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Judul Artikel:

**The effects of mouth rinsing and gargling with mouthwash containing povidone-iodine and hydrogen peroxide on the cycle threshold value of Severe Acute Respiratory Syndrome Coronavirus 2: A randomized controlled trial of asymptomatic and mildly symptomatic patients**

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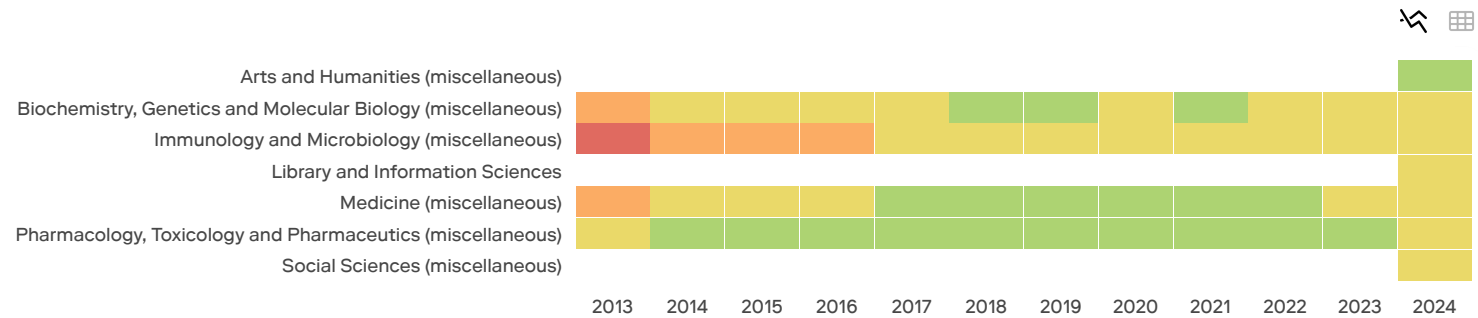
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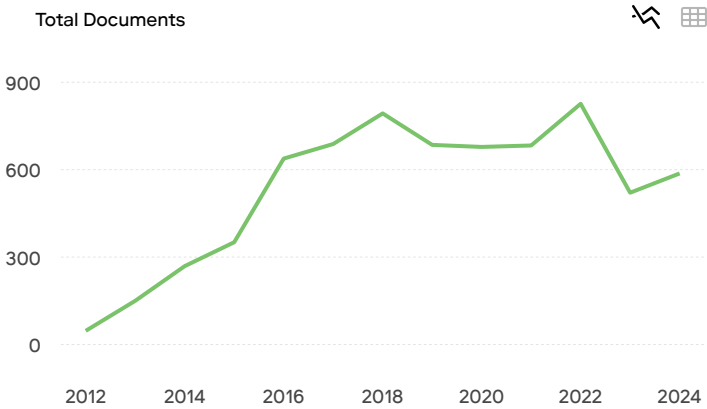
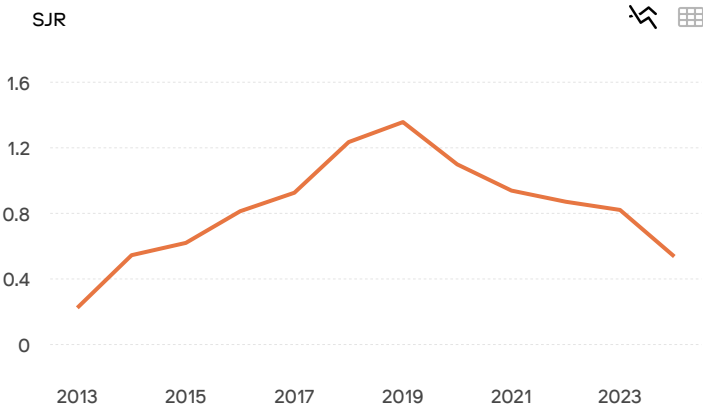
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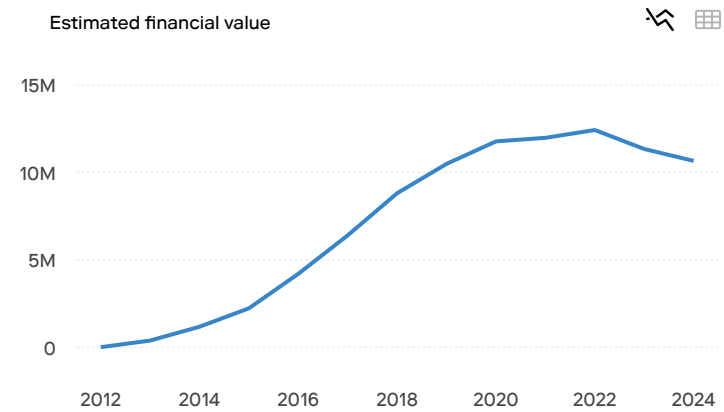
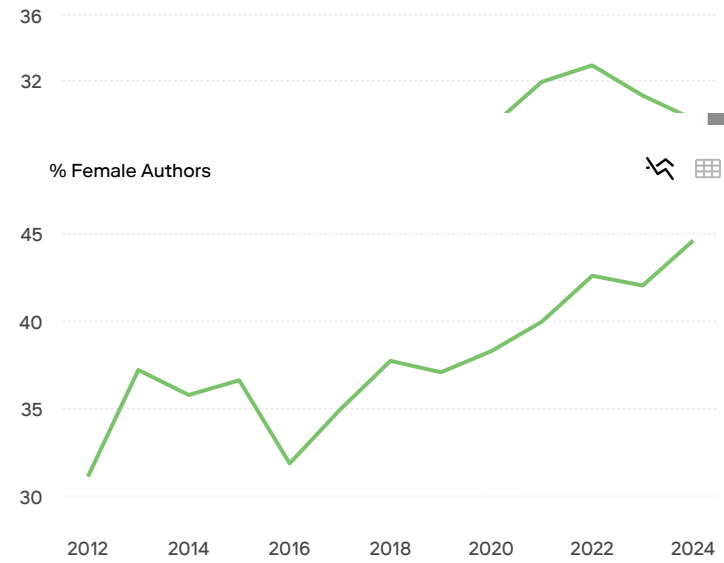
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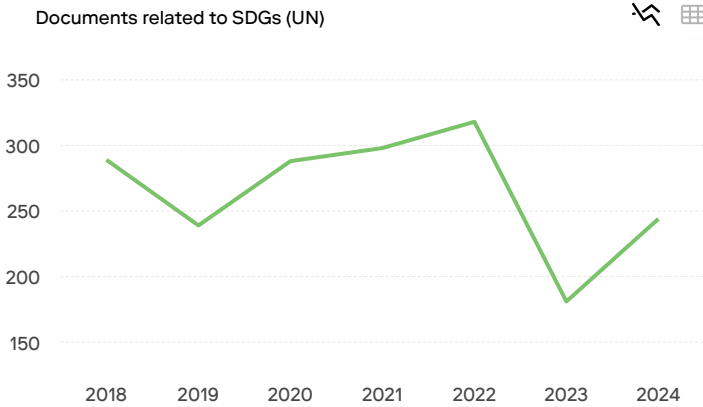
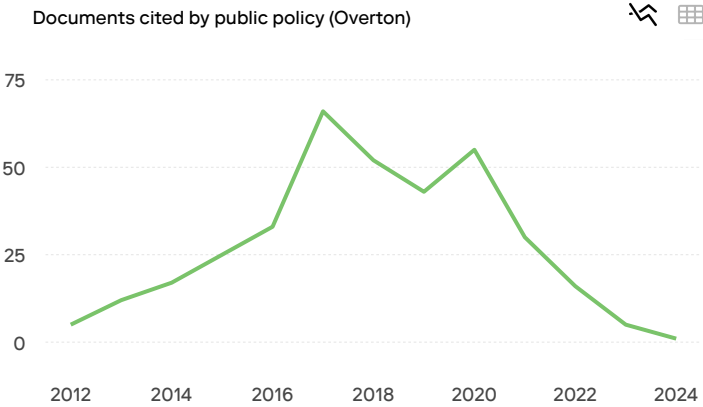
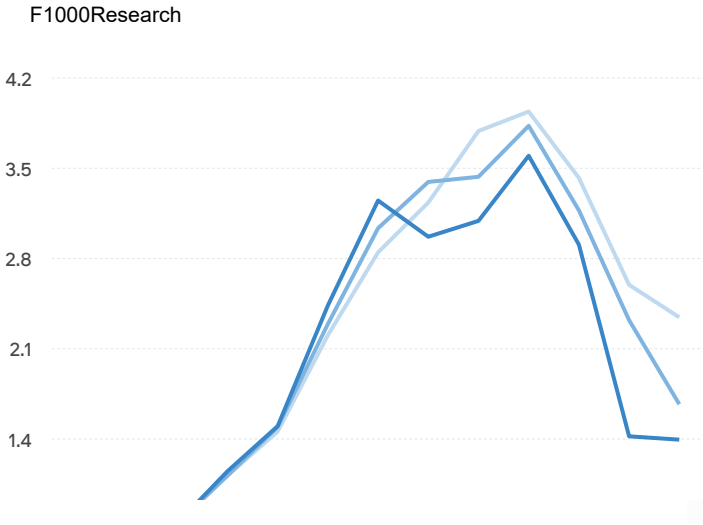
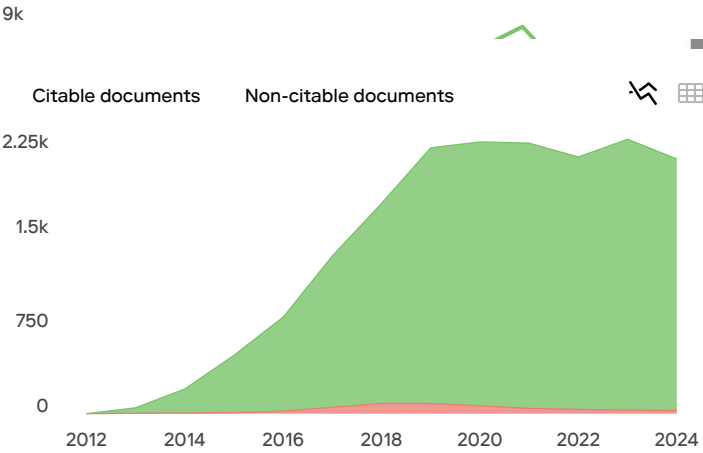
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Rosalina Tjandrawinata &lt;rosalina@trisakti.ac.id&gt;

