香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Role of Gastrointestinal Tract and Gut Microbiota in Pathogenesis of COVID-19: A Missing Site for Viral Replication & Transmission *(COVID190111)*

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Agenda

- What do we know about COVID-19 and the gut?
- What are our research findings?
- What are the implications for public health policy-making?
- How do our findings impact patient care?
- What is the global impact of our research?
- What are the future directions?

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COVID-19 research funding approved

April 27, 2020 Like 0

Food and Health Bureau
The Government of the Hong Kong Special Administrative Region

食物及衞生局研究處(研究基金秘書處)
Research Office (Research Fund Secretariat) Food

This will be the first study that simultaneously assess fecal SARS-CoV-2 viral load and gut microbiota in COVID-19

These data will not only have an impact on prevention and control of COVID-19, it will also offer a new prospect of potential therapeutics to modulate the gut microbiota to improve outcome in COVID-19 patients

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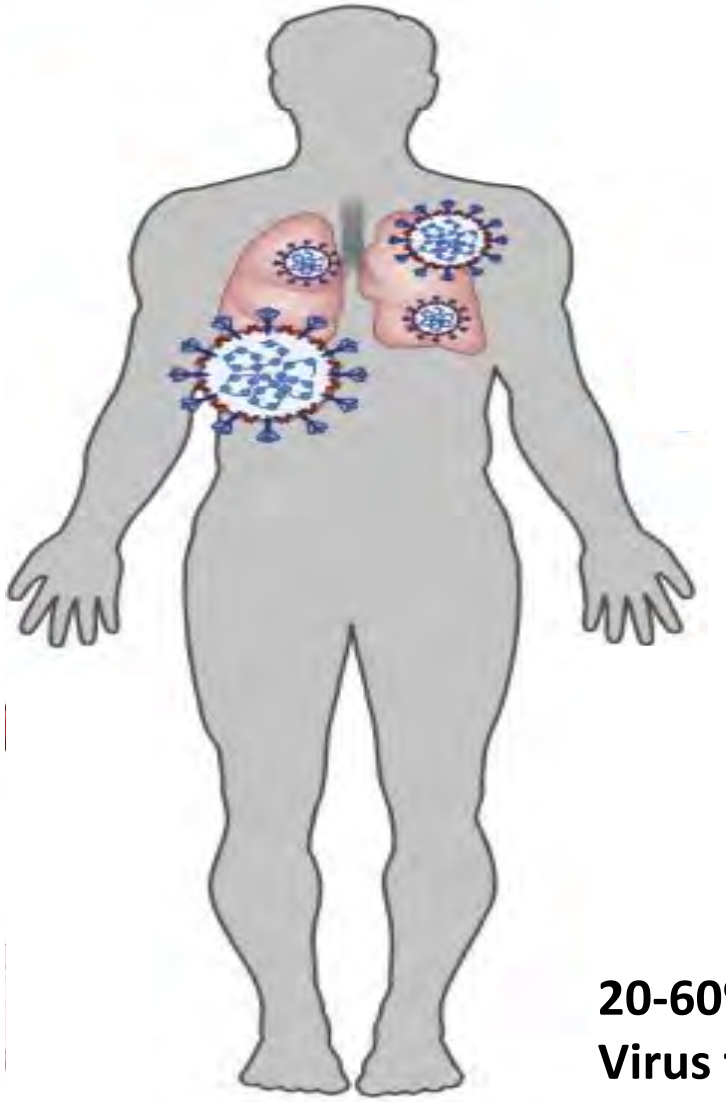
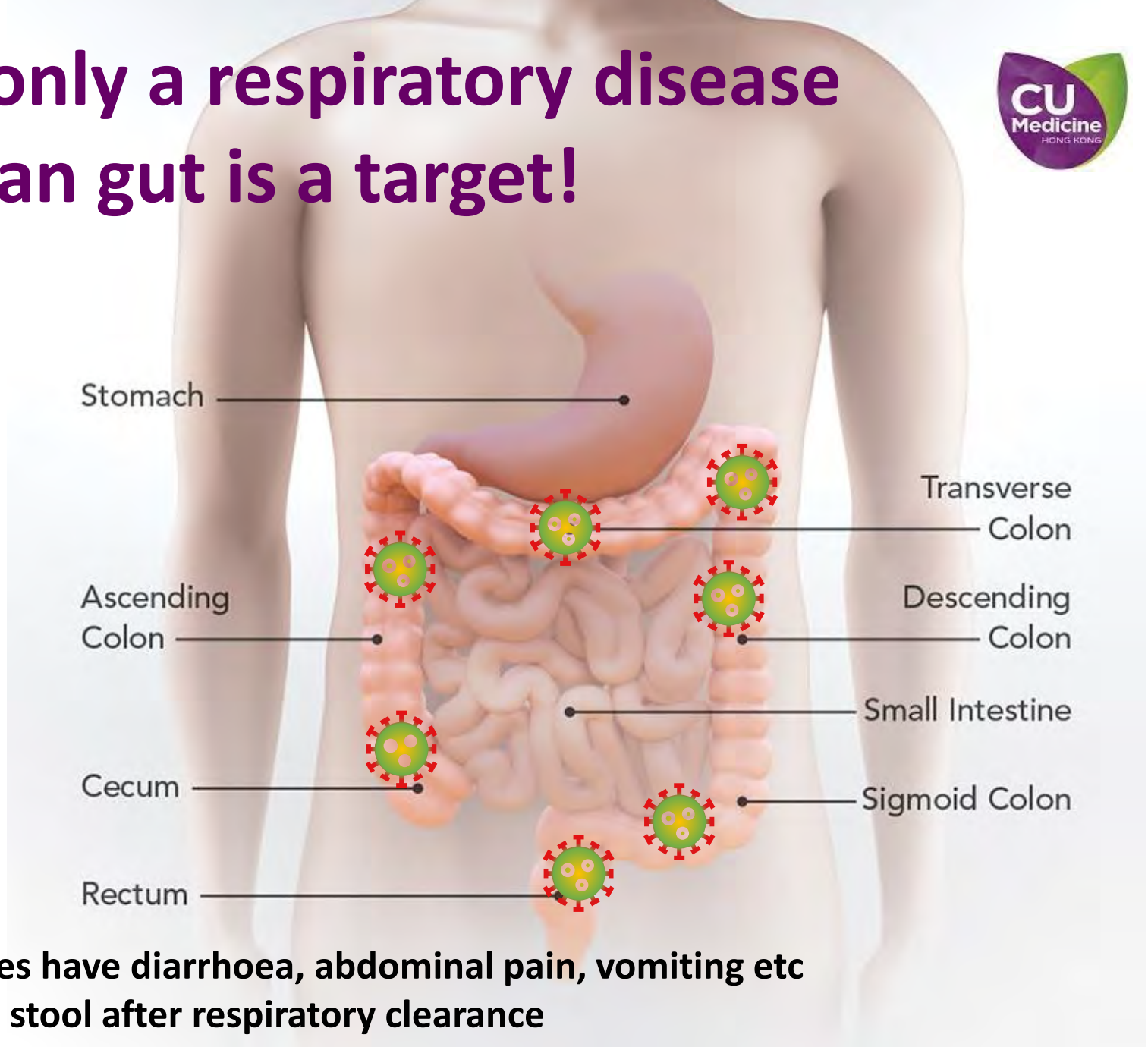
What do we know about COVID-19 and the Gut?

COVID-19 is not only a respiratory disease
The human gut is a target!

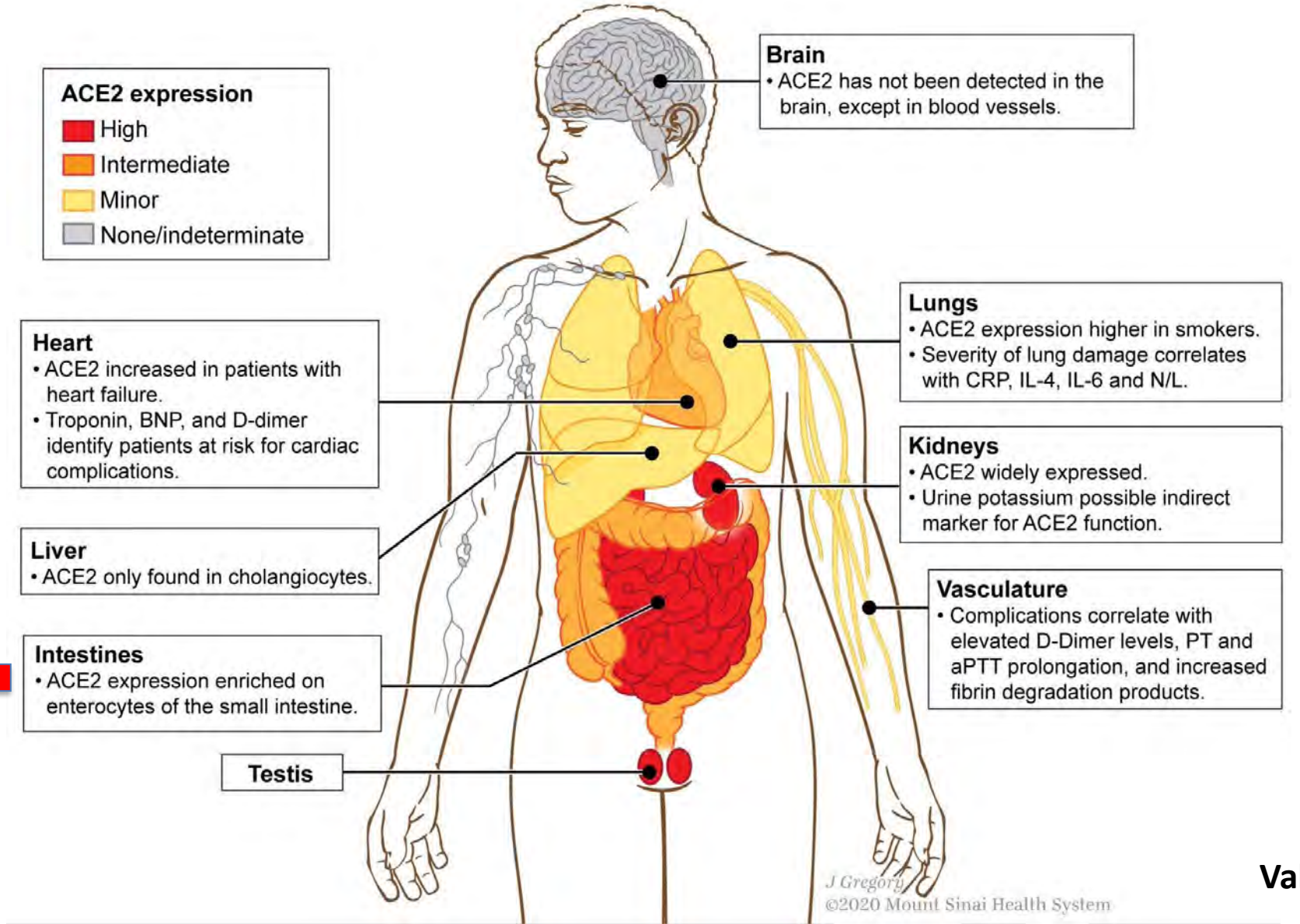




20-60% of cases have diarrhoea, abdominal pain, vomiting etc
Virus found in stool after respiratory clearance

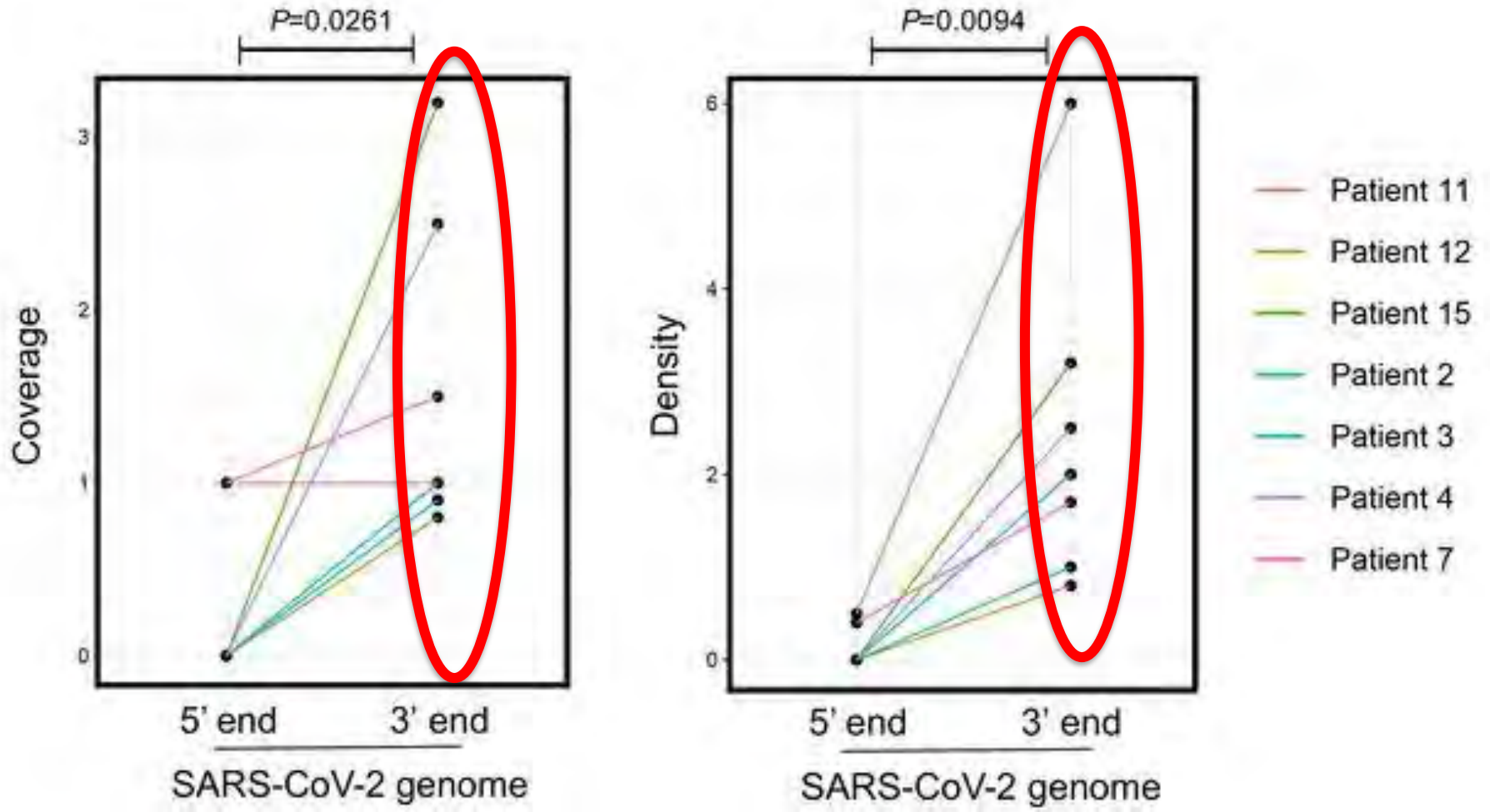
Ng and Tilg. Gut 2020

Viral entry receptor (ACE-2) is highly expressed in the human gut



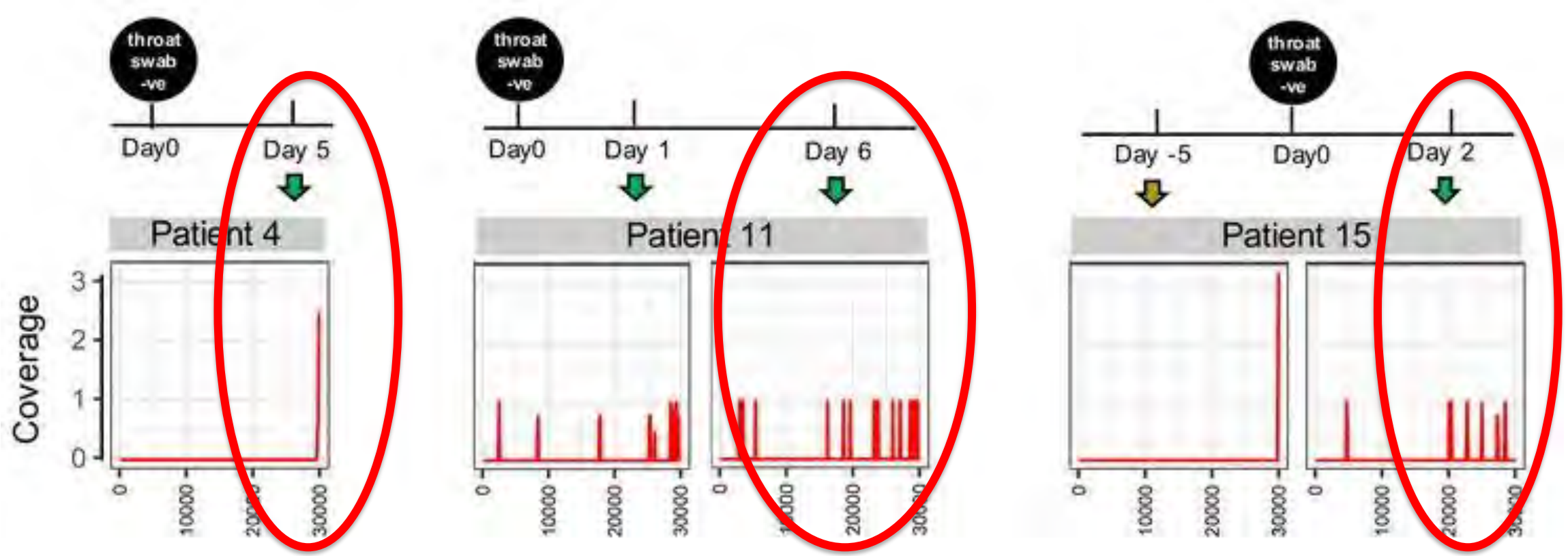
Vabret et al. Cell 2020

We found High 3' end coverage indicates active SARS-CoV-2 in the gut of COVID-19 patients

