

# Synbiotic for Prevention of SARS-Cov2 Infection in High Risk Hospital Staffs: A Randomized Controlled Trial

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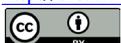
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## Abstract

**Introduction:** COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 increasingly involves people worldwide. Probiotics can improve immune system functions via different mechanisms. We proposed that Synbiotic Lactocare<sup>®</sup> may also reduce SARS-Cov2 infection in high-risk medical staff working in COVID-19 hospital wards. **Method:** In a randomized, controlled trial, 60 hospital staff without any history of clinical or laboratory evidence of SARS-Cov2 infection were received either once-daily oral synbiotic capsule (Lactocare<sup>®</sup>) that contains 1 billion CFU/Cap of *L. (Lactobacillus) casei*, *L. rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *L. acidophilus*, *Bifidobacterium infantis*, *L. bulgaricus*, and Fructooligosaccharide (Zist Takhmir, Tehran, Iran) or placebo with the same appearance for 30 days. They were followed for two months. **Result:** During the two-month period of this study, SARS-COV-2 RT-PCR test results were positive in three participants (9.67%) in placebo group compared to zero positive tests in synbiotic group. The differences were not statistically significant ( $p = 0.238$ ). During the study, two persons (7 %) of placebo group had respiratory complaints such as cough, rhinorrhea and/or dyspnea, compared with one in synbiotic group ( $p = 0.492$ ). **Conclusion:** This study showed that overall frequency of SARS-COV2 infection in participants receiving synbiotic and those receiving placebo did

not differ significantly. However, 3 hospital staff in placebo group compared to no one in synbiotic group had SARS-COV2 infection. Further studies with greater power and alternative probiotic strains and mixture are warranted to determine whether Synbiotic can prevent COVID-19 in at-risk hospital staff.

## Keywords

COVID-19, Synbiotic, Prevention, Lactocare, SARS-Cov2

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## 1. Introduction

COVID-19 pandemic caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is increasingly affecting people worldwide. To date, there is no established prevention or treatment protocol for this new virus. Millions of people suffer from COVID 19 despite social distancing, hand hygiene, healthy diet, and lifestyle and mask-wearing. In Iran, some provinces (Tehran, Alborz, Qom, Mazandaran, Gilan, Qazvin) are known as the main centers of the Coronavirus epidemic, which should be controlled and some provinces (including Golestan, Khorasan Razavi [Mashhad], North Khorasan) are the ring around the center of damage, which should be controlled. The main actors associated with a high number of cases are older age, high degrees of urbanization, higher average temperatures and the number of physicians [1] [2].

Although several brands of vaccines with different efficacy have been approved and vaccination started in some countries, it won't be available for all people especially in developing countries. It is necessary to work on other effective preventive measures that are able to reduce the risk of SARS-Cov2 infection with negligible side effects. This can be used in community or at least in high-risk groups such as health care providers [3].

One of the potential strategies can be probiotics with the ability to boost human immunity [4]. Recent studies revealed that gastrointestinal microbiota has an important role in balance and proper function of immune system [5] [6]. Probiotics have been used in different immune-mediated and inflammatory disorders [7] [8] [9] [10] [11]. Probiotics can improve immune system functions via different mechanisms. One of them is increasing IgA secreting plasma cell numbers in lamina propria of intestine, lung and mammary gland [12] [13] [14]. This immunoglobulin has a major role in mucosal immune system [15]. Besides humoral immunity, healthy commensal microbiota of intestine can increase CD4+ T cells and regulatory T cells of GI lamina propria.

Bradley *et al.* in 2019 showed that the intestinal microbiota influences the IFN- $\alpha/\beta$  receptor surface expression in respiratory epithelial cells, which in case of respiratory virus infection are able to respond more efficiently to type I IFNs stimulation with enhanced interferon-stimulated genes (ISGs) levels and impedes early virus replication [16]. A high-fiber diet (Prebiotic) increased the production of acetate by the intestinal microbiota and modulated the activity of respi-

ratory IFN- $\beta$  and increased the expression of ISGs in the lung [17]. Furthermore, gut microbial components and metabolites (postbiotic) including short-chain fatty acids (SCFA), are involved in gut-lung communication.

