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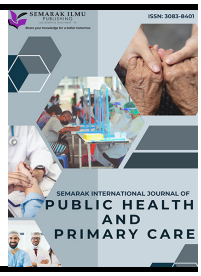

The Interplay Between Oral, Nasal, Lungs, and Gut Microbiome Ecology in Coronavirus Disease 2019 (COVID-19) Infection

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ABSTRACT

The human body's immune response to the Coronavirus Disease 2019 (COVID-19) virus is a complex phenomenon that is not fully understood. The presence of microorganisms within the body, known as the microbiome, can interact with different mucosal systems and influence the immune response to the virus. Individuals have also been reported to shed the severe acute respiratory syndrome Coronavirus 2 (*SARS-CoV-2*) despite being asymptomatic for COVID-19. The COVID-19 infection is complex and does not occur merely via the respiratory pathway. In this review, we would like to share about the possible involvement of nasal, oral, lung and gut ecological microbiome in the infectivity of COVID-19.

1. Introduction

The S*evere Acute Respiratory Syndrome Coronavirus 2* (*SARS-CoV-2*) is a new human coronavirus that was declared a pandemic on March 11, 2020, [1]. The *Coronavirus* Disease 2019 (COVID-19) lasted for almost three years and the pandemic was denounced on March 5, 2023, [2]. Malaysia ended the pandemic similarly and recently proposed nationwide "To live with COVID-19" steps which no longer require home surveillance orders (HSO) for infected individuals [3]. To date, there are numerous variants of the *SARS-CoV-2* namely the Alpha, Beta, Gamma, Delta, and Omicron variants [4,5]. It is projected that these variants may further evolve over time [4]. There are multiple efforts in mitigating and enhancing vigilance for future pandemics. Among the many, there are prediction models that could be applied to COVID-19 or similar pandemics as well as education through augmented reality application to create awareness [6,7].

Elsewhere, we read in amazement the study by Avanzato *et al.,* [8] that the *SARS-CoV-2* virus was shed beyond 100 days. Similarly, an asymptomatic COVID-19 patient continued to shed *SARS-CoV-2* for 33 days after being *SARS-CoV-2* free in the respiratory tract [9]. Although, prolonged shedding is incongruent with infectivity, the science behind this phenomenon is academically and clinically

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interesting[10–12]. Several identical receptors in the gut and lungs, and the constant communication between these tracts are essential for the transmission of *SARS-CoV-2* as well as the severity of COVID-19 [13,14].

In recent years, there have also been expansive discussions and proof of evidence of the gut-brain and gut-liver axes in COVID-19. These have been thoroughly discussed by Kalam and Balasubramaniam [15] and Assante *et al.,* [16] separately elsewhere, and is beyond the scope of this manuscript.

In this review, we would be narrating about the possible involvement of the nasal, oral, lung, and gut ecological microbiome in the infectivity and transmission of COVID-19. We review current knowledge and assess information on the microbiome, microbial ecology, microbiota cross-talks, shedding, *SARS-CoV-2,* and COVID-19.

2. The Human Microbial Ecology

The term “microbiome” and “microbiota” are often used interchangeably [17,18]. “Microbiota" refers to the live microbes that are present in certain environments such as the oral cavity or sinuses [17,18]. On the contrary, microbiome encompasses a more extensive catalogue of the microbes and their genes [17,18]. The human microbial ecology exhibits distinct inter-individual and biological variation. There are also complex inter-kingdom communications and relationships that may result in either symbiosis or dysbiosis of the mucosal systems. The mucous membranes are usually colonised by microbes, mycotic species as well as “viromes”, varying in symbiotic and other type of relationships [19,20]. Although viruses have long been major players in the human microbial ecology, the terms "nanobes" and "nanobiome" are scarcely used in medical literature. For brevity, “nanobes”, microbes, and mycotic species would collectively be referred to as “microbiome(s)”, “microbiota” or “microorganism(s)” in this review. *SARS-CoV-2* size is reported to be 70-110 nm and thus should be recognized as a nanobe [21].

The human body hosts around 100 trillion complex microorganisms which outnumber the body’s individual cells [22]. The mutualistic relationship between the host and the symbiotic microorganisms are vital to human health and is driven by the common evolutionary fate of both the aforementioned [23]. Among the functions of the microbiota are i) removal of pathogens and harmful dietary constituents, ii) development of the immunity, iii) differentiation and development of tissues and organs, iii) modulation of nutritional substrates and nutritive by-products, and iv) prevention of bowel cancer [24].

It is now known that in humans, there are six main bacteria phyla. These are *Actinobacteria, Firmicutes, Proteobacteria, Verrucomicrobia, Euryarchaeota,* and *Bacteroidetes* [25,26]. In addition, the bacterial colonies cluster by location rather than by individuals [26]. The nose and gut have approximately 10g and 1000g of microbiota respectively, whereas the mouth and lungs have 20g each [24].

There are contrasting data on the ratio and prevalence of *Firmicutes* and *Bacteroidetes* in the oral, nasal, and gut [27,28]. Huffnagle *et al.,* [28] reported high *Firmicutes* within the nasal microbiota. The oral and lung microbiota shared similar ratios [28]. We postulate that the contrast reported earlier might be due to unaccounted factors such as oral cavity pathologies (stomatitis, gingivitis, caries, periodontal disease, and chronic tonsillitis) owing to changes in microbiota constituents.

