)	Community-level masks promotion strategies (multiple levels of randomisation, including free surgical or cloth face masks with information on the importance of masking, role modelling by community leaders and imams, and in-person reminders) for community-living adults (≥18 years) vs no intervention on confirmed symptomatic SARS-CoV-2 infections (primary outcome) and self-reported symptoms of COVID-19 (secondary outcome). Results: Statistically significant difference of symptomatic SARS-CoV-2 infections favouring mask use promotion (overall: adjusted prevalence ratio 0.91(95% CI 0.82 to 1.00)). Statistically significant difference for surgical masks (adjusted prevalence ratio 0.89 (95% CI 0.78 to 1.00)) but no statistically significant reduction with cloth face masks (adjusted prevalence ratio 0.95(95% CI 0.79 to 1.11)).
NCT04668625	2020–12 to 2020–12	Spain	Mass event	1047	Access to an indoor music event with systematic same-day screening of attendees with antigen-detecting rapid diagnostic tests, use of face masks, and adequate air ventilation vs no access for community-living adults (18–59 years) on confirmed SARS-CoV-2 infections (primary outcome) and self-reported symptoms of COVID-19 (secondary outcome). Results: No SARS-CoV-2 infections in the intervention group and two infections in the control group were reported (reported incidence difference, estimated using a Bayesian approach −0.15% (95% CI −0.72 to 0.44)).
ISRCTN18100261	2021–04 to 2021–06	UK	Testing strategy	238 579 (201)	Daily testing of contact cases vs isolating contact cases of school staff and students (secondary school and further education college) on COVID-19-related absences from school among those otherwise eligible to be in school and confirmed symptomatic SARS-CoV-2 infections (co-primary outcomes) and confirmed SARS-CoV-2 infections in contact cases (secondary outcome). Results: The adjusted incidence rate ratio for symptomatic SARS-CoV-2 infections was 0.96 (95% CI 0.75 to 1.22) and for COVID-19-related absences 0.80 (95% CI 0.53 to 1.21).
NCT04872075†	2021–05 to 2021–06	France	Mass event	6678	Access to an indoor music event with systematic antigen-screening within 3 days, medical mask-wearing and optimised ventilation vs no access for community-living adults (18–45 years) on confirmed SARS-CoV-2 infections (primary outcome). Results: The estimated absolute difference between attendees and non-attendees for SARS-CoV-2 infections had a 95% CI −0.26% to +0.28% which did not exceed the prespecified, non-inferiority margin (0.35%).
Completed without published results (n=3)					
ISRCTN14602359	2020–03 to 2021–03	UK	Behaviour change	n.r. (6899)	Behaviour intervention on how to reduce the spread of infections using Germ Defence (interactive website helping users with preplanning about effective isolation of an infected household member, personalised goal setting for increasing a range of infection control behaviours, changing the home environment to support new habits, and problem-solving to overcome barriers) promoted by general practitioners to their adult patients (≥18 years) vs no intervention on COVID-19 diagnoses, COVID-19 symptoms presentation, primary care consultations, hospital admissions (secondary outcomes).

