

*Infectious Disease Control Training Centre, Hospital Authority (HA IDCTC)/
Infection Control Branch (ICB), Centre for Health Protection (CHP) and
Chief Infection Control Officer's Office,*



Microbiome Modulation in Combating MDRO during COVID Pandemic



Siew NG

**Director, Microbiota-I Center (MagIC)
Professor, Department of Medicine & Therapeutics
The Chinese University of Hong Kong
Honorary Consultant, Prince of Wales Hospital**

CONFLICT OF INTEREST DISCLOSURE

Presenter(s) : Siew C Ng

The authors have financial conflicts of interest:

Grant: Dr. Ng has received research grants from Olympus, Ferring, Janssen and Abbvie.

Advisory board member: Dr. Ng has served as for Pfizer, Ferring, Janssen and Abbvie.

Speaker's Fees: Dr. Ng has served as speakers for Janssen, Abbvie, Takeda, Ferring, Tilotts, Menarini, Pfizer.


She is scientific co-founder of *GenieBiome limited* and have filed patents related to microbiome and COVID-19 at CUHK.

Outline





1. Role of gut microbiome in COVID-19 risk and severity
2. Scientific development of a microbiome immunity formula
3. Gut microbiome and development of Long COVID
4. Impact of gut microbiome on MDRO
5. Microbiome modulation for MDRO

What Clinicians should know about COVID-19

- 
- GI symptoms are not uncommon (3-61%)
 - Detection of virus in stool does not correlate with GI symptoms (asymptomatic carrier)
 - SARS-CoV-2 RNA could be detected in gut of severe cases

Commentary

COVID-19 and the gastrointestinal tract: more than meets the eye

Siew C Ng ¹, Herbert Tilg ²

An outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome (SARS-CoV-2), has rapidly spread from China to almost all over the world affecting over 800,000 people across 199 countries. Whereas typical presentations of this infection, such as fever, cough, myalgia, fatigue and

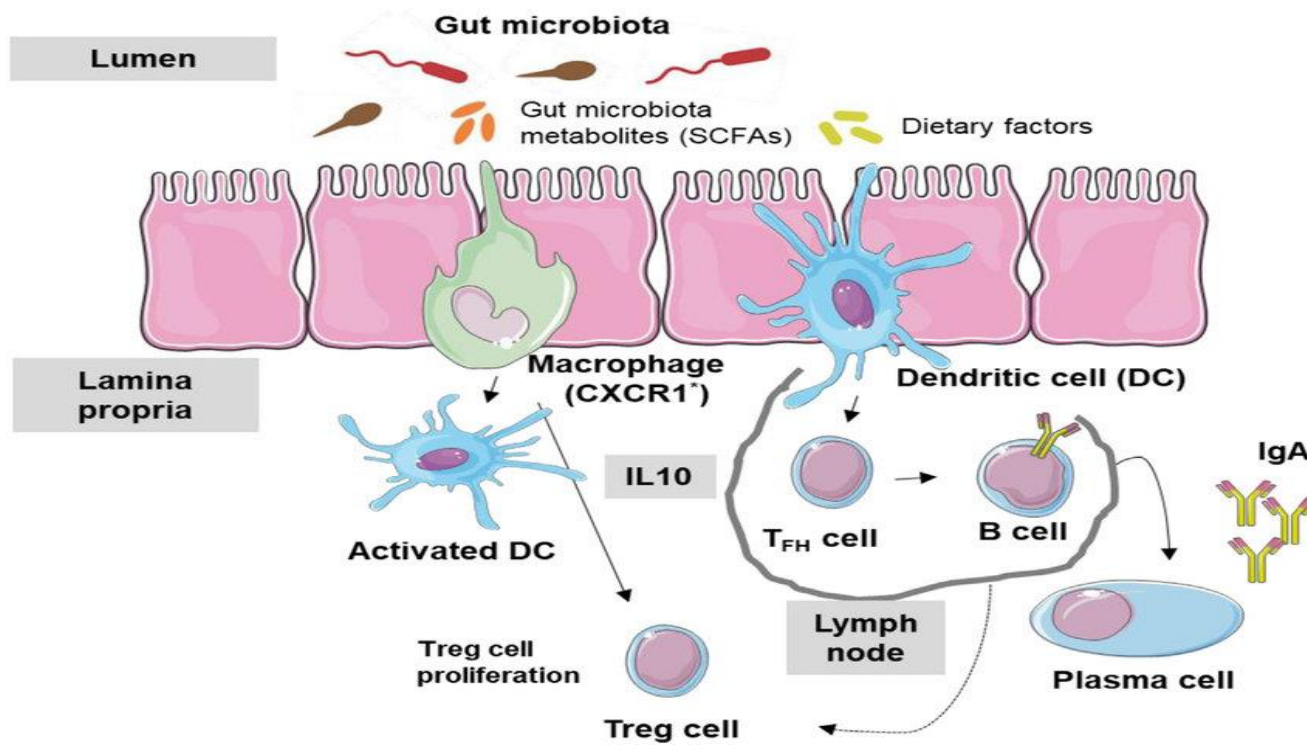
Overall, 58/95 cases (61.1%) showed evidence of GI symptoms with diarrhoea (24.2%), nausea (17.9%), vomiting (4.2%) and impaired liver function as assessed by elevated transaminases (32.6%) being the most relevant features. Importantly, they performed endoscopy in six subjects demonstrating that SARS-CoV-2 could be

RNA sequencing data, they found that ACE2 was highly expressed in the small intestine especially in proximal and distal enterocytes. They also found that two other viral entry receptors for human coronavirus 229E virus and Middle East respiratory syndrome CoV virus were highly expressed in enterocytes.¹¹ To take these findings further, Zhang *et al* examined ACE2-expressing cell composition and proportion in five public datasets with single-cell transcriptomes of lung, oesophagus, gastric, ileum and colon.⁸ They found that successful virus entry of SARS-CoV-2 depends not only on the presence of cell receptor ACE2 but also

Gut microbiota

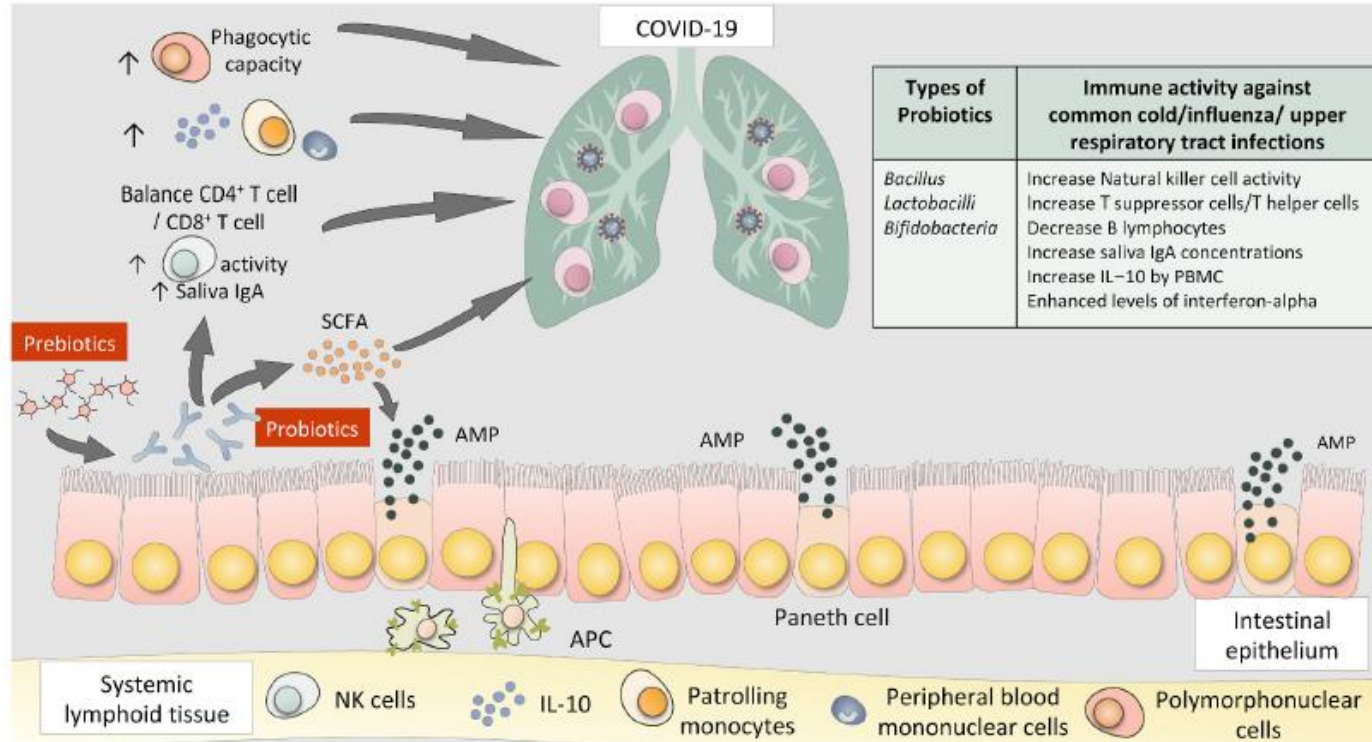
regulates immunity to maintain defense against
viral and bacterial infections

Frontiers in Immunology 2018





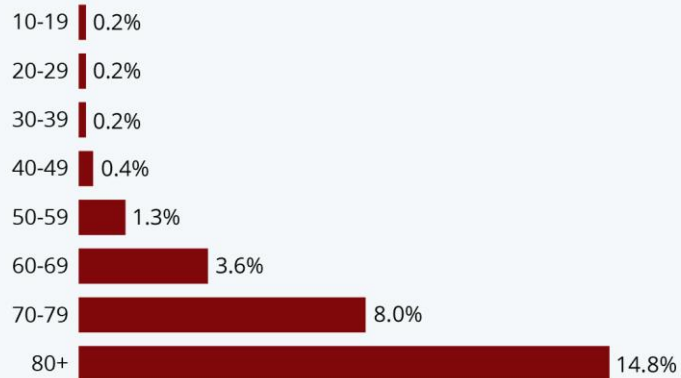
Gut-Lung Cross Talk



COVID-19 and the elderly

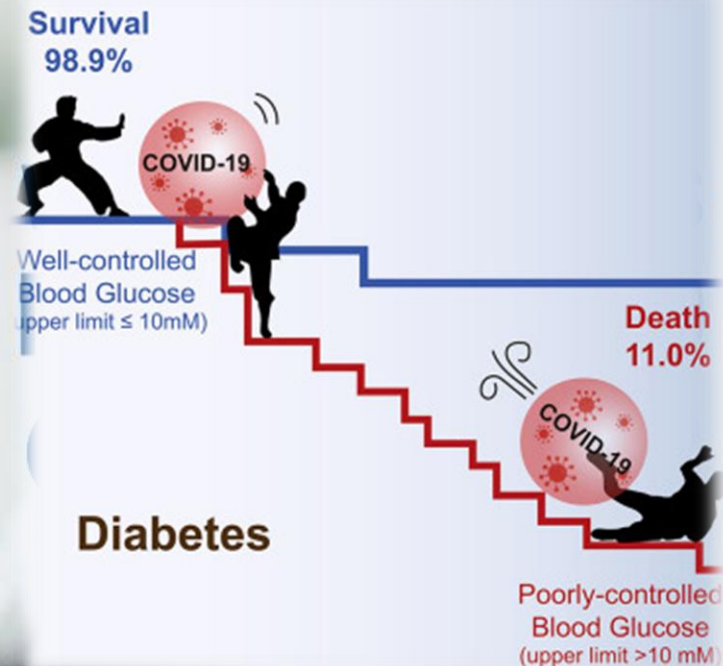
Study: Elderly Most At Risk From The Coronavirus

COVID-19 fatality rate by age (as of February 11, 2020)



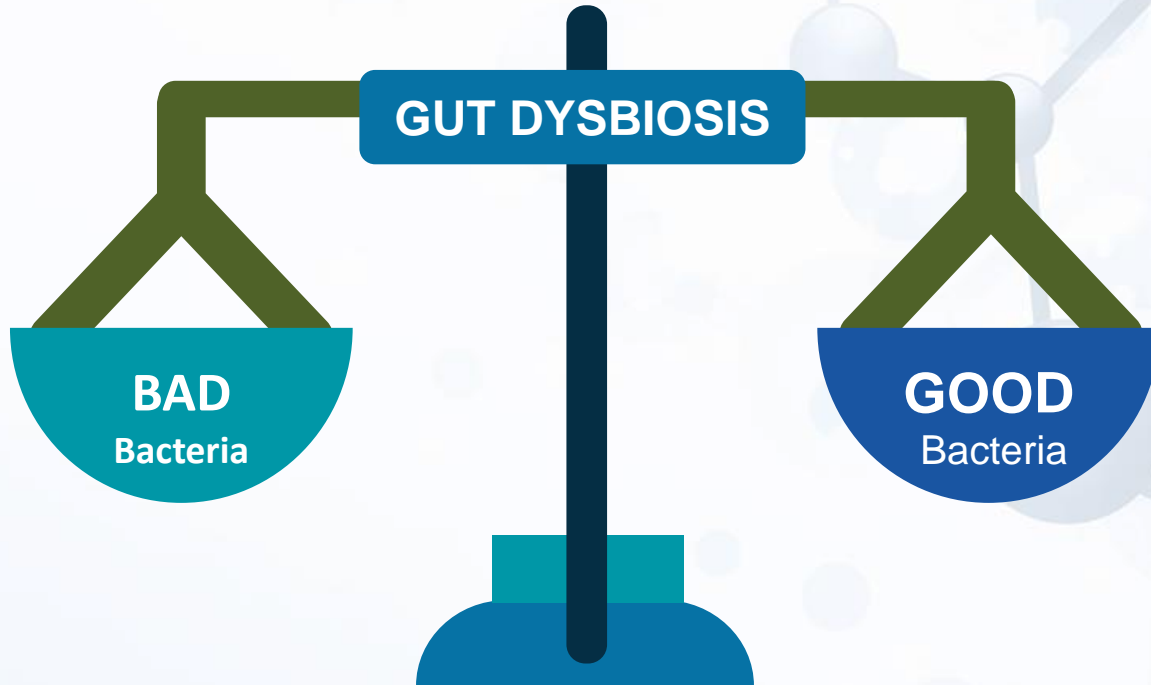
n=44,672 confirmed COVID-19 cases in Mainland China
Source: Chinese Centre for Disease Control and Prevention

Diabetics more prone to severe COVID-19



Microbiota “Out of Balance” = Increased Severity of COVID-19 patients

People with severe COVID outcomes most at risk of gut
"dysbiosis"



Gut microbiota in COVID-19: key microbial changes, potential mechanisms and clinical applications

Raphaella I. Lau^{1,2,3,4}, Fen Zhang^{1,2,3,4}, Qin Liu^{1,2,3}, Qi Su^{1,2,3}, Francis K. L. Chan^{1,2,3} & Siew C. Ng^{1,2,3}✉

Diet

- High-fibre, plant-based, prebiotic-rich diet
- Milder COVID-19 severity
- Rapid viral clearance
- Reduced clinical symptoms
- Enriched SCFA-producing gut bacteria
- Low-sugar diet
- Milder COVID-19 severity
- Rapid viral clearance



Probiotics and prebiotics

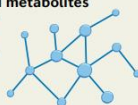
- Enhanced host antiviral capacity
- Milder COVID-19 severity
- Reduced symptoms and hospitalization
- Lowered risk of death and pro-inflammatory markers
- Positive gut microbiota modulation



Microbiota-based interventions for COVID-19

Microbiota-derived metabolites

- IPA, tryptamine, BIP
- Anti-SARS-CoV-2 properties in vitro



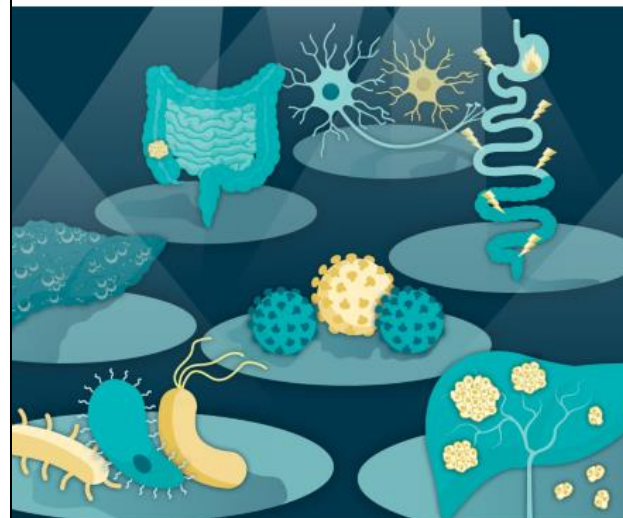
Faecal microbiota transplantation

- Rapid resolution of COVID-19
- Reduced gastrointestinal symptoms
- Improved blood immunity profile
- Positive gut microbiota modulation



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nature reviews gastroenterology & hepatology



YEAR IN REVIEW

Spotlight on key advances in research and clinical care in 2021

Cirrhosis-associated immune dysfunction
Mechanisms and modulation

IBD Risk in Patients With
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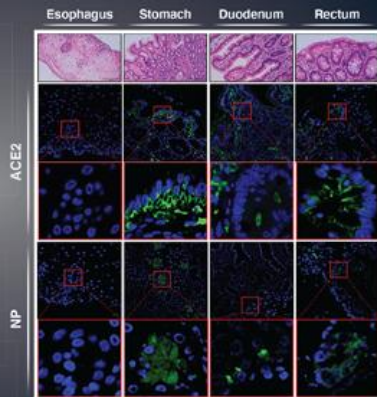
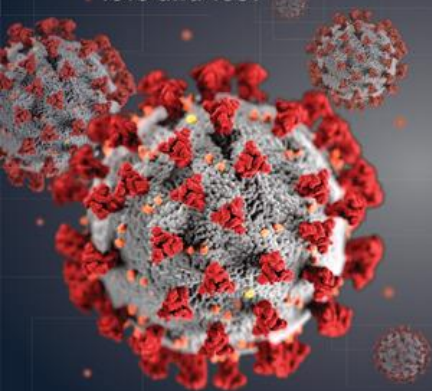
Gastroenterology

Volume 158 / Number 6 May 2020

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Evidence for GI Infection of SARS-CoV-2

1518 and 1831



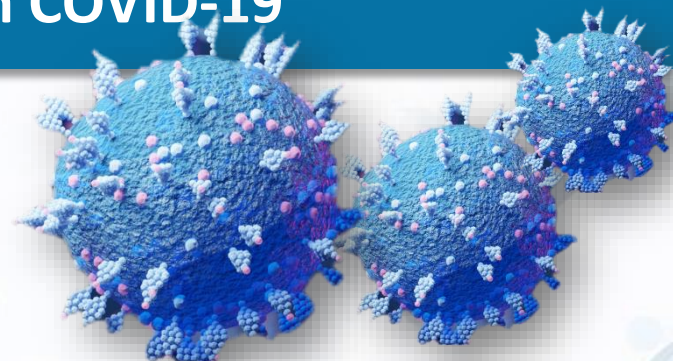
also
in this
issue

AGA Institute and the Joint Task Force on
Allergy-Immunology Practice Parameters Clinical
Guidelines for the **Management of Eosinophilic
Esophagitis** **1776**

AGA Clinical Practice Update on Screening and
Surveillance for **Hepatocellular Carcinoma in
Patients With Nonalcoholic Fatty Liver Disease:**
Expert Review **1822**

1st

in the world to define microbiota alterations (Gut Dysbiosis) in COVID-19



BASIC AND TRANSLATIONAL—ALIMENTARY TRACT

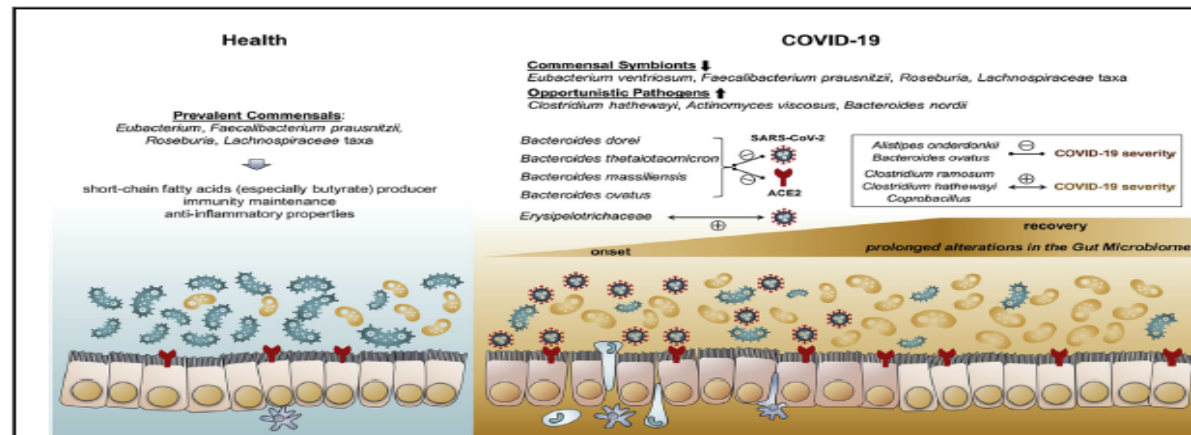
Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization



