Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

"modest efficacy".[1] The odds ratio in the cited Cochrane meta-analysis is 0·53 (95% CI 0·37–0·76).[4] We believe that the efficacy of a treatment that leads to twice as great a reduction in the number of cases is far from modest. The potential for probiotics to reduce the risk and severity of viral respiratory tract infections is supported by clinical and experimental studies on influenza, rhinovirus, and respiratory syncytial virus.[2] Although none of these effects have been tested with SARS-CoV-2, some probiotic stains do have antiviral activity against other coronaviruses.[2] Given the importance of strain-to-strain differences, the selection of probiotics for testing needs to made on the basis of documented attributes.

Mak and colleagues mention that the rationale for using probiotics in COVID-19 is based on indirect evidence.[1] This assertion is true for all interventions in the context of this novel disease. Ideally, preventive and therapeutic interventions should be tested in randomised controlled trials before implementation in clinical practice. In a pandemic affecting millions of people, disregarding practices that are not supported by solid evidence against this specific pathogen is not realistic. Clinicians have adopted a more pragmatic approach, and issued recommendations based on evidence from other viral infections, sepsis, and general intensive care management.[5] Currently, there is no evidence from randomised controlled trials that any medication can prevent or improve the outcomes of COVID-19, and there are hundreds of ongoing trials of antivirals, immune-modulating agents, convalescent plasma, and steroids. On the basis of limited evidence showing that Bacillus Calmette-Guérin (BCG) vaccination provides heterologous protection against respiratory tract infections, randomised trials have been launched to assess whether BCG vaccination can reduce the incidence and severity of COVID-19.[6] We propose that well documented probiotic strains deserve the same level of interest, and call for trials with probiotics to reduce the risk and help treat COVID-19.

EG is supported by the Leenaards Foundation. GRG reports grants from GlaxoSmithKline and Pukka Herbs, and personal fees from Clasado and Pepsico, outside the submitted work. GR reports personal fees from Seed, Danone Canada, KGK Science, and Acerus Pharma, and grants from Kimberly Clark, outside the submitted work. GR also has a patent issued on a probiotic strain to bind to heavy metals. GRG and GR are members of the Board of International Scientific Association for Probiotics and Prebiotics, a non-profit, non-lobbying group of researchers. DB and VDA declare no competing interests.

Eric Giannoni, David Baud, Varvara Dimopoulou Agri, Glenn R Gibson, Gregor Reid
eric.giannoni@chuv.ch

Clinic of Neonatology (EG, VDA) and Materno-Fetal and Obstetrics Research Unit (DB), Department Mother-Woman-Child, Lausanne University Hospital and University of Lausanne, Lausanne CH-1011, Switzerland; Food and Nutritional Sciences, St Joseph's Hospital, University of Reading, UK (GRG); Department of Microbiology and Immunology, University of Western Ontario, London, ON, Canada (GR); and Canadian R&D Centre for Human Microbiome and Probiotics, Lawson Health Research Institute, London, ON, Canada (GR)

1 Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterol Hepatol* 2020; **5:** 644–45.
2 Baud D, Dimopoulou Agri V, Gibson GR, Reid G, Gionnoni E. Using probiotics to flatten the curve of coronavirus disease COVID-2019 pandemic. *Front Pub Health* 2020; published online May 8. DOI:10.3389/fpubh.2020.00186.
3 Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: more than meets the eye. *Gut* 2020; **69:** 973–74.
4 Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev* 2015; **2:** CD006895.
5 Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020; **46:** 854–87.
6 Curtis N, Sparrow A, Ghebreyesus TA, Netea MG. Considering BCG vaccination to reduce the impact of COVID-19. *Lancet* 2020; **395:** 1545–46.

We read with interest Joyce Mak and colleagues' Correspondence[1] in *The Lancet Gastroenterology & Hepatology* on the role of probiotics in illnesses related to COVID-19. Although we largely agree with the authors' conclusions, we believe that use of probiotics in the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has wider implications.

