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SYNOPSIS

Review of "Medical Masks versus N95 Respirators for Preventing COVID-19 among Health Care Workers: A Randomized Trial"

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One-minute Summary

- The authors examined whether the effectiveness of medical masks was non-inferior to fit-tested N95 respirators worn by health care workers (HCWs) for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed symptomatic Coronavirus Disease 2019 (COVID-19) infection in HCWs providing routine care to patients with suspected or confirmed COVID-19.

- The authors used a pre-specified relative effect size (hazard ratio [HR]) margin of within 2 to consider medical masks non-inferior to N95 respirators. In other words, the study examined if wearing medical masks resulted in doubling the hazard of RT-PCR-confirmed symptomatic COVID-19 when compared to wearing N95 respirators during routine patient care.

- The study design was a randomized, non-inferiority trial. The study period was May 4, 2020 to March 29, 2022. HCWs were randomly assigned to wear medical masks (n=497) or N95 respirators (n=507) when providing routine care to patients with suspected or confirmed COVID-19 for 10 weeks (or up to 2 weeks following receipt of an mRNA vaccine). The trial was conducted in 29 health care facilities located in Canada (n=266 HCWs), Israel (n=34), Pakistan (n=186) and Egypt (n=518).

- Based on an intention-to-treat analysis, RT-PCR-confirmed symptomatic COVID-19 occurred in 10.46% of the medical mask group compared to 9.27% of the N95 respirator group (HR: 1.14; 95% confidence interval [CI]: 0.77, 1.69). The overall result was non-significant (CI includes null effect), and the upper limit of the CI was within the margin of 2; therefore, indicating medical masks to be non-inferior to N95 respirators, based on the pre-specified margin for this study.

- Post-hoc (i.e., not pre-planned) subgroup analyses demonstrated between-country differences in results. Results were as follows (proportion of confirmed symptomatic COVID-19 in medical mask versus N95 respirator group; HR [95% CI]): **Canada** (6.11% versus 2.22%; 2.83 [0.75, 10.72]); **Israel** (35.29% versus 23.53%; 1.54 [0.43, 5.49]); **Pakistan** (3.26% versus 2.13%; 1.5 [0.25, 8.98]); and **Egypt** (13.62% versus 14.56%; 0.95 [0.6, 1.5]).

- The authors concluded that while the results indicated non-inferiority, the margin was wide, meaning the results should be interpreted as ruling out a doubling in hazard of confirmed symptomatic COVID-19 for those wearing medical masks compared to N95 respirators. A hazard reduction of less than 2 but greater than 1 could not be determined based on this study's design. Additionally, based on the CI, the results cannot exclude up to a 69% relative increase, or a 23% relative decrease in infection risk in the medical mask group relative to the N95 respirator group.

Additional Information

- HCWs were excluded if they did not have a valid N95 respirator fit test, had one or more high-risk comorbidities for COVID-19, had previous laboratory-confirmed COVID-19, or had received one or more doses of a COVID-19 vaccine with >50% efficacy for the circulating strain (e.g., mRNA or vector-based COVID-19 vaccine against the original SARS-CoV-2 strain). HCWs could use N95 respirators at any time based on a point-of-care risk assessment, and all HCWs were required to wear N95 respirators for aerosol-generating medical procedures (as this was consistent with institutional policies at the time). HCWs were also recommended to wear eye protection, gowns and gloves when caring for patients with suspected or confirmed COVID-19.

- Participants were assessed twice weekly for signs and symptoms of COVID-19 via automated text messages. A nasopharyngeal swab sample was obtained for any one of the following signs or symptoms: fever (≥38°C), cough, or shortness of breath; or for any two of the following signs or symptoms: fatigue, myalgia, headache, dizziness, expectoration, sore throat, diarrhea, nausea, vomiting, abdominal pain, runny nose, altered taste or smell, conjunctivitis, or painful swallowing.

