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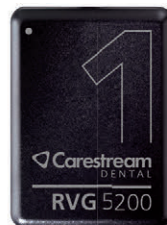
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# COVID-19 risk management in dental practice

## Part 2: The infection chain pathway of SARS-CoV-2

Johan Hartshorne<sup>1</sup> and Andre van Zyl<sup>2</sup>

**Keywords:** aerobiology, aerosols, airborne, droplets, coronavirus, co-morbidities, COVID-19, SARS-CoV-2, dentistry, risk management, reservoir, transmission, infection chain, susceptible host

### Executive Summary

#### Rationale

Understanding the coronavirus (SARS-CoV-2) and its pathways from its reservoir to host can help us understand how to fight the virus, and is critical in developing effective and sustainable infection prevention and control measures.

#### Key points

##### The pathogen – SARS-CoV-2

- SARS-CoV-2 is the most contagious of all the respiratory viral infections.
- The main sources of SARS-CoV-2 are asymptomatic, pre-symptomatic, symptomatic COVID-19 individuals in the population.
- SARS-CoV-2 transmission from asymptomatic and pre-symptomatic hosts are a fundamental fault line in the spread of COVID-19 because we do not know who they are.
- The average incubation period (infectious period) is 6.4 days (range 2-24 days)
- SARS-CoV-2 is very stable at room temperature, wide range of pH and on smooth surfaces (including glass, plastic, and stainless steel).
- SARS-CoV-2 is stable on stainless steel and plastic for up to 9 days.
- Detectable levels of infectious virus is still present on the outer layer of a surgical mask at 7 days.
- SARS-CoV-2 is very susceptible to standard disinfection materials, including 70% ethanol, household bleach and 7.5% povidone-iodine.

#### Reservoir

- SARS-CoV-2 infectious cycle can start in the lungs, naso-pharynx, oral mucosa, tongue and salivary glands.
- During the first 10 days of incubation the virus mainly accumulates in the pharyngeal, oral and nasal areas.
- SARS-CoV-2 is consistently detected in saliva.

#### Portal of exit (leaving the host reservoir)

- Individuals with infection produce respiratory droplets or aerosol particles from breathing, talking, singing, coughing and sneezing

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- Common exit portals for SARS-CoV-2 are the mouth, nose, respiratory tract and faecal route.

### Mode of transmission

- Transmission of SARS-CoV-2 can occur from asymptomatic and symptomatic individuals.
- SARS-CoV-2 is mainly transmitted through close physical contact and respiratory droplets.
- Airborne transmission is possible during aerosol generating procedures.
- Large droplets (>5 µm) settle faster due to gravity, thus contaminating surrounding surfaces.
- Smaller droplets (<5 µm) evaporate faster forming droplet nuclei that can stay airborne for hours.
- Aerosolized viral droplet nuclei particles can travel great distances and remain airborne and viable for up to 3 hours and can infect dental health care workers, patients and contaminate surfaces.

### Portal of entry and replication

- Portal of entry is through mouth, nose, respiratory tract.
- SARS-CoV-2 S-spike protein invades host target cells by using ACE2 as its receptor.

### Susceptible host and disease pathogenicity

- Infected hosts can present with clinically inapparent (asymptomatic) or mild (80%), moderate severe (14%) or critical illness requiring hospitalization (6%).
- Individuals with co-morbidities presented with increased COVID-19 severity and higher case fatality rates.
- Hypertension and hyperlipidaemia were the most frequent co-morbidities.
- Elderly and immune-compromised individuals are most vulnerable
- Individuals with periodontitis may be linked to more severe COVID-19

### Practice implications

- The disturbing reality is that we have no idea who among us is spreading the disease.
- Early recognition of an infected person (source of infection) and cutting off the route of transmission are key points to control COVID-19.
- A decrease in the oral viral load would diminish the amount of virus expelled and reduce the risk of transmission.
- Pre-procedural mouth rinse is a critical prophylactic measure for reducing oral viral load and risk of spreading SARS-CoV-2.
- The weight of combined evidence supports airborne

precautions for occupational health and safety of health workers treating asymptomatic or suspected patients with COVID-19.

- Ventilation is of critical importance to control airborne transmission of SARS-CoV-2

### Introduction

The global outbreak of coronavirus disease (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is the most contagious of all the viral respiratory pandemics (Part 1 – Table 1) and spreading fast with an increasing number of infected patients world-wide. The current global statistics on February 22, 2021 (11:39 GMT), show the total number of confirmed cases 112,026,236, total deaths 2,479,303 and total recovered /discharged 87,392,155 individuals. Current global active infected cases 22,154,178 (19,8%) of which 22,060,880 (99,6%) have a mild condition and 93,898 (0.4%) are serious / critical.<sup>1</sup> The COVID-19 statistics for South Africa on February 22, 2021 showed a total number of 1,503,796 cases, total deaths 49,053 and total recovered 1,412,015 cases. Current active COVID-19 cases in South Africa on February 23, 2021 were 41,872 of which 546 (1.3%) cases are serious/critical.

Outbreaks of newly emerging infectious viral diseases present unique challenges and threats to health care providers due to lack of immunity, absence of specific, effective, and safe antiviral drugs, and a limited understanding of the emerging threat and reliance on infection prevention and control measures.

A series of events has to happen to enable a pathogen such as SARS-CoV-2 to cause an infection (COVID-19). This series of events is referred to as the 'chain of infection'. The links of the infection chain consist of : (i) the pathogen (infectious agent), (ii) reservoir or source, (iii) portal of exit, (iv) mode of transmission, (v) portal of entry, and (vi) a susceptible host.<sup>2,3</sup> The chain of infection model holds that infectious diseases result when an agent (pathogen) leaves its reservoir or host through a portal of exit, is conveyed by some mode of transmission, and enters through an appropriate portal of entry to infect a susceptible host.

The spread of infection can be mitigated by breaking the infection chain at any of its links. Therefore understanding the setting and characteristics of each link of the infection chain and how SARS-CoV-2 spreads to a susceptible host is critical in developing effective and sustainable infection prevention and control measures in the absence of a vaccine and anti-viral drugs.

## Methodology and Purpose

The literature search methodology used for the data assimilation and knowledge synthesis in this series is described in Part 1. The epidemiological 'infection chain' model was also used to enhance data assimilation and knowledge synthesis. (Table 1)

Part 2 of this series will focus on the key parameters of the infection chain that impact directly on risk management in the dental practice (Table 1)<sup>2,3</sup>. In addition, Part 2 also provides a review of the current knowledge and understanding of aerobiology and flow physics implicated in the generation, expulsion, evolution and transmission of virus-laden droplets and aerosols generated during expiratory activities such as breathing, talking, coughing and sneezing and during aerosol generating procedures.

This knowledge will enhance dental practitioners understanding the what, the why, and the how, underpinning SARS-CoV-2 infection control and prevention.

## Pathways of the infection chain – What is our knowledge and understanding of SARS-CoV-2 (virus) and susceptible host characteristics?

