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COVID-19 – The efficacy of the LEAF-mask measured by assessing the viral load of the mask's inner and outer surface used by nurses in ICUs compared to the N95: a phase II, multicenter, randomized, controlled, open-label, clinical trial protocol

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Abstract:

Introduction: *The unprecedented, worldwide COVID-19 pandemic demanded the need for adequate personal protective equipment (PPE) for health care workers (HCWs). The commonly recommended N95-mask (N95) needs further optimization in the areas of technology, re-usability, and comfort. The LEAF-mask (LEAF) reportedly offers improved technology and innovative features, however, neither of them have been tested yet. Therefore, there is an ongoing need to study the efficacy of masks used by HCWs in the intensive care units (ICUs). The goal of this study is to demonstrate the superiority of LEAF for nurses working in COVID-19 ICUs when compared to the N95.*

Methods: *A phase-II, multicenter, randomized, controlled, open-label, clinical trial. A sample size of 98 nurses, working in COVID-19 ICUs, will be necessary to detect a significant difference in viral load of the inner and outer parts of both masks as the primary outcome. Secondary outcomes will be exploratory in nature, including adverse effects, wearing comfort of masks, and virus infection rate.*

Discussion: *The ongoing COVID-19 pandemic has already infected and killed millions of people and burdens healthcare systems worldwide. This led to the search for comprehensive measures to prevent the further spread of the SARS-CoV-2, in particular among HCWs in the frontline. Therefore, this study intends to demonstrate the superiority of the new LEAF compared to the N95, primarily in efficacy but also in re-usability and wearing comfort when used by nurses in COVID-19 ICUs. The possible findings from this study on improved technologies and innovative features possibly shown in the LEAF may greatly contribute to better working conditions for nurses working in COVID-19 ICUs.*

Keywords: *COVID-19, coronavirus, SARS-CoV-2, LEAF-mask, N95-mask, clinical trial*

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Abbreviations:

1 WHO: World Health Organization
2 COVID-19: Coronavirus (SARS-CoV-2) Disease 2019
3 PPE: Personal Protective Equipment
4 HCW: Health Care Worker
5 CDC: Centers for Disease Control and Prevention (USA)
6 ICU: Intensive Care Unit
7 FDA: Food and Drug Administration (USA)
8 HEPA: High Efficiency Particulate Airfilter
9 UVC: Ultraviolet light with wavelengths between 200-280 nm
10 RT-PCR: Real-Time-Reverse Transcriptase Polymerase Chain Reaction
11 CRS: Comfort Rating Scale
12 OSHA: Occupational Safety and Health Administration
13 RNA: Ribonucleid Acid
14 RedCap: Research Electronic Data Capture
15 PI: Principal Investigator
16 IDMC: Independent Data Monitoring Committee
17 GLIMMPSE: Online Power Computation for Linear Models with and without a Baseline Covariate.

INTRODUCTION

The [1]WHO declared the [2]COVID-19 pandemic an international public health emergency in 2020. The health system continues to be overwhelmed, leading to shortages of medical devices and [3]PPE (Ranney et al., 2020). Adequate PPE, however, is crucial for [4]HCWs` protection (Verbeek et al., 2020).

The main mechanism of infection from the SARS-CoV-2 virus is inhalation through droplets and aerosols (Liu et al., 2020). Aerosolization of the virus in the hospital environment increases the risk of exposure to HCWs and supports the use of all-day protection measures (Van Doremalen et al., 2020).

The N95 without valved respirator is currently the standard mask for HCWs (Lee et al., 2011), with a filter efficiency of a minimum of 95% for aerosol particles with a size of 0.3 μm (CDC, 1997). The N95 prevents the flow of aerosol particles through inertial impact and provides adherence of very small particles to its fibers, with electrostatic attraction (Konda et al., 2020). However, the use of N95 has limitations such as reported strong breathing difficulties (Rebmann et al., 2013) and an increase of breathing resistance that may constitute an adverse effect for users (Lee et al., 2011). A different - to the best of our knowledge - single opinion in the literature reports that the N95 breathing resistance is 50% lower than with N99 (Nirvana, year unknown), a statement which, however, is not based on validated scientific studies.

