International Journal of Oral Health Dentistry 2021;7(3):155–160

Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Oral Health Dentistry

Journal homepage: www.ijohd.org

Review Article

COVID-19 An update on oral symptoms, newer variants, second wave and vaccination drive in India — A Review

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ARTICLE INFO

Article history:
Received 01-07-2021
Accepted 06-08-2021
Available online 24-09-2021

Keywords:
Corona virus
Covid Tongue
Dyguesia
Vaccines

ABSTRACT

A serious threat to world now is the emergence of COVID-19 (Corona Virus Diseases-2019). When compared to its precursor virus, SARS (Severe acute respiratory syndrome – now called as SARS-CoV-1) and MERS (Middle East respiratory syndrome), this virus spreads more rapidly. The emergence of this virus happened in december 2019 in Wuhan. World Health Organisation announced this virus outbreak as a pandemic on March 20th 2020. The current threat to the world is the emergence of second wave of COVID -19 that has shaken many countries in world and its peak in India was in the month of may 2021 which had drastically affected the country. Hence this review gives a comprehensive update on corona virus and its newer oral symptoms and about treatment approaches and vaccines currently available in India.

1. Introduction

The disease caused by corona virus has been termed as COVID-19 (Corona Virus disease -2019) and is a new virus that has not been previously identified in humans.[1] Following the first wave, due to its rapid spread and numerous mutant strains that are developing, the second wave has totally wobbled many countries in the world and India had faced tragedy of second wave were the single day spike of COVID -19 case was above 3.5 – 4 lakhs. There has been a change in pattern of signs and symptoms and a variation in range of the affected age groups due to the development of newer strains of the virus. Apart from restrictions of gatherings and personal protective aids, researchers are now focussing on mass immunisation programs by vaccination.[2,3]

1.1. Mechanism of corona virus entry into human cell

Corona viruses are spherical enveloped particles containing single-stranded RNA with a nucleoprotein present within a capsid consisting of matrix protein. The envelope has club-shaped glycoprotein surface projections.[4] The genome of corona virus encodes five structural proteins such as, Spike protien, Membrane protein, Nucleocapsid protein, Hemagglutinin esterase (HE), and Small envelope protein.[5,6] Several mutations have been occurring in corona virus especially in its spike protein, that has resulted in numerous variants arousal in different parts of the world (Table 1, 2). Now a striking threat to the world is arousal of "Delta plus" variant.[7,8]

The entry of corona virus in the host cell is mediated by spike proteins. Corona viruses mostly recognize amino-peptidases or carbohydrates as an important receptor for entering into human cells. The spike protein contains a 3-dimensional structure in the receptor binding region to maintain the vander Waals forces. The 394 glutamine

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https://doi.org/10.18231/j.ijohd.2021.032

residues in the receptor binding region of SARS-CoV-2 is recognized by the lysine 31 residue on the human angiotensin converting enzyme receptor (ACE 2). This interaction between the virus and ACE receptor on human cell facilitate the virus to enter into the host cell.[9]

1.2. The outbreak and symptoms of COVID-19

The outbreak of novel corona virus and second wave hit is rapidly alarmed the world and resulted in a global health emergency. India experienced massive second wave of COVID -19 which was threatening the entire nation. This disease mainly affects the lung's efficiency to exchange oxygen and resulting in difficulty to breathe. Patients infected with SARS-CoV-2 have mainly shown pneumonia like symptoms that include fever, cough, shortness of breath, sputum production and myalgia or fatigue, indicating that corona virus affects the respiratory tract and causes acute respiratory disease. Apart from the respiratory symptoms, patients have developed other symptoms which appears within 2 to 14 days after exposure to the virus.[10,11]

1. Gastrointestinal[10,11] — Diarrhea, poor appetite, nausea, vomiting
2. Central nervous system[10,11] — Headache and confusion
3. Cardio vascular system[10,11] — Palmus, chest distress
4. Other symptoms[10,11] — Loss of smell and taste
5. Oral Symptoms — loss of taste and COVID tongue (Table 3)

