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The intestinal microbiota and improving the efficacy of COVID-19 vaccinations

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ABSTRACT

Most COVID-19 cases are mild or asymptomatic and recover well, suggesting that effective immune responses ensue, which successfully eliminate SARS-CoV-2 viruses. However, a small proportion of patients develop severe COVID-19 with pathological immune responses. This indicates that a strong immune system balanced with anti-inflammatory mechanisms is critical for the recovery from SARS-CoV-2 infections. Many vaccines against SARS-CoV-2 have now been developed for eliciting effective immune responses to protect from SARS-CoV-2 infections or reduce the severity of the disease if infected. Although uncommon, serious morbidity and mortality have resulted from both COVID-19 vaccine adverse reactions and lack of efficacy, and further improvement of efficacy and prevention of adverse effects are urgently warranted. Many factors could affect efficacy of these vaccines to achieve optimal immune responses. Dysregulation of the gut microbiota (gut dysbiosis) could be an important risk factor as the gut microbiota is associated with the development and maintenance of an effective immune system response. In this narrative review, we discuss the immune responses to SARS-CoV-2, how COVID-19 vaccines elicit protective immune responses, gut dysbiosis involvement in inefficacy and adverse effects of COVID-19 vaccines and the modulation of the gut microbiota by functional foods to improve COVID-19 vaccine immunisations.

1. Introduction

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections is a huge global medical issue. There are no current and specific anti-viral medicines to combat the infections. The vaccines to prevent spread of the virus has become the most effective approach to stop the further spread of the pandemic. Currently numerous COVID-19 vaccines have been developed or are under development and numerous studies are ongoing (Clinical-Trials-Org, 2020–2021). While most of the vaccines are in preclinical stages, 11 COVID-19 vaccines have been approved for emergent use worldwide (Vasireddy et al., 2021). Generally, the applications of these vaccines have sharply reduced the new cases in countries with high percentages of populations vaccinated such as USA and Isreal. However, improving efficacy and reducing adverse effects of the COVID-19 vaccines are still issues which need to be solved urgently. A small proportion of vaccinated people infected with SARS-CoV-2 virus have developed severe COVID-19 disease (Brazal, 2021; Frenck et al., 2021). In addition, vaccination has caused serious adverse effects (including deaths), which decreases the acceptance of COVID-19 vaccines by many people. Therefore, sufficient understanding of the mechanisms of human immune responses to SARS-CoV-2 infections and factors related to COVID-19 vaccine efficacy and adverse effects are necessary to solve the problems.

SARS-CoV-2 mainly enters through respiratory tract to infect humans but it may also enter through the gastrointestinal tract (Chen, J. et al., 2021). The virus enters cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors. As most human cells express ACE2, the virus can infect numerous organs contributing to inflammation from ACE2 signaling driving multiple organ failure in severe infections (Iwasaki et al., 2021). The consequences of the infections depend on the interactions of viral loads and human immune responses. Adequate immune responses could eliminate the virus, leading to complete recovery from the disease. Pathological immune responses are characterized by hyperinflammation and lymphopenia that causes acute respiratory distress syndrome (ARDS) and multi-organ failure, leading

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to death. Most COVID-19 cases are asymptomatic or mild, indicating sufficient immune responses for elimination of the virus. COVID-19 vaccines are designed to elicit strong and balanced immune responses to prevent SARS-CoV-2 infections or reduce the severity of the disease if still infected. Most vaccines produce antibodies against receptor binding domain (RBD) of the spike protein of the virus to prevent the virus from entering human cells. The efficacy of some vaccines such as those from Moderna and Pfizer can reach 95% with minor side-effects in most circumstances while others have reached 50–80% efficacy. The COVID-19 vaccines may become less effective in people with advanced age or underlying chronic diseases. New variants of SARS-CoV-2 may reduce vaccine efficacy (Kumar, A. et al., 2021; Xie et al., 2021; Zou et al., 2021). Therefore, it is important to study the factors that cause COVID-19 vaccine inefficacy and the adverse-effects that can develop.

In this narrative review, we summize human beneficial immune responses to the SARS-CoV-2 virus infections and immune responses to COVID-19 vaccines. We disscuss the aging intestinal microbiome and mucosal immunity, the effects of gut dysbiosis on vaccination for COVID-19, and modulation of the gut microbiota for improving the efficacy and the prevention of adverse effects from the vaccines.

2. Immunity and intestinal bacteria

The composition of the intestinal microbiome and its physiological functions have close links to host health, metabolic diseases as well as aging (Turroni et al., 2009). The intestinal microbiota is well-known to be associated with the development of immune cells and maintenance of adequate immune responses (Lynn et al., 2021; Vitetta et al., 2017). An important distinghuishing feature of the aging intestines is the overexpression of pro-inflammatory activity such as cytokine IL-6 which has an adverse effect on the function of the intestinal barrier and the mucosal immune system (Man et al., 2015). Immune decline is characteristic of advancing age (i.e., immunosenescence), and as such the immune system is subject to significant remodelling (Jiang et al., 2013; Weiskopf et al., 2009) with consequent deleterious outcomes to health and survival.

Intestinal dysbiosis has been linked to immunological disequilibrium (Baradaran Ghavami et al., 2021). The immunological disequilibrium has often been described as a T-helper 2 (Th_2) hyperactivity and T_{reg} deficiency (Baradaran Ghavami et al., 2021; Mezouar et al., 2018). The involvement of the intestinal microbiota and immune related outcomes has been recently reviewed (Zheng et al., 2020) and specific effects that the intestinal microbiota induces on end-organs such as the lungs and the liver are presented in Table 1.

Experimental and clinical epidemiological studies (Yu et al., 2016) highlight the importance of a pivotal cross-talk between the the intestine and lung that generates a gut-lung axis that progresses homeostasis (Dang and Marsland, 2019). The gut microbiome therefore can be seen as a functional mediator of lung health or disease. Adverse changes in the intestinal microbiome (i.e., dysbiosis) through injudicious dietary practices and obesity, the adminitration of antibiotics and disease processes (e.g., T2D) can disrupt the inflammatory tone of the gut skewed toward proinflammatory immune responses (see Table 2).

The lung microbiome has been recently reviewd (Yagi et al., 2021). Suffice in brief to add herewith that independent molecular techniques have reported that a diverse and low abundance of micro-organisms coexist in the lungs and associated airways. This given the constant exposure of the lungs to the external environment. In the lower airways of healthy individuals studies have reported the diverse presence albeit in low abundance of bacteria from the Streptococcus, Prevotella and Veillonella groups (Dickson et al., 2016; Hilty et al., 2010; Mathieu et al., 2018; Pattaroni et al., 2018; Yu et al., 2016). In lung disease states studies that have compared the lung microbiome in health and disease have reported significant differences

in composition (Philley et al., 2019; Yagi et al., 2021). Lung disese has been associated with the loss of bacterial diversity with the

Table 1
Laboratory animal studies: effects induced by the intestinal microbiota on end-organ immunity outcomes.

Intestinal microbiota…	Immune related outcome
…immune axis with the lungs	
SCFAs Prebiotics → SCFAs (i.e., butyrate)	↑ myeloid cells | shape beneficial immunity of the lung (Trompette et al., 2018)
C. orbiscindens → Desaminotyrosine	↑ Type I IFN signaling | influenza protection (Steed et al., 2017)
Pseudomonas Lactobacilli PneumotypeSPT	↑ Th_{17} type response | regulation basal inflammatory tone (Larsen et al., 2015; Segal et al., 2016; Yadava et al., 2016)
…immune axis with the liver	
LPS	TLR4 signaling → hepatic stellate cell induction → fibrosis (Ma et al., 2018; Paik et al., 2003)
MAMP	Kupffer cells | critical components of innate immunity (Corbitt et al., 2013)
Probiotics	NKT cells | antitumor immunosurveillance (Ma et al., 2018; Wang, X. et al., 2021)
Prebiotics → SCFAs (i.e., butyrate)	↑ Bacterial metabolites (e.g., butyrate) | anti-inflammatory (Golonka and Vijay-Kumar, 2021)
K. pneumoniae – translocated pathogen	↑ Th_{17} type responses | responses induced in the liver (Nakamoto et al., 2019)
…immune axis with the brain	
SCFAs (acetate | propionate | butyrate)	Microglial homeostasis | contribution by the microbiota metabolite signaling (Cryan and Dinan, 2015; Erny et al., 2015) ↑ T_{reg} cells | counter-regulate autoimmunity in the CNS (Bhutia and Ganapathy, 2015; Haghikia et al., 2015)

SCFAs = short chain fatty acids; LPS = Lipopolysaccharides; MAMP = Microbe Associated Molecular Patterns; *Clostridium orbiscindens Klebsiella pneumoniae;* CNS = Central Nervous System.