The N95 is designed for one-time, 8-hours continuous or intermittent use (CDC, 2020b). Its purchase price is US$ 2.50 per single unit on average. Neither decontamination of the N95, nor re-use is formally recommended by the CDC and the National Institute for Occupational Safety and Health (NIOSH) (CDC, 2020c), however the limited supply of N95s during the pandemic has caused the re-use of N95 masks by HCWs hereby increasing the risk of infection ([5]CDC, 2020a). A study by Rebmann et al. (2013) showed that nurses working in ICUs touched not only their face and eyes but also to the N95 itself during its lengthened use more than 20 times per shift. Additionally, the N95 may cause great discomfort and abrasions (Ha, 2020). Furthermore, the non-transparent design of a face mask like the N95 could be problematic for human connection between nurse and patient, especially because it does not allow nonverbal communication in particular for COVID-19 patients in [6]ICUs developing a "post intensive-care syndrome" (Brown-Johnson et al., 2020).

The LEAF, manufactured by Redcliffe Medical Devices Inc (Southfield, MI), is [7]FDA-registered and covers a bigger part of the face with a transparent and soft material. Technological features include a N100 series HEPA-Carbon filter with a filtration rate of a minimum of 99.97% for 0.3 μm particles – corresponding to the filter efficiency certified by NIOSH for N100 filters (CDC, 2020c). Moreover, the LEAF reportedly ensures a low breathing resistance and offers the following additional innovative features: a [9]UV-C-light-based self-sterilization technology, electronic active ventilation, and anti-fog technology. The HEPA filter cartridge can be used for up to one month before it has to be replaced while retaining the same face unit for a duration between 9 and 12 months. The one-time costs of the LEAF intended to be used in our study currently amounts to US$ 199 plus US$ 14.90 monthly for renewal of the filter cartridge (Redcliffe Inc., 2021).

UV-C-light has a germicidal function, hereby killing microorganisms without deleterious effects on human cells, due to their minimal reach (Welch et al., 2020).
However, there is a total lack of available scientific literature on these specific features. To the best of our knowledge, LEAF's efficacy and other features have not been tested yet in a clinical trial so far.

Therefore, the purpose of this study protocol is to show whether the LEAF provides a greater level of efficacy and wearing comfort for nurses working in COVID-19 ICUs when compared to the N95.

MATERIALS AND METHODS

Primary and secondary objectives

Our primary target is to test the efficacy of the LEAF compared to the N95 by assessing the mean difference in load of SARS-CoV-2 particles at the outer and inner parts of both masks after daily use by nurses working in COVID-19 ICUs. Secondary objectives are the infection rate with SARS-CoV-2 and its correlation with detected SARS-CoV-2 virions, examining the wearing comfort and potential events, and finally performing a viral culture to determine the viability of detected SARS-CoV-2 particles.

Trial Design

The trial is designed as a phase-II, multicenter, randomized, controlled, open-label, superiority clinical trial with two parallel arms and a 1:1 allocation ratio.

Study Setting

The trial will take place in tertiary and/or secondary hospitals treating COVID-19 patients in ICUs across the state of Sao Paulo, Brazil. (hereinafter "site centers"). Each site center will have a committed principal investigator (PI) and a sufficiently staffed research team. The study protocol must be approved by the ethics committee of each hospital prior to the initiation of the study.

Randomization

Nurses treating patients with SARS-CoV-2 infection in the participating site centers' ICUs will be considered as the accessible population. As important prognostic baseline characteristics, we consider the site centers as well as age, sex, race, and BMI of the nurses. Concerning the relatively small groups tested at the site centers, we will limit the pre-stratification to the covariate site center and include the other covariates like age, sex, race, and BMI of the nurses in our outcome regression model. After stratification, the randomization sequence list will be automatically generated by an external person not involved in the study using a web-based program. For allocation concealment, an envelope system will be used. The envelopes are opaque and numbered according to the randomization list containing the randomization code. The envelopes will be opened only after enrollment of the nurses into the study and subsequently registered and stored. Only nurses who give their informed consent to participate and who fulfill the eligibility criteria will be randomized.