1.3. Preventive measures and treament modalities in india

Routes of transmission of corona virus includes, Direct transmission (through cough, sneeze, or droplet inhalation), Contact transmission (through oro-nasal-ocular route) and Aerosol transmission. Following the outbreak of second wave Centers for Disease Control and Prevention (CDC) has updated its guidelines for the use of masks.[12]

1. **Doubling your mask**[12,13] — wearing a cloth mask over a surgical mask provides more protection.
2. **Knotting the ear loops**[12,13] — Knotting the ends of the ear loops is another way to ensure that the mask covers your mouth and nose completely and thus reducing the exposure by more than 95 per cent
3. **Using mask fitter**[12,13]- to improve the fitting of the mask, use a mask fitter or nylon covering over the mask is recommended and this will also prevent from inhaling the aerosol particles.
4. CDC does not recommend the use of N95 respirators for protection against COVID-19 in non-healthcare settings. N95 (filter up to 95% of particles in the air) respirators should be prioritized for healthcare personnel.[12,13]

2. Vaccination Drive in India

Government of India ensure to take all necessary steps to face the challenge and threat posed by COVID-19. At present, the priority of the government is to make COVID -19 vaccine available to all. COVID-19 vaccination drive has been initiated to cover healthcare and frontline workers from January 16^{th} 2021, for citizens — above 60 years of age from March 1^{st} 2021, above 45 years of age from April 1^{st} 2021, above 18 years of age from May 1^{st} 2021.

Co-WIN application is the digital platform for the vaccination drive in India. The CO-WIN application will help the citizen with an option to register and schedule the vaccination session online in centers of their choice. Covishield and Covaxin received first Emergency use Authorisation by National Regulator on January 16^{th} 2021. Vaccination drive to be expanded with Sputnik V, Pfizer and Moderna in India in upcoming days.[21]

2.1. Covaxin (BBV152)[22,23]

2.1.1. Development

By Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) — National Institute of Virology (NIV).

2.1.2. Technology

Inactivated vaccine developed using *Whole-Virion Inactivated Vero Cell.* Advantage of inactivated vaccines is that they do not replicate and are therefore unlikely to revert and cause pathological effects. They contain dead virus, incapable of infecting people but still able to trigger the immune response. Covaxin is able to induce both Th1 T-cell responses and humoral response in the host.

2.1.3. Special features

COVAXIN has immune-potentiators, also known as vaccine adjuvants – Algel – IMDG (Chemosorbed imidazoquinoline onto the aluminium hydroxide gel) that boost immunogenicity.

2.1.4. Dosage

Vaccine given in two doses, 4 to 6 weeks apart (28 to 48 days)

2.1.5. Storage temperature

2 to 8 degree Celcius.

2.1.6. Efficacy

Covaxin demonstrated efficacy of 81 percent in Phase 3 clinical trials**.** Effective against united kingdom, Brazil and Indian variants of corona virus.

Table 1: Corona virus variants reported in the different parts of the world

S.no	Corona virus variants	First reported country
1.	B.1.1.7 (Alpha)	United Kingdom, UK variant
2.	P.1 (Gamma)	Japan and Brazil
3.	P.2	Brazil
4.	B.1.351 (Beta)	South Africa
5.	B.1.427	United States (California)
6.	B.1.429	United States-(California)
7.	B.1.1.7 + B.1.429 (US-UK variant)	United States-(California)
8.	B.1.525	United kingdom
9.	B.1.617	India (double mutant)
10.	B.1.617.2 (Delta),	Delta variant - India
11.	B.1.617.2.1	Delta plus variant - Europe

Table 2: Significant key features of corona virus variants

S.no	Variants	Features
1.	B.1.1.7 B.1.427 B.1.1.7 + B.1.429 (US-UK variant)	Increased transmissibility rate
2.	P.1 B.1.351 B.1.427 B.1.429	Decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment.
3.	P.2	Escape the antibodies for other variants
4.	B.1.617 B.1.525	Evade host immune responses
5.	B.1.1.7 + B.1.429 (US-UK variant) B.1.429	Escape antibodies which is produced post vaccination.
6.	B.1.617.2	40-60% more contagious or transmissible than the Alpha variant (U.K./B.1.1.7)
7.	B.1.617.2.1	Evading immunity that people developed from vaccination well as natural immunity after recovering from COVID

