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aligners and/or refinements must be anticipated and communicated to patients as part of informed consent when treating with aligners.

Finally, the limitations mentioned in the letter are discussed in the original article, along with other variables that may have impacted our data collection and analysis.

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Recent evidence sustains the use of chlorhexidine-based mouthwash for dental patients during the coronavirus disease 2019 epidemic

It was with great interest that we read the Letter to the Editor by Singh and colleagues (Singh H, Sharma P, Kapoor P, Maurya RK. Virucidal mouth rinses for patients during the coronavirus disease 2019 outbreak. *Am J Orthod Dentofacial Orthop* 2021;159:707-9) on the use of prophylactic preprocedural mouth rinses (PPMR) to limit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and recommendation to use povidone iodine (PVP-1)-based PPMR. The letter did not consider recent data concerning the virucidal effects of chlorhexidine (CHX) and PVP-1 and could lead to some rash conclusions, raising unfounded choices.^{1,2} Therefore, we would like to highlight a few points.

The use of a specific compound in PPMR was not recommended in the last Guidance for Dental Settings by either the Centers for Disease Control and Prevention or the European Centre for Disease Prevention and Control, and the use is not sustained by clear evidence.³⁻⁶

The virucidal effect of CHX against SARS-CoV-2 is plain when the experiments are planned to avoid cell toxicity.⁷⁻⁹ Toxicity is present at 1:100 dilution and is known to be also caused by other components of commercial PPMR. Unfortunately, avoiding toxicity is tricky and expensive to achieve according to in vitro testing on the basis of European Standard EN 14476 and laboratories rated BioContainment level 3 or higher.¹⁰ PVP-1's better benefits reported by Lamas are based on data from unusual clinical trials,¹¹ including salivary tests in 2 patients, without statistical evaluation. Recently, a similar trial has shown CHX analogous benefit.⁹

PVP-1, hydrogen peroxide, and CHX mouthwashes significantly reduce SARS-CoV-2 burden in mouth fluid and respiratory droplets by reverse transcriptase polymerase chain reaction of RNA viruses and rapid antigen testing of virus protein.¹² Nevertheless, the reduction is time-dependent, and CHX seems more suitable before orthodontic care, which usually takes <60 minutes.

Evidence on CHX (0.2%, mouth rinsed for 30 seconds) and PVP-1 (1%, gargled for 30 seconds) was similar to a randomized-controlled clinical trial and cycle threshold values, the indicator of viral load in the salivary sample.¹³

Unlike hydrogen peroxide and PVP-1, CHX shows the highest affinity with SARS-CoV2 proteins from computational drug modeling.¹⁴ CHX shows strong binding sites in SARS-CoV-2's spike protein and on the ACE2-Spike (receptor-binding domain) interface of SARS-CoV-2, similar to those exerted by antiviral drugs. CHX affinity to spike proteins is remarkable: the binding energy for CHX, PVP, and hydrogen peroxide is respectively -10.4, -4.5, and -3.2 kcal/mol. In addition, only CHX binds to papain-like protease, known to be essential for viral RNA replication and controlling host cells.

Because of different optimal pH, CHX (pH 5.5-7.0), both PVP-1 (pH 2.0-7.0) and hydrogen peroxide (pH 2.5-3.6) are expected to differently influence dental demineralization, frequent in orthodontic patients.

In our opinion, we need sound data to sustain the preferential use of PVP-1 in favor of CHX. Dental teams deserve clarity and need updated guidelines on PPMR use in orthodontic patients.

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REFERENCES

1. Becker K, Gurzawska-Comis K, Brunello G, Klinge B. Summary of European guidelines on infection control and prevention during COVID-19 pandemic. *Clin Oral Implants Res* 2021;32(Suppl 21): 353-81.
2. Hong KS. A study on using mouthwash before providing dental treatment to patients in dental clinics during the COVID-19 pandemic. *Int J Clin Prev Dent* 2021;17:21-6.
3. Centers for Disease Control and Prevention. Guidance for Dental Settings. Interim infection prevention and control Guidance for Dental Settings during the coronavirus disease 2019 (COVID-19)