## Invitation to peer review an article by Lilies Dwi Sulistyani

1 message

editorial@f1000peerreview.com &lt;editorial@f1000peerreview.com&gt;

Wed, Mar 20, 2024 at 11:44 AM

To: rosalina@trisakti.ac.id

Dear Rosalina

The effects of mouth rinsing and gargling with mouthwash containing povidone-iodine and hydrogen peroxide on the cycle threshold value of Severe Acute Respiratory Syndrome Coronavirus 2: A randomized controlled trial of asymptomatic and mildly symptomatic patients

Sulistyani LD, Julia V, Soeprapto A, Swari RP, Rosmanato F, Haryanto B, Cahyarini C, Panjaitan R *et al.*

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On behalf of

Madhura  
The Editorial Team, F1000Research

### Article abstract

**Background:** Coronavirus disease 2019 can spread rapidly. Surgery in the oral cavity poses a high risk of transmission of severe acute respiratory syndrome coronavirus 2. The American Dental Association and the Centers for Disease Control and Prevention recommend the use of mouthwash containing 1.5% hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) or 0.2% povidone iodine (PI) to reduce the viral load in the upper respiratory tract and decrease the risk of transmission. The aim of the present study was to analyze the effect of mouth rinsing and gargling with mouthwash containing 1% PI, 0.5% PI, 3% H<sub>2</sub>O<sub>2</sub>, or 1.5% H<sub>2</sub>O<sub>2</sub> and water on the cycle threshold (CT) value obtained by real-time reverse transcription polymerase chain reaction (RT-PCR).

