Covid-19 & SivoMixx®800

The microbiome and immunity

✓ The gut is home to an ecosystem of diverse microbes including bacteria, archaea, eukaryotes, and viruses, known as the gut **microbiome**.

✓ More than 1,000 different bacterial species make up this ecosystem and are referred to as the **gut microbiota**.

✓ The gut microbiota play an important role in the development of the **immune system** and in preventing pathogen invasion through maintaining the **intestinal natural barrier**.
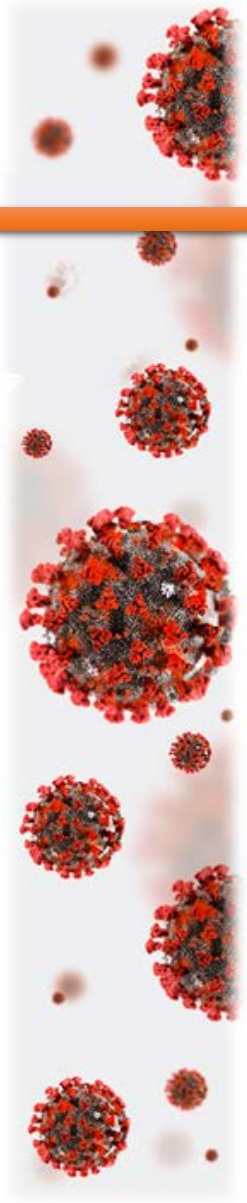
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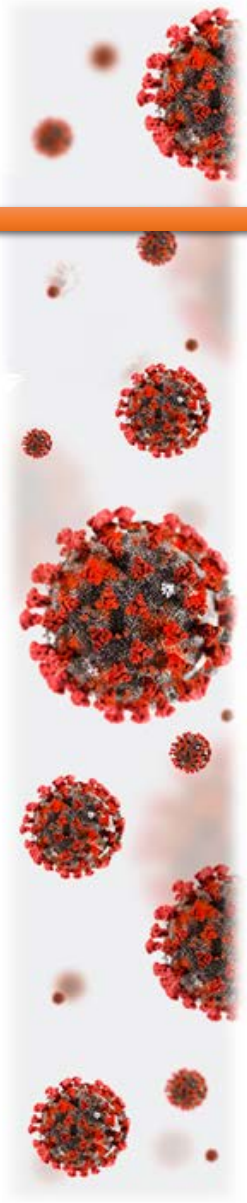
Probiotics and viruses

✓ A range of studies suggests probiotics can influence the course of **viral infections**, including viral respiratory tract infections.

✓ Interestingly, not all probiotics have the same health benefits, so selecting an appropriate product is vital.

✓ There may be interplay between the microorganisms in the gut and those in the lung – the so-called '**gut-lung axis**'

(Infusino F et al. 2020)
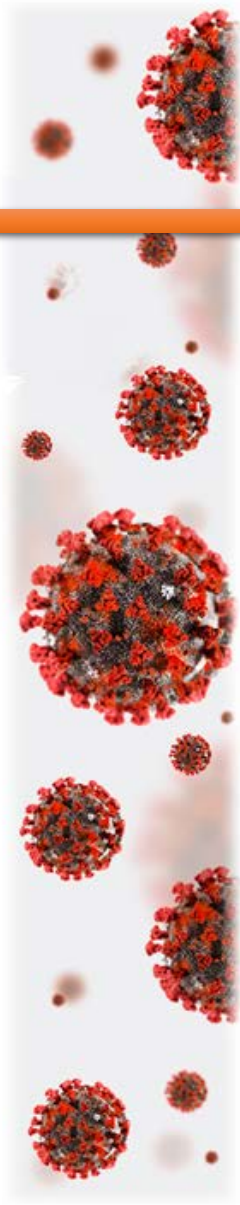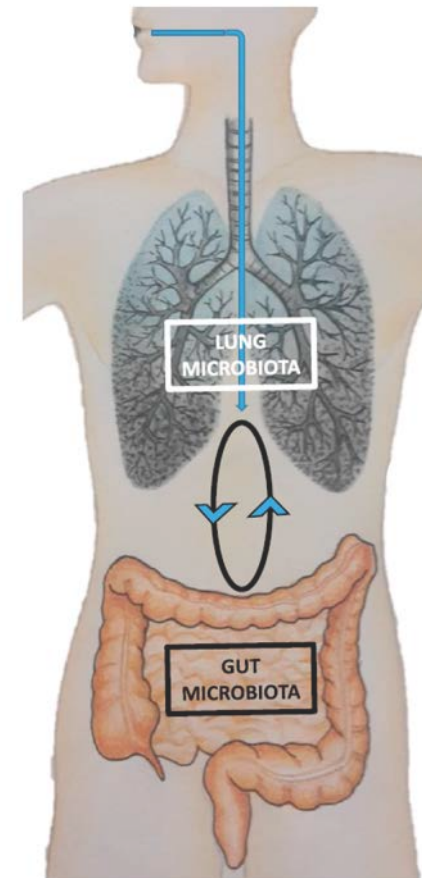
Gut-Lung Axis (GLA)

✓ The recently emerged GLA concept involves **host–microbe** as well as **microbe–microbe** interactions, based both on localized and long-reaching effects.

✓ GLA can shape immune responses and interfere with the course of respiratory diseases.

✓ Growing evidence indicates the key role of inter-kingdom crosstalks in maintaining host homeostasis and in disease evolution. (Enaud R et al, 2020)

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SARS-CoV-2 virus

✓ Gastrointestinal symptoms like diarrhea, nausea, vomiting and abdominal discomfort, frequently followed by typical respiratory symptoms, are commonly found in patients affected by COVID-19 and showed to be associated to disease severity.

Jin X, et al., 2019; Lin L, et al., 2020

✓ Both organs express the **ACE2 receptor**, through which the SARS-CoV-2 virus can enter cells.

✓ In the gut, where ACE2 receptors are abundantly present, coronavirus may multiply quickly.

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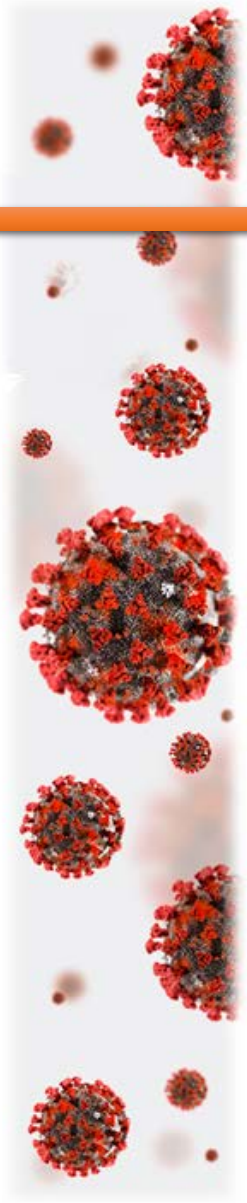
SARS-CoV-2 and ACE2 receptors

Previous studies have shown that:

✓ ACE2 expressed in the intestinal epithelium regulates the ecology
of the gut microbiome through intestinal amino acid homoeostasis.