Some anatomical landscapes may have an overlap of the phylum and microbiota [24]. This is due to physiologic flow and connection(s) between these landscapes. Others may harbour an entirely distinct community of microbiomes. These are due to the presence of different substances such as

keratin, sebum, and fluids at these anatomical locations. Other than that, oxygen levels, pH, and temperature may further influence the microbiota composition [24]. While the nasal cavity microbiome resembles the skin flora, the resemblance of oral cavity is of the gut [29,30]. Although both the respiratory and intestinal tracts exhibit similarities such as the presence of goblet cells, microvilli, and Immunoglobulin A (IgA), the differences in acidity, oxygen content, contact with food particles, types of gases, and direction of flow contribute to the variation in microbiome composition [13,14,31]. It is noteworthy that the microbiota of the nasal cavity may serve as a helpful stand-in for the more difficult-to-access sinus microbiota due to their proximity [32].

The gut microbiota of an individual in good health is made up of the phyla *Firmicutes, Bacteroidetes, Proteobacteria,* and *Actinobacteria*, accounting for more than 90% of the total gut microbiota [33,34]. It has also been studied that the gut microbiome of the elderly drifts away from *Firmicutes,* and is abundant in *Bacteroides, Alistipes,* and *Parabacteroides* instead [35]. As for children, they have different and distinct microbiota constituents compared to adults. Environmental exposures at birth and infancy, particularly nursing, have an impact on the microbiota. However, as the age advances, the nasal and oral microbiomes become quite similar [36].

3. Oral, Nasal, Lungs, and Gut Communications

The microbiome and its by-products could translocate from one mucosal lining to another. This interplay occurs between the oral, nasal, lungs, and gut mucosa via aspiration, regurgitation, sputum swallowing, blood, and lymphatic circulations [14]. Oral microbiome may cause respiratory infection via direct aspiration of the pathogens, periodontal disease-associated enzymes, and cytokine translocation from the mouth to the respiratory tract, leading to lung dysbiosis [20].

In a competent host, the interplay within the microbiome ensures eubiosis, as well as proper regulation of the innate and adaptive immunity for the deactivation of viruses [14]. In addition, the microbiome produces by-products such as indigestible polysaccharides and nutrients to modulate the gut immune system [13]. Figure 1 shows the crosstalk between the oral, nasal, lungs, and the gut. The by-products, constituents of the microbiome, pathogens, enzymes, and cytokines that may be translocated from one environment to another are also represented in the same figure. The arrows with red to green gradient and vice versa depict symbiosis and eubiosis, respectively, between different regions that are shown.

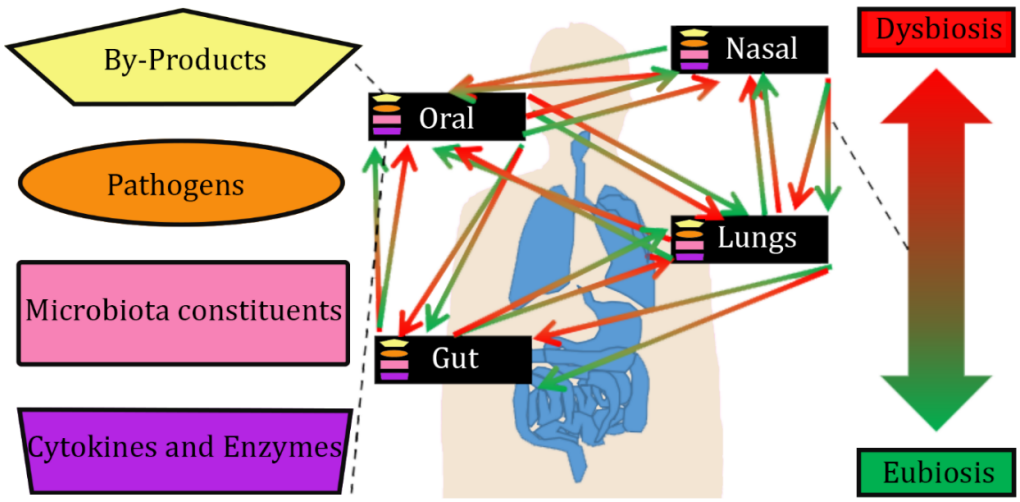

Fig. 1. The crosstalk between the oral, nasal, lungs and gut

4. Transmission: *SARS-CoV-2* Induced Response in the Lungs and Gut

SARS-CoV-2 may be present in both the alveoli and gut. In an immunocompetent host, there is good ciliary clearance at the terminal bronchioles. Firstly, recognition of the viral products would trigger an innate immune response [37]. In the alveoli, Type-II pneumocytes are responsible for ion and fluid transport as well as surfactant production [38]. As the surfactant contains lipases and proteases, it degrades protein-rich oedema fluid which is the product of inflammation. This mechanism is inversed during acute respiratory distress syndrome (ARDS), resulting in the inactivation of the surfactant [38].

Upon inflammation, the resident macrophages may shift into classically activated phenotype macrophage (M1) to stimulate interleukin (IL) such as Interleukin-1 (IL-1), Interleukin-alpha1B (IL-α1B), Interleukin-6 (IL-6), and Tumour Necrosis Factor-Alpha (TNF-α)[39,40]. In the later phase, the M1 shifts to the alternative activated phenotype macrophage (M2) for the clearance of apoptotic cells and fibrosis [39].

Figure 2 shows the effect of *SARS-CoV-2* to the lungs and gut. The lungs and gut are represented as a) and b), respectively, in immunocompetent individuals. Conversely, the lungs and guts are represented as c) and d), respectively, in mild COVID-19 infected individuals.