Table 2
Clinical trials on gut microbiota and COVID-19 vaccination efficacy (Clinicaltrials.gov).

NCT#*	Title	Intervention	Main aims	Location
04980560	Gut microbiota profile and its impact on immunity status in COVID-19 vaccinated cohorts	An observation study	Compare microbiome profile in subjects with different COVID-19 vaccination and subjects recovered from COVID-19	Prince of Wales Hospital, Hong Kong
04884776	Modulation of gut microbiota to enhance health and immunity	3 Bifidobacteria at 2×10^{10} CFU for 12 weeks	Restore gut microbiota to increase COVID-19 vaccine efficacy and reduce side-effects	Prince of Wales Hospital, Hong Kong
04798677	Efficacy and tolerability of ABBC1 in volunteers receiving the influenza or COVID-19 vaccine	ABBC1 including beta-glucans, Inactivated saccharomyces cerevisae, Selenium, and Zinc	Enhance immune responses including generation of T cells, IgM and IgG	Hospital Mare de Déu de la Merc, Spain

*NCT# is the National Clinical Trial Number.

dominance of one taxon or a small group of taxa (Tunney et al., 2013).

A microbiota fecal analysis cross sectional study with participants from different age groups, reported that age-related profiles in the intestinal microbiota presented changes in composition and diversity with advancing age (Claesson et al., 2011). Core microbiota families *Bifidobacteriaceae, Bacteroidaceae, Ruminococcaceae*, and *Lachnospiraceae* become less abundant in the older age groups (Biagi et al., 2016; Claesson et al., 2011; Rampelli et al., 2020; Wu et al., 2019). Vaccines continue to be the most effective means for preventing infectious diseases (de Jong et al., 2020). Plausible suggestions synthesized from murine studies and causal reports point to the impact of the microbiome on human immunity (de Jong et al., 2020). Yet, while there is a exponential growth in discussions of a connection between the intestinal microbiota as a whole and the immune system, the impact of the microbiota on immunity to vaccinations remains poorly understood. *In vitro* and *in vivo* experimentation models have reported that the genus *Bifidobacterium* with species such as *B. adolescentis*, was effective in decreasing the binding of a Norovirus to Caco-2 cells and HT-29 cells (Li et al., 2016) and Coxsackievirus B3 to HeLa cells (Kim et al., 2014). Tan and colleagues (Tan et al., 2016) demonstrated that in the intestines of germ-free mice, *B. adolescentis* induced a robust Th17 response without any adverse effects on gut inflammation. Furthermore, in low chronic inflammation animal models of intestinal diseases, Phillip and colleagues (Philippe et al., 2011) reported that *B. bifidum* and *B. animalis* strains restored immune markers and intestinal epithelial barrier integrity. *B. longum* CECT 7347 attenuated inflammatory cytokine production with a concomitant $CD4^+$ T cell-mediated immune response in the gut of a gliadin-induced enteropathy animal model (Laparra et al., 2012). Studies from more than a decade ago have supported the posit that the genus *Bifidobacterium* can exert beneficial outomes to the health of the host through immunomodulatory actions. In particular a recent review (c.f. Ruiz et al., 2017) has comprehensively reported on numerous animal and human studies supporting evidence that the genus *Bifidobacterium* within the phylum Actinobacteria exhibits significant immunomodulatory effects. Moreover, members of the genus *Bifidobacterium* are early colonizers of the neonate intestine and as such this genus is very much pronounced in infants during the lactation years (Milani et al., 2017).

The elderly have a significantly increased susceptibility to infections. Early clinical investigations have reported that probiotic bacteria from the genus *Bifidobacterium* can enhance certain aspects of cellular immunity in the elderly (Chiang et al., 2000; Gill et al., 2001). A systematic review (Miller et al., 2017) that evaluated clinical evidence from an albeit small study, concluded that *Bifidobacterium animalis* ssp. *lactis* HN019 enhanced natural killer (NK) cell and polymorphonuclear cell functionalities in healthy elderly adults.

Furthermore, it has been recently reported that aging in long-term surviviors can lead to a rearrangement of bacterial species co-occurrence networks that presented a feature of increased abundances of subdominant species (Rampelli et al., 2020). This observation correlated with intestinal bacterial enrichment and an increased abundance of bacterial health-associated species from such bacterial orders Verrucomicrobiales (i.e., *Akkermansia*), *Bifidobacteriales,* and *Christensenellaceae*. At the species level, the contributions from specific bacteria included *Bifidobacterium adolescentis, Bifidobacterium longum, Bacteroides uniformis, Faecalibacterium prausnitzii, Ruminococcus bromii, Subdoligranulum* sp.*, Anaerostipes hadrus, Blautia obeum, Ruminococcus torques, Coprococcus catus, Coprococcus comes, Dorea longicatena,* and *Roseburia* sp., were reported to be associated with improved intestinal health (Rampelli et al., 2020).

3. Immune responses to Sars-Cov-2 infections

Most patients infected by SARS-CoV-2 virus experience asymptomatic or mild disease manifestations. The immune reactions in these patients were efficacious with an adaptive immune response. Adaptive immune outcomes were indicative of immune system recognition with an appropriate response that effectively eliminated the viruses and enabled the patients to recover from the disease (Chen, J. et al., 2021; Maecker, 2021).

The initial characterization of such an adequate immune response were from a case study which showed the course of immune responses and the recovery from SARS-CoV-2 infections (Thevarajan et al., 2020). In a female patient diagnosed with mild to moderate COVID-19, both strong humoral and cellular immune responses were found in the early stages of SARS-CoV-2 infections. The specific IgG and IgM antibodies against the virus were produced at the early stage (day 7 and day 9 of symptom onset), which were concomitant with increased antibody secreting cells (day 7) and circulating T follicle helper cells (day 7) (Thevarajan et al., 2020). Cytotoxic $CD8^+$ T cells increased at day 7, reaching to the highest level at day 9 and decreased at day 20 with increased granzyme A, granzyme B and perforin (Thevarajan et al., 2020). The blood levels of $CD16^+CD14^+$ monocytes were lower than that of healthy donors, indicating homing of these cells to infection sites. No differences in NK cells were found in the blood samples from the patient and healthy patients. Slightly increased proinflammatory cytokines and chemokines were found, suggesting no cytokine storm was formed in this patient.

The following studies have further presented a wider picture of immune responses to SARS-CoV-2 infections, which involved both innate and adative immune responses (Fig. 1). The important roles of innate immunity in COVID-19 are demonstrated. Most importantly, temporal interferon I (IFN I) production, which inhibits viral replication and orchestrates proinflammatory responses, is associated with mild COVID-19 and delayed low IFN I production causes robust viral replication and severe disease (Zhou, Z. et al., 2020). Persistent/excessive IFN I and excessive inflammatory cytokine levels cause multiple tissue damage and can also cause severe disease.

Innate immune cells can prevent viral invasion. Dendritic cells (DC) and macrophages secrete appropriate amounts of IFN I as well as proinflammatory cytokines (IL-6, TNF-alpha and IL-1beta) and chemokines (CCL2 and CCL7) to exert protective effects (Zhou, R. et al., 2020). These cells also present antigens to adaptive immune cells. But over response with a cytokine storm is pathological, resulting in severe COVID-19. NK cells can secrete granzyme B and perforin to eliminate viral-infected cells to reduce viral replication (Zuo and Zhao, 2021). Neutrophils are quickly recruited to infectious sites by chemotactic factors from infected epithelial cells. Neutrophils can limit pathogenesis by phagocytosis, releasing anti-microbial molecules and forming neutrophil extracellular traps (Laforge et al., 2020). But activated neutrophils can produce reactive oxygen species, proteases and neutrophil extracellular traps, which if excessive can cause tissue damage (Kang et al., 2021). Adequate innate immune responses provide first line fast protection from SARS-CoV-2 infections. The failure of innate immune responses can cause increased viral loads and hyperinflammation, leading to severe disease. For example, decreased DCs are associated with severe COVID-19.

