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Research Article

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Real World Effectiveness of Benzydamine + Chlorhexidine on Sore Throat of COVID-19 Patients (Difflam-C® COVID-19)

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Abstract

Objective: *Severe acute respiratory syndrome coronavirus 2 caused a global pandemic with staggering speed. Various experimental drugs and non-pharmacologic interventions had been investigated to determine additional benefits for the management of COVID-19. This study explored the real-world effectiveness of benzydamine + chlorhexidine (Difflam-C®) solution in alleviating sore throat of Filipino patients, under condition of routine medical practice.*

Study Design: *Observational, uncontrolled study design*

Setting: *Ambulatory / out-patient health facilities*

Method: *This study included patients who were suspect, probable and confirmed to have COVID-19 who manifested with symptoms and signs of dysphagia / odynophagia. They were prescribed with benzydamine + chlorhexidine (Difflam-C®) solution as a supplement for the management of these conditions, regardless of RT-PCR and/or rapid antigen test result, in accordance with the respective local prescribing information and routine clinical practice.*

Results: *A decreasing trend can be observed in the median visual analogue scales (VAS) pain scores from baseline up to seven days. The difference from the baseline VAS score was significant in all observation period from day 1 to day 7 ($p<0.001$). The greatest difference was seen between days 4 and 5 (median VAS scores of 2 and 0, respectively). Almost all of the participants (95.9%) reported sore throat resolution at the end of the seventh day of observation. Majority did not experience adverse events and if so, were generally mild.*

Conclusion: *The benzydamine + chlorhexidine (Difflam-C®) gargle alleviated the signs of dysphagia and odynophagia among patients with suspected, probable and confirmed COVID-19 infection.*

Background

The novel coronavirus, SARS-CoV-2, first isolated in Wuhan City, in China last December 2019, caused a global pandemic with staggering speed. The situation in the Philippines also rapidly evolved, with a single case first identified last January 30, 2020, to over 3.6 million cases by February 2022 [1]. Initial cases in the Philippines were imported from China and other neighboring Asian countries. Eventually, sustained community transmission led to the implementation of intensified isolation and quarantine measures, as recommended by the Philippine Society for Microbiology and Infectious Diseases, as well as other interim guidelines regarding prevention and control [2].

Based on the latest 2022 epidemiological data from the World Health Organization (WHO), the Philippines continues to experience a surge in COVID-19 cases. Ongoing surveillance sees higher transmission in certain regions in the country with the rest of the Philippine archipelago remains with localized community transmission [3]. As of February 2022, there are more than 3.6 million confirmed COVID-19 cases and more than 56,000 deaths have been reported in the Philippines by the Department of Health (DOH) [4].

The clinical presentation of COVID-19 ranges from mild common cold-like illness to a severe viral pneumonia that may precipitate potentially fatal acute respiratory distress syndrome. According to the WHO, the most common symptoms of COVID-19 are fever, tiredness, and dry cough. Few patients experience generalized malaise with myalgia, nasal congestion, coryza, sore throat, or even diarrhea. Patients usually have mild symptoms, but may eventually present with more toxic manifestations, especially among those with existing comorbidities. Most patients recover without needing any special treatment [2]. The full vaccine coverage against COVID-19 in the Philippines has been reported at 56.74% [5]. Geriatric people and those with underlying medical conditions (e.g., hypertension, diabetes mellitus,

obesity, bronchial asthma, etc.), as well as the unvaccinated, are most likely to develop severe or critical forms of COVID-19. Breakthrough infections among the fully vaccinated have been documented by the US Centers for Disease Prevention and Control, especially among the delta variant infections [6].

Odynophagia is one of the most common otolaryngological dysfunctions of COVID-19 [7,8]. It can be caused by a variety of pathogens, but regardless of etiology, there is a need for symptom relief. Though odynophagia may be self-limiting and may resolve spontaneously in seven to ten days, patients often prefer to use medications to alleviate the throat discomfort [9].
Oral antiseptic solutions are among the identified interventions to decrease the viral load in the buccal cavity. The oral cavity is believed to play a pivotal role in the pathogenicity and transmission of SARS-CoV-2, the viral etiologic agent for COVID-19. It has been hypothesized that the identification of targeted anti-microbial mouth rinses to reduce salivary viral load can potentially contribute to lessening the burden of the COVID-19 pandemic. Because SARS-CoV-2 is an enveloped virus, many reagents target the outer lipid membrane of this obligate intracellular parasite. Moreover, some of them act on the viral capsid by denaturing proteins. To date, there has been no robust scientific evidence to recommend mouth rinse¬¬s with an anti-SARS-CoV-2 effect to control the viral load in the buccal cavity [10].