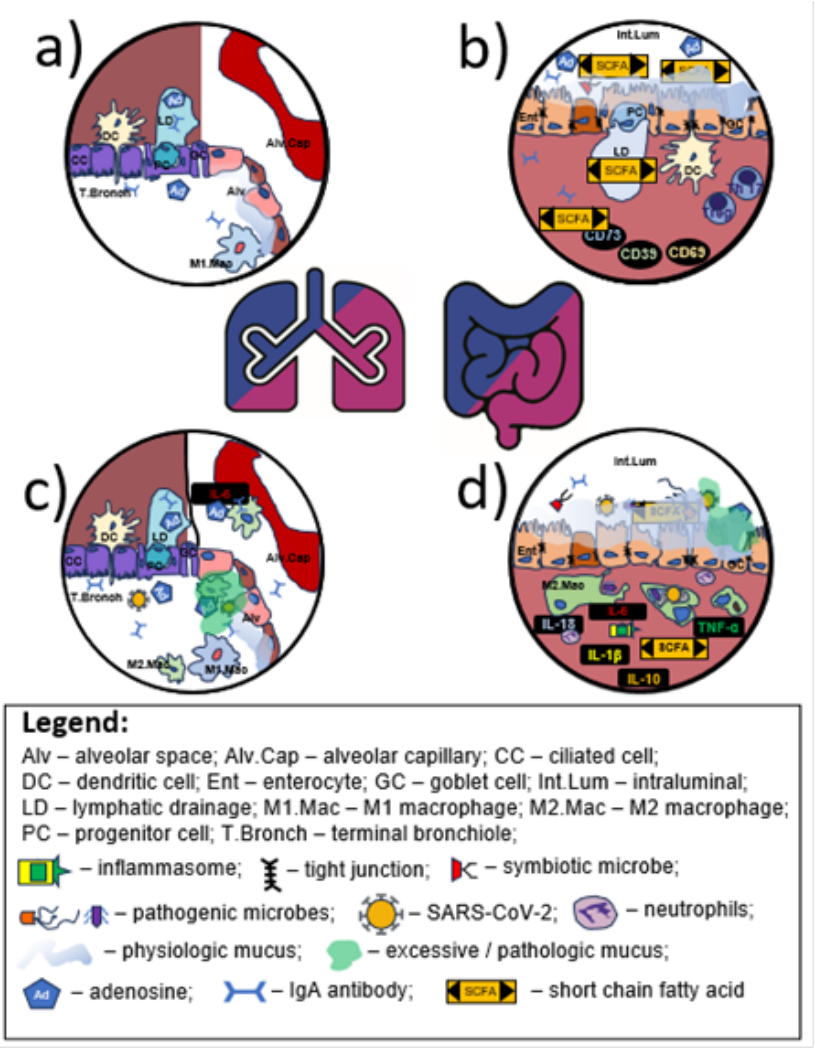

Fig. 2. The lungs and gut of an immunocompetent and mild COVID-19 infected individual

As inflammation remains a double-edged sword, the balance between a timely immune response and the inhibition of prolonged toxic response modulates against lung injury and poor outcome. The over-activation of pro-inflammatory cytokines, neutrophil hyper-responsiveness, neutrophil apoptosis, and M1 to M2 mismatch leads to lung injury [14,39,41]. Fibrosis may occur as a sequalae of excessive and repetitive inflammation and repair. Circulating IL-6, IL-10 and TGF-β stimulate the plasma cell to produce IgA in the gut [31]. While IL-22 protects the tissue, a low IL-10 is directly proportionate to unfavourable ARDS outcomes [41].

Paneth cells maintain the gut microbiota homeostasis by producing α-defensins, lysozymes, growth factors, and signals to the intestinal stem cells [42–44]. Morever, it has innate immune-sensing capability by utilising the TLRs and inflammasomes. The α-defensins act as chemo-attractants and modulate adaptive immunity [41,42].

The pyrin domain-containing protein 3 ($NLRP_3$) is a macromolecular platform that senses injury and modulates pro-inflammatory cytokines [45]. In extreme cases, the $NLRP_3$ may induce cell death via pyroptosis [45]. In fact, enhanced inflammasome activity is associated with poor prognosis and mortality [45]. This was also notable in COVID-19 cases [46].

Furthermore, the enterocytes are essential for nutrient absorption and activation of the immune system, while the M-cells and DCs are responsible for antigen presentation, delivery, and phagocytosis [47–49]. On the other hand, mucus or mucin glycoproteins are produced by the goblet cells [50]. The gut motility is dependent on intestinal cells of Cajal and smooth muscle cells [51,52]. It is important to note that other than lymphoid tissues in the gut mucosa, there are also Peyer's patches and appendix which make up the Gut-Associated Lymphoid Tissue (GALT) [53].

Plasmacytoid Dendritic Cell Precursors (pDCs) or Type-1 Interferon-Producing Cells produce Type-1 Interferon (IFN-I) [54]. IFN-I promotes the function of natural killer cells (NK), B-Cells, T-cells, and myeloid dendritic cells [54]. Upon viral infection, the pDCs differentiate into dendritic cells (DCs) resulting in naive CD4+ priming [54]. The IFN-I is required for the Antigen-Presenting Cell (APC) system for CD4+ priming. This priming produces IFN-γ and IL-10 [54]. The production of IFN-I and TNF-α during virus stimulation activates monocytes or myeloid DCs and secretes IL-12 [54]. The myeloid DCs induce strong Th1 and cytotoxic T-lymphocyte responses. pDCs derived DCs enhances generation and maintenance of memory T-cells through the IFN-I [54].

The microbiota sends out a variety of signals that cause the DCs to migrate to the draining lymph node and alter phenotypically. Within the mesenteric lymph nodes (MLN), DCs stimulate the activation of different T-cell subsets and the release of several regulatory cytokines, including IL-10, TGF-Beta, and IL-6, as well as stimulate T-cells differentiation into Tregs, Th17, CD4, and CD8. There is also production of B-cells that is stimulated by IL-6 and IL-10 [55].

