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Pre-Existing Immunity to COVID-19: Overview and Implications – Part 2

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Abstract

This review article comes in three parts: Part 1 introduced the subject and investigated how other coronaviruses provided pre-existing immunity to SARS-CoV-2; Part 2 considers pre-existing immunity from other micro-organisms, and Part 3 will investigate pre-existing immunity from non-COVID vaccinations and will conclude the article as a whole.

Studies of exposure to some of the more common viruses found that they are generally associated with worsening of COVID-19, while malaria exposure correlated with lower disease incidence and severity. The effect of the host microbiome on COVID-19 seemed to depend upon its composition. Poor microbiome diversity, lower levels of beneficial bacteria, especially short-chain fatty acid (SCFA)-producing bacteria, and increased inflammation were all associated with COVID-19 severity, although supplementation with beneficial oral bacteria appeared protective. Nevertheless, some studies showed that the presence of traditionally pathogenic bacteria in the microbiome may correlate with less severe disease. These results lead to questions as to why other viruses are associated with more severe COVID-19, while a parasite (malaria) and certain traditionally pathogenic bacteria in the microbiome are associated with protection. More research is needed to confirm findings and to determine the mechanism(s) producing these effects, but the studies suggest that, ideally, the influence of the human host's other viral exposures and microbiome composition on a particular pathogen must be considered, just as we would consider other disease risk factors to assess vulnerability.

Keywords: COVID-19, SARS-CoV-2, pre-existing immunity, viruses, commensal bacteria, microbiome

Pre-existing immunity from other micro-organisms

Studies suggest that the course of COVID-19 may be affected not only by other human coronaviruses but also by non-coronaviruses and bacteria. The principal micro-organisms are discussed below.

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Dengue virus

Dengue is a vector-borne positive-stranded RNA enveloped virus of the Flavivirus family, contracted through the bite of an infected Aedes mosquito. Population studies have shown that COVID-19 tended to be less severe in regions where dengue virus was endemic. (1–3) Nevertheless, a meta-analysis of African studies found that samples from high dengue areas with low malaria burden had negligible protective ability against COVID-19, while samples from high malaria areas showed correlation with protection regardless of dengue status, (4) suggesting that in Africa, and possibly elsewhere, it is malaria which is driving SARS-CoV-2 immunity.

Cytomegalovirus (CMV)

CMV is a beta-herpes virus, with global seroprevalence estimated at 60-90%. (5) Although CMV-

specific T cells were cross-reactive with SARS-CoV-2, (6,7) those seropositive for CMV suffered increased COVID risk, hospitalisation, ICU stay and ventilator use, with a longer duration of viral shedding, heightened inflammatory response and upregulation of the ACE2 receptor, the main entry for SARS-CoV-2 into the cells. (5,8)

Hepatitis B

A meta-analysis of 16 studies, comprising 14,682 patients, found that viral hepatitis correlated with increased risk of severe COVID-19. (9) This is supported by two later Asian studies showing that chronic hepatitis B infection appears to increase COVID-19 susceptibility and severity. (10,11)

Other viruses

The situation is somewhat confused as one study found that rhinovirus, respiratory syncytial virus and several herpes viruses showed no cross-reactivity with SARS-CoV-2, (24) while another showed that individuals infected with rhinovirus, enterovirus, respiratory syncytial virus, and human metapneumovirus were less likely to have a positive COVID test, (25) indicating some protective effect. Influenza virus, surprisingly, showed little cross-reactivity with SARS-CoV-2, (26) and was associated with more severe COVID-19. (27,28)