This real-world scenario observational, uncontrolled study determined the effectiveness of benzydamine + chlorhexidine (Difflam-C®) solution on alleviating throat pain of Filipino patients who were suspect, probable, or confirmed to have COVID-19 infection under condition of routine medical practice.

Methods

This study was conducted from November 2021 until February 2022, aligned with various guidelines and recommendations for good epidemiological practice for non-interventional studies and internationally accepted guidelines [13-17].

Patients eligible for participation in this study were adults (i.e., 18-59 years old), classified as suspect, probable, or confirmed COVID-19 cases, based on the Department of Health (DOH) Administrative Order [18]. Study subjects were excluded if they were hypersensitive to benzydamine or chlorhexidine; or if they used any other oral preparation, like povidone iodine, hexetidine, chlorine dioxide, carbenoxolone, dichlorobenzyl alcohol, amylmetacresol, hexylresorcinol, xylitol, cetylpyridinium for the past 48 hours prior to initiation of benzydamine + chlorhexidine (Difflam-C®) solution.

Partner physicians from several ambulatory / out-patient health facilities throughout the Philippines were tapped to recruit study subjects. As part of their routine medical care, the study subjects were prescribed with benzydamine + chlorhexidine (Difflam-C®) solution and were given for free as a supplement for the management of these conditions, in accordance with the respective local prescribing information and routine clinical practice.

There were 219 patients initiated with benzydamine + chlorhexidine (Difflam-C®) solution. Two (2) bottles of benzydamine + chlorhexidine (Difflam-C®) solution were provided for free upon consultation. No monetary compensation was given. Patients were followed up until the total resolution of the sore throat (i.e., odynophagia / dysphagia) or up to a maximum of seven (7) days. Development of adverse effects was monitored for a total duration of fourteen (14) days.

Patients consulted with their attending doctors, either through face-to-face appointments or through telemedicine sessions. Since this was an observational, uncontrolled study, there were no special protocol-mandated visits or procedures associated with the study. However, whenever applicable, evaluations documented in the case report form (CRF) were expected to be aligned with the local prescribing information recommendations and individual clinician practice.

The patients were instructed to gargle 15 ml of benzydamine + chlorhexidine (Difflam-C®) solution for 30 seconds to one (1) minute at 1.5 to 3.0 hours interval based on full product prescribing information. Duration of treatment should not exceed seven (7) days. Patients were asked to continue taking benzydamine + chlorhexidine (Difflam-C®) solution at least once a day for the subsequent second to seventh days. During the course of the study, patients were allowed to use other prescribed medications, except different mouth preparations, as deemed medically appropriate by their attending physician.

The primary endpoints were: (1) the decrease in pain from baseline visual analog scale (VAS) until the total resolution of odynophagia, possibly with no recurrence of throat symptoms, for a maximum of seven days; and (2) the time to total resolution of odynophagia after use benzydamine + chlorhexidine (Difflam-C®) solution with no recurrence of the odynophagia. Occurrence of adverse effects, including but not limited to hypersensitivity reactions, were recorded.

During the course of the study, a patient could discontinue his/her benzydamine + chlorhexidine (Difflam-C®) solution, if this patient was given another oral preparation. However, this patient would still remain in the study, and data were captured at the time of this change in treatment. For patients who voluntarily withdrew from the study for any reason at any time, their data would also be captured at the time of the withdrawal.

There were no mandatory visits in the context of this observational, uncontrolled study. However, physicians were encouraged to advise study subjects at least two follow-up periods (i.e., on day 7 and day 14 of the isolation / quarantine period). Follow-up consultation was done via face-to-face clinic visit or tele-medicine sessions.

Patient demographic profile and vital signs were collected on all patients, and these included age, sex, vaccination status, nature of work / profession and frequent use of voice at work. Data on relevant medical history / current medical conditions were also gathered. If possible, diagnoses (and not symptoms) were likewise recorded. The choice of treatment, as well as the decision to discontinue treatment, were at the sole discretion of the pre-

scribing physician and the patients, and were independent from participation in this study. Key selected adverse events (AE), their duration, intervention (if any), and time of resolution were also recorded.