Tao Zuo,^{1,2,3,*} Fen Zhang,^{1,2,3,*} Grace C. Y. Lui,^{3,4,*} Yun Kit Yeoh,^{1,5} Amy Y. L. Li,³ Hui Zhan,^{1,2,3} Yating Wan,^{1,2,3} Arthur C. K. Chung,^{1,2,3} Chun Pan Cheung,^{1,2,3} Nan Chen,^{1,2,3} Christopher K. C. Lai,⁵ Zigui Chen,⁵ Eugene Y. K. Tso,⁶ Kitty S. C. Fung,⁷ Veronica Chan,⁶ Lowell Ling,⁸ Gavin Joynt,⁸ David S. C. Hui,^{3,4} Francis K. L. Chan,^{1,3} Paul K. S. Chan,^{1,5} and Siew C. Ng^{1,2,3}

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Study Design

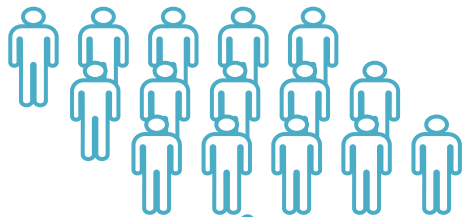
Yeoh.. Ng. *Gut* 2021

COVID-19 (n=15)

Control (n=15)

Pneumonia (n=30)

Mild
Moderate
Severe
Critical

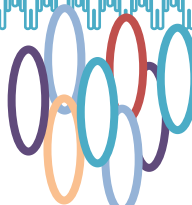


Standard diet captured

COVID-19 (n>100)

Control (n>1500)

>250 samples



Microbial profiling of fecal samples by metagenomics sequencing



Gut microbiome is linked to more severe COVID-19



Original research

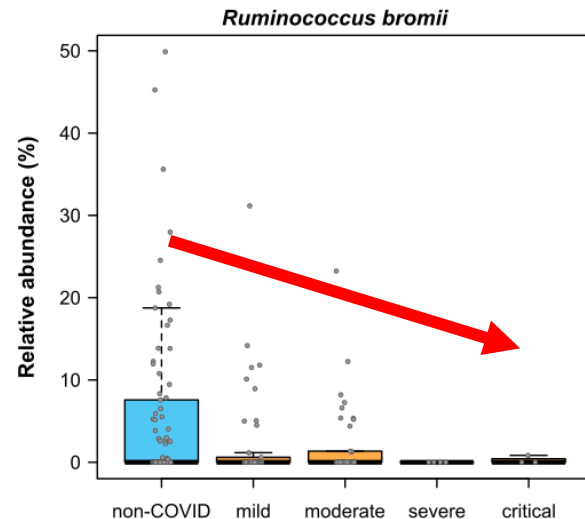
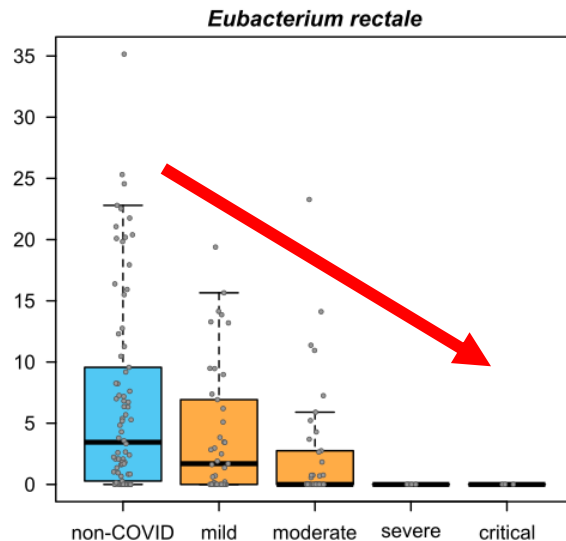
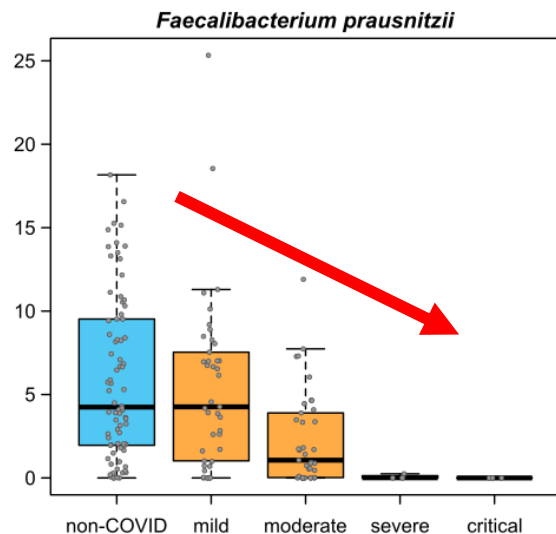
Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19

Yun Kit Yeoh ,^{1,2} Tao Zuo ,^{2,3,4} Grace Chung-Yan Lui,^{3,5} Fen Zhang,^{2,3,4} Qin Liu,^{2,3,4} Amy YL Li,³ Arthur CK Chung,^{2,3,4} Chun Pan Cheung,^{2,3,4} Eugene YK Tso,⁶ Kitty SC Fung,⁷ Veronica Chan,⁶ Lowell Ling,⁸ Gavin Joynt,⁸ David Shu-Cheong Hui,^{3,5} Kai Ming Chow ,³ Susanna So Shan Ng,^{3,5} Timothy Chun-Man Li,^{3,5} Rita WY Ng,¹ Terry CF Yip,^{3,4} Grace Lai-Hung Wong ,^{3,4} Francis KL Chan ,^{2,3,4} Chun Kwok Wong,⁹ Paul KS Chan,^{1,2,10} Siew C Ng ,^{2,3,4}

Gut 2021

Several gut commensals with known immunomodulatory functions were underrepresented in COVID-19 patients

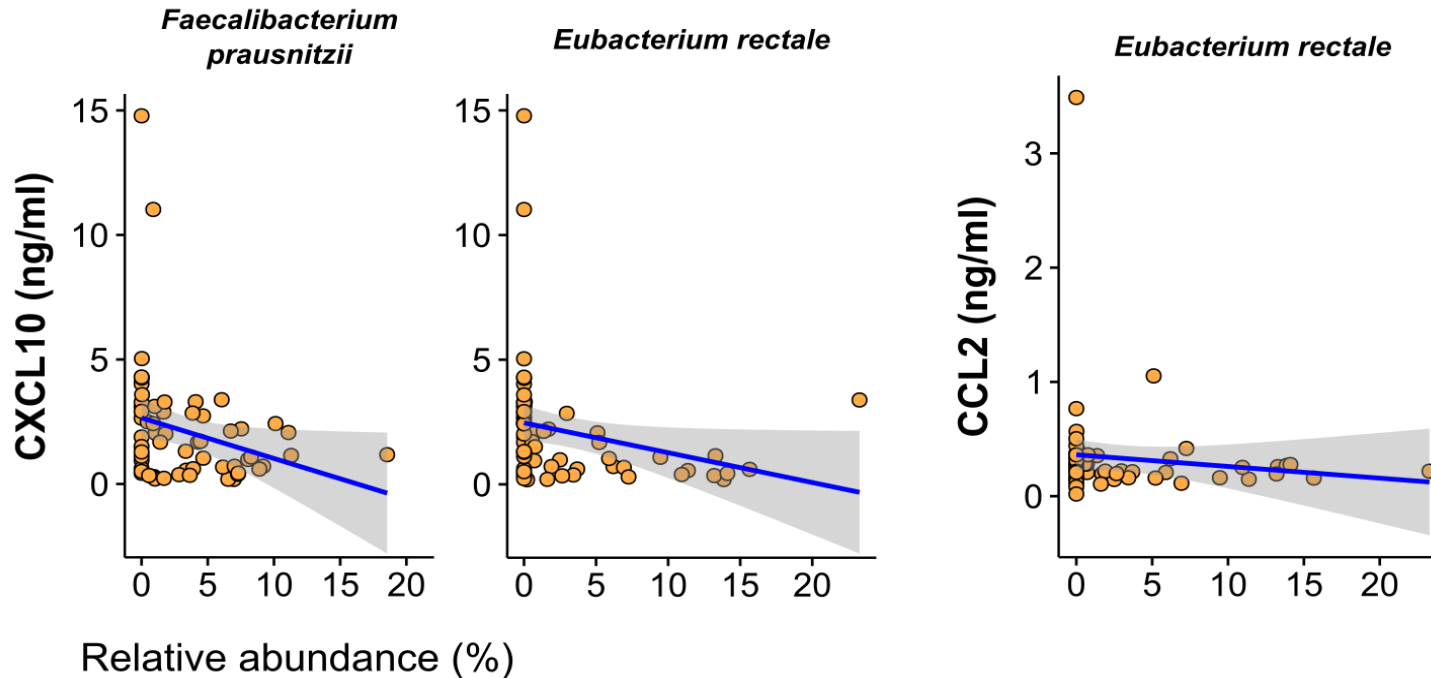
Yeoh.. Ng. Gut 2021



Several species depleted in COVID-19 are associated with increased inflammatory marker concentrations

Yeoh.. Ng, Gut 2020

Zuo.., Ng, Gastroenterology 2020

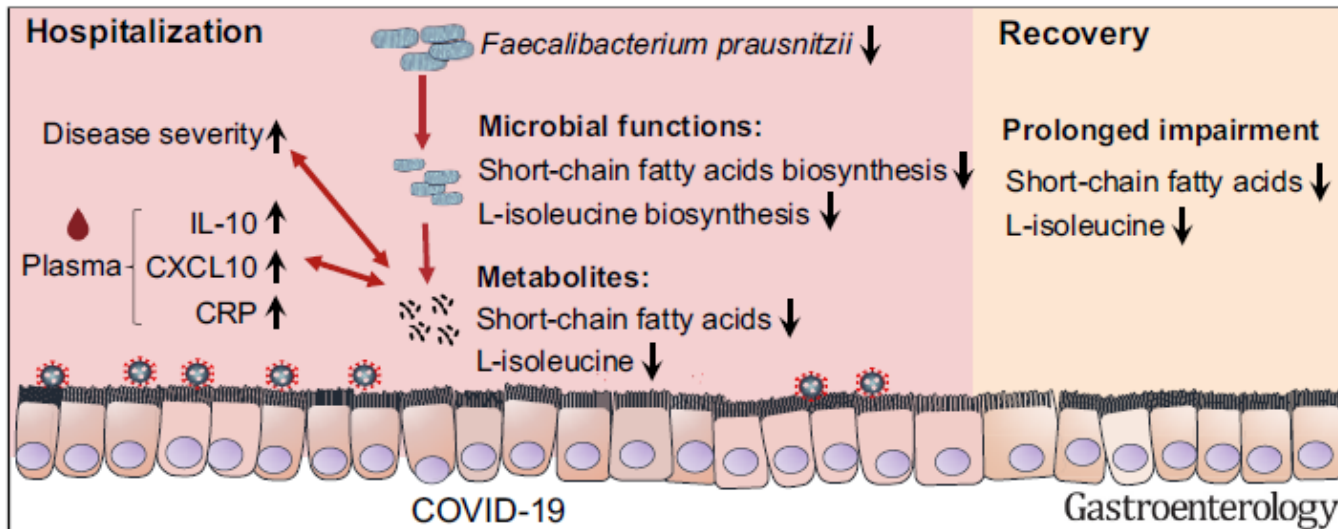


Prolonged Impairment of Short-Chain Fatty Acid and L-Isoleucine Biosynthesis in Gut Microbiome in Patients With COVID-19

Fen Zhang,^{1,2,3,4,*} Yating Wan,^{1,2,3,4,*} Tao Zuo,^{1,2,3,4} Yun Kit Yeoh,^{1,5} Qin Liu,^{1,2,3,4} Lin Zhang,^{1,2,3,4,6} Hui Zhan,^{1,2,3,4} Wenqi Lu,^{1,2,3,4} Wenye Xu,^{1,2,3,4} Grace C. Y. Lui,^{4,7} Amy Y. L. Li,⁴ Chun Pan Cheung,^{1,2,3,4} Chun Kwok Wong,⁷ Paul K. S. Chan,^{1,2,5,8} Francis K. L. Chan,^{1,3,4,9} and Siew C. Ng^{1,2,3,4,9}

Gastroenterology 2021

Antibiotic-naïve (n=150)



Lack of SCFA and L-isoleucine biosynthesis significantly correlated with disease severity and increased plasma CXCL-10, NT- pro B- type natriuretic peptide, and CRP

BASIC AND TRANSLATIONAL—ALIMENTARY TRACT

Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization

Tao Zuo,^{1,2,3,*} Fen Zhang,^{1,2,3,*} Grace C. Y. Lui,^{3,4,*} Yun Kit Yeoh,^{1,5} Amy Y. L. Li,³
Hui Zhan,^{1,2,3} Yating Wan,^{1,2,3} Arthur C. K. Chung,^{1,2,3} Chun Pan Cheung,^{1,2,3} Nan Chen,^{1,2,3}
Christopher K. C. Lai,⁵ Zigui Chen,⁵ Eugene Y. K. Tso,⁶ Kitty S. C. Fung,⁷ Veronica Chan,⁵
Lowell Ling,⁸ Gavin Joynt,⁸ David S. C. Hui,^{3,4} Francis K. L. Chan,^{1,3} Paul K. S. Chan,^{1,5} and
Stew C. Ng^{1,2,3}

Gastroenterology

BASIC AND TRANSLATIONAL—ALIMENTARY T

Alterations in Fecal Fungal Microbiome of Patients With COVID-19 During Time of Hospitalization until Discharge

Tao Zuo,^{1,2,3,*} Hui Zhan,^{1,2,3,*} Fen Zhang,^{1,2,3} Qin Liu,^{1,2,3} Eugene Y. K. T.
Grace C. Y. Lui,^{3,5} Nan Chen,^{1,3} Amy Li,^{2,3} Wenqi Lu,^{1,3} Francis K. L. Cha
Paul K. S. Chan,^{1,6} and Siow C. Ng^{1,2,3}

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BACKGROUND & AIMS: Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects gastrointestinal tissues, little is known about the roles of gut commensal microbes in susceptibility to and severity of infection. We investigated changes in fecal microbiomes of patients with SARS-CoV-2 infection during hospitalization and associations with

Impact Factor:
17.373

Gastroenterology

See Covering the Cover synopsis on page 1193.

BACKGROUND & AIMS: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects intestinal cells, and might affect the intestinal microbiota. We investigated changes in the fecal fungal microbiomes (mycobiome) of patients with SARS-CoV-2 infection during hospitalization and on recovery.

time of hospitalization until clearance of SARS-CoV-2 from nasopharyngeal samples. **RESULTS:** Patients with COVID-19 had significant alterations in their fecal mycobiomes compared with controls, characterized by enrichment of *Candida albicans* and a highly heterogeneous mycobiome configuration, at time of hospitalization. Although fecal mycobiomes of 22 patients with COVID-19 did not differ significantly from those of controls during times of hospitalization, 8 of 30 patients with

COVID-19

Gut

Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19 

Chen^{1, 6}, Siaw Shi Boon⁶, Francis Kl Chan^{1, 3}, Paul KS Chan^{1, 6}, Siew C Ng^{1, 2, 3}

Author affiliations +

Abstract

Objective Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was detected in faeces of patients with COVID-19, the activity and infectivity of the virus in the GI tract during disease course is largely unknown. We investigated temporal transcriptional activity of SARS-CoV-2 and its association with longitudinal faecal microbiome alterations in patients with COVID-19.

Design We performed RNA shotgun metagenomics sequencing on serial faecal viral extractions from 15 hospitalised patients with COVID-19. Sequencing coverage of the SARS-CoV-2 genome was quantified. We assessed faecal microbiome composition and microbiome functionality in association with signatures of faecal SARS-CoV-2 infectivity.

Results Seven (46.7%) of 15 patients with COVID-19 had stoc

Impact Factor: 19.819

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Gut

Gut microbiota
Original research

Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19

¹Yun Kit Yeoh ^{1, 2}, ³Tao Zuo ^{2, 3, 4}, Grace Chung-Yan Lui ^{3, 5}, Fen Zhang ^{2, 3, 4}, Qin Liu ^{2, 3, 4}, Amy Yi Li ³, Arthur CK Chung ^{2, 3, 4}, Chun Pan Cheung ^{2, 4}, Eugene YK Tao ⁴, Kitty SC Fung ⁷, Veronica Chan ⁶, Lowell LING ⁸, Gavin Joyns ⁸, David Shu-Cheng Hung ^{3, 5}, ⁶Kai Ming Chow ³, Susanna So Shan Ng ^{3, 5}, Timothy Chun-Man Li ^{3, 5}, Rita WY Ng ¹, Terry CF Yip ^{3, 4}, ⁹Shi-Lai Hung Wong ^{3, 4}, ¹⁰Francis KL Chan ^{2, 3, 4}, Chun Kwok Wong ⁹, Paul KS Chan ^{1, 2, 10}, ¹⁰Siew C Ng ^{3, 4}.

[Author affiliations](#)

Abstract

Objective Although COVID-19 is primarily a respiratory illness, there is mounting evidence suggesting that the GI tract is involved in this disease. We investigated whether the gut microbiome is linked to disease severity in patients with COVID-19, and whether perturbations in microbiome composition, if any, resolve with clearance of the SARS-CoV-2 virus.

Methods In this two-hospital cohort study, we obtained blood, stool and patient records from 100 patients with laboratory-confirmed SARS-CoV-2 infection. We collected stool samples from 27 of the 100 patients up to 30 days after clearance of infection. We performed metagenomic sequencing and identified SARS-CoV-2 in 10 patients. We performed whole-genome sequencing total DNA extracted from stools. We identified 10 patients with SARS-CoV-2 in stool samples collected from plasma.

Factor:
19.819

Conclusion Associations between gut microbiota composition, levels of cytokines and inflammatory markers in patients with COVID-19 suggest that the gut microbiome is involved in the magnitude of COVID-19 severity possibly via modulating host immune responses. Furthermore, the gut microbiota dysbiosis after disease resolution could contribute to persistent symptoms, highlighting a need to understand how gut microorganisms are involved in inflammation and COVID-19.



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Intestinal bacteria may affect severity of coronavirus, researchers find

Although the coronavirus is primarily a respiratory disease, there is increasing evidence that suggests the GI tract is involved

By Yaron Steinbuch | New York Post



Dr. Siegel on coronavirus vaccine rollout: 'Political posturing' needs to end

Fox News medical contributor Dr. Marc Siegel provides insight into the coronavirus vaccine rollout on 'America's Newsroom.'

The bacteria lurking in COVID-19 patients' intestines may play a role in how sick they get from the illness, according to new research.

Although the coronavirus is primarily a respiratory disease, there is increasing evidence that suggests the GI tract is involved, scientists at the Chinese University of Hong Kong said.



"Based on several patients surveyed in this study for up to 30 days after clearing SARS-CoV-2, the gut microbiota is likely to remain significantly altered after recovery from COVID-19," they said. (iStock)

The team studied samples from 100 patients treated at two Hong Kong hospitals to see how the so-called microbiome in the digestive system might affect the deadly bug.

"Gut microbiome composition was significantly altered in patients with COVID-19 compared with non-COVID-19 individuals (respectively, with and without antibiotic medication)," they wrote in the *British Medical Journal*.

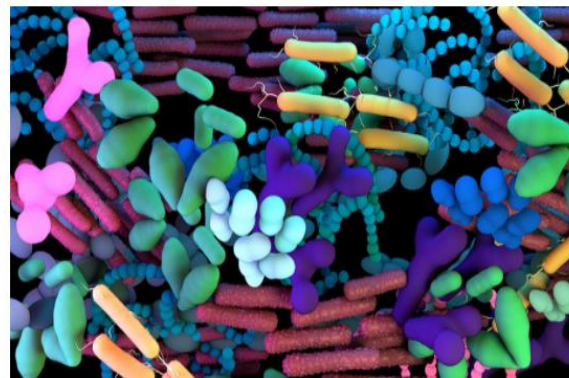
**Fox News
(United States)**

Infectious Disease > COVID-19

Gut Microbiome and COVID-19 Severity: New Evidence for Link

— Lab study finds certain patterns associated with more serious illness

by Molly Walker, Associate Editor, MedPage Today January 11, 2021



The gut microbiome may play a role in COVID-19 severity, a lab study suggested.

Patients with depleted levels of certain species of bacteria were associated with elevated concentrations of inflammatory cytokines, and blood markers including C-reactive protein, lactate dehydrogenase, and aspartate aminotransferase, reported Siew Ng, PhD, of The Chinese University of Hong Kong, and colleagues, in *Gut*.

