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David Baud

Varvara Dimopoulou Agri

Glenn R Gibson

Gregor Reid

Lawson Health Research Institute, gregor@uwo.ca

Eric Giannoni

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Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic

David Baud¹, Varvara Dimopoulou Agri², Glenn R. Gibson³, Gregor Reid^{4,5} and Eric Giannoni^{2*}

¹ Materno-Fetal and Obstetrics Research Unit, Department Woman-Mother-Child, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland, ² Clinic of Neonatology, Department Woman-Mother-Child, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland, ³ Food and Nutritional Sciences, St Joseph's Hospital, The University of Reading, Reading, United Kingdom, ⁴ Department of Microbiology and Immunology, The University of Western Ontario, London, ON, Canada, ⁵ Canadian R&D Centre for Human Microbiome and Probiotics, Lawson Health Research Institute, London, ON, Canada

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INTRODUCTION

Despite strategies based on social distancing, hygiene, and screening, COVID-19 is progressing rapidly throughout the world, with healthcare systems at risk of being overwhelmed. While identification of effective drug therapies is ongoing, vaccines will not be available in the near future. Therefore, additional preventive strategies are urgently needed.

COVID-19 presents with a spectrum of disease severity, ranging from mild and non-specific flu-like symptoms, to pneumonia, and life-threatening complications such as acute respiratory distress syndrome (ARDS) and multiple organ failure. While transmission of SARS-CoV-2 is thought to occur mainly via respiratory droplets, the gut may also contribute toward the pathogenesis of COVID-19 (1). SARS-CoV-2 RNA has been detected in the gastrointestinal tract and stool samples from patients (2–4), and in sewage systems (5). Coronaviruses, including SARS-Cov-2 can invade enterocytes, thereby acting as a reservoir for the virus (4). Indeed, large clinical studies from China indicate that gastrointestinal symptoms are common in COVID-19, and are associated with disease severity (3, 4).

Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit on the host (6). Clinical evidence shows that certain probiotic strains help to prevent bacterial and viral infections, including gastroenteritis, sepsis, and respiratory tract infections (RTIs). The reason for adding probiotic strains to the overall prevention and care strategy is founded in science and clinical studies, albeit hitherto none directly on the etiological agent of this pandemic.

CLINICAL DATA SUPPORTING THE USE OF PROBIOTICS TO PREVENT COVID-19

Probiotics can prevent antibiotic-associated diarrhea, and infections in the gastrointestinal tract, but also infections at other sites, including sepsis, and RTIs (7–13). Meta-analyses are the gold standard for evidence-based medicine. In one analysis of more than 8,000 preterm infants included in randomized control trials (RCTs), patients receiving enteral supplementation with probiotics showed a reduction in necrotizing enterocolitis, nosocomial sepsis, and all-cause mortality (14). A well-conducted RCT including >4,000 newborns in India found a reduction in sepsis and lower RTIs in infants treated with a strain of *Lactobacillus plantarum* combined with prebiotics (which are growth substrates specific for beneficial microorganisms) (15).

Viruses are etiologic agents of over 90% of upper RTIs. The positive impact of probiotics on prevention of upper RTIs is documented in a number of studies. A meta-analysis of 12 RCTs

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Irene Lenoir-Wijnkoop,
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*Correspondence:

Eric Giannoni
eric.giannoni@chuv.ch

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including 3,720 adults and children reported a 2-fold lower risk of developing upper RTI in subjects taking probiotics, and a small but significant reduction in disease severity in those infected. A randomized, double-blind, placebo-controlled intervention study of 479 adults showed that *Lactobacillus gasseri* PA 16/8, *Bifidobacterium longum* SP 07/3, and *Bifidobacterium bifidum* MF 20/5 with vitamins and minerals lowered not only the duration of common cold episodes but also days with fever (16). The impact of probiotics on prevention of upper RTIs caused by specific viruses has also been documented. An RCT including 94 preterm infants showed that galactooligosaccharide and polydextrose prebiotic mixture (1:1), or probiotic *Lactobacillus rhamnosus* GG given between 3 and 60 days of life lowered the incidence of clinically defined virus-associated RTI by 2- to 3-fold compared to placebo (17). The incidence of rhinovirus-associated episodes, which comprised 80% of all RTIs in this study, was also strongly reduced with probiotics or prebiotics. The incidence of influenza RTI was reduced following consumption of *Lactobacillus brevis* in an open label study of 1,783 school children (18). Pertinent to the pandemic affecting adults more than children, these positive findings were confirmed in an RCT that included 27 elderly subjects receiving *Bifidobacterium longum* or placebo (19). Furthermore, lactic acid bacteria, from which many probiotics are selected, are part of the upper respiratory tract microbiota in healthy people, and some strains are being considered for prevention of recurrent otitis media (20, 21). This makes their use for contributing to slow down progression of the coronavirus pandemic worthy of consideration.