Table 3: Oral manifestations of COVID -19

Oral manifestations	Pathophysiology
Loss of taste [14–16]	ACE2 is expressed in human oral tissues, especially enriched in dorsal tongue. SARS-CoV-2 would cause direct damage to ACE2-expressing cells of taste buds during the cellular entering process, resulting in gustatory dysfunction. Patients presented a prevalence of 45% for taste disorders, 38% for dysgeusia, 35% for hypogeusia, and 24% for ageusia. Zinc deficiency is considered as one of causative factors for gustatory dysfunction associated with COVID-19. A decreased zinc level favours the interaction of zinc-dependent metalloenzyme ACE2 with spike proteins of SARS-CoV-2 but an increased zinc level inhibits ACE2 expression.
Hyposalivation – reduced secretion of saliva [15]	Human salivary glands express ACE2 and TMPRSS2, salivary gland infection with SARS-CoV-2 affects saliva secretion, thereby disrupting the taste sensation.
Sialadenitis and Xerostomia [8]	SARS-CoV-2 could cause acute sialadenitis by binding to ACE2 receptors in the epithelia of salivary glands, resulting cell lysis. Zinc deficiency also an added factor for sialadenitis The SARS-CoV-2 enters the peripheral nervous system (supplying the salivary gland) and damage it during their neuroinvasion, affecting the function of salivary glands. Viral invasion by trans-synaptic pathway.
Mucosal lesions [17,18]	Reports shows COVID-19 patients developed ulcers on hard palate, tongue and buccal mucosa, erosions of lips and buccal mucosa. The most common site of lesions is tongue (38%), followed by labial mucosa (26%) and palate (22%). Hyper-inflammatory response secondary to the viral infection are linked to oral mucosal lesions associated with COVID-19. Expression of higher inflammatory cytokines IL-6 may contribute to mucosal lesions.
COVID tongue 18 - Association between geographic tongue (GT) and SARS-CoV-2 infection	Presents with irregular areas of depapillation on the dorsal surface of the tongue. Few literatures shows evidence suggesting that Geographic tongue might be associated with elevated levels of the infammatory cytokine interleukin-6 (IL-6). This is the cytokine that is upregulated in severe COVID-19 disease.
Periodontal Diseases [19,20]	ACE 2 and furin are expressed in sulcular and periodontal pocket epithelium which aid in viral invasion. Therefore, SARS-CoV-2 infects these epithelial cells resulting in periodontal diseases. Literature shows Prevotella intermedia is frequently detected in COVID-19 patients, SARS-CoV-2 could predispose individuals to a periodontal disease through bacterial co-infection by Prevotella intermedia.

2.1.7. Side effects

Pain at the injection site, Headache, fatigue and fever. No severe or life-threatening (i.e grade 4 and 5) adverse events were reported**.**

2.2. Covishield[24,25]

2 to 8 degree celcius

2.2.1. Development

developed by Oxford University in collaboration with AstraZeneca and manufactured in India by Pune's Serum Institute of India.

2.2.2. Technology

ChAdOx1 nCoV-19 vaccine (AZD1222) is a chimpanzee adenoviral vectored vaccine with full length SARS-CoV-2 spike insert. A viral vector vaccine uses a harmless version of a different virus, called a "vector," to deliver information to the body that helps it protect and trigger the immune response.

2.2.3. Special features

Vector technology, previously the same technology used for preparation of vaccine for EBOLA virus, other incredients in covishield are L-Histidine, L-Histidine hydrochloride monohydrate, Magnesium chloride hexahydrate, Polysorbate 80, Ethanol, Sucrose, Sodium chloride, Disodium edetate dihydrate (EDTA) and Water.

2.2.4. Dosage

Two doses**,** 6 to 8 weeks (42 to 56 days).

2.2.5. Storage temperature

To 8 degree Celcius

2.2.6. Efficacy

Trial shows when doses were given one month apart, efficacy was 60-70 percent. Another trial shows when two doses given 2-3 months apart, efficacy was 90 per cent.