To date several studies revealed that probiotics could reduce upper respiratory infections incidence, duration and disease severity [18] [19]. A Cochrane review concluded that probiotics were better than placebo in reducing the number of episodes of acute upper respiratory infection (URTI), the mean duration of an episode of acute URTI, antibiotic use and school absence [20]. A recent systematic review and meta-analysis in 2020 concluded that synbiotic interventions reduced the incidence rate of respiratory tract infections (RTIs) by 16% and the proportion of participants experiencing RTIs by 16% [21]. Sly *et al.* showed that when using Immunostimulant OM-85 in infants, the cumulative frequency of severe lower respiratory tract infection and the number of days with symptoms were significantly lower compared to placebo, suggesting a reduction in the overall inflammatory burden in the lower airways [22].

The immunomodulatory effects of probiotics are strain-dependent [6]. Many trials using *Lactobacillus rhamnosus* GG, *Lactobacillus plantarum*, *Lactobacillus casei* and *paracasei* and some strains of Bifidobacterium could have preventive effects against respiratory infections. These scientific pieces of evidences have opened the possibility of exploring particular strains of beneficial probiotics with immunomodulatory capacities (immunobiotics) in order to increase antiviral defenses in the respiratory tract, especially the combination of probiotics and prebiotics which is called synbiotic [16] [21].

David Baud and colleagues provided a list of probiotic products with documentation in human studies that may have relevance to reducing the burden of the coronavirus pandemic [3]. We recently showed that synbiotic Lactocare<sup>®</sup> intervention can reduce the episodes of viral respiratory infections in asthmatic children [1]. Interestingly, some probiotic strains in Synbiotic Lactocare<sup>®</sup> are similar to Strains suggested by David Baud. After COVID-19 pandemic, we proposed that Synbiotic Lactocare<sup>®</sup> may also reduce SARS-Cov2 infection in high-risk medical staff working in COVID-19 hospital wards.

## 2. Method

1) Participants: this study was a randomized, double blind, placebo-controlled trial that was done during the second wave of COVID-19 pandemic (July to August 2020) in Mashhad, the second most popular city in Iran. Subjects were recruited from employees of emergency department of Imam Reza and Akbar hospital, COVID 19 referral centers in Mashhad. Participants were invited through banners. Inclusion criteria: hospital staff (nurse, physician, nurse aid), no history of clinical or laboratory evidence of SARS-Cov2 infection, active participation in inpatient corona wards. Exclusion criteria: History of COVID-19 infection, Positive antibody or RT-PCR against SARS-Cov2, history of autoimmune disorders, antibiotic prescription during the study, noncompliance (missing more than 5

days synbiotic use), pregnancy, immunosuppressive drugs use, or any chronic lung diseases. All participants signed informed consent form (Figure 1).

2) Study design: participants in synbiotic group received once daily oral synbiotic capsule (Lactocare<sup>®</sup>) that contains 1 billion CFU/Cap of *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium infantis*, *Lactobacillus bulgaricus*, and Fructooligosacharide (Zist Takhmir, Tehran, Iran) or placebo in the same appearance for 30 days. They were followed up at 15 and 45 days by phone call and after first and second month visited in clinic. If suspected symptoms and signs of COVID-19 were occurred, SARS-Cov2 RT-PCR with nasal or oral swab was done.

3) Sample size and randomization: all participants (60 persons) were active hospital staff of emergency department in Imam Reza and Akbar hospital, working at least 40 hours per week, and who had no evidence of novel coronavirus infection at the time of trial entrance or before it. They were randomly divided to synbiotic and placebo groups. According to previous studies that showed a 20% - 30% reduction [1] in common colds with a probiotic, we estimated a sample size of 28 in each group using an  $\alpha$  value of 0.05 with a power of 90% and possible 20% follow-up loss.