- pandemic. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/dental-settings.html>. Accessed July 1 2021.
4. ECDC2020. COVID-19 infection prevention and control measures for primary care, including general practitioner practices, dental clinics and pharmacy settings: first update. Available at: <https://www.ecdc.europa.eu/en/publications-data/covid-19-infection-prevention-and-control-primary-care>. Accessed July 1 2021.
 5. Burton MJ, Clarkson JE, Goulao B, Glenny AM, McBain AJ, Schilder AG, et al. Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to improve patient outcomes and to protect healthcare workers treating them. *Cochrane Database Syst Rev* 2020;9:CD013627.
 6. Kelly N, Nic Iomhair A, McKenna G. Can oral rinses play a role in preventing transmission of COVID-19 infection? *Evid Based Dent* 2020;21:42-3.
 7. Geller C, Varbanov M, Duval RE. Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses* 2012;4:3044-68.
 8. Jain A, Grover V, Singh C, Sharma A, Das DK, Singh P, et al. Chlorhexidine: an effective antiCovid mouth rinse. *J Indian Soc Periodontol* 2021;25:86-8.
 9. Yoon JG, Yoon J, Song JY, Yoon SY, Lim CS, Seong H, et al. Clinical significance of a high SARS-CoV-2 viral load in the saliva. *J Korean Med Sci* 2020;35:e195.
 10. Steinhauer K, Meister TL, Todt D, Krawczyk A, Pavogel L, Becker B, et al. Comparison of the in-vitro efficacy of different mouthwash solutions targeting SARS-CoV-2 based on the European Standard EN 14476. *J Hosp Infect* 2021;111:180-3.
 11. Martínez Lamas L, Diz Dios P, Pérez Rodríguez MT, Del Campo Pérez V, Cabrera Alvargonzalez JJ, López Domínguez AM, et al. Is povidone iodine mouthwash effective against SARS-CoV-2? First in vivo tests. *Oral Dis*. Epub 2020 Jul 2.
 12. Jayaraman BG, Rajan G, Kannian P, Lavanya C, Ravichandran K, Kumarasamy N, et al. Povidone iodine, hydrogen peroxide and chlorhexidine mouthwashes reduce SARS-CoV2 burden in whole mouth fluid and respiratory droplets. *medRxiv* 2021 [Preprint]. Available from: <https://www.medrxiv.org/content/10.1101/2021.02.25.21252488v1>
 13. Elzein R, Abdel-Sater F, Fakhreddine S, Hanna PA, Feghali R, Hamad H, et al. In vivo evaluation of the virucidal efficacy of chlorhexidine and povidone-iodine mouthwashes against salivary SARS-CoV-2. A randomized-controlled clinical trial. *J Evid Based Dent Pract* 2021;21:101584.
 14. Sette-DE-Souza PH, Costa MJF, Amaral-Machado L, Araújo FADC, Almeida Filho AT, Lima LRA. Dental workers in front-line of COVID-19: an in silico evaluation targeting their prevention. *J Appl Oral Sci* 2021;29:e20200678.

Authors' response

The viewpoint of Berenghi et al on chlorhexidine (CHX) based mouthwash during the coronavirus disease 2019 (COVID-19) pandemic raises an interesting hypothetical question. The recent articles by Becker et al¹ and Hong² do not consider the available scientific evidence supporting the virucidal effects of either CHX or povidone iodine (PVP-1) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and thus were

somewhat inconclusive. We respectfully maintain that when we wrote our Letter to the Editor, emerging robust scientific data concerning the virucidal effects of CHX and PVP-1 were taken into consideration. In reference to the other queries put forth by Berenghi et al, we wish to supplement evidence-based literature regarding the use and composition of preprocedural mouthrinses as has been recently updated in scientific literature.

We acknowledge that in the early stages of a pandemic, health authorities such as the Centers for Disease Control and Prevention³ recommended preprocedural mouthrinses for dental treatment even without robust clinical evidence. However, we would like to highlight the fact that despite relatively fewer in vitro studies being published during the first wave of the pandemic, the Guidance for Dental Settings by the Centers for Disease Control (last updated on December 9, 2020) did not reflect the emerging evidence supporting virucidal effectiveness of PVP-1 against SARS-CoV-2.

Regarding the European Centre for Disease Prevention and Control⁴ guidance, there is no mention regarding the use of prophylactic preprocedural mouth rinse (PPMR). In addition, the Cochrane review by Burton et al⁵ could identify only ongoing studies, including 14 randomized controlled trials (RCTs) but found no completed studies worth including. Given the unprecedented dynamic nature of COVID-19 infection and being a translational research field, it is not surprising that Cochrane reviews are likely to conclude as low certainty or unclear evidence because of a lack of RCTs. However, we firmly believe that the absence of evidence may not necessarily reflect evidence of absence.⁶ On further exploration, we found that at the time of publishing of the review commentary by Kelly et al,⁷ only insufficient direct in vitro evidence of the efficacy of specific compounds in PPMR against SARS-CoV-2 was available. The majority of the evidence was extrapolated from other viruses, including influenza, HIV, and herpes simplex.

A critical analysis of the studies by Jain et al⁸ and Yoon et al⁹ revealed that cell toxicity effects were not considered while assessing virucidal effects of CHX against SARS-CoV-2. In contrast, after the use of a suspension assay on the basis of EN14476 methodology, no cytotoxic effects have been reported with the use of 1% PVP-1 mouthwash at a concentration of 0.63 mg/mL or a 1:16 or lower dilution of the product.¹⁰ Moreover, in early periods of the outbreak, a first report on the in vitro efficacy of PVP-1 (1.0%, 1.5%, and 3% concentration) also demonstrated complete inactivation of SARS-CoV-2 without any cytotoxic effects.¹¹ In accordance with EN 14476 standards, a recent in vitro study¹²