Blinding

The trial will be open-label since blinding is not fully feasible due to the specific nature and the entirely different optical design of the masks to be compared. In particular, the LEAF is fully transparent whereas the N95 is not. Therefore, the nurses and data collectors being aware of the group assignment cannot be blinded. The laboratory staff, statisticians and other research staff members will be blinded to reduce bias, given they are not aware of group assignment.

Eligibility Criteria

Inclusion criteria:

- All nurses in the site centers using a face mask in the COVID 19-ICU and who
- work 30 hours/3-days weeks in COVID 19-ICUs,
- passed the fit-test for the masks based on the rules of OSHA-Respiratory Protection Standards,
- are vaccinated against or tested negative for SARS-CoV-2 via RT-PCR and for IgG-antibodies via Elecsys® serology (Roche Diagnostics Deutschland GmBH, Mannheim, Germany),
- >18 years of age,
- agreed on all study protocol requirements,
- agreed to and signed the informed consent form.

Exclusion criteria:

- All nurses of the site centers who
- are tested positive for SARS-CoV-2 and IgG antibodies titer levels
- present flu-like symptoms (e.g., congestion, fever, cough) prior to the beginning of the trial,
- present a high-risk profile to SARS-CoV-2 infection such as diabetes, pregnancy, asthma, chronic obstructive pulmonary disease, and obesity (Jordan et al., 2020) with a BMI > 29,
- participate in another clinical trial.

Recruitment Strategy

Recruitment will be conducted by displaying posters in hospitals, preferably in the entry of the ICUs, cafeteria, and emergency departments as well as through invitation letters, leaflets, and advertisements sent to institutional email addresses.

Educational meetings will be organized to explain the study project and its goals to potentially interested participants, addressing any questions or concerns during meetings and other visits at the site centers. Recruitment interviews take place via video call or on-site in person. Eligible nurses will be given an informed consent form and receive an explanation of its contents.

Adherence

During recruitment, participants will receive emails or telephone calls from the research team giving detailed information and updates on the study, as well as promoting an appropriate understanding of the study protocol.

Enrolled nurses will be closely followed during the study until the 14th day after the last swab by trained research team members at each site center who will consistently be reachable for the nurses on a specific phone number. Nurses will be regularly reminded by personal phone calls about each upcoming appointment, such as mask fit tests and swabs.

Psychological support by a psychotherapist will be available online for the nurses on demand all the time concerning the compatibility of their workload and adherence to the study requirements.

Each nurse will be given a gift card in the equivalent of in total of US$ 50 as an incentive that can be used in their site center cafeteria.

Timeline

The nurses will be recruited by using convenience sampling. After enrollment, the nurses will be screened regarding their eligibility criteria before randomization and allocation to one arm of the study. The study duration is limited to ten shifts during which the nurses will participate in the study including after-shift activities, such as filling out questionnaires. The timeline is described via the CONSORT diagram attached hereto (**Figure 1**).

Interventions

General procedure

Before the trial, the nurses will undergo a fit test for the masks following [12]OSHA-recommendations and will take part in a workshop regarding CDC-guidelines for donning and doffing techniques (CDC, 2020b).