Antigen-specific adaptive immune responses including humoral and cellular responses are activated by antigen presentation through macrophages and DCs. The important role of antibodies in containing SARS-CoV-2 infections has been highlighted (Leslie, 2020). Another study showed that neutralizing antibody levels were associated with protection capabilities (Khoury et al., 2021). It was sufficient to protect the host from infection and severe COVID-19 if the levels of neutralizing antibodies reached 20.2% and 3% of the convelescent mean value respectively. Mantus et al. (2021) characterized the humoral responses in hospitalized COVID-19 patients and found the antibodies produced included anti-RBD, anti-full-length-spike, anti-nucleoprotein with high levels of IgG against RBD being associated with major virus neutralization (Mantus et al., 2021). Sterlin et al. (2021) found IgA was robustly secreted in early stage infections and that the IgA antibody neutralised SARS-CoV-2 virus more robustly than did IgG and IgM (Sterlin et al.,

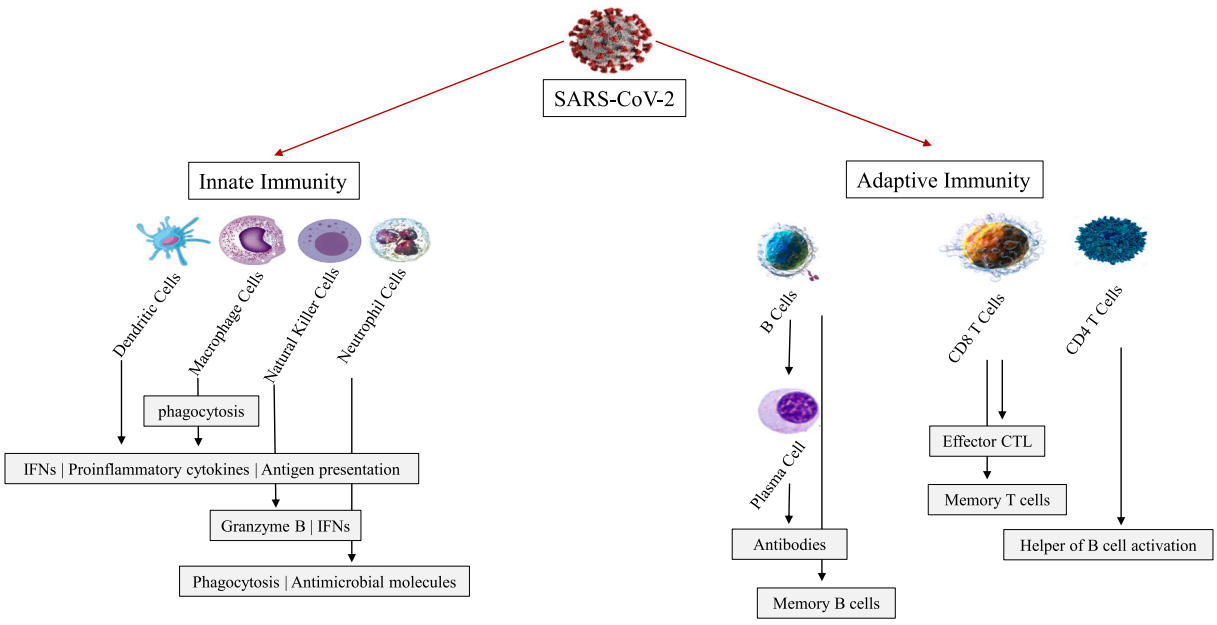

Fig. 1. Natural immune responses to SARS-CoV-2. SARS-CoV-2 infections elicit both innate and adaptive immune responses. Activation of innate immune cells including DCs, Macrophages, NKs and neutrophils results in secretion of IFNs, proinflammatory cytokines granzymes, antimicrobial molecules and phagocytosis to contain the virus. DCs and macrophages also present antigens to adaptive immune cells to elicit humoral and cellular immune responses. Antibodies produced can neutralize the virus and cytotoxic $CD8^+$ T-cells can eliminate virus-infected cells. Memory B cells and memory T cells are produced which provide rapid responses with subsequent infections of the virus.

2021).

A model of T cell responses in COVID-19 has been proposed. In mild forms of the disease, IL-2, type I and type III interferon promotes clonal expansion of activated T cells, which become effector T cells, terminally differentiated T cells or memory T cells (Chen and John Wherry, 2020). Consistently, Liao et al (2020) found highly clonally expanded CD8 + T cells in moderate cases of the disease (Liao et al., 2020). In severe disease, IL-6, IL-10, CXCL proteins (such as CXCL8) and TNF-alpha may reduce the T cell pool and number of activated T cells and lead to exhausted or terminally differentiated T cells (Chen and John Wherry, 2020). This can also be supported by recent findings that PD-L1/PD-1 axis were increased, which could result in T cell exhaustion (Chen, J. and Vitetta, L., 2021; Vitte et al., 2020). Therefore, T cell responses are also critical in combating SARS-CoV-2 infections.

Convalescent immune profiles of recovered COVID-19 patients have revealed various protective effects to subsequent SARS-CoV-2 infections. Immune responses to endemic coronavirus infections have been shown to be unable to protect hosts from subsequent infections but able to reduce disease severity (Tan et al., 2021). Similarly, convalescent immune responses from asymptomatic or mild SARS-CoV-2 infections are not able to elicit strong immunity against subsequent infections (Sui et al., 2021). Moderate and severe COVID-19 infections resulted in the ability to elicit strong humoral and cellular immune responses, which could protect the hosts from subsequent infections (Yan et al., 2020; Zhang, J. et al., 2021). Zhang et al. (2021) showed that there were high titers of anti-S1 and anti-S2 antibodies in convalescent sera in severe COVID-19 compared with non-severe COVID-19 (Zhang, J. et al., 2021). Antigen-specific $CD4^+$ T-cells particularly subset of $CXCR3^+$ were correlated with antibody titers. These cells also secreted IL-21 and IFN-gamma. The duration of convalescent antibodies has also been questioned. It has been shown that IgG and IgA begin to decline after 6 to 10 weeks following the onset of symptoms and the neutralizing ability of the antibodies decreases after a few weeks (Beaudoin-Bussières et al., 2020). Memory B cells and T cells may exert protective effects for longer periods even after mild COVID-19 infections (Gaebler et al., 2021; Rodda et al., 2021). These cells will allow rapid expansion of antigen-specific T cells and B-cells as well as rapid production of antibodies when encounting second infections (Cox and Brokstad, 2020; Sokal et al., 2021; Tavukcuoglu et al., 2021).

How immune responses to SARS-CoV-2 become pathological has been an important topic of enquiry. This could be related to chronic inflammatory status and decreased anti-inflammatory mechansisms (Chen, J. et al., 2021). Gut dysbiosis is closely associated with such a status, which facilitates the formation of hyperinflammation. In severe COVID-19, pro-inflammatory macrophages are abundant (Grau and Félez, 1987). Hyperinflammation could activate PD-L1, leading to $CD8^+$ T-cell exhaustion, which delays the elimination of the virus (Chen, J. and Vitetta, L., 2021). Similarly, gut dysbiosis could disturb the appropriate immune responses elicited from vaccinations, which will be discussed in a later section in greater detail.

In summary, the innate and adaptive immune responses provide first line and second line protection to SARS-CoV-2 infections. Adequate responses could eliminate invading viruses, leading to the recovery from the disease. However, insufficient responses such as delayed type I IFN secretion with rapid replication of the viruses or over-responsive immunity with hyperinflammation can result in severe disease and fatality. The various convalescent immune profiles in preventing reinfections have been studied with short-term protection by antibodies and long-term by memory B cells and memory T cells.