The researchers noted that patients with severe disease exhibit high blood plasma levels of inflammatory markers, and that there is "substantial involvement" of the gastrointestinal tract in SARS-CoV-2 infection, given "altered gut microbiota composition in SARS-CoV-2 infected subjects." They hypothesized gut microbiota would be associated with host inflammatory immune

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PODCAST
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Global Impact of Our Scientific Discoveries



Lost microbes of COVID-19: *Bifidobacterium*, *Faecalibacterium* depletion and decreased microbiome diversity associated with SARS-CoV-2 infection severity

Sabine Hazan,¹ Neil Stollman,² Husevin S Bozkurt,³ Sonva Dave,^{4,5}
Andreas J Papoutsis,¹ Jordan Dani,¹ Eamonn MM Quigley,⁶ Thomas

How might it impact on clinical practice in the foreseeable future?

- ▶ Boosting of *Bifidobacterium* or *Faecalibacterium* through probiotic supplementation or faecal microbiota transplant is worthy of exploration in the management of patients with acute severe disease or protracted infection. If the changes that we document precede SARS-CoV-2 infection in those who are most severely affected, this therapeutic approach may be of particular interest. Conversely, if the reduction follows infection, then repopulation of the gut microbiome may reduce long-term effects related to gut microbiome composition changes with SARS-CoV-2 infection.



Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs



Review article: Probiotics, prebiotics and dietary approaches during COVID-19 pandemic

Jielun Hu^{a,b,c,1}, Lin Zhang^{a,b,1}, Winnie Lin^{a,b,d}, Whitney Tang^{a,b}, Francis K.L. Chan^{a,b,d},
Siew C. Ng^{a,b,d,*}

^a Center for Gut Microbiota Research, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China

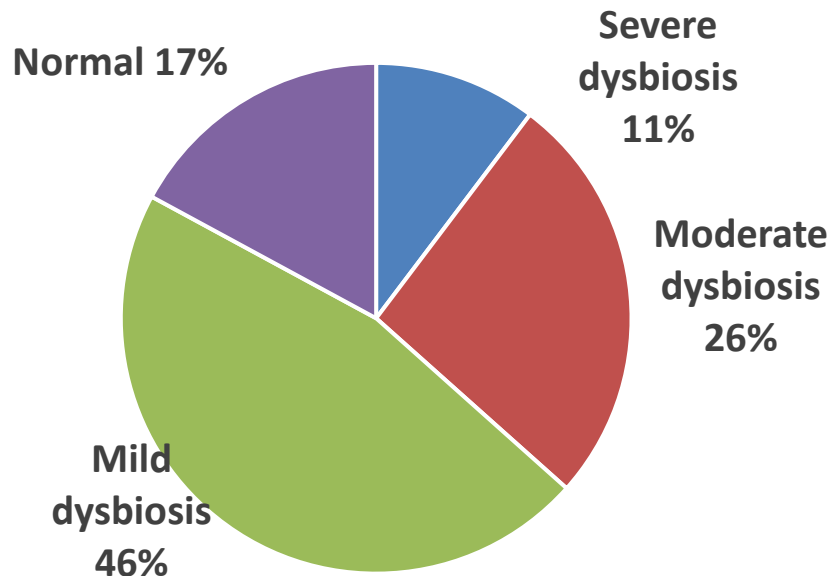
^b Institute of Digestive Disease, State Key Laboratory of Digestive Disease, LKS Institute of Health Science, The Chinese University of Hong Kong, Hong Kong, China

^c State Key Laboratory of Food Science and Technology, China-Canada Joint Lab of Food Science and Technology (Nanchang), Nanchang University, Nanchang, China

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***Almost 40% of healthy HK population has
Moderate/severe imbalanced gut microbiota
(marker of impaired immunity) comparable to COVID-19 patients***

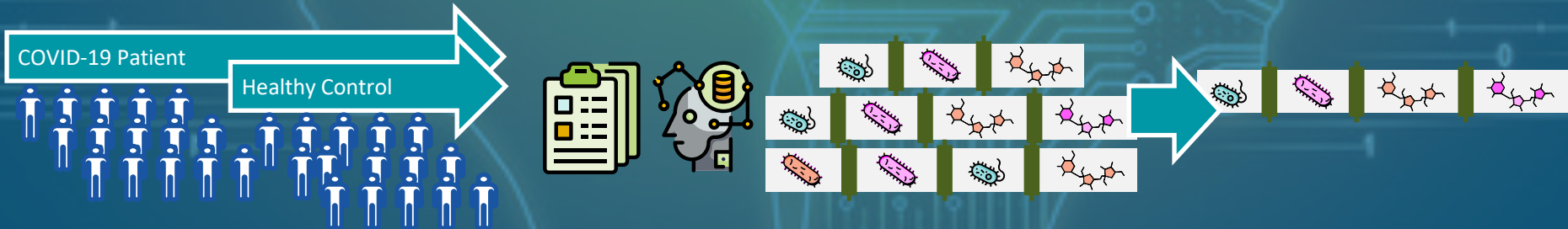


Outline



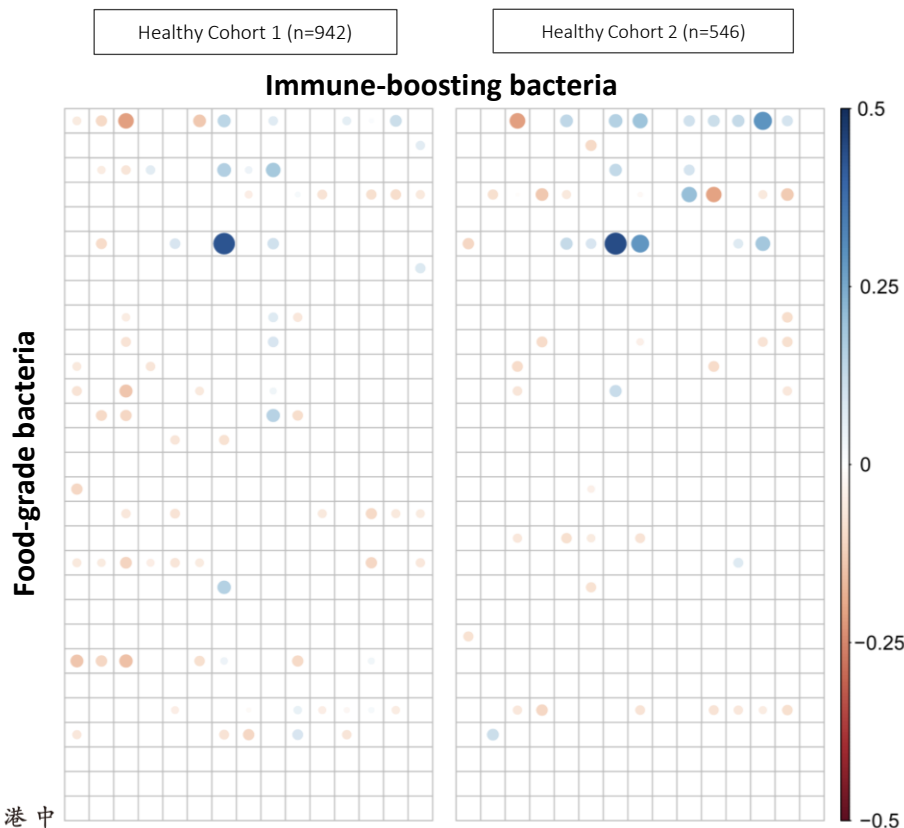
1. Role of gut microbiome in COVID-19 risk and severity
- 2. Scientific development of a microbiome immunity formula**
3. Gut microbiome and development of Long COVID
4. Impact of gut microbiome on MDRO
5. Microbiome modulation for MDRO

We successfully identified
23 gut microbiota
associated with severity of COVID-19, and
4 of them are **consumable probiotics**



Using our Microbiome datasets

Big Data Analysis and Machine Learning



Food-grade bacteria that are positively correlated with immune-boosting bacteria (blue)

Food-grade bacteria that are negatively correlated with immune-boosting bacteria (red)

Blue indicates positive correlation; red indicates negative correlation. Color intensity and size of circle represents correlation coefficient, which is between -0.5 to 0.5.

A unique microbiome immunity formula (SIM01) was developed using big data analysis and machine learning



Coronavirus: Hong Kong's Chinese University researchers craft supplement to help balance body's bacteria amid Covid-19 battle

- Team moved forward with project after discovering many recovering patients had microbe imbalance in intestines
- 'Good bacteria are supposed to help with immunity, so we think the missing bacteria make [patients] more susceptible to infection,' researcher says



Zoe Low

Published: 11:09pm, 11 Jun, 2020

Why you can trust SCMP



Chinese University's Francis Chan speaks at a Thursday press conference where his team unveiled a new probiotic formula designed to help balance the 'good' and 'bad' bacteria found in the gut. K.Y. Cheng

CU Medicine Develops a Probiotic Formula to Target Imbalance in Gut Microbiota in COVID-19








June 11, 2020, 8:33 PM GMT+8

HONG KONG, June 11, 2020 /PRNewswire/ -- The Faculty of Medicine of The Chinese University of Hong Kong (CU Medicine) is the first to discover a series of good bacteria missing in the gut of COVID-19 patients. The research team recently confirmed this discovery with a large number of healthy subjects and COVID-19 patients. Using big data analysis and machine learning, CU Medicine has successfully developed a probiotic formula that aims to target gut dysbiosis, thereby offering hope to boost immunity against COVID-19 and other emerging viral infections. They anticipate that the formula will soon be turned into a probiotic supplement to go with our daily diet to improve our defense against infection.



CLINICAL TRIAL

Gut microbiota-derived synbiotic formula (SIM01) as a novel adjuvant therapy for COVID-19: An open-label pilot study

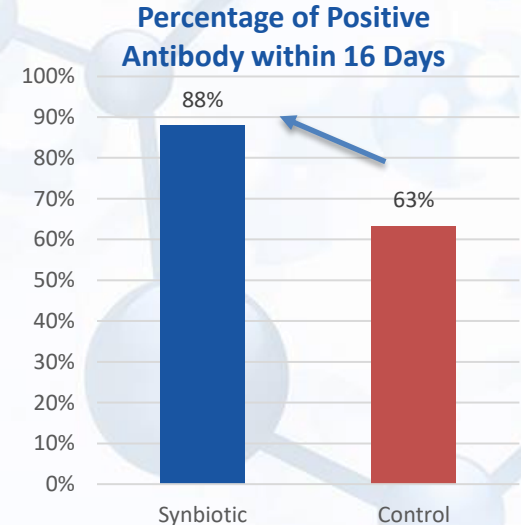
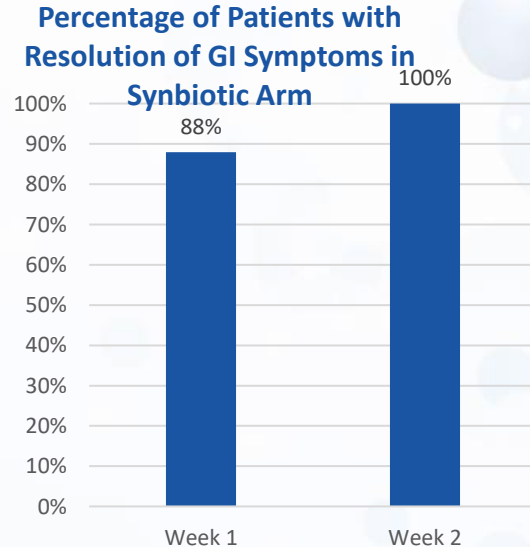
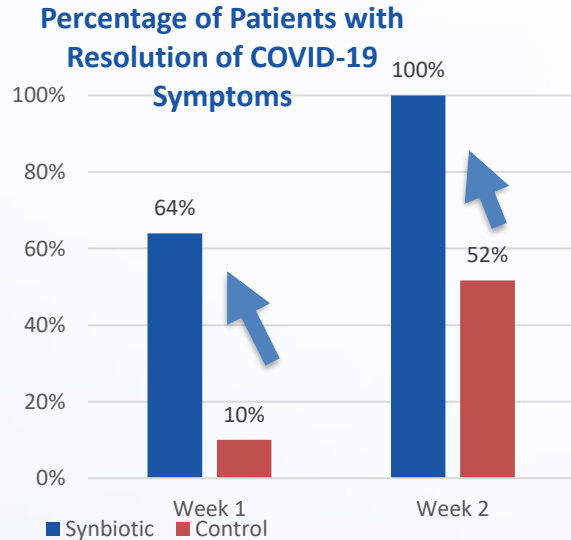
Lin Zhang,^{*,†,‡1}  Zhilu Xu,^{*,†,‡1}  Joyce W Y Mak,^{*,†,‡}  Kai Ming Chow,[†] Grace Lui,^{†,§} Timothy C M Li,[†] Chun Kwok Wong,[¶] Paul K S Chan,^{**}  Jessica Y L Ching,[†]  Yasuhiro Fujiwara,^{††} Francis K L Chan^{*,†,‡}  and Siew C Ng^{*,†,‡} 

^{*}Microbiota I-Center (MagIC), [†]Department of Medicine and Therapeutics, Faculty of Medicine, [‡]State Key Laboratory of Digestive Disease, Institute of Digestive Disease, Li Ka Shing Institute of Health Sciences, Faculty of Medicine, [§]Stanley Ho Centre for Emerging Infectious Diseases, Faculty of Medicine, [¶]Department of Chemical Pathology, Faculty of Medicine, ^{**}Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China; and ^{††}Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka, Japan

More patients on Immunity Formula achieved resolution of COVID-19 symptoms & positive antibody

Lin...Chan, Ng. Journ Gastro Hep 2022

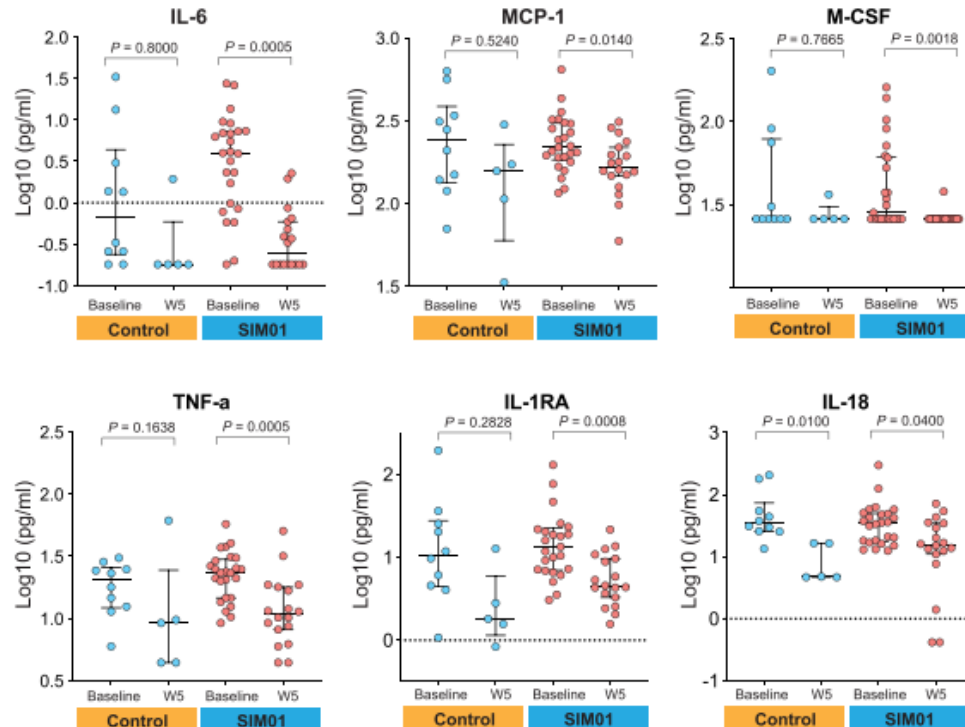
Clinical Study



*1 subject in control arm was admitted to ICU at week 1, this subject was not included in week 2 analysis

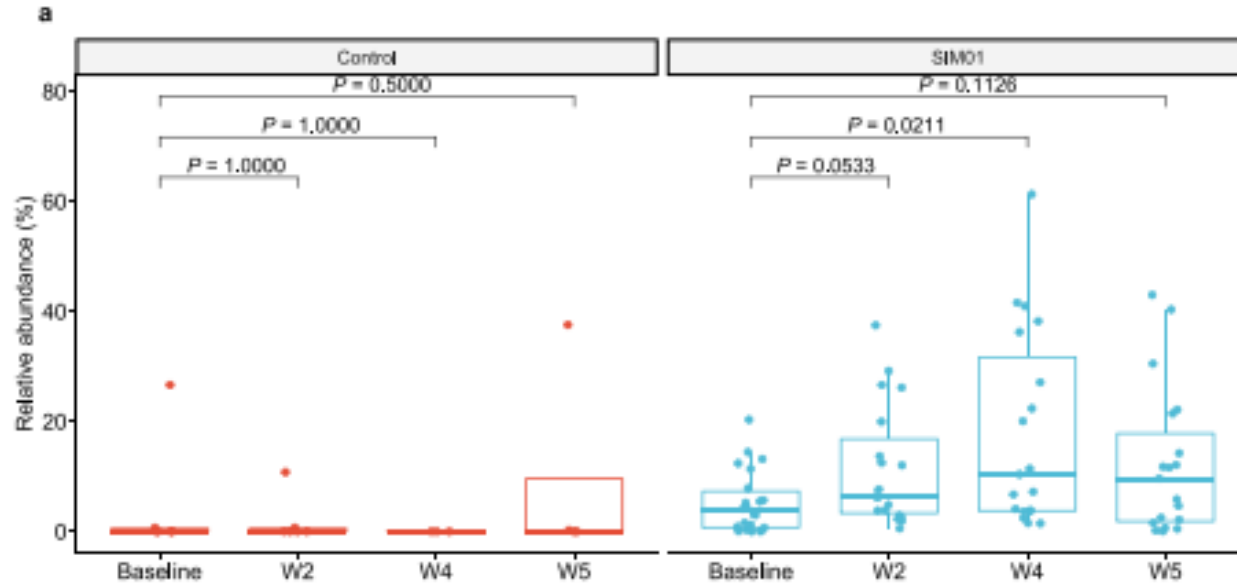
Blood level of pro-inflammatory cytokines was significantly reduced in the microbiome immunity formula group (SIM01)

Lin...Chan, Ng. Journ Gastro Hep 2022



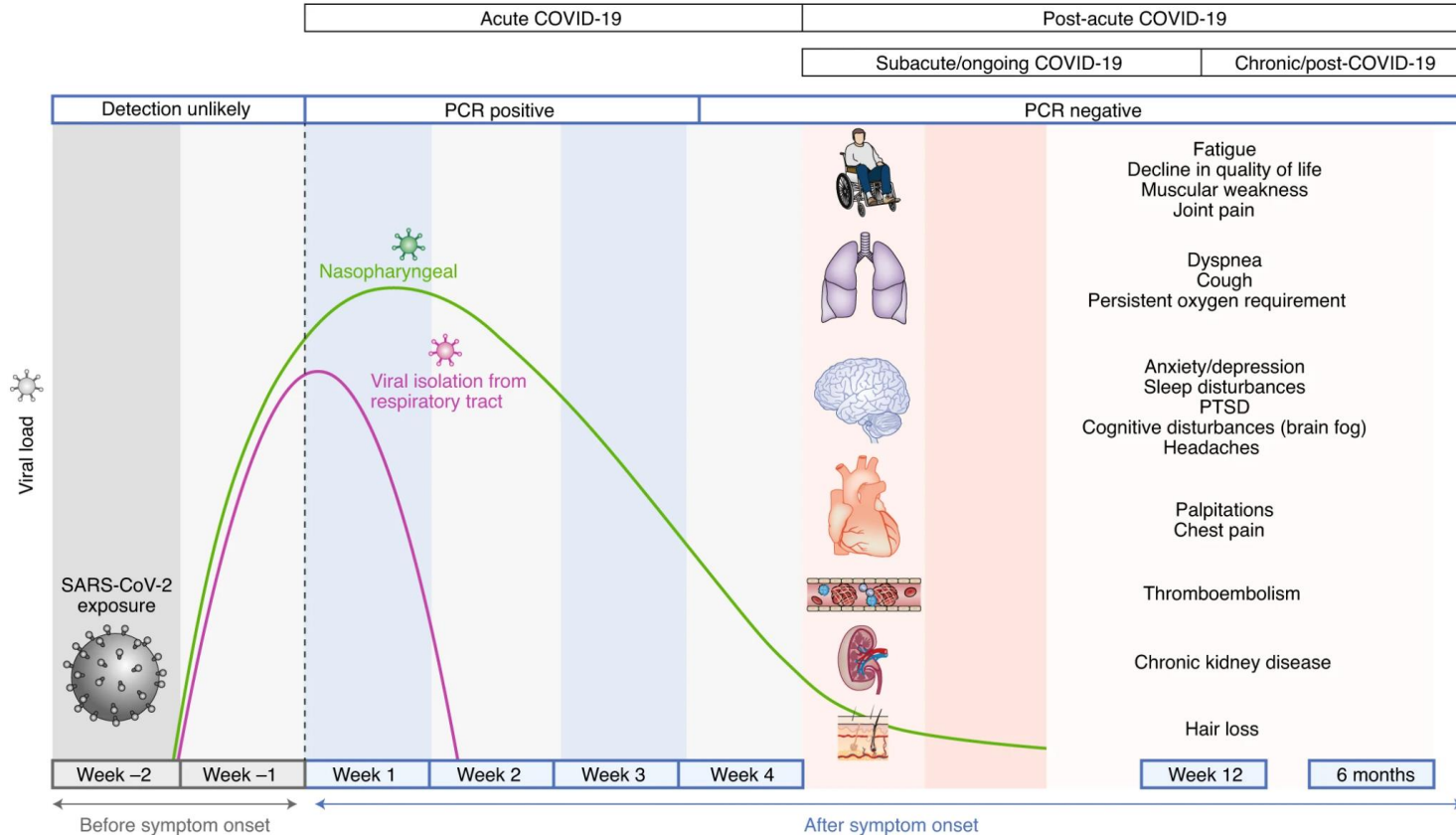
Abundance of three probiotic species contained in SIM01 increased in stool of intervention group