- Baseline characteristics were balanced overall and similar within each country. Seropositivity at baseline varied between countries, with few seropositive participants in Canada (2.3% in medical mask group, 1.6% in N95 group) and a majority (81.6% in medical mask group, 80.5% in N95 group) seropositive in Egypt. Across all settings, there were 185 (37.5%) participants in the medical group and 185 (37.2%) in the N95 respirator group who were seronegative at baseline. Enrollment in Canada, Israel and Pakistan ended before Omicron circulation, and enrollment in Egypt began in December of 2021 and included the period when Omicron was in circulation.

- HCWs' adherence with their assigned device was self-reported as "always" in 91.2% of the medical mask group and 80.7% of the N95 respirator group. Adherence was reported as "always" or "sometimes" in 97.7% of the medical mask group and 94.4% of the N95 respirator group. Audits of adherence were also conducted which involved random selection of 20% of shifts at a participating facility where trial participants were observed. Observed adherence was similar between the medical mask (98.3%) and N95 respirator (96.6%) groups.

- Results from the study's secondary outcomes of interest are reported below. Overall, there were no statistically significant differences between the two groups (medical mask versus N95 respirator) for any secondary outcome. These also varied by country, and detailed results for each country can be found in the study's supplementary document.
    - Serologic evidence of infection: 10.8% (medical mask) versus 11.9% (N95 respirator); HR: 0.88; 95% CI: 0.43, 1.81
    - Acute respiratory illness: 5.4% (medical mask) versus 6.1% (N95 respirator); HR: 0.89; 95% CI: 0.53, 1.49
    - Lower respiratory tract infection or pneumonia: 0.6% (medical mask) versus 0.6% (N95 respirator); HR: 1.02; 95% CI: 0.21, 5.04
    - Absenteeism: 9.7% (medical mask) versus 8.9% (N95 respirator); HR: 1.12; 95% CI: 0.74, 1.68
    - Intensive care unit admission or deaths: no cases across all participants
- Post-hoc subgroup analysis of the effect of medical masks versus N95 respirators only in those seronegative at baseline found similar point estimates to the analysis that included seropositive participants. Post-hoc subgroup analysis comparing those with no reported household or community exposures versus one or more reported household or community exposures also found no significant difference between groups. These analyses suggest no significant impact of illness exposure outside of the work setting or pre-existing antibodies on overall results.
- Adverse effects related to assigned devices included discomfort, skin irritation and headaches. Of the total medical mask group, 10.8% reported any of these adverse effects, and 13.6% of the N95 respirator groups reported any adverse effect. One participant in the medical mask group and three in the N95 respirator group withdrew from the study due to discomfort or adverse events related to their assigned device.

PHO Reviewer's Comments

The results of this study have been commented on in a published editorial.[1] There are some important considerations and limitations to this study, which are described below.

- **Research question**. The study addresses a very specific question of using an N95 respirator in place of a medical mask for providing direct care for patients with suspected or confirmed COVID-19 in the context of universal medical mask use, N95 respirator use based on HCW point of care risk assessment, and N95 respirator use for aerosol generating medical procedures. The study was not designed to evaluate other policies such as universal N95 respirator use and did not prevent HCWs assigned to the medical mask group from using N95 respirators.

- **Generalizability.** These study results are applicable to HCWs in health care facility settings, not to patients, visitors, or the general public in other settings. Health care workers have access to N95 respirator fit testing and are trained to check for correct fit and seal, are in close contact or provide direct care to patients with suspected or confirmed COVID-19, and use other IPAC precautions required for all HCWs in a health care facility.