**Methods:** This study is a randomized single blind controlled clinical trial which has been registered in the International Standard Randomized Controlled Trial Number (ISRCTN) registry on the 3<sup>rd</sup> February 2022 (Registration number: ISRCTN18356379). In total, 69 subjects recruited from Persahabatan General Hospital who met the inclusion criteria were randomly assigned to one of four treatment groups or the control group. The subjects were instructed to gargle with 15 mL of mouthwash for 30 s in the oral cavity followed by 30 s in the back of the throat, three times per day for 5 days. CT values were collected on postprocedural days 1, 3, and 5.

**Results:** The results of the Friedman test significantly differed among the groups (n=15). The CT values increased from baseline (day 0) to postprocedural days 1, 3, and 5.

**Conclusions:** Mouth rinsing and gargling with mouthwash containing 1% PI, 0.5% PI, 3% H<sub>2</sub>O<sub>2</sub>, or 1.5% H<sub>2</sub>O<sub>2</sub> and water increased the CT value.

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Rosalina Tjandrawinata &lt;rosalina@trisakti.ac.id&gt;

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**Your peer review report is due soon**

1 message

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**editorial@f1000research.com** <editorial@f1000research.com>

Fri, Mar 29, 2024 at 9:36 AM

To: rosalina@trisakti.ac.id

Dear Rosalina

[The effects of mouth rinsing and gargling with mouthwash containing povidone-iodine and hydrogen peroxide on the cycle threshold value of Severe Acute Respiratory Syndrome Coronavirus 2: A randomized controlled trial of asymptomatic and mildly symptomatic patients](#)

Sulistiyani LD, Julia V, Soeprapto A, Swari RP, Rosmanato F, Haryanto B, Cahyarini C, Panjaitan R *et al.*

Thank you again for agreeing to review this article, we really appreciate your help with the peer review process. This is just a reminder that your report is due on 3 April, but please let us know if you need more time. (If you submitted your report not long before this email was dispatched, we apologize for bothering you.)

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Best regards,

Madhura

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### **3. Bukti review artikel**



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## RESEARCH ARTICLE

**REVISED** The effects of mouth rinsing and gargling with mouthwash containing povidone-iodine and hydrogen peroxide on the cycle threshold value of Severe Acute Respiratory Syndrome Coronavirus 2: A randomized controlled trial of asymptomatic and mildly symptomatic patients

[version 2; peer review: 2 approved]

Lilies Dwi Sulistyani<sup>1</sup>, Vera Julia<sup>1</sup>, Andrianto Soeprapto<sup>1</sup>,  
Rumartha Putri Swari<sup>1</sup>, Febriadi Rosmanato<sup>1</sup>, Budi Haryanto<sup>2</sup>,  
Cahyarini Cahyarini<sup>2</sup>, Rinaldi Panjaitan<sup>2</sup>, Diah Ayu Maharani<sup>3</sup>

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<https://doi.org/10.12688/f1000research.110843.2>

**Abstract****Background**

Coronavirus disease 2019 can spread rapidly. Surgery in the oral cavity poses a high risk of transmission of severe acute respiratory syndrome coronavirus 2. The American Dental Association and the Centers for Disease Control and Prevention recommend the use of mouthwash containing 1.5% hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) or 0.2% povidone iodine (PI) to reduce the viral load in the upper respiratory tract and decrease the risk of transmission. The aim of the present study was to analyze the effect of mouth rinsing and gargling with mouthwash containing 1% PI, 0.5% PI, 3% H<sub>2</sub>O<sub>2</sub>, or 1.5% H<sub>2</sub>O<sub>2</sub> and water on the cycle threshold (CT) value obtained by real-time reverse transcription polymerase chain reaction (RT-PCR).

**Open Peer Review****Approval Status** ✓✓

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1. **Muhammad Ruslin**, Hasanuddin University, Makassar, Indonesia

2. **Rosalina Tjandrawinata**, Universitas Trisakti, West Jakarta, Indonesia

Any reports and responses or comments on the article can be found at the end of the article.

## Methods

This study is a randomized single blind controlled clinical trial which has been registered in the International Standard Randomized Controlled Trial Number (ISRCTN) registry on the 3<sup>rd</sup> February 2022 (Registration number: ISRCTN18356379). In total, 69 subjects recruited from Persahabatan General Hospital who met the inclusion criteria were randomly assigned to one of four treatment groups or the control group. The subjects were instructed to gargle with 15 mL of mouthwash for 30 s in the oral cavity followed by 30 s in the back of the throat, three times per day for 5 days. CT values were collected on postprocedural days 1, 3, and 5.

## Results

The results of the Friedman test significantly differed among the groups (n=15). The CT values increased from baseline (day 0) to postprocedural days 1, 3, and 5.

## Conclusions

Mouth rinsing and gargling with mouthwash containing 1% PI, 0.5% PI, 3% H<sub>2</sub>O<sub>2</sub>, or 1.5% H<sub>2</sub>O<sub>2</sub> and water increased the CT value.

## Keywords

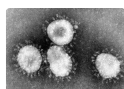
mouthwash, severe acute respiratory syndrome coronavirus, povidone iodine



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**Corresponding author:** Lilies Dwi Sulistyani ([liliesdwi\\_s@yahoo.co.id](mailto:liliesdwi_s@yahoo.co.id))

**Author roles:** **Sulistyani LD:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Julia V:** Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Soeprapto A:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Swari RP:** Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Rosmanato F:** Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Haryanto B:** Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation; **Cahyarini C:** Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Supervision, Validation; **Panjaitan R:** Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Supervision, Validation; **Maharani DA:** Data Curation, Formal Analysis, Methodology, Software, Validation

**Competing interests:** No competing interests were disclosed.

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**REVISED Amendments from Version 1**

There is a change in the second sentence in the conclusion which leads to a specific conclusion related to patients infected with SARS-CoV-2.