### 1. The pathogen – How virulent and infectious is SARS-CoV-2?

#### • The origin and identification of the coronavirus SARS-CoV-2

In December 2019, a cluster of fatal pneumonia outbreaks originated in Wuhan City, China.<sup>4</sup> All patients had been associated with the Wuhan Wholefood Market, where seafood and live animals are sold. The disease spread rapidly to most provinces in China and subsequently the rest of the world.<sup>5,6</sup>

Chinese researchers quickly isolated a new virus from a patient and sequenced its genome (29,903 nucleotides).<sup>7</sup> The infectious agent of this viral pneumonia that originated in Wuhan was finally identified as a novel coronavirus (2019-nCoV), the seventh member in a family of coronaviruses that affect humans.<sup>8</sup> After analysis of respiratory samples, the Peoples Republic of China Centers for Disease Control declared that the pneumonia was caused by a novel coronavirus now referred to as SARS-CoV-2.<sup>9</sup>

Coronaviruses (CoV) are respiratory pathogens. They belong to the Coronaviridae family. Currently there are four genera of coronaviruses:  $\alpha$ -CoV,  $\beta$ -CoV,  $\lambda$ -CoV, and  $\delta$ -CoV.<sup>10</sup> SARS-CoV-2 is an enveloped single stranded RNA virus. Six corona viruses were previously known to cause disease in humans, SARS-CoV-2 is the seventh member of

the coronavirus family that infects humans after SARS-CoV, MER-CoV.<sup>4</sup> and the Middle East respiratory syndrome coronavirus (MERS-CoV)<sup>12</sup> that occurred in 2002-2003 and in 2012 respectively. SARS-CoV, MERS-CoV and SARS-CoV-2 belong to  $\beta$ -CoV.<sup>7,13</sup>

#### • The morphologic and genetic structure, replication and pathogenic mechanisms

The morphologic structure of SARS-CoV-2 is similar to SARS-CoV, with virion size ranging from (60-140 nm) (0.06-0.14 $\mu$ m).<sup>14</sup> The virus has distinctive spikes of 9-12 nm that give the appearance of "coronas" around the sun. Spike, membrane and envelope surface viral proteins of the coronavirus are embedded in its host-derived lipid bilayer membrane encapsulating the helical nucleocapsid comprising viral RNA.<sup>15</sup>

SARS-CoV-2 presents with two notable genomic features: (i) it is optimized for binding to human receptor angiotensin-converting enzyme 2 (ACE) and, (ii) the receptor binding domain in the spike S-protein has a site at the S1-S2 boundaries (the two subunits of the spike) through which insertion of nucleotides takes place. The cleavage site on the S-protein allows effective cleavage by furin (protease) and other proteases that allows nucleotides of SARS-CoV-2 to enter host cells through human cell receptor ACE2, to allow viral entry, duplication, infectivity and host range.<sup>16-18</sup>

ACE2 is an important receptor for SARS-CoV-2<sup>19</sup> and found in many target cells including type II alveolar cells of lung<sup>20-22</sup>, epithelial cells of the oesophagus, adsorptive enterocytes from the ileum and colon<sup>22</sup>, cholangiocytes<sup>23</sup>, myocardial cells, kidney proximal tubule cells, bladder and urothelial cells<sup>20</sup>, salivary gland epithelial cells<sup>24,25</sup> and oral mucosa.<sup>26</sup>

Viral entry and cell infection trigger the host's immune response, and the inflammatory cascade is initiated by antigen presenting cells.<sup>27</sup> It is suggested that the severity of the virus infection is closely related to the maturity and binding capacity of ACE2.<sup>28</sup> Gao and co-workers<sup>29</sup> have suggested that a lower level of ACE2 and weaker binding could be a major contributing factor that leads to the absence of any clinical manifestations in asymptomatic cases.

#### • What is known about the incubation period of SARS-CoV-19?

Incubation period is the time from moment of exposure to the corona virus until signs and symptoms appear. The best current estimates of the incubation of SARS-CoV-2 range from 2-14 days with an average of 6.4 days.<sup>27,30,31</sup>



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**Table 1 : The infection chain pathway from pathogen to host and appropriate infection control strategies to mitigate or contain transmission of the coronavirus between health care workers and patients in the dental practice setting**

Infection chain pathway and definition	Infection chain characteristics	Infection control strategy
<p><b>Pathogen</b> of sufficient virulence and adequate number (load) to cause disease</p>	<ul style="list-style-type: none"> <li>Contagion: Coronavirus (SARS-CoV-2)</li> <li>Single stranded RNA</li> <li>Enveloped – lipid bi-layer membrane</li> <li>Diameter 60-140nm (0.06-0.14µm)</li> <li>Spike protein 9-12nm - viral entry key</li> <li>Very susceptible to standard disinfection methods</li> <li>Very contagious</li> </ul>	<ul style="list-style-type: none"> <li>Hand sanitizing – removes virus</li> <li>Surface disinfection – Kills virus</li> <li>Universal masking – evade virus</li> <li>Social distancing – evade virus</li> <li>Isolation</li> <li>HEPA filters (virus scavenging) &amp; UV light sterilization</li> <li>HOCL fogging - airborne disinfection</li> <li>Anti-viral drugs</li> <li>Vaccine – antibody immune resistance</li> </ul>
<p><b>Reservoir or source (carrier)</b> (A place that allows the pathogen to survive or multiply)</p>	<ul style="list-style-type: none"> <li>Incubation (infectious period) 6.4 days</li> <li>Human COVID-19 pre-symptomatic</li> <li>Human COVID-19 asymptomatic</li> <li>Respiratory tract (naso-pharynx and lungs)</li> <li>Oral cavity (Oral mucosal epithelial cells, salivary glands, tongue and periodontium)</li> <li>Gastro-intestinal tract (intestinal epithelium)</li> <li>Possible environmental reservoirs: Biofilm in waterlines and Ventilation systems</li> </ul>	<ul style="list-style-type: none"> <li>Patient and staff screening for symptoms</li> <li>Universal masking (evade) and hand sanitation (remove virus)</li> <li>Maintain good hygiene and sanitation</li> <li>Pre-procedural mouth rinse – kills virus and reduces viral load</li> <li>Asepsis / sterilization</li> <li>Waterline Disinfection</li> <li>HEPA filters &amp; UV sterilization</li> </ul>
<p><b>Portal of exit</b> (Ways in which the virus leaves the reservoir)</p>	<ul style="list-style-type: none"> <li>Mouth (talking) aerosols</li> <li>Mouth - Contaminated saliva (aerosols)</li> <li>Mouth - Respiratory secretions (air droplets (coughing or talking))</li> <li>Nose - Respiratory secretions (air droplets) -sneezing</li> <li>Faecal</li> </ul>	<ul style="list-style-type: none"> <li>Pre-procedural rinse &amp; gargle</li> <li>Rubber dam isolation</li> <li>High volume evacuation</li> <li>PPE (Masks and gloves)</li> <li>Hand sanitation</li> </ul>
<p><b>Mode of transmission from source to host</b> (Ways in which the virus spreads from reservoir to the susceptible host)</p>	<ul style="list-style-type: none"> <li>Direct contact (touch) with contagion (pathogen) in saliva or surfaces</li> <li>Indirect contact with contaminated surface/objects (fomites)</li> <li>Contact with conjunctiva, nasal or oral mucosa with contaminated droplets (coughing, sneezing and talking)</li> <li>Inhalation of airborne microorganisms suspended in air</li> <li>Aerosol generating procedures</li> <li>Faecal-oral route</li> <li>Superspreading events</li> </ul>	<ul style="list-style-type: none"> <li>Hand sanitizing</li> <li>Pre-procedural mouth rinse</li> <li>Isolation – use of rubber dam</li> <li>High volume evacuation</li> <li>Appropriate PPE (Masks, Gloves, Gowns, Shields)</li> <li>Appropriate surface disinfection</li> <li>Ventilation, HEPA filters &amp; UV sterilization</li> <li>Prevent &amp; control Superspreading events</li> </ul>
<p><b>Portal of entry</b> (Ways through which the pathogen can enter a susceptible host)</p>	<ul style="list-style-type: none"> <li>Deposition</li> <li>Attachment (ACE2 receptors) &amp; Entry</li> <li>Replication and release</li> <li>Respiratory tract</li> <li>Nose (nasal mucosa)</li> <li>Mouth (oral mucosal)</li> </ul>	<ul style="list-style-type: none"> <li>Preprocedural mouth rinse</li> <li>Surgical masks (FFP2) or N95 respirators (FFP3)</li> <li>Goggles and/or face shields</li> <li>Appropriate disinfection</li> </ul>
<p><b>Susceptible host</b> Is an individual who is not immune  Susceptible individuals may have co-morbidities that affect their susceptibility to, and severity of COVID-19</p>	<ul style="list-style-type: none"> <li>Healthy individual</li> <li>Immune compromised individual</li> <li>Elderly</li> <li>Co-morbidities</li> <li>Smoking</li> <li>Patients receiving ACE2-increasing drugs</li> <li>Disease: COVID-19</li> <li>Asymptomatic</li> <li>Pre-symptomatic</li> <li>Symptomatic</li> </ul>	<ul style="list-style-type: none"> <li>Pre-screening&amp; risk identification</li> <li>Isolation</li> <li>Diagnostic testing</li> <li>Universal masking</li> <li>Hand sanitize</li> <li>Preprocedural mouth rinse</li> <li>Maintain good hygiene</li> <li>Special precautions for individuals at high risk &amp; co-morbidities</li> <li>Enhance the immune system</li> <li>Vitamin D supplementation</li> <li>Healthy nutrition, reduce stress, adequate sleep</li> <li>Eliminate smoking</li> <li>Social distancing</li> <li>Mucus modification</li> <li>Anti-viral drugs</li> <li>Designer antibodies &amp; Vaccination</li> </ul>



