

# GUT MICROBIOME, player in the COVID-19 infection?

---

May 15, 2020

Over the past weeks, the world has been hit by a new virus called SARS-CoV-2. This virus, infinitely small and infinitely threatening, has brought most of the planet to a standstill. Scientific research has been very active and many teams around the world were rapidly mobilized to build up knowledge about this new virus and to fight a major public health crisis. Numerous publications have been published, including some on the gut microbiome and COVID-19.

We wanted to make a short, non-exhaustive synthesis on this topic in order to highlight some of the up-to-date discoveries and to share experts' opinion of **Pr. Joël Doré, Scientific Director of MetaGenoPolis and Micalis INRAE France** and **Pr. Harry Sokol, Hepato-gastroenterologist at the Saint Antoine Hospital in Paris, France**.

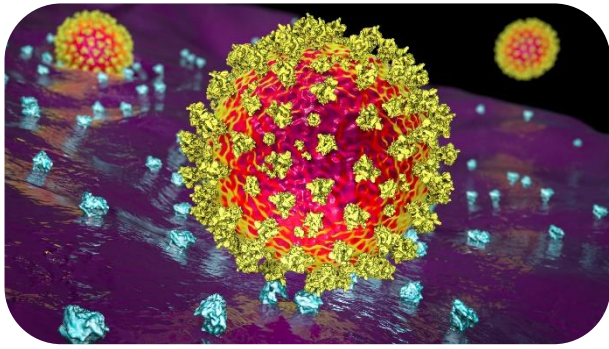


## COVID-19 in a few words

— Since December 2019, the SARS-CoV-2 virus has generated an unprecedented global pandemic. This virus, which belongs to the coronavirus family, is responsible for the infection known as COVID-19. Recent studies have revealed that the SARS-CoV-2 virus has a angiotensin-2 converting enzyme (ACE2) receptor and is therefore able to infect all human cells that express it. (Zhou et al., 2020 ; Lekto et al., 2020). Current data suggest that the infection would take place in two phases: a first phase of infection due to the virus for about a week, then a second phase of exacerbated reaction of the immune system, also called cytokine storm, for a reduced number of people resulting in hospitalization in intensive care units. (Shi et al., 2020 ; Tay et al., 2020). The SARS-CoV-2 virus has a high level of contagiousness and causes different reactions in individuals. Some people will not realize that they are infected, some will have mild symptoms, while others will experience severe cases of infection ranging from severe acute respiratory syndrome to multiple organ dysfunction leading to death. Most individuals with severe cases of infection have been found to have co-morbidities. Indeed, age and some chronic diseases appear to influence the individuals prognosis infected with COVID-19. Nevertheless, severe forms have also been observed in younger individuals without risk factors.

## Can the SARS-CoV-2 virus colonize our intestines ?

— The SARS-CoV-2 virus is detected in samples from the upper respiratory tract, particularly the nasopharynx, and targets the lungs. ACE2, which is recognized as a receptor by the SARS-CoV-2 virus, has been shown to be expressed primarily in type II alveolar epithelial cells and ciliated cells (Qi et al., 2020 ; Zhao et al., 2020).



While it has long been known that the ACE2 enzyme is highly expressed in the small intestine but weakly expressed in the colon, a recent study also showed that the intestine is another organ targeted by the SARS-CoV-2

virus, with the ACE2 enzyme being highly expressed on differentiated enterocytes. (Lamers et al., 2020). The microscopic and transcriptomic methods also revealed that the intestinal epithelium promotes replication of the SARS-CoV-2 virus.

## Is the SARS-CoV-2 virus detected in the feces of infected patients ?

— SARS-CoV-2 virus traces are detected in feces of individuals who were tested positive for COVID-19 infection. However, at this time, it has not yet been demonstrated whether SARS-CoV-2 virus can be transmitted via stools of infected patients and whether it is

infectious. An initial study showed persistence of traces of the SARS-CoV-2 virus in stools up to 60 days after the onset of symptoms. (Zheng et al., 2020). The SARS-CoV-2 detection time was significantly longer in fecal samples than in respiratory and serum samples. Another



study carried out on five patients admitted and followed up at Bichat-Claude Bernard University Hospital (Paris, France) and Centre Hospitalier Universitaire Pellegrin (Bordeaux, France) for COVID-19 infection also showed detection by RT-PCR of the SARS-CoV-2 virus in the feces of 2 of these patients. The quantified fecal viral load was in the range of 6 to 8 log<sub>10</sub> copies per gram of stool (Lescure et al., 2020).