Lin...Chan, Ng. Journ Gastro Hep 2022



Post-acute COVID-19 Syndrome (Long COVID)

Nalbandian et al. Nature Medicine 2021



中大發現新冠康復者腸道「壞菌多」

中大研究顯示，新冠肺炎會影響患者的腸道，導致免疫力下降，導致「長新冠」症狀，即是患者康復之後，腸道微生態失衡仍然持續，

■中大研究顯示，
影響患者的腸道。



長期病徵包括疲倦、呼吸困難、失眠、記性差及脫髮。中大研究團隊於去年二至五月收集一百名新冠康復者的糞便及其血液樣本，與七十八名沒有染疫人士的樣本作比對，結果顯示新冠患者的腸道微生態較平常人差，腸道的「壞菌」較常人多，包括扭鏈瘤胃球菌、擬桿菌屬等；而腸道內亦缺少可調節免疫力的「好菌」，如幾種雙歧桿菌、普拉梭菌等等。

中大醫學院腸道微生物群研究中心副主任黃秀娟教授說，由於患者腸道內「壞菌」比「好

菌」多，這情況稱為「長新冠」。香港中文大學醫學院的研究發現，患新冠肺炎的嚴重程度，與患者腸道微生態失衡程度一致，相信幫助患者改善失衡問題，可減低出現長新冠的風險。

缺乏益菌

或導致長新冠

中大醫學院院長、中大醫學院腸道微生物群研究中心主任陳家亮教授指，過去已有研究表明，腸道微生態主宰人體免疫力，以對抗病毒侵襲。由於腸道失衡影響腸胃，如感染新冠肺炎，康復後失調狀態或會持續，繼而出現長新冠情況。

八成人症狀持續

外國研究指出，多達75%新冠患者康復後持續出現相關症狀。至於香港方面，中大醫學院內科及藥物治療學系腸胃及肝臟科助理教授麥詠欣醫生表示，於2020年2月至4月期間抽驗了住院的30名新冠患者，年齡介乎20至72歲，當中40%為男性，



和相關，當中能測到腸胃免疫力的發現降臨，而在腸道和胃腸菌，患者的數量降低了1.6倍至2.6倍不等，而前者更與新冠肺炎病情嚴重程度有關；而腸3種益菌減少，炎症細胞因子濃度愈高，即發炎情況愈嚴重，同時患者亦擁有較多壞菌，如沙雷菌屬、梭狀芽孢桿菌和腸桿菌屬。另外，患者於病毒清除後30天，益菌水平仍然偏低，康復後補充，「長新冠」患者的腸道微生態情況亦在分析當中，相信很快可確定兩者間的關係。」

保護腸道環境

陳家亮續指，如果在治療新冠肺炎的同時改善腸道微生態平衡狀態，相信可以減低長新冠的風險。「早前研究發現有因成人腸道微生態有不同程度的失



建議對康復者作全面治療。
記者：李明俊 編輯：黎家豪 美術：陳冠廷

出院後腸道仍欠特定益菌
失眠疲倦記性差

8成新冠康復者有後遺症

中大醫學院今年1月用電話跟進去年30名新冠肺炎康復者情況，發現8成人有腸道微生態失衡，可導致免疫力下降，患者出現後遺症比例高，令人憂慮，建議對康復者作全面治療，除治療外，改善腸道微生態減少後遺症風險。

Symptoms linger long after recovery for 80pc of patients

Ethan Paul
ethan.paul@scmp.com

Eighty per cent of recovered Covid-19 patients in Hong Kong continue to experience at least one of the disease's symptoms six months later and nearly a third report suffering from more than three, researchers have found.

The study by a Chinese University team examined the role that imbalances in gut

30 after they had recovered six months later. Out of that group, 24 said they still suffered from at least one symptom, while nine reported having more than three, the study found.

Analysis of the samples showed many of the patients suffered from a deficiency in certain types of "good" bacteria that regulated and directed the body's immune system, paired with an excess of "bad" bacteria that tended to disrupt it.



香港中文大學
The Chinese University of Hong Kong

CU Medicine
Faculty of Medicine
The Chinese University of Hong Kong

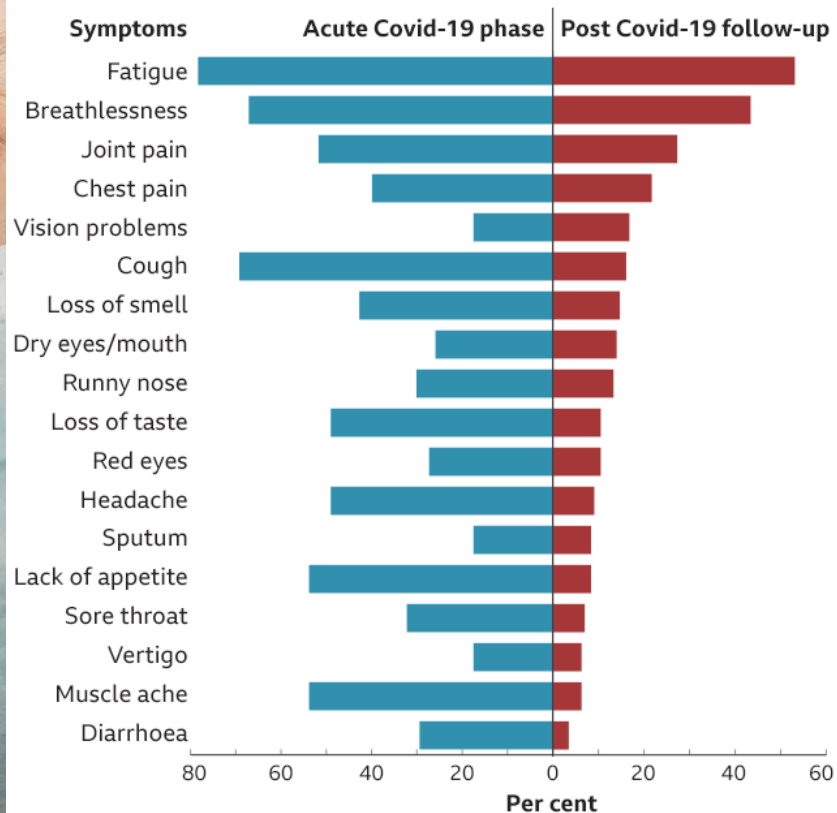


Press Conference 18 Jan 2021

'Long-COVID': 75% COVID-19 patients suffer from symptoms post-recovery

Persistent symptoms in Covid-19 patients

Patients followed up on average 60 days after first symptoms*



*143 patients assessed in Rome in April and May 2020

Source: Jama/Carfi, Bernabei, Landi et al

① JANUARY 25, 2022

Make-up of gut microbiome may be linked to long COVID risk

by British Medical Journal

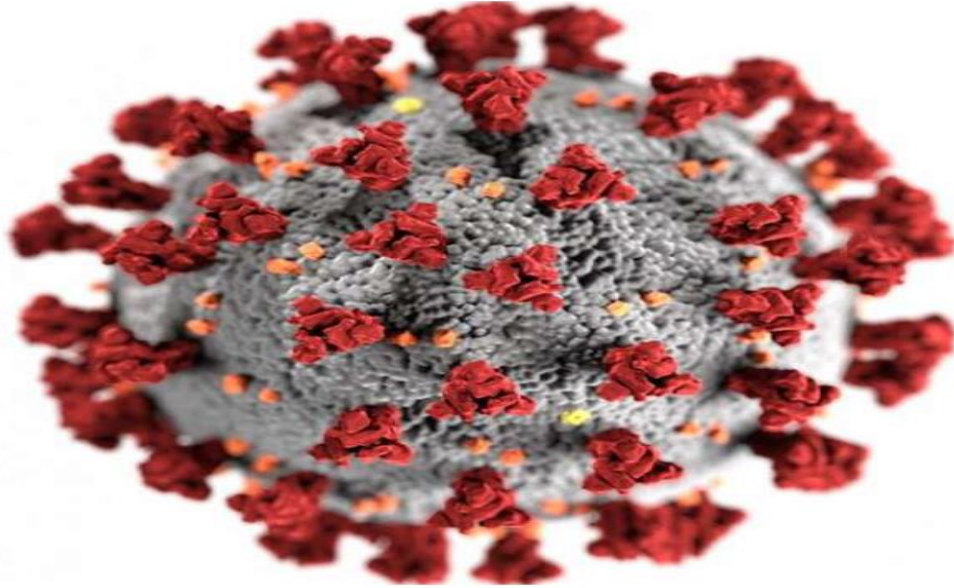


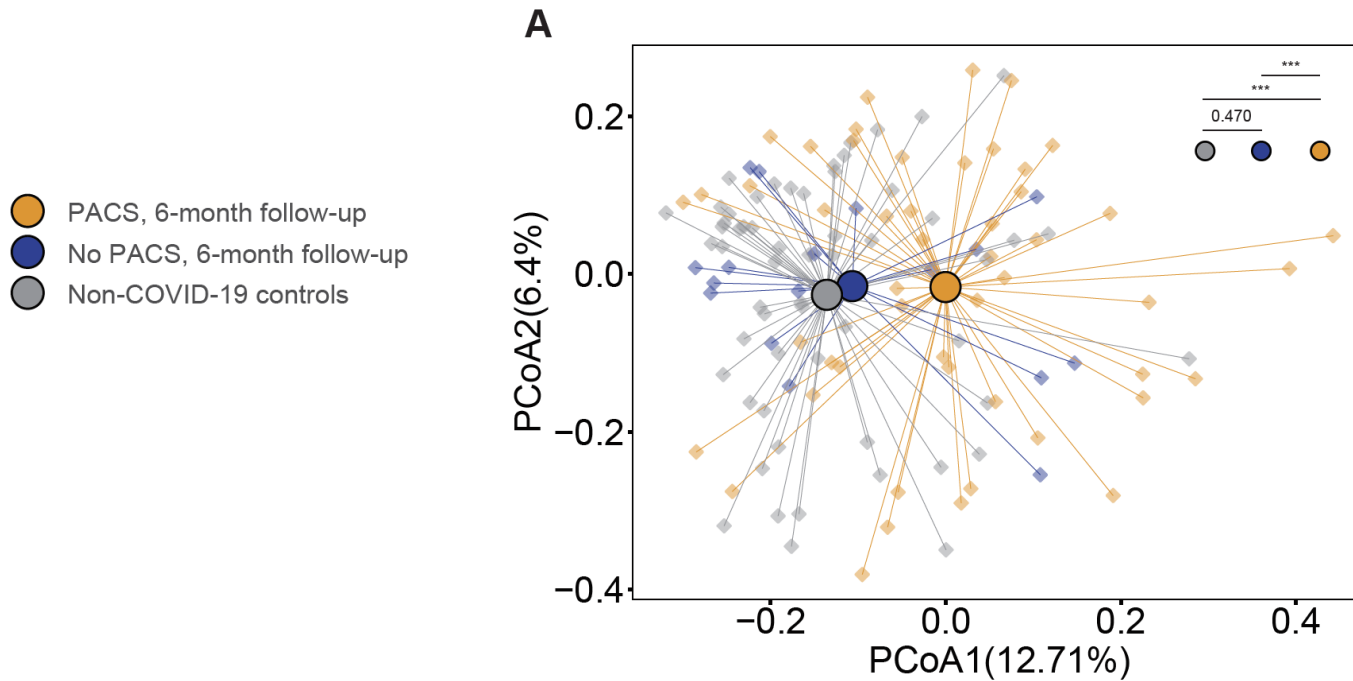
Image of the ultrastructural morphology exhibited by the 2019 Novel Coronavirus (2019-nCoV). Credit: CDC

The make-up of the gut microbiome may be linked to a person's risk of developing 'long COVID' many months after initial infection with SARS-CoV-2, the virus responsible for COVID-19 infection, suggests research published online in the journal *Gut*.

Microbiome 'profiling' might help identify those who are most susceptible to developing the condition, suggest the researchers.

Patients with Long COVID have distinct gut microbiome dysbiosis

Liu.. Ng. Gut 2021

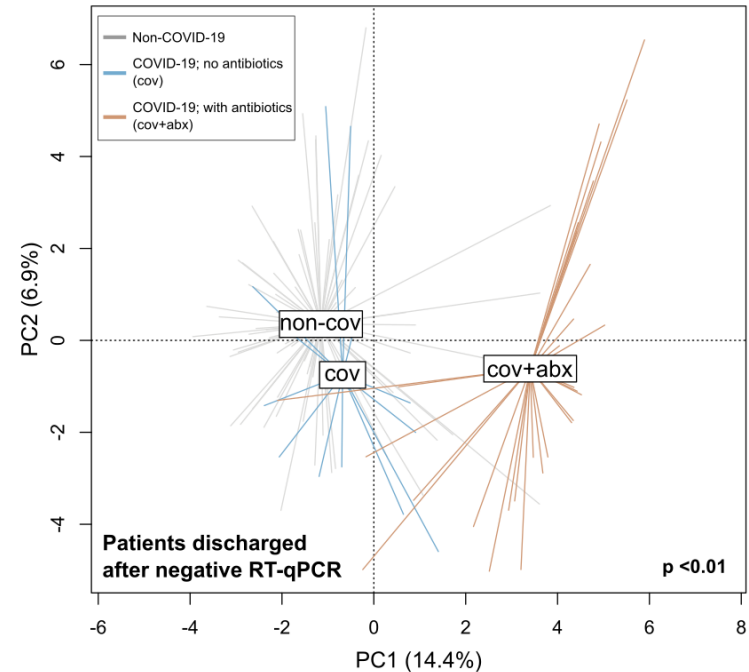


106 patients with varying degrees of COVID-19 severity, treated at 3 different hospitals between February and August 2020, and 68 people who didn't have COVID-19

Gut microbiota composition remains altered after clearing virus -> LONG COVID symptoms

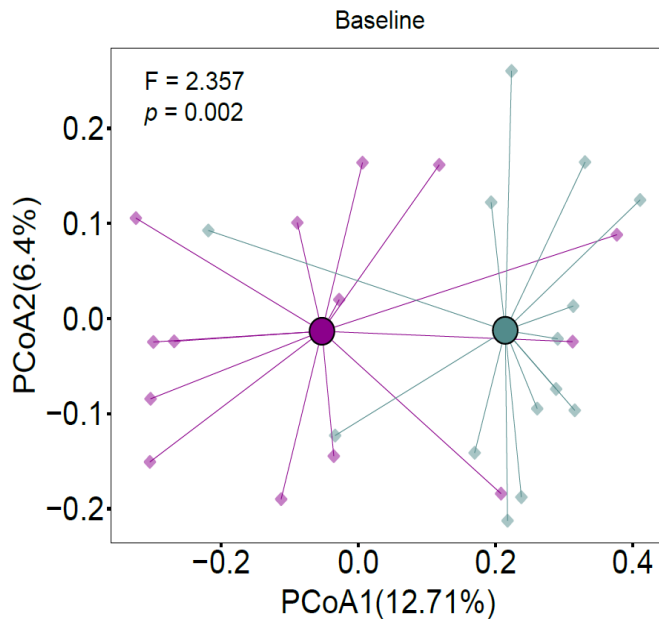
Yeoh... Ng. Gut 2021

- Lower levels of *E. rectale*, *R. bromii* and *F. prausnitzii*, *Bifidobacteria* compared with non-COVID subjects
- Could contribute to persistent symptoms associated with COVID



Gut microbiota composition at admission predicts Long COVID

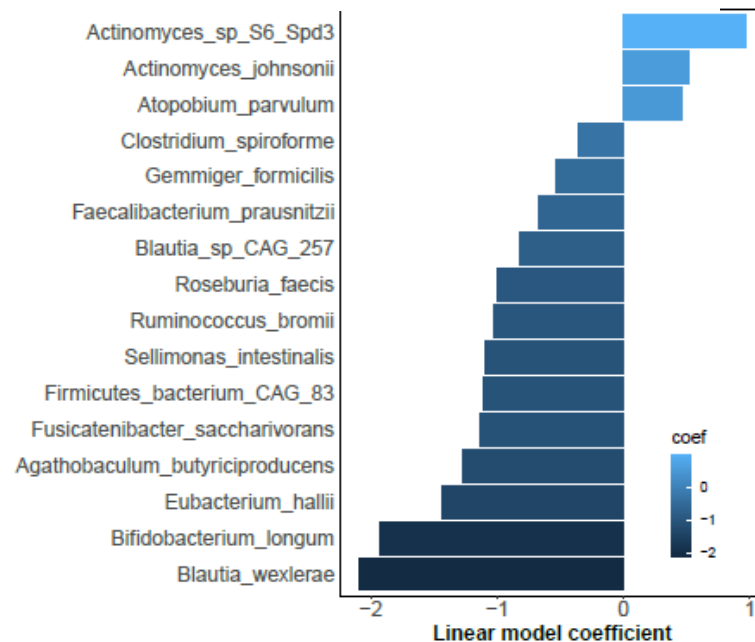
Liu... Ng. Gut 2021



● No PACS, baseline samples at admission

● PACS, baseline samples at admission

Baseline bacteria taxa associated with PACS

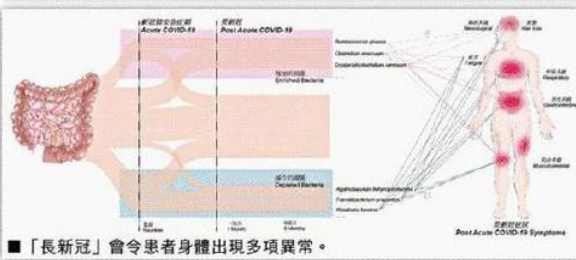


腸道 多惡菌

中大研究：疲倦記性差脫髮 新冠後遺症纏身



■中大研究發現新冠患者腸道細菌失衡，與出現「長新冠」風險相關。



■「長新冠」會令患者身體出現多項異常。



本港醫院迄今已治愈1.2萬多名新冠肺炎患者，但該症不少患者均有後遺症，一般被稱為「長新冠」或稱「新冠肺炎後遺症」，意指這些新冠患者康復後仍持續超過12周出現下列徵狀，如疲倦、脫髮、記憶力差甚至焦慮等。香港中文大學醫學院昨日公布一項最新研究，發現超過75%的新冠肺炎患者出現「長新冠」，這類患者也被發現腸道細菌出現失衡。中大醫學院院長兼腸道微生物群研究中心主任陳家亮表示，全球有數以百萬計人士感染新冠肺炎，相關研究顯示透過調節腸道內的細菌，可以促進患者痊癒及減少新冠肺炎後遺症出現。

中大研究團隊指，76%新冠患者康復後6個月內出現至少一種症狀，當中最常見的症狀，包括有31%是疲倦、28%為記憶力差；而脫髮、焦慮和睡眠困難同樣是21%。而腸道微生物失衡是導致「長新冠」的主因。

研究發現，「長新冠」患者的腸道微生物生態異常，「好菌」明顯較少，而「惡菌」則較多。相反，沒有後遺症人士的腸道微生物則較豐富及多樣化，與從未染疫人士相似。團隊又發現，「長新冠」患者在年齡、性別、其他疾病、使用抗生素和抗病毒藥物、感染新冠肺炎的嚴重程度上，與未有出現

後遺症人士無分別。

團隊又指，多達81種腸道細菌與多種新冠後遺症有關，當中不少細菌更與3種或以上持續症狀有密切關聯。同時，他們亦發現「長新冠」患者腸道中缺少了幾種能提高人體免疫力的腸道細菌。

籲及早調節腸道微生態

陳家亮表示，研究顯示新冠患者的腸道微生態可以預測出現後遺症的風險，透過調節腸道內的細菌，可以促進患者痊癒及減少新冠肺炎後遺症出現。

Gut feeling on long Covid pays off

Leone Xue

A lack of diversity of microorganisms in one's guts is associated with "long Covid," which causes fatigue, poor memory, and hair loss months after an infection, Chinese University researchers have found.

Long Covid refers to how patients suffer from at least one persistent symptom for four weeks after being cleared of the Covid virus.

Published in international journal *Gut*, the study found 76 percent of patients had at least one symptom six months after recovery, with 31 percent reporting fatigue, 28 percent poor memory, 21 percent hair loss, 21 percent anxiety and 21 percent sleeping difficulties.

The symptoms were observed in patients across all ages and genders, regardless of whether they had used antibiotics or antiviral drugs, or the severity of their infections.

The research found that what is inside the gut may affect one's susceptibility to long-term complications, as patients with long Covid had a less diverse gut microbiome, meaning they have significantly fewer "favorable" bacteria and a greater abundance

of "unfavorable" bacteria. Patients without long Covid have normal gut conditions.