The maximum incubation period observed is as high as 24 days which suggests that this may increase the risk of virus transmission. Studies also suggest that elderly people have shorter incubation periods; thus, faster disease progression.<sup>32</sup> Transmission of SARS-CoV-2 can occur in the pre-symptomatic and symptomatic period.<sup>33</sup> Recent studies have revealed important transmission features of SARS-CoV-2, including infectiousness of asymptomatic<sup>34-38</sup> and pre-symptomatic cases.<sup>39-41</sup>

#### • **How long do individuals shed infectious SARS-CoV-2 RNA after infection?**

Although a precise estimate of residual risk of SARS-CoV-2 transmission after recovery from COVID-19 cannot be generated at this time, it is likely substantially less than the risk during illness when most person to person transmissions occurs.<sup>42</sup> It is impossible to say with 100% certainty that all recovered individuals are no longer infectious. Persons who are immunocompromised may have prolonged viral shedding.<sup>42</sup> COVID-19 testing is not always possible and/or accurate to make a determination whether a patient is infectious or not. The viral burden in saliva usually declines after onset of illness.<sup>42</sup>

The CDC recommends that isolation be maintained for at least 10 days after illness onset (Illness onset is defined as the date symptoms began), and least 3 days after recovery. Recovery is defined as resolution of fever without use of fever-reducing medication or resolution of other symptoms.<sup>42</sup> Duration of infectious period for COVID-19 is approximately 10 days after the incubation period.<sup>43</sup>

#### • **What is the stability of the virus in different environmental conditions?**

The virus is highly stable at 4°C, but sensitive to heat. Infectious virus could be recovered from printing or tissue paper after 3 hours whereas no virus could be detected from wood and cloth on day 2. By contrast SARS-CoV-2 was more stable on smooth surfaces on day 4 (glass and banknote) or day 7 (stainless steel and plastic.) Strikingly, a detectable level of infectious virus could still be present on the outer layer of a surgical mask on day 7.<sup>44</sup>

No infectious virus could be detected after a 5-minute incubation with various disinfectants (household bleach, 70% ethanol, 7.5% povidone-iodine, 0.5% chlorhexidine and 0.1% Benzalkonium chloride) at room temperature, and therefore very susceptible to standard disinfection methods.<sup>44</sup> SARS-CoV-2 is extremely stable in a wide range of pH values (pH 3-10) at room temperature.

#### • **Transmission kinetics of SARS-CoV-2**

The efficiency of transmission for any respiratory virus has important implications for containment and mitigation strategies. (Infection prevention and control strategies) Studies suggest an estimated reproduction number (R<sub>0</sub>) of 2.2, which means that on average, each infected person will spread the infection to an additional two individuals. Until the number falls below 1.0, it is likely that the outbreak will continue to spread.<sup>45</sup>

Serial interval of COVID-19 is defined as the time duration between a primary case (infecter) developing symptoms and the secondary case (infectee) developing symptoms.<sup>46,47</sup>

The basic reproduction number, which has been widely used and misused to characterize the transmissibility of the virus, hides the fact that transmission is stochastic, is dominated by a small number of individuals, and is driven by super-spreading events (SSE's).<sup>48</sup>

#### **2. Reservoirs (source or target organ): SARS-CoV-2 infectious cycle**

The reservoir of an infectious agent is the habitat in which the agent or pathogen normally starts its infectious cycle, lives, grows, and replicates. Reservoirs include animals, humans, and the environment. The reservoir may or may not be the source from which the pathogen is transferred to the host.

#### • **Zoonosis and animal reservoirs**

Similar to other viruses, SARS-CoV-2 has many potential natural- intermediate- and final hosts. This poses great challenges to prevention and treatment of virus infections.

Humans are also subject to diseases that have animal reservoirs. Many of these diseases are transmitted from animal to animal, with human as incidental hosts. The term zoonosis refers to an infectious disease that is transmissible under natural conditions from vertebrate animals to humans. Genomic characterization of SARS-CoV-2 has shown that it is of zoonotic origin. Scientists agree that the coronavirus SARS-CoV-2 very likely originated in bats (natural source)<sup>8</sup> whilst pangolins and snakes may be intermediate hosts.<sup>18</sup>

#### • **Human reservoirs**

Many common respiratory infectious diseases have human reservoirs. Diseases that are transmitted from person to person without intermediaries. Human reservoirs may or may not show the effects of illness. Asymptomatic or passive carriers are those who do not experience symptoms despite being infected. Incubatory carriers are those who can

transmit the pathogen (virion) during the incubation period (pre-symptomatic) before clinical illness begins.<sup>3</sup> Researchers have shown the role of the oral mucosa and salivary gland epithelial cells with high expression in ACE2 in SARS-CoV-2 infection.<sup>24,26</sup>

Current evidence suggests that SARS-CoV-2 transmitted by asymptomatic infected individuals may originate from infected saliva.<sup>25</sup> Asymptomatic carriers commonly transmit disease because they do not realize they are infected, and consequently take no special precautions to prevent transmission. Symptomatic persons who are aware of their illness, on the other hand, may be less likely to transmit infection because they are too sick to be out and about, take precautions to reduce transmission, or receive treatment that limits the disease.<sup>3</sup>

At present it is considered that the main source of SARS-CoV-2 are pre-symptomatic, symptomatic and asymptomatic COVID-19 individuals in the population.<sup>18,49</sup>