Continued

Table 1 Continued

Trial ID	Start to end date	Country	Intervention topic	N individuals (clusters*)	Description (population, intervention and comparison, and outcomes related to SARS-CoV-2 infections) Results (we report information on published results for primary outcomes related to SARS-CoV-2 infections where available, and for secondary outcomes only where the primary outcome was not related to SARS-CoV-2 infections; of note, outcomes reported in published results might differ from the registry information)
NCT04620798	2020–09 to 2020–12	USA	Behaviour change	1700	Immediate vs delayed provision of COVID-19 antibody test results in addition to assessment of engagement with COVID-19 prevention behaviours following testing of university students (≥18 years) on confirmed SARS-CoV-2 infections (secondary outcome).
NCT04647305	2021–01 to 2021–03	Colombia	Masks and behaviour change	233	Closed face shield, surgical face mask, and an educational video intervention vs surgical face mask alone and an educational video intervention for community-living adults (≥18 years) on confirmed SARS-CoV-2 infections (primary and secondary outcome).
Ongoing (n=17)					
NCT04359264	2020–04 to 2020–05	Canada	Income support	392	Income support of US$1000 to community-living adults (≥18 years) suffering from COVID-19-related financial disruptions vs no income support on self-reported symptoms consistent with COVID-19 (primary outcome) and confirmed SARS-CoV-2 infections (secondary outcome).
NCT04296643	2020–04 to 2021–04	Canada, Israel	Masks	576	Surgical masks vs N95 respirator worn when providing care to patient with febrile respiratory illness for hospital-based nurses (≥18 years) on confirmed SARS-CoV-2 infections (primary outcome) and COVID-like symptoms, absenteeism from work, pneumonia, intensive care unit admissions, mechanical ventilations, and mortality (secondary outcomes).
NCT04321928	2020–04 to 2021–08	Hungary	Behaviour change	7576	Health education regarding lifestyle changes (questioning and recommendations in mental health, smoking habits, physical activity, dietary habits, and alcohol consumption) in addition to personalised vs general health education aiming towards improvement of these factors with general recommendations following the WHO principles for community-living adults (≥60 years) on intensive care unit admissions, hospital admissions, and mortality in participants with confirmed SARS-CoV-2 infections (combined primary outcome) and general practitioner visits, emergency, hospital and intensive care admissions, length of hospitalisations and intensive care unit stay and organ dysfunction (secondary outcomes).
NCT04464486	2020–04 to 2022–03	USA	Symptom tracking	300	COVID-19 and cancer-related symptom tracking, automated self-management support messages for symptoms reported, and a nurse practitioner monitoring and responding to alerts for COVID-19 symptoms and poorly controlled or worsening cancer symptoms vs information by research staff reviewing COVID-19 symptoms, home precautions, and instructions on what to do to address concerns that arise in adult cancer outpatients (≥18 years) on self-reported COVID-19 symptoms (secondary outcome).
NCT04471766	2020–07 to 2021–08	Guinea-Bissau	Masks	40 000	Certified cloth face masks plus information on COVID-19 prevention vs information alone for community-living children and adults (≥10 years) on self-reported COVID-like illnesses, consultations for COVID-19 like illness or/and confirmed SARS-CoV-2 infections, self-reported COVID-19 like illnesses plus hospitalisations or mortality, and all-cause mortality (co-primary outcomes).
ISRCTN69564614	2020–08 to 2022–01	UK	Special housing	1200	Settled housing temporarily accommodated by the local authority vs business-as-usual accommodation provided by local authorities for community-living homeless individuals (no details concerning age) on self-reported SARS-CoV-2 infections (primary outcome).

Continued

Table 1 Continued

Trial ID	Start to end date	Country	Intervention topic	N individuals (clusters*)	Description (population, intervention and comparison, and outcomes related to SARS-CoV-2 infections) Results (we report information on published results for primary outcomes related to SARS-CoV-2 infections where available, and for secondary outcomes only where the primary outcome was not related to SARS-CoV-2 infections; of note, outcomes reported in published results might differ from the registry information)
NCT04753645	2020–09 to 2021–05	Bangladesh	Behaviour change	3840 (194)	Multicomponent hygiene intervention (handwashing stations, in-person demonstration, hygiene meetings) and soap distribution vs multicomponent hygiene intervention without no soap distribution vs soap distribution without multicomponent hygiene intervention vs no intervention for community-living children and adults (≥10 years) on self-reported symptoms of transmissible diseases (no details if limited to COVID-19; co-primary outcome).
PACTR202102616421588	2020–11 to 2021–07	Congo	Behaviour change	1312 (121)	Multicomponent hygiene intervention (construction of water points, latrines and improved access to water and sanitation) for community-living children and adults (with no restriction on age) vs no intervention on self-reported COVID-19-like illnesses (co-primary outcome).
NCT04565509	2020–11 to 2022–09	USA	Behaviour change	2500 (6)	General vs targeted messaging on COVID-19 and the importance of testing to students, families and school staff (5–90 years) on confirmed SARS-CoV-2 infections (phase 1; secondary outcome). In phase 2, an adapted messaging strategy based on phase one and its implementation barriers and facilitators will be tested.
NCT04499391	2020–12 to 2022–07	USA	Information and education	24560 (200)	Multiple real-time, interactive videoconferencing information courses on COVID-19-related guideline implementation with refresher course vs multiple information courses alone for nursing home staff (≥18 years) on SARS-CoV-2 infections (no details if confirmed, diagnosed, or self-reported infections; primary outcome) and COVID-19 hospitalisations, mortality due to COVID-19 and influenza-like illnesses (secondary outcomes).
NCT04726371	2021–01 to 2022–10	USA	Information and education	5350 (400)	Tailored vs generic education and information on guidelines for COVID-19 mitigation for congregate care home staff and residents (≥18 years) on confirmed SARS-CoV-2 infections (co-primary outcome).
NCT04591015	2021–02 to 2021–08	USA	Information and education	172	COVID-19 support messages that provide information addressing identified barriers in Hispanic underserved communities (eg, obtaining testing supplies and medications, accessing routine medical care and completing other important diabetes self-management behaviours such as healthful eating, exercise, social distancing, quarantine, and stay-at-home/lockdown guidelines) for outpatients with diabetes (≥18 years) vs usual intervention on self-reported COVID-19 diagnoses (secondary outcome) and any hospital readmissions (tertiary outcome).
NCT04830761	2021–03 to 2022–04	Switzerland	Behaviour change	710	Combination of diverse hygiene behaviour change strategies (habit, motivation, social norms) for community-living adults (≥18 years) on self-reported influenza-like infection symptoms and self-report of confirmed SARS-CoV-2 infections (secondary outcomes).
NCT04765475	2021–03 to 2022–09	USA	Behaviour change	600	Motivational interviewing (preventive behaviours and COVID-19 testing when experiencing symptoms, and isolation and care-seeking when positively tested) and supportive services (provision of supportive services such as referrals to needed medical, mental or behavioural healthcare and delivery of a hygiene kit containing basic hygiene supplies; participants will also be provided information on COVID-19 and nearby testing locations, mask wearing, how to prevent the spread in the home, and managing stress during COVID-19) vs COVID-19 symptom monitoring system (alerts and information to request home testing after first symptoms) and supportive services vs motivational interviewing, COVID-19 symptom monitoring system, and supportive services vs supportive services alone community-living for young adults (18–34 years) and older adults (≥65 years) on confirmed SARS-CoV-2 infections (co-primary outcome).