A further look at microbiomes led to 81 bacterial species linked to long Covid being identified, many of them associated with three or more persistent symptoms hitting the respiratory, neuro, digestive systems, skin, muscles and bones and causing fatigue.

Persistent respiratory symptoms are strongly linked to opportunistic pathogenic microbes – which do not usually infect the healthy – while species known to boost immunity were depleted in those with long Covid.

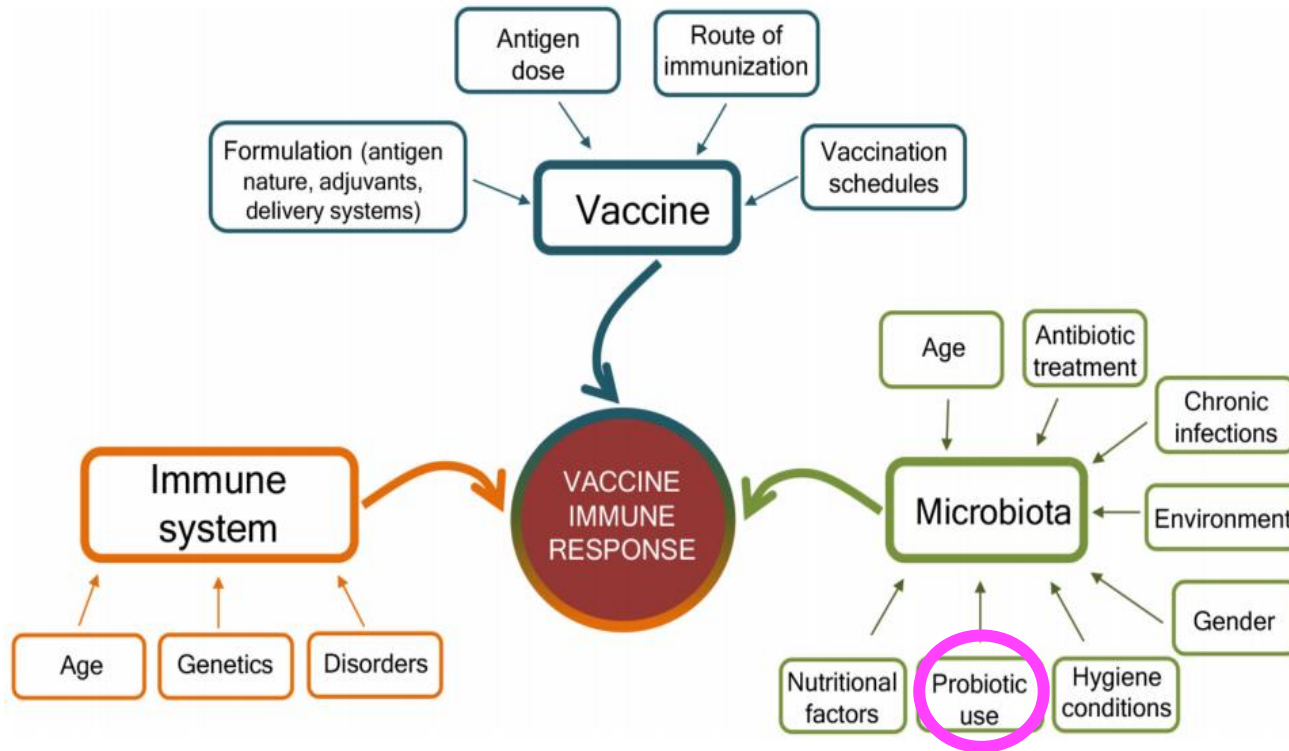
CUHK's Centre for Gut Microbiota Research associate director Ng Siew-chien said the study is the world's first to demonstrate an imbalance of microorganisms in the guts at six months after Covid recovery and the link between altered gut microbiota and common lingering symptoms.

Center director and dean of medicine Francis Chan Ka-leung said: "The findings are the impetus for consideration of microbiota modulation to facilitate timely recovery and reduce the burden of post-acute Covid syndrome."



Francis Chan, far left, and Ng Siew-chien with the team of researchers that discovered the link between long Covid and persistent effects on health.

Gut Microbiota can influence Immune Response to Vaccination

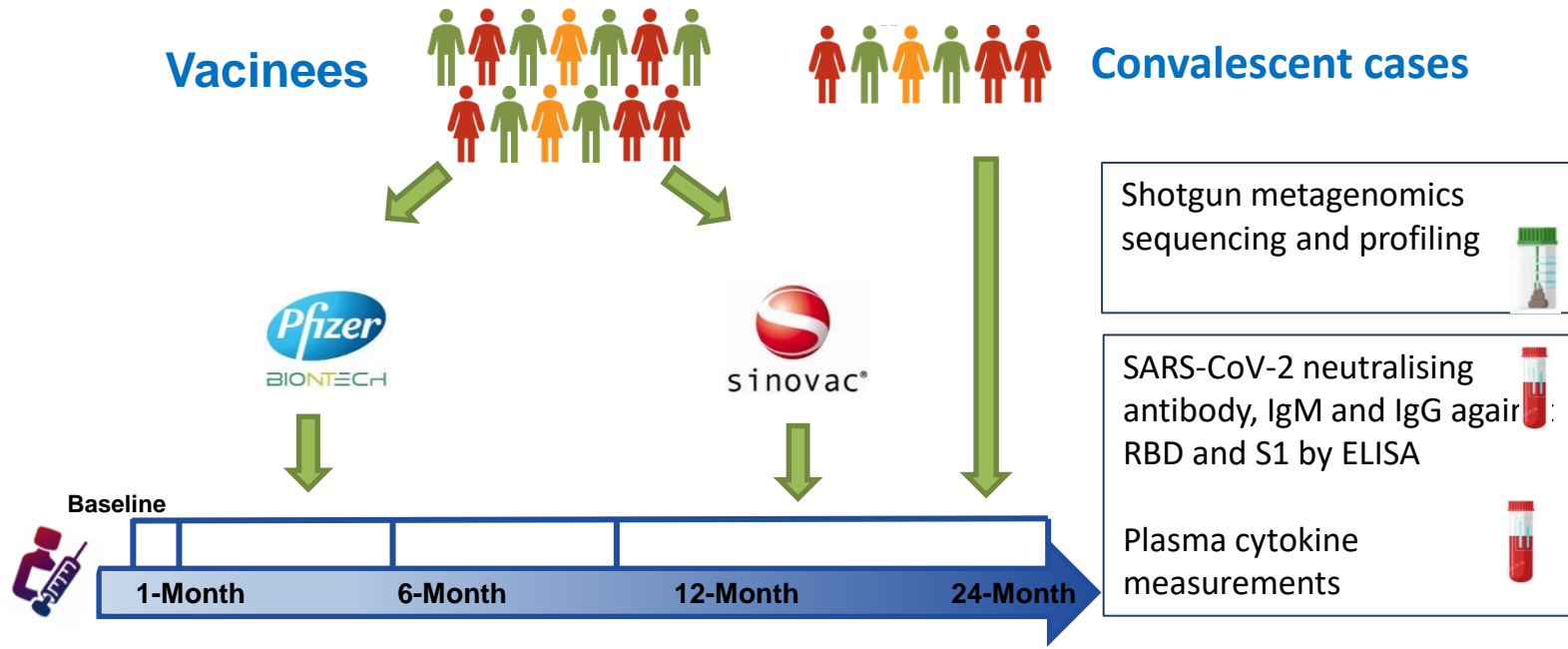




Original research

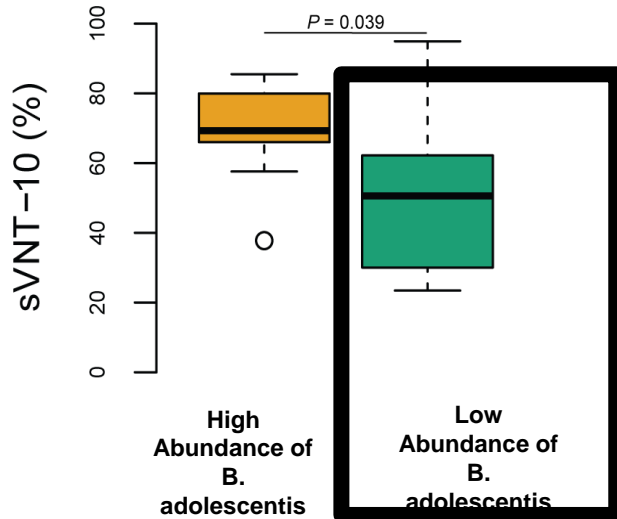
Gut microbiota composition is associated with SARS-CoV-2 vaccine immunogenicity and adverse events

Siew C Ng ^{1,2,3,4} Ye Peng ^{5,6} Lin Zhang ^{1,2,4,7} Chris KP Mok,^{3,8} Shilin Zhao,^{5,6} Amy Li,¹ Jessica YL Ching ¹ Yingzhi Liu,^{4,7} Shuai Yan,^{4,7} Dream L S Chan,⁴ Jie Zhu,^{5,6} Chunke Chen,^{3,8} Adrian CH Fung,⁹ Kenneth KY Wong ⁹ David SC Hui,^{1,10} Francis KL Chan ^{1,2,3,4} Hein M Tun ^{5,6}



People lacking *Bifidobacterium adolescentis* showed poor antibody response to COVID-19 vaccines

Subjects who received SinoVac (inactivated vaccine) with **low abundance of *B.adolescentis*** showed lower antibody response.



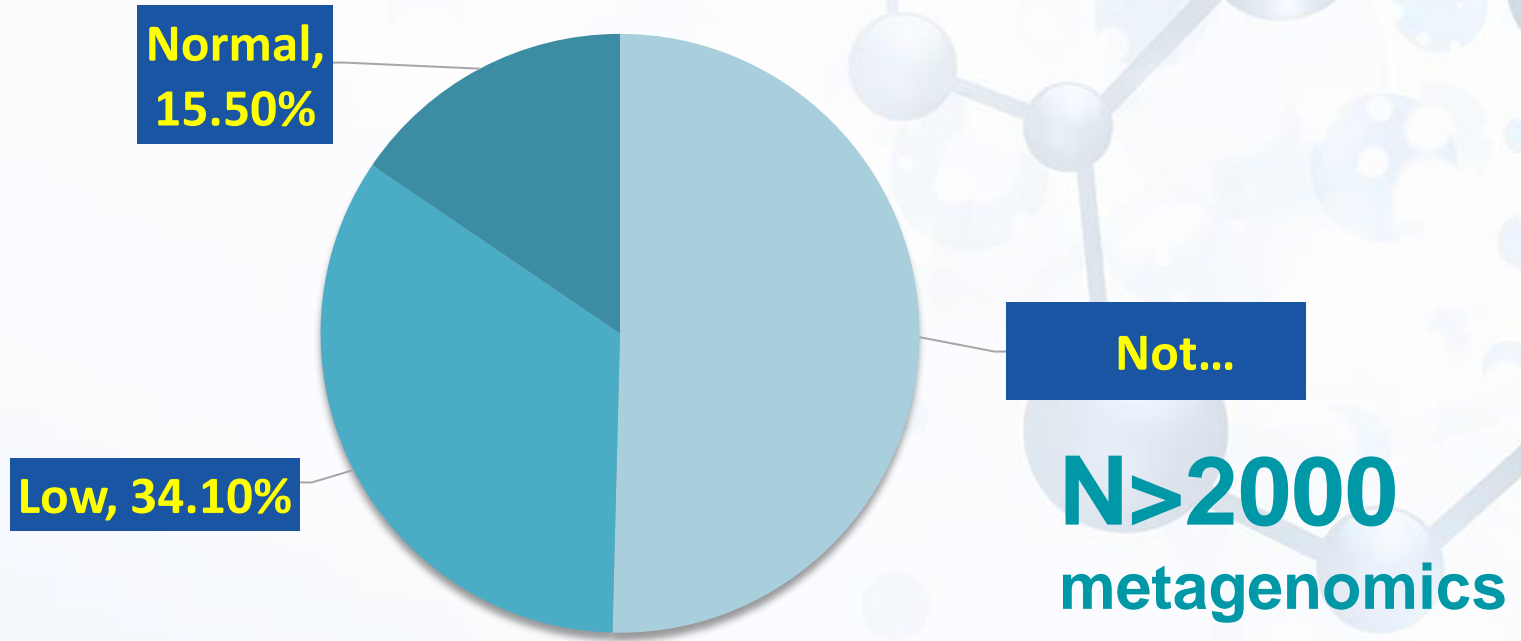
Subjects who received BioNTech (mRNA vaccine) and showed the **lowest quarter of antibody response** are also lack of *B. adolescentis* and *R. faecis*.

Antibody level



Lacking
R. faecis and *B. adolescentis*

85% of the population are depleted in *B. adolescentis* in the gut



青春雙岐桿菌 *Bifidobacterium adolescentis*

Beneficial bacteria that
regulates immunity



Acquired after birth



antibiotics



Diet

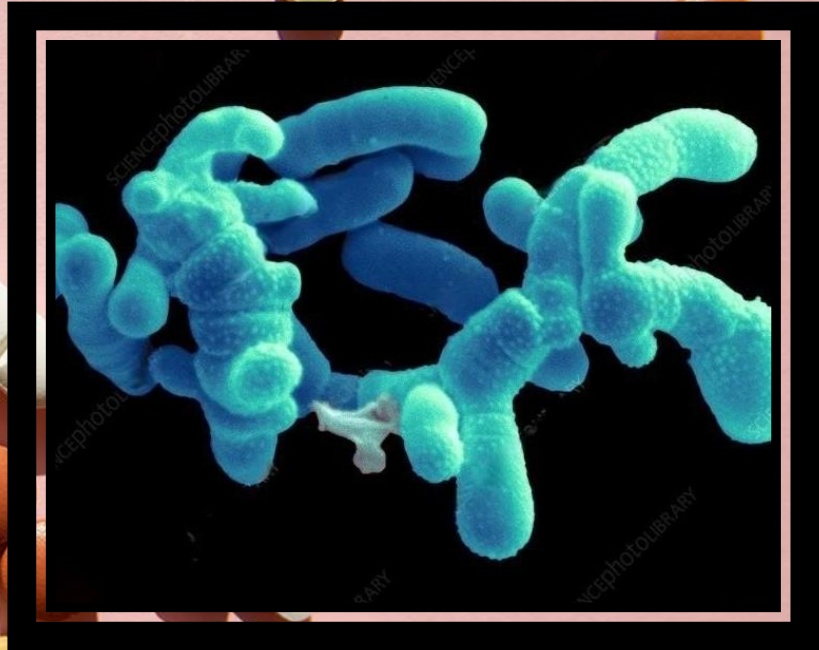


stress



Lower Abundance





Few commercial probiotic contain bifidobacteria adolescentis

...fragile and requires special microencapsulation technology

To maintain survival and colonisation

Joint CUHK-HKU study discovers efficacy of COVID-19 vaccines correlates with a probiotic bacterium, *Bifidobacterium Adolescentis*



Dr Hein Tun from HKU, Professor Ng Siew Chien from CUHK, Professor Francis Chan Ka-leung from CUHK, and Professor Lin Zhang of CUHK yesterday. Photo: K.Y. Cheng

Gut bacteria helps boost vaccine response: study

Gigi Choy
g@choy@scma.com

A type of probiotic bacteria in the gut has the potential to improve a person's antibody response to Covid-19 vaccines, researchers at two Hong Kong universities have found.

The joint study by Chinese University (CUHK) and the University of Hong Kong (HKU) discovered that the efficacy of the Sinovac and BioNTech Covid-19 vaccines correlated with the amount of *Bifidobacterium adolescentis* people had in their gut, meaning that low antibody response corresponded to inadequate levels of that bacteria.

role in modulating the efficacy of Covid-19 vaccines," said Professor Ng Siew Chien, associate director of CUHK's Centre for Gut Microbiota Research. "The inactivated vaccine (developed by Sinovac) is known to have fewer side effects but suffers from relatively lower antibody response. Our study offers a potential solution to enhance [its] efficacy."

The researchers collected blood and stool samples from 138 people aged between 18 and 67 to measure their antibody levels in relation to their gut bacterial composition. The samples were taken before vaccination and one month after their second dose between April and August this year.

Dr Hein Tun, assistant professor of public health at HKU, noted that there were two possible ways for gut microbiota to boost antibody response to vaccines.

"First, some components of gut bacteria such as flagellin serve as natural adjuvants to enhance antibody production," he said. "Second, gut microbiota produce metabolites such as short chain fatty acids that can enhance immune cell metabolism to support energy demands for antibody production."

In an earlier CUHK study involving more than 2,000 residents, researchers found that 85 per cent either had very low levels of *Bifidobacterium adolescentis*

to oxygen, so it dies very easily when exposed to it. It's also very fragile in terms of the environment that it likes to live in," she said.

"We can't get it through our diet because it's not sufficient to give you enough of this bacteria. A lot of what's available in terms of probiotics may not have this bacteria because you need special technology to encapsulate the bacteria so that it can survive and actually reach your gut when you consume it."

Asked if the public should

check whether they had an adequate amount of *Bifidobacterium adolescentis* in their body, Professor Francis Chan Ka-leung, dean of CUHK's medical school, said it would be costly and recommended against it.

"This bacteria can be measured using metagenome analysis but this type of analysis is only available in university-level laboratories, so it is not widely available and will be pretty expensive," said Chan, who is also a director of the Centre for Gut Microbiota Research.

"[People] should focus on improving their overall immune system through [a balanced] diet, exercise and possibly taking

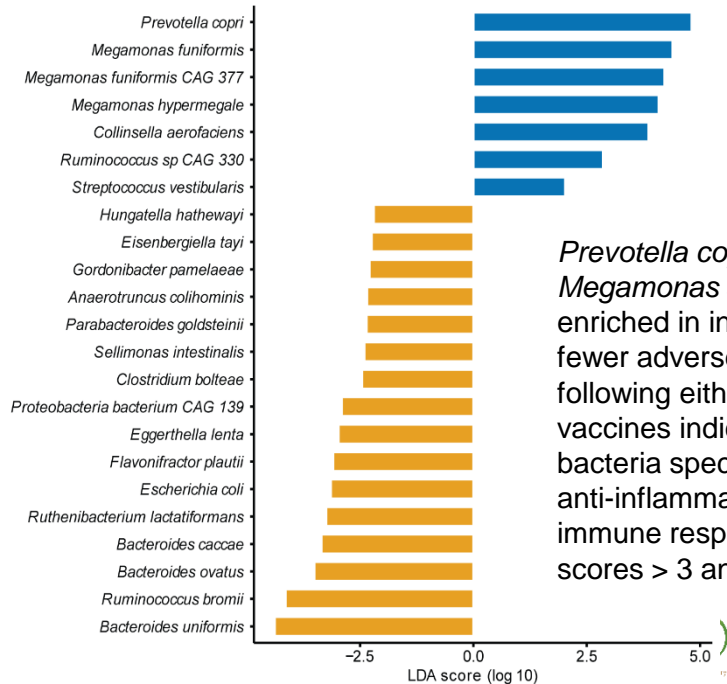
GUT CHECK PROVIDES JABS A POWER BOOST



The experts from Chinese University.

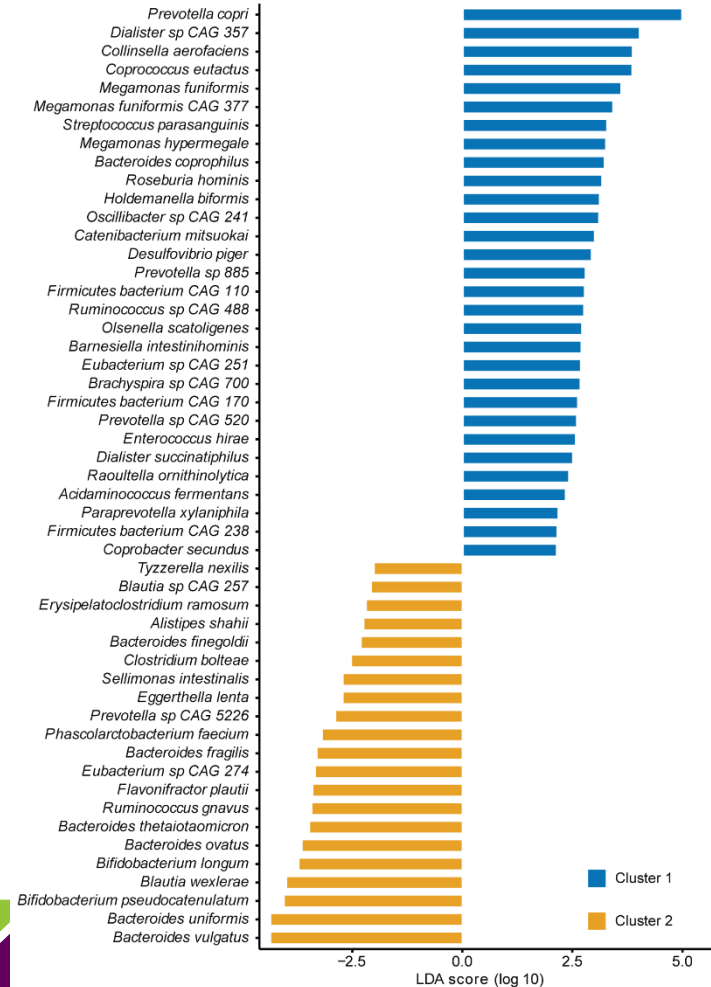
Specific Bacteria associated with less side effects after COVID-19 vaccine

Coronovac



Prevotella copri and two *Megamonas* species were enriched in individuals with fewer adverse events following either of the vaccines indicating that these bacteria species may play an anti-inflammatory role in host immune response (LDA scores > 3 and $p < 0.05$).