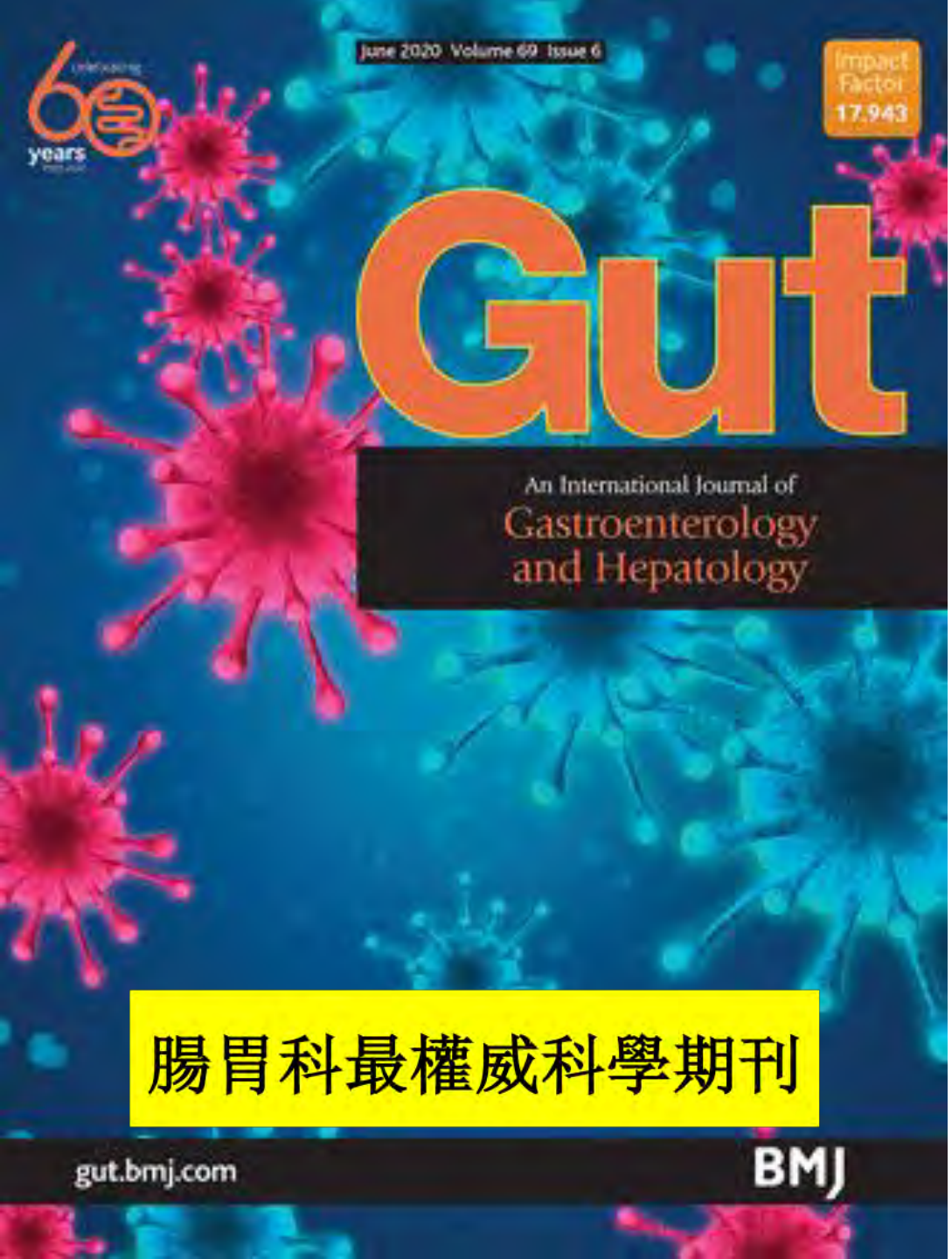


Zuo.. Chan, Ng. Gut 2020

SARS-CoV-2 is still active even after disease resolution (nasopharyngeal clearance of SARS-CoV-2 virus)



Zuo.. Chan, Ng. Gut 2020



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

Patients with COVID-19 had active and prolonged SARS-CoV-2 activity in the gut, even in the absence of GI manifestation

中大研究發現 無腸胃不適者糞便樣本仍帶病毒

新冠肺炎康復者腸道病毒尚具傳染性

新冠病毒橫行肆虐，中文大學醫學院證實，沒有腸胃不適的新冠肺炎患者，其糞便可發現活躍的新型冠狀病毒，即使患者康復後其呼吸道樣本偵測不到病毒，但腸道內的病毒仍然具傳染性，尤其是嬰幼兒。研究已於國際醫學期刊《GUT》發表。 本報記者報道

■陳家亮（中）表示，一些國家機構如美國食品藥物管理局正與中大醫學院接洽，進一步了解糞便檢測的細節和安排。

■中大醫學院成立新冠病毒檢測中心，以提升本港新冠病毒檢測量。

中大醫學院院長兼腸道微生物群研究中心主

疫患康復者腸道逾月帶病毒

【香港商報訊】記者馮仁業報道：香港中文大學醫學院昨日公布一項研究發現，即使患者已經康復或沒有腸胃不適，其腸道及糞便仍有可能載有活躍的新冠肺炎病毒逾1個月，因此患者出院後必須作健康監測及跟進，避免出現經糞便傳播的機會。

中大醫學院發現 促跟進監測

為了解新冠肺炎病毒在患者

2歲童糞便帶新冠病毒36天

含量或高成人千倍 中大揭腸細菌成隱形傳播鏈

中大醫學院發現，新冠肺炎患者即使無腸胃不適，腸道及糞便都帶有活躍的新冠病毒，即使呼吸道樣本檢測不到病毒，腸道內偵測到的病毒亦有複製能力和傳染性，造成隱形傳播鏈，是全球首次證實。研究團隊透過糞便檢測，發現6名細菌感嬰幼兒染疫，其中一名2歲確診女童的糞便持續36天含高濃度的新冠病毒，病毒量更比成人高出100至1000倍；而成人確診者即便呼吸道已無病毒，糞便仍含病毒。團隊指出，病毒能長期在腸道內存活及繁殖，提醒市民要經常用源日水消毒廁所，如廁後及為嬰兒「換

■中大醫學院成立新冠病毒檢測中心，模擬糞便給測，協助找出隱性患者。

Press Conference 8 sept 2020

What are the Implications for public health policy-making?

Implications

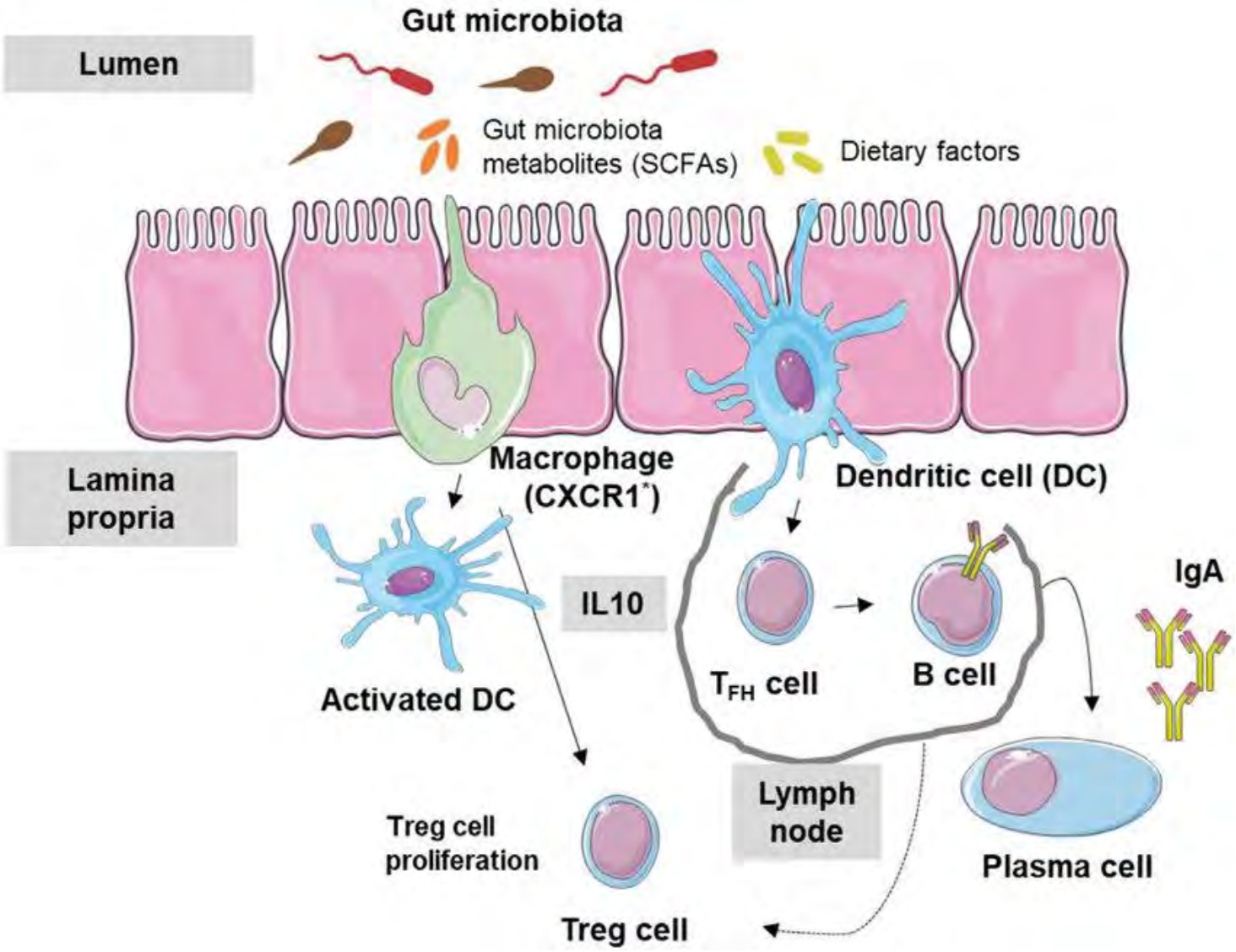
SARS-CoV-2 can be easily detected in the stool and persist after recovery

Stool test is accurate and safe *(suitable and more effective for COVID-19 screening for specific groups of people)*

Caution on potential threat of faecal-oral viral transmissions

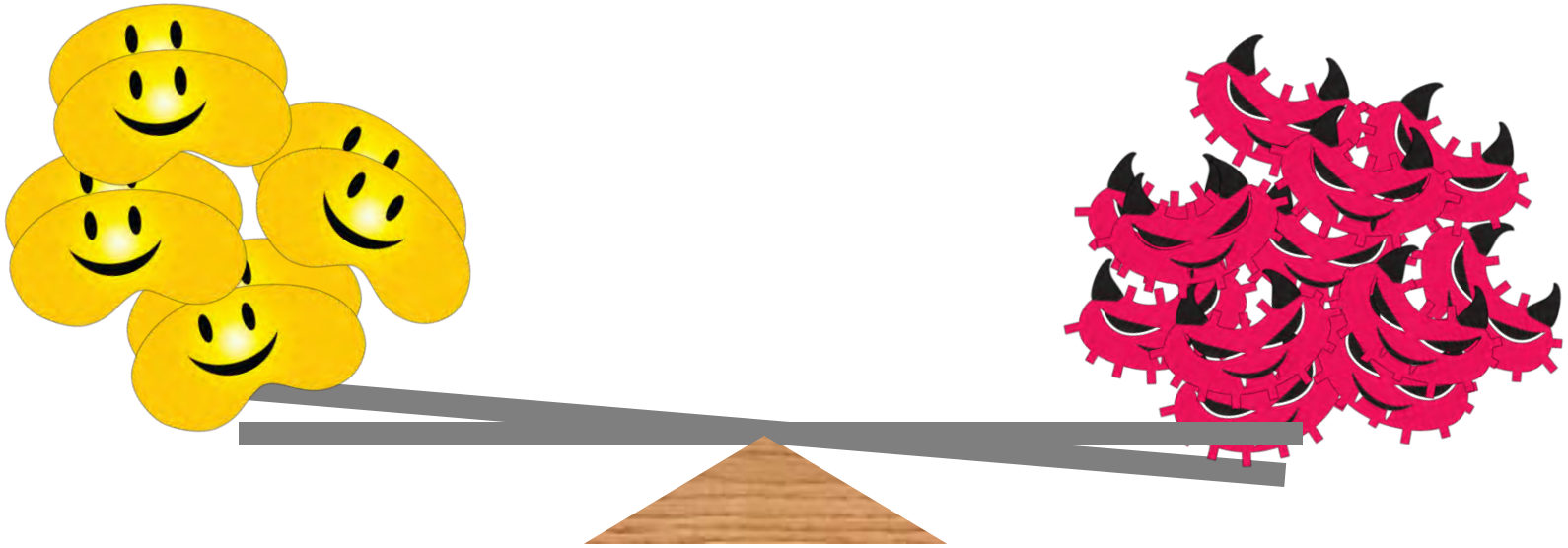
Gut microbiota

regulates immunity to maintain defense against viral and bacterial infections



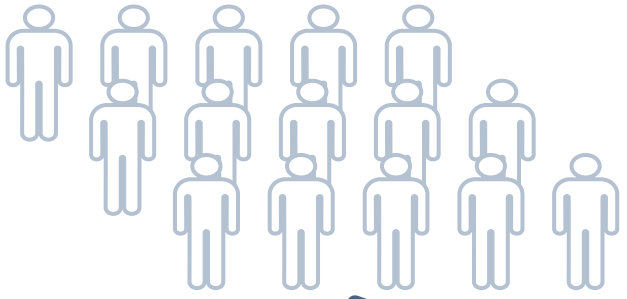
Frontiers in Immunology 2018

Gut dysbiosis makes us susceptible to infections (including COVID-19) with worse outcomes



What are our key research findings?