Hashimoto T et al. Nature. 2012;487:477–481

✓ ACE2 receptors are markedly downregulated by the entry
of SARS-CoV-2 into cells through membrane fusion.

Verdecchia P et al. Eur J Intern Med. 2020;76:14–20

✓ The intestinal downregulation of ACE2 can consequently lead to an
altered microbiota that confers susceptibility to inflammation of the gut.

Perlot T et al. Microbes Infect. 2013;15:866–873
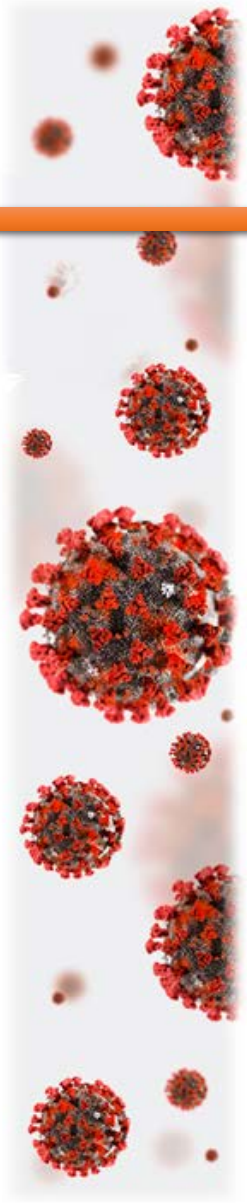
Possible mechanism of intestinal involvement in COVID-19

Infusino F, et al.
Diet Supplementation, Probiotics, and Nutraceuticals in SARS-CoV-2 Infection: A Scoping Review.
Nutrients. 2020;12(6):1718

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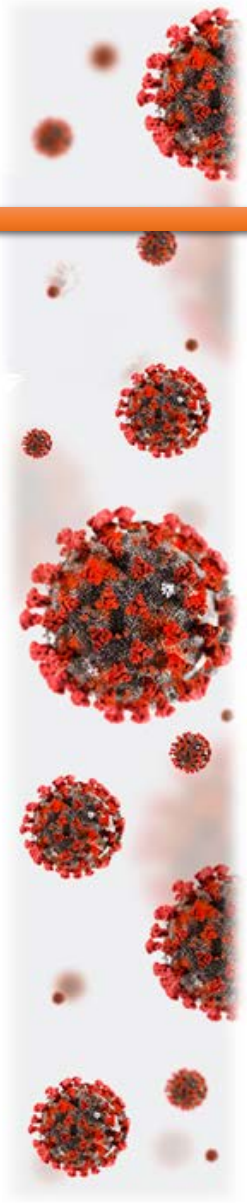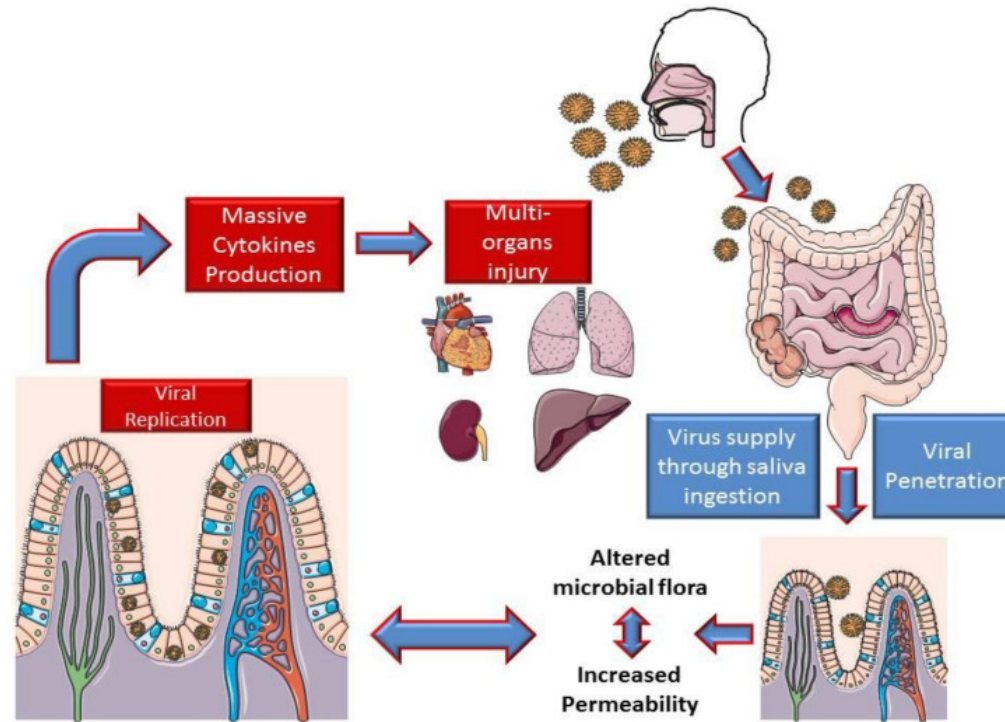
What probiotics can do

✓ Probiotics may play a role in preventing the **cytokine storm** and related acute respiratory distress syndrome (ARDS) or multi organ failure (MOF) in high-risk individuals with established SARS-CoV-2 infection

✓ A number of suggestions indicate that probiotics could represent a complementary tool to decrease SARS-CoV-2-related inflammation and favor the recovery of intestinal mucosa damage. (Infusino et al. 2020)

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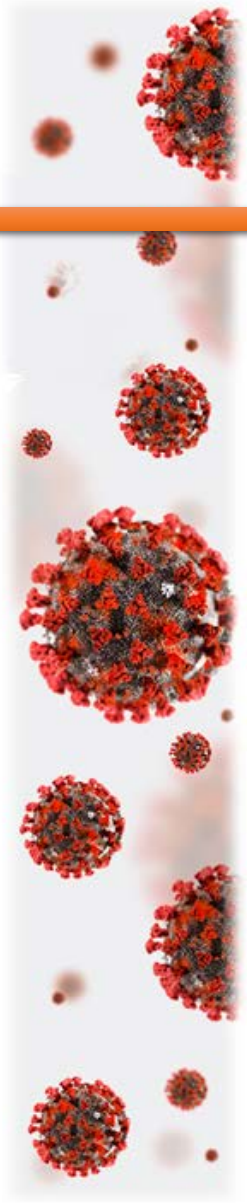
What probiotics can do against viruses

Probiotics could act against viruses in three ways:

✓ by reinforcing the 'innate' immune response in the cells of the gut lining (the mucosa);

✓ by reducing the permeability of the intestine to pathogens;