Biontech



THE SECRET TO TREATING LONG COVID MAY LIE IN THE GUT MICROBIOME

Bacterial populations may predict who gets Long Covid.

Alissa Eckert/SCIENCE PHOTO LIBRARY/Science Photo Library/Getty Images

Feedback

WHEN COVID-19 HIT the world with a sucker punch, [Siew C. Ng](#) didn't flinch. Her research experience on the gut microbiome and its role in immunity told her it's likely involved in Covid-19 infection — but further, Ng hypothesized it could also help treat [features of Covid-19](#). Now, in the journal [Gut](#), Ng and her team report the fruit of their labor: They show how healthy gut bacteria could protect against [Long Covid](#).

Home / News & Opinion

Gut Microbiome May Help or Hinder Defenses Against SARS-CoV-2

The health of the microbial community is associated with COVID-19 severity, but it's not yet clear if the relationship is causal.



Bianca Nogrady

Aug 31, 2021

PDF VERSION

Facebook Twitter Plus 333

When SARS-CoV-2 first began rampaging around the world, it was thought to primarily affect the respiratory system. It soon became clear that the virus had more [far-reaching effects](#), including on the gastrointestinal system and its bacterial symbionts.

This came as no surprise to Siew Ng, a gastroenterologist in the Center for Gut Microbiota Research at the Chinese University of Hong Kong. "We previously had found quite a lot of impaired gut microbiome in different conditions, including people with infectious disease," says Ng. COVID-19 patients were no different. "In quite a substantial proportion of people, they also have gut manifestations, such as diarrhea, such as abdominal pain."

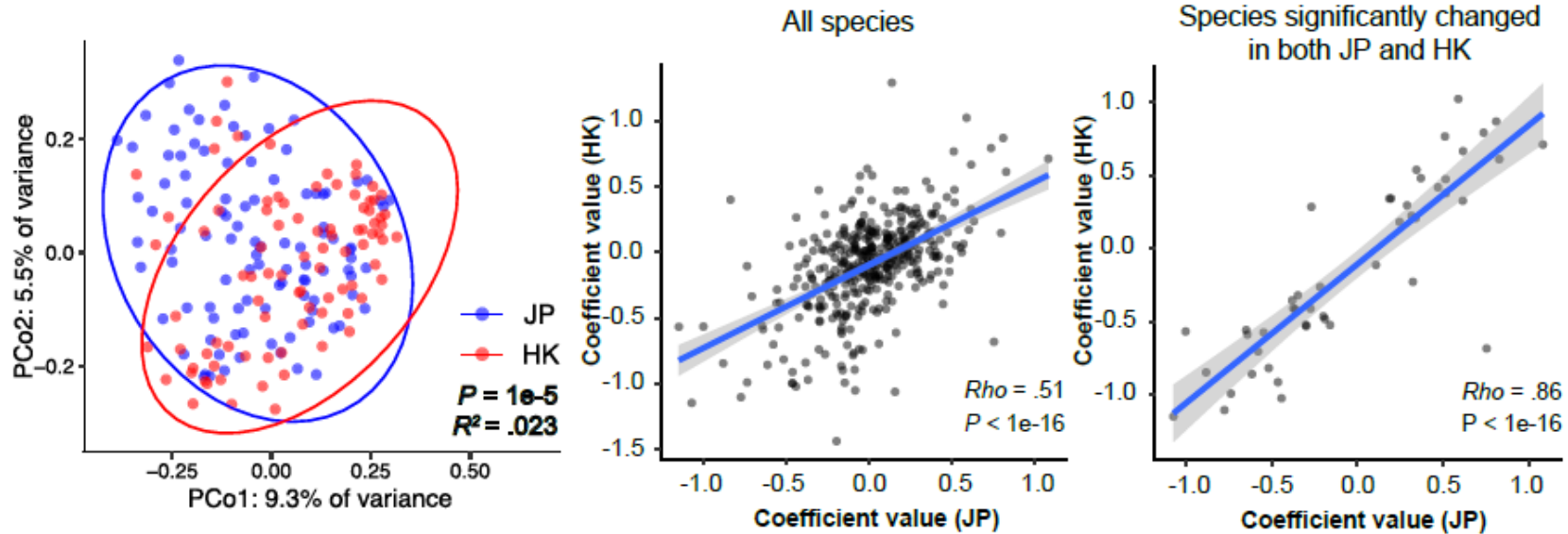
One early [study](#) suggested that nearly 20 percent of patients with confirmed SARS-CoV-2 infection had gastrointestinal symptoms. That same study found that COVID-19-infected people shed viral RNA in their feces—another clue that the virus was getting into the gut.

ABOVE: © ISTOCK.COM,
[DR_MICROBE](#)

Are Microbiome Signatures Population-Specific?

Overlapping microbial signatures for COVID-19
independent of geographical microbial differences (Japanese, Chinese)

Nagata .. Ng et al. *Gastroenterology* 2022 (in press) (CUHK, Tokyo Medical University)



Outline



1. Role of gut microbiome in COVID-19 risk and severity
2. Scientific development of a microbiome immunity formula
3. Gut microbiome and development of Long COVID
- 4. Impact of gut microbiome on MDRO**
5. Microbiome modulation for MDRO



***Superbugs are
on the rise***

***The pandemic
might have
make it worse***

COVID-19 CREATED A PERFECT STORM

The U.S. lost progress combating antimicrobial resistance in 2020

A detailed 3D rendering of a virus particle, likely SARS-CoV-2, showing its characteristic spherical shape with a textured surface and numerous red, spike-like protrusions. The background is a dark blue field with out-of-focus purple and pink circular shapes, suggesting a microscopic environment.

↑15%

Antimicrobial-resistant infections and deaths increased in hospitals in 2020.

~80%

Patients hospitalized with COVID-19 who received an antibiotic March-October 2020.



Delayed or unavailable data, leading to resistant infections spreading undetected and untreated.

**INVEST IN
PREVENTION.**

**Setbacks to fighting
antimicrobial resistance
can and must be temporary.**

Learn more: <https://www.cdc.gov/drugresistance/covid19.html>

ANTIBIOTICS?

EVIL

EDITORIAL

Combating antimicrobial resistance during the COVID-19 pandemic

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Hong Kong Med J 2021;27:396–8

<https://doi.org/10.12809/hkmj215124>

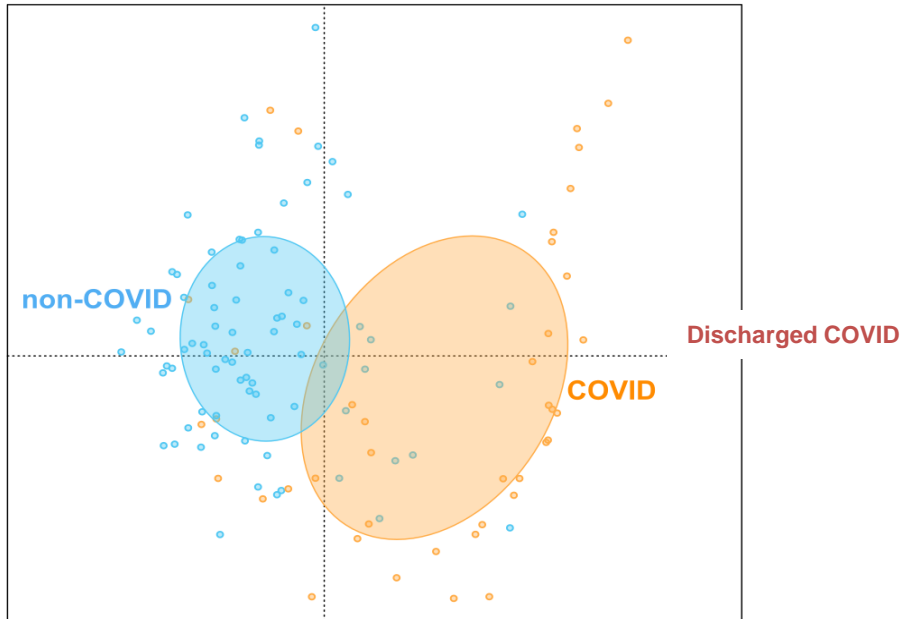
Are We too liberal? Too Much Antibiotics?

- Empirical treatment of patients with COVID-19 using antibiotics is common
- A meta-analysis involving 154 studies and over 30 000 patients revealed that 74.6% of patients with COVID-19 received antibiotics, significantly higher than the estimated prevalence of bacterial co-infection
- In Hospitalised patients with COVID-19, 72% (1450/2010) of patients received antibiotics but only 8% (62/806) had bacterial or fungal co-infections

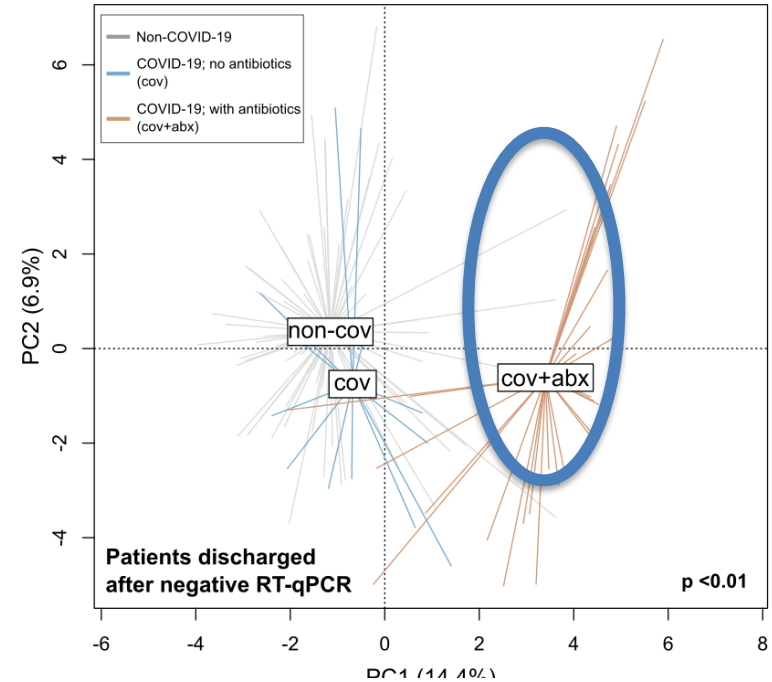


Gut Microbiota “Dysbiosis” Persist after Disease Resolution and Worsened with Antibiotic Use

Yeoh... Ng. *Gut* 2021



Differences in gut microbiota composition in discharged COVID-19 patients vs non-COVID-19 subjects depicted by separation of the two ellipses



Lower levels of *E. rectale*, *R. bromii* and *F. prausnitzii*, *Bifidobacteria* compared with non-COVID subjects



RESEARCH PAPER



Antibiotics and probiotics impact gut antimicrobial resistance gene reservoir in COVID-19 patients

Qi Su^{a,b,c,d#}, Qin Liu^{a,b,c,d#}, Lin Zhang^{a,b,c,d}, Zhilu Xu^{a,b,c,d}, Chenyu Liu^{a,b,c,d}, Wenqi Lu^{a,b,c}, Jessica YL Ching^b, Amy Li^{a,b,c}, Joyce Wing Yan Mak^{a,b,c}, Grace Chung Yan Lui^{b,e}, Susanna So Shan Ng^{b,f}, Kai Ming Chow^b, David SC Hui^{b,f}, Paul KS Chan^e, Francis Ka Leung Chan^{a,b,c,d}, and Siew C Ng^{a,b,c,d}

^aMicrobiota I-Center (Magic), Hong Kong SAR, China; ^bDepartment of Medicine and Therapeutics, the Chinese University of Hong Kong, Hong Kong SAR, China; ^cLi Ka Shing Institute of Health Sciences, State Key Laboratory of Digestive Disease, Institute of Digestive Disease, the Chinese University of Hong Kong, Hong Kong SAR, China; ^dCenter for Gut Microbiota Research, Faculty of Medicine, the Chinese University of Hong Kong, Hong Kong SAR, China; ^eDepartment of Microbiology, the Chinese University of Hong Kong, Hong Kong SAR, China; ^fStanley Ho Centre for Emerging Infectious Diseases, Faculty of Medicine, the Chinese University of Hong Kong, Hong Kong SAR, China

ABSTRACT

Dysbiosis of gut microbiota is well-described in patients with coronavirus 2019 (COVID-19), but the dynamics of antimicrobial resistance genes (ARGs) reservoir, known as resistome, is less known. Here, we performed longitudinal fecal metagenomic profiling of 142 patients with COVID-19, characterized the dynamics of resistome from diagnosis to 6 months after viral clearance, and reported the impact of antibiotics or probiotics on the ARGs reservoir. Antibiotic-naïve patients with COVID-19 showed increased abundance and types, and higher prevalence of ARGs compared with non-COVID-19 controls at baseline. Expansion in resistome was mainly driven by tetracycline, vancomycin, and multidrug-resistant genes and persisted for at least 6 months after clearance of SARS-CoV-2. Patients with expanded resistome exhibited increased prevalence of *Klebsiella* sp. and post-acute COVID-19 syndrome. Antibiotic treatment resulted in further increased abundance of ARGs whilst oral probiotics (synbiotic formula, SIM01) significantly reduced the ARGs reservoir in the gut microbiota of COVID-19 patients during the acute infection and recovery phase.

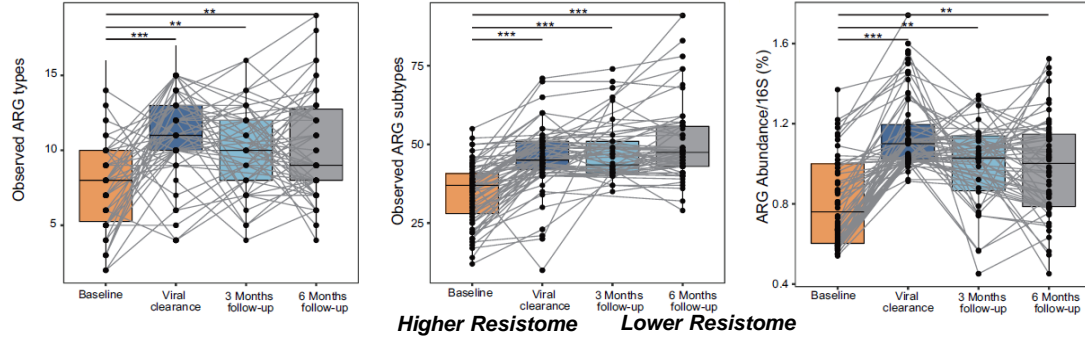
ARTICLE HISTORY

Received 24 May 2022
Revised 18 August 2022
Accepted 20 September 2022

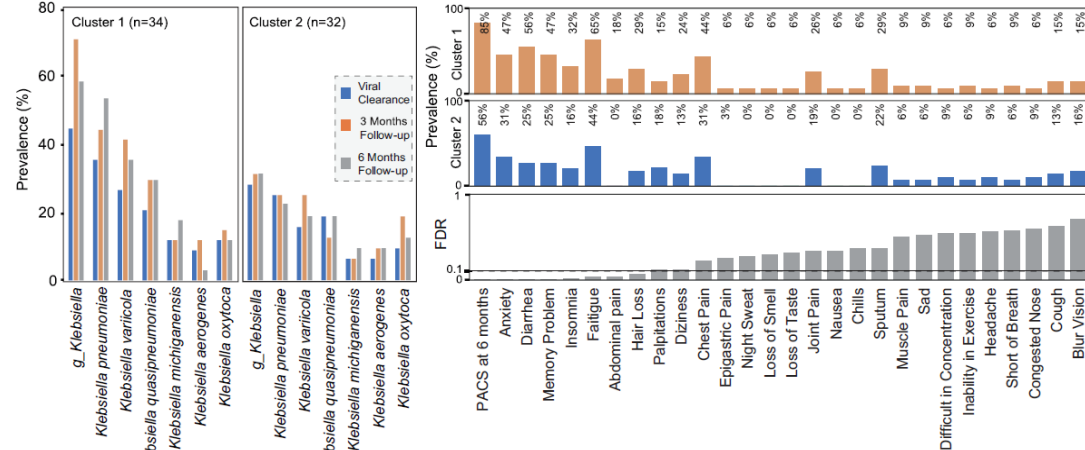
KEYWORDS

COVID-19; gut microbiome;
antimicrobial resistance
gene; synbiotic formula;
SIM01

Increased Antimicrobial Resistance Gene Reservoir (resistome) in COVID-19



COVID-19 patients exhibited an enlarged gut antimicrobial resistance gene reservoir (resistome)



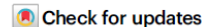
Resistome maintained for at least six months, which was associated with higher possibility of *Klebsiella* co-infection and long-COVID symptoms

Gut microbiome dysbiosis in antibiotic-treated COVID-19 patients is associated with microbial translocation and bacteremia

Received: 13 June 2022

Accepted: 12 September 2022

Published online: 01 November 2022



Lucie Bernard-Raichon^{1,20}, Mericien Venzon^{1,2,20}, Jon Klein^{3,20}, Jordan E. Axelrad^{4,20}, Chenzhen Zhang^{5,20}, Alexis P. Sullivan⁵, Grant A. Hussey⁵, Arnau Casanovas-Massana⁶, Maria G. Noval⁷, Ana M. Valero-Jimenez⁷, Juan Gago^{2,8}, Gregory Putzel^{7,9}, Alejandro Pironti^{7,9}, Evan Wilder⁴, Yale IMPACT Research Team*, Lorna E. Thorpe^{8,9}, Dan R. Littman^{1,10}, Meike Dittmann⁷, Kenneth A. Stapleford⁷, Bo Shopsis^{7,9,11}, Victor J. Torres^{7,9}, Albert I. Ko⁶, Akiko Iwasaki^{3,10}, Ken Cadwell^{1,4,7,9}✉ & Jonas Schluter^{5,7,9}✉

SARS-CoV-2 infection induces gut microbiome dysbiosis in mice, which correlated with alterations to Paneth cells and goblet cells, and markers of barrier permeability

Gut microbiome dysbiosis is associated with translocation of bacteria into the blood during COVID-19

Outline



1. Role of gut microbiome in COVID-19 risk and severity
2. Scientific development of a microbiome immunity formula
3. Gut microbiome and development of Long COVID
4. Impact of gut microbiome on MDRO
- 5. Microbiome modulation for MDRO**

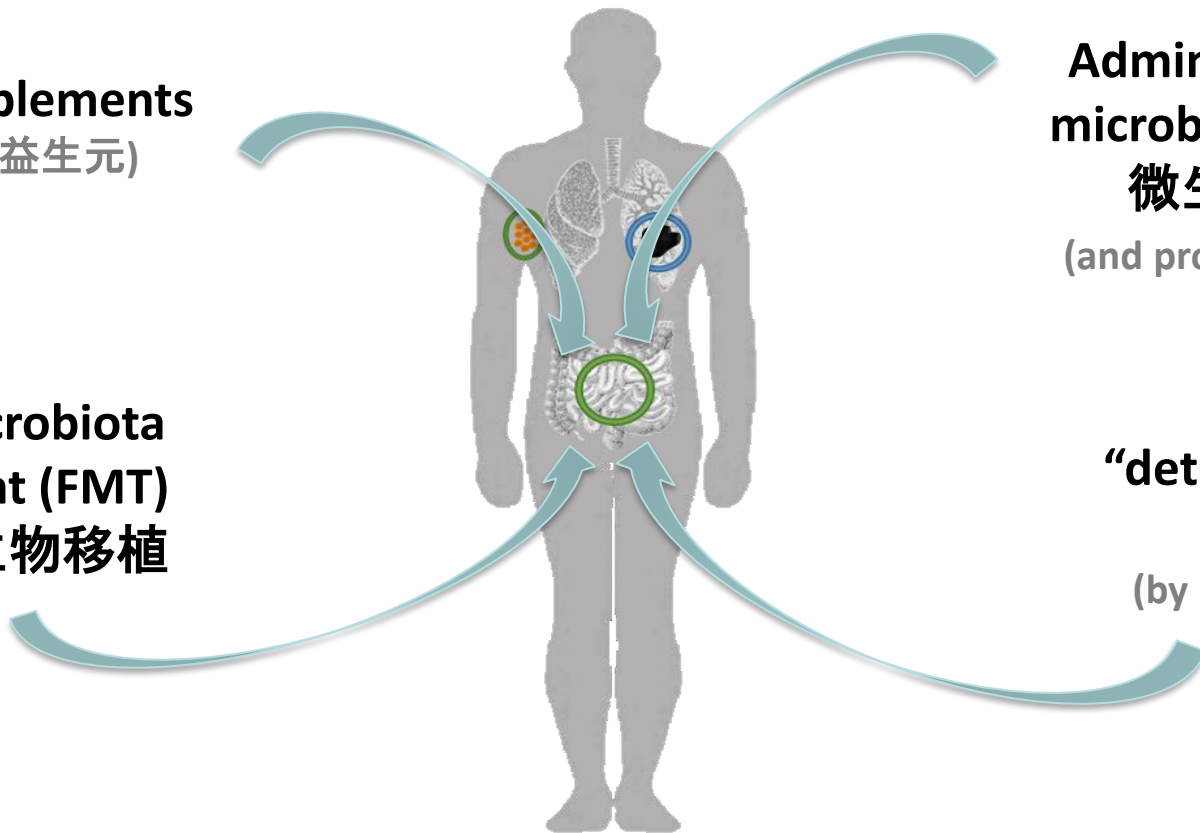
How to Modulate the Gut Microbiota?