Probiotics have also been used to prevent bacterial lower RTIs in critically ill adults. Meta-analyses of RCTs including close to 2,000 patients found that probiotic strains reduce the incidence

of ventilator-associated pneumonia (22, 23). But low quality of evidence and conflicting results among different studies calls for additional well-conducted RCTs.

It should be noted that not all probiotics, even those with gastrointestinal benefits, necessarily contribute in every way to reducing the risk of respiratory infection. For example, *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* ssp. *lactis* may contribute to intestinal benefits, but do not reduce the number of viruses in the nasopharynx (24). Examples of products that could be considered, depending on availability in a given country, are provided in **Table 1**.

MECHANISTIC BASIS FOR THE ACTION OF PROBIOTICS TO PREVENT INFECTIONS AND RELEVANCE TO COVID-19

Mechanisms that might explain clinical success of probiotics include enhancement of the intestinal epithelial barrier, competition with pathogens for nutrients and adhesion to the intestinal epithelium, production of anti-microbial substances and modulation of the host immune system (28). An RCT of 55 infants showed that enteral supplementation with a combination of *Bifidobacterium bifidum* and *Streptococcus thermophilus* reduced the incidence of diarrhea and shedding of rotaviruses (29), an effect that has been confirmed in subsequent studies (30). This would indicate interference with viral entry into cells and/or inhibition of viral replication in the intestine. While this mechanism may have a role in reducing dissemination of coronavirus via the gut, the probiotic strains were not administered to the respiratory tract. So, direct inhibition may

TABLE 1 | The following are examples (not exclusive) of probiotic products, or web sites listing products, with documentation in human studies that may have relevance to reducing the burden of the coronavirus pandemic.

Products	Basis for inclusion	When to administer	References
<i>Lactobacillus casei</i> DN-114 001; DanActive/Actimel Fermented drink, Danone	Reduced incidence and duration of RTIs	Once daily for duration of the pandemic	(12, 13)
<i>Lactobacillus gasseri</i> PA 16/8, <i>Bifidobacterium longum</i> SP 07/3, and <i>B. bifidum</i> MF 20/5; Tribion harmonis, Merck	Lowering duration and severity of flu-like illness	Once daily for duration of the pandemic	(16)
<i>Lactobacillus rhamnosus</i> GG; Culturelle or other brand names	For digestive health and gut barrier integrity, and prevention of viral RTIs	One capsule daily for duration of the pandemic	(17)
<i>Lactobacillus plantarum</i> DR7; Malaysia	Prevention of upper RTIs, immune modulation	2 g sachet per day for duration of pandemic	(25)
<i>Bifidobacterium breve</i> Yakult, and <i>Lactobacillus casei</i> Shirota; available as fermented drinks	Lower incidence of ventilator-associated pneumonia	One of each day for duration of the pandemic	(26)
<i>Bifidobacterium longum</i> BB536; Morinaga, and sold in many formulations	Enhances innate immunity, prevents influenza infection	One each day for duration of the pandemic	(19)
<i>Pediococcus pentosaceus</i> 5-33:3, <i>Leuconostoc mesenteroides</i> 32-77:1, <i>L. paracasei</i> ssp. <i>paracasei</i> 19, <i>L. plantarum</i> 2,362 plus inulin, oat bran, pectin, and resistant starch; Medipharm, Sweden	To reduce rate of SIRS, infections, sepsis, days of stay in the intensive care unit, days under mechanical ventilation, and mortality	For COVID-19 patients	(27)

A list of probiotics available in Canada for various health issues; www.probioticchart.ca
A list of probiotics available in the USA for various health issues; www.usprobioticguide.com

We must emphasize that none have been tested or proven to have an effect against SARS-CoV2, the virus causing COVID-19, nor are they proven treatments or cures for this condition.

appear impossible at this site. Having said that, lungs have their own microbiota and a gut-lung connection has been described whereby host-microbe, microbe-microbe and immune interactions can influence the course of respiratory diseases (31). RTIs such as influenza are associated with an imbalance in the microbial communities of the respiratory and gastrointestinal tracts (32, 33). This dysbiosis may alter subsequent immune function and predispose to secondary bacterial infection. As reports from China indicate that COVID-19 might be associated with intestinal dysbiosis causing inflammation and poorer response to pathogens (34, 35), the case exists for probiotic strains that restore gut homeostasis (36). It is feasible that orally administered probiotic strains could further influence this gut-lung axis, as some can migrate from the gut to distant sites, such as the breast to treat mastitis (37).