Apart from that, CD73 is expressed by Th17 cells [56]. CD73 up-regulation has been associated with reduction of mortality in ARDS patients [56]. In the gut, CD73 produces adenosine which has antibacterial properties, and it is downregulated during intestinal infection [57,58]. A direct effect of adenosine is the reduction ability of pneumococci to bind to pulmonary epithelial cells via A1 adenosine receptor signaling and this may reduce co-infection [59]. Th17 is found to be high in COVID-19 patients [60]. Both CD73 and CD39 are found in the gut and have a protective role in lung injury [61,62]. Elevated extracellular adenosine promotes pro-inflammatory and profibrotic mediators in the lung. IL-6 and TGF-β are profibrotic mediators [63]. On another note, when there is good gut barrier and eubiosis, short chain fatty acids (SCFA) are produced. The presence of SCFA and adenosine would help the gut microbiota to overcome invaders. SCFA are also involved in homeostasis of the IgA production, tight junction, and microbiome population. These would be discussed further in a later subtopic of this review.

At low concentrations, the pro-inflammatory proteins serve as regulatory proteins to achieve homeostasis. Subsequently, both IL-1 and IL-18 participate in the initiation and amplification of the inflammatory responses. Figure 3 depicts the amplified inflammatory response in both the lung and gut, labelled as a) and b), respectively, in a severe COVID-19 infected individual.

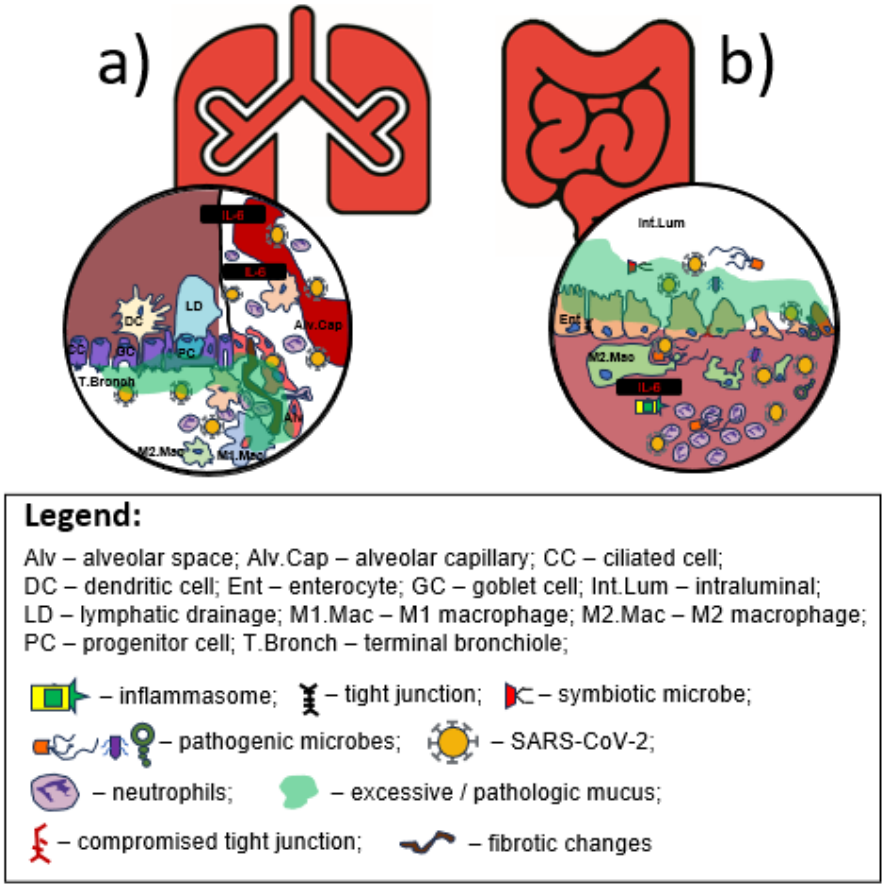

Fig. 3. The lungs and gut in severe COVID-19 infection

5. Infectivity: *SARS-CoV-2* Fate and Microbiome Ecology

One factor contributing to the complex nature of the host immune response to COVID-19 is the involvement of Transmembrane Protease Serine 2 and 4 (TMPRSS2 and TMPRSS4) in facilitating the entry of the virus into the host via angiotensin-converting enzyme-2 (ACE-2). The ACE-2 is also found along the gut lining [64]. It is noteworthy that enterocytes could also be infected by *SARS-CoV-2* via TMPRSS2 and TMPRSS4 [65].

The TMPRSS2 is known to regulate the tryptophan level in the gut. As the metabolism of tryptophan promotes differentiation of T-Reg and induces IL-10, on the contrary, its degradation produces IL-22 [66]. A different author has reported that high IFN levels promote tryptophan degradation, which correlates to ARDS severity [67]. In some lung pathologies, TMPRSS4 is upregulated for its role in epithelial migration and mesenchymal transition [68]. This may explain the fibrosis and scarring mechanisms seen as a complication of the COVID-19 infection [69,70]. Alternatively, COVID-19 infection causes macrovascular and microvascular complications that may also play a role in fibrosis [69].

ACE-2 which is physiologically known to block the renin–angiotensin–aldosterone system (RAAS) was also found to be a functional receptor for *SARS-CoV-2* [71]. The underexpression of ACE-2 in an

immunocompetent host makes them less susceptible to COVID-19 infections [72]. These were also echoed in the paediatrics population and would be discussed further in a subsequent subtopic of this review. While the usage of pharmaceuticals such as angiotensin-converting enzyme inhibitor (ACE-i) and angiotensin receptor blocker (ARB) were controversial during the pandemic, recent research has mixed findings about it. In a retrospective study of approximately 7,600 COVID-19 patients on ARB or ACE-i showed that the former was superior in reducing the length of hospital stay duration. However, the mortality rate did not differ [73]. Elsewhere, an open label randomised control trial of ARB and ACE-i in critically ill COVID-19 patients worsened the outcome and survival rate compared to those who did not receive both the medications [74]. Finally, a multicentred retrospective observational study stated that their finding was consistent with the International Society of Hypertension which was not to discontinue both the medications during COVID-19 [75]. The findings from these three research show that the ACE-2 could be modulated accordingly at different instances and severity of COVID-19.