4) Statistical analysis: statistical analysis was done by statistical package for social sciences (SPSS) software version 16.0 (IBM Inc., Chicago, IL, USA). The

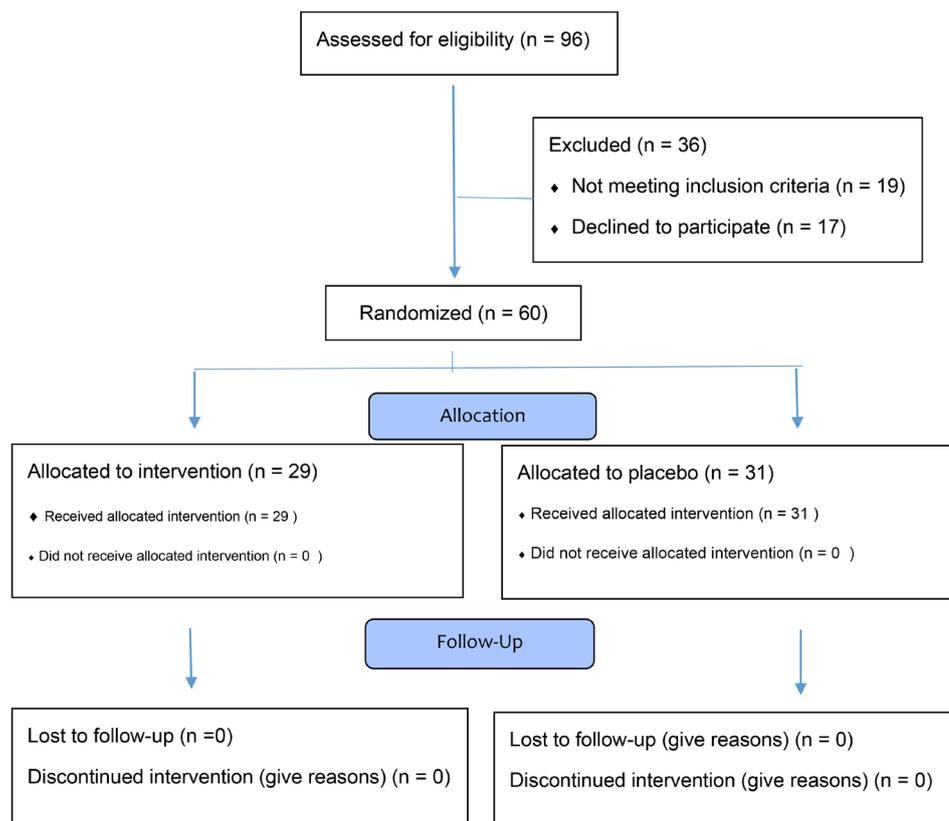


Figure 1. Flow chart of the study.

IBM SPSS Statistical Software for Windows version 22.0 (IBM Corp., Armonk, N.Y., USA) was used for the statistical analyses. The standard descriptive statistics were applied to describe the pattern of the data. The Chi-square and Fisher's exact tests were used to examine the significance of associations between categorical data. All tests were two-tailed, and the probability value of 0.05 was considered significant.

**Ethical consideration:** This trial protocol was approved by Mashhad University of Medical Sciences ethical committee (code: IR.MUMS.REC.1399.240). The study protocol was registered in Iranian registry of clinical trials. (Code: IRCT-20101020004976N6). The authors have no conflict of interests. This article was funded by the Deputy of Research at Mashhad University of Medical Sciences.

### 3. Result

Among sixty participants who were enrolled in the study, fourteen (23%) of them were physicians, forty-one (68%) were nurses and five (9%) were nurse aids. Most of them (forty-six, 77%) were older than 30 years. There was no significant difference between two groups. Detailed distributions between groups are shown in **Table 1**.

During the two month period of this study, SARS-COV-2 RT-PCR test results were positive in three participants (9.67%) in placebo group compared to no positive test in synbiotic group. The difference was not statistically significant ( $p = 0.238$ ).