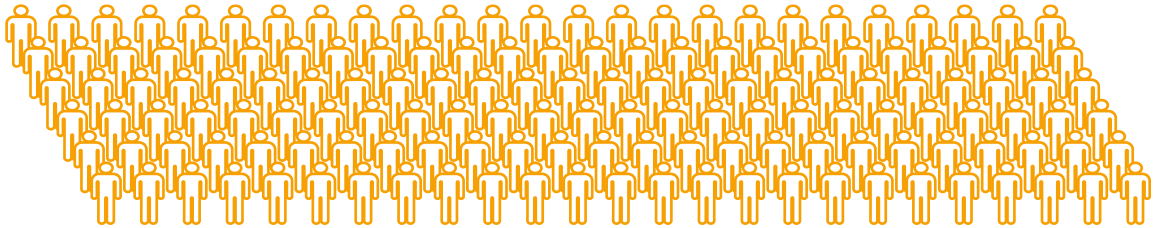
COVID-19 (n=15) | **Control (n=15)** | **Pneumonia (n=30)**

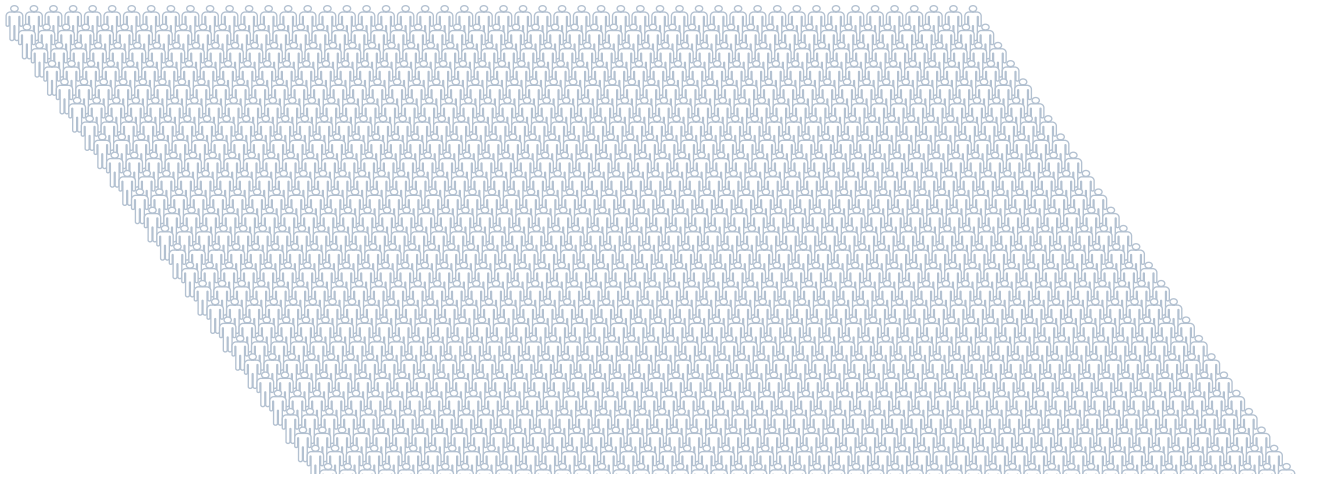


Mild
Moderate
Severe
Critical

COVID-19 (n=100)

Control (n=1500)

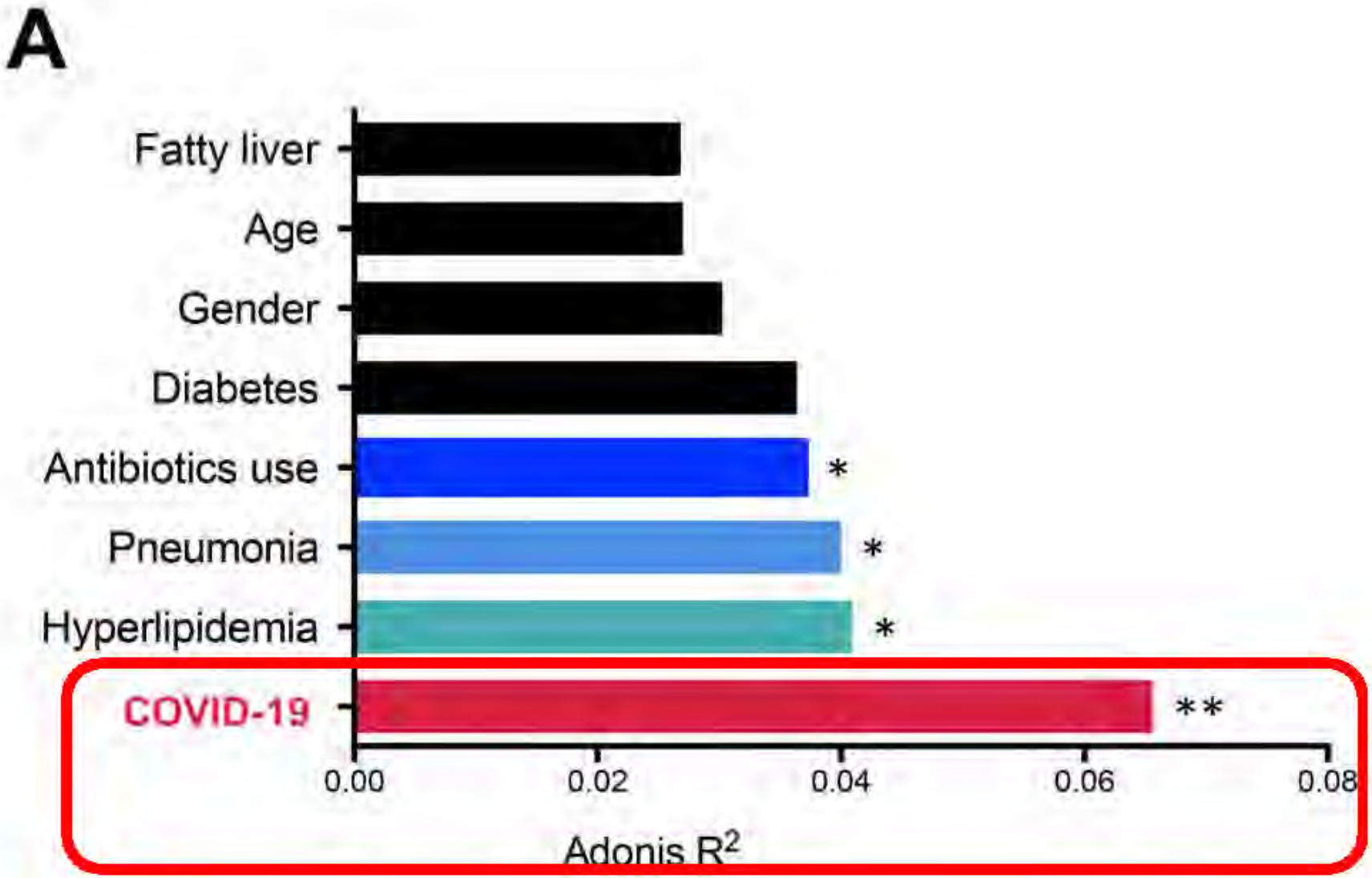




230 samples

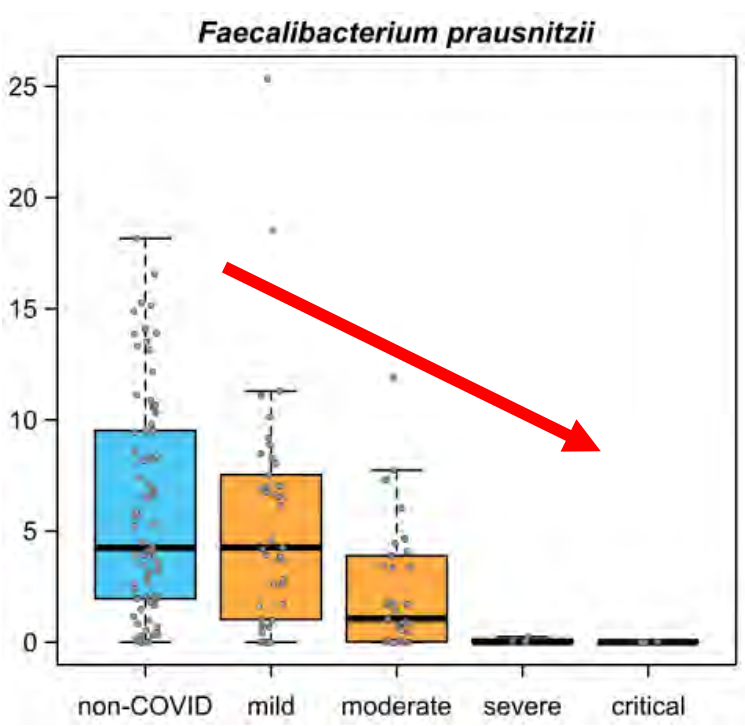
We then expanded our study cohort to 100 patients with COVID-19 and 1,500 healthy controls and collected their microbiota data. With big data analysis, we developed a symbiotic formula that aims to target gut dysbiosis, thereby boosting immunity against COVID-19

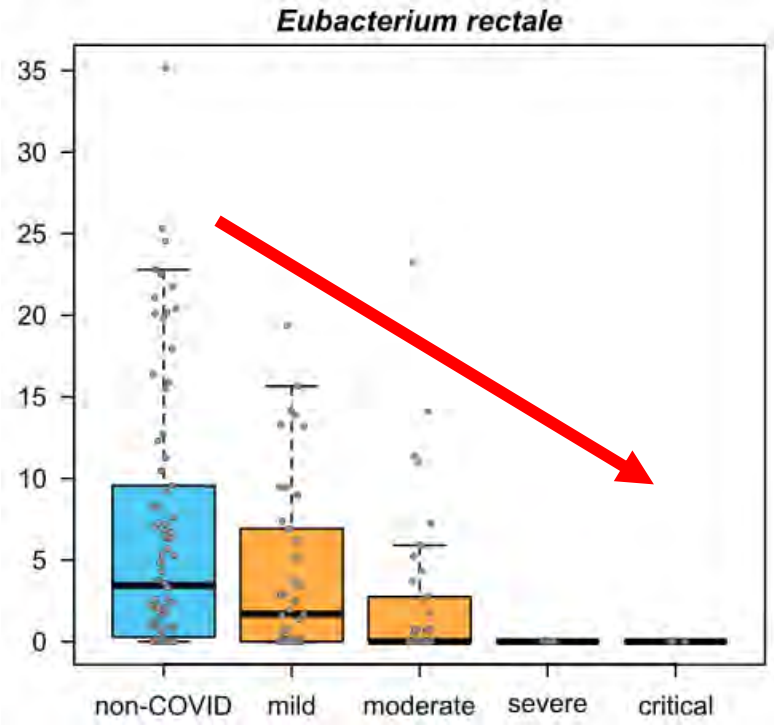
Gut microbiome is significantly altered in COVID-19