When a person is infected with COVID-19, the neutrophil counts are high even with leukopenia [76]. Toll-like receptors (TLRs) recognise viral products thus initiating innate immune response. There is also elevation of C-Reactive Proteins (CRP), lactate dehydrogenase (LDH), and procalcitonin [76–78]. Elsewhere, there were abundant bacteria that were reported to cause co-infection with *SARS-CoV-2* [79]. On top of that, there were also reports of fungal and other viruses as co-infectors [80].

Recently, Morens *et al.,* [81] have implied that infections with *SARS-CoV-2* may not be fully controlled by human immune responses and exhibit interindividual variations. They have suggested that future strategies should target non-conventional host immune mechanisms [81].

A recent study that investigated the expression of ACE2 and TMPRSS2 in COVID-19 patients found that there was no discernible variation in the blood expression the aforementioned levels in adults nor children [82]. In addition, children had low expression of TMPRSS2 and ACE2 in the nasal and bronchial regions compared to adults [82].

6. Shedding of *SARS-CoV-2* in COVID-19

The degree of disease severity, the type of sample tested, and the clinical spectrum of *SARS-CoV-2* all influence the viral RNA shedding patterns and duration of shedding. A study on *SARS-CoV-2* in which human intestinal biopsy tissues were obtained from patients with COVID-19 and uninfected control individuals for microscopic examination concluded that there were no pro-inflammatory reactions in the GI tract [83]. Surprisingly, there were considerable decrease in the severity of the illness and mortality in those with GI symptoms [83].

In a systematic review, 364 patients collectively showed a longer shedding time in stool samples with a median of 19 days when compared to the airway which recorded 14 days [84]. In children, the median time were 34 and 9 days for airways and stool, respectively [85]. There was also delayed clearance of SARS-CoV-2 in stool samples of children despite testing negative in the airway. This lasted up to 20 days as reported by Xing *et al.,* [86]. Figure 4 shows the varying symptoms, COVID-19 antigen and/or PCR test results and shedding amongst symptomatic and asymptomatic individuals.

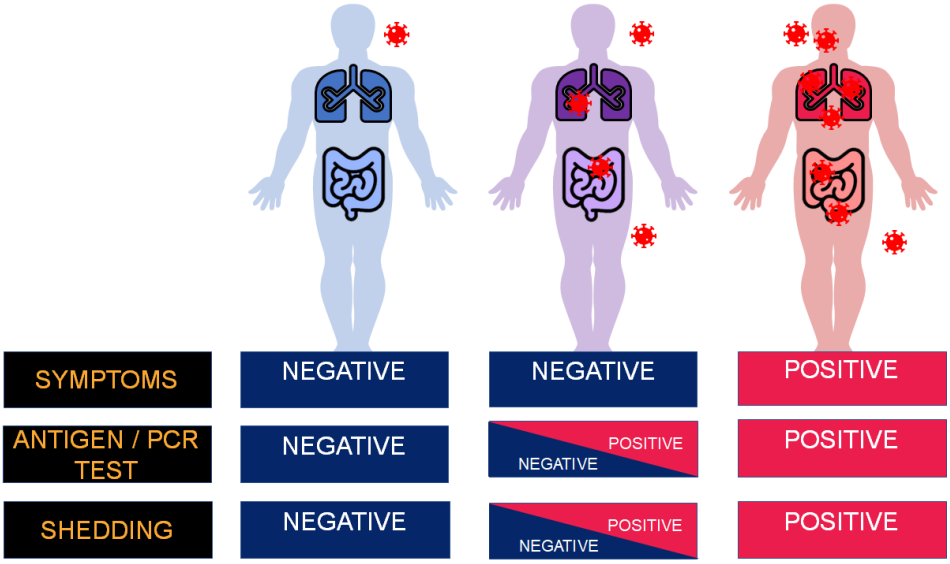

Fig. 4. The symptoms, test results and shedding among the asymptomatic and infected COVID-19 individuals

To our best knowledge, the coverage of "virobiota" in literature is limited. Phagosomes constitute majority of the gut virobiota [87]. Manrique and colleagues reported that healthy phagosome colonies are absent in those with gastrointestinal diseases [88]. There is also evidence of viral presence in the gut with constant shedding since early childhood without any clinical symptoms [89]. Hence this enhances the notion that shedding is a common phenomenon in viral infections.

7. Altered Gut Microbiota, Dysbiosis and Leaky Gut in COVID-19

The intestinal epithelial cell (IEC) barrier, which is functional, supports the symbiotic gut microbiota [90]. The microbiota in the intestinal lumen is contained in a steady state of mucus, antimicrobial peptides, and secretory IgA [90]. The intestinal immune system in the gut lamina propria becomes mostly tolerant of the resident symbiotes when it is tightly controlled by IECs [90]. DCs facilitate the growth of regulatory T (Treg) cells, which release TGF-β and IL-10. These two factors work in concert to cause the synthesis of commensal specific IgA [90]. IgA has a bidirectional relationship with the microbiota. Microbiota may modulate and induce IgA synthesis and secretion. Likewise, IgA can influence microbiota composition and diversity [91].