✓ by regulating the anti-inflammatory effects of the immune response.
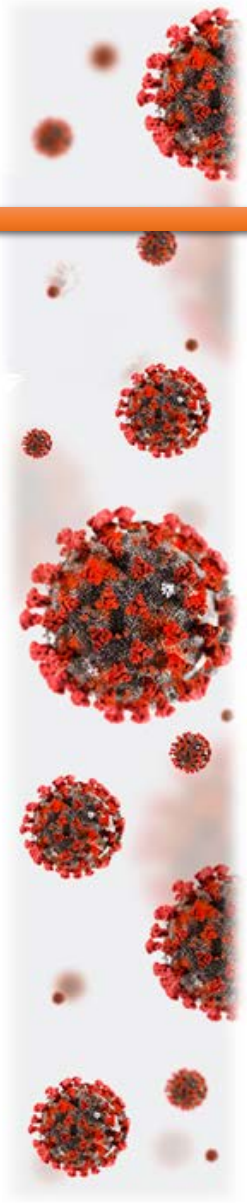
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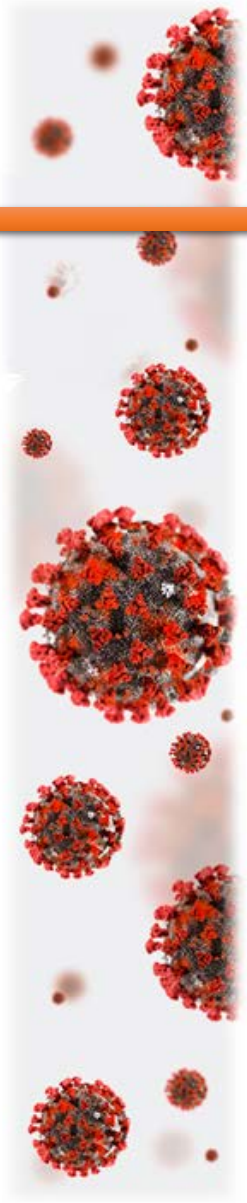
What probiotics can do against viruses

The ability of probiotic strains to modify the balance between **pro-inflammatory** and **immunoregulatory cytokines** can allow:

✓ Viral clearance
✓ Decreased immune response-mediated damage to the lung.

This mechanism might be particularly relevant, in preventing or mitigating the exacerbated inflammatory processes that lead patients affected by COVID-19 to death.

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Challenges in the Management of SARS-CoV2 Infection: The Role of Oral Bacteriotherapy as Complementary Therapeutic Strategy to Avoid the Progression of COVID-19

Gabriella d'Ettorre [1†], Giancarlo Ceccarelli [1*†], Massimiliano Marazzato [1], Giuseppe Campagna [2], Claudia Pinacchio [1], Francesco Alessandri [3], Franco Ruberto [3], Giacomo Rossi [4], Luigi Celani [1], Carolina Scagnolari [5], Cristina Mastropietro [1], Vito Trinchieri [1], Gregorio Egidio Recchia [1], Vera Mauro [1], Guido Antonelli [5], Francesco Pugliese [3] and Claudio Maria Mastroianni [1]

- ✓ **70 patients positive for COVID-19**, hospitalized between March 9th and April 4th, 2020.

- ✓ All the patients had fever, required non-invasive oxygen therapy and presented a CT lung involvement on imaging more than 50%.

- ✓ Forty-two patients received hydroxychloroquine, antibiotics, and tocilizumab, alone or in combination.

- ✓ A second group of 28 subjects received the same therapy added with oral bacteriotherapy, using **SivoMixx®800**.
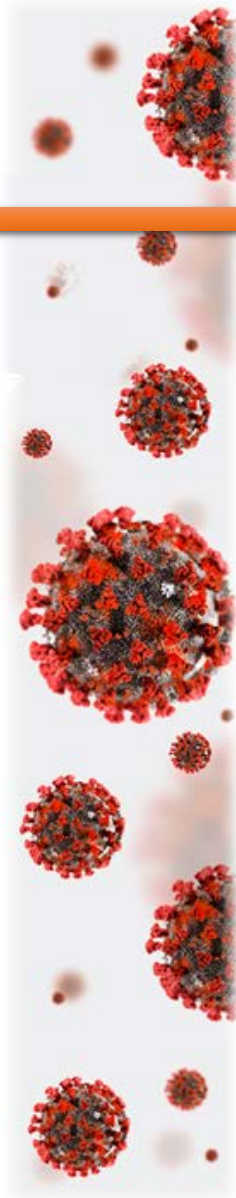
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Oral bacteriotherapy in Covid-19

✓ Almost half the patients were suffering from diarrhoea at the beginning of the study. After 7 days, diarrhoea had resolved in all the Sivomixx®-treated patients but less than half of the control group.

✓ The estimated risk of developing respiratory failure was eight-fold lower in patients receiving oral bacteriotherapy