Data were analyzed using Stata version 10 software. Quantitative variables were expressed as mean with standard deviation or the median (i.e., minimum and maximum), as appropriate. To determine differences in VAS scores between baseline and up to 7 days, Wilcoxon signed rank test was used with p-value <0.05 as cut off for significance.

Results

There were a total of 219 participants with mean age 37.1, SD ± 11.9 years, 64.8% of whom were females and 35.2% were males. Fifty percent (50%) were vaccinated with Sinovac, and almost 100% received the required doses for each vaccine type. Frequent use of voice was observed more among those with blue-collared work (80.0%), than white-collared jobs (15.5%) (Table 1).

Table 1: Demographic Profile of Subjects

Gender: n (%)	n = 219	Age in Years: (mean, SD)		37.1, 11.9
Male	77 (35.2%)	Female		142 (64.8%)
Vaccination Status				
Vaccine Type	With First Dose	With Second Dose		Total No. (%)
Sinovac	109	107		109 (49.8%)
Astra Zeneca Oxford	59	59		59 (26.9%)
Pfizer BioNTech	20	20		20 (9.1%)
Moderna	9	9		9 (4.1%)
Janssen	8	N/A		8 (3.7%)
Sputnik Gamaleya	2	N/A		2 (0.9%)
No Response		12		
Nature of Work				
Nature of Work	Does your job require frequent use of your voice?			
	Yes No. (%)	Yes No. (%)	No Response	Total
White-collared (i.e., businessman, lawyer, health professional, office employee, etc.)	110 (84.0%)	20 (15.3%)	1	131
Blue-collared (i.e., driver, construction worker, etc.)	30 (78.9%)	8 (21.1%)	0	38
Unemployed (i.e., retired, housewife, student, etc.)	3(7.5%)	3(7.5%)	34	40
No response			10	10

Heart rate, respiratory rate, blood pressure, temperature, and oxygen saturation were within normal in most of the participants; however, mild to moderate grade fever was noted in 23 participants. Hypertension, dyslipidemia, and diabetes mellitus ranked highest in terms of existing medical comorbidities, and most of the study subjects were allegedly compliant with their maintenance medications (Table 2).

Table 2: Clinical Profile of Study Subjects

Vital Signs	No. (%)		
Heart Rate (beats / minute)	Normal (60-100)	Tachycardic (> 100)	
	194 (97.5%)	5 (2.5%)	
Respiratory Rate (breaths / minute)	Normal (15-20)	Tachypneic (> 20)	
	152 (77.2%)	45 (22.8%)	
Systolic Blood Pressure (mmHg)	Normal (90-130)	Elevated (> 130)	
	177 (90.8%)	18 (9.2%)	
Diastolic Blood Pressure (mmHg)	Normal (60-100)	Elevated (> 100)	
	192 (98.5%)	3 (1.5%)	
Oxygen Saturation	> 95%	< 95%	
	173 (93.5%)	12 (6.5%)	
Temperature (oC)	Normal (< 37.6oC)	Low Grade Fever (37.6oC - 37.9oC)	Moderate to High Grade Fever (> 38.0oC)
	178 (88.6%)	9 (4.5%)	14 (7.0%)

Medical Co-Morbidities and Maintenance Medications					
	TotalNo. (%)	With Maintenance Medications		Compliance with Medications	
		Yes	No	Good	Poor
Hypertension	47 (21.5%)	31	16	30	
Dyslipidemia	16 (7.3%)	10	1	8	1
Diabetes Mellitus	13 (5.9%)	10	1	9	1
Allergic Rhinitis	15 (6.8%)	6	3	6	
Bronchial Asthma	11 (5.0%)	7	1	7	
Chronic Obstructive Pulmonary Disease	4 (1.8%)	2	1	1	1
Dyspepsia / Acid-Related Disorders	2 (0.9%)		2		
Rheumatic Heart Disease	2 (0.9%)		2		
Thyroid Pathology	2 (0.9%)	1	1	1	
Bipolar Disorder / Schizophrenia	1 (0.4%)	1		1	
Gastroesophageal Reflux Disease	1 (0.4%)		1		
HIV+ Infection	1 (0.4%)		1		
Chronic Kidney Disease	1 (0.4%)		1		
Cardiac Dysrhythmia	1 (0.4%)		1		
Coronary Artery Disease	1 (0.4%)		1		
Endometriosis	1 (0.4%)	1		1	
Pulmonary Tuberculosis	1 (0.4%)	1			