4. Intestinal dysbiosis-caused inefficacy of vaccines and mechanisms

Various COVID-19 vaccines have been developed to initiate proper immune responses to defend from SARS-CoV-2 infections. However, the risk factors that interfere with immune responses to SARS-CoV-2 could also reduce the efficacy of COVID-19 vaccines. Gut dysbiosis has been associated with the severity of COVID-19 caused by many risk factors (Chen, J. et al., 2021). Indeed, the roles of the gut microbiota in immune responses to vaccination against viruses other than SARS-CoV-2 have been well demonstrated in both animal experiments and clinical studies (Lynn et al., 2021; Vitetta et al., 2017). In animal models, germ-free (GF) mice or antibiotics-treated mice had decreased immune responses in various aspects. Kim et al. (2016) showed that the immune responses to

intranasal cholera toxin mucosal vaccination were reduced in GF or antibiotics-treated mice including reduction in B cell numbers, antigen-specific IgG, recall-stimulated cytokine responses and follicular helper T cell responses (Kim et al., 2016; Kim et al., 2019). Ichinohe et al. (2011) revealed that combination treatment of mice with a mix of antibiotics including vancomycin, neomycin, metronidazole and ampicillin reduced immune responses to respiratory influenza virus infection (Ichinohe et al., 2011). Both $CD4^+$ T-cells, $CD8^+$ T-cells and virus-specific antibody titers were decreased while viral titers in the lung was increased. In an LCMV (lymphocytic choriomeningitis virus) mouse model, Abt et al. (2012) demonstrated that antibiotic-treated mice had delayed virus clearance with decreased $CD8^+$ T-cell and LCMV-specific IgG production (Abt et al., 2012). The study also showed that macrophages had also decreased responses to type I and type II IFNs and impaired capacity to limit virus replication. These animal experiments indicate that gut commensal bacteria are necessary for effective immune responses to defend from viral infections. Indeed, *Bifidobacterum longum* subsp. *infantis* has been correlated with antigen-specific T cell responses in vaccines for tuberculosis, polio virus and tetanus toxin (Huda et al., 2014). Furthermore, dysbiosis caused by deficient protein diets also resulted in reduced immune responses to oral attenuated human rotavirus vaccination such as decreased cell number of antibody secreting cells, $CD4^+$ T cells, $CD8^+$ T cells and Tregs as well as decreased cytokine production (Kim et al., 2020; Michael et al., 2020; Miyazaki et al., 2018).

In humans, the roles of the gut microbiota in vaccine efficacy have been evidenced by various approaches. The same vaccines elicited different responses in lower middle income countries (LMICs) and high income countries (HICs) and the low efficacy in LMICs was accounted for by gut dysbiosis in the populations (Lynn et al., 2021). Gut dysbiosis in infants with short-term breast-feeding, malnutrition and diarrhea was linked with the lower efficacy of oral polio vaccines (Haque et al., 2014). Gut dysbiosis was also associated with the effect of pre-vaccination immune status on vaccine efficacy. The immune responses to vaccination has been associated with immune status before vaccination. For example, influenza vaccine efficacy was only 30–50% in a population older than 65 years compared to 70–90% in younger adults (Osterholm et al., 2012). In elderly RSV (respiratory syncytial virus) vaccine non-responders, there were baseline immune profiles with higher ($HLA\text{-}DR^+$) $CD4^+$ and $CD8^+$ T cells and increased expression of CCR7, CD127 and CD69, indicating a chronic inflammatory status (Lingblom et al., 2018). Fourati et al. (2016) found that pre-vaccination inflammation was associated with hyporesponse to HepB vaccination (Fourati et al., 2016). These could be explained by gut dysbiosis-caused chronic inflammation that causes decreased immune responses to vaccination.

The mechanisms for the roles of gut microbiota in vaccine efficacy have been attributed to pattern recognition receptors (PRRs) of antigen presenting cells activated by gut bacterial molecules such as flagellin and peptidoglycan (Lynn et al., 2021). PRRs are abundant in innate immune cells, which will respond to stimuli rapidly once activated by gut bacterial molecules (i.e., termedimmune training) (Smith et al., 1988; Yakabe et al., 2021). Binding of the PRR, Nucleotide-binding oligomerization domain-containing protein 2 (Nod2), by peptidoglycans increased cAMP production, which promotes DCs to secrete cytokines (Kim et al., 2016; Kim et al., 2019). Activation of Nod2 with synthetic agonists reconstituted cholera toxin-caused immune responses in GF or antibiotic-treated mice, indicating the critical role of Nod-2 in gut microbiota-stimuated immune responses (Kim et al., 2016; Kim et al., 2019). It was reported that Nod2 stimulation by symbiotic/commensal bacteria contributed to the optimal CT-mediated antigen-specific oral vaccination efficacy and that this was meditated through the induction and subsequent increased levels of IL-1β. Toll-like receptor 5 (TLR5) requires activation by flagllin for plasma cell development and antibody production (Oh et al., 2014; Pabst and Hornef, 2014). TGF-β can be stimulated by clusters IV and XIVa clostridia to activate regulatory T cells (Treg cells), which are important for maintaining in equillibrium immune responses (Atarashi et al., 2011). In contrast, gut dysbiosis causes chronic inflammation and reduced anti-inflammatory mechanisms through altered commensal bacterial metabolites such as butyrate (Chen, J. et al., 2021). Butyrate is well-known to activate regulatory T cells to exert anti-inflammatory effects (Chen and Vitetta, 2018; Furusawa et al., 2013). In a mouse model, butyrate facilitated IgA production in the colon through activation of GPR41 and GPR109a, and inhibition of histone deacetylases (Isobe et al., 2020). Butyrate is also important in maintaining the integrity of the gut barrier. Decreased butyrate production results in the translocation of endotoxin and bacteria into the circulation system and extra-intestinal organs, facilitating the formation of hyperinflammation caused by SARS-CoV-2 that cause direct tissue damage (Chen, J. et al., 2021). Intestinal microbial dysbiosis that can disrupt immune responses through hyperresponses and inflammation could possibly disturb immune response elicited by COVID-19 vaccinations and thus affect COVID-19 vaccine efficacy (Ferreira et al., 2020a, 2020b).

5. Intestinal dysbiosis linking risk factors to inefficacy of COVID-19 vaccines

Based on the effects that the gut microbiota has on the efficacy of vaccines against various microbes and the role of dysbiosis in the severity of COVID-19, it is not surprising that the gut microbiota may be critical for the efficacy of COVID-19 vaccinations (Ferreira et al., 2020a; Stefan et al., 2021) and that gut dysbiosis could reduce COVID-19 vaccine efficacy (Lynn et al., 2021). It has been proposed that the vulnerable population that presents with severe COVID-19 and high mortality should be vaccinated with priority (Leong et al., 2021; Russo et al., 2021; Wingert et al., 2021). The vulnerable population is characterized by advanced age, underlying chronic diseases (such as obesity, diabetes, chronic cardiovascular, pulmonary, liver and kidney diseases) and psychiatric disorders (such as stress, anxiety and depression) (Chen, J. et al., 2021; Koff et al., 2021; Stefan et al., 2021). Gut dysbiosis is one of the mechanisms by which these risk factors cause a pathological immune response. Risk factors that reduce defences againts SARS-CoV-2 infections could also reduce their responses to COVID-19 vaccines and increase adverse effects. A recent study showed that aging, obesity and hypertension markedly reduced the efficacy of the Pfizer/BioNTech vaccine (Koff et al., 2021; Pellini R et al., 2021; Stefan et al., 2021).

The efficacy and adverse effects in aged people, particularly those with underlying diseases have been a critical issue for COVID-19 vaccinations (Connors et al., 2021; Soiza et al., 2021). Indeed, aging has been considered to be the most important risk factor for severe COVID-19 infections (Wingert et al., 2021). Aging is associated with chronic inflammation and reduced immune responses. These changes could be caused by the aging gut microbiota, which causes both immunosenesence and inflammaging (Bosco and Noti, 2021; Connors et al., 2021). Studies have shown that aging populations respond to vaccinations poorly (Bosco and Noti, 2021). A meta-analysis showed that vaccines were unable to evoke optimal antibody responses in older adults although vaccines could reduce hospitalization and mortality rates (Almasri and Holtzclaw, 2021). Importantly biological aging indicated by a frailty index is more correlated with an associated gut dysbiosis change than chronological aging (Kim and Jazwinski, 2018; Maffei et al., 2017). Muller et al. (2021) compared the immune responses to the Pfizer vaccine in two groups of patients less than 60 years and more than 80 years of age (Müller et al., 2021). The latter had significantly lower antibody titers. Even after second doses, no neutralizing antibodies were detected in the older age group in 31.3% and only 2.2% in the younger group (Müller et al., 2021). It was hence suggested to promote earlier revaccinations or increased vaccine doses. However, a recent clinical trial reported that Astrazeneca is well tolerated in the older aged population and produced similar immunogenicity results (Ramasamy et al., 2021). A systemic review showed that the older aged population were usually excluded in most clinical trials of COVID-19 vaccines, leading to

insufficient data to analyse vaccine efficacy (Hou et al., 2021). The involvement of gut dysbiosis in inefficacy of COVID-19 in the older age groups warrants extensive studies. Modulation of the gut microbiota may comprise a better approach at increasing COVID-19 efficacy.