The gut microbiome has a critical impact on systemic immune responses, and immune responses at distant mucosal sites, including the lungs (38, 39). Administration of certain bifidobacteria or lactobacilli has beneficial impact on influenza virus clearance from the respiratory tract (39, 40). Probiotic strains improve levels of type I interferons, increase the number and activity of antigen presenting cells, NK cells, T cells, as well as the levels of systemic and mucosal specific antibodies in the lungs (16, 19, 39). There is also evidence that probiotic strains modify the dynamic balance between proinflammatory and immunoregulatory cytokines that allow viral clearance while minimizing immune response-mediated damage to the lungs. This might be particularly relevant to prevent ARDS, a major complication of COVID-19. An RCT with *Lactobacillus plantarum* DR7 showed suppression of plasma pro-inflammatory cytokines (IFN- γ , TNF- α) in middle-aged adults, and enhancement of anti-inflammatory cytokines (IL-4, IL-10) in young adults, along with reduced plasma peroxidation and oxidative stress levels (25). Given the cytokine storm that appears to occur in many COVID-19 patients, this type of modulation may prove to be very important. The manner in which orally administered probiotic strains contributes to this appears to involve the immune response emanating from the intestine, a focal point of the body's defenses. Therefore, probiotic strains documented to enhance the integrity of tight junctions, for example through increasing butyrate, a fuel for colonocytes could theoretically reduce SARS-Cov-2 invasion.

Evidence for antiviral activity of probiotic strains against common respiratory viruses, including influenza, rhinovirus, and respiratory syncytial virus comes from clinical and experimental studies (17–19, 41). While none of these effects or mechanisms have been tested on the new SARS-CoV-2 virus, this should not negate considering this approach, especially when effects of probiotics against other coronavirus strains have been reported (42–45). Furthermore, patients are dying from secondary bacterial infections. A recent study in mice has shown that oral

administration of *Lactobacillus acidophilus* CMCC878, started 24 h after pulmonary inoculation of *Pseudomonas aeruginosa* and *Staphylococcus aureus* reduced bacterial load in the lungs, and decreased lung damage and systemic inflammation (46).

SAFETY OF PROBIOTICS

Probiotics are generally safe, even in the most vulnerable populations and in intensive care settings (14, 47). Cases of probiotic-associated bacteremia and fungaemia have occurred on extremely rare occasions, mainly in premature and immunocompromised patients treated with preparations lacking adequate quality control (48, 49). Rather than consider intensive care patients too ill to receive probiotic and prebiotic therapy, RCTs of probiotics for the prevention of ventilator-associated pneumonia provide a reason to consider them (22, 23, 26). Moreover, in an RCT of 65 critically ill, mechanically ventilated, multiple trauma patients, the synbiotic *Pediococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *L. paracasei* ssp. *paracasei* 19, *L. plantarum* 2,362 plus inulin, oat bran, pectin, and resistant starch resulted in reduced rate of infections, systemic inflammatory response syndrome, sepsis, days of stay in the intensive care unit, days under mechanical ventilation, and mortality (27).

SUMMARY

In summary, orally administered probiotic strains can reduce the incidence and severity of viral RTIs. At a time when doctors are using drugs with little anti-COVID-19 data, probiotic strains documented for anti-viral and respiratory activities (not low-quality undocumented imitations) should become part of the armamentarium to reduce the burden and severity of this pandemic. Government funding is being used to test numerous drugs but just as important, they should fund probiotic trials. In addition, use of recognized prebiotics (e.g., fructans, galactans) to enhance propagation of probiotic strains and indigenous beneficial microbes should be recommended as part of the overall strategy to flatten the curve (11, 50).

AUTHOR CONTRIBUTIONS

EG, DB, and VD contributed conception of the manuscript. EG and VD wrote the first draft. DB, GG, and GR wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of Interest: GG and GR provide advice to probiotic and prebiotic companies.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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