- **Margin of non-inferiority.** A key point of discussion is related to the margin of non-inferiority. The pre-specified margin for this study was a HR of 2, therefore the study aimed to determine if medical masks were associated with double the hazard compared to N95 respirators. If the upper limit of the 95% confidence interval of the HR result was below 2, medical masks were considered non-inferior in this study. The authors estimated COVID-19 would occur in 5% of the N95 respirator group and that a clinically significant effect would include a 10% infection risk or higher in the medical mask group. This margin means results would need to show a relatively large significant difference in device effectiveness (i.e. 50% reduced hazard by wearing N95) to determine medical masks to be inferior. A smaller and potentially clinically important difference in the effect size cannot be excluded in this study. The choice of non-inferiority margins are often debated and study investigators may need to balance study feasibility (i.e. larger sample size would be required for a smaller margin) with clinically important effect sizes. There are questions and critiques regarding the margin used in this study.[1]

- **Certainty and power.** In the post-hoc analysis stratified by country, reported CIs were relatively wide and in some cases overlapping, indicating imprecision and a high degree of uncertainty. Power calculations were based on the primary outcome of RT-PCR-confirmed symptomatic COVID-19 for all participants. The post-hoc sub-analyses by country were underpowered and several were conducted with very small sample sizes (e.g., total of 34 participants from Israel). Approximately one quarter of the study population were recruited in Canada. The Canadian arm of the study found confirmed COVID-19 in 8/131 (6.11%) HCWs in the medical mask group and 3/135 (2.22%) HCWs in the N95 respirator group (HR 2.83, 95% CI: 0.75, 10.72). While a benefit from N95 respirators is suggested by this subgroup analysis, it is underpowered to draw any firm conclusions.

- **Confounders.** Enrollment for this study was staggered time-wise across the different countries, beginning with Canada, then Israel, Pakistan and finally Egypt. Therefore, beyond the baseline differences between countries, results also represent potentially different periods of the pandemic, such as absence/presence of Omicron and other VOCs, various public health measures and institutional policies being implemented or lifted, vaccine roll-out, and community transmission levels. There were potentially multiple important between-country differences that could explain the observed heterogeneity, such as a higher risk of community exposures in Egypt or general infection prevention and control (IPAC) adherence. For instance, self-reported eye protection use was 88% in Canada compared to 22%–25% in Egypt (Supplement Table 13).

- **Testing parameters.** RT-PCR testing of participants was triggered by self-reported signs or symptoms of infection; therefore, results do not account for potential asymptomatic infections and are subject to self-report bias. The authors also looked at seroconversion in participants who were seronegative at baseline and found similar results between study groups (Supplement Table 2).

- **Study design and critical appraisal.** Randomized controlled trials (RCTs) are challenging in the field of public health which largely operates in uncontrolled environments. When results are somewhat uncertain, such as in this complex study, the implications of an inconclusive result remain relevant to decision-making around harms and benefits. One example from this study is the result related to differences in device tolerability and adherence between medical masks and N95 respirators. The reported differences are not a weakness of study design, but likely reflect the reality of using these devices. This can be considered along with effectiveness results in overall harm-benefit interpretations of this study. See Appendix A for details of a critical appraisal checklist applied to this study. Finally, ambiguous results can support the generation of additional more focused or nuanced hypotheses for researchers to investigate moving forward.

Appendix A: Critical Appraisal

Appraisal of this study using the Critical Appraisal Skills Programme (CASP) Randomized Controlled Trial Standard Checklist was conducted by the authors of this synopsis.[2] Subject matter experts provided input. This checklist does not provide one final quality rating of the study, but divides appraisal into four main sections with questions to consider (answer options: yes, no, or can't tell). Please see below for the full appraisal, in a format adapted directly from the CASP Randomized Controlled Trial Standard Checklist.[2]

Table 1. Critical appraisal using CASP Randomized Controlled Trial Standard Checklist