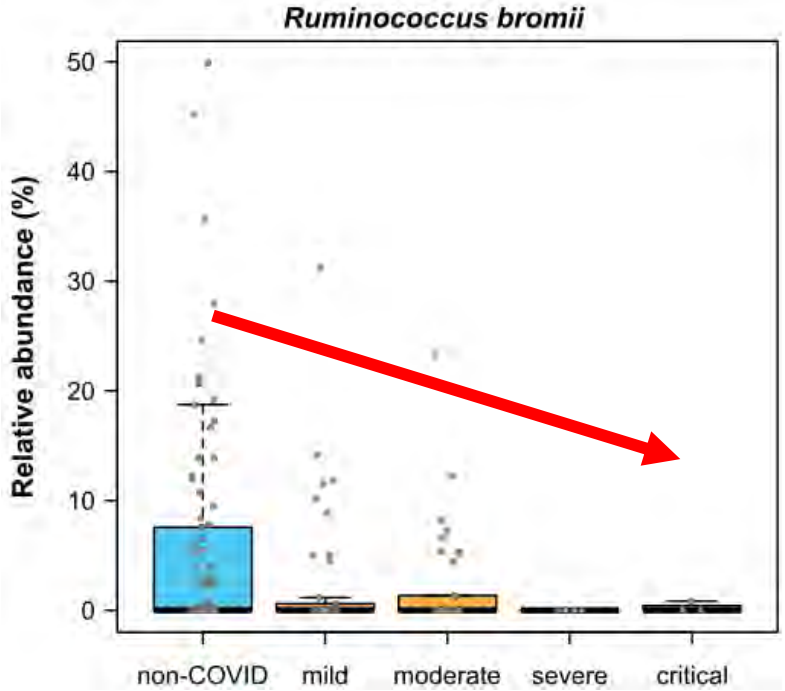


Zuo..Ng et al. Gastro 2020

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



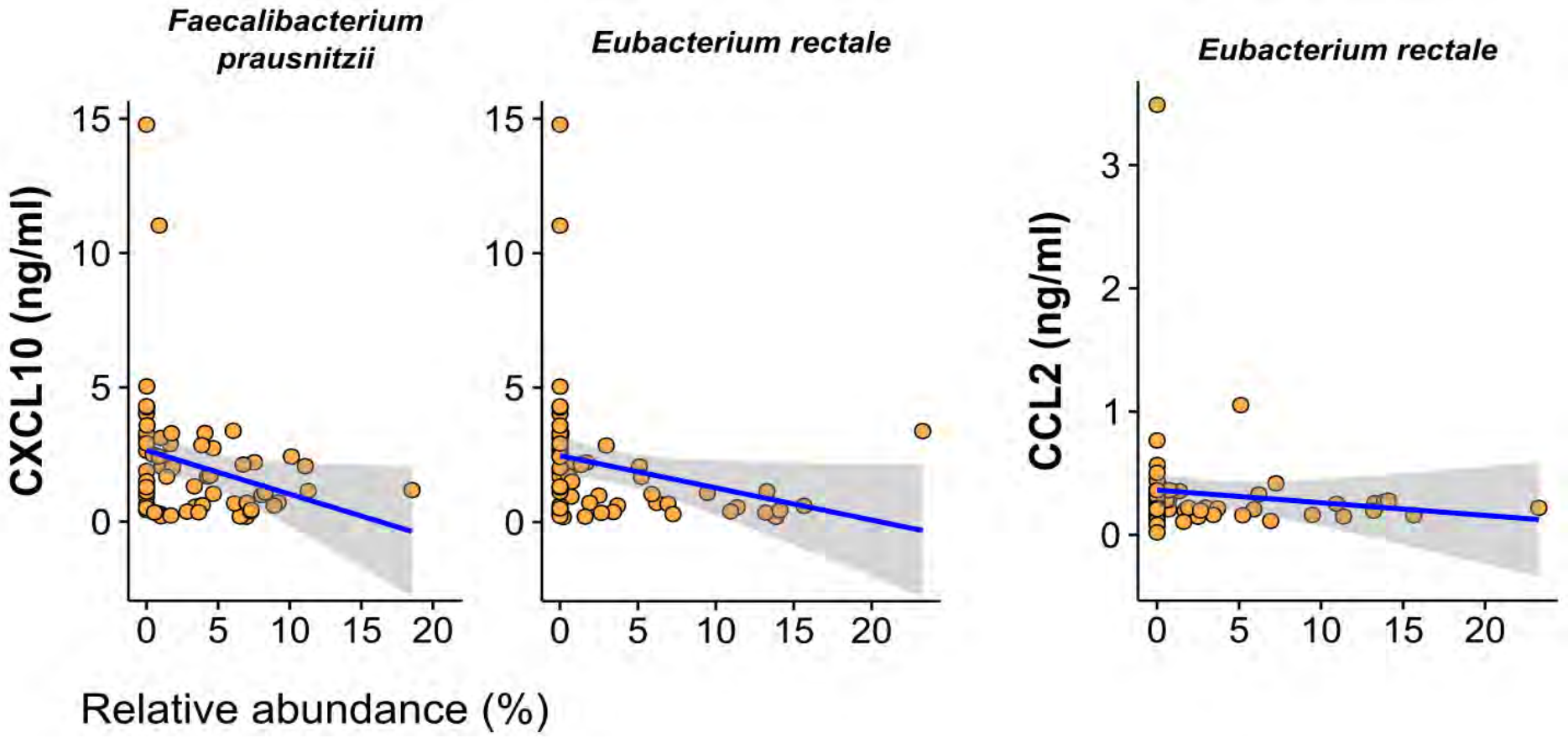




Yeoh.. Chan, Ng, Gut 2020

Zuo.. Chan, Ng, Gastroenterology 2020

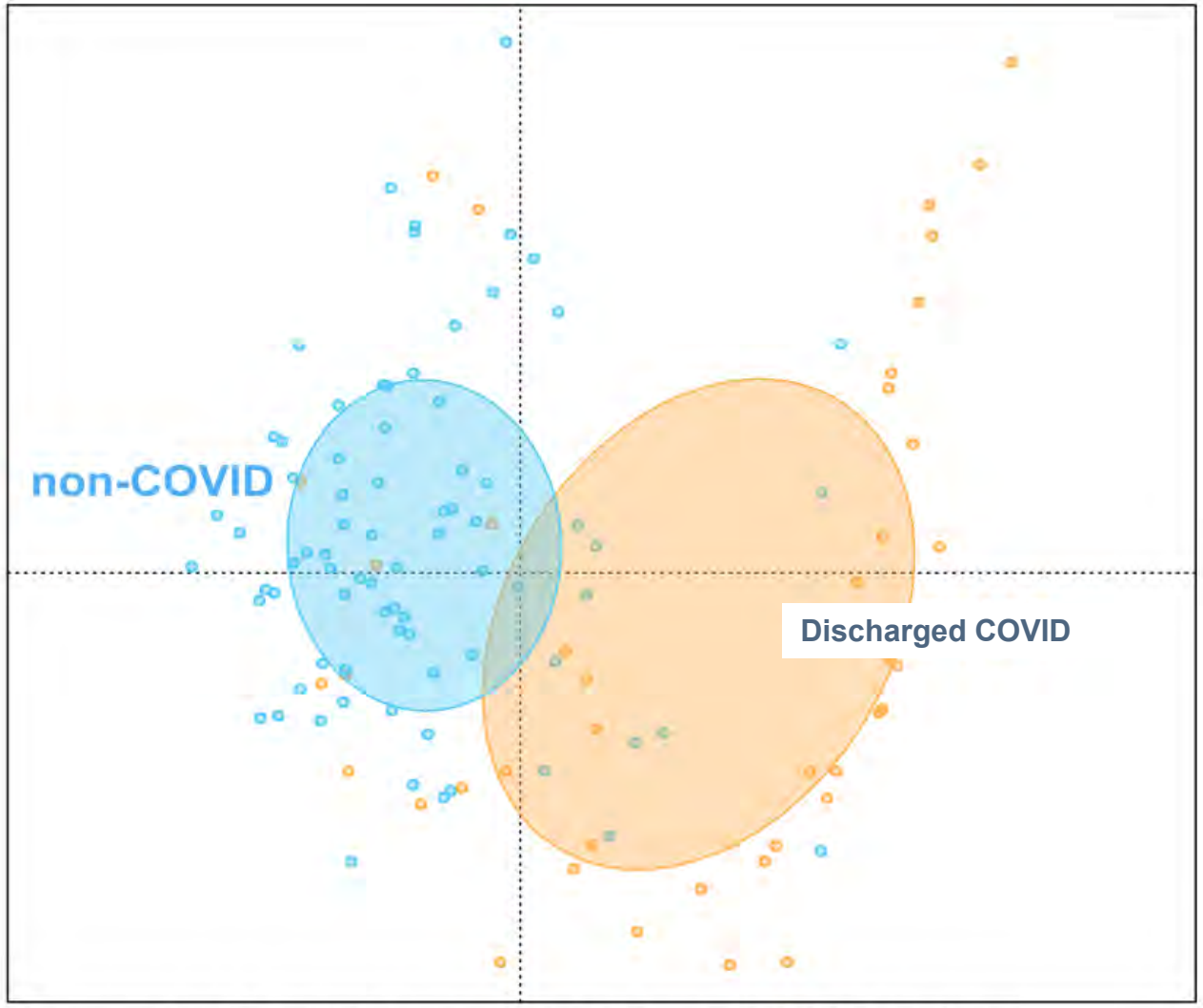
Several species depleted in COVID-19 are associated with increased inflammatory marker concentrations



- Short-chain fatty acids biosynthesis
- L-isoleucine biosynthesis

Yeoh.. Chan, Ng, Gut 2020
Zuo.. Chan, Ng, Gastroenterology 2020
Fen .. Ng. Gatstroenterology 2021

Gut microbiota dysbiosis persist after disease resolution (Up to 30 days)

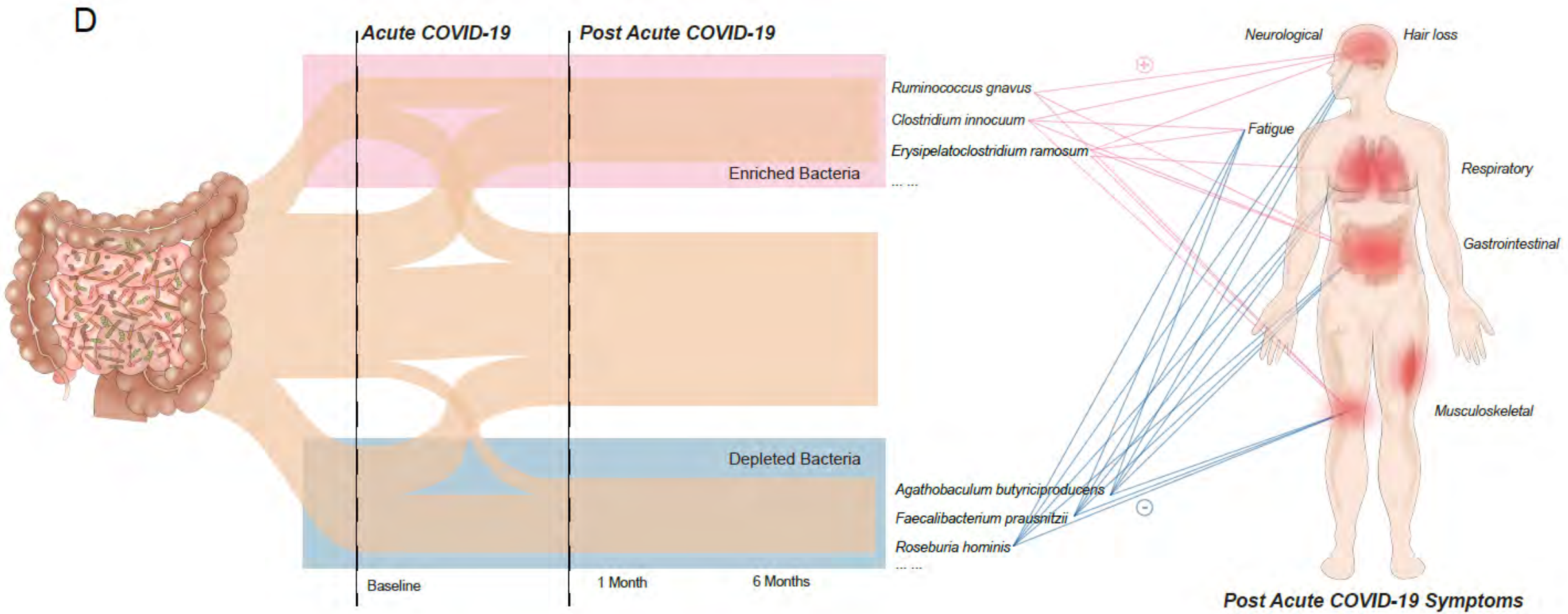


Differences in gut microbiota composition in discharged COVID-19 patients vs non-COVID-19 subjects depicted by seperation of the two ellipses

Yeoh..Chan, Ng, Gut 2020

Zuo.. Chan, Ng, Gastroenterology 2020

Gut microbiota composition at admission predicts Long COVID (Post-acute COVID syndrome)



Liu..Ng. Gut 2021

Gastroenterology

Top International Medical Journal

First Evidence in the World

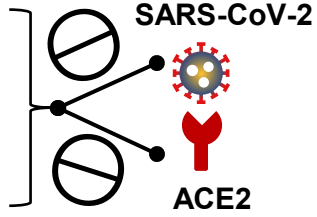
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

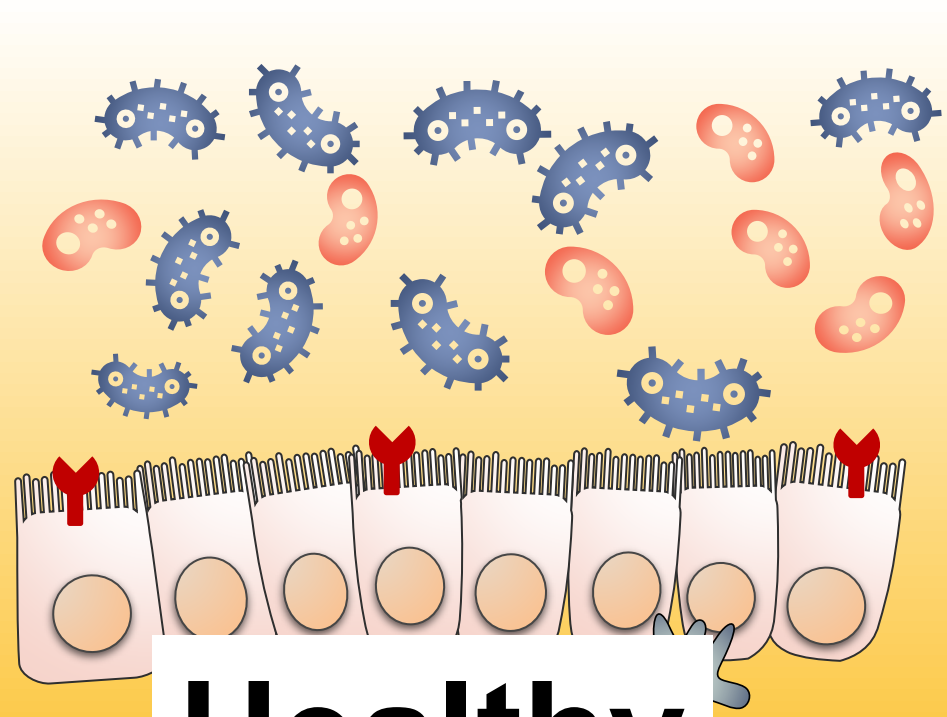
Commensals:
Faecalibacterium prausnitzii
Roseburia
Eubacterium
Lachnospiraceae taxa

Commensal Symbionts
Faecalibacterium prausnitzii, *Roseburia, Eubacterium ventriosum*, *Lachnospiraceae* taxa

Opportunistic Pathogens
Clostridium hathewayi, *Actinomyces viscosus*, *Bacteroides nordii*

Bacteroides dorei
Bacteroides thetaiotaomicron
Bacteroides massiliensis
Bacteroides ovatus



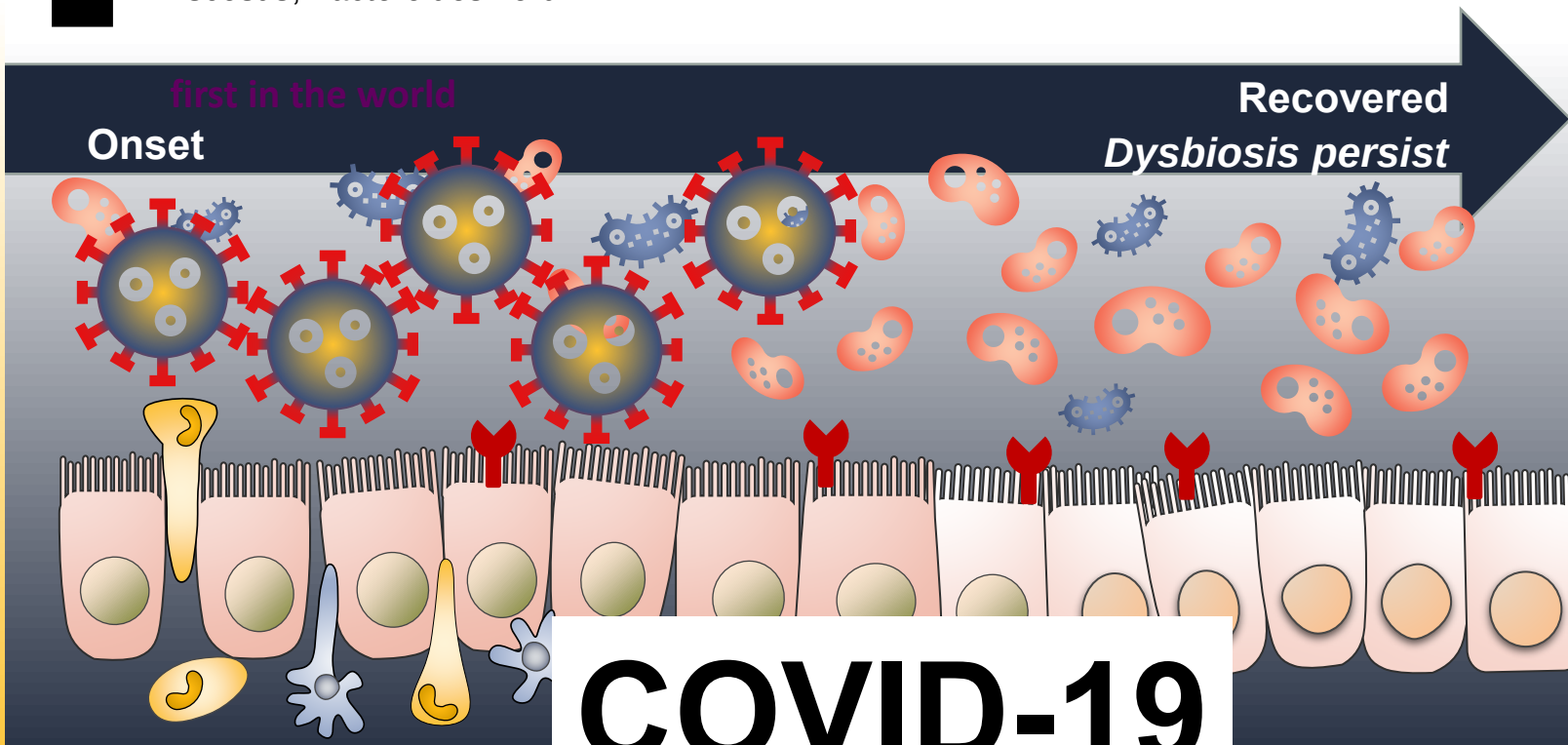


Healthy

first in the world

Onset

Recovered
Dysbiosis persist



COVID-19

晴報 News

12.6.2020 Fri | skypost.hk

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讀者人數免費報第2位

COVID-19 新冠肺炎

中大醫學院昨發表全球首份證實新冠肺炎病者腸道微生態失衡研究，發現腸內惡菌增加，令抑制病毒入侵的益菌量減少，致免疫力下降。團隊經大數據分析逾千份樣本後，研發出益生菌組合配方，預計約3個月能製成益生菌補充劑，加入日常飲食，改善整體腸道健康，增強免疫能力，但強調配方屬健康食品，非作治療新冠肺炎之用。

黃秀娟(左)稱團隊研究的益生菌配方，較市面上產品耐熱、耐氧及耐胃酸；中為陳家亮，右為陳基湘。

中大證新冠患者腸道失衡 致免疫力減

研益生菌組合配方改善

研發益生菌配方 有望增強免疫力

中大全球首證新冠患者腸道微生態失衡

己於中國及美國申專利

腸道微生物重要如器官

新冠患者缺益生菌腸道失衡

中大醫學院研發配方 洽產膳食補充劑惠民

香港中文大學醫學院根據總體基因體學，首度發現新冠肺炎患者腸道缺乏一系列的益生菌，故透過大數據分析，成功研發耐熱、耐氧、耐胃酸的益生菌配方，可添加於膳食中，平衡腸道微生態，增強免疫力以減低受感染機會。中大醫學院院長陳家亮期望，能在數月內推出該款益生菌補充劑惠及全民。