## The gut microbiome, a key player in our health

— In recent years, many studies have been conducted to better understand the role of the gut microbiome in human health. It has been shown that a decrease of the gut microbiome bacterial diversity, a marker of dysbiosis, is associated with short and long-term health problems such as immune diseases, chronic intestinal diseases, allergies, diabetes (type 1 and 2), obesity, autism, colorectal cancer or cirrhosis (Valdes et al., 2018).

The role of the gut microbiome in systemic inflammation is well known and its disruption has been associated with impaired intestinal permeability. It has also been shown that individuals may react differently to the intake of probiotic drugs or food supplements depending on the composition of their gut microbiome (Zmora et al., 2018 ; Veiga et al., 2020).



Pr. Joël Doré

*« Humans are inherently microbial and if the microbiome can influence susceptibility to infection by the influenza virus, therefore in an extra-intestinal sphere, it is probably first and foremost through its close relationship with the immune system (the natural defenses). Research is now documenting chain relationships between the microbiota, intestinal permeability, inflammation and the resulting oxidative stress. »*

In viral infections such as influenza, the intestinal microbiota appears to influence the infection severity with risks of bacterial superinfections of the lungs in individuals with decreased gut microbiome diversity (Sencio et al., 2020).

## Does the gut microbiome play a role in COVID-19 infection and the associated immune response ?

— In the case of COVID-19 infection, several data suggest that the gut microbiome may be involved. Since the beginning of the pandemic, physicians have observed that some people infected with SARS-CoV-2 have experienced digestive symptoms, such as diarrhea or vomiting (Jin et al., 2020 ; Lin et al., 2020). The altered gut microbiome and intestinal permeability could lead to an inflammatory state that may be involved in the second phase of COVID-19 infection. The microbiome plays a fundamental role in the host immune system functioning and has an impact on systemic immune responses, even at distant mucosal sites, particularly the lungs (Abt et al., 2012 ; Zelaya et al., 2016).

*« The immune system is connected to the gut microbiome. When balanced, immune homeostasis is promoted. In the case of obesity, hypertension and diabetes, which are recognized risk factors for severe COVID-19 infections, this symbiotic host-microbiome relationship is altered, leading to a loss of bacterial diversity, a reduction in the permeability of the intestinal barrier, an increase in pathogenic bacteria and an inflammatory state. »*



Pr. Joël Doré

People with metabolic syndromes, such as obesity and diabetes, are at high risk of developing severe forms of COVID-19 infection. In recent years, multiple studies have shown that the gut microbiome is depleted and the intestinal barrier is impaired in obese and diabetic patients.



Pr. Harry Sokol

*« It is possible that some bacteria of the gut microbiome play a role in susceptibility to COVID-19 infection. However, there is currently no solid data to incriminate any specific bacteria. »*



This suggests that the initial state of the microbiome in individuals may help predict the development of severe forms of COVID-19.

## COVID-19 infection in children and gut microbiome ?

— Children's gut microbiome is different from that of adults. At birth, the microbiome-host symbiosis is established with a poorly diversified microbiome comprising mainly bacteria capable of developing in the presence or absence of oxygen. These bacteria will create an oxygen-free, so-called anaerobic environment favorable to the development of other bacteria, such as *Bifidobacteria*, some of which will become predominant in children's gut microbiome.

The composition of the gut microbiome will change considerably with the introduction of solid foods, and then it will continue to evolve throughout childhood until adulthood. Indeed, the gut microbiome of healthy children differs functionally and taxonomically from that of adults in the first decade of life, suggesting that the gut microbiome may mature more slowly than previously thought (Derrien et al., 2019). Among these differences, *Bifidobacteria* appear more abundant in the gut microbiome of children than in that of adults, and will progressively decrease until adulthood.