Reservoirs are places where SARS-CoV-2 infectious cycle starts, where it can replicate and survive i.e., lungs, nasopharynx, oral cavity (oral mucosa, salivary glands, tongue and possibly the periodontium), and gastro-intestinal tract. Viruses are obligate intracellular parasites. They cannot produce outside of a cell. The sum total of all the events that take place in a virus infected cell or reservoir is called the infectious cycle, or viral replication. Once inside the cell, the virus hijacks the cellular machinery forcing it to produce more viruses.<sup>50</sup> These events consist of: (i) attachment, (ii) entry of the virion, (iii) uncoating and translation of mRNA into protein, (iv) genome replication, (v) assembly of new particles, (vi) and release of new particle (virions) from the host cell.<sup>51</sup> SARS-CoV-2 has been identified in both upper and lower respiratory tract samples from patients.<sup>52</sup> Higher viral loads have been detected in nasal passages and the upper respiratory tract of individuals infected with SARS-CoV-2, which means that coughs and sneezes may contain higher viral loads. One factor that is contributing to the rapid growth of COVID-19 infections is the higher viral load of the SARS-CoV-2 virus in the upper respiratory tract of asymptomatic hosts who shed virus-laden droplets during normal activities such as talking and breathing.<sup>34</sup>

Oral viral load of SARS-CoV-2 has been associated with severity of COVID-19, and thus, a reduction in the oral viral load could be associated with a decrease in the severity of the condition.<sup>53</sup> A decrease in the oral viral load would diminish the amount of virus expelled and reduce the risk of transmission.<sup>53</sup>

SARS-CoV-2 is primarily thought to infect lungs with

transmission via the respiratory route. However clinical evidence suggest that the oral cavity,<sup>26</sup> salivary gland epithelial cells<sup>24</sup> and intestine<sup>54</sup> may present as viral target organs or potential reservoirs for SARS-CoV-2.

ACE2 is an important receptor for SARS-CoV-2 19 and highly expressed in salivary gland epithelial cells.<sup>24</sup> and the oral mucosa.<sup>26</sup> It is suggested that there may be an increased dental risk due to SARS-CoV-2 transmitted by asymptomatic infection that may originate from saliva especially during aerosol generating procedures.<sup>25</sup> It is also hypothesized that periodontal pockets may be a plausible reservoir for SARS-CoV-2.<sup>55</sup>

The SARS-CoV-2 receptor ACE2 is also highly expressed on differentiated enterocytes.<sup>56</sup>

- **Environmental reservoirs**

The environment such as ventilation systems, sanitation facilities, waterlines and biofilms may also be reservoirs for SARS-CoV-2.<sup>57-59</sup> However, no studies have reported or suggested the possibility of ventilation systems, sanitation systems and waterlines being possible reservoirs or source of infection.

### 3. Portal of exit – How does the coronavirus leave the host reservoir?

Portal of exit is the path by which a pathogen leaves its host, corresponding to the site where the pathogen is localized.<sup>3</sup> During the infectious period, every individual emits potentially infectious aerosols all the time, not just when sneezing or coughing.<sup>60</sup>

Common portals of exit for SARS-CoV-2 include the mouth (breathing, talking, coughing, singing, aerosol generating procedures), nose (sneezing), respiratory tract (oro-pharynx and nasopharynx) (sputum production), and now added, the faecal route.<sup>59</sup>

Production of infectious respiratory droplets or particles are dependent on the type and frequency of respiratory activity, type and site of infection and viral load. Furthermore, relative humidity, particle aggregation, and mucous properties influence expelled particle size and subsequent transmission.<sup>61</sup>

- **Respiratory droplets and aerosols**

Individuals with infections produce particles between 0,05 and 500µm from breathing, talking, coughing and sneezing.<sup>61</sup> This indicates that expelled particles carrying pathogens do not exclusively disperse by droplet or airborne transmission but avail of both methods simultaneously and current infection control precautions should be updated to





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include both methods of aerosolized transmission.<sup>61</sup>

Respiratory droplets are formed from the fluid lining of the respiratory tract (oro- and naso-pharyngeal complexes).<sup>62,63</sup> The mechanisms of formation are usually associated with distinct locations in the respiratory tract and both the characteristics of the respiratory tract as well as the viral load carried by the lining are functions of the location.<sup>63,64</sup> One key mechanism for the generation of respiratory droplets is the instability and eventual fragmentation of the mucous lining due to shear stress induced by the airflow.<sup>65</sup> The Rayleigh-Taylor instability (the instability between two fluids when the lighter fluid is pushing the heavier one) is particularly important in spasmodic events such as coughing and sneezing.<sup>66,67</sup>

The second mechanism for droplet formation is associated with the rupture of the fluid lining during the opening of a closed respiratory passage.<sup>68</sup>

These submillimetre-sized passages collapse during exhalation, and the subsequent reopening during inhalation ruptures the mucus meniscus, resulting in the generation of micron sized droplets.<sup>63,64</sup> A similar mechanism probably occurs in the larynx during activities such as talking and coughing, which involve the opening and closing of the vocal folds.<sup>69</sup> Finally, movement and contact of the tongue and lips, particularly during violent events such as sneezing, generate salivary droplets.<sup>70</sup> Higher viral loads have been detected in nasal passages and the upper respiratory tract of individuals infected with SARS-CoV-2, which means that coughs and sneezes may contain higher viral loads.<sup>34</sup>

- **Saliva – oral droplets and aerosol generating procedures**

Several studies have confirmed that the viral load in human saliva is very high and that pre-operative mouth rinses can reduce this but cannot eliminate it.<sup>71,72</sup> In terms of coronavirus, Wang and co-workers examined the oral cavity of SARS patients and found large amount of SARS-CoV-2 RNA in their saliva (7.08×10<sup>3</sup> to 6.38×10<sup>8</sup> copies/mL).<sup>73</sup> This suggests a strong possibility of coronavirus transmission through oral droplets. According to Chowell and co-workers, evidence shows that the majority of SARS-CoV and MERS-CoV cases are associated with nosocomial transmission in hospitals, partly from aerosol-generating procedures.<sup>74</sup>

Recent reports of high viral load in the oropharynx early in the course of the disease aroused concern about increased infectivity during the period of minimal symptoms.<sup>43,75</sup> The potential for individuals infected with SARS-CoV-2 to shed

and transmit the virus while asymptomatic is greater, and those in the latent stages of the diseases often shed the virus at a higher rate.<sup>34</sup>

- **Gastrointestinal system – faecal route a potential portal of exit for SARS-CoV-2**

Evidence suggests that SARS-CoV-2 can infect and be shed from the gastrointestinal tract (faecal-oral route).<sup>56,59</sup> In addition, researchers have also detected SARS-CoV-2 in stool samples, gastrointestinal tract, saliva and urine.<sup>18</sup> There is evidence of ingestion, penetration of enterocytes and excretion of live SARS-CoV-2 through the faecal route.