Malnutrition such as a deficiency of proteins has been demonstrated to reduce antibody secreting cells, leading to decreased IgA and IgG production in rotavirus infections in animal models (Michael et al., 2020; Miyazaki et al., 2018). This may suggest that nutritional status could be important in COVID-19 vaccine efficacy. Indeed, nutraceuticals such as vitamin C, vitamin D, lactoferrin, omega-3 fatty acids and trace elements such as zinc, selenium and magnesium can improve the gut microbiota and reduce COVID-19 severity (Chen, J. and Vitetta, L., 2021). Deficiency of these components causes severe COVID-19.

Obesity is also a major concern for reduced efficacy in COVID-19 vaccinations (Kipshidze et al., 2021; Ledford, 2020; Townsend et al., 2021). Although it has been shown that under-weight and normal weight patients have much high efficacy in antibody titers than over-weight and obese patients, other immune responses could be further investigated (Pellini R et al., 2021). Obesity, characterized by chronic inflammation, is a risk factor for severe COVID-19 and gut dysbiosis is one of the mechanisms that results in ineffective immune responses (Chen, J. et al., 2021). How gut dysbiosis is involved in the inefficacy of COVID-19 vaccination warrants further dedicated studies. It has also been reported that humoral immune responses in kidney or liver transplantation patients, which usually are excluded in clinical trails, were reduced (Marjot et al., 2021; Mossad, 2021; Sui et al., 2021). A recent study reported that as much as 61% of liver transplantation patients and 24% of other chronic liver diseases had poor antibody responses to COVID-19 vaccinations (Thuluvath et al., 2021). The low immunogenicity of COVID-19 vaccine in liver transplantation were associated with factors of age, renal function and immunosuppressive medications (Rabinowich et al., 2021). In contrast, a study demonstrated that NAFLD did not affect the efficacy of a COVID-19 vaccines (Wang, J. et al., 2021). It may be necessary to distinguish mild and severe liver diseases on vaccine efficacy (Cornberg and Eberhardt, 2021). A study reported that chronic kidney disease was associated with decreased vaccine efficacy (Hou et al., 2021) due to the uremic milieu-vitamin D deficiency- and insufficient erythropoitin-caused antigen presenting cell dysfunction and reduced B cell numbers. Both a uremic milieu and vitamin D deficiency are known to cause gut dysbiosis (Chaves et al., 2018; Chen, J. et al., 2021).

Gender differences in COVID-19 severity has been well demonstrated, an outcome that is due to the difference in immune responses elicited (Alwani et al., 2021; Mateus et al., 2021). These immune responses could also underpin differences in COVID-19 vaccine efficacy. Sex steroids are known to regulate the gut microbiota (Manosso et al., 2021; So and Savidge, 2021) and thus could mediate vaccine efficacy through the gut microbiota. As such studies are warranted that would investigate the role of the gut microbiota in gender differences in COVID-19 vaccine efficacy.

6. Efficacy of COVID-19 vaccines

Currently numerous COVID-19 vaccines have been developed, including live-attenuated virus vaccines, inactivated virus vaccines, protein subunit vaccines, replication-deficient vectors and genetic vaccines (DNA and RNA vaccines) (Min and Sun, 2021). Currently at least more than 10 COVID-19 vaccines have been approved for emergency use worldwide. These vaccines have been shown to elicit immune responses against SARS-CoV-2 with various levels of efficacy from clinical trials. Three USA vaccines (Pfizer/BioNTech, Moderna and Johnson and Johnson) and one UK vaccine (Astrazenica) have been used extensively in Western countries.

6.1. mRNA vaccines

mRNA vaccines are the most successful vaccines. mRNAs were designed to encode viral proteins, which are then translated into antigen proteins to elicit immune responses. Pfizer-BioNtech mRNA vaccine encodes RBD of the S protein while Moderna vaccine encodes the S-2P antigen (Noor, 2021). Nanotechnology has been applied for the delivery of mRNAs to prevent quick degradation in human bodies. Lipid nanoparticles (LNP) are employed to formulate both mRNA vaccines. The route of mRNA vaccines to produce immune responses are shown in Fig. 2 (Kowalczyk et al., 2016). After the vaccine particles are engulfed (i.e., phagocytosis) by dendritic cells, mRNAs are released into the cytosol, where mRNAs are translated into antigen proteins. The antigens are bound to MHC I in the endoplasmic reticulum and presented to the cell surface, which activate B-cells produce antigen-specific antibodies and activate $CD8^+$ T cells into antigen-specific cytotoxic T cells in draining lymph nodes (Kowalczyk et al., 2016). The released mRNAs in the circulation can also activate the innate immune system through recognization by TLRs 3,7,8 and RIG-I (retinoic acid-inducible gene), leading to increased production of INF I and stimulation of Th1cells (Cagigi and Loré, 2021). LNPs in the formulae can also elicit immune responses through TLR pathways (Chung et al., 2020). Both mRNA vaccines reach very high rates of efficacy with Moderna being 94.1% and Pfizer/BioNTech 95.0% in clinical trials (Baden et al., 2021; Polack et al., 2020). These clinical trials have excluded immunosuppressed individuals, who are likely to have lower response rates to the vaccines. For example, the use of ocrelizumab, an anti- B cell CD20 antibody and fingolimod, an immune-modulator that sequesters lymphocytes decreased Pfizer/BioNTech humoral immune response efficacy rates to 22.7% and 3.8% respectively (Achiron et al., 2021).

6.2. Adenovirus-based vaccines

Adenovirus-based vaccines express SARS-CoV-2 antigens from transgenes in an adenoviral backbone using a strong adenoviral promoter. Astrazenica-Oxford vaccine (AZD1222) employs a chimpanzee adenovirus developed by Oxford University (chAdOx1), which enter but do not replicate in human cells (Derikvand et al., 2020). The AZD1222 transgene is the spike protein from SARS-CoV-2. The following phase II/III trial confirmed previous results with efficacy of 70.4% (Ramasamy et al., 2021; Voysey et al., 2021). Jansen Pharmaceuticals vaccine (Johnson and Johnson) produced Ad26.COV2.S, which only needs one dose immunization. The vector is the replication-incompetent adenovirus 26 and the transgene is the full length SARS-CoV-2 spike protein (Bos et al., 2020). A single dose immunization has been shown to elicit robust immune responses with antigen-specific antibodies sufficient to protect from SARS-CoV-2 infections with overall efficacy of 66.3% (Mercado et al., 2020; Sadoff et al., 2021). Sputnik V developed in Russia has been made from two adenovirus types, 26 and 5, to carry cDNA encoding for the spike protein of COVID-19 (Logunov et al., 2020). Phase I/II clinicals showed it safety and tolerability; the vaccine produced 100% of antibody and cellular immune responses and 91.6% efficacy (Logunov et al., 2021; Logunov et al., 2020). Sputnik has been now used in many countries worldwide. Ad5-nCoV (Convidecia) from CanSino Biologicals (Wu et al., 2020) have been approved by some countries including China, Hungary, Chile, Mexico and Pakistan for emergent use; but not yet by WHO. A clinical trial (PhaseI/II) showed that it is safe and efficacious (Zhu et al., 2020a; Zhu et al., 2020b).

Animal models have been used to test the immunogenicity of adenovirus-based vaccines. In a recent adult rhesus macaques experiment, both $1x10^{11}$ Ad26.COV2.S viral particles (vp) and $5x10^{10}$ vp produced robust immune responses at week two, which further increased at week four. The higher dosage vp immunization had 1.6-fold higher binding and 2.1-fold higher neutralization antibodies than that of the lower dosage (Solforosi et al., 2021). In both cases, binding antibodies declined more rapdly than neutralizing antibodies. A second dose