Malaria

Malaria is caused by parasites that are transmitted through the bites of infected female Anopheles mosquitoes. Reports suggest that in malaria-endemic areas, there was a lower incidence and severity of COVID-19. (12–14) A large 2023 meta-analysis of African studies found that >11% of pre-pandemic blood samples tested positive for anti-SARS-CoV-2 antibodies, (4) and a later survey of 53 African countries showed that each 10% increase in the prevalence of malaria was associated with a 28% decrease in the cumulative incidence of COVID-19. (15) Globally, systematic and other reviews found that in malaria-endemic areas, individuals had lower incidence and severity of COVID-19. (16–18) In studies of individuals, co-infection with malaria was associated with less severe COVID-19 and faster viral clearance. (19) A previous acute malarial infection appeared to provide elevated anti-SARS-CoV-2 antibodies, (20–22) although one study found these antibodies were non-neutralising. (23)

Human commensal bacteria

Studies of the intestinal, oral, and respiratory tract microbiomes have shown a clear positive association of COVID-19 incidence and severity with poor diversity, lower levels of beneficial bacteria, especially those producing short-chain fatty acids (SCFAs), increased inflammation, and colonisation by opportunistic pathogens. (29–40) SCFA-producing bacteria are important to provide a key energy substrate for epithelial cells to maintain immune homeostasis and promote the production of mucosal regulatory T cells, which inhibit the production of excessive inflammation. (29) In the intestines, certain elements of the microbiome were cross-reactive with SARS-CoV-2 (41) and can play a vital role in the induction of an adaptive immune response to viral infection. (31,42)

In the human oral microbiome, pre-existing infections are common and are associated with COVID-19 severity; (35,39,43–46) this is thought to be due to induction of ACE 2 expression, production of inflammatory cytokines, (40) increased adhesion of pathogens to oral mucosal surfaces, breathing the oral pathogen into the lungs (47) or decreased mucosal secretory IgA (sIgA). (38) Nevertheless, several species of oral bacteria, particularly *Streptococcus salivarius*, can beneficially induce anti-SARS-CoV-2 spike IgG antibodies, (48) and oral bacteria supplementation (combined with an intranasal vaccine) could protect against SARS-CoV-2 infection. (42)

In the upper respiratory tract, two *Streptococcus* strains stimulated the expression of the ACE2 receptor *in vitro*, increasing viral entry to the body, (44,49) while a decreased level of bacteria producing the SCFA butyrate was seen in PCR-positive individuals compared to PCR-negative individuals. (35,36,49)

Some lower respiratory tract bacteria increase the production of beneficial type I interferons, cytokines, chemokines, and antiviral factors, and can enhance the antiviral defences of epithelial cells. (44) Remarkably, in the lower airways of COVID-19 patients requiring mechanical ventilation, the presence of the otherwise pathogenic *Escherichia coli*, *Staphylococcus aureus,* and *Klebsiella pneumoniae* correlated with increased odds of survival compared with death from COVID-19. (46) Similarly, another study identified six so-called pathogenic bacteria from the intestine or respiratory tract, which share significant homology with SARS-CoV-2 proteins but far from being pathogenic in their effect, pre-exposure generated T cells, which were associated with protection against SARS-CoV-2. (50)

Studies talk of the ability of SARS-CoV-2 to alter

the microbiome, but since none of these studies measured the microbiome prior to COVID-19, this may not be a true reflection of what is occurring. Since we all harbour a number of different, generally dormant, microbes, it is perhaps more likely that the pre-existing microbiome affects the course of COVID-19. And not always in the expected direction.

Part 2 Conclusion

As well as the common cold coronaviruses, SARS-CoV-2 may also be influenced by other micro-organisms, although the studies focus much less on cross-reactivity and tend merely to investigate whether or not the micro-organism was protective.