#### 4. Mode of transmission

Human-to-human transmission of SARS-CoV-2 from its reservoir to a susceptible host occurs primarily via four routes: (i) large droplets from infected respiratory or saliva secretions that are expelled with sufficient momentum (i.e., coughing, sneezing, talking, singing) so as to directly impact the host recipients' mouth, nose or conjunctiva (droplet transmission)<sup>76</sup> (ii) physical contact with infected droplets deposited on a surface (fomite transmission) and subsequent transfer to the recipients' respiratory mucosa, conjunctiva or oral mucosa (contact transmission)<sup>76,77,78</sup> (iii) inhalation by the recipient of aerosolized droplet nuclei that are delivered by ambient air currents (airborne transmission)<sup>70,81</sup> and (iv) faecal-oral route of transmission.<sup>59</sup>

According to current evidence, SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes.<sup>9,18,30,82-85</sup> However recent evidence suggest that the airborne transmission route may be highly virulent and dominant for the spread of SARS-CoV-2.<sup>80</sup> SARS-CoV-2 is mainly transmitted through close physical contact and respiratory droplets, while airborne transmission is possible during aerosol generating procedures.<sup>78,86</sup>

- (i) **Droplet and aerosol transmission**

Transmission of SARS-CoV-2 is primarily via virus-laden fluid particles, namely droplets (>5 µm) and aerosols (<5 µm) (also referred as droplet nuclei) that are formed in the respiratory tract of an infected person and expelled from the mouth and nose during breathing, talking, coughing and sneezing or during aerosol generating procedures.<sup>60,72,87</sup> Viral transmission can occur when viral particles are aerosolized by a cough, sneeze or during dental procedures. According to Froum and Strange, particles can travel up to a distance of 6m from an infected person and have the potential to incite secondary infections.<sup>88</sup>

- **Respiratory droplets and aerosols**

Asymptomatic and pre-symptomatic individuals, by definition do not cough or sneeze to any appreciable extent. This leaves direct or indirect contact modes and aerosol (airborne) transmission as the main possible modes of transmission. Both breathing and talking emit large quantities of aerosol particles, typically about 1  $\mu\text{m}$  in diameter and are large enough to carry viruses such as SARS-CoV-2 to be readily inhaled deep into the respiratory tract of another individual.<sup>60</sup>

Ordinary speech aerosolizes significant quantities of respiratory particles. Studies suggest that speech emits more aerosol particles than breathing<sup>89</sup> and the louder one speaks, the more aerosol particles are produced.<sup>90</sup> It is plausible that a face-to-face conversation with an asymptomatic infected individual, even if both individuals take care not to touch or to maintain social distancing, might be adequate to transmit SARS-CoV-2.

Respiratory droplet transmission (droplet particle size >5-10 microns) occurs when a person is in close contact (within 1 m) with someone who has respiratory symptoms e.g., coughing or sneezing and is therefore at risk of having his/her mucosae (mouth or nose) or conjunctiva (eyes) exposed to infective droplets.<sup>86</sup> It is conceivable that infectious particles sized less than 10  $\mu\text{m}$  have more serious health implications as they are able to penetrate into the lower respiratory tract to establish infection.

- **Aerosol generating procedures**

Aerosol generating procedures (AGP) are defined as any dental and medical care procedure that results in the production of airborne particles (aerosols). AGP's can produce particles <5  $\mu\text{m}$  in size which can remain suspended in the air and travel over a distance, causing infection when inhaled. AGP create the potential for airborne transmission of infections that may otherwise be transmitted by droplet route.

Aerosols and droplets are produced during many dental procedures (i.e., use of air turbines during restorative procedures, surgical handpieces, air abrasion, use of a 3-in-1 syringe, ultrasonic or sonic scalers, air polishing devices and use of ErYAG laser with water coolant function). Splatter droplets are much larger than aerosol particles (<50 micron). The size of the coronavirus-shaped spherical particle is estimated to be about 0.125 microns (125 nm) (range: 0.06 microns to 0.14 microns).<sup>4</sup> It is therefore plausible that both aerosol particles and splatter droplets can contain SARS-CoV-2 and therefore a potential hazard for health care workers, including dentists.

- **Aerobiology and physics of aerosolization: Determining the fate of droplets and aerosols and transmission rates**

Size, velocity, inertia, gravity and evaporation are key determinants of the fate of droplets, pathogen carriage, aerosolization, and transmission.<sup>61</sup>

- **Temperature, humidity and evaporation**

Higher temperatures and lower relative humidity lead to larger evaporation rates that increase the critical droplet size.<sup>91,92</sup> Wells' simple but elegant analysis predicted that the critical size that differentiates large from small droplets is approximately 100 $\mu\text{m}$ .<sup>91</sup> Subsequent analysis has shown that typical temperature and humidity variations expand the critical size range from approximately 50 to 150 $\mu\text{m}$ .<sup>92</sup>

Droplet evaporation plays a significant role in the eventual fate of a droplet.<sup>91</sup> Large droplets settle faster than they evaporate, and so contaminate surrounding surfaces. Smaller droplets evaporate faster, so forming droplet nuclei that can stay airborne for hours and may be transported over long distances.<sup>70</sup>

Dependence of evaporation rates on ambient temperature and humidity has implications for the very important, and as yet unresolved, questions regarding seasonal and geographic variations in transmission rates.<sup>93,94</sup> as well as airborne transmission in various indoor environments.<sup>95,96</sup>

- **Velocity**

The number, density, velocity and size distributions of droplets ejected by expiratory events have important implications for aerosolization, pathogen carriage and transmission of respiratory infectious disease.<sup>61,70</sup> A single sneeze can generate 40,000 or more droplets, with velocities upwards of 20  $\text{ms}^{-1}$ .<sup>97</sup> Coughing generates approximately 3,000 droplets, with velocities of approximately 10  $\text{ms}^{-1}$ , but even talking can generate approximately 50 particles per second.<sup>90</sup> Breathing and talking generate jet velocities that seldom exceed 5  $\text{ms}^{-1}$  and mostly expel small droplets.<sup>98</sup> Recent studies have noted that, while breathing and talking generates droplets at much lower rate, it probably accounts for more expired bioaerosols over the course of a day than intermittent events such as coughing and sneezing.<sup>99,100</sup>

Droplet characteristics (number, density, size distribution and velocity) continues to be elusive due to the multifactorial nature of the phenomena as well as difficulty of making such measurements.<sup>89,97,101</sup>

- **Turbulence and cloud dynamics**

It has also been shown that the respiratory jet transforms into a turbulent cloud or puff.<sup>102</sup> While large droplets are mostly not affected by the cloud dynamics, small and



medium-sized droplets can be suspended in the turbulent cloud for a longer time by its circulatory flow, thereby extending the air travel distance significantly.<sup>102</sup> This also has important implications for transmission via indirect contact with contaminated surfaces, since SARS-CoV-2 is able to survive on many types of surfaces for hours to days.<sup>103</sup> In addition, the turbulent cloud also moves upwards due to buoyancy<sup>102</sup> thereby enabling small droplets and droplet nuclei to reach heights where they can enter the ventilation system and accelerate airborne transmissions.<sup>70</sup> The notion of critical droplet size that was introduced by Wells<sup>91</sup> might need to be re-examined in view of our rapidly evolving knowledge about these expiratory events.<sup>92,102</sup>

#### - Diffusion

Diffusion mainly occurs through coughing, sneezing, talking, singing and saliva aerosols. For the droplet transmission route, an important consideration is the horizontal distance travelled by large droplets. The 3-6 feet social distancing guidelines probably originate from Wells' original work.<sup>70</sup> However, studies indicate that while this distance might be adequate for droplets expelled during breathing and coughing,<sup>92,104-106</sup> large droplets expelled from sneezes may travel 20 feet or more.<sup>92,102</sup> Studies also suggest that social distancing in indoor environments could be complicated by ventilation-system-induced air currents.<sup>107</sup>

#### (ii) Direct and indirect contact transmission (Fomite transmission)

Direct or indirect contact modes require a susceptible individual to physically touch themselves i.e., oral, nasal, and eye mucous membranes with, for example, a virus-contaminated hand.<sup>72</sup> "Direct" indicates that person-to-person contact transfers the virus between infected and susceptible host (such as by hand shake), while "indirect" implies transmission via a "fomite" which is an object like a light handle or x-ray tube that has been contaminated with infectious virus.<sup>60</sup> SARS-CoV-2 can also be transmitted to fomites aerosol generating procedures. SARS-CoV-2 may also be transmitted directly to surfaces, handles or equipment (fomites) due to poor hand sanitation.