✓ At the end of the study period, **none of the 28 Sivomixx®-treated patients had died or been admitted to the ICU**, whereas 4 of the 42 controls (9.5%) had died.
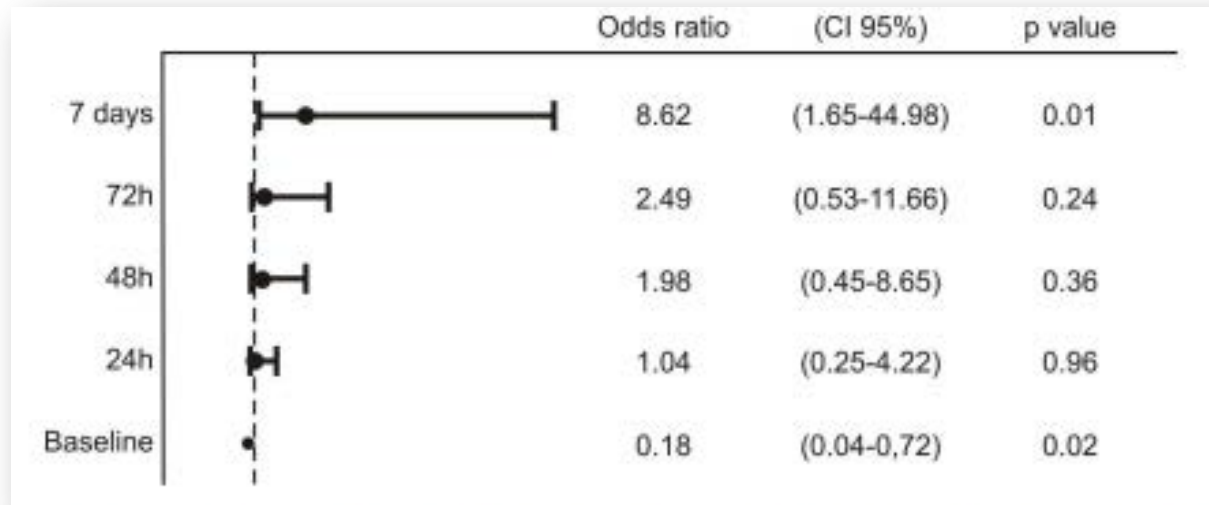
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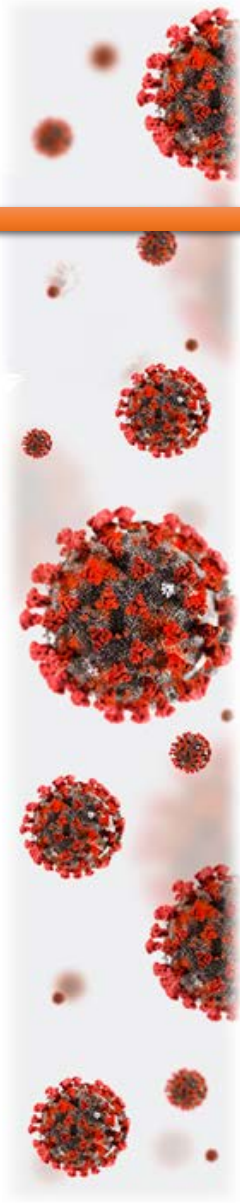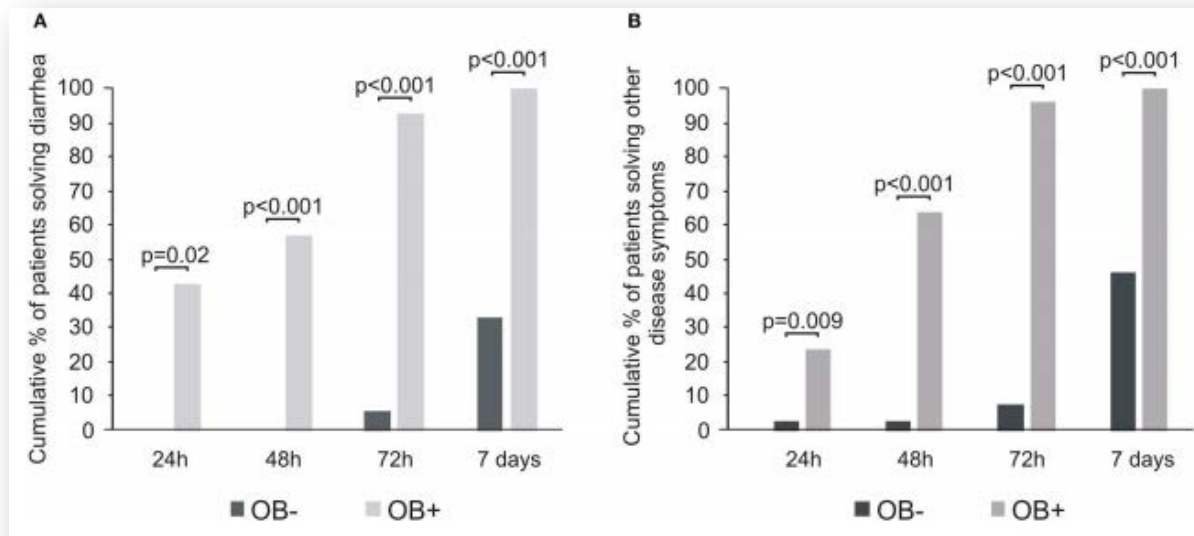
Color-coded barplots based on probiotic administration showing the disappearance of diarrhea (A) as well as other symptoms (B) at different time points. Statistical significance between the group at alpha level 0.05 was also reported.

Within 72h, nearly all patients treated with bacteriotherapy (OB+) showed remission of diarrhea and other symptoms as compared to less than half of the not supplemented group.

	Odds ratio	(CI 95%)	p value
7 days	8.62	(1.65-44.98)	0.01
72h	2.49	(0.53-11.66)	0.24
48h	1.98	(0.45-8.65)	0.36
24h	1.04	(0.25-4.22)	0.96
Baseline	0.18	(0.04-0,72)	0.02

Analysis of the longitudinal data for the respiration variable in relation to the "OB– vs. OB+" group performed by GLIMMIX. For each time point, the odds ratio, the confidence interval 95% and the statistical significance were reported.

The estimated risk of developing respiratory failure was eight-fold lower in patients receiving oral bacteriotherapy (OB+).
Both the prevalence of patients transferred to the Intensive Care Unit (ICU) and mortality were higher among the patients not treated with oral bacteriotherapy (OB-).

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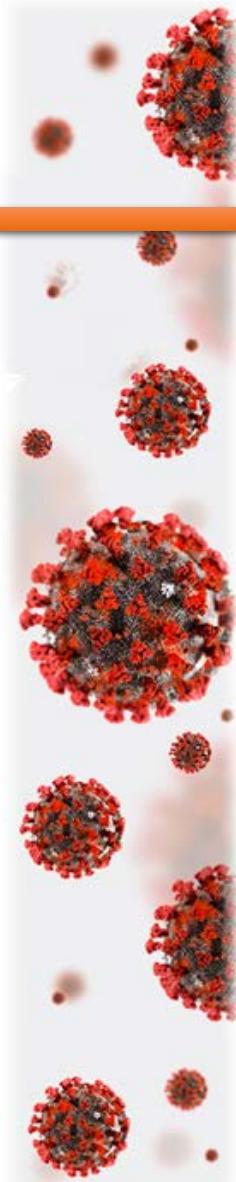
Conclusions

Challenges in the Management of SARS-CoV2 Infection: The Role of Oral Bacteriotherapy as Complementary Therapeutic Strategy to Avoid the Progression of COVID-19

Gabriella d'Ettorre [1†], Giancarlo Ceccarelli [1*†], Massimiliano Marazzato [1], Giuseppe Campagna [2], Claudia Pinacchio [1], Francesco Alessandri [3], Franco Ruberto [3], Giacomo Rossi [4], Luigi Celani [1], Carolina Scagnolari [5], Cristina Mastropietro [1], Vito Trinchieri [1], Gregorio Egidio Recchia [1], Vera Mauro [1], Guido Antonelli [5], Francesco Pugliese [3] and Claudio Maria Mastroianni [1]

The initiative aimed to modulate the gut-lung axis, facilitate patient management and possibly determine the outcome of lung infection.

Oral bacteriotherapy has shown a statistically significant impact on the clinical conditions of COVID-19 patients.
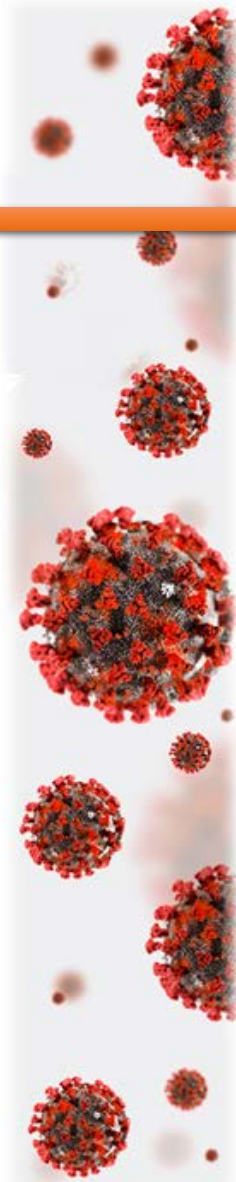
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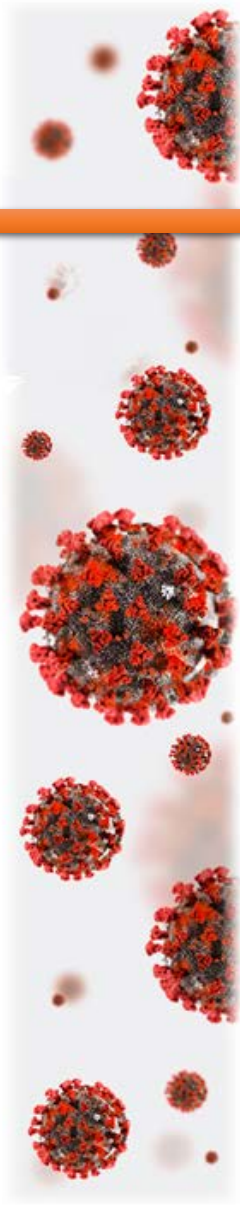## Oral bacteriotherapy in patients with COVID-19: a retrospective cohort study