人體內有數量巨大、種類繁多的微生物，它們共同組成了人體微生態系統。而人體的微生態主要包括眼睛、口腔、皮膚、腸道、生殖道等七大系統，當中最重要的是微生物數量最多的腸道微生態。腸道微生態對促進人體生理機能的完善 特別是免疫功能的成熟有着非常重要的作用。

惡菌增加一成至九成

中大醫學院研究團隊今年2至3月為15名介乎20至70歲新冠肺炎患者，採集他們住院至出院期間的糞便樣本，並與15名健康人士的樣本作比對，結果發現無論病情輕微抑危重病人，都有腸道微生態嚴重失衡問題，導致惡菌增加10%至90%，且抑制病毒入侵的四種益菌數量少一半，當中維持人體免疫力的普拉梭菌更完全消失。團隊其後擴大研究範圍，分析150名新冠肺炎患者及1,500名健康人士的腸道微生態，對比結果亦與上述情況一樣。

中大團隊成功研發出益生菌補充劑，有望幫助市民增強免疫力。

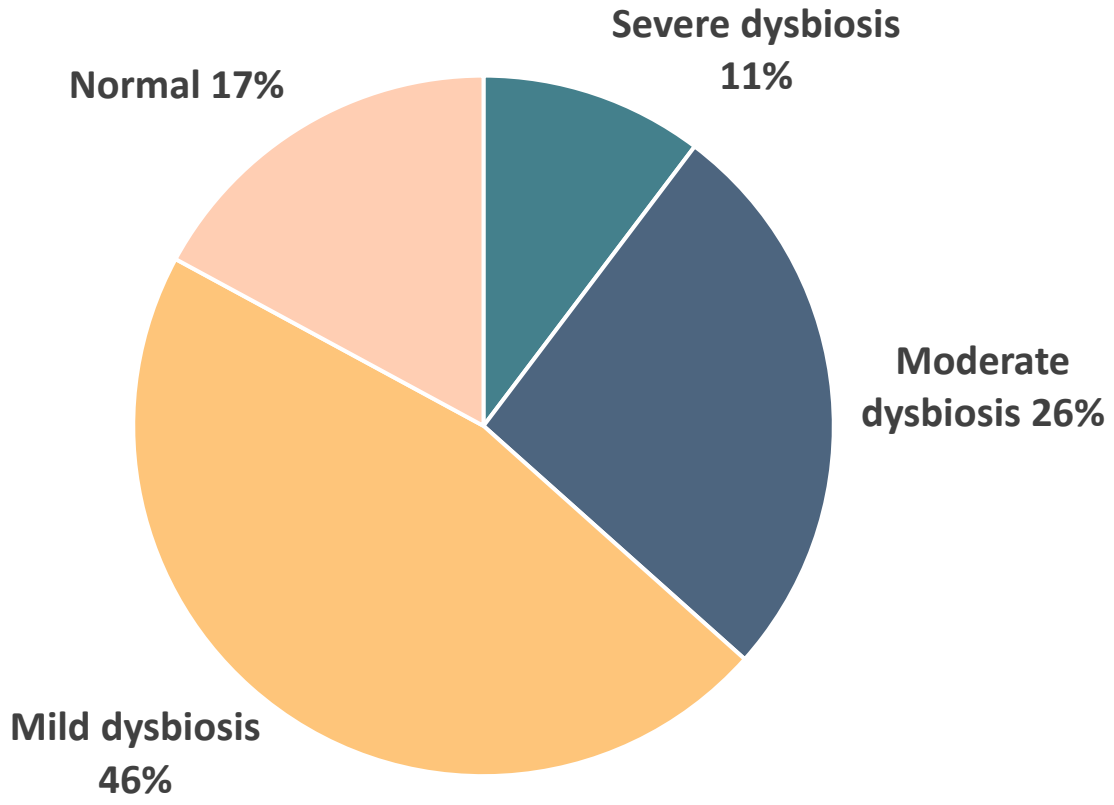
中大醫學院微生物學系系主任陳基湘表示，腸道微生態中存有大量益菌，可合成維他命，增加免疫力及調節中樞神經系統等，而微生態有機會受各種因素如飲食，運動，壓力甚至出生方法等影響，因此組合因人而異。

中大醫學院腸道微生物群研究中心副主任黃秀娟表示，人體肺部和消化道均有ACE2受體，是導致新冠病毒入侵的受體，而腸道微生態的平衡有機會影響ACE2受體數量，數量愈多代表惡菌愈多，而23種腸道細菌則與病情嚴重程度有關。她補充，接受研究的15名患者中，所有人都有微生態失衡情況，相信是因失衡導致免疫力下降，從而感染新冠肺炎。

該團體日前以大數據分析，成功研發針對腸道微生態失衡的益生菌配方。陳家亮指出，新配方使用新技術，令益生菌更耐熱，耐氧，耐胃酸，提升活菌量及穩定性，令更多益生菌能到達腸道。配方已在內地和美國申請專利，正與創科及食品公司洽商大規模生產成補充劑，添加在日常膳食中，並於短期內面世，希望能在坊間廣泛應用。他續指，盼年底前能與亞洲其他醫學院合作進行大型臨床研究，把配方在一至兩年內變成治療藥物。

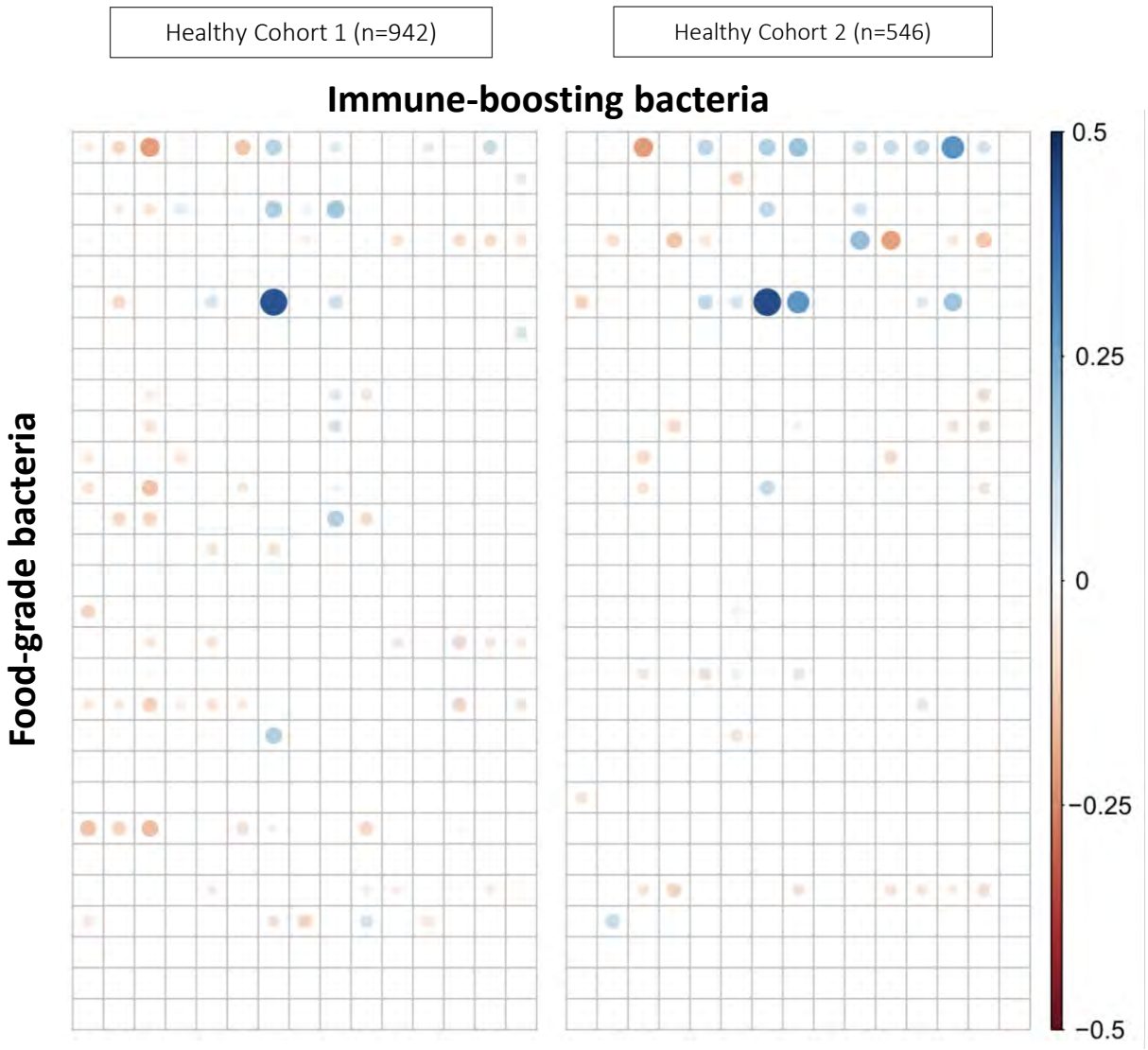
How do the research impact patient care?

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



Data on file

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 was developed using big data analysis and machine learning

Hong Kong / Health & Environment

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

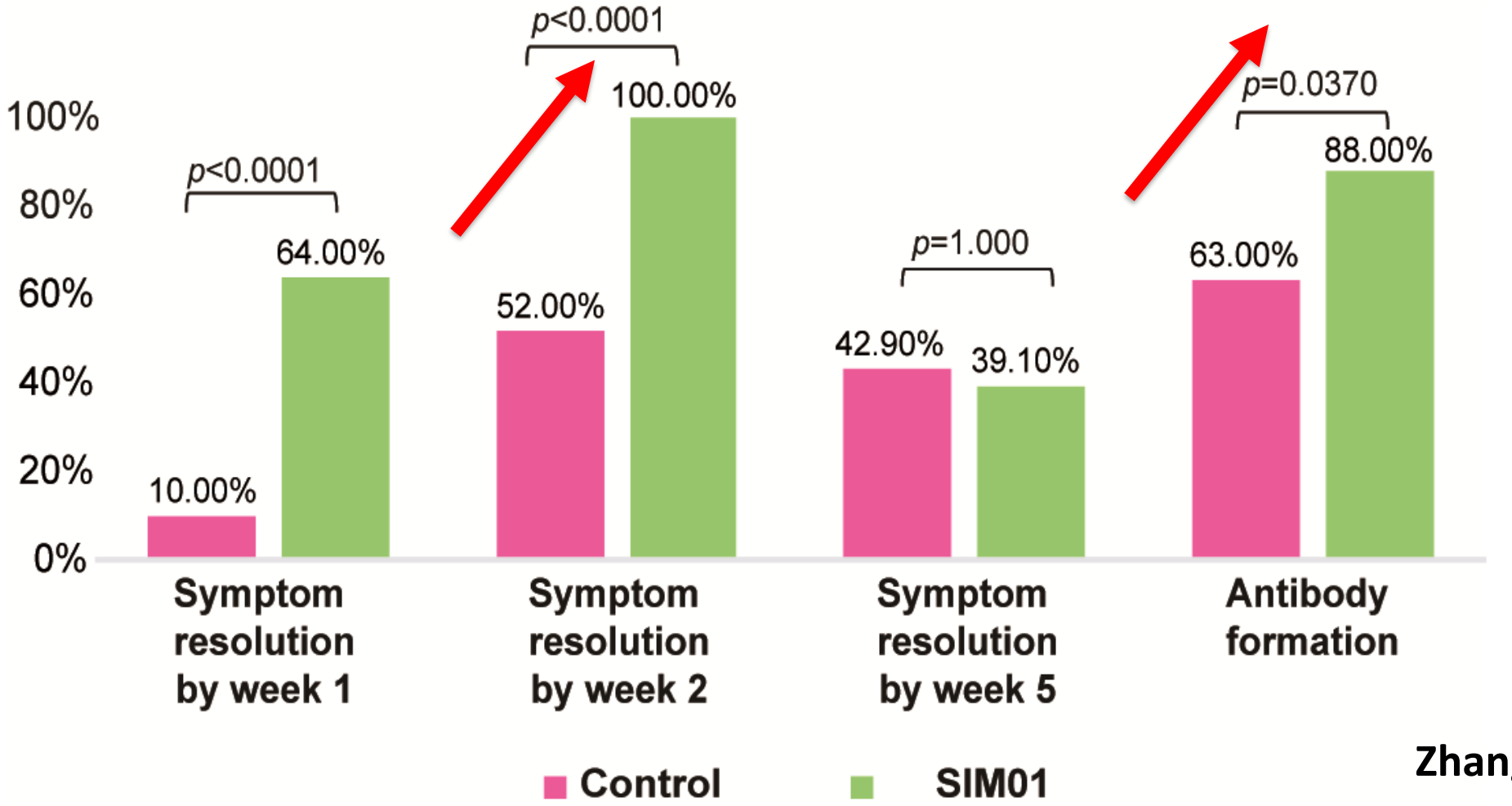
Chinese University's Francis Chan speaks at a Thursday press conference where his team unveiled a new probiotic formula designed to help balance the 'good' and 'bad'

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.

More patients on immunity formula achieved resolution of COVID-19 symptoms & antibody formation



Zhang.. Ng. APDW 2021

Zhang et al. JGH (revision)

What are the global impact of our research?

2 editorials
5 publications
5 media press

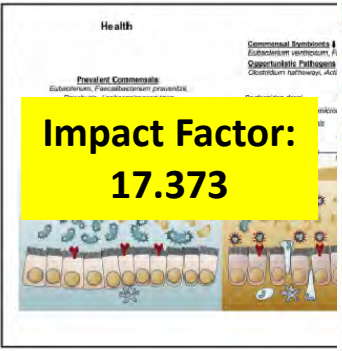
Gastroenterology aga
Gastroenterology 2020;159:944–955

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]

[1]Center for Gut Microbiota Research, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, China; [2]State Key Laboratory for Digestive Disease, Institute of Digestive Disease, Li Ka Shing Institute of Health Science, The Chinese University of Hong Kong, Shatin, Hong Kong, China; [3]Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, China; [4]Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong, China; [5]Department of Microbiology, The Chinese University of Hong Kong, Shatin, Hong Kong, China; [6]Department of Pathology, United Christian Hospital, Hong Kong, China; [7]Department of Pathology, Prince of Wales Hospital, Hong Kong, China; [8]Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong,



Impact Factor: 17.373

BACKGROUND & AIMS: Although severe acute respirator syndrome coronavirus 2 (SARS-CoV-2) infects gastrointestin tissues, little is known about the roles of gut commensal m crobes in susceptibility to and severity of infection. We inve tigated changes in fecal microbiomes of patients with SARS CoV-2 infection during hospitalization and associations wit

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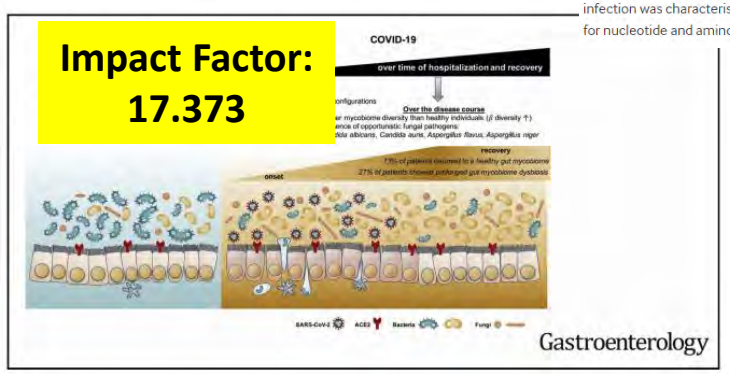
BASIC AND TRANSLATIONAL—ALIMENTARY T

Alterations in Fecal Fungal Microbiome of Patients Witl COVID-19 During Time of Hospitalization until Discharg

Tao Zuo,[1,2,3,*] Hui Zhan,[1,2,3,*] Fen Zhang,[1,2,3] Qin Liu,[1,2,3] Eugene Y. K. Ts Grace C. Y. Lui,[3,5] Nan Chen,[1,3] Amy Li,[2,3] Wenqi Lu,[1,3] Francis K. L. Char Paul K. S. Chan,[1,6] and Siew C. Ng[1,2,3]

[1]Center for Gut Microbiota Research, Faculty of Medicine, The Chinese University of Hong Kong, Sh [2]State Key Laboratory for Digestive Disease, Institute of Digestive Disease, Li Ka Shing Institute of Hea University of Hong Kong, Shatin, Hong Kong, China; [3]Department of Medicine and Therapeutics, Fa Chinese University of Hong Kong, Shatin, Hong Kong, China; [4]Department of Medicine and Geriatri Hospital, Hong Kong, China; [5]Stanley Ho Centre for Emerging Infectious Diseases, The Chinese Un Shatin, Hong Kong, China; and [6]Department of Microbiology, The Chinese University of Hong Kong, S

Impact Factor: 17.373



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 *Candia 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

BMJ Journals
Gut

COVID-19

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

Tao Zuo [1, 2, 3], Qin Liu [1, 2, 3], Fen Zhang [1, 2, 3], Grace Chung-Yan Lui [3, 4], Eugene YK Tso [5], Yun Kit Yeoh [1, 6], Zigui Chen [1, 6], Siaw Shi Boon [6], 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 stool
Even in the absence of GI manifestations, all seven patients sh
of the 3'
continue
respirato
Collinsel
nucleoti
SARS-Co
sterconis, Alistipes onderdonkii and *Lachnospiraceae bacteriu*

Conclusion This pilot study provides evidence for active and p
manifestations and after recovery from respiratory infection o
infection was characterised by enrichment of opportunistic pa
for nucleotide and amino acid biosynthesis and carbohydrate

Impact Factor: 19.819

BMJ Journals
Gut

Gut microbiota
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]

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 inf
27 of the 100 patients up to 30 days after clearance of SARS-CoV-2. Gut microbio
sequencing total DNA extracted from stools.
Concentrations of inflamn
red from plasma.