Continued

Table 1 Continued

Trial ID	Start to end date	Country	Intervention topic	N individuals (clusters*)	Description (population, intervention and comparison, and outcomes related to SARS-CoV-2 infections) Results (we report information on published results for primary outcomes related to SARS-CoV-2 infections where available, and for secondary outcomes only where the primary outcome was not related to SARS-CoV-2 infections; of note, outcomes reported in published results might differ from the registry information)
NCT04875520	2021–05 to 2023–03	USA	Testing strategy	10 000 (16)	Weekly testing and symptomatic testing for SARS-CoV-2 vs symptomatic testing alone of students and school staff (≥4 years) on confirmed SARS-CoV-2 infections (primary outcome).
NCT04832919	2021–07 to 2022–05	USA	Behaviour change and testing strategy	810 (270)	Information on the importance of infection control measures, developing, implementing and follow-up an infection control plan tailored to the unique circumstances of the household, training on infection control skills necessary for optimal implementation of the plan, and offering of tests during home visits by nurses vs standard access to COVID-19 testing sites and standard COVID-19 public health messaging to community-living households (≥10 years) on self-report of COVID-19 symptoms or diagnoses (co-primary and secondary outcome).
ACTRN12621000567820	2021–08 to 2022–10	Australia	Air-sterilisation strategy	400 (10)	Air-sterilisation strategy using commercially available upper-room germicidal ultraviolet light in nursing homes vs no intervention on confirmed respiratory infections including SARS-CoV-2 (primary outcome) and hospitalisations (secondary outcome).
Not yet recruiting (n=9)					
NCT04453553	2020–07 to 2020–09	UK	Testing strategy	n.r. (50)	Screening for COVID-19 via nasopharyngeal swab taken at day 0 and 14, with the addition of daily nasal swabs tested via rapid test system vs screening for COVID-19 via nasopharyngeal swab taken at day 0 and 14 alone of nursing home residents (without age limit) on confirmed SARS-CoV-2 infections (primary outcome) and suspected or confirmed SARS-CoV-2 infections, COVID-19-related hospitalisations and mortality of residents, staff, and visitors (secondary outcomes).
PACTR202008485004797	2020–08 to 2021–03	South Africa	Information and protective equipment	720	Printed information material (transmission and COVID-19 caring at home), daily information delivered via Whatsapp, protective equipment (masks, hand sanitiser, bleach, gloves), and lay healthcare worker support vs printed information and on demand hotline service for community-living household contacts (≥12 years) of persons diagnosed with SARS-CoV-2 on confirmed SARS-CoV-2 infections of household contacts (primary and secondary outcome).
CTRI/2020/07/026796	2020–08 to n.r.	India	Masks	10 000 (45)	Cotton face masks vs no intervention for community-living adults (≥18 years) on confirmed SARS-CoV-2 infections (primary and secondary outcome).
CTRI/2020/12/029805	2020–12 to n.r.	India	Goggles	30	Ventilated goggles vs standard goggles for healthcare workers inside COVID-19 intensive care unit (18–50 years) on confirmed SARS-CoV-2 infections (secondary outcome).
NCT04756609	2021–02 to 2021–06	France	Testing strategy	104 000 (18)	Systematic offer of nurse-driven SARS-CoV-2 screening following a self-administered questionnaire about COVID-19 symptoms, possibilities of close contacts, risk exposure situations and sociodemographic characteristics combined with usual emergency department practice with physician-directed diagnostic testing vs usual emergency department practice alone for adults (≥18 years) in the emergency department on confirmed SARS-CoV-2 infections (primary and secondary outcome) and description of the symptomatology (secondary outcome).
NCT04823351	2021–04 to 2021–11	Switzerland	Masks	1200 (n.r.)	FFP2 masks vs surgical masks for nurses (≥18 years) working in nursing homes on confirmed SARS-CoV-2 infections (primary outcome).
NCT04898127	2021–05 to 2021–12	Norway	Mass event	30 000	Rapid test before access to a concert vs no access for community-living adults (18–45 years) on confirmed SARS-CoV-2 infections (primary outcome) and diagnosed SARS-CoV-2 infections and hospital admissions (secondary outcomes).