During the study, two persons (7 %) of placebo group had respiratory complaint such as cough, rhinorrhea and/or dyspnea, compared with one in synbiotic group ( $p = 0.19$ ). Three persons in placebo group revealed gastrointestinal manifestations like diarrhea, vomiting and abdominal pain while two patients in intervention group revealed diarrhea, nausea and/or vomiting ( $p = 0.67$ ). Only one case in placebo group had disturbance in gustatory and smell senses (**Table 2**).

### 4. Discussion

This study showed that 3 participants in placebo group got SARS-COV2 infection

**Table 1.** Characteristics of study participants (n = Number).

	Synbiotic group (n = 29)	Placebo group (n = 31)	P-value (Chi-2)
<b>Age</b>			
<30 years	8	6	0.451
>30 years	21	25	
<b>Career (n)</b>			
Nurse	18	23	0.101
Physician	10	4	
Nurse aid	1	4	
<b>Risk factors:</b>			
Hypertension, Diabetes mellitus Hypothyroidism	5	4	0.393

**Table 2.** Comparing laboratory data and clinical manifestations between synbiotic and placebo group.

	Synbiotic group	Placebo group	P-value (Chi-2)
<b>SARS-COV-2 RT-PCR</b>			
First month	0	1	
Second month	0	2	
<b>Total</b>	<b>0</b>	<b>3</b>	<b>0.238</b>
<b>Respiratory</b>			
First month	0	2	
Second month	1	2	
<b>Total</b>	<b>1</b>	<b>4</b>	<b>0.19</b>
<b>Gastrointestinal</b>			
First month	1	1	
Second month	1	2	
<b>Total</b>	<b>2</b>	<b>3</b>	<b>0.67</b>
<b>Fever and Chill</b>			
First month	0	1	
Second month	1	1	
<b>Total</b>	<b>1</b>	<b>2</b>	<b>0.61</b>
<b>Loss of smell</b>			
First month	0	0	
Second month	0	1	
<b>Total</b>	<b>0</b>	<b>1</b>	<b>0.48</b>

in comparison to no participant in synbiotic group. Although there was a lower number of involved persons in synbiotic group, the difference was not statistically significant. This may be partly due to small sample size, however, as even a small reduction in COVID-19 involvement is still promising, larger studies are critically needed.

While vaccines will not be widely available in the near future for general population in many countries, additional preventive strategies are urgently needed especially in high risk groups including health care providers and hospital staffs.

There are many evidences that communications exist between gut and lung, which is called the gut-lung axis. To our knowledge, this is the first report of synbiotic application for prevention of COVID-19 and there is no other published trial using probiotic or prebiotic for prevention or treatment of this novel disease. There are some animal studies and very nice reviews that suggest specific strains of probiotics are effective against corona viruses and presumably, SARS-COV2. Julio Villena and Haruki Kitazawa have summarized the information regarding the effect of *L. rhamnosus* CRL1505 in the beneficial modulation of the mucosal antiviral immune response and suggest that this strain could be beneficial in the prevention and/or the reduction of the severity of infections caused by SARS-COV2 [16]. They also concluded that immunobiotic interventions are mostly effective in the prevention of respiratory infections while they rarely influence the course of infection once the pathogen has started its replication in the host and immunobiotics should be considered as a strategy for prevention rather than as a therapeutic option.

Some patients with COVID-19 have intestinal microbial dysbiosis with low numbers of probiotic species such as Bifidobacterium and Lactobacillus which could be an indicator of their weak immunity, and therefore prebiotic, probiotic or synbiotic supplementation will help to re-normalize the intestinal flora balance and decrease the risk of infection [16].

Zuo and coworkers compared the fecal microbiota of fifteen patients infected with SARS-Cov2 to healthy controls and showed that *Coprobacillus* spp. *Clostridium ramosum* and *Clostridium hatherwayi* were associated with severity of COVID-19 symptoms [23]. Geva-Zatorsky demonstrated that *Coprobacillus* spp. can upregulate ACE2 (which is a receptor for virus entry) in the murine guts [24]. Beneficial effects include enhancement of the intestinal epithelial barrier, competition with pathogens for nutrients and adhesion, production of anti-microbial agents and modulation of the host immune system [25].