SARS-CoV-2 has been postulated to affect gut inflammation both directly and indirectly, infecting intestinal epithelial cells through the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2, and inducing pro-inflammatory chemokine and cytokine release.[2,3] Recent studies suggest that SARS-CoV-2 instigates an acute intestinal inflammatory response, highlighted in laboratory tests by elevated levels of faecal calprotectin and serum interleukin-6, and clinically evidenced by diarrhoea.[2]

Although gastrointestinal disorders are frequent in COVID-19, nothing is known regarding the ability of SARS-CoV-2 to affect the host microbial flora. However, previous studies have shown that ACE2 expressed in the intestinal epithelium regulates the ecology of the gut microbiome through intestinal amino acid homoeostasis[4] and that ACE2 receptors are markedly downregulated by the entry of SARS-CoV-2 into cells through membrane fusion.[5] The intestinal downregulation of ACE2 can consequently lead to an altered microbiota that confers susceptibility to inflammation of the gut.[4–6] Moreover, other coronaviruses, such as the porcine epidemic diarrhoea virus, are able to directly cause microbial dysbiosis, with decreases in the proportion of beneficial bacteria and increases in harmful bacteria.[7]

Given this evidence, bacteriotherapy could represent a complementary resource for the prevention and restoration of SARS-CoV-2 intestinal mucosa damage through the modulation of gut microbiota and decreasing related inflammation. In other infections, such as HIV, in which intestinal inflammation and related microbiota impairment can affect gut epithelial barrier function, bacteriotherapy (through microbiota surface compounds and metabolites)

has been shown to inhibit apoptosis, regulate signalling pathways to produce cytokines, maintain intestinal epithelial homoeostasis, and allow recovery of gut mucosal health, thereby attenuating inflammation.[8,9] We believe that studies of bacteriotherapy in SARS-CoV-2 are needed to evaluate the potential effects on intestinal mucosal inflammation and microbiome homoeostasis.

Finally, products available for bacteriotherapy are not the same and have different potential effects. Thus, the conclusions of each study must be considered separately, and the results of meta-analyses that collate data obtained from studies done with different products can be misleading.

We declare no competing interests.

*Giancarlo Ceccarelli, Carolina Scagnolari, Francesco Pugliese, Claudio M Mastroianni, Gabriella d'Ettorre
giancarlo.ceccarelli@uniroma1.it

Department of Public Health and Infectious Diseases (GC, CMM, Gd'E), Department of Anaesthesia and Intensive Care Medicine (FP), and Laboratory of Virology, Department of Molecular Medicine (CS, FP), Sapienza University of Rome, Rome 00161, Italy; Azienda Ospedaliero, University Policlinico Umberto I of Rome, Rome, Italy (GC, FP, CMM, Gd'E); and Pasteur Institute Italy, Cenci Bolognetti Foundation, Rome, Italy (CS, FP)

1 Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterol Hepatol* 2020; **5:** 644–45.
2 Effenberger M, Grabherr F, Mayr L, et al. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut* 2020; published online Apr 20. DOI:10.1136/gutjnl-2020-321388.
3 Zhang H, Kang Z, Gong H, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut* 2020; **69:** 1010–18.
4 Hashimoto T, Perlot T, Rehman A, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012; **487:** 477–81.
5 Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med* 2020; **76:** 14–20.
6 Perlot T, Penninger JM. ACE2—from the renin-angiotensin system to gut microbiota and malnutrition. *Microbes Infect* 2013; **15:** 866–73.
7 Tan Z, Dong W, Ding Y, Ding X, Zhang Q, Jiang L. Changes in cecal microbiota community of suckling piglets infected with porcine epidemic diarrhea virus. *PLoS One* 2019; **14:** e0219868.
8 Ceccarelli G, Statzu M, Santinelli L, et al. Challenges in the management of HIV infection: update on the role of probiotic supplementation as a possible complementary therapeutic strategy for cART treated people living with HIV/AIDS. *Expert Opin Biol Ther* 2019; **19:** 949–65.
9 Liu Q, Yu Z, Tian F, et al. Surface components and metabolites of probiotics for regulation of intestinal epithelial barrier. *Microb Cell Fact* 2020; **19:** 23.