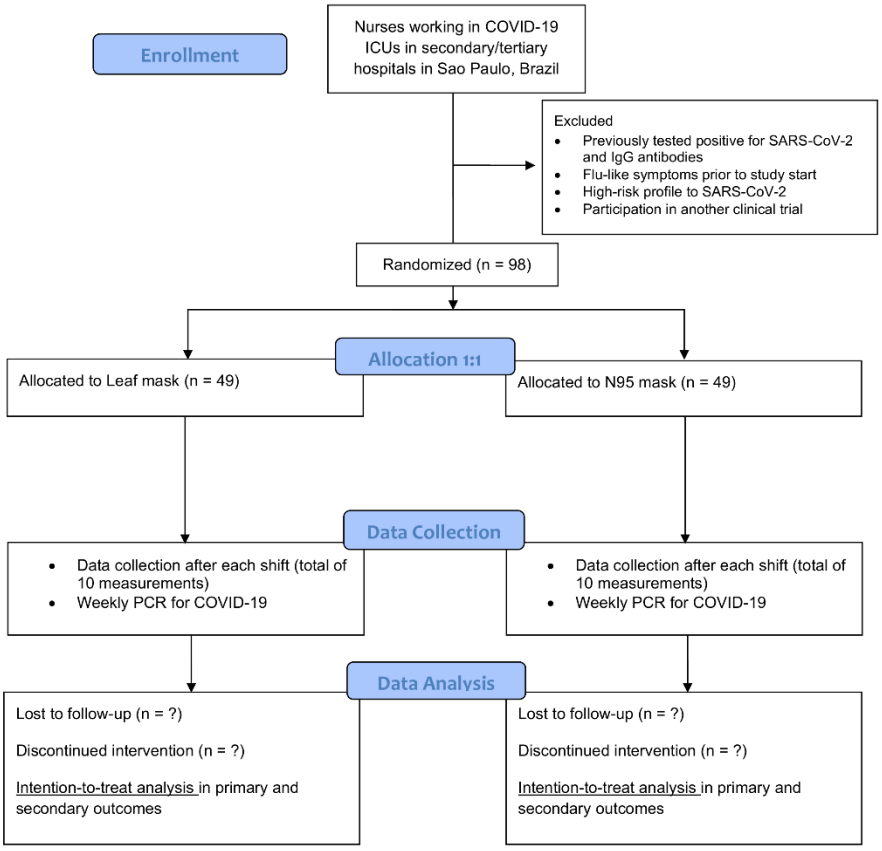

Figure 1. Timeline

Before each shift, the nurses of both groups will receive identically sealed boxes with one of the masks of the group the nurses are allocated to. The boxes will be opened at shift`s start and the mask will be used over 10-hour shifts. After the shift, the masks will be forwarded to study personnel who will first check for the masks` integrity and will then swab the inner and outer parts of the masks via RT-PCR according to the following standardized protocol:

- For the N95:
  swab of the center inner and center outer surface of the mask in an area of 3 x 3 cm (9 cm2).

- For the Leaf:
  swab of the whole inner and center outer surface of the mask filter in an area of 3 x 3 cm (9 cm2).

These standardized mask areas were chosen for swabbing because they concentrate aerosol particles that could go to or might come directly from the nurses` mouths and noses.

Nasopharyngeal specimens will be collected from each nurse following CDC-instructions as well (CDC, 2020a).

The RT-PCR swabs will be placed into sterile 15ml falcon tubes, containing 2ml of sterile saline, and stored at the site center`s local freezer at 2-8ºC. The samples will be delivered to a specialized laboratory within 72 hours after the samples have been taken.

By the end of each shift, the nurses will complete two questionnaires: the first one interrogating the number and the length of time the masks were taken off and the reasons therefore as well as asking for (open-question) potential adverse events (**Appendix 1**), and a second one asking for the mask`s wearing comfort via CRS[11] (**Appendix 2**).

Nurses may request withdrawal from the study for any reason and at any time they wish. Nurses presenting symptoms of COVID-19 - or flu infection in the course of the study, request to switch to the other study group, withdraw their informed consent, or drop out for any other reason will be excluded from the study.

Intervention group:
Nurses will receive a LEAF corresponding to their face according to the fit-test done before each shift in a sealed box.

After each shift, the LEAFs will first be cleaned from impurities by study personnel. After sterilization with the UV-C technology-kit for re-use, the LEAF will be stored in a sealed box again and handed over to the nurses when the next shift starts. Reportingly, the LEAF filter cartridge can be re-used for one month provided the cleaning and sterilization procedure is performed as described.

Control group:
Nurses will receive a new N95 fitting to their face in accordance with the fit-test conducted before each shift in a sealed box.

Laboratory procedures:
[13]RNA-extraction will be performed using QIAamp® Viral RNA Mini Kit (QIAGEN) according to the manufacturer's instructions. RNA will be extracted from 140µl of sample and eluted in 60µl of elution buffer. For RT-PCR assays, the method described by Chu (Chu et al., 2020) will be adopted. For samples with viral RNA-detection, a viral culture will be performed according to a recently described protocol recommended by WHO (Harcourt, 2020).