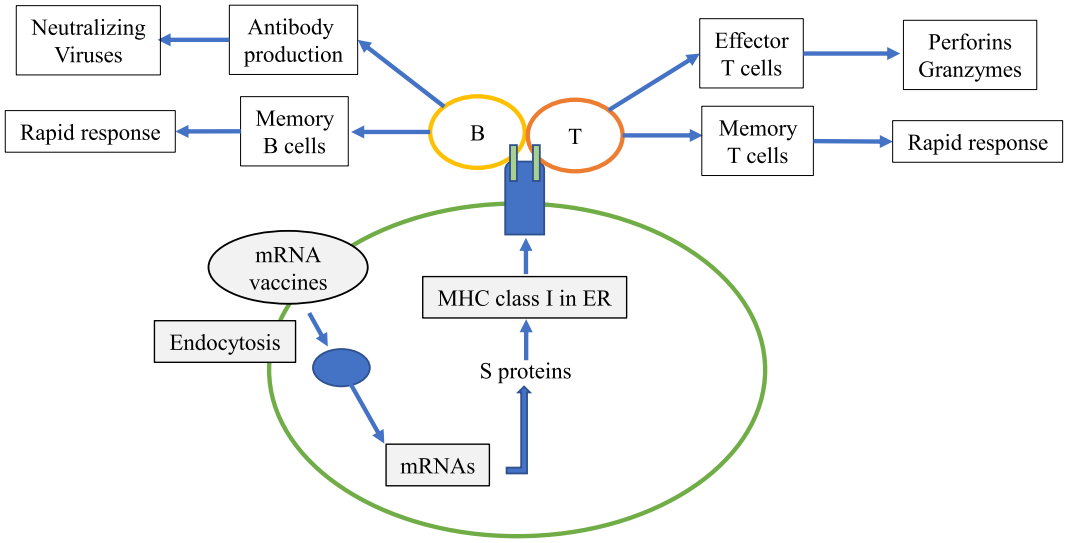

Fig. 2. Immune responses to COVID-19 mRNA vaccines. mRNA vaccines enter into antigen-presenting cells through endocytosis. mRNAs are released into cytoplasm and translated into S proteins. S proteins bind to MHC class I in ER and are presented by MHC class I to the cell surface. The antigens then activate B cells to produce antigen-specific antibodies and memory B cells and T cells to produce effector T cells and memory T cells.

immunization given 4 or 8 weeks later increased binding antibodies by 5.7- and 11.8 fold, respectively, and neutralizing antibodies by 7.6- and 15.2 fold, respectively; measured 2 weeks after the second dose (Solforosi et al., 2021). The immune reponses were also sufficient to protect most aged rhesus macaques although the protection ability may be weakened.

Recently, a new adenovirus-based anti-COVID-19 vaccine has been developed to target the S1 protein (a protease degradation product fo the S protein; Ad5.SARS-CoV-2-S1) and tested in mice through subcutaneous and intranasal administrations (Kim et al., 2021). A single dose immunization produced robust responses including production of S1-specific IgG, IgG1 and IgG2a that peaked at 2 weeks and induction of S1-specific B cells in cervical and axillary lymph nodes. The vaccine also elicited antigen-specific T-cell responses. In an experimental model of rehesus macaques, an adenovirus-vectored COVID-19 vaccine elicited strong humoral immune responses and protected from SARS-CoV-2 virus challenge (Feng et al., 2020).

6.3. *Inactivated or attenuated virus vaccines*

Inactivated or attenuated virus vaccines are traditional approaches which require both destruction of infectivity and retaining immunogenicity (Xia et al., 2020; Xia et al., 2021). Sinovac Biotech developed a formaldehyde-inactivated whole-virus SARS-CoV-2 vaccine – CoronaVac, which was approved by WHO for emergent use (Gao et al., 2020; Mallapaty, 2021). The vaccine formulae includes alum as adjuvant. The immune responses activated include monocyte-secreted IFN, $CD4^+$ T cells, B-cells, antibodies and $CD8^+$ T cells. The clinical trial (Zhao Y, 2020) showed that the vaccine was safe and was tolerated in aged participants (Wu et al., 2021). Sinopharm also produced an inactivated vaccine called BBIBP-CorV (approved by WHO), which are in clinical trials (Garcia C, 2020; Yang Y, 2020). The results reported from the a phase III clinical trial (Yang Y, 2020) showed that inactivated vaccines from SARS-CoV-2 WIV04 and HB02 reached 72.8% and 78.1% efficacy, respectively (Al Kaabi et al., 2021b). Covaxin home-grown and produced vaccine by Bharat Biotech will be widely available and administered to millions of healthcare workers (Kumar, V. M. et al., 2021). The phase I clinical trial showed efficacy, safety and tolerability (Thiagarajan, 2021). An ongoing clinical trial with 25,800 participants predicted an efficacy of 81% (Thiagarajan, 2021). Therefore, inactivated vaccines could produce sufficient protection effects although the efficacies are lower than that of mRNA vaccines.

6.4. *Vaccination of patients recovered from covid-19*

The COVID-19 vaccines have been shown to further increase immune responses of the population that has had SARS-CoV-2 infections. Mazzoni et al. (2021) revealed that one dose of Pfizer/BioNTech vaccination was sufficient to increase hormural and cellular immunity in COVID-19 recovered patients and second dose vaccination did not further increase immune responses (Mazzoni et al., 2021). In contrast, second dose vaccination is necessary for naïve vaccinated patients to reach high immune responses. Levi et al. (2021) showed that after the first dose of Pfizer/BioNTech vaccination there was an exponential increase in the levels of IgG after 5–8 days in previously exposed COVID-19 patients compared to naïve patients (Levi et al., 2021). However, asympotamic and naïve patients required a second dose of the vaccine to reach optimal immune responses. Sasikala et al. (2021) showed that single dose of mRNA vaccines dramatically increased neutralizing antibodies (1124.73 ± 869.13 vs94.23 ± 140.06 AU/ml) in 280 healthcare workers who previously infected with SARS-CoV-2 (Sasikala et al., 2021). Therefore, vaccination is able to further increase immune profiles in the population who had SARS-CoV-2 exposure but with not sufficient immune responses elicited.

6.5. *Influence of variants on vaccine efficacy*

With the expanding COVID-19 pandemic and increased infections of the population, many SARS-CoV-2 variants have emerged. It has been demonstrated that various variants produce resistance to vaccination-caused immune responses, this, to different extent. According to the scope of resistance, WHO distinguishes variants into variants of concern and variants of interest. There are now four strains of variants of concern including B1.1.7, B. 1.351, P1 of B.1.1.28 and B.1.167 (Jia and Gong, 2021). It has also been shown that antibodies isolated from natural infections and vaccinations are less effective against variants (Chen, R. E. et al., 2021; Hoffmann et al., 2021; Jia and Gong, 2021; Khoury et al., 2021; Röltgen et al., 2021; Wang, Z. et al., 2021). A meta-analysis showed that neutralizing antibodies induced by natural infections or vaccinations had 1.5-fold reduction against B.1.1.7, 8.7-fold reduction against B1.351 and 5-fold reduction against P1 (Chen, X. et al., 2021). The newly found variant B.1.167.1 was also 6.8 fold more resistant to these antibodies than the wild type (Edara et al., 2021). The two mRNA vaccines elicited robust T cell responses to wild type spike and nucleocapsid proteins (even more than that in convalescent plasma) but their

effects on variants (B1.1.7, B. 1.351, P1 of B.1.1.28 and B.1.167) were greatly diminished (Gallagher et al., 2021). According to a CDC report, 64% COVID-19 breakthrough cases were mutant variants ("COVID-19 Vaccine Breakthrough Infections Reported to CDC - United States, January 1-April 30, 2021," 2021).

7. Adverse effects of covid-19 vaccines

Adverse-effects for all COVID-19 vaccines have been reported during emergency use. In clinical trials, side-effects could be underestimated due to the selection criteria of patients for vaccinations (Klimek et al., 2021). Non-serious adverse-effects have been reported frequently, including local pain, redness, swelling and systemic symptoms of fever, fatigue, headache, and muscle and joint pain (Polack et al., 2020). Recent clinical trials for two inactivated COVID-19 vaccines showed that non-serious adverse effects happened in 41.7% to 46.5% of participants, most of which were reporting local pain (Al Kaabi et al., 2021a; Zhao Y, 2020). Serious adverse-effects are rare but have resulted in fatalities, which has greatly affected acceptance of vaccinations. There were 23 deaths of frail elderly patients reported in Norway after COVID-19 vaccination (Torjesen, 2021). How to avoid severe adverse-effects is an important issue with the requisite being for an urgent resolution.

Allergic reactions have been caused by the two mRNA vaccines (Castells and Phillips, 2021; Klimek et al., 2021; Selvaraj et al., 2021). Allergy is known to be caused by over production of IgE. IgE binds to a high affinity IgE receptor (Fc epsilon RI) on mast cells and basophils, causing the release of histamine, prostaglandins, leukotrienes, proteases and pro-inflammatory cytokines. The guidance for vaccination participants has been developed to avoid anaphylaxis (Banerji et al., 2021; Klimek et al., 2021). A computerized model showed that the possible allergen could be the amino acid residues at 437–508 of RBD (spike protein sub-unit) that is expressed by mRNA vaccines (Selvaraj et al., 2021). The components of the nano-delivery system used could also cause allergy such as PEG, TRIS and glycophospholipids (Hatziantoniou et al., 2021; Selvaraj et al., 2021; Troelnikov et al., 2021).