Unlike adults, children infected with the SARS-CoV-2 virus develop milder symptoms in the vast majority of cases. Nevertheless, some severe forms have been found in children. Data from 2,143 cases of children with COVID-19 reported to the China Center for Disease Control and Prevention could be analysed and showed that children of all



ages and genders were infected. Severe forms of the disease were observed in infants (Dong et al., 2020).

A recent report highlighted the case of 8 children with hyperinflammatory shock described as Kawasaki-like syndrome during the COVID-19 pandemic (Ripaghen et al., 2020). This may suggest that some children, as well as adults with severe forms, may have an exacerbated immune response to COVID-19 infection. Since then, several other similar cases have been detected in France and other countries around the world.

*« Healthy young patients with no known risk factors for the severe form of COVID-19 infection are very rare and probably genetically predisposed. Studies are underway to determine which genetic predispositions are involved. »*



Pr. Harry Sokol

Could these differences between the gut microbiome of children and adults be one of the factors explaining children develop less severe forms of COVID-19 infection? This question remains without scientific evidence to date and will likely be the subject of future investigations.

Is it possible to predict severe forms of COVID-19 from the gut microbiome ?

— Several initiatives are rapidly emerging to better understand the involvement of the gut microbiome in COVID-19 infection, particularly the severe forms.

Among them, two French clinical studies: the first named COVI-Biome, coordinated by Prof. Harry Sokol - APHP was launched at the end of April to collect and analyze the feces of 300 patients infected with SARS-CoV-2. In these patients, the composition of the gut microbiome, its function and intestinal inflammation markers will be analysed.



Pr. Harry Sokol

*« The COVI-Biome study is promoted by APHP. It is an ancillary study to the COVIDeF cohort whose objective is to collect stool from patients infected with COVID-19 in order to determine whether alterations exist and whether the microbiome can predict the occurrence of severe forms of the infection. »*

The second study named EDIFICE was also launched at the end of April by the start-up LUXIA Scientific in partnership with the Medical Research Institute of the Saint Jean l'Ermitage Clinic in Melun. The objective will be to determine in 160 individuals whether the loss of diversity of the gut microbiome is associated with COVID-19 infection.

## How can we best help our gut microbiome ?

— Today there is a lack of fibers in our diet in both adults and children, which has a negative impact on our gut microbiome, for which



Pr. Joël Doré

*« Eating a wide variety of fibers is linked to better health. Fiber will feed our gut microbiome. A diverse gut microbiome supports our immune system and its ability to defend itself against infections. It is therefore becoming necessary to consume more fibers and in greater variety, especially in these days of the COVID-19 pandemic. »*

fibers are an important fuel. (Makki et al., 2018). The bacterial diversity of our gut microbiome decreases and inflammatory diseases increase. Consuming a wide variety of fibers daily is recommended to take care of our gut microbiome.



Although to date no effect or mechanism has been demonstrated on the novel SARS-CoV-2 virus, probiotic strains can reduce the severity of viral infections and some appear to have an effect on other coronavirus strains. (Baud et al., 2020).

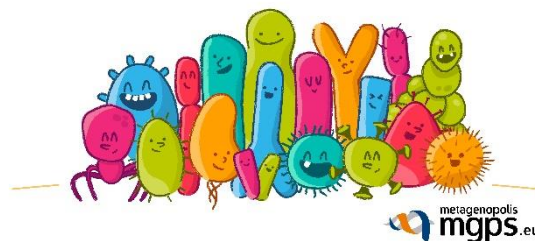
*« To date, there is very limited evidence on the use of probiotics to control respiratory viral infections. So it is difficult to imagine any effectiveness with current probiotics. Nonetheless, some probiotics have shown some efficacy in reducing the severity of intestinal infection, and it is therefore conceivable that the digestive symptomatology of COVID-19 infection could be an interesting target. »*



Pr. Harry Sokol

Could probiotics play a role in reducing the viral load of SARS-CoV-2 and the severity of COVID-19 infection? The International Association for Probiotics and Prebiotics (ISAPP) indicates that it is essential to continue scientific advances in the prevention or treatment of coronavirus.