At specified time intervals, median VAS scores showed a decreasing trend from baseline to bedtime on day 1 and was significantly different from baseline values ($p<0.001$). There were two participants whose sore throat pain were relieved within 30 minutes of first use of the solution which persisted until bedtime (Table 3).

Table 3: VAS Scores at Baseline and at Different Timepoints on Day 1

Time	VAS scores		p-value*
	Median	min, max	
Baseline	5	1, 10	
After 30 min	5	0, 10	<0.001
After 60 min	4	0, 9	<0.001
After 6 hours	4	0, 9	<0.001
After 12 hours	3	0, 9	<0.001
At bedtime	3	0, 9	<0.001

*Wilcoxon signed-rank test

A decreasing trend was observed in the median VAS scores from baseline up to seven days. The difference from the baseline VAS score was significant in all observation days, from day 1 to day 7 ($p<0.001$). The greatest difference was seen between days 4 and 5. Likewise, a decreasing trend can be observed in the frequency of use of the study solution from day 1 to day 7, and the difference was significant in comparison with day 1 ($p=0.004$ and $p<0.001$) (Table 4).

Table 4: VAS Scores at Baseline and Up to Day 7, as well as Frequency of Use of Difflam-C® from Day 1 to Day 7

Time	VAS scores		p-value*	Frequency of Use		p-value*
	Median	min, max		Median	Median	
Day 0 (Baseline)	5.0	1, 10	4		4	
Day 1	3.0	0, 9	4	0.004	4	0.004
Day 2	3.0	0, 9	3	<0.001	3	<0.001
Day 3	2.0	0, 8	3	<0.001	3	<0.001
Day 4	2.0	0, 6	3	<0.001	3	<0.001
Day 5	0	0, 8	3	<0.001	3	<0.001
Day 6	0	0, 6	2	<0.001	2	<0.001
Day 7	0	0, 4	4	<0.001	4	<0.001

*Wilcoxon signed-rank test

The proportion of those whose sore throat resolved was highest after five days of treatment (24.2%). Nine participants (4.1%) had recurrence of symptoms despite treatment (Table 5).

Table 5: Number of Days to Resolution of Sore Throat and Treatment Failure

Number of Days	No. (%)
< 1	8 (3.7%)
1	10 (4.6%)
2	24 (11.0%)
3	28 (12.8%)
4	30 (13.7%)
5	53 (24.2%)
6	33 (15.1%)
7	16 (7.3%)
>7	17 (7.8%)
Treatment Failure	9 (4.1%)

Majority did not experience adverse events. For those who experienced adverse events, they were mostly mild and spontaneously resolved within the study period. No intervention was made, and no hospitalization was warranted (Table 6). None of those who experienced adverse reactions discontinued use of the study solution. In this study, there were no drop-outs. None of the study subjects was shifted to a different oral gargle regimen.

Table 6: Frequency of Adverse Events

Adverse Events	Severity: No. (%)			
	None	Mild	Moderate	Severe
Taste Disturbance	139 (64%)	60 (27%)	18 (8%)	2 (1%)
Mucosal Numbness	134 (61%)	56 (26%)	27 (12%)	2 (1%)
Oral Burning Sensation	175 (80%)	35 (16%)	9 (4%)	0 (0)
Food After taste	183 (84%)	28 (13%)	7 (3%)	1 (0.5%)
Thirst	193 (88%)	13 (6%)	12 (6%)	1 (0.5%)
Dry Mouth	185 (84%)	8 (4%)	24 (11%)	2 (1%)
Nausea	207 (95%)	8 (4%)	3 (1%)	1 (0.5%)
Dyspepsia	209 (96%)	10 (4%)	0 (0)	0 (0)
Vomiting	210 (96%)	7 (3%)	1 (0.5%)	1 (0.5%)

Discussion

The period of study subject recruitment coincided with the surge of the COVID-19 omicron variant in the Philippines. Epidemiologic studies had shown that the omicron variant, though more transmissible in behavior, often presented with less severe upper respiratory tract infection symptoms, and would typically include odynophagia and/or dysphagia, with or without fever [16]. This appeared to be consistent with the collected data, since only 11.5% of the study subjects developed febrile episodes, but all experienced throat irritation. However, genetic sequencing was never performed for all RT-PCR confirmed COVID-19 patients, so it could only be assumed that majority of these study subjects

were infected with the omicron variant, based on the clinical manifestations self-reported by the study subjects.