**Any further responses from the reviewers can be found at the end of the article**

## 1. Introduction

Coronavirus disease 2019 (COVID-19) spreads quickly and deadly and, thus, has been especially challenging to healthcare workers.<sup>1</sup> COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of the respiratory tract, was first reported in Wuhan, China in December 2019 and declared a pandemic on March 11, 2020.<sup>2–4</sup> According to the World Health Organization, SARS-CoV-2 accounted for 262 million infections and 5.2 million deaths globally as of December 1, 2021.<sup>5</sup> The average incubation period of SARS-CoV-2 is about 3–9 days.<sup>6</sup> Clinical manifestations appear after the incubation period and vary from asymptomatic to severe respiratory disease and life-threatening multiple organ failure.<sup>1,7</sup>

Up to 80% of cases exhibit mild localized symptoms in the upper respiratory tract (URT) accompanied by non-specific symptoms, especially fever and cough.<sup>6,8,9</sup> Virus transmission in about 44% of cases occurs before the onset of symptoms.<sup>10</sup> About 18% of cases are asymptomatic but can transmit the virus to others.<sup>6</sup> It is difficult to distinguish between truly asymptomatic and pre-symptomatic patients because of the lack of visible symptoms.<sup>11</sup> Asymptomatic patients and those with mild symptoms greatly contribute to the transmission of SARS-CoV-2 because of the lack of awareness of an active infection, reluctance to seek medical care, and poor understanding of transmission prevention.<sup>12</sup>

SARS-CoV-2 is mainly transmitted by inhalation of respiratory droplets or contact with contaminated surfaces.<sup>7,13</sup> SARS-CoV-2 rapidly replicates in the URT, producing large numbers of pathogenic progeny at an early stage of disease development that can be transmitted by respiratory droplets.<sup>1,14</sup> Further replication in the lower respiratory tract leads to the development of lung disease.<sup>15,16</sup> Saliva contains high amounts of SARS-CoV-2 that enters through the lower respiratory tract, URT, or infected salivary glands and acts as a potential source of virus transmission in the oral cavity.<sup>17–20</sup>

Reducing the amount of SARS-CoV-2 in the URT and oral cavity in the early stages of disease is important to prevent virus transmission and reduce the severity and progression of disease.<sup>18,21,22</sup> Various active ingredients of mouthwash have virucidal activities that disrupt the lipid envelope of the virus.<sup>23</sup> Active ingredients of mouthwash recommended before medical procedures in the oral cavity include 21%–26% ethanol with essential oils, chlorhexidine, povidone iodine (PI), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), cetylpyridinium chloride, chlorinated water, and hypertonic saline.<sup>23–25</sup> The American Dental Association (ADA) and the Centers for Disease Control and Prevention (CDC) recommend gargling with mouthwash containing 0.2% PI or 1.5% H<sub>2</sub>O<sub>2</sub> before medical procedures in the oral cavity because SARS-CoV-2 is susceptible to oxidation.<sup>26,27</sup> Current recommendations include mouth rinsing and gargling with mouthwash for 30 s in the oral cavity followed by 30 s in the back of the throat.<sup>24</sup>

The objective of this study was to semi-quantitatively evaluate the effect of mouth rinsing and gargling with mouthwash containing various concentrations of PI and H<sub>2</sub>O<sub>2</sub> on the amount of SARS-CoV-2 in the URT using the cycle threshold (CT) value during real-time reverse transcription polymerase chain reaction (RT-PCR) in asymptomatic and mildly symptomatic patients.

## 2. Methods

### 2.1 Study design

The cohort of this single-blind randomized controlled trial included four intervention groups and one control group. The study protocol was approved by the Health Research Ethics Committee of Persahabatan Central General Hospital (CGH) with registration number: 68/KEPK-RSUPP/06/2021. This study has been retrospectively registered in the International Standard Randomized Controlled Trial Number (ISRCTN) registry on the 3<sup>rd</sup> February 2022 with registered number ISRCTN18356379 (<https://doi.org/10.1186/ISRCTN18356379>).

### 2.2 Sample selection

In total, 69 patients infected with SARS-CoV-2 were recruited from Persahabatan CGH, a national COVID-19 referral center hospital, from July to September 2021. SARS-CoV-2 infection was confirmed by RT-PCR. The sample size was calculated using G\*Power (RRID:SCR\_013726) 3.1.9.2 software (<https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower>). The inclusion criteria were age 19–60 years, CT values ≤ 30,

asymptomatic or mild symptoms, and diagnosis of COVID-19 within 3 days prior to recruitment. The exclusion criteria consisted of refusal to participate, comorbid disease, thyroid disease, pregnancy, routine use lithium drugs, radioactive iodine treatment, and allergy to PI and H<sub>2</sub>O<sub>2</sub>. All subjects signed an informed consent form after being provided with information regarding the study objective and possible risks and benefits of gargling with mouthwash. The subjects were randomly assigned by one researcher to one of the four treatment groups or the control group using a simple randomization method where each research subject was assigned to a group with specific order: 1% PI, 3% H<sub>2</sub>O<sub>2</sub>, control, 0.5% PI, and 1.5% H<sub>2</sub>O<sub>2</sub> consecutively. This study is single blinded where only the research subjects were blinded from their group allocation.

### 2.3 Intervention

The subjects were instructed on how to rinse and gargle with mouthwash via video conference and supplied with repackaged mouthwash. The 1% PI group rinsed their mouth with BETADINE® Mouthwash and Gargle solution (Napp Pharmaceuticals Ltd., United Kingdom). The 3% H<sub>2</sub>O<sub>2</sub> group rinsed their mouth with *OneMed*™ solution (Inti Medicom Retailindo, Indonesia). The group treated with 0.5% iodine peroxide and 1.5% H<sub>2</sub>O<sub>2</sub> rinsed their mouth with a diluted solution of 1% PI BETADINE® Mouthwash and Gargle solution and 3% H<sub>2</sub>O<sub>2</sub> *OneMed*™ added with sterile distilled water in accordance with the formula  $\text{Volume}_1 \times \text{Concentration}_1 = \text{Volume}_2 \times \text{Concentration}_2$ . The control group was instructed to rinse their mouth with AQUA™ mineral water (Danone, France). The subjects were instructed to rinse their mouth with 15 mL of mouthwash for 30 s in the oral cavity followed by gargling 30 s in the back of throat three times per day for 5 days. Mouth rinsing and gargling with mouthwash were conducted in a self-isolation room and monitored via video conference.