Transmission may also occur through fomites in the immediate environment around the infected person.<sup>108</sup> Currently there is no evidence linking transmission of SARS-CoV-2 conclusively to contaminated environmental surfaces.<sup>109</sup>

#### (iii) Airborne transmission

Studies suggest that coronavirus has been detected on

particles of dust or polluted air thus enabling coronavirus to be carried over longer distances air borne, potentially increasing the risk of infection.<sup>110-113</sup>

The airborne transmission route is associated with small droplets that are suspended and transported in air currents over longer distances. Under certain humidity and temperature environments, airborne droplets (aerosols) can remain in flight for hours.<sup>27</sup> Smaller droplets evaporate faster than they settle, forming droplet nuclei that can stay airborne for hours and may be transported over long distances.<sup>70</sup> Most of these droplets evaporate within a few seconds<sup>92</sup> to form droplet nuclei. The nuclei consist of virions and solid residue<sup>114</sup> but water may never be completely removed.<sup>115</sup>

Droplet nuclei are sub-micrometer to approximately 10µm in size, and remain suspended in the air for hours.<sup>70</sup> Each droplet nucleus could contain multiples virions, and, given the approximately one hour viability half-life of the SARS-CoV-2 virus,<sup>103</sup> and the fact that SARS-type infections in a host may potentially be caused by a single virus,<sup>116</sup> droplet nuclei play a singularly important role in the transmission of SARS-CoV-2.<sup>60</sup> The transport of droplet nuclei over larger distances is primarily driven by ambient airflows. Indoor environments such as homes, offices, hospitals, malls, aircraft and public transport vehicles pose a particular challenge to disease transmission. The importance of ventilation in controlling airborne transmission of infections is well known.<sup>95,96</sup>

In the context of dental practice, airborne transmission may be possible where aerosol generating procedures are performed; (e.g., ultrasonic scalers, use of air turbines, 3-in-1 syringes).<sup>86</sup> However, there have been no evidence-based reports on aerosol generated transmission to date. Studies are needed to determine whether viable SARS-CoV-2 is found in air samples in dental rooms where non-aerosol and aerosol generating procedures are performed. Current available evidence suggests that long-range aerosol-based transmission is not the dominant mode of SARS-CoV-2 transmission.<sup>117</sup>

Once infected droplets have landed on surfaces, their survivability on those surfaces determines if contact transmission is possible. Based on the current evidence, SARS-CoV-2 can remain infective, from 2 hours up to 9 days on inanimate surfaces, with increased survival in colder or dryer environments.<sup>118-120</sup> A study of people with Influenza found that 39% of people exhaled infectious aerosols.<sup>121</sup> If SARS-CoV-2 is transmitted in aerosols, then it is possible that virus particles can be transmitted over greater distances. Yan and co-workers also suggested that infected aerosols are

also produced during breathing and talking.<sup>121</sup> Therefore, it is suggested that when an air space is being shared, such as in a dental practice, breathing in infected air by airborne transmission is possible.<sup>121</sup>

#### **(iv) Faecal-Oral route transmission**

Many pathogens that cause gastroenteritis follow the so-called “faecal-oral” route because they exit the source host in faeces, are carried on inadequately washed hands to a vehicle such as food, water, or utensil, and enter a new host through the mouth.<sup>3</sup> SARS-CoV-2 has been detected in the faeces of some patients.

Thus taken together with fomite transmission, there is a potential possibility that SARS-CoV-2 could transmit via the faecal-oral route. The faecal-oral route describes a route of transmission where the virus particles can pass from one person to the mouth of another. Main causes included lack of adequate hand sanitation and poor hygiene and sanitation practices.<sup>56</sup>

### **5. Portal of entry and life cycle of SARS-CoV-2**

The portal of entry refers to the manner in which a pathogen enters a susceptible host to initiate its lifecycle and pathogenicity. The portal of entry must provide access to tissues in which the pathogen can replicate. Often infectious agents use the same portal to enter a new host that they used to exit the source host.<sup>3</sup>

Viruses are basically molecular nanomachines that take over the host cell after entry and force it to produce numerous copies of themselves.<sup>122</sup> The life cycle of a coronavirus consists of the following stages: (i) deposition, (ii) attachment and entry, (iii) transcription and replication, and (iv) assembly and maturation, and (v) release.<sup>51</sup>

#### **• Deposition of droplets and aerosols (droplet nuclei)**

Infection entry points are through the mouth (oral mucosa), nose (nasal mucosa) and eyes (conjunctiva).<sup>72</sup> Inhalation or direct contact of virus-laden droplets and aerosols (droplet nuclei) and the deposition of the virus in the respiratory mucosa, oral mucosa, nasal mucosa, or conjunctiva of the host is the final stage of droplet or airborne transmission.<sup>70</sup> The nose typically filters air particles above 10µm. Therefore, if a particle is less than 10 µm, it can enter the respiratory system. Fine aerosol particle (<2.5µm) can enter the alveoli. Ultrafine aerosol particles (<0.1µm) such as SARS-CoV-2 can enter the bloodstream and target organs such as the brain and heart.

There are six mechanisms that determine the deposition location: impaction, sedimentation, interception, diffusion, electrostatic precipitation and convection.<sup>124</sup> The relative importance of these mechanisms depends on the particle size and the region of the airway where deposition occurs. For small droplet nuclei-sized particles, sedimentation will drive significant deposition in the upper respiratory tract of the host<sup>125</sup> and relies completely on turbulent diffusion, whereas deposition of larger droplets are driven by impaction, sedimentation and interception<sup>126</sup> and rely mostly on deposition velocity. Large droplets, despite a higher deposition velocity, probably deposit in the upper respiratory tract, and could be deactivated by the first defensive layer of the mucosa.<sup>127</sup> On the other hand, small droplet nuclei, despite their smaller deposition velocity, will penetrate deeper into the respiratory system, and this could affect the progression and intensity of infection.