In addition, the study focused primarily on the ambulatory out-patient clinics. All study subjects only required supportive medical management, including prescription with benzydamine + chlorhexidine (Difflam-C®) solution. Likewise, geriatric patients were also not included in this study, for this population was at a higher risk for developing severe forms of COVID-19 infection, due to the presence of complicated forms of comorbidities, which could potentially influence the prognosis of the COVID-19 infection [18].

In addition, since 95% of the study subjects were fully vaccinated already, this could have influenced the degree of severity of the COVID-19 infection. To date, more than 120 million doses of COVID-19 vaccines had been administered already, while roughly 8 million booster shots had been given during the DOH vaccination roll-out drive [19].

Though the presence of comorbidities was not evaluated on its potential impact on the severity of the COVID-19 infection among the study subjects, it was notable that hypertension, dyslipidemia, and diabetes mellitus ranked highest in this cohort of patients. These non-communicable diseases had been frequently observed among COVID-19 patients, and the link between severe COVID-19 infection and presence of such medical comorbidities had been established already [16, 20].

Supportive care and intensive respiratory management remain the standard of care for COVID-19. Supportive care includes the use of antipyretics for fever, oral fluids for hydration, and strict isolation at home or in temporary treatment and monitoring facilities. Nonetheless, from a clinical perspective, prescribing an agent to address the throat discomfort could be viewed as beneficial for patients suffering from COVID-19 infection [21].

The baseline median VAS of our participants was 5, a value similar to that of the pain severity seen in a world-wide survey involving the Philippines, ranging between 1-6 (63%). Similarly, data on sore throat severity from the other 12 countries (i.e., Australia, Brazil, China, France, Germany, Italy, Russia, Saudi Arabia, South Africa, Thailand, the UK and the USA) revealed comparable results [21].

However, with the use of the study solution by the study subjects, there was a noticeable shortening of the course of the sore throat. Current data showed resolution of the throat irritation by day 5, compared to 7-10 days when no active medical intervention was prescribed [9]. Thus, Difflam-C® oral solution could be viewed as a promising remedy for patients with odynophagia, even among those with possible COVID-19 infection.

Benzydamine is an anti-inflammatory agent which is widely available and used for the treatment of several buccal cavity conditions. After topical administration, benzydamine is absorbed and retained transdermally, thereby, becoming concentrated in inflamed tissue. Although benzydamine is classified as a non-steroidal anti-inflammatory drug (NSAID), it has a different chemical structure to other NSAIDs. In contrast, its anti-inflammatory activity is considered a result of reducing the cell response to injury by preventing the synthesis of TNF- , preventing the oxidative burst of neutrophils and respiratory burst of monocytes, and stabilizing the membranes of neutrophils, erythrocytes, and liposomes [11, 22].

Aside from its anti-inflammatory property, benzydamine also has local anesthetic activity. This is an important attribute as pain is often associated with inflammation. The therapeutic indications for benzydamine are: (1) sore throat, (2) post-tonsillectomy and post-operative sore throat, (3) aphthous stomatitis/mucositis post-chemoradiotherapy, and (4) gingivitis and dental surgery pain [11, 22]. The aims of treatment are to reduce pain and inflammatory signs of swelling (i.e., erythema and edema), to improve dysphagia and to alleviate ear ache [11, 22]. In addition, it has been purported to also have anti-viral activity, and this cellular property is proportional to its concentration [23-26].

On the other hand, chlorhexidine is a cationic bisbiguanide used in general medical practice as a broad-spectrum antiseptic. Chlorhexidine is known to have anti-viral activity and is effective against lipid-enveloped viruses but not against non-enveloped viruses. Thus, a recent review recognizes its use in reducing the risk of spreading SARS-CoV-2 through aerosols, although its action against this virus remains controversial [10, 23].