Results Gut microbiome c
with COVID-19 compared with non-COVID-19 individuals irrespective of whether pa
gut commensals with known immunomodulatory potential such as *Faecalibacterium prausnitzii, Eubacterium rectale* and bifidobacteria were underrepresented in patients and remained low in samples collected up to 30 days after disease resolution. Moreover, this perturbed composition exhibited stratification with disease severity concordant with elevated concentrations of inflammatory cytokines and blood markers such as C reactive protein, lactate dehydrogenase, aspartate aminotransferase and gamma-glutamyl transferase.

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.

Impact Factor: 19.819

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The Chinese University of Hong Kong
Faculty of Medicine
The Chinese University of Hong Kong

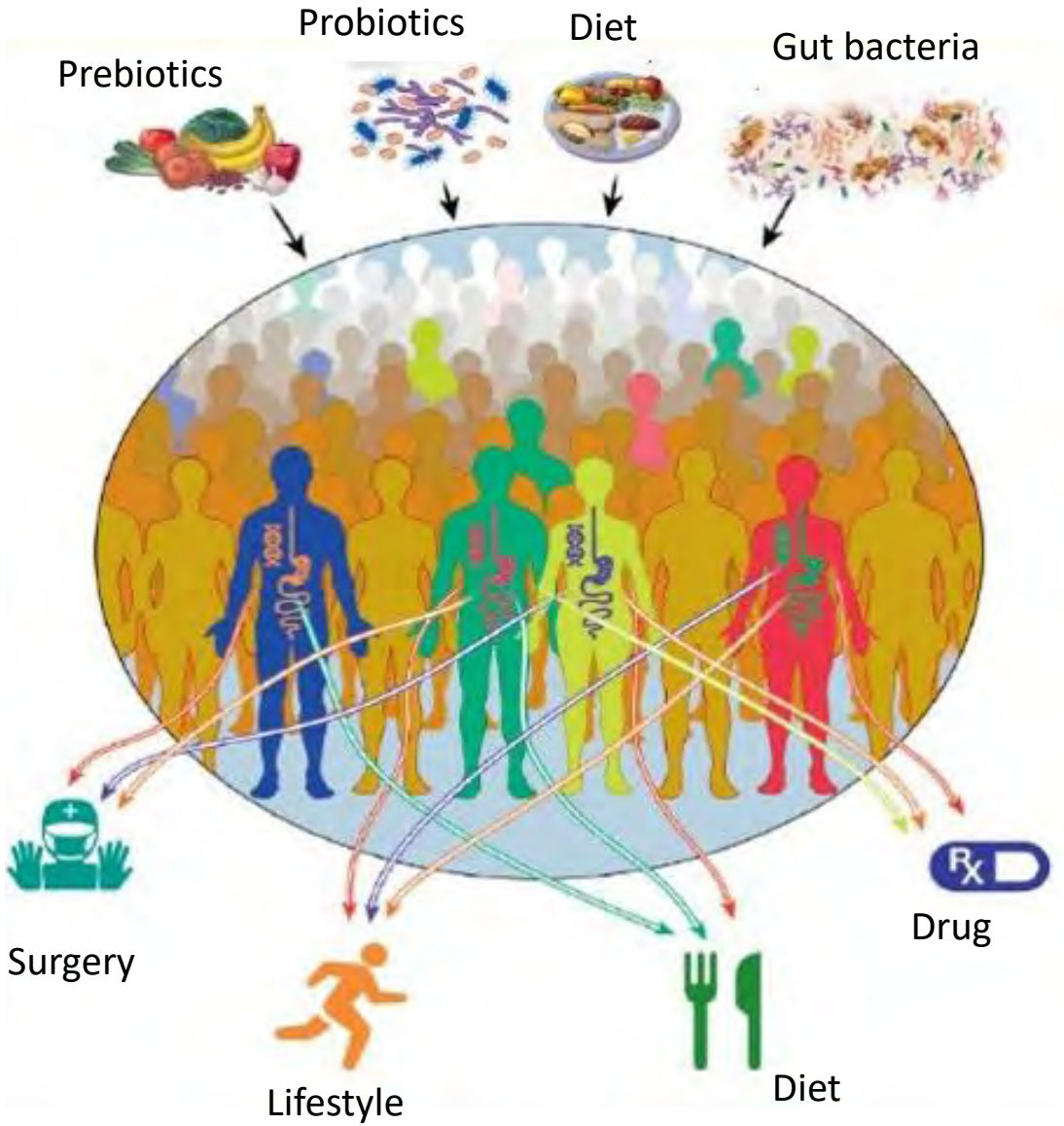
Global Impact of our Work

What are our future directions?

Durability of vaccine response?

Durability of COVID-19 vaccine remains unclear and some countries are offering third vaccine doses

Can we modulate gut microbiome to improve vaccine response?



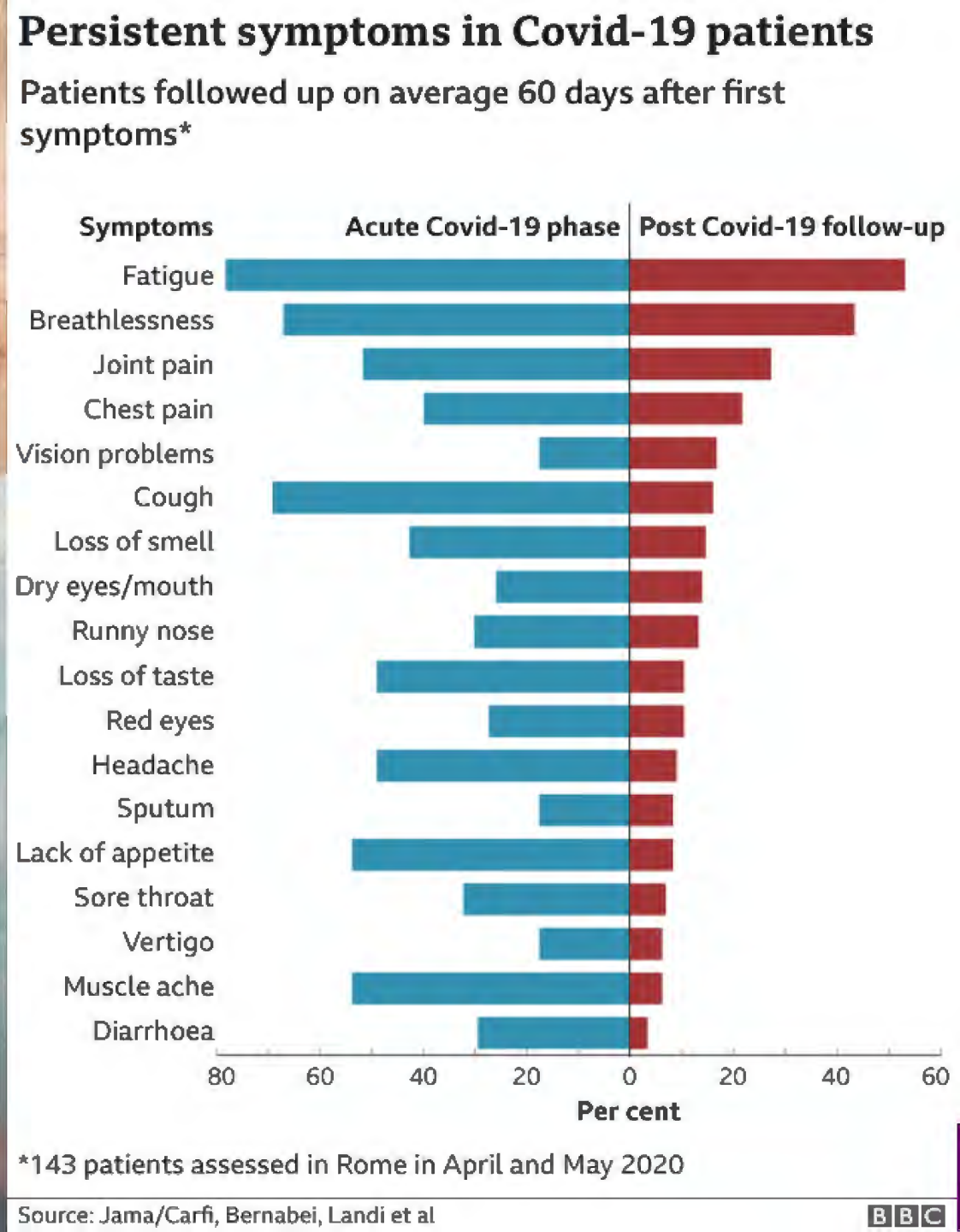
香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Novel strategies to facilitate early detection, prevention and Intervention for long-Term Health problems related to COVID-19 (NovITor-COVID study) *(COVID1903002)*

Siew Ng, Francis Chan, Grace Wong, Martin Wong, YK Wing
Department of Medicine and Therapeutics
The Chinese University of Hong Kong

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



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，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

■中大研究顯示，新影響患者的腸道。

Symptoms linger long after recovery for 80pc of patients

Ethna Paul

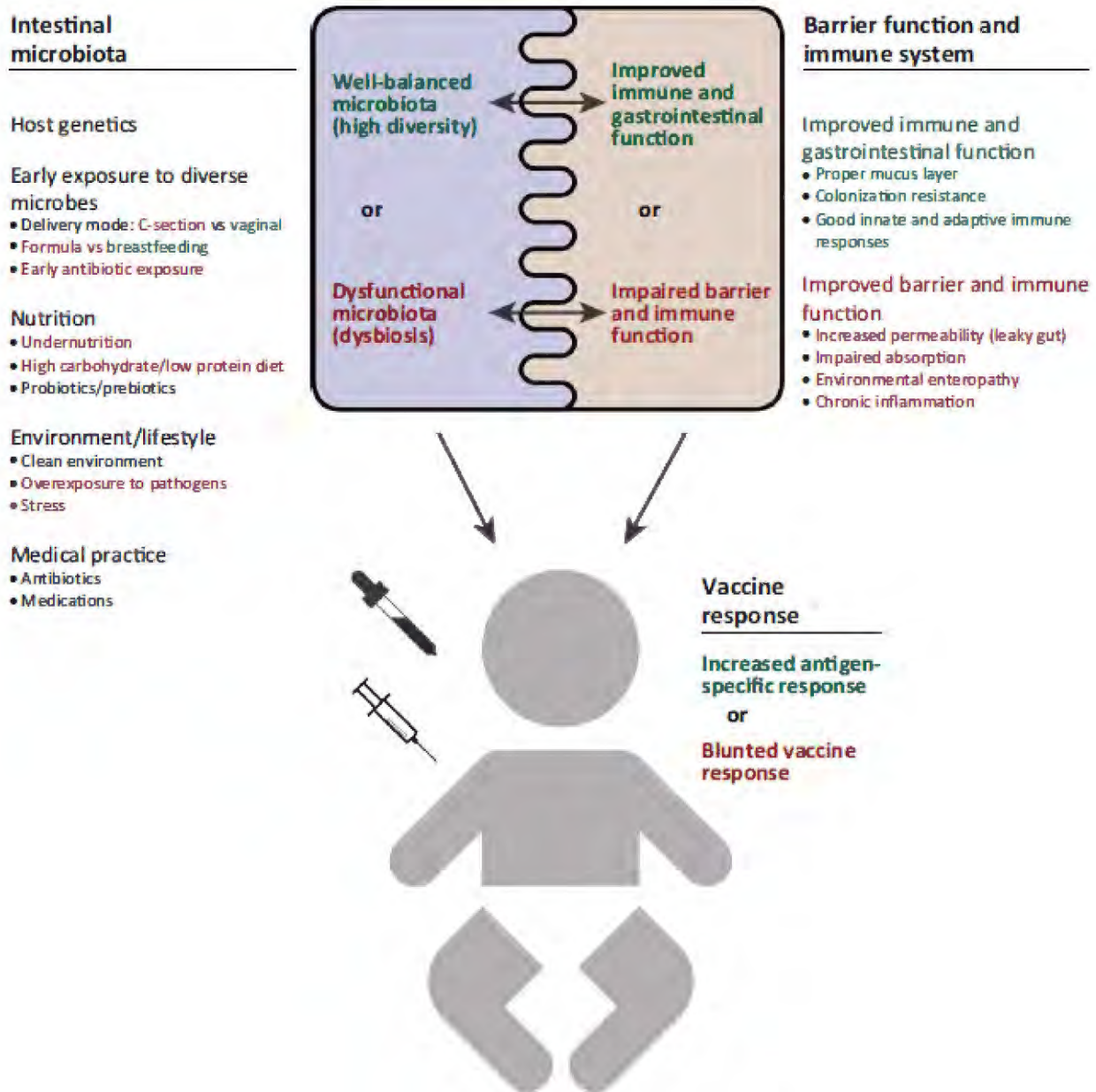
Eighty per cent of recovered Covid-19 patients in Hong Kong continue to experience at least one of the disease's symptoms six months after the first report suffering from more than three researches have found.

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

30 after they had recovered six months later. Of this group, 23 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 disarm it.