Giancarlo Ceccarelli[1*], Cristian Borrazzo[2], Claudia Pinacchio[2], Letizia Santinelli[2], Giuseppe Pietro Innocenti[2], Eugenio Nelson Cavallari[2], Luigi Celani[2], Massimiliano Marazzato[2], Francesco Alessandri[2], Franco Ruberto[2], Francesco Pugliese[2], Mario Venditti[2], Claudio M. Mastroianni[2], Gabriella d'Ettorre[2]

This retrospective, observational cohort study included **200 adults** (≥18 years) with severe COVID-19 pneumonia hospitalized in the period March 6 and April 26, 2020.

All patients received therapeutic regimens (**BAT, Best Available Therapy**) including hydroxychloroquine (200 mg twice a day for 7 days), azithromycin (500 mg once a day for 7 days), lopinavir–ritonavir (400/100 mg twice a day) or darunavir–cobicistat (800/150 mg once a day) for 14 days, and low molecular weight heparin.

In addition to the standard therapy, 88 patients were administered with the probiotic bacterial blend **SIVOMIXX®**.

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**Oral bacteriotherapy in patient with COVID-19:
a retrospective cohort study**

Out of the 200 patients:

- ✓ 112 received BAT without oral bacteriotherapy
- ✓ 88 received BAT with oral bacteriotherapy

Crude mortality was 22%. Ten patients (11%) died in the group of 37 patients treated with BAT plus oral bacteriotherapy versus 34 (30%) subjects in the group of 38 patients managed only with BAT (p<0.001).
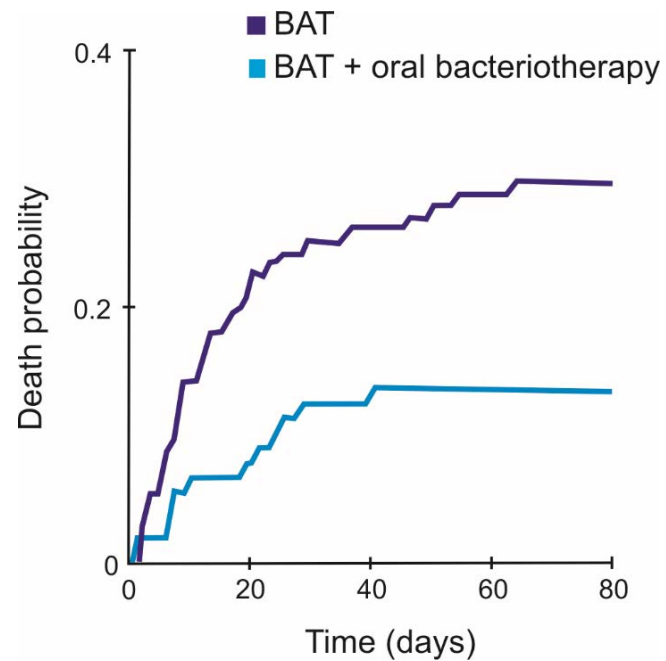
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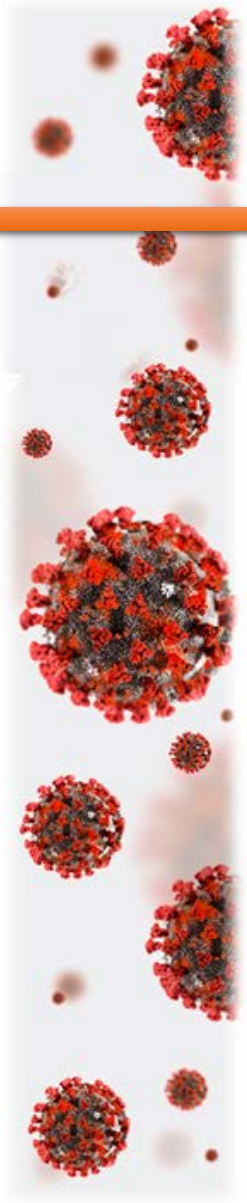
RESULTS – 2nd Study
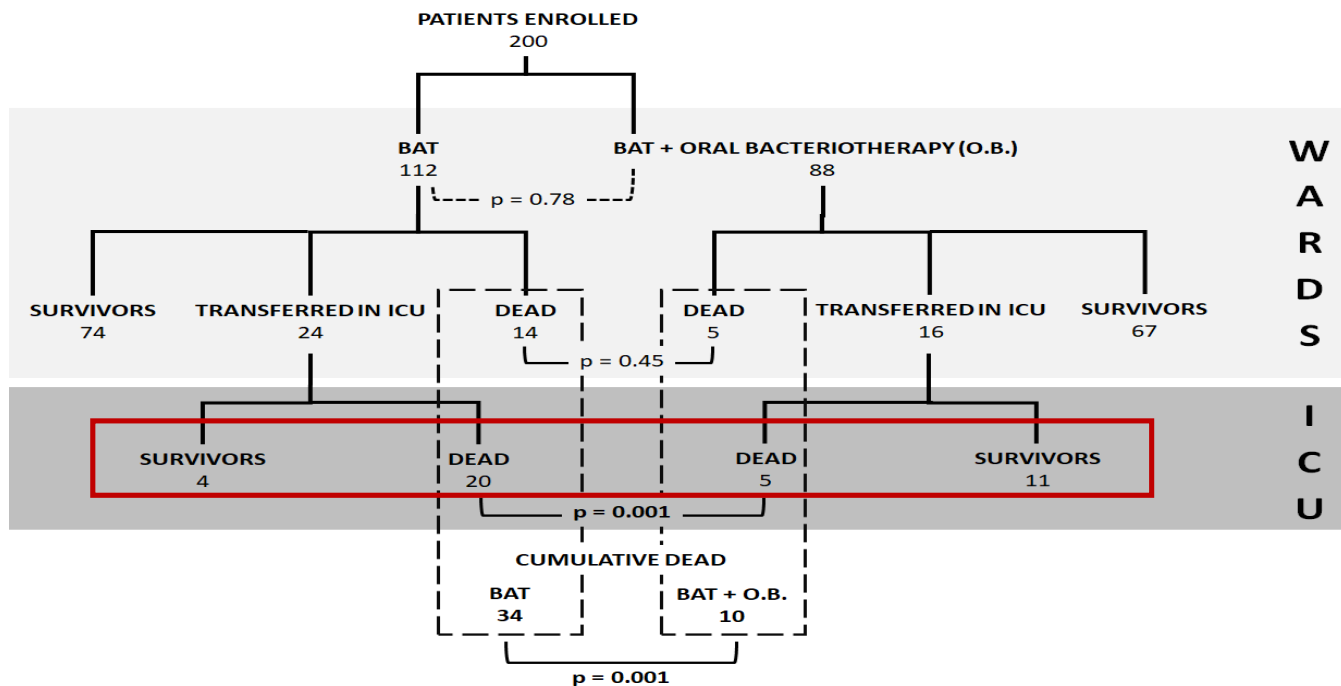
The deaths in ICU of individuals who had taken oral bacteriotherapy
in addition to BAT were 5, while 20 of those treated only with BAT died (p.<0.001).
The percentage of subjects who died in ICU was therefore equal to 83,3%
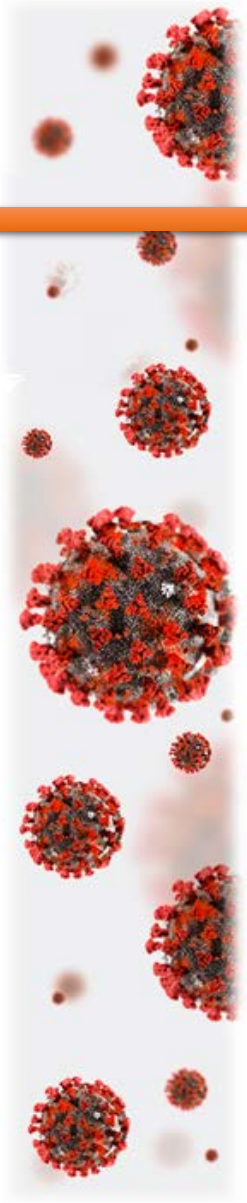for the first group and 31,3% for the BAT + OB group (p<0,001).