Gut dysbiosis may be caused by gut microbiota disruption such as SIBO (Small Intestinal Bacterial Overgrowth), LIBO (Large Intestinal Bacterial Overgrowth), SIFO (Small Intestinal Fungal Overgrowth), and IMO (Intestinal Methanogen Overgrowth) [92]. These are beyond the scope of this review but have been discussed thoroughly elsewhere [92]. Dysbiosis are potentiated by i) circulatory cytokines, ii) direct binding of SAR-CoV-2 to enterocytes and, iii) leakage of *SARS-CoV-2* into the gut [93]. Dysbiosis also causes high faecal calprotrectin and low synbiotics [93].

In dysbiosis, there is increased gut exposure to toxins, apoptotic debris, and pro-inflammatory cytokines that cause microbial dysbiosis and an overabundance of "pathobionts," which are symbiotic bacteria that have undergone transformation and are now pathologic [90]. Overgrowth of pathobionts causes the IEC barrier to break and subsequently lose its integrity. Microorganisms and their components can translocate and activate TLRs, which in turn set off potentially dangerous effector T-cell responses intended to eliminate invasive microorganisms [90]. In the end, IECs' release of IL-1 and IL-6 stimulate DCs' and macrophages' TH1 and TH17 responses, which in turn raises B-cells' production of commensal-specific IgG [90].

Notably, dysbiosis is the prognostic marker for the severity of COVID-19 infection [64]. In a recent study by Yeoh *et al.,* [94] it was stated that the gut microbiome of COVID-19 patients were altered irrespective of the treatment modalities utilised. However, these treatment modalities did not include any agents that would act on the microbiome or its axes. In addition, the gut symbiotes were underrepresented in these patients. Upon dysbiosis, *SARS-COV-2* causes dysregulation of the ACE-2, dysregulation to the vascular permeability, induces coagulopathy and cytokine storm. Eventually, dysbiosis is again accentuated by *SARS-CoV-2* [64].

A study has shown elevated levels of interleukins (ILs) such as IL-1β, IL-7, IL-8, IL-9, IL-10, TNF-α, and vascular endothelial growth factor (VEGF) in infected individuals [39]. Nevertheless, the results regarding the production of interferon-gamma (IFN-γ) are conflicting, with some studies showing elevated levels while others reporting decreased production [39]. These discrepancies may be due to the virus's ability to manipulate the host's ubiquitin system, leading to a weakened antiviral response including those of IFN-I[95]. Consequently, this may also explain the mismatch between TNF-α, IL-1β, IL-2, and IL-6 with low T-Reg concentrations leading to cytokine storm [96]. At the point of writing this manuscript, a 2022 article reported low IFN-γ levels while the opposite was found in a 2024 article [97,98]. The plasma of COVID-19 patients had elevated levels of IFN-γ [97]. T-cells from COVID-19 patients expressed higher IFN-γ upon simulation with the spike protein [97]. There was also evidence that IFN-γ downregulated CD8+ T-Cells [97]. Elsewhere, a low of IFN-γ was one of the predictors for hospitalisation [98]. There was also a significant inverse correlation between low IFN-γ response and high level of IL-6 [98]. We gather that these differences are due to discrepancies in the levels and need for IFN-γ at different spectrums of the disease such as mild COVID-19 to the extreme end of COVID-19 with cytokine storm release.

As for leaky gut, it is a phenomenon in which there is increased permeability of the gut. Intestinal barrier is a functional structure that divides the gut lumen from the inner host [99]. It is made up of humoral (defensins, IgA, mechanical (mucus, epithelial layer), immunological (lymphocytes, innate immune cells), muscular, and neurological components [99]. Tight junction defects, apoptotic leaks, and erosion ulcers during dysbiosis cause impaired intestinal permeability [99]. When there is increased gut permeability as the gut barrier is diminished, translocation of bacteria, lipopolysaccharide (LPS) into blood stream would enhance pro-inflammatory immune response and possibly trigger cytokine storm as discussed separately by Vignesh *et al.,* [53] and Hussain *et al.,* [93].

A study that investigated the gut barrier dysfunction in almost 150 COVID-19 patients, found that COVID-19 patients had considerably greater levels of fatty acid binding protein 2 (FABP2), peptidoglycan, and LPS, which support the existence of leaky gut [100]. Additionally, COVID-19 infection increased *Firmicutes* to *Bacteroidetes* ratio [100].

8. The case of Prebiotics, Probiotics, Synbiotics and Postbiotics

Probiotics are live bacteria that, when administered in adequate proportions, improve host health by colonising the body [101]. Probiotics can modify the composition of human microbiota [101]. The presence of probiotic and symbiote microorganisms in the lung-gut axis aids the modulation of gut bacteria, regulation of antioxidant enzymes, scavenging of free radicals, and chelation of metal ions [102].

The prebiotics are usually substrates that are non-digestible and yet may benefit the microbiota [103]. Prebiotics may further aid the productivity, efficacy, and proliferation of certain probiotic strains [104]. It is noteworthy that synbiotics are the combination of prebiotics and probiotics [105].

The SCFA are made of propionic and butyrate. These are also considered as postbiotics which are the byproducts of the microbes and mycoplasma that utilises the prebiotics. The prebiotics does not

cause any harm to the mucosal lining of the guts. The SCFA enhances intestinal epithelial barrier function by increasing mucus production via the goblet cells and fortifying the tight junctions [14]. Other than that, the SCFA also stimulates IgA production and G-Protein receptors (GPR) such as GPR 109A and promotes T-cells such as the T helper 1, 17 and IL-10 Tregs [106]. On another note, butyrate increases Th9 which reduces lung inflammation[107].