Checklist Section	Checklist Question	Answer and Notes
Section A: Is the basic study design valid for a randomised controlled trial?	1. Did the study address a clearly focused research question? Consider: • Was the study designed to assess the outcomes of an intervention? • Is the research question 'focused' in terms of: population studied, intervention given; comparator chosen; outcomes measured?	**Yes.** Study objective is clearly stated: To determine whether medical masks are non-inferior to N95 respirators to prevent COVID-19 in health care workers providing routine care.
Section A: Is the basic study design valid for a randomised controlled trial?	2. Was the assignment of participants to interventions randomised? Consider: • How was randomisation carried out? Was the method appropriate? • Was randomisation sufficient to eliminate systematic bias? • Was the allocation sequence concealed from investigators and participants?	**Yes**. Participants were randomly assigned centrally by a study statistician who generated the sequence using a computerized random number generator. Randomization was stratified by site in permuted blocks of 4. The randomization scheme was provided by an interactive web response system and performed centrally.
Section A: Is the basic study design valid for a randomised controlled trial?	3. Were all participants who entered the study accounted for at its conclusion? Consider: • Were losses to follow-up and exclusions after randomisation accounted for? • Were participants analysed in the study groups to which they were randomised (intention-to-treat analysis)? • Was the study stopped early? If so, what was the reason?	**Yes**. Reasons provided for all participants originally assigned, but not included in final analysis. E.g., withdrew, previously positive for COVID-19. Participants were analyzed in their assigned groups. The study was not stopped early.

Checklist Section	Checklist Question	Answer and Notes
Section B: Was the study methodologically sound?	4. Were the participants 'blind' to intervention they were given? Were the investigators 'blind' to the intervention they were giving to participants? Were the people assessing/ analysing outcome/s 'blinded'?	**No**. This was not possible. **Yes**. Investigators were blinded to treatment allocation. **Yes**. Laboratory personnel doing COVID-19 testing were blind to treatment allocation.
Section B: Was the study methodologically sound?	5. Were the study groups similar at the start of the randomised controlled trial? Consider: • Were the baseline characteristics of each study group (e.g. age, sex, socio-economic group) clearly set out? • Were there any differences between the study groups that could affect the outcome/s?	**Yes**. Baseline characteristics reported (Table 1 in the study) and differences reported, including by country. Differences addressed in sub-group/sensitivity analyses.
Section B: Was the study methodologically sound?	6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)? Consider: • Was there a clearly defined study protocol? • If any additional interventions were given (e.g. tests or treatments), were they similar between the study groups? • Were the follow-up intervals the same for each study group?	**Can't tell**. A clearly defined protocol was described, changes to protocol, and justification for same are described in supplementary document. Very challenging/unfeasible to fully account for all additional factors/influences in a real-world environment. The authors did assess both self-reported and observed adherence to assigned device, ventilation standards by country, other IPAC practices, and community exposures. There were differences in self-reported adherence to assigned device. Participants also required to follow local institutional policies, and free to don N95 for any aerosol generating procedures or when required by point-of-care risk assessment. The per-protocol analysis was defined as including participants with at least 80% follow up.

Checklist Section	Checklist Question	Answer and Notes
Section C: What are the results?	7. Were the effects of intervention reported comprehensively? Consider: • Was a power calculation undertaken? • What outcomes were measured, and were they clearly specified? • How were the results expressed? For binary outcomes, were relative and absolute effects reported? • Were the results reported for each outcome in each study group at each follow-up interval? • Was there any missing or incomplete data? • Was there differential drop-out between the study groups that could affect the results? • Were potential sources of bias identified? • Which statistical tests were used? • Were p values reported?	**Yes**. Power calculation was undertaken for main analysis. A non-inferiority margin of 2 was determined a priori. A lower margin could have been considered to determine if there were smaller, but clinically important differences in the effectiveness of devices. Post-hoc analyses by country were underpowered. Outcomes were clearly defined and measured Results were expressed as HRs with 2-sided 95% CIs. Results for all planned analyses were reported, and several post-hoc sub-analyses' results were reported. Amount of missing responses in each group (mask, N95) reported (<1%). No attempt was made to impute missing post-randomization values, and only observed values were used in the analysis. All withdrawals post-randomization reported with reasons. Limitations addressed: community exposure, heterogeneity between countries, uncertainty in estimates of effect, self-reported adherence, baseline antibodies, and differences in vaccination/VOCs between countries. Cox proportional hazards model stratifying by health care facility. The analysis fulfilled the Schoenfeld residual test for the assumption of proportional hazards in Cox analysis. The cumulative incidence of RT-PCR–confirmed COVID-19 was estimated using Kaplan–Meier methods.
Section C: What are the results?	8. Was the precision of the estimate of the intervention or treatment effect reported? Consider: • Were confidence intervals (CIs) reported?	**Yes**. CIs reported, and imprecision/interpretation of results discussed.