### 2.4 Measurement

Samples were collected with oropharyngeal and nasopharyngeal swabs using a disposable virus sampling tube (Baicare Biotechnology Co., Ltd., China) by a trained staff member of Persahabatan CGH on postprocedural days 1, 3, and 5 after gargling with mouthwash. The samples were appropriately packaged, labeled, and sent to the Department of Microbiology for RT-PCR analysis. The specimens were vortexed with an LMS® UZUSIO VTX-3000L vortex mixer (LMS Co., Ltd., Japan) for 20 s and allowed to stand for 15 min. Then, 250 µL of MagNA Pure 96 extraction reagent (Roche Life Science, Germany) were loaded into the cartridge and mixed with 200 µL of the specimen. The cartridge was loaded into the Rosche MagNA Pure 96 instrument for sample extraction. The reaction mix of the mBioCoV-19 RT-PCR Kit (Bio Farma, Indonesia) was used to detect the open reading frame 1b and RNA-dependent RNA polymerase genes. In brief, 15 µL of reaction mix were added to each well and mixed with 5 µL of the extracted specimen. CT values were obtained automatically with an Exicycler™ 96 (Ver.4) (RRID:SCR\_022144) Real-Time Quantitative Thermal Block (Bioneer Corporation, South Korea) ([https://us.bioneer.com/products/instrument/Exicycler96\\_V4-overview.aspx](https://us.bioneer.com/products/instrument/Exicycler96_V4-overview.aspx)) upon detection of SARS-CoV-2 genetic material.

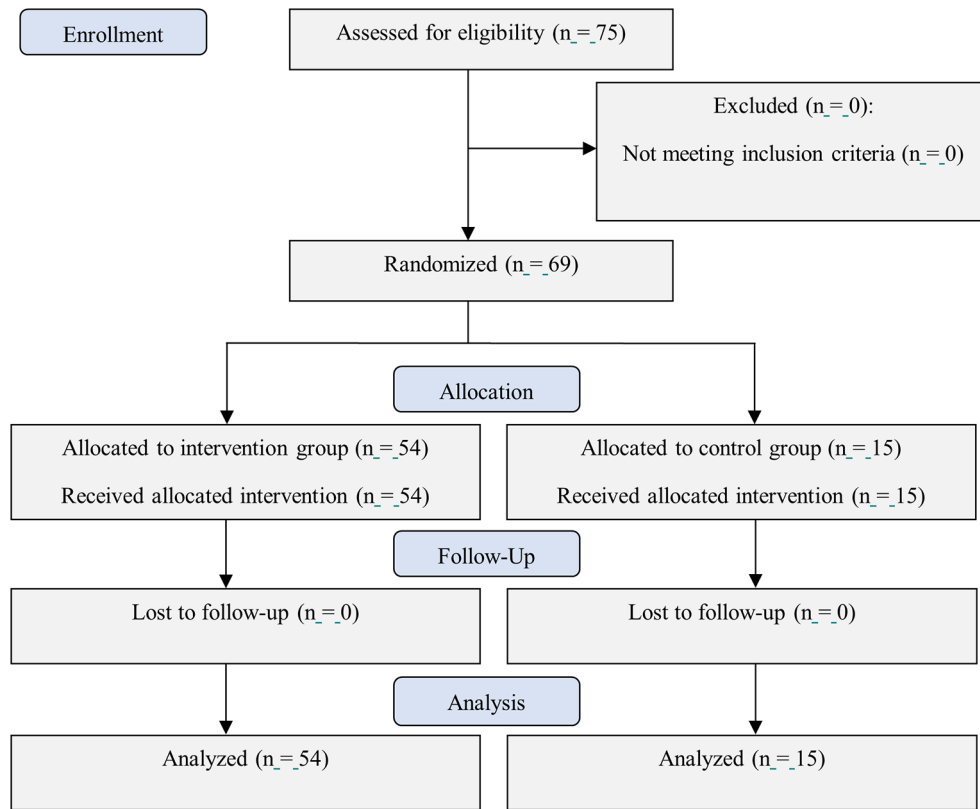
### 2.5 Statistical analysis

CT values of the open reading frame 1b target gene were analyzed using IBM SPSS Statistics for Windows, version 22.0. (IBM Corporation, USA) (RRID:SCR\_016479) (<https://www.ibm.com/products/spss-statistics>). The data were not normally distributed; thus a nonparametric test was used for analysis. Repeated measurements of each group were analyzed using the Friedman nonparametric test. Comparisons between groups from baseline (day 0) to postprocedural days 1, 3, and 5 were conducted using the Kruskal–Wallis nonparametric test. A probability (*p*) value of <0.05 was considered statistically significant.

## 3. Results

The total size estimation was 75 patients with *n*=15 for each group. However, due to the significant decrease in new COVID-19 cases in Indonesia, only 69 patients were recruited from July to September 2021, as it was difficult to recruit subjects who met the inclusion criteria (Figure 1). Numbers of participants for each group were 1% PI = 15, 0.5% PI = 12, 3% H<sub>2</sub>O<sub>2</sub> = 15, 1.5% H<sub>2</sub>O<sub>2</sub> = 12, and control = 15.

Of the 69 patients, 39 (56.5%) were male and 30 (43.5%) were female. The average age of the subjects was 32.8 (range, 25–44) years. Cough (66.7%) was the most common early symptom of COVID-19 (Table 1). As shown in Table 2, the mean CT values increased in each group from baseline (day 0) to postprocedural days 1, 3, and 5. The results of the Friedman test showed significant differences in CT values among the groups. *Post-hoc* analysis (Table 3) showed significant differences in most of the CT values with the exceptions of between days 1 and 3 in the 0.5% PI and 3% and 1.5% H<sub>2</sub>O<sub>2</sub> groups and between days 3 and 5 in the 3% H<sub>2</sub>O<sub>2</sub> and control groups. Comparisons of CT values among the groups using the Kruskal–Wallis test showed no significant differences due to the increases in CT values of each group.



