

Correspondence

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Response to letter of concern regarding »Reduction in COVID-19 infection using surgical facial masks outside the healthcare system«

We thank Noah A. Haber, Sarah E. Wieten and Emily R. Smith[1] for their interest, questions and comments on the design article published in DMJ entitled “Face masks for the prevention of COVID-19 - Rationale and design of the randomised controlled trial DANMASK-19” [2]. In order to increase the use of evidence-based practices at hospitals and in the community, it is crucial to conduct properly designed randomised controlled trials (RCT). We welcome these questions as proper understanding is crucial to support the interpretation of trial findings by decision-makers, media and other academics without a medical background.

Some of the questions raised by Haber et al. relate to the concept of a RCT; whether we collected information on compliance, relative risk reduction and the study period. We have answered each question separately below in order to provide proper clarification. First, it is important to highlight that Haber et al. have correctly understood the purpose of the trial as we investigated whether face masks prevent the wearer from becoming infected. We did not investigate source control in the current trial although multiple researchers around the world have asked us to also investigate the latter. To perform a pragmatic RCT of face masks as source control would probably require inclusion of actively SARS-CoV-2 infected participants, and the outcome would then be how many persons around the diseased individual (hospital staff, family, friends, co-workers, etc.) would be infected if the infected person used – or did not use – face masking. This would be a very challenging study to design and perform, not least for ethical reasons.

The primary question from Haber et al. relates to the study arms of the trial. The 6,000 participants were randomised 1:1 to wear face masks outside the home or not to wear face masks. Both groups were repeatedly and strongly recommended to follow the authorities’ general COVID-19 precautions throughout the study period. As in any RCT, we delivered all materials free of charge to participants as economic status should not result in a biased study population. Haber et al. propose that the trial will primarily investigate whether a delivery of face masks induces mask-wearing behaviour. We instructed participants in the use of face masks and used weekly follow-up questionnaires to reinforce and assess compliance very carefully. The compliance will be reported

in the paper. On this basis, we are able to report whether the recommended use of face masks protects the wearer against corona virus infection. The second question relates to compliance in both study arms during the trial period. Again, similar to when we are performing drug RCTs, we agree that compliance with an intervention according to randomisation is of utmost importance in any RCT and that non-compliance will dilute the effect of the intervention. Information on face mask use compliance, psychological factors and opinion on future behaviour was collected on a weekly basis during the study period as we believe that such information was highly relevant to assess the efficiency of face masks. These data will be collected for both groups – including use of face mask in the participants randomised to not wear a face mask. It should be noted that, during the study period, face masks were very rarely (< 5%) worn in the community in Denmark – outside this trial. The pragmatic RCT will most likely more accurately represent actual adherence to the intervention as opposed to idealised laboratory studies or in parallel to observational community studies in which adherence to interventions is often unrealistically high. The third question raised by Haber et al. relates to the COVID-19 incidence rate during the trial period and the findings from the systematic review on face masks published in the Lancet currently offering the highest level of evidence [3]. Haber et al. acknowledge that data on this new and emerging virus are limited, which is especially true for physicians like us who initiated COVID-19 RCTs in the emerging phase. Nonetheless, Haber et al. state that Denmark almost certainly experienced a SARS-CoV-2 incidence that was a much lower than the predicted 2% over the course of the trial. The official SARS-CoV-2 infections rates are based on PCR identification of nasal/oropharyngeal swab specimens. During the trial period, the test volume in Denmark was rather limited, most likely underestimating the true prevalence of SARS-CoV-2 infection. In order to capture all SARS-CoV-2 infections in the DANMASK-19 trial, we used a combination of the three; 1) PCR, 2) hospital-diagnosed COVID-19 and – most importantly – 3) antibody testing. On this basis, the officially reported SARS-CoV-2 infection rates and the rate of infection in our study may not be compared. The estimated reduction in infection rate by wearing a face mask was in good agreement with the later findings in the meta-analysis published by Chu et al. in the Lancet (2020) [2]. As correctly noted by Haber et al., the systematic review also reported a relative risk reduction in a sub-analysis of three small observational studies conducted in China and Vietnam on SARS-CoV-1 rather than SARS-CoV-2 in a non-healthcare setting, which yielded a relative risk (RR) of 0.56, 95% confidence interval (CI) 0.40 to 0.79. We therefore consider that a 50% relative risk reduction is a reasonable estimate. Additionally, the Danish government introduced a lock-down by mid-March 2020, which reduced transmission gradually; and mid-May a partial re-opening was launched. However, we only recruited participants who were still exposed to transmission (outside home among other people for more than three hours per day), i.e. not citizens staying at home. This is expected to yield a higher incidence rate in our study cohort. A full list of eligibility criteria can be found in the design article [1]. We made a conservative estimate of the expected number of participants to be infected during the study period; 2% in the control group and 1% in the face-mask group. With a sample size of 4,636 participants randomised 1:1, we needed $4,636 / 2 \times 2\%$ a total of 46 participants in the control group to reach a composite primary outcome and $4,636 / 2 \times 1\%$ a total

of 23 participants in the face mask group to reach a primary outcome, i.e. combined, 69 participants needed to reach a primary outcome (power 80%, 2-sided alpha < 0.05). In an idealised setting, we would have conducted a RCT on the use of face masks over the course of several months, but this was not considered feasible.

Haber et al. seem to ignore that several of the potential limitations in pragmatic trials are optimally addressed by a randomised design. We need evidence to improve our fight against COVID-19 – and RCTs are urgently needed to document that the present general precautions issued by health authorities are effective – or to establish that they need adjustments.

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Conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

LITERATURE

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