Microbial dysbiosis can cause blunted vaccine response



Cell Host Microbe. 2020;
Trends in Immunology 2014

Four Integrated Programs

(Prevention is better than cure)

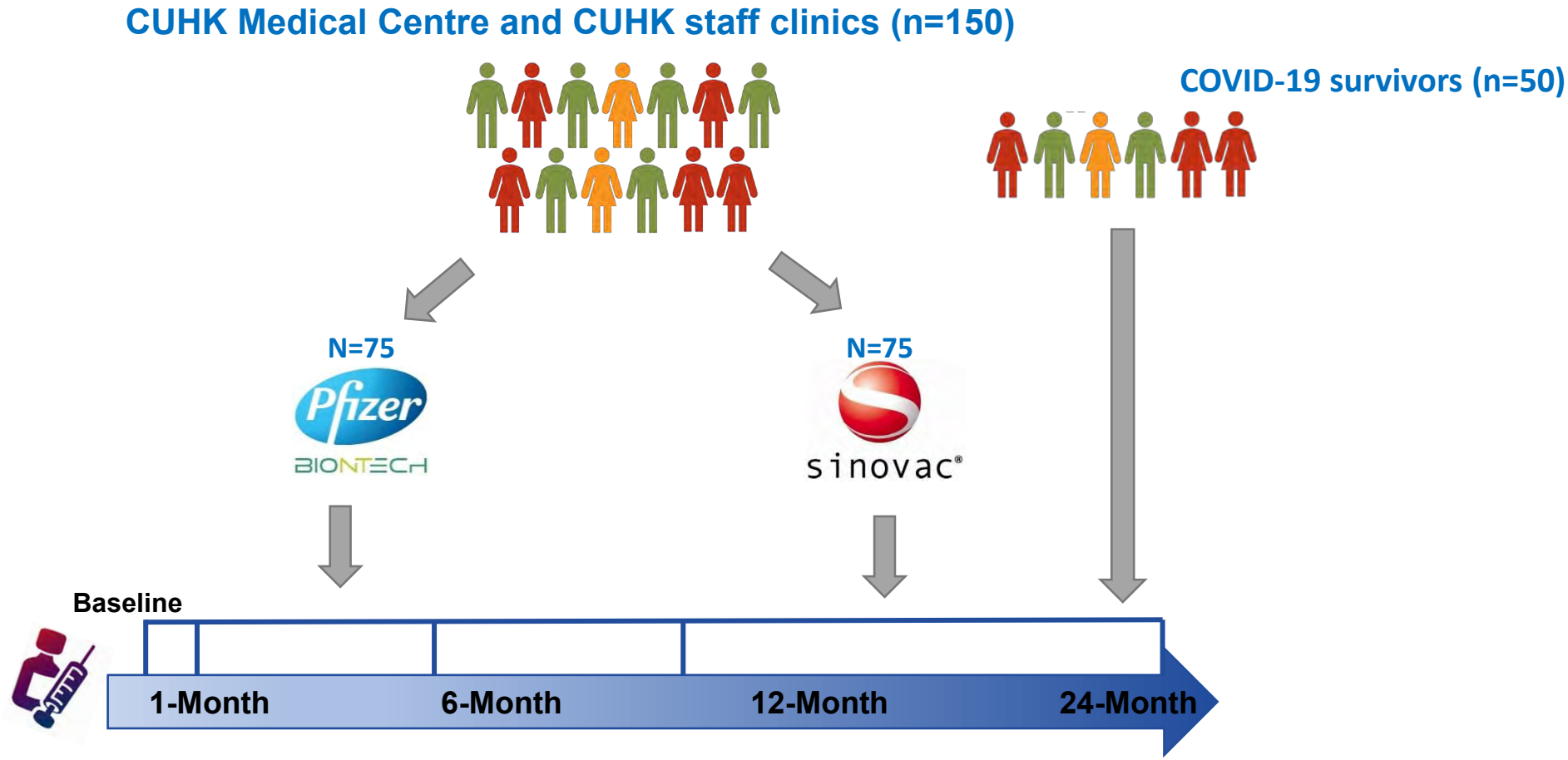
1. **Big data analytics** to capture new-onset long-term comorbidities of COVID-19

2. Integrated primary care of patients with **long-COVID**

3. Identification of **neuropsychiatric complications** and early intervention in COVID-19 survivors

4. Modulation of gut microbiota to prevent complications in COVID-19 patients and **boost vaccine response**

Gut microbiota Affects Vaccine Response



SARS-CoV-2 neutralising antibody, IgM and IgG against RBD and S1 by ELISA

Plasma cytokine measurements

Shotgun metagenomics sequencing and profiling

Targeted and untargeted metabolomics sequencing and profiling

Impact Summary

- 40% of HK people have imbalanced gut microbiota and are at risk of COVID-19
- COVID-19 patients have missing gut bacteria with immunomodulatory potential
- Gut microbiota in COVID-19 patients is concordant with disease severity
- Restoration of gut dysbiosis is an adjuvant treatment to hasten recovery
- Microbiota-targeted interventions can help increase vaccine antibody response and provides hope to prolong vaccine durability

Food and Health Bureau
The Government of the Hong Kong Special Administrative Region

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Faculty of Medicine
The Chinese University of Hong Kong

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The Chinese University of Hong Kong

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Faculty of Medicine
The Chinese University of Hong Kong

Modulation of gut microbiota to enhance health and immunity of vulnerable individuals during COVID-19 pandemic *(COVID19F07)*

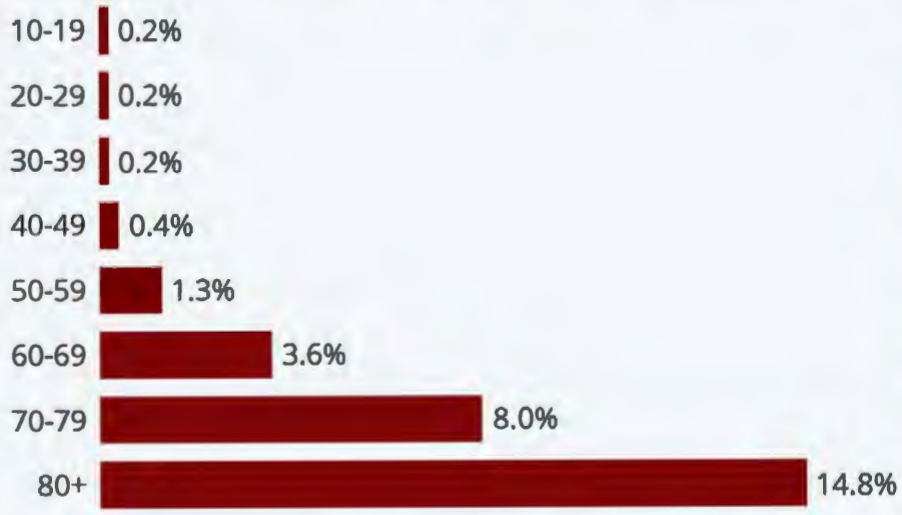
Joyce WY Mak
Department of Medicine and Therapeutics
The Chinese University of Hong Kong

IMPACT

COVID-19 and the elderly

Study: Elderly Most At Risk From The Coronavirus

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

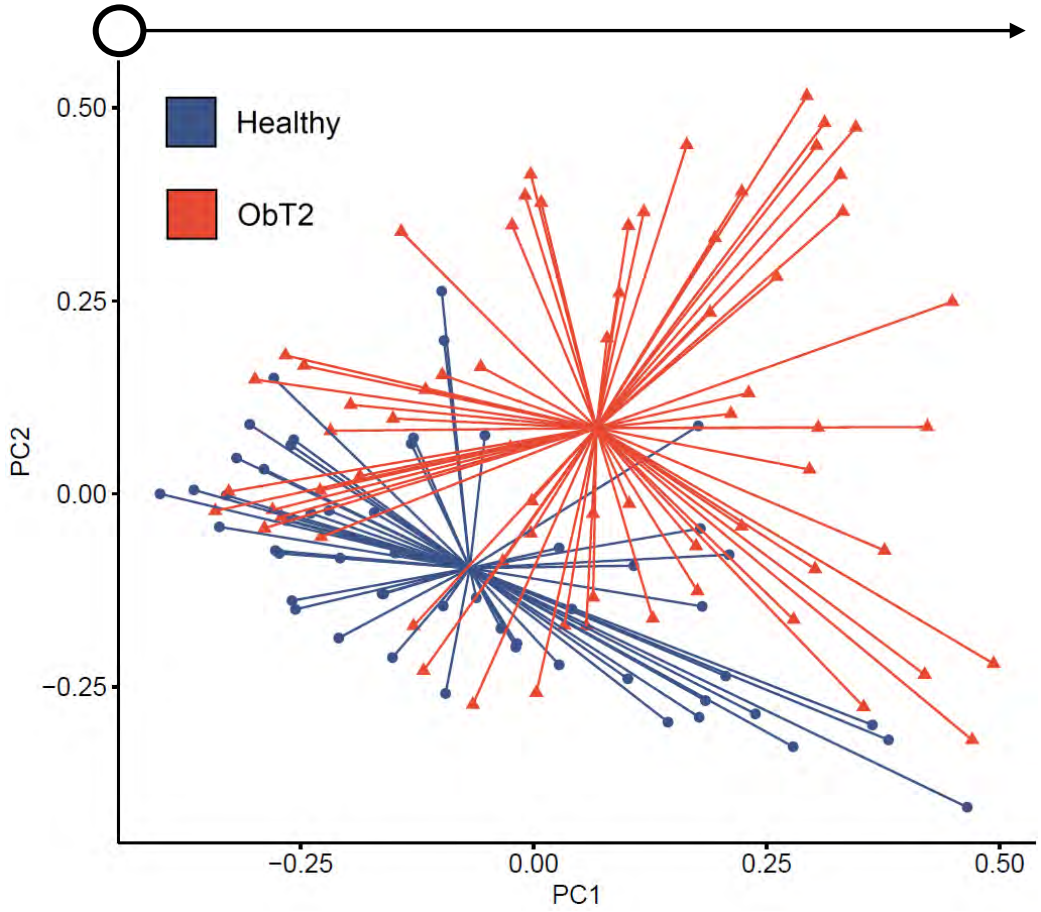


n=44,672 confirmed COVID-19 cases in Mainland China
Source: Chinese Centre for Disease Control and Prevention

Diabetics more prone to severe COVID-19

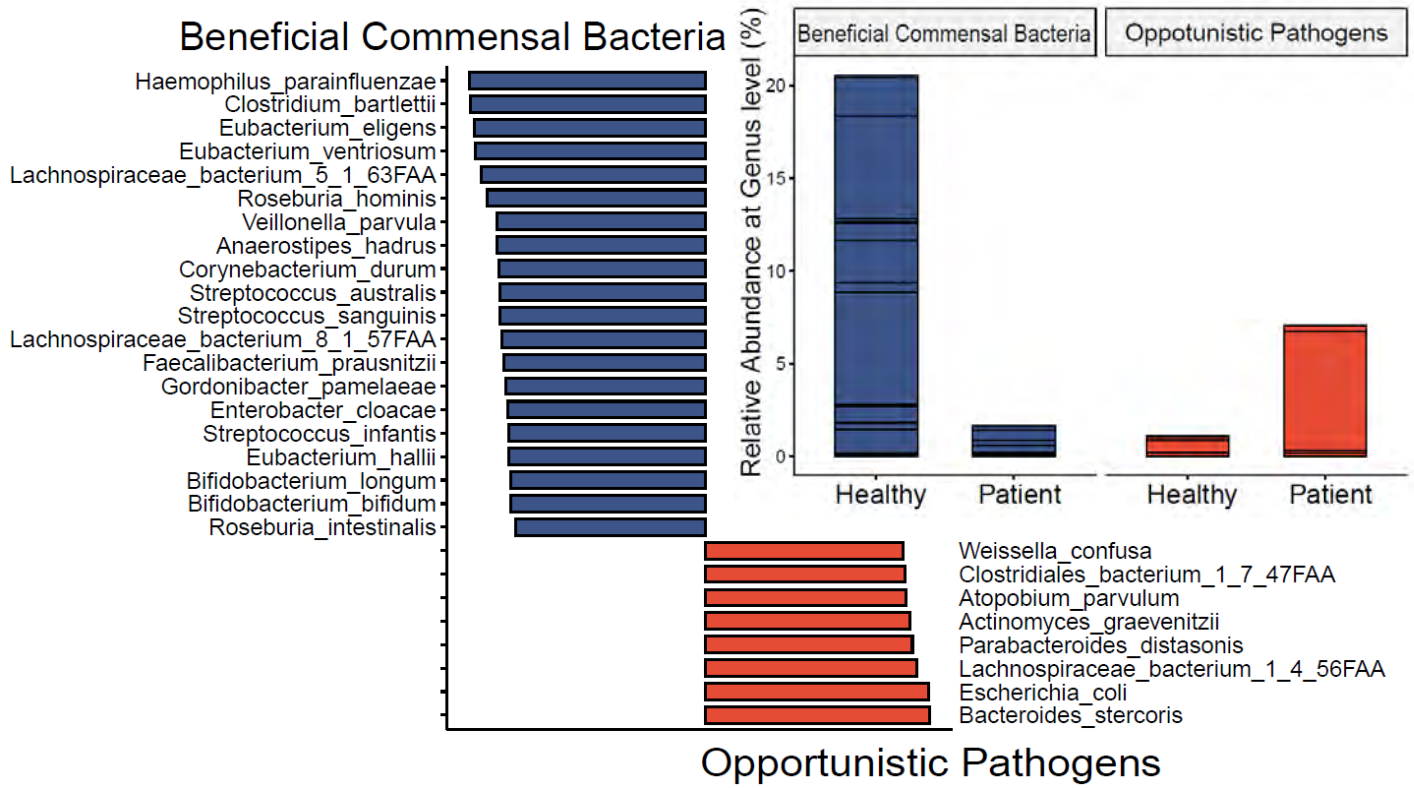
Patients with Diabetes Mellitus have severe dysbiosis

The microbiome in DM patients are distinct from that of healthy subjects, with depletion of beneficial commensal bacteria and expansion of opportunistic pathogens (including E.coli and some Bacteroides spp. that were shown to affect response to vaccination).

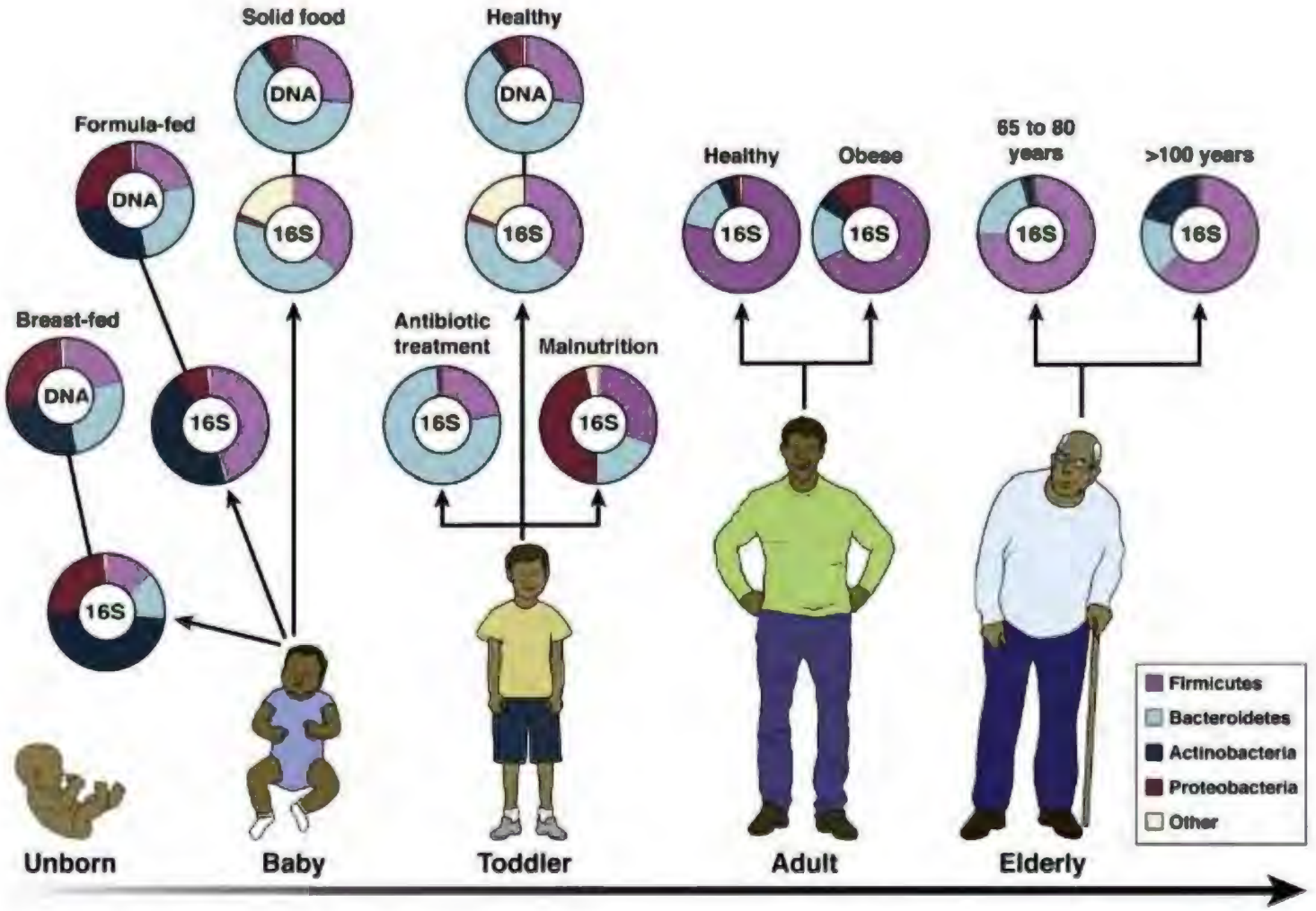


The beneficial commensal bacteria constitute an average of 20.6% of the microbiome, and the opportunistic pathogens constitute an average of 1.1% of the microbiome in healthy subjects.