Another severe adverse effect reported in COVID-19 vaccination is thrombosis, which is also life-threatening. Adenovirus-based vaccines including Janssen's, Astrazenica (Covishield in India) and Sputnik V (Gamaleya Research Institute, Moscow, Russia) have been associated with thrombosis (Gupta et al., 2021; See et al., 2021). No thrombosis has been reported in Ad5-nCOV recipants and clinical trials, although the latter has 1% rate of serious adverse effects at a dose of 5×10^9 vp and 9% at a dose of 1×10^{11}, such as high fever and severe fatigue (Zhu et al., 2020a; Zhu et al., 2020b). Activation of platelets were considered to be the cause of the thrombosis. As most thrombosis happened in adenovirus-based vaccines, the vector and the encoded full length spike protein have been considered to be the causal material. Currently only one case of mRNA-induced thrombosis has been reported (Carli et al., 2021). A study showed that antibodies against platelet factor 4 were found in both adenovirus-based and mRNA vaccination (Thiele et al., 2021). IgG antibodies that react with and activate platelet factor 4 have been detected in high percentage of vaccination participates (19/281). However, the titers of the antibodies are usually very low and not sufficient to activate platelets.

Rarely, a cytokine storm has been reported after vaccination with BTN162b2 in a patient with colorectal cancer under anti-PD-1 immunotherapy (Au et al., 2021). There were highly increased proinflammatory cytokines CRP, IFN-gamma, IL-2, IL-18, IL-16 as well as anti-inflammatory cytokine IL-10 accompanied by thrombocytopenia. The cytokine storm could be explained by stimulation of vaccines together with increased sensitivity of cellular immune responses. Anti-PD-1 could increase activation of $CD8^+$ T cells.

8. Approaches to improve gut microbiota for COVID-19 vaccinations

As gut dysbiosis in COVID-19 has affected the efficacy and adverse effects of COVID-19 vaccines, improvement of the gut microbiota could increase COVID-19 vaccine efficacy as well as reduce side effects (Lynn et al., 2021). Indeed, there are several ongoing clinical trials that are testing the modulation of gut microbiota on COVID-19 vaccines. A clinical trial that is investigating a yeast-based probiotic called ABBC1 to enhance the efficacy of a vaccine against COVID-19 detected by both humoral and cellular responses (Mateus Rodríguez JA, 2020). ABBC1 includes β1,3/β1,6-glucan and inactivated *Saccharomyces cerevisae* as well as trace elements selenium and zinc. Another clinical trial has also used a formulae with 3 Bifidobacteria to increase COVID-19 vaccine efficacy and reduce adverse-effects in elderly type 2 diabetes patients (Mak JWY, 2020). A third clinical trial is investigating a functional food including 5-ALA-phosphate to increase the efficacy of COVID-19 vaccines (Darwish A, 2020). 5-ALA-phosphate is known to maintain gut microbiota homestasis (Chang et al., 2021).

Lactobacteria and Bifidobacteria could strengthen the immune responses to COVID-19 vaccinations. MAMPs from these bacteria can stimulate TLRs to promote both innate and adaptive immune responses (Moradi-Kalbolandi et al., 2021; Vlasova et al., 2013) (Fig. 3). Also a clinical trial is ongoing to examine microbiota profiles in vaccinated and infected participants (i.e., NCT04980560) (Fig. 3). Various approaches are available to improve the diversity of the gut microbiota including administration of probiotics, prebiotics, synbiotics, nutraceuticals, trace elements, fecal microbiota transplantation (FMT) and food/energy restriction such as FMD (fasting mimicking diets). All these approaches have been applied to various conditions with different levels of success. FMT has been successfully used in the treatment of *C. difficile* infections that result from antibiotic-caused gut dysbiosis. FMT is the preferred approach for restoring the gut microbiota from *C. difficile* disruptive infections. But it may have severe adverse effects such as pathogenic infections. Therefore, it may not be suitable for an adjuvant approach for COVID-19 vaccines. Probiotics, prebiotics and synbiotics have been used to treat many chronic infectious diseases such as inflammatory bowel disease (Chen, J. et al., 2021; Walton et al., 2021). They are highly safe with minimal side-effects reported. Most commonly used probiotics are from a narrow range of organisms such as Lactobacteria and Bifidobacteria. Common prebiotics include fructose oligosaccharides, galactooligosaccharides, beta-glucans and resistant starches. Some prebiotics could have direct anti-viral effect. For example, epigallocatechin gallate not only improves gut microbiota but also exerts potent anti-viral effect through inhibiting Nsp15 (Hong et al., 2021). Both probiotics and prebiotics have been reported to increase influenza vaccine efficacy markedly (Lei et al., 2017). These could improve COVID-19 vaccine efficacy as well as has been indicated (Akatsu, 2021). A synbiotic could be better than a probiotic or a prebiotic alone as it not only provides commensal bacteria but also dietary fibre that can elevate levels of butyrate production in the gut (Holscher, 2017). Butyrate also increases the transition of antigen-activated $CD8^+$ T cells into long-live memory cells (Bachem et al., 2019; Ji and Hu, 2019). In addition, indole-producing bacteria and bile acid-modulating bacteria could also be studied for possible use in COVID-19 vaccination (Fig. 3). So far 85 species of bacteria have identified to produce tryptophanase that converts tryptophan into indole (Lee and Lee, 2010). Indole has anti-inflammatory effect through activation of aryl hydrocarbon receptor (Rothhammer et al., 2016). Commensal bacteria can produce some derivatives of secondary bile acids such as 3-oxolithocholic acid, isoallolithocholic acid and isoDCA which have anti-inflammatory effect through activation of Tregs (Campbell et al., 2020; Hang et al., 2019).

Newer generation probiotics have an expanded bacterial range, and in future could include a formulae for complementing COVID-19 vaccines. Butyrate-producing bacteria such as *F. prausnitzii* that can produce butyrate directly are being included in experimental probiotic

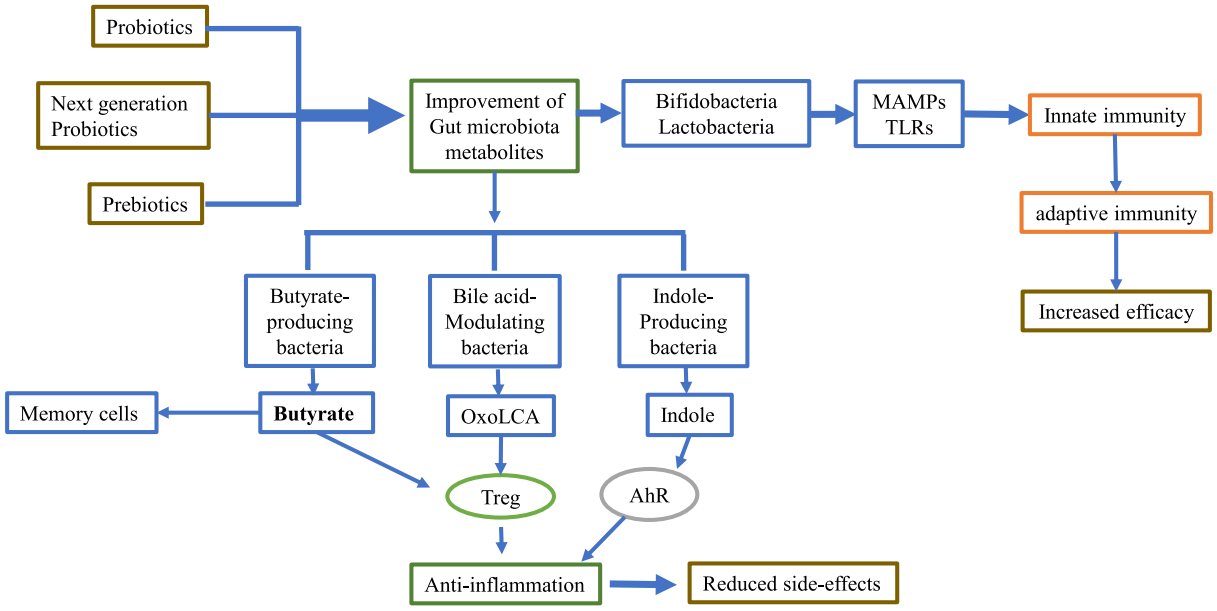

Fig. 3. Probiotics and prebiotics for Covid-19. Probiotics and next generation probiotics as well as prebiotics can improve the abundance of the gut microbiota and increase commensal bacterial metabolites, which strengthen both innate and adaptive immune responses to increase COVID-19 vaccine efficacy. Some commensal bacterial metabolites can also activate regulatory T cells to balance immune responses. Improved gut microbiota can also reduce adverse effects of COVID-19 vaccines.