Written by Anne-Sophie ALVAREZ  
Microbiota Scientist & Communication Manager MetaGenoPolis  
by INRAE  
<http://mgps.eu/>  
[@MgpsLab](#)



## References

- Zhou et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579, 270–273 (2020). <https://doi.org/10.1038/s41586-020-2012-7>
- Letko et al. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 5, 562–569 (2020). <https://doi.org/10.1038/s41564-020-0688-y>
- Shi et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 27, 1451–1454 (2020). <https://doi.org/10.1038/s41418-020-0530-3>
- Tay et al. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* (2020). <https://doi.org/10.1038/s41577-020-0311-8>
- Qi et al. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem. Biophys. Res. Commun.* 526, 135–140 (2020). [doi:10.1016/j.bbrc.2020.03.044](https://doi.org/10.1016/j.bbrc.2020.03.044) [pmid:32199615](https://pubmed.ncbi.nlm.nih.gov/32199615/)
- Zhao et al. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. *bioRxiv* 2020.01.26.919985 [Preprint]. 9 April 2020. [doi:10.1101/2020.01.26.919985](https://doi.org/10.1101/2020.01.26.919985)
- Lamers et al. SARS-CoV-2 productively infects human gut enterocytes. *Science* 2020. DOI: [10.1126/science.abc1669](https://doi.org/10.1126/science.abc1669)
- Zheng et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study *BMJ* 2020; 369 :m1443
- Lescure et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis* 2020. [https://doi.org/10.1016/S1473-3099\(20\)30200-0](https://doi.org/10.1016/S1473-3099(20)30200-0)
- Valdes Ana M, Walter Jens, Segal Eran, Spector Tim D. Role of the gut microbiota in nutrition and health *BMJ* 2018; 361 :k2179 [doi: https://doi.org/10.1136/bmj.k2179](https://doi.org/10.1136/bmj.k2179)
- Zmora et al.  
Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features. *Cell* 2018 Sep 6;174(6):1388-1405.e21. [doi: 10.1016/j.cell.2018.08.041](https://doi.org/10.1016/j.cell.2018.08.041)
- Veiga, P., Suez, J., Derrien, M. et al. Moving from probiotics to precision probiotics. *Nat Microbiol* (2020). <https://doi.org/10.1038/s41564-020-0721-1>
- Sencio et al. Gut Dysbiosis during Influenza Contributes to Pulmonary Pneumococcal Superinfection through Altered Short-Chain Fatty Acid Production. *Cell Rep.* 2020 Mar 3;30(9):2934-2947.e6. [doi: 10.1016/j.celrep.2020.02.013](https://doi.org/10.1016/j.celrep.2020.02.013).

Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. (2020). doi: 10.1136/gutjnl-2020-320926

Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut*. (2020). doi: 10.1136/gutjnl-2020-321013.

Abt MC, Osborne LC, Monticelli LA, Doering TA, Alenghat T, Sonnenberg GF, et al. Commensal bacteria calibrate the activation threshold of innate antiviral immunity. *Immunity*. (2012) 37:158–70. doi: 10.1016/j.immuni.2012.04.011

Zelaya H, Alvarez S, Kitazawa H, Villena J. Respiratory antiviral immunity and immunobiotics: beneficial effects on inflammation-coagulation interaction during influenza virus infection. *Front Immunol*. (2016) 7:633. doi: 10.3389/fimmu.2016.00633

Derrien M, Alvarez AS, de Vos WM. 2019. The Gut Microbiota in the First Decade of Life. *Trends Microbiol* (12):997-1010. doi:<https://doi.org/10.1016/j.tim.2019.08.001>

Dong et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics* 2020. DOI: <https://doi.org/10.1542/peds.2020-0702>

Riphagen et al. Hyperinflammatory shock in children during COVID-19 pandemic. *The lancet* 2020. DOI:[https://doi.org/10.1016/S0140-6736\(20\)31094-1](https://doi.org/10.1016/S0140-6736(20)31094-1)

Makki et al. The Impact of Dietary Fiber on Gut Microbiota in Host Health and Disease. *Cell Host and microbiome*/2018.:<https://doi.org/10.1016/j.chom.2018.05.012>

Baud David, Dimopoulou Agri Varvara, Gibson Glenn R., Reid Gregor, Giannoni Eric. Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic. *Frontiers in Public Health* DOI=10.3389/fpubh.2020.00186