2.2.7. Side effects

Pain or tenderness at the injection site, Headache, Tiredness, Muscle or joint aches, Fever, Chills, Nausea, enlarged lymph nodes, excessive sweating, itchy skin or rash.

2.3. Sputnik V[26]

2.3.1. Development

developed by Gamaleya Research Institute and the Russian defence ministry partnered with Dr Reddy's in September 2020 to conduct clinical trials of Sputnik V in India.

2.3.2. Technology

Two-dose adenoviral vector vaccine using two different adenoviruses for each dose.

2.3.3. Special feature

A vector vaccine based on adenovirus DNA (adenovirus serotypes 5 and 26 are used), in which the SARS-CoV-2 coronavirus gene is integrated. Adenovirus is used as a "container" to deliver the coronavirus gene (the antigen insert is an unmodified full-length S-protein) to cells and start the synthesis of the new coronavirus's envelope proteins triggering the immune system.

2.3.4. Dosage

Days to three months

2.3.5. Storage temperature

2-8 degree Celcius.

2.3.6. Efficacy

Clinical trials reported 91.6% efficacy rate.

2.3.7. Side effects

Slight body temperature rise and pain around the injection site.

2.4. Pfizer (BNT162b2)[27]

-73 degree celcius

2.4.1. Development

By Pfizer and BioNTech

2.4.2. Technology

mRNA vaccine, consist of genetic information (spike protein) from the virus in the form of messenger RNA.

2.4.3. Special feature

Uses lipid nanoparticles that encase the RNA, protect it and helps it to slide inside the cell. Active incredients are nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2, lipids, salts and sucrose.

2.4.4. Dosage

Two doses, 21 days apart.

2.4.5. Storage temperature:

Degree celcius

2.4.6. Efficacy

Phase 3 trial of the BNT162b2 vaccine showed 95% efficacy

2.4.7. Side effects

Pain at injection-site, headache, fatigue.

3. Drugs Used For COVID -19 in India

3.1. Remdesivir

Remdesivir recommended candidate for the treatment of Covid-19. Remdesivir formerly known as GS-5734, is a monophosphoramidate prodrug of an adenosine analog that was developed in response to the Ebola virus outbreak in West Africa in 2014. Mechanism of action is a viral RNA-dependent RNA polymerase (RdRp) inhibitor, targeting the viral genome replication process thus halting the replication of virus.[28,29]

Baricitinib is an oral selective inhibitor of Janus kinase (JAK) 1 and JAK 2 (used to treat moderate to severe active rheumatoid arthritis) is now recommended for COVID-19 treatment because of its inhibitory effect on SARS-CoV-2 endocytosis and on the intracellular signaling pathway of cytokines that is responsible for the hyperinflammatory state that results in severe illness. Remdesivir in combination with baricitinib has been granted a Emergency Use Authorization by the FDA for clinical use in adult and pediatric patients two years of age or older hospitalized with COVID-19 requiring supplemental oxygen (SpO2</= 94%).[30,31]

3.2. Virafin

Virafin, the antiviral drug by Zydus Cadila, has received emergency use authorization by the Drugs Controller General of India (DCGI) for treatment of moderate cases of COVID-19. It was originally used for treating Hepatitis C virus infection.Virafin is Pegylated Interferon alpha - 2b can be used in moderate cases of COVID-19, studies reported its use reduced the need for supplemental oxygen therapy, thus preventing severe respiratory distress and failure.[32–34]

4. Conclusion

Corona virus has massively striked the entire world and various clinical studies has reported arousal of newer symptoms, of which oral symptoms also plays important role in identification of the diseases. Dentist should take the responsibility to screen and identify the oral symptoms of COVID- 19, that is likely occur as co-infection or secondary manifestation of COVID-19. India is now in serious thrive to come out of this second wave of COVID-19. Health care professionals are working hard to bring back the nation to a normal pace. Government of India is taking necessary steps to vaccinate each and every citizen of India.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Jayakumar S, Srinivas Vineetha C, Meera John B, Arumugam K, Sridhar D. COVID-19 An update on oral symptoms, newer variants, second wave and vaccination drive in India — A Review. *Int J Oral Health Dent* 2021;7(3):155-160.