Deposition of virus-bearing droplets in the respiratory tract does not always result in infection, since the mucus layer provides some level of protection against virus invasion and subsequent infection.<sup>128</sup>

#### **• Attachment and entry**

The S-protein of the virus interacts and binds to ACE2 in the first stage of virus replication called “attachment”.<sup>26,49</sup> The specificity of this binding or “attachment” determines which cell type a virus can infect, a phenomenon called cell tropism.<sup>51</sup> ACE2 plays an important role in cellular entry,<sup>29</sup> thus ACE2-expressing cells are target cells and are susceptible to SARS-CoV-2 infection.<sup>26,129</sup> High ACE2 expression was identified in type II alveolar cells of lung,<sup>20,21,22</sup> epithelial cells of the oesophagus, adsorptive enterocytes from the ileum and colon,<sup>22</sup> cholangiocytes,<sup>23</sup> myocardial cells, kidney proximal tubule cells, bladder and urothelial cells.<sup>20</sup> Cells with high ACE2-expression should be considered as potential high risk for SARS-CoV-2 infection.<sup>26</sup> A recent study demonstrated that the ACE2 is expressed on the epithelial cells of the oral mucosa.<sup>26</sup> Interestingly, the ACE2 receptor was also highly expressed on the cells of the tongue. These findings support the plausible evidence that the oral cavity is potentially high risk for SARS-CoV-2 infection susceptibility.<sup>26</sup> Following receptor binding the virus enters the host cell cytoplasm.<sup>51</sup>

#### **• Transcription and replication**

Direct translation of the RNA-genome leads to the synthesis of structural and non-structural proteins (S, E, and M proteins)<sup>51,123</sup>

- **Assembly and maturation release**

Following replication and sub-genomic RNA synthesis, the S, E, M proteins are translated and inserted into the endoplasmic reticulum where the viral genomes are encapsulated by a membrane via budding and resulting in the formation of mature virions.<sup>51,123</sup>

- **Release of virions and initiation of pathogenicity**

Mature virions then travel to the cell surface inside vesicles and exit the cell by exocytosis to proceed with its pathogenic journey within the host.<sup>51,123,130</sup>

## 6. Susceptible host, co-morbidities and COVID-19

The final link in the chain of infection is the susceptible host. Susceptibility of a host depends on genetic factors, specific and non-specific immunity status, and factors that affect an individual's ability to resist infection such as age, immunodeficiencies, co-morbidities, stress, and nutritional deficiencies.<sup>49</sup>

- **Susceptible host and risk factors**

An individual's genetic makeup or inborn errors of immunity may influence the immune response to infection thus either increasing or decreasing susceptibility and severity of developing the infectious disease COVID-19.<sup>131,132</sup> However, the role of human genetics in determining clinical response to the virus remains unclear.<sup>132</sup>

All groups are susceptible to COVID-19 regardless of age or gender. Patients aged 30-79 accounted for 86,6% of all cases.<sup>30</sup> Elderly male citizens are more susceptible to COVID-19 and studies showed a median age of death was 75. Most elderly affected had underlying comorbidities (e.g., diabetes, hypertension, heart disease etc)<sup>133</sup> or a history of surgery before admission.<sup>32</sup>

Factors that may increase susceptibility to infection by disrupting host immune defences include age (elderly), malnutrition, vitamin D deficiency, alcoholism, smoking, stress, obesity in males, hypertension, and therapies (e.g. cancer therapy, immune suppressors, ACE2 modulators) that may impair the non-specific or specific immune response.<sup>134</sup> Specific immunity refers to protective antibodies that are directed against a specific agent. Because this is a novel virus, individuals have no protective antibodies nor is there a vaccine available at this point in time (October 2020). Non-specific immunity that defend the host against infection include the skin, mucous membranes, the cough reflex, and non-specific immune responses.

With what we know about the pathogenesis of the SARS-

CoV-2 virus, it seems reasonable to assume that those with higher levels of expression of ACE-2 receptors may be at greatest risk.<sup>27</sup>

- **Diagnosis of COVID-19**

The detection of SARS-CoV-2 viral nucleic acid (RNA) by reverse transcriptase polymerase chain reaction (TR-PCR) serological test is the standard for non-invasive diagnosis of COVID-19.<sup>29</sup> However, the possibility of false negatives and the relative long testing time and availability of serological tests and resources for testing is a big problem.<sup>18</sup> The radiographic features of coronavirus are similar to that found in community acquired pneumonia caused by other organisms. Chest CT-Scan is important to diagnose this pneumonia.<sup>135</sup>

- **What are the clinical manifestations of COVID-19?**

Covid-19 is an acute viral infection with a mean incubation period of 6.4 days from onset of infection.<sup>30,31</sup> The most common clinical symptoms of COVID-19 observed in patients admitted to hospital in Wuhan, China were fever (89.9%), cough (67,7%), fatigue (38,1%), whereas diarrhoea (3.7%) and vomiting (5%) were rare.<sup>133</sup> In comparison symptoms commonly observed at hospital admission in Italy were fever (75%), dyspnoea (71%), cough (40%) and diarrhoea (6%).<sup>136</sup> A recent systematic review and meta-analysis showed that COVID-19 is characterized by the following most prevalent symptoms: fever [91.3% (95%CI: 86%-96%)], cough [67.7% (95%CI: 59-76%)], fatigue [51%, (95%CI: 34%-68%)], and dyspnoea, [34% (95%CI: 21%-40%)].<sup>137</sup> The typical clinical manifestations of patients who suffered from the novel viral pneumonia were fever, cough, and myalgia or fatigue with abnormal chest CT.<sup>9,138,139</sup> COVID-19 is now classified in 4 levels based on the severity of the symptoms: Mild (mild symptoms and no radiographic features); Moderate (fever, respiratory symptoms, radiographic features); Severe (one of the following : dyspnoea- (RR>30times /min); Oxygen saturation (<93; PaO<sub>2</sub>/FIO<sub>2</sub> , 300mmHg); Critical (one of the following: respiratory failure, septic shock or multiple organ failure).<sup>30</sup>

Laboratory examinations revealed the following findings: lymphopenia (82.1%), thrombocytopenia (36.2%), elevated level of C-reactive protein (CRP), elevated levels of lactate dehydrogenase (LDH) and creatine kinase (CK).<sup>9</sup> Lymphocytopenia and cytokine storms are not exclusive to COVID-19 severity. Both are hallmarks of many other types of severe respiratory infections.<sup>140</sup> Increased ferritin levels and relatively low procalcitonin levels were commonly found



in individuals with severe COVID-19 compared to those with moderate disease. Hypertension and hyperlipidaemia were the most frequent comorbidities. Individuals with severe Covid-19 had underlying pulmonary disease and the majority of individuals with severe COVID-19 presented with moderate to severe Acute Respiratory Distress Syndrome and hospital mortality was 25% within this group.<sup>141</sup> The presence of bacterial co-infection was also a common finding in individuals with severe COVID-19.<sup>141</sup> The potential role of periodontitis in bacterial co-infection or as a co-morbidity remains unclear and should be further investigated.<sup>142</sup>

A recent study has demonstrated that broad innate and adaptive leukocyte perturbations may be the cause of a dysregulated host immune response resulting in severe COVID-19 infection.<sup>141</sup> The general immune response landscape and their perturbations in severe COVID-19 presented with (i) elevated white blood cells and polymorphonuclear leukocytes, and (ii) lower frequencies of dendritic cells, CD8+ cells, innate lymphoid cells and natural killer cells.<sup>141</sup>

The neutrophil-to-lymphocyte ratio (NLR) has been proposed to be an independent risk factor for severe COVID-19. Both NLR as well as the neutrophil : T-cell ratio (NTR) were high in individuals with severe COVID-19, emphasizing and suggesting both as potential biomarkers of COVID-disease severity.<sup>141</sup> The data also indicate an exacerbated plasmablast response in severe COVID-19 cases. According to Kuri-Cervantes and co-workers, the top parameters driving the clustering of severe COVID-19 were associated with T-cell activation in the CD4+ and CD8+ T-cell memory subsets, frequency of plasmablasts and neutrophils.<sup>141</sup> According to the latter authors, the abovementioned immune dysregulation may necessitate targeted strategies to effectively manage clinical care.<sup>141</sup>

Currently there is no underpinning evidence to indicate what viral and/or human factors underpin whether a person with COVID-19 will develop a severe infection.