Diet & supplements
(prebiotics益生元)

**Fecal Microbiota
Transplant (FMT)**
腸道微生物移植

**Administration of
microbial consortia**
微生物組合
(and probiotics益生菌)

**Targeting of
“detrimental有害的”
microbes**
(by antibiotics抗生素 /
phage噬菌體)



Role of Probiotics, Prebiotics in Combating MDRO

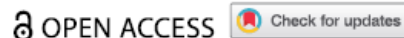
- The use of microbiome manipulation with prebiotics, probiotics, and synbiotics is in its infancy compared with other measures
- No direct conclusions regarding the efficacy of these measures
- For now, these supplements seem safe to use and are well tolerated in most populations
- These nutritionally based therapies should continue to be used in conjunction with other proven techniques, such as antibiotic stewardship and improvement in hygiene and sterilization practices, to aid in the reduction of colonization with MDROs.

Companies Developing Microbiome-based Therapies for MDRO

Company	Product Name or Prefix	Therapy Type	Proposed Mechanism	Trials Specifically for MDRO
Rebiotix	RBX2660	FMT (enema)	Displacement of MDRO	Phase 1/2
Kaleido	KB109	prebiotic	Feed healthy bacteria to out-compete MDRO	Clinical Food Study
ExeGi	Visbiome (US), Vivomixx (EU)	probiotic	Displacement of MDRO	Yes [31]
Vedanta	VE707	rationally selected microbiota	Displacement of MDRO	Preclinical
SciBac	SCB	engineered probiotic	Transfer of plasmids to enhance good bacteria	Preclinical
Rise Therapeutics	R	delivery technology for protein therapies	Immune modulation	Preclinical
Finch	CP & FIN	FMT, rationally selected microbiota	Displacement of MDRO	No
OpenBiome	unbranded pills	FMT (pills)	Displacement of MDRO	No
Seres	SER	FMT, rationally selected microbiota	Displacement of MDRO	No
Evelo	EDP	monoclonal microbials	Immune modulation	No
Enterome	EB	small molecule	Immune modulation	No
PureTech Health	numerous	hydrogel	Physical clearing of gut	No
Atterx	C-1205	lyophilized <i>E. coli</i>	Prevents growth of MDRO	On website, no NCT
Atterx	GN-4474	bacterial conjugation + killer plasmid	Transfer of toxic plasmid to target bacteria	On website, no NCT



RESEARCH PAPER



Antibiotics and probiotics impact gut antimicrobial resistance gene reservoir in COVID-19 patients

Qi Su^{a,b,c,d#}, Qin Liu^{a,b,c,d#}, Lin Zhang^{a,b,c,d}, Zhilu Xu^{a,b,c,d}, Chenyu Liu^{a,b,c,d}, Wenqi Lu^{a,b,c}, Jessica YL Ching^b, Amy Li^{a,b,c}, Joyce Wing Yan Mak^{a,b,c}, Grace Chung Yan Lui^{b,e}, Susanna So Shan Ng^{b,f}, Kai Ming Chow^b, David SC Hui^{b,f}, Paul KS Chan^e, Francis Ka Leung Chan^{a,b,c,d}, and Siew C Ng^{a,b,c,d}

^aMicrobiota I-Center (Magic), Hong Kong SAR, China; ^bDepartment of Medicine and Therapeutics, the Chinese University of Hong Kong, Hong Kong SAR, China; ^cLi Ka Shing Institute of Health Sciences, State Key Laboratory of Digestive Disease, Institute of Digestive Disease, the Chinese University of Hong Kong, Hong Kong SAR, China; ^dCenter for Gut Microbiota Research, Faculty of Medicine, the Chinese University of Hong Kong, Hong Kong SAR, China; ^eDepartment of Microbiology, the Chinese University of Hong Kong, Hong Kong SAR, China; ^fStanley Ho Centre for Emerging Infectious Diseases, Faculty of Medicine, the Chinese University of Hong Kong, Hong Kong SAR, China

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KEYWORDS

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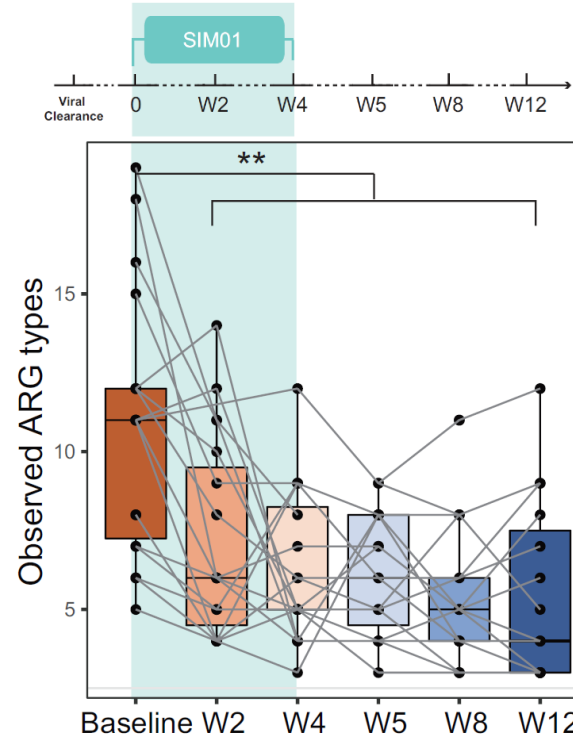
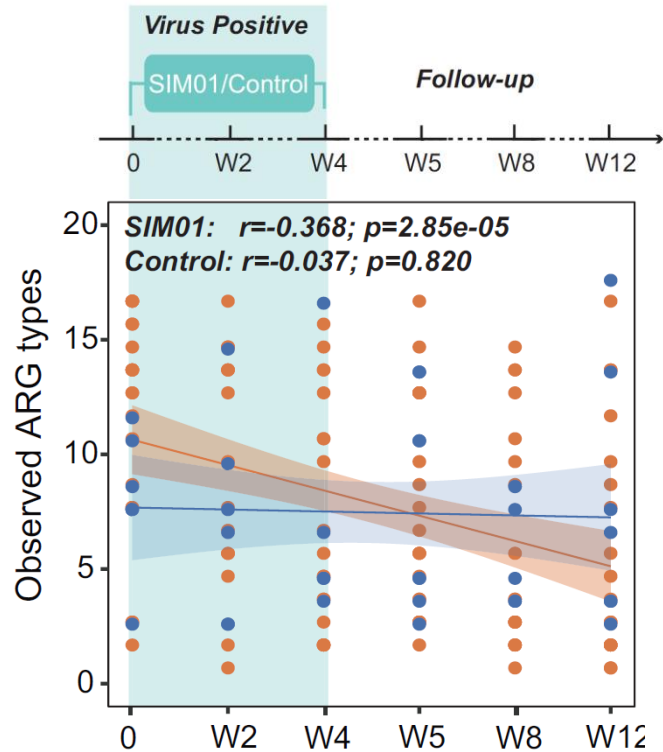
CU Medicine Develops a Probiotic Formula to Target Imbalance in Gut Microbiota in COVID-19

June 11, 2020, 8:33 PM GMT+8

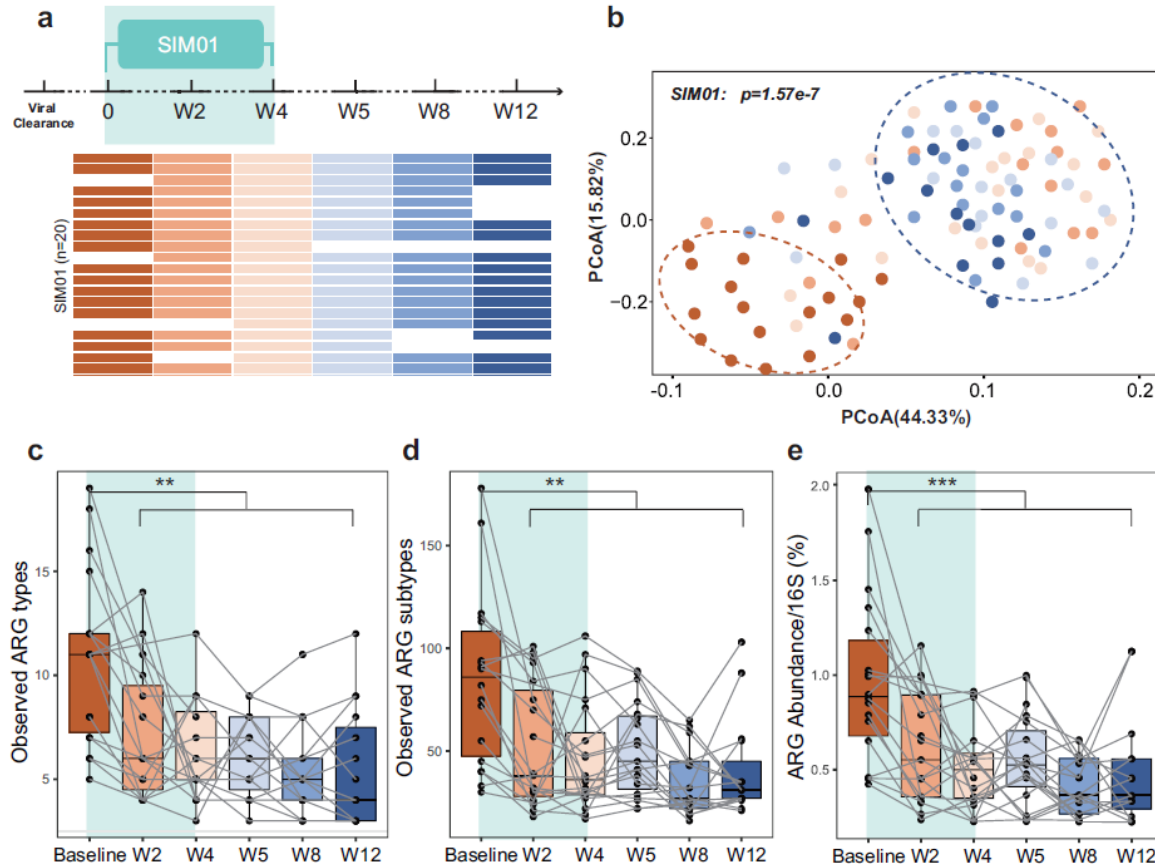
HONG KONG, June 11, 2020 /PRNewswire/ -- The Faculty of Medicine of The Chinese University of Hong Kong (CU Medicine) is the first to discover a series of good bacteria missing in the gut of COVID-19 patients. The research team recently confirmed this discovery with a large number of healthy subjects and COVID-19 patients. Using big data analysis and machine learning, CU Medicine has successfully developed a probiotic formula that aims to target gut dysbiosis, thereby offering hope to boost immunity against COVID-19 and other emerging viral infections. They anticipate that the formula will soon be turned into a probiotic supplement to go with our daily diet to improve our defense against infection.



Synbiotics (SIM01) during acute infection or recovery phase significantly reduced the ARGs reservoir in the gut microbiota of COVID-19 patients



SIM01 probiotic supplementation significant decreases in observed ARG types and relative abundance of ARGs



Resistome remained stable and did not expand spontaneously despite stopping probiotics

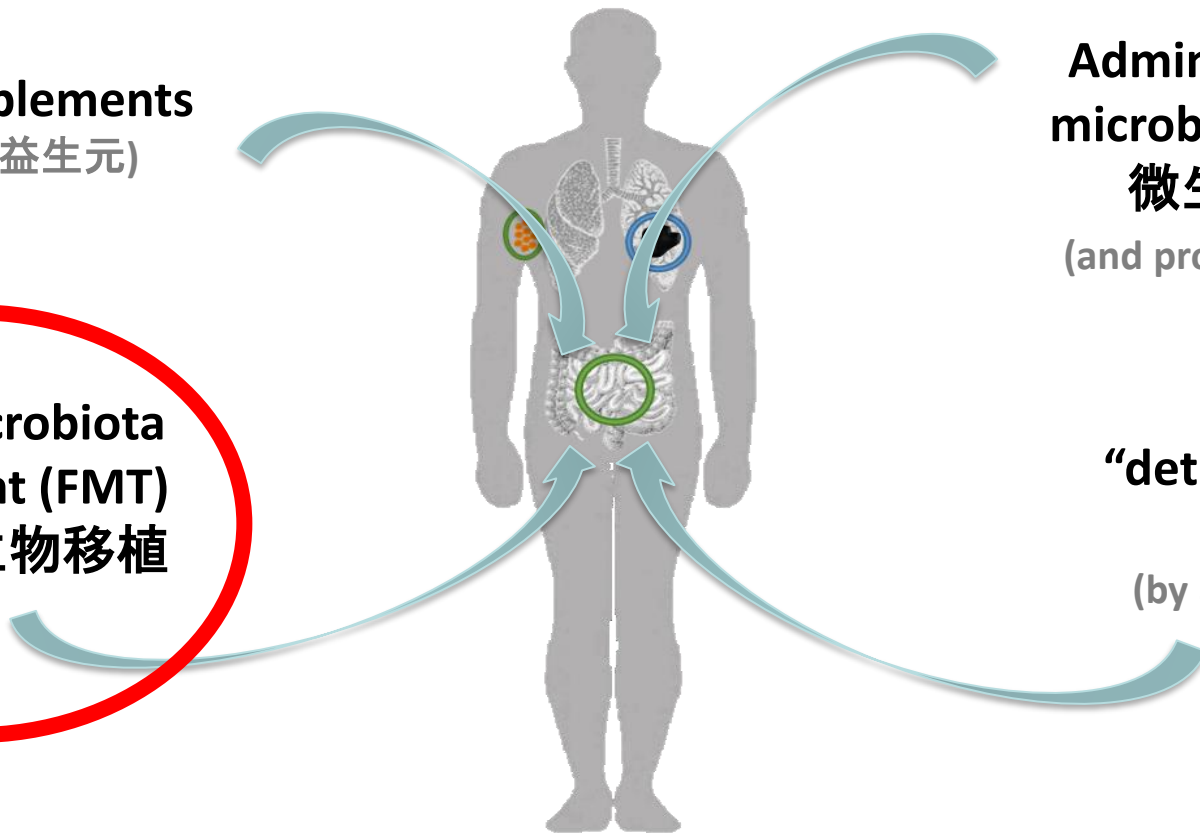
How to Modulate the Gut Microbiota?

Diet & supplements
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**Fecal Microbiota
Transplant (FMT)**
腸道微生物移植

**Administration of
microbial consortia**
微生物組合
(and probiotics 益生菌)

**Targeting of
“detrimental 有害的”
microbes**
(by antibiotics 抗生素 /
phage 噬菌體)



Fecal microbiota transplantation

腸道微生物移植



2 TOP NEWS

Standard 標準

Wednesday, October 7, 2015

NOSE SHIT, SHERLOCK!

Jane C. Young

It's not a joke with a potential deadly twist. Hospital-acquired infections are a leading cause of death in the United States, and a new study from the University of Hong Kong's Faculty of Medicine.

Since 2011, the hospital has been using a new method of treating patients with a nasal catheter to deliver a mixture of fecal matter and antibiotics.

The procedure, known as fecal microbiota transplantation (FMT), involves inserting a tube into the patient's nose and delivering a mixture of fecal matter and antibiotics.

The study, published in the journal *Antonie van Leeuwenhoek*, found that the procedure was effective in treating patients with hospital-acquired infections.



ing the procedure and the results of the study. The study found that the procedure was effective in treating patients with hospital-acquired infections.

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Minors' technique

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Minors' technique

Minors' technique

Minors' technique

Minors' technique

Minors' technique

Minors' technique

Fecal Transplant : 2000 year of history

Zhang et al. AJG 2012

4th century hand book of emergency medicine

“Yellow soup” a slurry of stool (黃龍湯)

253ml human fecal suspension by mouth for patients

With poisoning or severe diarrhoea



Ge Hong 283-363 AD

World war II

German soldiers used camel stool to treat dysentery

Sole provider of FMT service to the Hospital Authority in Hong Kong for *Clostridium difficile* infections 難辨梭菌感染:



中大研發糞便移植治難辨梭菌



治療學系名譽臨床助理教授林朗昕直言，雖然以糞便樣本作藥，聽起來不舒服，但病人接受度高，笑言反而菌生更難以啓齒。他呼籲健康人士向研究所捐贈糞便樣本，以協助臨床研究。

難辨梭菌感染醫院常見

中大醫學院副教授黃秀娟於簡報會介紹，人體有超過 400 種腸道微生物，當中細菌分爲具侵略性的微生物與具保護性的微生物兩種，如腸道微生物生態失衡，好微生物不足以制衡壞微生物，難辨梭菌入侵，引發腸道微生物生態失衡，故復發率較高，超過一成會復發，甚至會有二成半重症患者於 60 天內死亡；團隊於今年年初起針對症狀嚴重的難辨梭菌患者進行研究，將 15 位病人分成兩組治療，抗生素的治療率只得二成半，但「腸道微生物移植」卻高達八成半。

向健康人士收集糞便樣本

林朗昕表示，「腸道微生物移植」於 2013 年經中大團隊引入本地，程序涉及向健康人士收集約 50 至 100 毫升糞便，經處理後植入患者腸道。

中大籲捐糞移植 助治腸惡菌

【本報訊】人體腸道有 100 兆腸道微生物，當中有好也有壞，服用抗生素有機會令腸道微生物生態失衡，令難辨梭菌乘虛而入。患者會有腹瀉、發燒及腹痛等症狀，嚴重會出現脫水、敗血症甚至死亡。中大醫學院腸胃科團隊今年初研究，以移植糞便治療難辨梭菌的嚴重患者，結果

人發病率在 2009 年至 13 年間大增三倍，每年約有 400 宗新症，約 25% 患者因併發症死亡。今年初研究使用「腸道微生物移植」，透過移植糞便進行治療，15 名病人中有 7 人接受糞便移植，其中 6 人首次移植後已痊癒，治療率達 85% 以上，餘下一人在第二次移植後也痊癒，惟使用傳統抗生素治療的 8 名病人，只有兩人痊癒，治療率僅 25%。

經過濾後灌入患者小腸

「腸道微生物移植」是收集捐贈者 50 至 100 克糞便樣本，加入生理鹽水並經過過濾後，以鼻喉管灌入患者小腸。67 歲的鄭

ORIGINAL ARTICLE

Faecal microbiota transplantation for treatment of recurrent or refractory *Clostridioides difficile* infection in Hong Kong

Rashid N Lui, Sunny H Wong, Louis HS Lau, TT Chan, Kitty CY Cheung, Amy YL Li, ML Chin, Whitney WY Tang, Jessica YL Ching, Kelvin LY Lam, Paul KS Chan, Justin CY Wu, Joseph JY Sung, Francis KL Chan, Siew C Ng *

Laboratory for Fecal Microbiota
Transplantation (FMT)
腸道微生物移植實驗室

Professor Ng Siew Chien | 黃秀娟 教授

Ng et al. Gut 2019
Lynch..Ng..Nature Rev Gastro Hep 2019
Tao...Ng. Nature Communications 2018

FMT for Eradicating MDRO

As of December 2019, 197 studies in clinicaltrials.gov were completed or actively enrolling subjects for FMT therapy, mostly for *Clostridioides difficile* infection (CDI), which was the genesis for treating MDROs with FMT.

21 studies in clinicaltrials.gov are for MDRO decolonization or treatment.