Outcomes

Primary outcome
The primary outcome, being the difference in viral load (copies/µL) between the inner and outer surfaces of the N95 and the LEAF, will be measured daily via RT-PCR. The mean difference of viral load will be subsequently calculated by the average difference of the daily viral load measurements over the ten shifts measured. The choice of the difference in viral load as a surrogate outcome is unique, but the feasibility of our study would be compromised by a huge sample size and study time needed if we would have chosen the viral infection of the nurses as the primary outcome. The COVID-19 pandemic requires fast solutions with the lowest possible cost - this applies also to clinical trials where surrogate outcomes are an option to be considered (Svensson et al., 2013).

We are aware of the existing uncertainty of assuring via RT-PCR or otherwise, that a nurse could be asymptomatically diseased (Pollock et al., 2020). However, for practical purposes, we think that a positive RT-PCR result from the mask surfaces will potentially indicate a contaminated surface with a high chance of infection for each nurse, considering that exposure to upper airways is the preferred SARS-CoV-2 entrance route (Cao et al., 2020).

Secondary outcomes
The wearing comfort of masks will be self-reported and assessed by CRS adapted to the COVID-19 context

(Malik et al., 2006) at the end of every shift (**Appendix 2**).

A combined self-report questionnaire (**Appendix 1**) on both the number/time of nurses` donning and doffing of their masks and possible adverse events (open-question) will be filled out by the nurses at the end of every shift.

SARS-CoV-2-infection rate of nurses will be assessed by RT-PCR in nasopharyngeal samples collected after each shift.

A culturing of viral cells will be assessed according to the protocol already referred to above but only to the extent that RNA-detection shows a viral load on the masks' surfaces.

Data Management

All data being necessary for the trial`s specific purposes will be collected and stored in [14]REDCap for a period of 10 years after the study ends. Participants' information will be de-identified, treated strictly confidential, and not be used for any unauthorized purposes. Only the [15]PI and in case of the PI`s hindrance the appointed representative will have full access to the electronic database at any time.

An [16]IDMC, consisting of three persons accomplished in clinical trials, will be implemented. The PI will consult the IDMC via ad hoc meetings in cases of any serious adverse effects, of a necessity to unblind for emergency reasons, of any protocol violation or change, or if the trial has to be terminated. Due to the short duration of the trial, no interim analysis will be performed.

It is intended to terminate the trial in case of a positive SARS-CoV-2 infection rate being larger than 10% in the intervention group. The IMDC will be consulted in advance.

Sample Size Calculation

The sample size calculation was performed to find a difference in viral load between the LEAF and the N95 considering a statistical power of 80% and a significance level of 5%. For effect size determination we used a previous, similar experimental study (Eninger et al., 2008). On this basis, we calculated the estimated effect size with Cohen`s d 0.136, using G*Power 3.1.9.2.

In order to calculate the intra-class correlation between the ten measurements (ten shifts) within each nurse two linear exponent autoregressive (LEAR) correlation models with a mean correlation of 0.5 or 0.8 and with a consistent decay rate of 0.3 were considered. As the most conservative approach, the mean correlation value of 0.8 was selected, given the lack of evidence about repeated measurements of viral load on the surface of a mask. Therefore, taking into consideration a dropout rate of 10%, we specified the total sample size with 98 nurses, using [17]GLIMMPSE" (Kreidler et al., 2013).

Statistical Analysis for primary and secondary outcomes

Our data will be presented as mean and standard deviation (±) or as median and IQR for continuous variables or as percentages and frequencies for categorical variables. All tests will be two-sided. The alpha significance level for statistically significant results for both primary and secondary outcome(s) will be 5%.

The primary outcome will be assessed using a linear mixed regression model considering the type of mask as a fixed factor and the nurse as a random effect. This statistical model considers potential correlations between the ten repeated measures within each nurse. As already referred to above, we will – besides the pre-stratification of the site centers – provide additional control for the covariates age, sex, race, and BMI of the nurses as potential confounding factors for the outcome in the same linear regression model. The outcome regression analysis will be multivariate adjusting for further potential confounding variables, such being longer shifts of nurses (i.e. exceeding the foreseen 10 h per shift), the number and time duration of donning and doffing of the masks per shift, the different handling of masks by nurses (e.g., frequency of mask touching), the different sizes of the mask models, the potential risk that the different type of respirator may modulate the viral load in the respective ICU-room and the specific UV-C-sterilization of the LEAF.