In this subject with T2DM however, the beneficial commensal bacteria constitute only 1.6% of the microbiome, whereas the opportunistic pathogens constituted 7.1%.

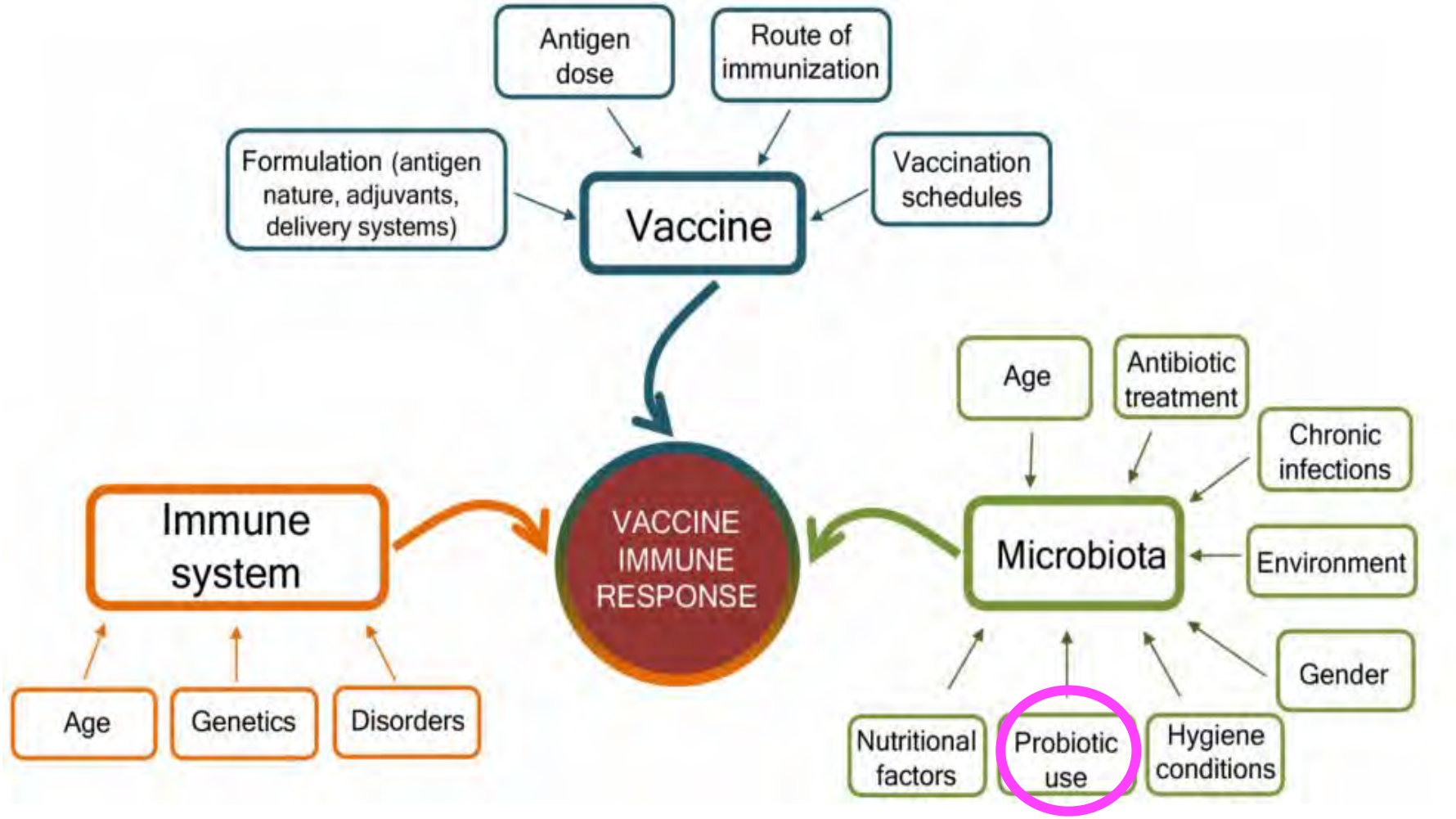


Dysbiosis in elderly subjects

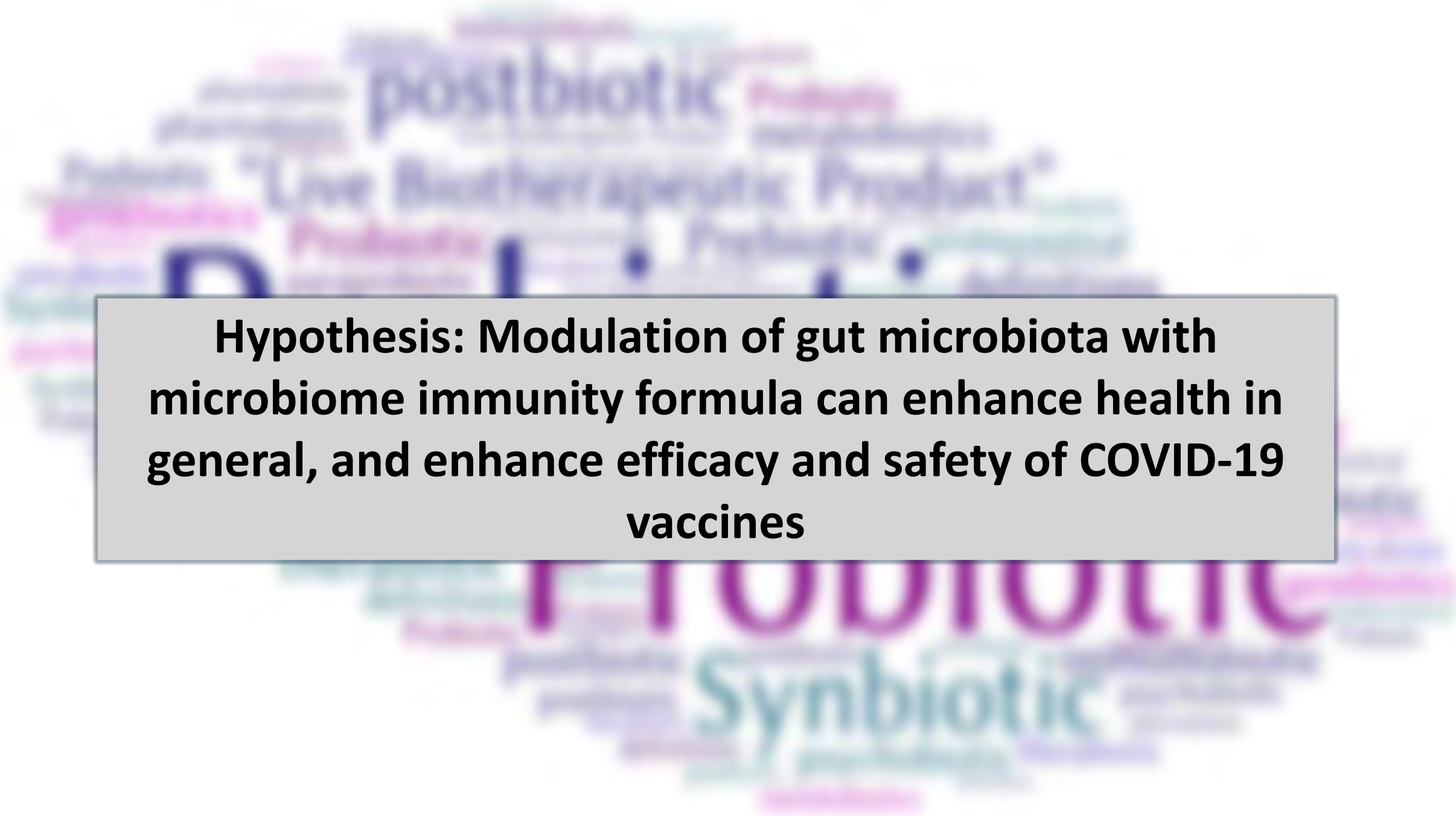


Haran JP, McCormick BA. Gastroenterology. 2021 Jan;160(2):507-523.

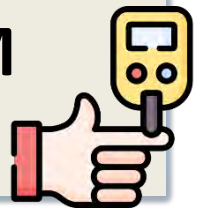
Influence of Gut Microbiota on the Immune Response to Vaccination



Ciabattini et al, Frontiers in Microbiology, 2019



Hypothesis: Modulation of gut microbiota with microbiome immunity formula can enhance health in general, and enhance efficacy and safety of COVID-19 vaccines

Sub-Study 1	Sub-Study 2
Double-blinded RCT	Open-labelled RCT
Recruit 222 Type 2 DM patients aged 18 -65 	Recruit 262 Elderly subjects aged > 65 years 
Randomised into microbiome immunity formula/ placebo x 6 months in 1:1 ratio	Randomised into microbiome immunity formula for 3 or 6 months in 1:1 ratio
50% of the subjects need to have COVID-19 vaccination	50% of the subjects need to have COVID-19 vaccination

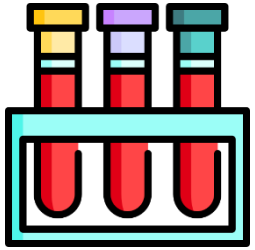
Primary Outcome

- Proportion of patients achieving **restoration of gut dysbiosis** at 6 months

Secondary Outcomes

- **Immunogenicity of the COVID-19 vaccine** as measured by serum neutralization assay against pseudo virus and live virus, and IgM and IgG against receptor-binding domain [RBD] and S1 by ELISA

- Adverse events within 6 months
- Number of unscheduled hospitalisation and clinic visits at different time points (month 1, 3,6,9 and 12)
- Changes in the gut microbiome over time

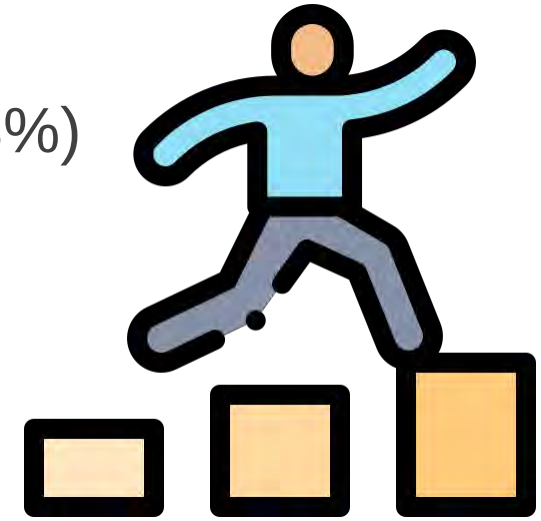


- Changes in plasma **immune response** markers over time
- Quality of life as measured by EQ-5Q-5L

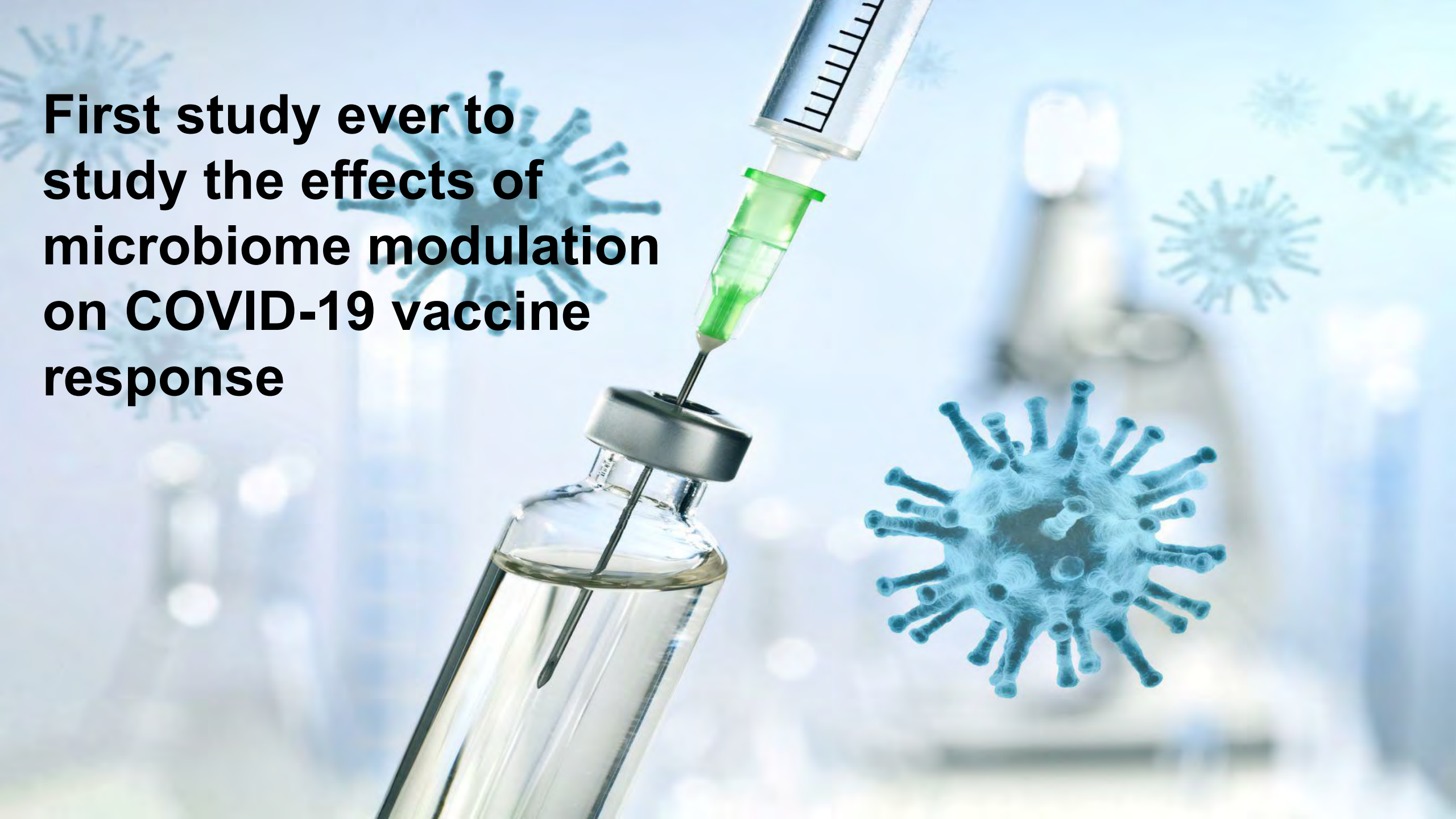
Current Progress

Sub-study 1 (DM) 59 DM subjects recruited (26.6%)

Sub-study 2 (Elderly) 82 elderly subjects recruited (31.3%)



First study ever to study the effects of microbiome modulation on COVID-19 vaccine response



Thank you! Comments welcome