FMT for Eradicating MDRO




RESEARCH ARTICLE

May/June 2022 Volume 7 Issue 3 e01510-21

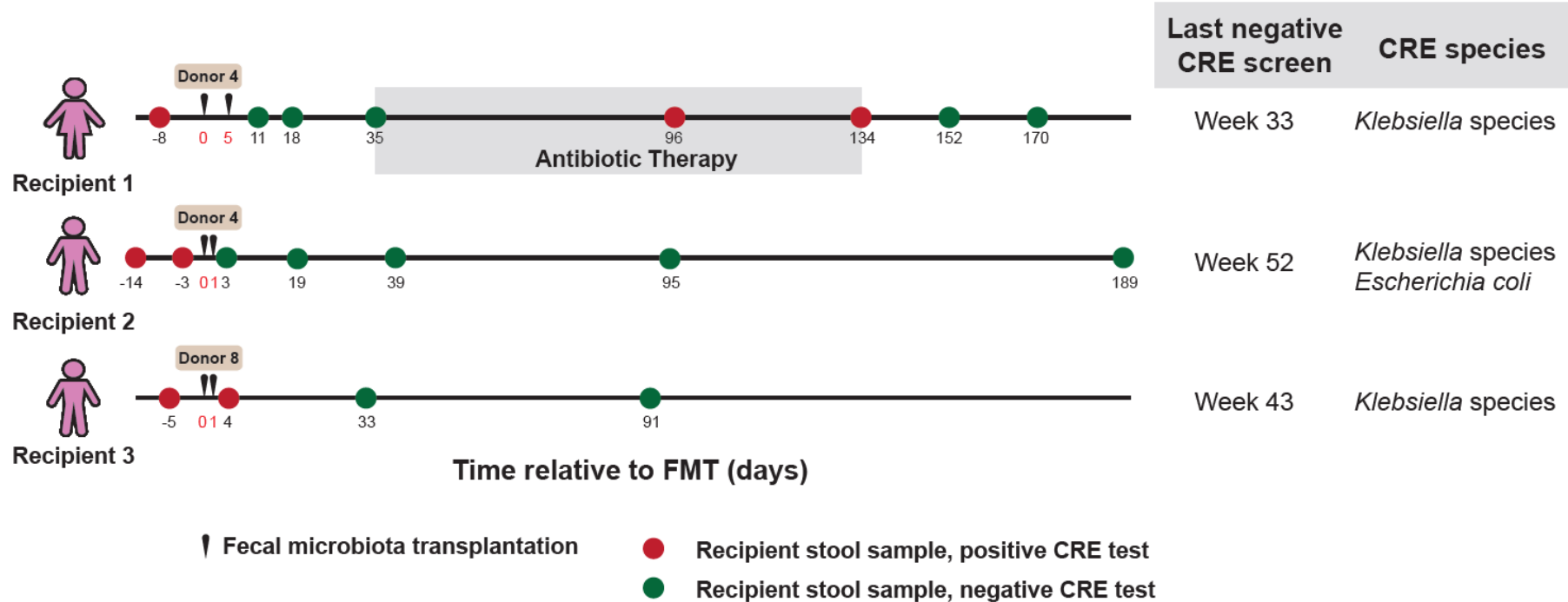
<https://doi.org/10.1128/msystems.01510-21>

Longitudinal Evaluation of Gut Bacteriomes and Viromes after Fecal Microbiota Transplantation for Eradication of Carbapenem-Resistant *Enterobacteriaceae*

Qin Liu ^{a,b,c,d}, Tao Zuo^{a,b,c,d}, Wenqi Lu^{a,b,c,d}, Yun Kit Yeoh^{a,e}, Qi Su^{a,b,c,d}, Zhilu Xu^{a,b,c,d}, Whitney Tang^{a,b,c,d}, Keli Yang^{a,b}, Fen Zhang^{a,b,c,d}, Louis H. S. Lau^b, Rashid N. S. Lui^b, Miu Ling Chin^e, Rity Wong^b, Chun Pan Cheung^{a,b,c,d}, Wenyi Zhu^{a,b,c,d}, Paul K. S. Chan ^{a,e}, Francis K. L. Chan^{a,b,c,d}, Grace C. Lui^b, Siew C. Ng^{a,b,c,d}

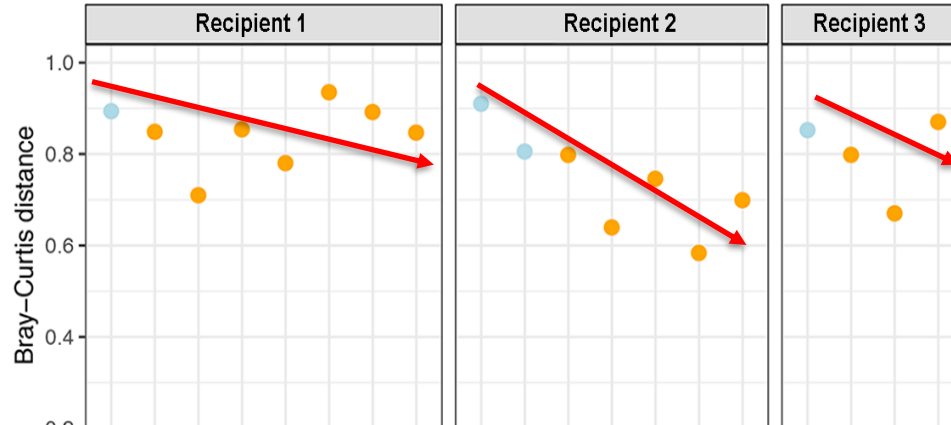
Liu, Q.,Ng, S. C. 2022. Longitudinal Evaluation of Gut Bacteriomes and Viromes after Fecal Microbiota Transplantation for Eradication of Carbapenem-Resistant Enterobacteriaceae. *mSystems*, e01510-21.

Successful Eradication of Carbapenem-resistant *Enterobacteriaceae* with FMT

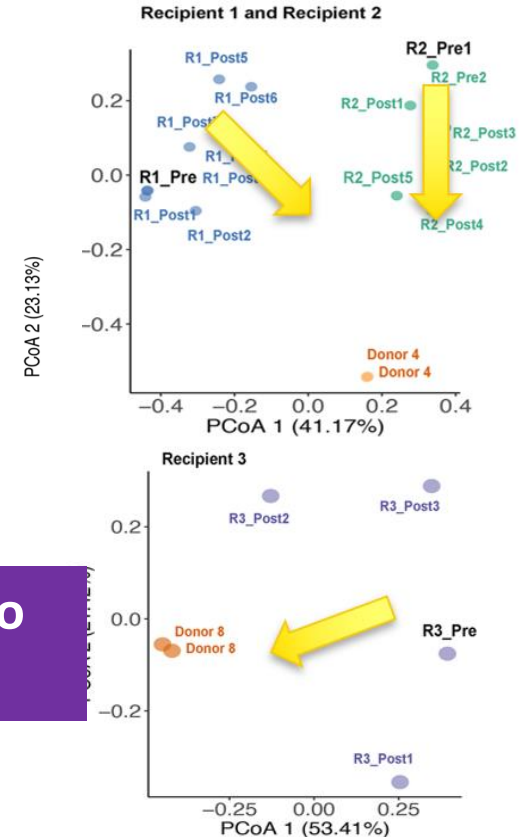


Similarity of Bacteria composition towards donor after FMT

Bray-Curtis dissimilarity of pre- and post-FMT samples compared to donor

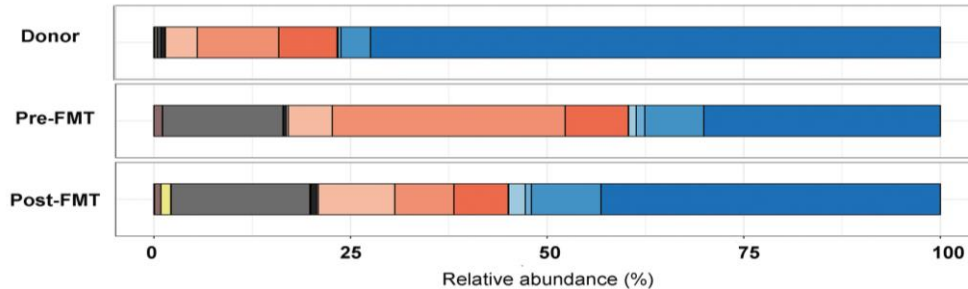


Increased similarity of bacterial composition to that of donor following FMT

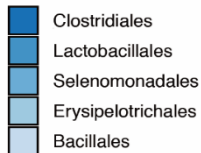


Repopulation of bacteriome in recipients by FMT

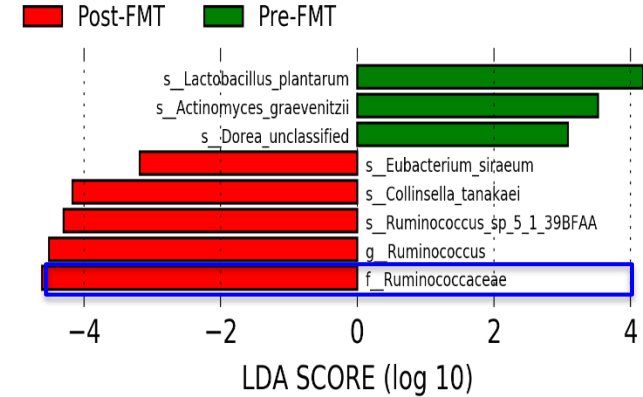
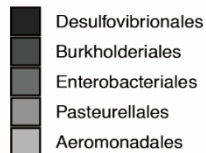
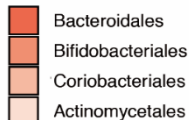
Marked shift towards an increased Firmicutes after FMT



Firmicutes



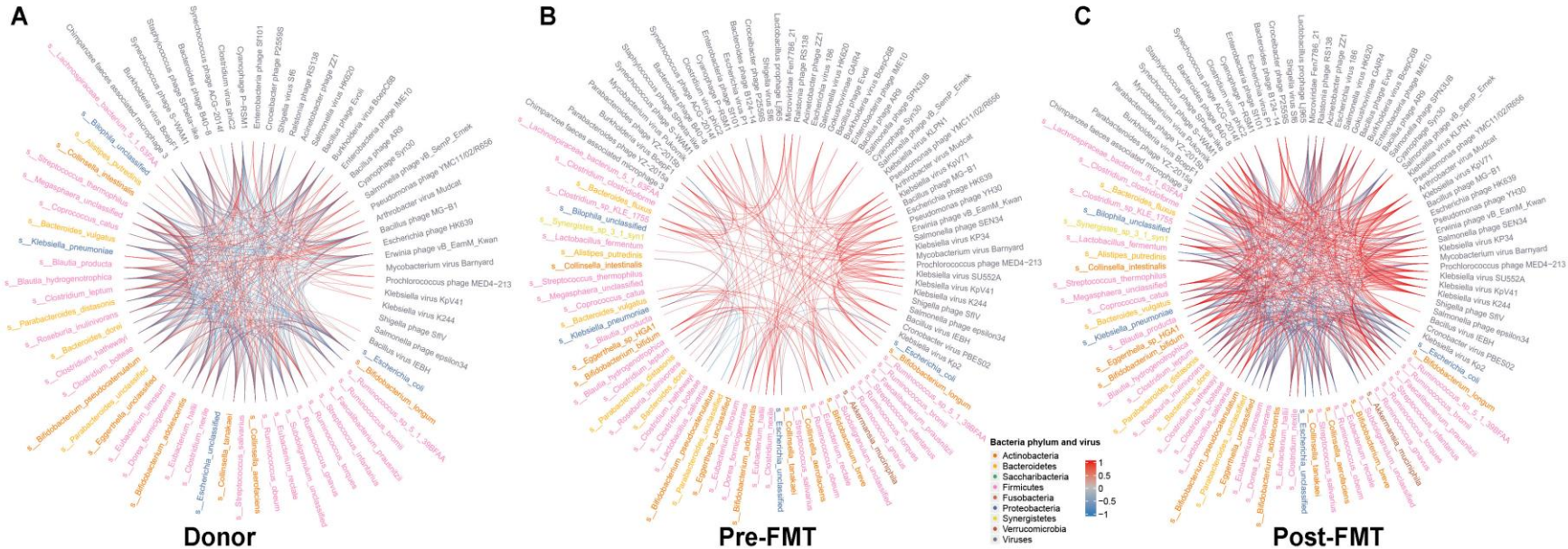
Actinobacteria



Enriched *Ruminococcaceae* may play an important role for CRE clearance by FMT

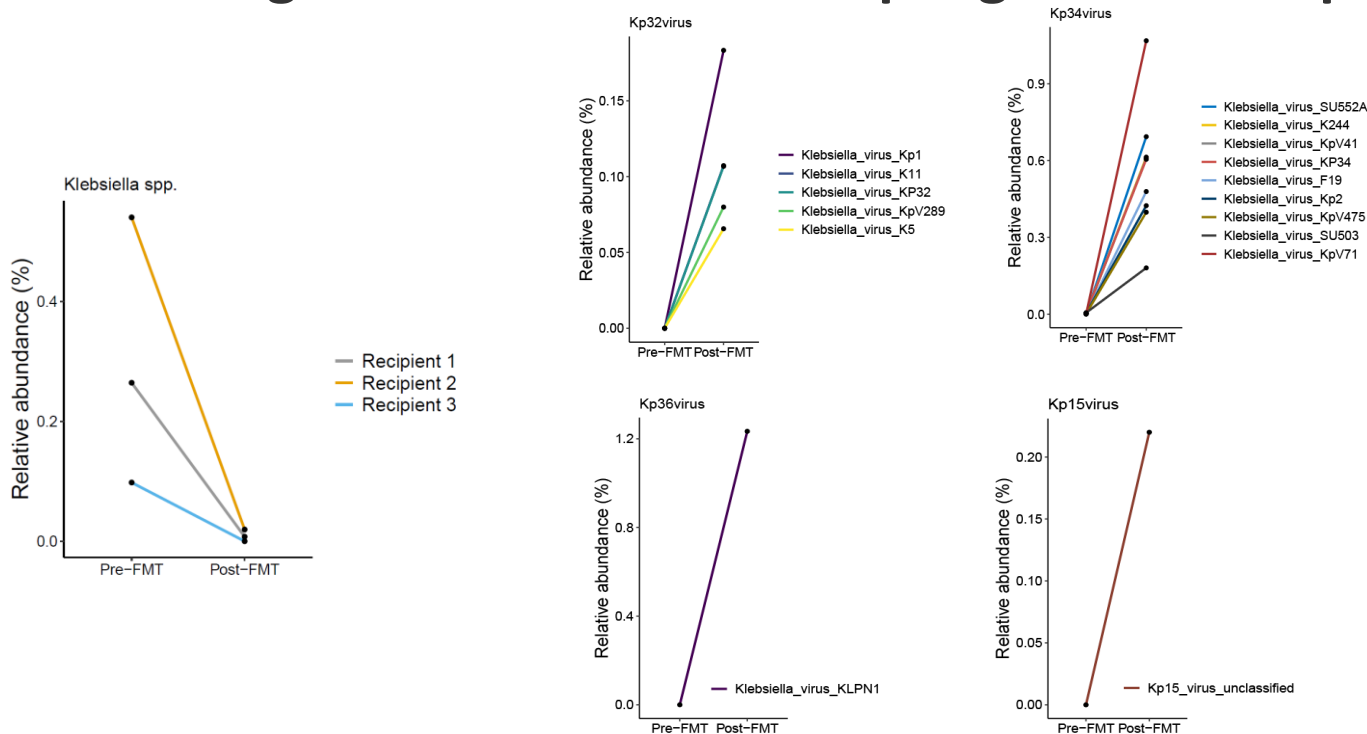
Tight connection between gut bacteriome and virome in donor and post-FMT

FMT impacts the trans-kingdom interactions of gut microbiome composition



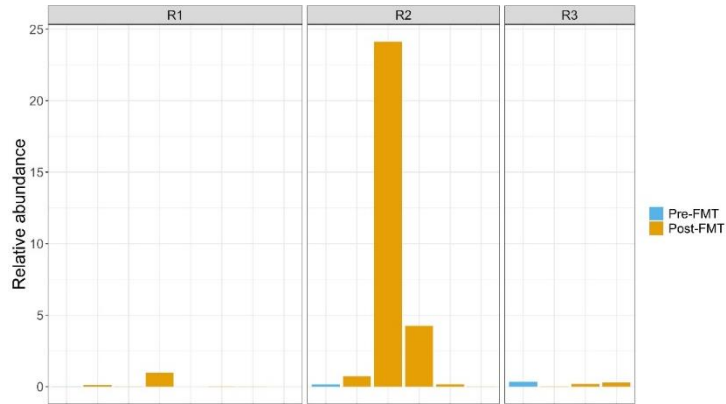
Alterations of Gut Virome after FMT

Striking increase in *Klebsiella* phages in all recipients



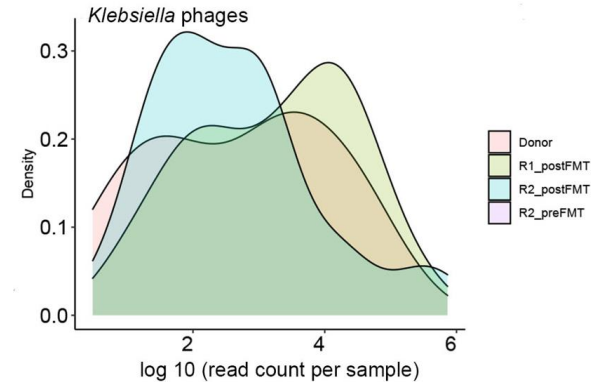
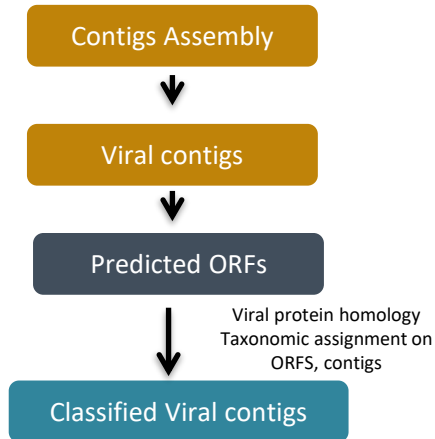
Alterations of Gut virome after FMT

Escherichia virus in VLP metagenomes



Recipient 2
Only CRE *E.coli* carrier

**Targeted bacteriophage expansion for
CRE causative bacteria**



The bloom of bacteriophages after FMT were donor origin

FMT and MDRO

- In a small pilot study, all patients had CRE clearance after 2 FMTs
- Bacterial, viral communities responded differently to FMT
- Bacterial communities showed engraftment with donor-derived symbiont (*Ruminococcaceae*)
- Transkingdom interactions between the virome and bacteriome communities may have evolved in part to support efficient FMT for treating CRE

FMT play a major role in modulating not just bacteria but also virome communities in CRE

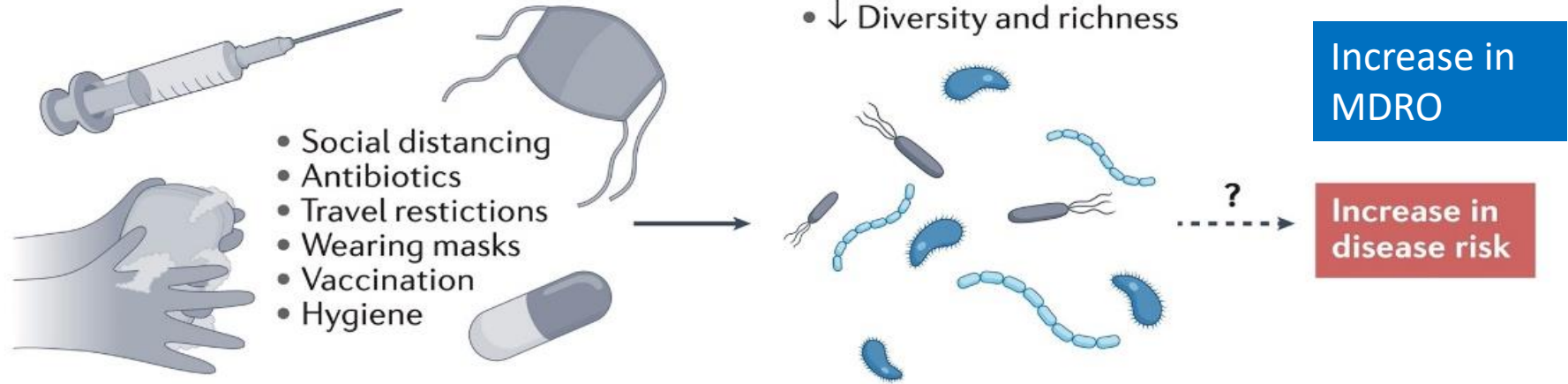
What We Don't Know (yet)



Beyond the Pandemic

Lau... Ng, Nature Reviews Gastroenterology & Hepatology (2022)

c Post-pandemic?



How does microbiota modulation help in MDRO, COVID-19 Patients and General Public?

Hasten recovery and reduce long covid symptoms

Reduce resistome and has potential to reduce MDRO

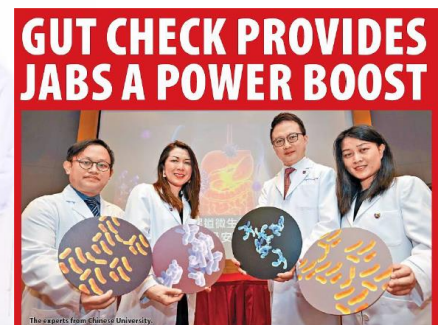
Helps to boost Immunity to fight against the virus with scientific evidence

Improves Vaccine antibody response and reduces vaccine side effects

Take Home Messages

- Gut microbiome impact COVID-19 risk, severity and long covid
- Antibiotics are associated with “**worsened dysbiosis**” in COVID-19 patients
- COVID-19 patients had increased antimicrobial resistance gene reservoir
- ***A synbiotic formula (SIM01)*** used in acute infection or recovery phase can significantly reduced ARGs reservoir in COVID-19 patients
- Fecal microbiota transplant may have potential role in clearing MDRO and the mechanisms should be explored
- ***Think before you prescribe antibiotics (Before it is too late!)***

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