People infected with this highly contagious virus can present with clinically inapparent (asymptomatic), mild, moderate severe or critical illness requiring hospitalization.<sup>143</sup> Estimates show that about 80% of people with COVID have mild or asymptomatic disease, 14% severe disease, and 6% become critically ill.<sup>6,144</sup> Although the true case fatality rate is yet unknown, current model-based estimates ranged from 0.3% to 1.4% for countries outside China.<sup>145</sup>

Efforts to understand the pathogenesis and define the risk factors of severe COVID-19 has been hampered by our inability or unavailability of resources to identify all infected

individuals, irrespective of clinical symptoms.<sup>146</sup>

There is increasing evidence that many infections of COVID-19 are asymptomatic, but they can transmit the virus to others.<sup>29</sup>

- **Asymptomatic infections**

Asymptomatic infections are defined as positive detection of nucleic acid of SARS-CoV-2 in patient samples by reverse transcriptase polymerase chain reaction (TR-PCR) serological test, with no clinical symptoms or signs, and no apparent abnormalities in diagnostic images, including lung computed tomography.<sup>29</sup> The incidence of asymptomatic infections with COVID-19 in six different studies reported in a recent systematic review, ranged between 1.6% and 56.5%.<sup>29</sup> New evidence has emerged from China that 78% of new infections identified were asymptomatic.<sup>147</sup> In general, asymptomatic cases cannot be recognised if they are not confirmed by RT-PCT or other laboratory testing, and symptomatic cases may not be detected if they do not seek medical attention.<sup>36</sup> Nishiura and co-workers estimated asymptomatic ratio amongst 565 Japanese evacuees was 30.8% (95%CI:7.7%- 53.8%)<sup>36,148</sup> This approximates the percentage of asymptomatic case ratio (33.3%) reported from a study done in South Korea.<sup>149</sup>

Studies have shown that asymptomatic infections are more common in populations of young and middle-aged individuals with functional performance status without underlying diseases and comorbidities.<sup>29</sup> Asymptomatic cases have the same infectivity as symptomatic COVID-19 cases.<sup>29, 151</sup> Asymptomatic cases may play a key role in the transmission and therefore pose a significant challenge to infection control. It is also reported in the literature that the incidence of asymptomatic infections in children is lower than that of the whole population and might be related to the immune response and ACE2 levels in children.<sup>29</sup>

Transmission of SARS-CoV-2 from infected but still asymptomatic individuals has been increasingly reported.<sup>34,38,150</sup> Asymptomatic carriers during the incubation period can be a potential infection source of COVID-19.<sup>34,38</sup> Infection transmission by asymptomatic patients can make infection control and prevention very challenging. Viral loads peak within the first few days of symptoms, but asymptomatic patients can have a similarly high viral load.<sup>43</sup>

Early recognition of an infected person and cutting off the route of transmission is critical to controlling COVID-19. In addition most asymptomatic cases do not seek medical care which contributes to rapid spread of COVID-19.<sup>29</sup>

#### • **Co-morbidities and increased risk of COVID-19 severity**

Individuals who are at higher risk of severe illness include people older than 65 years, people at any age that have severe medical conditions, including asthma, cardiovascular conditions, hypertension, haemoglobin disorders, liver disease, severe obesity, people in nursing homes and long-term care facilities<sup>152</sup> and individuals with immune compromised conditions such as diabetics, HIV and TB.<sup>153</sup> The most prevalent co-morbidities associated with COVID-19 are: hypertension [21% (95%CI: 13.0%-27.2%)], diabetes [9.7% (95%CI: 7.2%-12.2%)], cardiovascular disease [8.4% (95%CI: 3.8%-13.8%)], and respiratory disease [1.5% (95%CI: 0.9% - 2.1%)]<sup>137</sup> The major finding that hypertension is a host factor for severe COVID-19 may underscore the involvement of the renin-angiotensin system (RAS) in the pathogenesis of COVID-19.<sup>154</sup> Other co-morbidities associated with COVID-19 severity included malignancy (1%), chronic liver diseases (4.5%) and chronic renal disease (1.4%)<sup>154</sup> It is also suggested that patients with cardiac diseases, hypertension or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection.<sup>129,155</sup> It is now also suggested that periodontitis may be linked to COVID-19 severity.<sup>142,156,157</sup>

Individuals with comorbidities presented with increased COVID-19 severity and higher case fatality rates compared to those individuals without comorbidities.<sup>30,136</sup>

#### **Conclusion**

The disturbing reality is that we have no idea who among us is spreading the disease. This extreme evasiveness of SARS-CoV-2 makes it harder to control.

Understanding the characteristics of the infection chain pathway is critical in the adoption of appropriate infection prevention and control strategies in the dental practice setting. Breathing, talking, sneezing, coughing and aerosol generating procedures are all implicated in the generation, expulsion, evolution, and transmission of virus-laden droplets and aerosols.

The infection chain can be blocked at various levels by applying infection control and prevention strategies, thus mitigating the risk of spreading infection. An effective risk mitigation strategy for dental practices has to be based on a combined approach of breaking the links of the infection chain and should include (i) screening and isolation of high risk patients as well as oral health care workers to reduce the risk of exposure, (ii) universal masking and hand sanitation

remains the basic foundation of infection disease prevention and control strategy, (iii) pre-procedural mouth rinse to reduce the oral and naso-pharyngeal viral load remains an important but neglected strategy, (iv) use of appropriate personal protective equipment, (v) use of rubber dam and high volume suction (evacuation) to reduce exposure to contaminated aerosols and respiratory droplets and splatter, (vi) cleaning and surface disinfection, (vii) ventilation and airborne disinfection (HEPA- filters and UV lights, foggers), (viii) immune boosting, designer antibodies to neutralize the viral spike protein and use of a vaccine.

The current understanding and available evidence-based knowledge of the how and why of these infection prevention and control measures in the dental practice clinical setting will be discussed in Part 3 of the series.

Fundamental questions that remain unanswered include: (i) How does SARS-CoV-2 primarily spread in a dental clinical setting?; (ii) What is the viral titre in the respiratory fluid and the emitted aerosol particles during breathing, speech, coughing and sneezing and AGP (iii) What is the SARS-CoV-2 viral load in the saliva and pharyngeal mucus of asymptomatic and symptomatic salivary samples?; (iv) What is the infectious dose and length of exposure that will give an individual a significant chance of being infected? (v) What percentage of patients are asymptomatic and how do their infectiousness compare to those of symptomatic patients?; (vi) Who are the infectors and how does an infected individual's age and co-morbidities affect the risk of transmitting infection to others?; (vii) Is viable SARS-CoV-2 present in air samples in dental rooms where non-aerosol and aerosol generating procedures are performed? (ix) How effective are fogging devices at disinfecting airborne virus particles?

SARS-CoV-2 transmission from asymptomatic and pre-symptomatic hosts makes it more critical than ever that methods of rapid diagnosis are developed that provide better and faster prediction of COVID-19 infection and infectiousness. One of our greatest challenges globally is prophylactic prevention and control of transmission of SARS-CoV-2 from asymptomatic patients.

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