Table 1. Results of population studies of the effect of exposure to non-coronaviruses and malaria on COVID-19

VIRUS/PARASITE	EFFECT ON COVID-19 INCIDENCE	EFFECT ON COVID-19 SEVERITY
Dengue	Not assessed	Associated with protection but malaria exposure may be an unadjusted confounding factor
Cytomegalovirus	Not assessed	Associated with increased severity
Hepatitis B	Associated with increased incidence	Associated with increased severity
Influenza	Not assessed	Associated with increased severity
Rhinovirus, respiratory syncytial virus, several herpes viruses	Results are mixed	Not assessed
Malaria	Associated with lower incidence	Associated with improved outcomes

As **Table 1** shows, pre-exposure to other viruses was generally associated with increased COVID-19 incidence and severity, although meta-analyses of observational studies show that prior malaria exposure correlates with protection against COVID-19 incidence and severity. Although some studies suggest that dengue virus exposure, exceptionally, was associated with protection against COVID-19, this may be due to failing to take account of malaria exposure as a confounding factor.

With respect to commensal bacteria, poor microbiome diversity, lower levels of beneficial bacteria, especially SCFA-producing bacteria, and increased inflammation are all associated with COVID-19 severity, although supplementation with beneficial oral bacteria was associated with protection. Curiously, some studies showed that the presence of traditionally pathogenic bacteria in the microbiome may correlate with less severe disease. Although several authors talk of the ability of SARS-CoV-2 to alter the microbiome, since no study measured the microbiome prior to COVID-19, it may instead be the pre-existing microbiome which affects the course of COVID-19.

An interesting question is why non-coronaviruses are not associated with protection from COVID-19, but exposure to a pathogenic parasite and certain traditionally pathogenic bacteria correlates with less severe disease. Further research is required to confirm these findings and investigate mechanisms for this phenomenon. Essentially, these studies have shown that we must consider the influence of the human host's exposure to other micro-organisms on a particular pathogen, just as we would consider other disease risk factors, particularly since the presence of a pathogenic bacterium may help protect us against SARS-CoV-2.