A recent systematic review and meta-analysis in 2020 concluded that synbiotic interventions reduced the incidence rate of respiratory tract infections (RTIs) by 16% and the proportion of participants experiencing RTIs by 16% [21]. Interestingly, Synbiotic intervention reduced the episodes of viral respiratory infections even in asthmatic children [16].

Our study showed that participants in synbiotic had less gastrointestinal symptoms. This era is another potential beneficial effect of the application of immunobiotics as diarrhea is a frequent symptom in 10% to 30% of patients infected with SARSCoV-2. Animal studies demonstrated that *L. plantarum* Probio-38 and *L. salivarius* Probio-37 were capable of reducing the replication of transmissible coronavirus. A mixture of probiotic strains was also capable of improving the immune system of pigs infected with coronavirus and improved their reproductive performance (Tsukahara *et al.*, 2018). Interestingly, it was recently reported that a multi-strain probiotic mixture significantly reduced the fecal shedding of the feline coronavirus in cats infected with the pathogen [16].

Mak *et al.* reported that 58% - 71% of patients with COVID-19 in China were consumed antibiotics, and antibiotic-associated diarrhea occurred in 2% - 36% of patients. Probiotics intervention has been proposed to make these COVID-19 patients less prone to secondary infections [26].

In our study, one participant in placebo group versus no one in synbiotic group had anosmia. Dysgeusia and anosmia are common comorbidities in COVID-19 patients. Epidemiological studies have demonstrated that the incidence rate of olfactory problems in COVID-19 patients varies from 33.9% - 68% with female dominance [27]. There are some ongoing trials using intranasal probiotics for prevention and treatment of COVID-19. Their results will be interesting as to whether local use or probiotics produce inhibitory effects on olfactory problems (ClinicalTrials.gov Identifier: NCT04458519).

In COVID-19 patients, the main manifestations are fever and cough, lymphocytopenia and ground-glass changes on chest computed tomography [27]. In the current trial, fever and chill were seen in two cases in placebo group com-

pared to one case in synbiotic group with no statistically significant difference.

Finally, although it seems that probiotics and synbiotic should be used mainly as a preventive strategy against COVID-19, there are some evidences that show they may also help patients after infection with SARS-COV2 [28]. Interestingly, in an RCT of 65 critically ill, mechanically ventilated patients, a multi-strain synbiotic containing *Pediococcus pentosaceus*, *Leuconostoc mesenteroides*, *L. paracasei* ssp. *Paracasei* 19, *L. plantarum* plus inulin, oat bran, pectin, and resistant starch lowered the rate of infections, sepsis, days of admission in the intensive care unit, days under mechanical ventilation, and mortality [29].

Controversy still exists as some experts believe that blind use of probiotics for COVID-19 is not recommended until we have a better understanding of the pathogenesis of SARS-CoV-2 and its effect on gut microbiota [30].

The main limitation of this study was the small sample size. Many hospital staff was excluded from the study for their positive past clinical history or laboratory results of COVID-19. Some small differences between two groups may influence results for example one study showed a high proportion of COVID-19 health care workers had engaged in night shift-work and felt working under pressure than uninfected staffs [31]. The strengths of this study were the novelty of application of synbiotic in COVID-19 and the study population, health care workers, which are in high risk group and any data regarding the prevention of COVID-19 in this population are highly needed.

## 5. Conclusion

This study showed that overall frequency of SARS-COC2 infection in participants receiving synbiotic and those receiving placebo did not differ significantly. However, 3 hospital staff in placebo group compared to no one in synbiotic group had SARS-COC2 infection. This is encouraging regarding the importance of morbidity and mortality of COVID-19 especially in health care workers. Further studies with greater power and alternative probiotic strains and mixture are warranted to determine whether Synbiotic can prevent COVID-19 in at-risk hospital staff.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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