**Figure 1.** CONSORT flow diagram of this study.

**Table 1.** Demographic data.

| Sex                                              | n  | Percentage (%) |
|--------------------------------------------------|----|----------------|
| Male                                             | 39 | 56.5           |
| Female                                           | 30 | 43.5           |
| <b>Age (years)</b>                               |    |                |
| 19–25                                            | 14 | 20.3           |
| 25–44                                            | 45 | 65.2           |
| 45–60                                            | 10 | 14.5           |
| <b>Early symptoms</b>                            |    |                |
| Fever                                            | 38 | 55.1           |
| Cough                                            | 46 | 66.7           |
| Fatigue                                          | 41 | 59.4           |
| Sore throat                                      | 29 | 42.0           |
| Runny nose                                       | 40 | 58.0           |
| Headache                                         | 38 | 55.1           |
| Digestive disorders (diarrhea, nausea, vomiting) | 25 | 36.2           |
| Anosmia                                          | 30 | 43.5           |
| Ageusia                                          | 18 | 26.1           |

**Table 2.** Comparisons of cycle threshold (CT) values among the povidone iodine, hydrogen peroxide, and control groups (\* $p < 0.05$ ).

|                                    | CT Value         |       |        |       |        |       |        |       | <i>p</i> (Friedman test) |
|------------------------------------|------------------|-------|--------|-------|--------|-------|--------|-------|--------------------------|
|                                    | Baseline (Day 0) |       | Day 1  |       | Day 3  |       | Day 5  |       |                          |
|                                    | Mean             | SD    | Mean   | SD    | Mean   | SD    | Mean   | SD    |                          |
| PI, 1%                             | 23.974           | 4.017 | 29.105 | 6.041 | 34.035 | 5.765 | 36.879 | 4.406 | 0.001*                   |
| PI, 0.5%                           | 24.153           | 4.856 | 32.907 | 8.621 | 35.319 | 7.476 | 37.781 | 3.984 | 0.001*                   |
| H <sub>2</sub> O <sub>2</sub> 3%   | 23.132           | 3.806 | 33.097 | 5.783 | 35.679 | 5.590 | 37.861 | 3.310 | 0.001*                   |
| H <sub>2</sub> O <sub>2</sub> 1.5% | 25.405           | 3.639 | 32.390 | 6.627 | 35.639 | 5.757 | 38.531 | 1.960 | 0.001*                   |
| Control                            | 24.685           | 3.737 | 31.147 | 6.351 | 35.313 | 5.689 | 36.773 | 6.369 | 0.001*                   |
| <i>p</i> (Kruskal-Wallis test)     | 0.562            |       | 0.307  |       | 0.850  |       | 0.969  |       |                          |

\* $p < 0.05$ .**Table 3.** Wilcoxon *post-hoc* analysis of the Friedman test.

|                                    | Baseline–Day 1 | Baseline–Day 3 | Baseline–Day 5 | Days 1–3 | Days 1–5 | Days 3–5 |
|------------------------------------|----------------|----------------|----------------|----------|----------|----------|
| PI, 1%                             | 0.006*         | 0.001*         | 0.001*         | 0.026*   | 0.004*   | 0.037*   |
| PI, 0.5%                           | 0.005*         | 0.004*         | 0.002*         | 0.093    | 0.012*   | 0.043*   |
| H <sub>2</sub> O <sub>2</sub> 3%   | 0.001*         | 0.001*         | 0.001*         | 0.158    | 0.019*   | 0.114    |
| H <sub>2</sub> O <sub>2</sub> 1.5% | 0.012*         | 0.003*         | 0.002*         | 0.066    | 0.008*   | 0.028*   |
| Control                            | 0.005*         | 0.001*         | 0.001*         | 0.013*   | 0.003*   | 0.176    |

\* $p < 0.05$ .

#### 4. Discussion

SARS-CoV-2 infection can spread rapidly and cause severe morbidity and mortality.<sup>28</sup> The oral cavity and URT have high viral loads and are potential sources of SARS-CoV-2.<sup>29</sup> Kim *et al.*<sup>30</sup> found that viral shedding was high in the URT from the prodromal phase to day 5 after symptom onset. Yoon *et al.*<sup>19</sup> found that the viral load was greater in the saliva than the oropharynx in the early stages of disease. A high viral load in saliva can originate from the respiratory tract or secretions from infected salivary glands.<sup>18</sup> Chen *et al.*<sup>20</sup> reported the expression of angiotensin converting enzyme 2, a cell receptor for SARS-CoV-2, in the salivary glands, suggesting possible SARS-CoV-2 infection of the salivary glands.

Reducing the amounts of SARS-CoV-2 in the URT and oral cavity is important to prevent virus transmission.<sup>21,22</sup> The ADA and the CDC recommend preprocedural mouth rinsing and gargling with mouthwash containing H<sub>2</sub>O<sub>2</sub> or PI because SARS-CoV-2 is susceptible to oxidation.<sup>26,27</sup> PI consists of iodine and the water-soluble polymer polyvinylpyrrolidone. Iodine released from polyvinylpyrrolidone penetrates microorganisms and causes oxidation of amino acids and nucleic acids, resulting in disruption of metabolic pathways and cell membranes.<sup>17,25</sup> Frank *et al.*<sup>21</sup> claimed that mouthwash containing 2.5% PI is safe to use in the oral cavity for up to 5 months.

An *in vitro* study by Eggers *et al.*<sup>31</sup> reported that 0.023% PI exhibited virucidal activities against betacoronaviruses, including SARS-CoV and Middle East respiratory syndrome–related coronavirus (MERS-CoV), after contact for 15 s. The use of mouthwash containing 1% PI to reduce the load of SARS-CoV-2 was also confirmed by an *in vitro* study conducted by Anderson *et al.*<sup>3</sup> which reported that 1% PI reduced the load of SARS-CoV-2 by more than 99.99% or more than 4log<sub>10</sub> after 30 s of contact. An *in vitro* study by Hassandarvish *et al.*<sup>32</sup> reported that 1% PI reduced of the load of SARS-CoV-2 by more than 5log<sub>10</sub> after exposure for 15, 30, and 60 s. An *in vitro* study by Bidra *et al.*<sup>29</sup> found that PI at 0.5%, 1.25%, and 1.5% fully inactivated SARS-CoV-2 after contact for 15 and 30 s. The results of the present study showed that mouth rinsing and gargling with mouthwash containing 0.5% or 1% PI increased the CT values on postprocedural days 1, 3, and 5.