9. Haemophagocytic Lymphohistiocytosis (HLH), Cytokine Storm, Macrophage Activation Syndrome (MAS) in COVID-19 and the aftermath to the Microbiota

During the COVID-19 pandemic, it was common to hear interchangeable terms such as Haemophagocytic Lymphohistiocytosis (HLH), cytokine storm and cytokine storm syndromes [108]. Cytokine storm was first discussed as “cytokine dysregulation” in host versus graft disease [109]. HLH is eponymous to histocyte disease and while primary HLH, mainly affects children, the secondary HLH is commonly seen in adults [110,111]. Newer HLH classifications of GLH is beyond the scope of this review but has been discussed elsewhere by Ponnat *et al.,* [110]. In severe COVID-19, it is proven that there is presence of cytokine storm [108,112].

The main outcome of cytokine storm is immune exhaustion, reduced perforin, and inadequate cytolysis [108,112]. On the other hand, macrophage activation syndrome (MAS) is a kind of "Cytokine Storm Syndrome" that is typical of many rheumatic disorders, such as Still's disease and systemic juvenile idiopathic arthritis [113,114]. Elsewhere, Liu *et al.,* [111] echoed that it could also be immunologically induced in origin.

To our best knowledge, there are at least three scoring systems that have been utilised during the COVID-19 pandemic to fulfil the criteria of HLH, cytokine storm and/or MAH which are Delphi score, H-Score and COVID-19-associated hyperinflammatory syndrome (cHIS) scale, respectively [115–117]. A few authors including Hakim *et al.,* have argued that COVID-19 is not HLH as proven by H-score.

At the point of writing this review, the debate to stratify severe COVID-19 as HLH, cytokine storm or MAS remains. There are issues and discrepancies with the scoring system and inhomogeneous finding in COVID-19. Interestingly, the strategy to blunt HLH, cytokine storm and MAH are similar and resolves around high dose steroids, antivirals, immunomodulators, convalescent plasma therapy, therapeutic plasma exchange and hemadsorption, other immunosuppressive agents and cytokine-targeted therapies [108].

Severe COVID-19 infections and cytokine storm impact the gut microbiota. To date, there are two theories to support this notion. The first being severe COVID-19 infection alters the gut milieu resulting in: i) overgrowth of *Coprobacillus, Clostridium ramosum, and Clostridium hathewayi* ii) dysregulation of substrates such as low citrulline, citric acid and increased kynurenine to tryptophan ratio and succinic acid [118–120]. Notably, low citrulline and high succinic acid are pathognomonic to dysbiosis and leaky gut [121,122]. The second theory is the alteration of the microbiota due to antibiotic usage during severe COVID-19 [123,124]. It is common in clinical medicine for extensive antibiotics use during cytokine storm [125,126].

10. Flipped Kindergarten: Lessons Through the Low *SARS-CoV-2* Infectivity in Paediatric Population

Surprisingly, the infectivity of COVID-19 in the paediatric population has been globally low. Separate studies from China, Italy, Spain, and USA have shown similar results[127]. In a recent meta-analysis, less than 3.5% children who tested positive for COVID-19 were hospitalised [128]. There is also low seroprevalence of *SARS-CoV-2* in children [129]. ICU admission and death were also

uncommon among this population [128]. Possible explanations for the mild illness reported in this patient group include elevated ACE2 receptor concentrations, trained immunity, and a constitutionally high lymphocyte count, especially NK cells in paediatrics population [130]. In addition, children have better thymic function against COVID-19 compared to adults [131,132]. The innate immunity in children is more efficient compared to adults in upper airway contact with *SARS-CoV-2* [133]. Remarkably, children may have IgM for *SARS-CoV-2* despite being asymptomatic [129]. Another interesting theory is that children have higher melatonin levels [134,135]. Inflammasomes including $NLPR_3$ activated by *SARS-CoV-2* as discussed earlier accentuate lung injury. These inflammasomes are blocked by melatonin [136]. Besides, melatonin also reduces infection associated oxidative stress and reduces immunosuppression from sleep deprivation and chronic stress as discussed extensively elsewhere [136]. In a separate study by Köken *et al.,* [137] found that non-COVID-19 patient group had greater levels than the COVID-19 group and concluded that melatonin has protective effects against COVID-19.

It is noteworthy that certain virus infections are severe in children such as Respiratory Syncytial Virus (RSV) and metapneumovirus [133]. Also, children less than six months are susceptible to RSV and influenza [133].

Intriguingly, children carry high *SARS-CoV-2* viral load regardless of being asymptomatic [138]. This supports the earlier subtopic discussion and report of prolonged shedding in a paediatric case. Although children were less susceptible to COVID-19 infections, they were more prone to complications such as multisystem inflammatory syndrome in children (MIS-C, myocarditis, neuroinflammation and long COVID [139]. Children who are susceptible to COVID-19 include those with comorbidities and prematurity [140].

Elsewhere, it is reported that children's Th2 responses are greater, which result in a decrease in pro-inflammatory chemicals [53]. Th1 is linked to the inflammatory condition referred to as "inflammaging." [53].

All of these “flip-kindergarten” findings have been summarised in Figure 5.