References

1. Mallick A, Sukla S, De A, Biswas S. Evidences support that dengue virus can impart broad-spectrum immunity against betacoronaviruses in dengue endemic regions. J Med Virol. 2024 Jun;96(6):e29771.
2. Dutta D, Ghosh A, Dutta C, Sukla S, Biswas S. Cross-reactivity of SARS-CoV-2 with other pathogens, especially dengue virus: A historical perspective. J Med Virol. 2023 Feb;95(2): e28557.
3. Silvestre OM, Costa LR, Lopes BVR, Barbosa MR, Botelho KKP, Albuquerque KLC, et al. Previous dengue infection and mortality in coronavirus disease 2019 (COVID-19) Clin Infect Dis. 2021;73:e1219–e1221.
4. Ioannidis JPA, Contopoulos-Ioannidis DG. Pre-pandemic cross-reactive humoral immunity to SARS-CoV-2 in Africa: Systematic review and meta-analysis. Int J Infect Dis. 2023 Sep;134: 160–167.
5. Payen SH, Adhikari K, Petereit J, Uppal T, Rossetto CC, Verma SC. SARS-CoV-2 superinfection in CD14+ monocytes with latent human cytomegalovirus (HCMV) promotes inflammatory cascade. Virus Res. 2024 Jul;345:199375.
6. Mahajan S, Kode V, Bhojak K, Karunakaran C, Lee K, Manoharan M, et al. Immunodominant T-cell epitopes from the SARS-CoV-2 spike antigen reveal robust pre-existing T-cell immunity in unexposed individuals. Sci Rep. 2021 Jun 23;11(1):13164.
7. Pothast CR, Dijkland RC, Thaler M, Hagedoorn RS, Kester MGD, Wouters AK, et al. SARS-CoV-2-specific CD4+ and CD8+ T cell responses can originate from cross-reactive CMV-specific T cells. Elife. 2022 Nov 21;11: e82050.
8. Perera MR, Greenwood EJD, Crozier TWM, Elder EG, Schmitt J, Crump CM, et al. Human Cytomegalovirus Infection of Epithelial Cells Increases SARS-CoV-2 Superinfection by Up-regulating the ACE2 Receptor. J Infect Dis. 2023 Feb 14;227(4):543–553.
9. Hariyanto TI, Jodhinata C, Halim DA, Kurniawan A. Association between viral hepatitis and increased risk of severe coronavirus disease 2019 (COVID-19) outcome: a systematic review and meta-analysis. Gastroenterol Hepatol Bed Bench. 2022 Winter;15(1):9–14.
10. Liu Z, Song L, Chen J, Zhou Y, Wang Y, Tang L, et al. Causal associations between chronic hepatitis B and COVID-19 in East Asian populations. Virol J. 2023 Jun 1;20(1):109.
11. Wang J, Lu Z, Jin M, Wang Y, Tian K, Xiao J, et al. Clinical characteristics and risk factors of COVID-19 patients with chronic hepatitis B: a multi-center retrospective cohort study. Front Med. 2022 Feb;16(1):111–125.
12. Woodford J, Sagara I, Diawara H, Assadou MH, Katile A, Attaher O, et al. Recent malaria does not substantially impact COVID-19 antibody response or rates of symptomatic illness in communities with high malaria and COVID-19 transmission in Mali, West Africa. Front Immunol. 2022 Aug 3;13:959697.
13. Arshad AR, Bashir I, Ijaz F, Loh N, Shukla S, Rehman UU, et al. Is COVID-19 Fatality Rate Associated with Malaria Endemicity? Discoveries (Craiova). 2020 Dec 11;8(4):e120.
14. Iesa MAM, Osman MEM, Hassan MA, Dirar AIA, Abuzeid N, Mancuso JJ, et al. SARS-CoV-2 and Plasmodium falciparum common immunodominant regions may explain low COVID-19 incidence in the malaria-endemic belt. New Microbes New Infect. 2020 Nov;38:100817.
15. Habibzadeh F. Malaria and the incidence of COVID-19 in Africa: an ecological study. BMC Infect Dis. 2023 Feb 3;23(1):66.
16. Osei SA, Biney RP, Anning AS, Nortey LN, Ghartey-Kwansah G. Low incidence of COVID-19 case severity and mortality in Africa; Could malaria co-infection provide the missing link? BMC Infect Dis. 2022 Jan 22;22(1):78.
17. Anyanwu MU. The association between malaria prevalence and COVID-19 mortality. BMC Infect Dis. 2021 Sep 19;21(1):975.
18. Raham TF. Influence of malaria endemicity and tuberculosis prevalence on COVID-19 mortality. Public Health. 2021 May;194:33–35.
19. Rathi PM, Mahajan NN, Srivastava V, Junare PR, Bansal S, Kaushal N, et al. Early virus clearance of SARS-CoV-2 among co-infection with malaria. J Vector Borne Dis. 2023 Apr-Jun;60(2):211–214.
20. Lapidus S, Liu F, Casanovas-Massana A, Dai Y, Huck JD, Lucas C, et al. Plasmodium infection is associated with cross-reactive antibodies to carbohydrate epitopes on the SARS-CoV-2 Spike protein. Sci Rep. 2022 Dec 22;12(1): 22175.
21. Aguilar R, Jiménez A, Santano R, Vidal M, Maiga-Ascofare O, Strauss R, et al. Malaria and other infections induce polyreactive antibodies that impact SARS-CoV-2 seropositivity estima-