The virucidal action of  $H_2O_2$  involves the release of oxygen free radicals that disrupt lipid membranes.<sup>17</sup> O'Donnell *et al.*<sup>23</sup> suggested that the target of  $H_2O_2$  is the lipid envelope of SARS-CoV-2. The swine flu, rubella, rabies, corona, and influenza viruses are also sensitive to  $H_2O_2$ .<sup>24,33</sup> Caruso *et al.*<sup>33</sup> claimed that mouthwash containing 3%  $H_2O_2$  was safe for mucous membranes after 6 months of use. An *in vitro* study by Kampf *et al.*<sup>34</sup> reported that  $H_2O_2$  at a concentration of at least 0.5% effectively inactivated SARS-CoV and MERS-CoV on the surface of inanimate objects in 1 min. The results of the present study showed that mouth rinsing and gargling with mouthwash containing 1.5% and 3%  $H_2O_2$  increased the CT values on postprocedural days 1, 3, and 5. In contrast with an *in vitro* study by Bidra *et al.*,<sup>29</sup> which reported that mouthwash containing 1.5% and 3%  $H_2O_2$  had minimal virucidal activity after contact for 30 s, Gottsauner *et al.*<sup>35</sup> showed that mouth rinsing and gargling with mouthwash containing 1%  $H_2O_2$  in the mouth and back of the throat for 30 s did not reduce the load of SARS-CoV-2. The difference in the results of the present study and the report by Gottsauner *et al.*<sup>35</sup> was likely due to differences in  $H_2O_2$  concentrations.

Vergara-Buenaventura *et al.*<sup>24</sup> recommended mouth rinsing and gargling with mouthwash for 30 s in the oral cavity and 30 s at the back of the throat. The control group in the present study gargled with water, which surprisingly increased the CT values on postprocedural days 1, 3, and 5. Flushing the URT with fluids can clear excess mucus and mechanically reduce the viral load in the respiratory tract with impaired mucociliary function.<sup>36–38</sup> A study by Koparal *et al.*<sup>39</sup> found a delay in mucociliary clearance time in COVID-19 patients as compared to healthy individuals. Robinot *et al.*<sup>40</sup> reported that SARS-CoV-2 infection in ciliated epithelial cells causes loss of ciliary motility, short cilia deformity, and impaired mucociliary clearance, thereby increasing the spread of SARS-CoV-2 in the respiratory tract and increasing the risk of secondary infection in COVID-19 patients. Whirling water can mechanically wash out the virus and virus-infected cells from the oral cavity and pharynx.<sup>41</sup> A study by Satomura *et al.*<sup>41</sup> reported that mouth rinsing and gargling with tap water three times per day effectively reduced the incidence of URT infections by 36%.

Several current guidelines regarding the management of discharge of COVID-19 patients are based on the timing from onset of symptoms and a CT value > 30.<sup>42</sup> CT values are often associated with the risk of SARS-CoV-2 transmission.<sup>43</sup> Patients with high CT values are reportedly incapable of transmitting infectious virus particles.<sup>44</sup> A study by Hiroi *et al.*<sup>45</sup> reported that a CT value >30 indicates a very low infectious virus titer and a lower risk of infecting others. Scola *et al.*<sup>46</sup> concluded that patients with CT values  $\geq 34$  are incapable of transmitting SARS-CoV-2 and could be discharged from the infectious disease ward. The entire cohort of the present showed an increase in mean CT score of 34 on day 3 after gargling.

This study may be limited by its limited and uneven sample number due to the significant decrease in new COVID-19 cases in Indonesia, thus only 69 patients were found to fulfil the inclusion criteria during the recruitment period, with two groups (0.5% PI and 1.5%  $H_2O_2$ ) had only 12 samples per group where others had 15 per group.

## 5. Conclusion

Mouth rinsing and gargling with mouthwash containing 1% PI, 0.5% PI, 3%  $H_2O_2$ , or 1.5%  $H_2O_2$  and water increased the CT values. The results of this study suggest that rinsing for 30 s in the oral cavity and 30 s at the back of the throat three times per day for at least 3 days can be used to increased the CT value in patients infected with SARS-CoV-2 and could become a new preoperative protocol in oral and maxillofacial surgery and other medical procedures in the oral cavity.

## Data availability

### Underlying data

Zenodo: [Effects of Mouthrinsing and Gargling to CT Values of SARS CoV-2 DATASET]. <https://doi.org/10.5281/zenodo.6358988> [Version 1.0].

The project contains the following underlying data:

- [informed-consent-back.jpg] (informed consent form page 2).
- [informed-consent-front.jpg] (informed consent form page 1).
- [Metadata (Eng).xlsx] (metadata to read the data file)
- [Research\_Data\_Revised.pdf] (raw data of each research subject)
- [research-information-form.jpg] (information sheet for research participants)

- [research-subject-screening-form.jpg] (form filled by the research subject on screening)
- [subject-consent-form.jpg] (consent form signed by research participants)

### Reporting guidelines

Zenodo: CONSORT checklist for 'The effects of mouth rinsing and gargling with mouthwash containing povidone-iodine and hydrogen peroxide on the cycle threshold value of Severe Acute Respiratory Syndrome Coronavirus 2: A randomized controlled trial of asymptomatic and mildly symptomatic patients'. <https://doi.org/10.5281/zenodo.6409184> [Version 1].

Data are available under the terms of the [Creative Commons Attribution 4.0 International](#) (CC BY 4.0).