In a recent study, the salivary load of SARS-CoV-2 was evaluated before gargling with chlorhexidine, and after one, two, and four hours. A transient decrease in the viral load was observed for two (2) hours post-gargling, but it increased again after that. The main limitations of this study were the small number of subjects and the absence of controls (i.e., gargling with saline). Thus, if the results may be corroborated by other clinical trials, chlorhexidine oral antiseptic may potentially help prevent the spread of SARS-CoV-2 [10, 23-27].

Despite the potential benefit derived from the use of Difflam-C® oral solution, nine study subjects reported that their sore throat did not completely resolve even after seven days of regular gargling with benzydamine + chlorhexidine (i.e., median 2, range from 1-4). Technically, this could be explained by two possibilities. First, on top of viral etiologies, other potential causative agents (i.e., bacterial species) could also aggravate the odynophagia, especially among those with mixed type of infection of acute tonsillopharyngitis, thereby precipitating longer episodes of sore throat, possibly even beyond ten days. Second, persistence of symptoms could be explained possibly by the long COVID-19 syndrome. Health experts now recognize the post-COVID syndrome or the long COVID-19 syndrome. Though the exact mechanisms for this pathology have not yet been fully elucidated, it has been documented that a small proportion of COVID-19 patients may experience symptoms for protracted periods, or even possibly have recurrence of other clinical manifestations (i.e., sore throat) despite being labeled as "COVID-19, recovered." Post-COVID conditions are a wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19. These conditions can present as different

types and combinations of health problems for varying lengths of time [28].

The most common adverse effect experienced by the participants in this study was mucosal numbness, as this was expected with the use of benzydamine [7]. The second most common was burning sensation in the buccal area [24]. In this study, these adverse events were not too troublesome for the study subjects to discontinue usage, and the reported adverse events spontaneously resolved, without requiring any additional intervention [21]. The taste alteration was believed to be secondary to chlorhexidine [23, 27].

Conclusion

Among adult patients presenting with odynophagia given benzydamine + chlorhexidine (Difflam-C®) oral solution, 96% of them experienced complete relief of throat pain at the end of seven days of treatment. In addition, Difflam-C® shortened the duration of sore throat to just five days, as seen in majority of the study subjects (69.86%).

Limitations

The nature of the medical consultation (i.e., face-to-face vs. tele-consult) curtailed thorough physical examination of the buccal cavity and respiratory tract. More so, given the public health burden of COVID-19 in the country, on top of the popularity of other over-the-counter medications as COVID-19 therapy, it would be difficult to ascertain the effectiveness of a monotherapy regimen, like that of benzydamine + chlorhexidine (Difflam-C®) gargle, in addressing the sore throat pain of the study subjects.

This is a real world effectiveness study, and all well-known limitations of such an epidemiologic design may be evident. Nonetheless, this study has provided local data on primary care management of COVID-19 odynophagia.

Data Availability Statement

The data used to support the results of this study are available from the corresponding author upon reasonable request.

Competing Interests

R. S. is employed with iNova. J.N and R.J. have received consultancy honoraria from iNova.

Authors' Contributions

J. N., R. J. , and R. S. - all the authors, conceptualized the study, acquired and analyzed data, drafted and revise the paper, and approved the version to be published.