Continued

Table 1 Continued

Trial ID	Start to end date	Country	Intervention topic	N individuals (clusters*)	Description (population, intervention and comparison, and outcomes related to SARS-CoV-2 infections) Results (we report information on published results for primary outcomes related to SARS-CoV-2 infections where available, and for secondary outcomes only where the primary outcome was not related to SARS-CoV-2 infections; of note, outcomes reported in published results might differ from the registry information)
NCT04868942	2021–05 to 2022–05	France	Mass event	4500	Access to an indoor concert respecting protective measures (individual protection kit with (1) disposable FFP2 masks, hydroalcoholic solution, disposable tissues, garbage bag, and water bottle, (2) health mediation with information on barrier measures, (3) physical distancing and sitting participation and (4) person flow management vs no access for community-living students (18–29 years) on confirmed SARS-CoV-2 infections (primary and secondary outcome).
NCT04979858	2021–08 to 2022–02	USA	Masks	200	Newly developed reusable form-fitting fabric focal masks vs own masks and masking practices for students (≥18 years) living on the university campus on SARS-CoV-2 infections (no details if confirmed, diagnosed, or self-reported infections; primary outcome).
Withdrawn or terminated early (n=3)					
ISRCTN44152751 (w)	2020–03 to 2020–09	Norway	School opening	238 125 (1905)§	School opening vs school closing for 5–10 level pupils on confirmed SARS-CoV-2 infections of household contacts (primary outcome) and confirmed SARS-CoV-2 infections, and hospitalisation or mortality of grandparents and great grandparents (secondary outcomes).
NCT04377165 (t)	2020–05 to 2020–08	Australia	Information and education	9000 (n.r.)	Newsfeed on reliable accurate information on the COVID-19 pandemic with gamification function and reward system (links to resources for infection control, watching or completing tasks, and playing games to earn points) vs newsfeed alone for healthcare workers in nursing homes (≥18 years) on SARS-CoV-2 infections in the facility (no details if confirmed, diagnosed, or self-reported infections; secondary outcome).
NCT04896970 (w)	2021–06 to 2021–07	France	Mass event	1390	Access to an indoor concert vs no access respecting safety measures (masks, hydroalcoholic gel) for community-living adults (18–59 years) on confirmed SARS-CoV-2 infections (primary outcome).

*For cluster randomised trials only.

†Published as preprint results as of 14 November 2021.

‡Intervention was done twice (first on Thanksgiving, second on Christmas), numbers separated by semicolon for the first and second trial part.

§Planned sample size was calculated by the mean of the reported minimum and maximum for number of participants (116 750–359 500) and clusters (934 and 2876).

GP, General practitioner; n.r., not reported; t, Terminated early (due to 'engagement issues, poor recruitment to study'); w, Withdrawn (trial did and will never start: no reasons provided in the registry (ISRCTN44152751), abandonment (NCT04896970)).

Conclusions

Overall, during the first 18 months of the pandemic, the worldwide clinical research agenda failed to provide urgently needed evidence determining best strategies to prevent COVID-19 in schools, workplaces, nursing homes and other settings substantially affected. A long-term research agenda including behavioural, environmental, social and systems level interventions is urgently needed to guide policies and practices in the current and future public health emergencies.

Twitter Lars G. Hemkens @LGHemkens

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ORCID iDs
Julian Hirt http://orcid.org/0000-0001-6589-3936
Perrine Janiaud http://orcid.org/0000-0001-7684-8014
Lars G. Hemkens http://orcid.org/0000-0002-3444-1432

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