SIVOMIXX®800 is a decisive factor for the survival of the patient


Kaplan-Meier curves displaying death probability of patient treated with best available therapy (BAT) versus patient additionally treated with Sivomixx® 800.

Oral bacteriotherapy in patient with COVID-19: a retrospective cohort study

✓ In senior patients, immunocompromised patients, and people with **comorbidities** such as type 2 diabetes, heart disease, and vascular disorders COVID-19 infection may represent a dramatic challenge.

✓ The significant reduction in risk of death present for patients treated with both BAT and oral bacteriotherapy confirms the potential **antiviral and anti-inflammatory activity** exerted by the bacteria strains contained in Sivomixx®800 which are based on the synergic effects produced by the release of specific enzymes and the modulation of host immune response.

✓ Data show that the administration of more drugs in combination does not mean a better therapeutic outcome for COVID-19 patients.
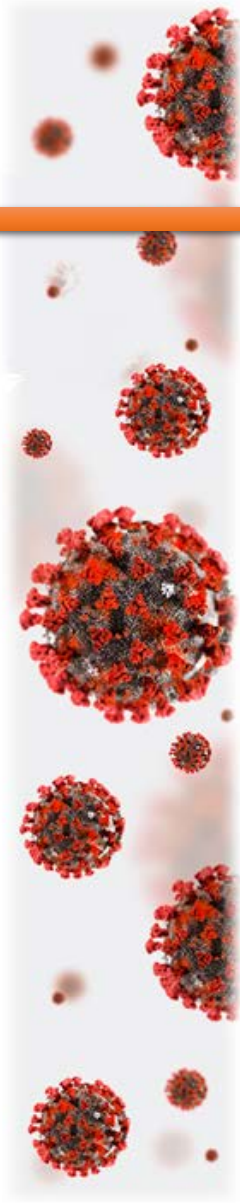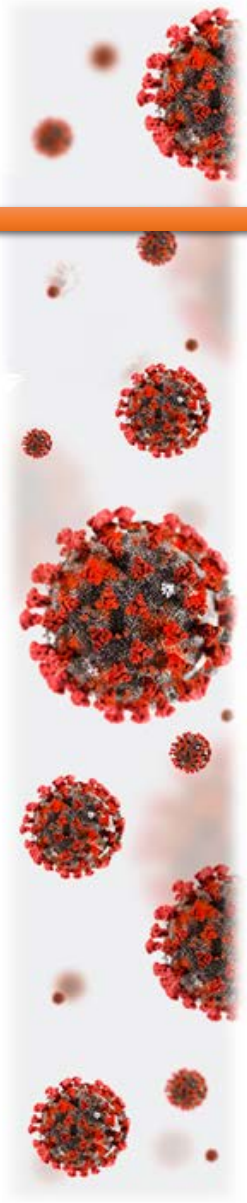
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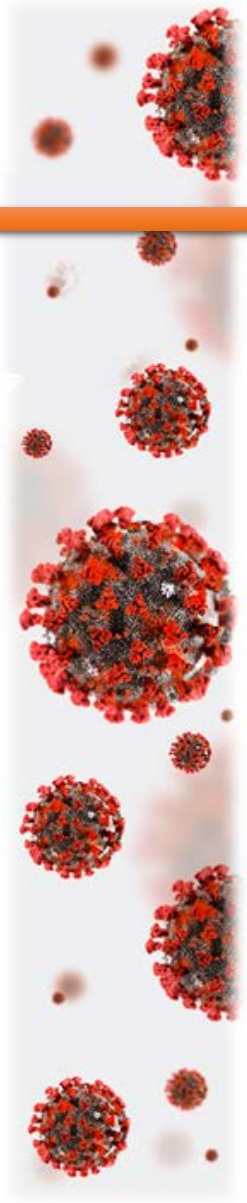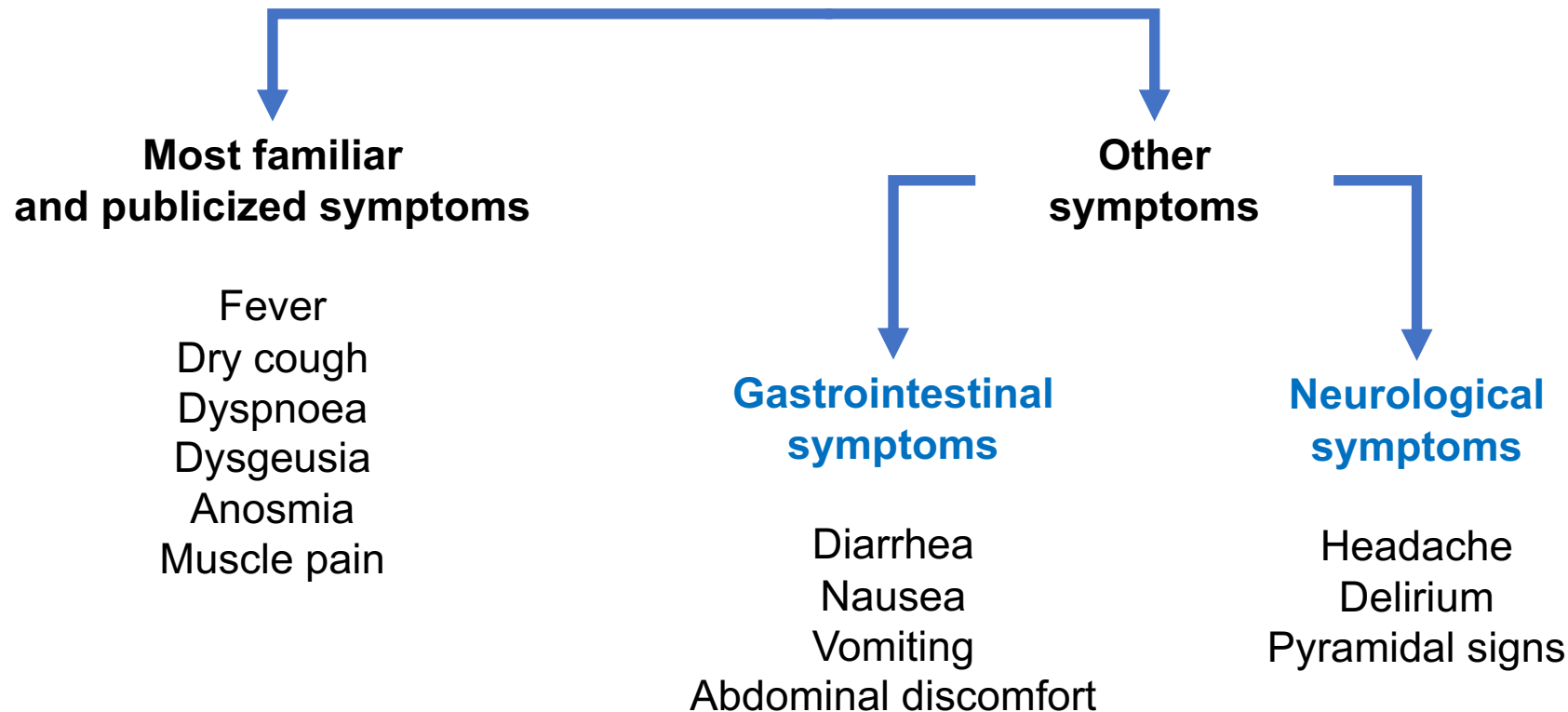
Data suggest a possible role for oral bacteriotherapy in the management of patients hospitalized for COVID-19 pneumonia.