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References

1. Coronavirus, N. (2020). Cases, provided by JHU CSSE. Reference Source.
2. Department of Health. Interim Guidance on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection Version 3.1, Department of Health Memorandum No. 2020-0381; July 2020.
3. WHO. (2021). COVID-19 in the Philippines Situation Report 84 [Internet]. World Health Organization Philippines.
4. Department of Health. (2021). COVID-19 Tracker. Philippine Department of Health.
5. Live COVID-19 Vaccination Tracker [Internet] Feb 2022.
6. US Centers for Disease Prevention and Control. (2021). Delta Variant: What we need to know about the science [Internet].
7. Krajewska, J., Krajewski, W., Zub, K., & Zatoński, T. (2020). COVID-19 in otolaryngologist practice: a review of current knowledge. European Archives of Oto-Rhino-Laryngology, 277(7), 1885-1897.
8. El-Anwar, M. W., Elzayat, S., & Fouad, Y. A. (2020). ENT manifestation in COVID-19 patients. Auris Nasus Larynx, 47(4), 559-564.
9. Wolford RW, Goyal A, Belgam Syed SY, and Schaefer TJ. Pharyngitis. (2021). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
10. Carrouel, F., Gonçalves, L. S., Conte, M. P., Campus, G., Fisher, J., Fraticelli, L., ... & Bourgeois, D. (2021). Antiviral activity of reagents in mouth rinses against SARS-CoV-2. Journal of dental research, 100(2), 124-132.
11. Almazan N. (2010). Benzydamine HCl 0.15% for Oropharyngeal Diseases and Surgeries: A Review of Clinical Trials: Semantic Scholar [Internet]. Semantics Scholar. Philippine Scientific Journal, 42.
12. Lebedeva, V. V., Fedyakina, I. T., Latyshev, O. E., Burtseva, E. I., Kukes, I. V., Blinov, D. V., ... & Grebennikova, T. V. (2021). Antiviral activity of benzydamine hydrochloride against SARS-CoV-2 in vitro model. Epidemiologiya i Vaktsinoprofilaktika, 83-90.
13. The Rules Governing Medicinal Products in the European Union. Guidelines on Pharmacovigilance for Medicinal Products for Human Use. 2008.
14. Annual Report of the European Medicines Agency [Internet]. 2005.
15. Guidelines for Good Pharmacoepidemiology Practices (GPP) [Internet]. International Society for Pharmacoepidemiology. 2008 [cited 2022].
16. Yawson, A. E., Oduro-Mensah, E., Tetteh, J., Adomako, I., Adjei-Mensah, E., Owoo, C., & Lartey, M. (2020). Clinical features of COVID-19 in Ghana: symptomatology, illness severity and comorbid non-communicable diseases. Ghana Medical Journal, 54(4s), 23-32.
17. Dixon, J. R. (1999). The international conference on harmonization good clinical practice guideline. Quality Assurance, 6(2), 65-74.
18. Further Amendment to Administrative Order No. 2020-0013, "Revised Administrative Order No. 2020-0012, 'Guidelines for the Implementation for the Inclusion of the COVID-19 in the List of Notifiable Diseases for the Mandatory Reporting to the Department of Health' Dated March 17, 2020." Department of Health, April 2020.
19. National COVID-19 Vaccination Dashboard. Department of Health website [Internet]. doh.gov.ph. 2012 [cited 2022 Feb 26].
20. Barek, M. A., Aziz, M. A., & Islam, M. S. (2020). Impact of

age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: a meta-analysis with 55 studies and 10014 cases. Heliyon, 6(12), e05684.
21. Van der Velden AW, Sessa A, Altiner A, Pignatari ACC, and Shephard A. (2020). Patients with Sore Throat: A Survey of Self-Management and Healthcare-Seeking Behavior in 13 Countries Worldwide. Pragmatic and Observational Research, 11, 91-102.
22. Fedorowicz, Z., Al-Muharraqi, M. A., Nasser, M., & Al-Harthy, N. (2010). Oral rinses, mouthwashes and sprays for improving recovery following tonsillectomy. Cochrane Database of Systematic Reviews, (1).
23. Lovato, A., & De Filippis, C. (2020). Clinical presentation of COVID-19: a systematic review focusing on upper airway symptoms. Ear, Nose & Throat Journal, 99(9), 569-576.
24. Chen, M. H., & Chang, P. C. (2021). The effectiveness of mouthwash against SARS-CoV-2 infection: A review of scientific and clinical evidence. Journal of the Formosan Medical Association.
25. Reis, I. N. R., do Amaral, G. C. L. S., Mendoza, A. A. H., das Graças, Y. T., Mendes-Correa, M. C., Romito, G. A., & Pannuti, C. M. (2021). Can preprocedural mouthrinses reduce SARS-CoV-2 load in dental aerosols?. Medical Hypotheses, 146, 110436.
26. Testori, T., Wang, H., Basso, M., Bordini, G., Dian, A., Vitelli, C., & Del Fabbro, M. (2020). COVID-19 and Oral Surgery: A narrative review of preoperative mouth rinses.
27. Richards, D. (2017). Chlorhexidine mouthwash plaque levels and gingival health. Evidence-based dentistry, 18(2), 37-38.
28. Center for Disease Control [Internet] cited 2022 February 24.