tions in endemic settings. J Med Virol. 2024 Jun;96(6):e29713.
22. Traoré A, Guindo MA, Konaté D, Traoré B, Diakité SA, Kanté S, et al. Seroreactivity of the Severe Acute Respiratory Syndrome Coronavirus 2 Recombinant S Protein, Receptor-Binding Domain, and Its Receptor-Binding Motif in COVID-19 Patients and Their Cross-Reactivity With Pre-COVID-19 Samples From Malaria-Endemic Areas. Front Immunol. 2022 Apr 27;13:856033.
23. Manning J, Zaidi I, Lon C, Rosas LA, Park JK, Ponce A, et al. SARS-CoV-2 cross-reactivity in prepandemic serum from rural malaria-infected persons. Cambodia. Emerg Infect Dis. 2022; 28:440–444.
24. Reche PA. Potential Cross-Reactive Immunity to SARS-CoV-2 From Common Human Pathogens and Vaccines. Front Immunol. 2020 Oct 16;11:586984.
25. Boschiero MN, Duarte A, Palamim CVC, Alvarez AE, Mauch RM, Marson FAL. Frequency of respiratory pathogens other than SARS-CoV-2 detected during COVID-19 testing. Diagn Microbiol Infect Dis. 2022 Feb;102(2):115576.
26. Chaisawangwong W, Wang H, Kouo T, Salathe SF, Isser A, Bieler JG, et al. Cross-reactivity of SARS-CoV-2- and influenza A-specific T cells in individuals exposed to SARS-CoV-2. JCI Insight. 2022 Sep 22;7(18):e158308.
27. Li ZN, Liu F, Jefferson S, Horner L, Carney P, Johnson MDL, et al. Multiplex Detection of Antibody Landscapes to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/Influenza/Common Human Coronaviruses Following Vaccination or Infection With SARS-CoV-2 and Influenza. Clin Infect Dis. 2022 Oct 3;75(Suppl 2):S271-S284.
28. Bai L, Zhao Y, Dong J, Liang S, Guo M, Liu X, et al. Coinfection with influenza A virus enhances SARS-CoV-2 infectivity. Cell Res. 2021 Apr;31(4):395–403.
29. Tang L, Gu S, Gong Y, Li B, Lu H, Li Q, et al. Clinical Significance of the Correlation between Changes in the Major Intestinal Bacteria Species and COVID-19 Severity. Engineering (Beijing). 2020 Oct;6(10):1178–1184.
30. Chen L, Yin Z, Zhou D, Li X, Yu C, Luo C, et al. Lymphocyte and neutrophil count combined with intestinal bacteria abundance predict the severity of COVID-19. Microbiol Spectr. 2024 Jan 11;12(1):e0302723.
31. Taufer CR, da Silva J, Rampelotto PH. In Silico Analysis of Probiotic Bacteria Changes Across COVID-19 Severity Stages. Microorganisms. 2024 Nov 18;12(11):2353.
32. Cao B, Wang X, Yin W, Gao Z, Xia B. The human microbiota is a beneficial reservoir for SARS-CoV-2 mutations. mBio. 2024 May 8;15(5):e0318723.
33. Polo PG, Çolak-Al B, Sentürk H, Rafiqi AM. Gut bacteria after recovery from COVID-19: a pilot study. Eur Rev Med Pharmacol Sci. 2022 Nov;26(22):8599–8611.
34. Li S, Zhou Y, Yan D, Wan Y. An Update on the Mutual Impact between SARS-CoV-2 Infection and Gut Microbiota. Viruses. 2022 Aug 15;14(8):1774.
35. Mostafa HH, Fissel JA, Fanelli B, Bergman Y, Gniazdowski V, Dadlani M, Carroll KC, Colwell RR, Simner PJ. Metagenomic Next-Generation Sequencing of Nasopharyngeal Specimens Collected from Confirmed and Suspect COVID-19 Patients. mBio. 2020 Nov 20;11(6):e01969–20.
36. Gao M, Wang H, Luo H, Sun Y, Wang L, Ding S, Ren H, Gang J, Rao B, Liu S, Wang X, Gao X, Li M, Zou Y, Liu C, Yuan C, Sun J, Cui G, Ren Z. Characterization of the Human Oropharyngeal Microbiomes in SARS-CoV-2 Infection and Recovery Patients. Adv Sci (Weinh). 2021 Oct;8(20):e2102785.
37. Qin T, Wang Y, Deng J, Xu B, Zhu X, Wang J, et al. Super Dominant Pathobiontic Bacteria in the Nasopharyngeal Microbiota Cause Secondary Bacterial Infection in COVID-19 Patients. Microbiol Spectr. 2022 Jun 29;10(3):e0195621.
38. Soffritti I, D'Accolti M, Fabbri C, Passaro A, Manfredini R, Zuliani G, Libanore M, Franchi M, Contini C, Caselli E. Oral Microbiome Dysbiosis Is Associated With Symptoms Severity and Local Immune/Inflammatory Response in COVID-19 Patients: A Cross-Sectional Study. Front Microbiol. 2021 Jun 23;12: 687513.
39. Gupta A, Bhanushali S, Sanap A, Shekatkar M, Kharat A, Raut C, Bhonde R, Shouche Y, Kheur S, Sharma A. Oral dysbiosis and its linkage with SARS-CoV-2 infection. Microbiol Res. 2022 Aug;261:127055
40. Takahashi Y, Watanabe N, Kamio N, Kobayashi R, Iinuma T, Imai K. Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19. J Oral Sci. 2020 Dec 23;63(1):1–3.
41. Bartolo L, Afroz S, Pan YG, Xu R, Williams L, Lin CF, et al. SARS-CoV-2-specific T cells in unexposed adults display broad trafficking potential and cross-react with commensal antigens. Sci Immunol. 2022 Oct 21;7(76):