### Author contributions

- Lilies Dwi Sulistyani conceived and designed the analysis, verified the analytical methods, gaining resources, supervised the study, in charge of overall direction and planning, wrote and revised the paper
- Vera Julia conceived and designed the analysis, verified the analytical methods, supervised the study, wrote and revised the paper
- Andrianto Soeprapto performed the experiment and analysis, drafted and revised the paper
- Rumartha Putri Swari performed the experiment and analysis, drafted the paper
- Febriadi Rosmanato performed the experiment and analysis, drafted the paper
- Budi Haryanto verified the analytical methods, gaining resources, supervised the study
- Cahyarini verified the analytical methods, supervised the study
- Rinaldi Panjaitan verified the analytical methods, supervised the study
- Diah Ayu Maharani designed and verified the statistics

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## Version 2

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**Muhammad Ruslin**

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Thank you for your revision on the article. Currently the conclusions are aligned with the data and the presentation looks clearer. I now approve the current version to be indexed.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** dentistry, oral and maxillofacial surgery

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 08 July 2024

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**Rosalina Tjandrawinata**

Universitas Trisakti, West Jakarta, Jakarta, Indonesia

I read the revised version of the article and approved the revision. This article will be useful for standard operating procedures in oral and dental treatment.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Dental materials

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Version 1

Reviewer Report 02 April 2024

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**Rosalina Tjandrawinata**

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I learn the authors' paper "The effects of mouth rinsing and gargling with mouthwash containing povidone-iodine and hydrogen peroxide on the cycle threshold value of Severe Acute Respiratory Syndrome Coronavirus 2: A randomized controlled trial of asymptomatic and mildly symptomatic patients" is very interesting and add more information for COVID-19-related cases.

However, there are some questions about the effectivity of different concentration, which would be very useful. Statistical analysis should be taken to analyse which mouthwash is the most effective mouthwash for the cases.

The conclusion is "that rinsing for 30 s in the oral cavity and 30 s at the back of the throat three times per day for at least 3 days preoperatively as a new preoperative protocol in oral and maxillofacial surgery and other medical procedures in the oral cavity"; while the statistics (Table 3) showed that both concentration of Hydrogen Peroxide and PI 0.5% mouthwash do not have significant difference between 1 day and 3 days and that CT value is already  $\geq 30$ .

So, that 1-day rinsing would be effective enough for reducing the virus. It is quite interesting that your data (Table 2) showed PI 0.5% increase CT value similar or more than PI 1%.

The most interesting condition is rinsing with mineral water (control group) is also rising the CT value, similar to the treated group. So, should we use mouth rinsing instead of mineral water if we can get similar result? It should be reconfirmed by authors. It will be very useful if the authors compare the difference among the mouth rinses and the control group.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Dental materials

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 22 Apr 2024

**Lilies Dwi Sulistyani**

Thank you to Rosalina Tjandrawinata. We appreciate your review and questions.

Mouth rinsing and gargling for 1 day shows effectiveness in reducing the number of viruses as seen from the increase in CT values. Based on research by Scola BL et al (Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards) which states that CT values equal or above 34 do not excrete infectious viral particles. Our research data showed an increase in mean CT value equal or above 34 for the five groups after mouth rinsing and gargling for 3 days. Therefore we recommend mouth rinsing and gargling at least 3 days.

Surprisingly we found that mouth rinsing and gargling with mineral water could increase the CT values as well. This is due to whirling water can mechanically wash out the virus and virus-infected cells from the oral cavity and pharynx. Mouth rinsing and gargling with mouthwash can disrupt the balance of flora in the oral cavity, therefore mouth rinsing and gargling with mineral water can be an alternative gargling procedure to prevent the attachment of the SARS-CoV-2 virus at an early stage that is safe for long-term use.

**Competing Interests:** No competing interests were disclosed.

Reviewer Response 27 May 2024

**Rosalina Tjandrawinata**

Dear doctors,

Thank you for the explanation. Now it is clear that whirling water can mechanically wash out

the virus and virus-infected cells from the oral cavity and pharynx, and it is clearly shown in Table 2 that the content of the liquid does not make any significant difference to the result.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 06 December 2022

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**Muhammad Ruslin**

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I appreciate the authors for presenting "The effects of mouth rinsing and gargling with mouthwash containing povidone-iodine and hydrogen peroxide on the cycle threshold value of Severe Acute Respiratory Syndrome Coronavirus 2: A randomized controlled trial of asymptomatic and mildly symptomatic patients". This will add more information to the existing literature on COVID-19-related cases.

However, there are some mismatches between the conclusions and the data presented. In the whole manuscript, the authors never mentioned cases specific to oral and maxillofacial surgery; how come they finally recommend this rinsing solution/method for oral and maxillofacial surgery? From my point of view, it would be better to draw a specific conclusion related to the Covid-19 patients, since this is your main issue in the article. Based on the results of your study, what can you recommend for these patients?

(please see the conclusion part, the second sentence, the sentence does not sound appropriate, please modify)

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

I cannot comment. A qualified statistician is required.

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** dentistry, oral and maxillofacial surgery

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 30 Jan 2023

**Lilies Dwi Sulistyani**

Thank you Prof Muhammad Ruslin. We appreciate your review and suggestions. In the introduction, we mentioned that this study departed from a large number of asymptomatic COVID-19 patients and mild symptoms which made a significant contribution to the spread of SARS-CoV-2 both to medical personnel and the people around the patient because there were no visible signs of active infection. These patients are often difficult to distinguish from healthy people, so there is a lack of awareness from health workers, especially those who perform procedures in the oral cavity, to apply transmission prevention protocols to these patients. We did not use samples for specific cases in the field of oral and maxillofacial surgery but instead used asymptomatic and mildly symptomatic COVID-19 patients. Reducing the amount of virus in the oral cavity and back of the throat before the medical procedure with mouth rinsing and gargling protocol is easy to perform. It can be applied in the field of oral and maxillofacial surgery. Not only oral and maxillofacial surgeons, but colleagues such as anesthesiologists, ENT, and others who perform any medical procedures in the oral cavity can also apply this mouth rinsing and gargling protocol as we stated in the second sentence of the conclusion.

**Competing Interests:** No competing interests were disclosed.

Author Response 22 Apr 2024

**Lilies Dwi Sulistyani**

Hi Prof Ruslin. Thank you for reviewing the article.  
I have modified the second sentence in the conclusion as per your suggestion.

**Competing Interests:** No competing interests were disclosed.

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