The one-time ratings of mask comfort will be analyzed with an independent t-test. The categorical outcomes (i.e. infection of SARS-CoV-2 and viral culture) will be analyzed with a Chi-Square test using the same in between-subject factor (i.e., type of mask). Lastly, the correlation between the SARS-CoV-2 infection rate and the difference in the viral load between the outer and inner parts of the mask will be tested using the Point-Biserial Correlation Coefficient.

The data analysis will be performed using Stata/IC 16.1 (StataCorp LLC, College Station, TX).

Missing Data

Data will be analyzed according to the intention-to-treat principle. If the dropout rate is lower than 10%, the

missing data will be analyzed via the worst-case scenario carried forward. If the dropout rate, however, exceeds 10% at maximum the likelihood approach will be used. Moreover, a sensitivity analysis will be performed in order to estimate the impact of missing data on the robustness of our final analysis and the accuracy of the results achieved.

DISCUSSION

Most of the studies so far have examined the efficacy of various face masks only in a laboratory setting and the recent SARS-CoV-2 outbreak emphasizes the need to test and develop new technologies of face masks in a clinical environment as would be COVID-19-ICUs. Therefore, this study addresses outcomes that might be of interest for a broader interpretation of the data. Initially, we discussed the infection rate as a potential primary clinical outcome but finally scrapped it due to both an expected huge sample size, making the trial infeasible, and expected insignificant effect size, too. We, therefore, selected for the primary outcome the mean difference in viral load of the masks as a surrogate of possible SARS-CoV-2 infection of the nurses. Moreover, the increasing vaccination of HCWs against SARS-Cov-2 in ICUs is going to make the choice of infection rate increasingly infeasible. The correlation between the surrogate marker of the viral load and the clinical outcome of a possible SARS-Cov-2-infection rate might also provide significant evidence to the current guidelines of face masks in health care settings.

The running pandemic has also shown the importance of wearing comfortable face masks when used under the current conditions. In this aspect, the testing of LEAF`s comfort during a ten shifts period compared to the standard N95 might be of urgent practical need in the daily work of HCWs in COVID-19 ICUs.

The expected findings will be novel and, due to the ongoing presence of the SARS-CoV-2, of great interest and significance for both the scientific and clinical community.

In case of negative results, our findings might also provide evidence of how the virus is propagated in a clinical setting, considering other factors regardless of the mask type used. The establishment of a correlation between SARS-CoV-2 load and the corresponding cell culture infectious dose (infectivity) as well as the value of information on the viral load itself is indeed not well understood (Jones et al., 2020). But we assume that this study may contribute to elucidate better this important scientific question.

It may be ethically objectionable that nurses in particular under the current pandemic situation tend to desire preferably using the new, but not tested LEAF but it has to be considered that the control group uses not any mask but a mask which is the current standard mask also in this pandemic situation.

The lack of previous evidence concerning the LEAF might be an obstacle in the interpretation of data. Furthermore, the viral testing procedure has some limitations, too, namely the detection threshold which implies that very small quantities of viral load might not be reliable to screen. Thus, every data below the detection threshold will be considered as a null result to control this limitation. Moreover, the characteristics of the LEAF demand the need to perform an open-label design, bearing the reported difficulties in blinding, which may create bias. Due to the nature of the measurements, there are a couple of confounders mentioned hereabove in the statistical analysis section which might substantially influence the results and which therefore we will adjust for in our outcome regression analysis.

The LEAF provides a novel mask technology and other innovative features which may be of significant importance particularly in extraordinary circumstances as with the current COVID-19 pandemic. Therefore, our study proposes to test LEAF`s efficacy under a real clinical COVID-19-ICU setting.

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Conflicts of Interests

The authors declare no conflict of interests.

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