The reduction in progression to severe disease and a lower mortality were highlighted in subjects in whom BAT is associated with oral bacteriotherapy.

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Coronavirus Disease 2019 (COVID-19)

**Most familiar
and publicized symptoms**

Fever
Dry cough
Dyspnoea
Dysgeusia
Anosmia
Muscle pain

**Other
symptoms**

**Gastrointestinal
symptoms**

Diarrhea
Nausea
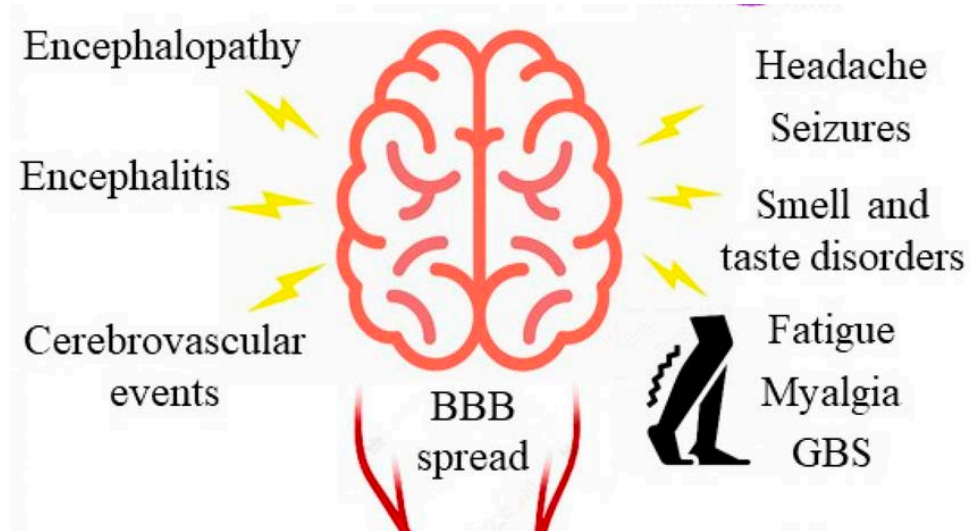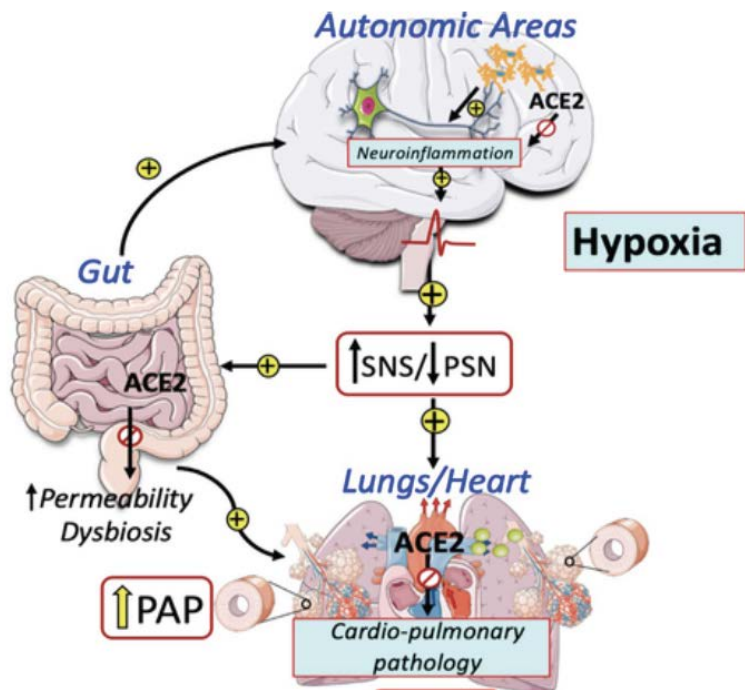Vomiting
Abdominal discomfort

**Neurological
symptoms**

Headache
Delirium
Pyramidal signs
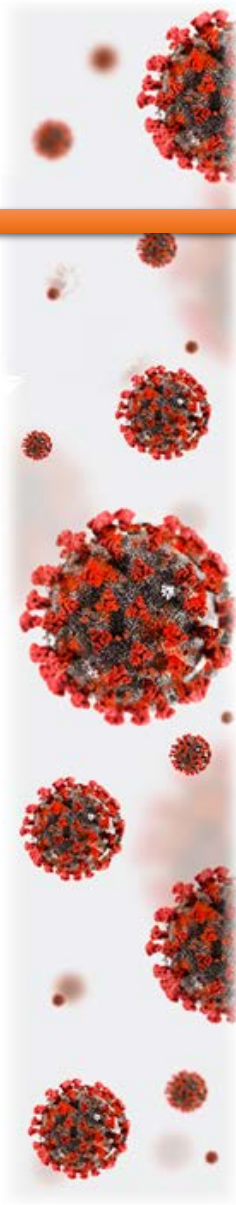
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Other symptoms of COVID-19

One-third of COVID-19 patients suffer potentially from permanent brain damage, and other symptoms such as headache, smell and taste disorder, some pyramidal disturbance, encephalopathy, depression and anxiety.