eabn3127.
42. Nagai M, Moriyama M, Ichinohe T. Oral Bacteria Combined with an Intranasal Vaccine Protect from Influenza A Virus and SARS-CoV-2 Infection. mBio. 2021 Aug 31;12(4):e0159821.
43. Di Pierro F, Iqtadar S, Mumtaz SU, Bertuccioli A, Recchia M, Zerbinati N, Khan A. Clinical Effects of Streptococcus salivarius K12 in Hospitalized COVID-19 Patients: Results of a Preliminary Study. Microorganisms. 2022 Sep 28;10(10):1926.
44. Andrade BGN, Cuadrat RRC, Tonetti FR, Kitazawa H, Villena J. The role of respiratory microbiota in the protection against viral diseases: respiratory commensal bacteria as next-generation probiotics for COVID-19. Biosci Microbiota Food Health. 2022;41(3):94–102.
45. Chagas ALD, Araújo JCDS, Serra JCP, Araújo KM, Cunha MO, Correia ADR, Gonçalves LMB, Carneiro LC. Co-Infection of SARS-CoV-2 and Klebsiella pneumoniae: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2024 May 30;14(11):1149.
46. Sulaiman I, Chung M, Angel L, Tsay JJ, Wu BG, Yeung ST, et al. Microbial Signatures in the Lower Airways of Mechanically Ventilated COVID-19 Patients Associated With Poor Clinical Outcome. Nat Microbiol (2021) 6(10): 1245–58.
47. Patel J, Sampson V. The role of oral bacteria in COVID-19. Lancet Microbe. 2020 Jul;1(3): e105.
48. Bondareva M, Budzinski L, Durek P, Witkowski M, Angermair S, Ninnemann J, et al. Cross-regulation of antibody responses against the SARS-CoV-2 Spike protein and commensal microbiota via molecular mimicry. Cell Host Microbe. 2023 Nov 8;31(11):1866–1881.e10.
49. Rosas-Salazar C, Kimura KS, Shilts MH, Strickland BA, Freeman MH, Wessinger BC, Gupta V, Brown HM, Rajagopala SV, Turner JH, Das SR. SARS-CoV-2 infection and viral load are associated with the upper respiratory tract microbiome. J Allergy Clin Immunol. 2021 Apr;147(4):1226–1233.e2.
50. Eggenhuizen PJ, Ng BH, Chang J, Cheong RMY, Yellapragada A, Wong WY, et al. Heterologous Immunity Between SARS-CoV-2 and Pathogenic Bacteria. Front Immunol. 2022 Jan 27;13:821595.