Authors' reply

We thank Eric Giannoni and colleagues and Giancarlo Ceccarelli and colleagues for their comments on our Correspondence.[1] New data have since highlighted that patients with COVID-19 have an altered gut microbiome with depletion of beneficial commensals (*Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, *Roseburia* and *Lachnospiraceae* taxa) and enrichment of opportunistic pathogens (*Clostridium hathewayi*, *Actinomyces viscosus*, *Bacteroides nordii*) during hospitalisation.[2] Importantly, gut microbiome configuration was associated with COVID-19 disease severity, and altered gut microbiota persisted even after clearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), suggesting that the virus might inflict prolonged harm to human microbiome homoeostasis.[2] Other risk factors for severe COVID-19, including old age, obesity, and diabetes mellitus,[3] have been shown to be associated with gut dysbiosis, which might contribute to the poor prognosis of COVID-19.[4]

During this crucial moment, with more than 6 million confirmed cases of COVID-19 globally, we understand that the situation is desperate, and it is not uncommon to try all alternative measures. In the absence of a vaccine or effective therapy for COVID-19, we agree that probiotics represent a complementary approach for the prevention and restoration of SARS-CoV-2-induced mucosal damage or inflammation through the modulation of gut microbiota. Probiotics exert their beneficial effects through several different mechanisms, and substantial differences appear to exist between different probiotic bacterial species and strains. Organisms therefore need to be selected in a rational manner to treat different diseases.[5] Currently, questions remain concerning which patients should receive probiotics, what is the best way to deliver probiotics, how to ensure optimal delivery, and whether there is variation in efficacy among different populations. As the world waits in semi-lockdown mode, continued scientific progress for COVID-19 prevention or treatment is highly important, and probiotics represent one option. We call for robust and well planned studies that can facilitate the identification of probiotic strains, including both well documented probiotics and novel COVID-19-specific probiotics, that might result in reduced susceptibility to COVID-19 or less severe disease.

JWYM reports grants from Janssen, the Hong Kong College of Physicians, and the Hong Kong Society of Gastroenterology, outside the submitted work. FKLC reports grants from Olympus Hong Kong and China, Pfizer, AstraZeneca, Takeda Pharmaceuticals, Takeda (China) Holdings, and Given Imaging, and personal fees from the American Gastroenterological Association, Medical Association of Guangdong Province, Olympus Hong Kong and China, Pfizer, AstraZeneca, Takeda Pharmaceuticals, EA Pharma, Takeda (China) Holdings, Associação dos Médicos Hospitalares da Função Pública de Macau, Pfizer Upjohn Korea, Fujifilm, Ministry of Health Singapore, and Japanese Gastroenterological Endoscopy Society. FKLC is also an advisor and commentator for evidence-based medicine for the Ministry of Health of the People's Republic of China, Pfizer, AstraZeneca, Ministry of Health Singapore, American College of Physicians Journal Club, and *Nature Reviews Gastroenterology & Hepatology*, outside the submitted work. SCN reports grants from Ferring and personal fees from Takeda, AbbVie, Janssen, and Tillotts, outside the submitted work.

*Joyce W Y Mak, Francis K L Chan, *Siew C Ng
siewchienng@cuhk.edu.hk

Center for Gut Microbiota Research, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (JWYM, FKLC, SCN)

1 Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterol Hepatol* 2020; **5:** 644–45.
2 Zuo T, Zhang F, Lui GCY, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. *Gastroenterology* 2020; available online May 20. DOI:10.1053/j.gastro.2020.05.048.