Checklist Section	Checklist Question	Answer and Notes
Section C: What are the results?	9. Do the benefits of the experimental intervention outweigh the harms and costs? Consider: • What was the size of the intervention or treatment effect? • Were harms or unintended effects reported for each study group? • Was a cost-effectiveness analysis undertaken? (Cost-effectiveness analysis allows a comparison to be made between different interventions used in the care of the same condition or problem.)	**Can't tell**. Discussion/conclusion address the pre-specified margin meaning a doubling of hazard, and that firm conclusions about non-inferiority may not be applicable given the between-country heterogeneity. Results include adverse events from each group (discomfort, headache, skin irritation) No cost-effectiveness analysis (not an aim of this study).
Section D: Will the results help locally?	10. Can the results be applied to your local population/in your context? Consider: • Are the study participants similar to the people in your care? • Would any differences between your population and the study participants alter the outcomes reported in the study? • Are the outcomes important to your population? • Are there any outcomes you would have wanted information on that have not been studied or reported? • Are there any limitations of the study that would affect your decision?	**Can't tell**. Result from other countries may not be applicable. Canadian results were obtained from study period earlier in pandemic (enrolled from May 4, 2020 to May 22, 2021 in Canada), which could be considered quite different from the current Ontario context (i.e., community transmission, VOCs, public health measures in place versus currently lifted). Canadian participants were 2nd largest group of the countries (n=266), however alone is a relatively small (underpowered) sample. Designed to assess for symptomatic infections, no process in place to detect asymptomatic infections (e.g., routine PCR test instead of symptom-prompted test).

Checklist Section	Checklist Question	Answer and Notes
Section D: Will the results help locally?	11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions? Consider: • What resources are needed to introduce this intervention taking into account time, finances, and skills development or training needs? • Are you able to disinvest resources in one or more existing interventions in order to be able to re-invest in the new intervention?	**Can't tell**. Based on this study – uncertain. The results provide a range of effect sizes that are less than doubling of the hazard. There is uncertainty in the effect size, and challenges with generalizability to the current Ontario context. Mask/N95 resources in Ontario context – not formally assessed, assume there is currently supply for both devices in health care facilities; however, cost assessment or comparison not conducted by study, or by this synopsis review team. N95s are more expensive, include fit testing/training, etc.
Appraisal summary	What is your conclusion about the paper? Would you use it to change your practice or to recommend changes to care/interventions used by your organisation? Could you judiciously implement this intervention without delay?	Overall, the methods of this study are sound. However, the precision of results and direct applicability to the current Ontario context are uncertain.

Additional References

1. Chou R. Comparative effectiveness of mask type in preventing SARS-CoV-2 in health care workers: uncertainty persists. Ann Intern Med. 2022 Nov 29 [Epub ahead of print]. Available from: https://doi.org/10.7326/m22-3219

2. Critical Appraisal Skills Programme. CASP randomized controlled trial standard checklist [Internet]. Oxford: CASP UK; 2020 [cited 2022 Nov 30]. Available from: https://casp-uk.net/images/checklist/documents/CASP-Randomised-Controlled-Trial-Checklist/CASP-RCT-Checklist-PDF-Fillable-Form.pdf

Note:

The article summarized in this synopsis was co-authored by a PHO employee. RJ, MN, VS, RM, KB, MS and KS declare that they are employed in similar organizational unit at PHO. KS co-published with other authors of the article in the past.

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