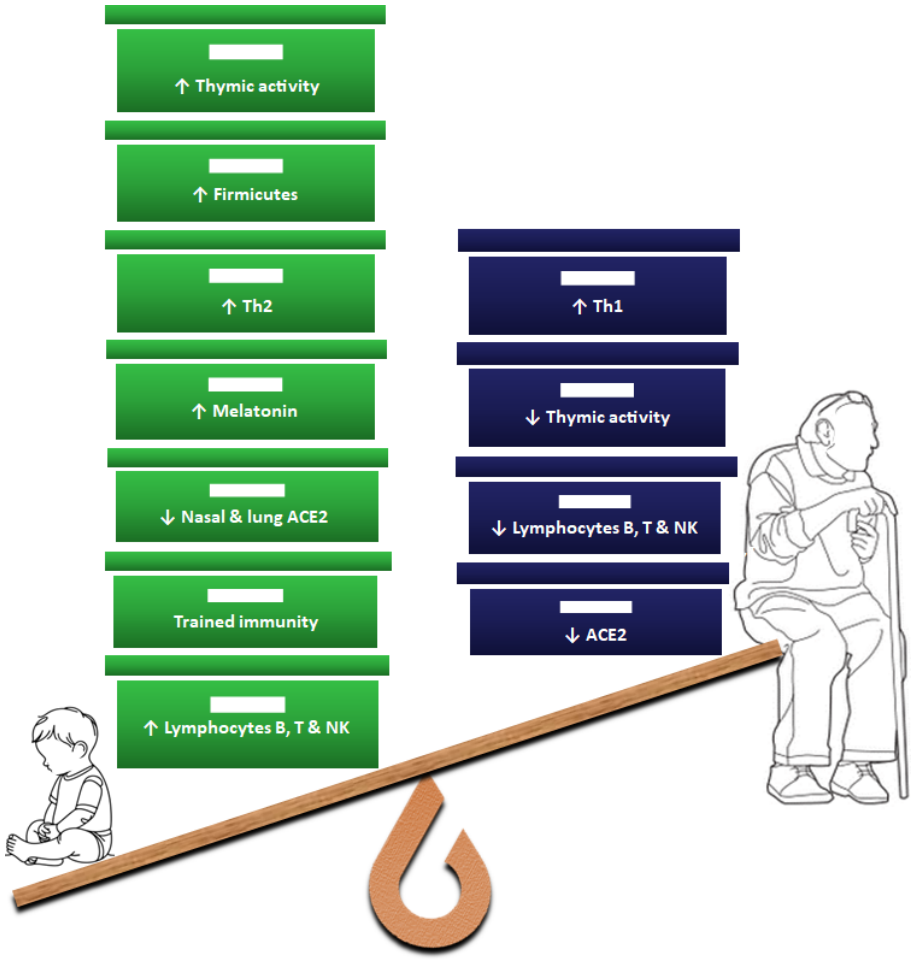

Fig. 5. Protective factors that contribute to low SARS-CoV-2 infectivity in padiatrics population

11. Future Aspects for the Interplay between Oral, Nasal, Lungs and Gut Microbiome *and SARS-CoV-2*

Mounting data illustrate that the host's immune response to COVID-19 and the microbiome ecology contributes to the growing understanding of the relationship. Nevertheless, future aspects of the interplay could be divided into research and clinical modulation. Figure 6 shows the overall summary that has been discussed in this narrative review.

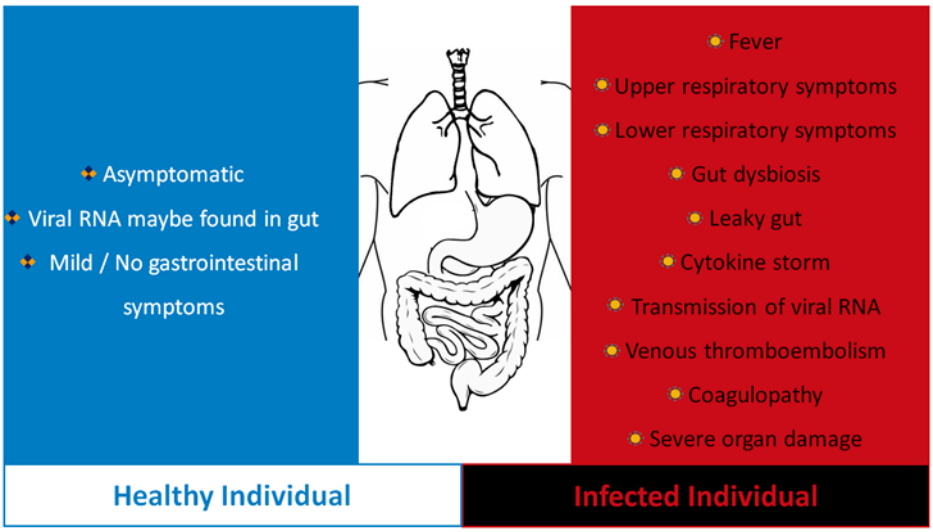

Fig. 6. *SARS-CoV-2* induced responses in the lungs and gut of a healthy and infected individual.

As for research, understanding the various microbiome, the nutrigenomics and nutrigenetic aspects could help with synthesis of new pharmaceutical and nutraceuticals. This could also lead to looking back at the existing arsenal and conducting non-biased evidence-based research. Other than that, other diagnostic tools should be readily available to distinguish *SARS-CoV-2* with other respiratory viruses, bacteria and even mycoses. This should be used as an adjuvant with the PCR, antigen, and antibody test. Pattern recognition, bioinformatics, the study of relevant 'omics', machine learning, deep learning and simulation should be utilised at best to address Hazard Identification, Risk Assessment and Risk Control (HIRARC) for future similar occurrences. Further research is needed to determine the precise mechanism and magnitude of gut dysbiosis's contribution to disease severity on a personalised and diverse community scale.

Based on the narration of this manuscript, it is lackadaisical to believe that we can successfully interfere in the interactions between humans and microbes without considering microbial ecology and evolution. Minimising harm to the health-associated equilibrium between humans and their microbiota should be re-prioritized in policy making, education, research, and medical intervention during illness(es). This could be one of the strategies to prepare for similar pandemics such as the COVID-19.

12. Conclusion

The existence and importance of crosstalk between the oral, nasal, gut and lung microbiome should not be undermined in the *SARS-CoV-2* transmission and COVID-19 infection. We believe that understanding of the complex interactions between the virus and the host immune system opens a plethora of considerable alternative, synergistic and adjuvant diagnostic, and therapeutic means not only for *SARS-CoV-2,* but also other similar viruses.

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