Protective activity of Sivomixx®
against neurodegeneration

SLAB51/SIVOMIXX® supplementation reduced the plasma concentration of pro-inflammatory cytokines, enhanced the synthesis of critical metabolic gut hormones considered therapeutic targets in neurodegeneration.

SLAB51/SIVOMIXX® markedly reduced oxidative stress in AD mice brain by activating SIRT1-dependent mechanisms, thus representing a promising therapeutic adjuvant in AD treatment.

SCIENTIFIC REP⚙RTS

OPEN

Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels

Laura Bonfili[1], Valentina Cecarini[1], Sara Berardi[1], Silvia Scarpona[1], Jan S. Suchodolski[2], Cinzia Nasuti[3], Dennis Fiorini[4], Maria Chiara Boarelli[4], Giacomo Rossi[1] & Anna Maria Eleuteri[1]

CrossMark

SLAB51 Probiotic Formulation Activates SIRT1 Pathway Promoting Antioxidant and Neuroprotective Effects in an AD Mouse Model

Laura Bonfili[1] · Valentina Cecarini[1] · Massimiliano Cuccioloni[1] · Mauro Angeletti[1] · Sara Berardi[1] · Silvia Scarpona[1] · Giacomo Rossi[1] · Anna Maria Eleuteri[1]
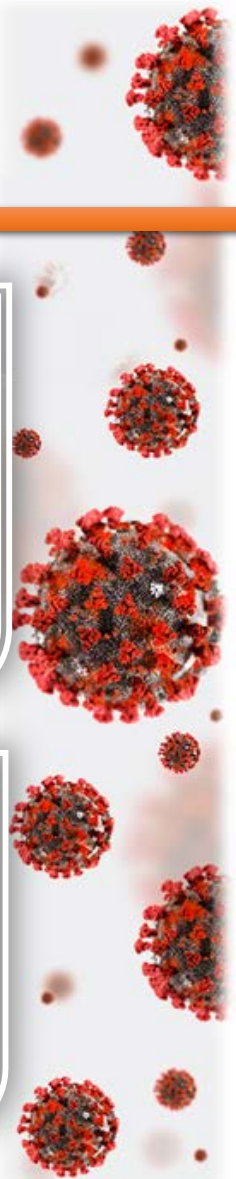
Protective activity of Sivomixx®
against neurodegeneration

SLAB51/SIVOMIXX® showed to protect dopaminergic neurons, counteract neuro-inflammation and oxidative stress and improve behavioral impairments, both *in vivo* and *in vitro*, by reverting some underlying molecular pathways.

Effects of the probiotic formulation SLAB51 in *in vitro* and *in vivo* Parkinson's disease models

Vanessa Castelli[1], Michele d'Angelo[1], Francesca Lombardi[1], Margherita Alfonsetti[1], Andrea Antonosante[1], Mariano Catanesi[1], Elisabetta Benedetti[1], Paola Palumbo[1], Maria Grazia Cifone[1], Antonio Giordano[2,3], Giovambattista Desideri[1], Annamaria Cimini[1,3]

The experimental data show that SLAB51/Sivomixx® can protect neurons, can reduce the inflammation in the brain and reduce the oxidative stress.

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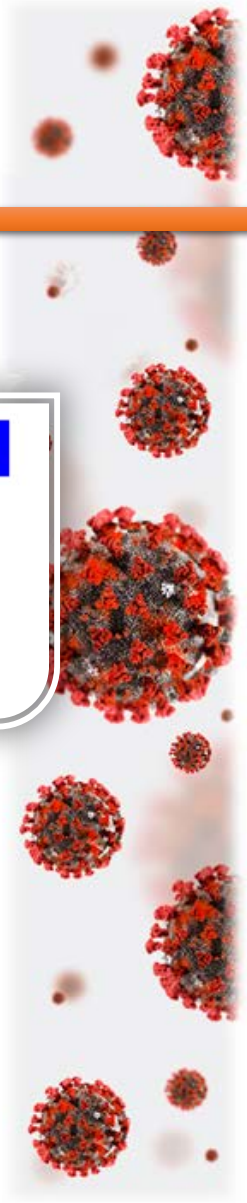
Conclusions

Slab51/Sivomixx® shows to have a valuable impact on:

✓ **The GUT**, by promoting a healthy intestinal microbiota and improving intestinal **barrier function** against invading pathogens

✓ **The Gut-lung axis**, by influencing key local and systemic signaling molecules to sustain the immune response and tissue homeostasis, confirming the potential **antiviral and anti-inflammatory activity**

✓ **The Gut-brain axis**, by protecting neurons and reducing the inflammation in the brain, with a positive effect on the **neurological symptoms** linked with the infection by SARS-COVID-2.

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SIVOMIXX®

slab51®
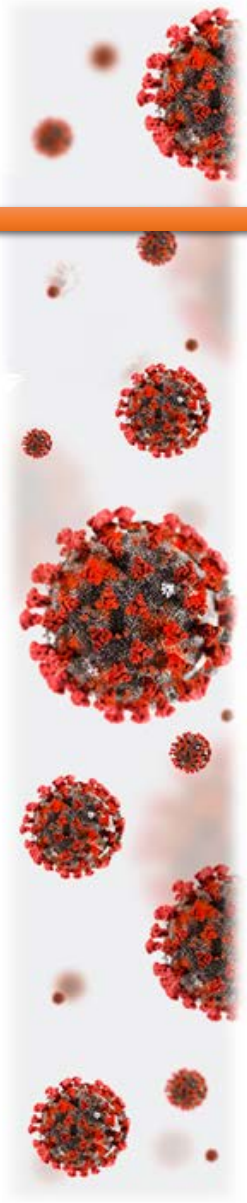
320 billion	• *Streptococcus thermophilus* DSM 32245
2 bifidobacteria **200 billion**	• *B. lactis* DSM 32246 • *B. lactis* DSM 32247
5 lactobacilli **280 billion**	• *L. acidophilus* DSM 32241 • *L. helveticus* DSM 32242 • *L. paracasei* DSM 32243 • *L. plantarum* DSM 32244 • *L. brevis* DSM 27961

www.ormendes.ch
www.sivomixx800.net

Mix of lactic acid bacteria and bifidobacteria, maltose

OrMendes