formulations (Gautier et al., 2021; O'Toole et al., 2017), which has numerous beneficial effects (Leylabadlo et al., 2020) as for example improving the efficacy and safety of COVID-19 vaccines (Moradi-Kalbolandi et al., 2021). An interventional clinical trial showed that *F. prausnitzii* was tolerated and improved metabolic pathways (Lorenzon M, 2020) Other next generation of probiotics such as *Bacteroides acidifaciens*, *Bacteroides ovatus*, *Bacillus pumilus* and *Bacillus megaterium* are less well studied. *B. acidifaciens* increased IgA in gnotobiotic mice and *B. ovatus* increased Ig M and Ig G. It has been included in a mixture of 9 probiotics for the treatment of *C. difficile* infections (Graham DY, 2020). This study is an update of previous work (Tvede and Rask-Madsen, 1989) that administered through rectal instillation homologous faeces to one patient and a mixture of ten different facultatively aerobic and anaerobic bacteria diluted in sterile saline to five other patients for the treatment of chronic relapsing diarrhoea caused by *C. difficile*. Recent studies have reported that *B. pumilus* and *B. megaterium* have been found to increase *F. prausnitzii* in a mouse model, indicating complex bacterial interactions (Kotowicz et al., 2019). Whether next generation probiotics produce more beneficial effects for COVID-19 vaccines warrants further studies.

Modulation of the gut microbiota could also reduce the side-effects of COVID-19 vaccines. It has been shown that probiotics can effectively ameliorate allergy (Jing et al., 2020). Several probiotics including *B. longum*, *B. breve*, *L. plantarum*, *L. casei*, *L. fermentum* and *L. rhamnosus* have been demonstrated to have anti-allergic effects through animal studies and clinical trials (Shu et al., 2019). The mechanisms are not well-elucidated (Shu et al., 2019). Butyrate could be an important mediator. It has been shown that decreased butyrate-producing bacteria in gut microbiota are associated with food allergy (Lee et al., 2020). Butyrate is known to activate regulatory T cells, which could reduce antibody IgE production. The inhibition of pro-inflammatory signalling pathways could also be important for butyrate to exert anti-allergic effects. There are possibilities that next generation probiotics could have strong preventive effects on allergic responses as some of them can produce butyrate. Instead, inclusion of butyrate into COVID-19 vaccine formulations may also reduce adverse effects of the vaccines. Prebiotic polysaccharides have been proposed for the prevention and treatment of COVID-19 (Barbosa and de Carvalho Junior, 2021). Each type of polysaccharides could have different effects on the immune system; either stimulation or suppression (Barbosa and de Carvalho Junior, 2021). How these polysaccharides affect COVID-19 vaccine efficacy could be studied in animal models first.

A synbiotic formulation (i.e., probiotic + prebiotic) could provide a profound impact on COVID-19 vaccine efficacy and for the prevention of adverse effects. An optimal formulation could be advanced. Next generation probiotics could be included, particularly butyrate-producing bacteria. Some prebiotics can be added to facilitate the production of butyrate, which is a major mediator for gut microbiota to increase immune responses in the intestines.

9. Conclusions

It is recognised that the intestinal microbiota is subject to changes with increasing age (Zhang, S. et al., 2021). There are physiological and extrinsic changes that accompany aging such as age-associated inflammation, immunosenescence, lifestyle nutritional and physical activity changes, medication use and the presence of chronic health conditions (DeJong et al., 2020; Zhang, S. et al., 2021). The extent of these changes remain to be clarified. What is advanced is that gut dysbiosis (Ragonnaud and Biragyn, 2021) has been recognized to be a concomitant factor with aging and is observed in severe COVID-19 infections (Chen, J. et al., 2021; Prasad et al., 2021).

COVID-19 vaccines have now been extensively administered in developed countries, which have progressed to makerdly reduce COVID-19 new cases. However, vaccine efficacy may need to be increased further, particularly in vulnerable people who are fragile and aged and/or diagnosed with underlying chronic diseases. Several studies have demonstrated that COVID-19 vaccine efficacy is markedly reduced in patients with advanced age or with chonic diseases (Soiza et al., 2021). Although most adverse effects are minor, the adverse effects, which cause severe complications and deaths comprise a major unresolved issue. Gut dysbiosis may be linked to the efficacies and adverse effects of COVID-19 vaccines. Certainly the Norwegian study investigating deaths in elderly frail patients post vaccination (Torjesen, 2021) adds to the plausibility of involvement of a dysbiotic gut. Improvement of gut microbiota in risk populations could increase vaccine efficacies and

reduce severe adverse effects. Intestinal dysbiosis effects could be a major factor for inefficacy and adverse effects of COVID-19 vaccines in susceptible individuals and in the frail and elderly population (Lynn et al., 2021). Modulation of the intestinal microbiota with *Bifidobacteria* and bacterial metabolites such as butyrate (Chen and Vitetta, 2020; Lynn et al., 2021) could be a practical approach as an adjuvant for vaccine COVID-19 efficacy improvement in the frail elderly. Incorporation of next generation probiotics with or without prebiotics, particularly inducing butyrate-producing bacteria, could be necessary requisites for improving the abundance and diversity of the gut microbiota, as important adjuvant mediators COVID-19 vaccine efficacy and the abrogation of vaccine adverse effects.

Ethics statement

The study upon which the narrative review was based did not require ethical approval. None was required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abt, M., Osborne, L., Monticelli, L., Doering, T., Alenghat, T., Sonnenberg, G. F., Paley, M. A., Antenus, M., Williams, K. L., Erikson, J., Wherry, E. J., & Artis, D. (2012). Commensal bacteria calibrate the activation threshold of innate antiviral immunity. *Immunity, 37*(1), 158–170. https://doi.org/10.1016/j.immuni.2012.04.011

Achiron, A., Mandel, M., Dreyer-Alster, S., Harari, G., Magalashvili, D., Sonis, P., Dolev, M., Menascu, S., Flechter, S., Falb, R., & Gurevich, M. (2021). Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies, 175628642110128 *Therapeutic Advances in Neurological Disorders, 14*. https://doi.org/10.1177/17562864211012835.

Akatsu, H. (2021). Exploring the effect of probiotics, prebiotics, and postbiotics in strengthening immune activity in the elderly. *Vaccines (Basel), 9*(2), 136. https://doi.org/10.3390/vaccines9020136

Al Kaabi, N., Zhang, Y., Xia, S., Yang, Y., Al Qahtani, M. M., Abdulrazzaq, N., Al Nusair, M., Hassany, M., Jawad, J. S., Abdalla, J., Hussein, S. E., Al Mazrouei, S. K., Al Karam, M., Li, X., Yang, X., Wang, W., Lai, B., Chen, W., Huang, S., Wang, Q., Yang, T., Liu, Y., Ma, R., Hussain, Z. M., Khan, T., Saifuddin Fasihuddin, M., You, W., Xie, Z., Zhao, Y., Jiang, Z., Zhao, G., Zhang, Y., Mahmoud, S., ElTantawy, I., Xiao, P., Koshy, A., Zaher, W. A., Wang, H., Duan, K., Pan, A., & Yang, X. (2021a). Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: A randomized clinical trial. *JAMA, 326*(1), 35. https://doi.org/10.1001/jama.2021.8565

Al Kaabi, N., Zhang, Y., Xia, S., Yang, Y., Al Qahtani, M. M., Abdulrazzaq, N., Al Nusair, M., Hassany, M., Jawad, J. S., Abdalla, J., Hussein, S. E., Al Mazrouei, S. K., Al Karam, M., Li, X., Yang, X., Wang, W., Lai, B., Chen, W., Huang, S., Wang, Q., Yang, T., Liu, Y., Ma, R., Hussain, Z. M., Khan, T., Saifuddin Fasihuddin, M., You, W., Xie, Z., Zhao, Y., Jiang, Z., Zhao, G., Zhang, Y., Mahmoud, S., ElTantawy, I., Xiao, P., Koshy, A., Zaher, W. A., Wang, H., Duan, K., Pan, A., & Yang, X. (2021b). Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: A randomized clinical trial. *JAMA, 326*(1), 35. https://doi.org/10.1001/jama.2021.8565

Almasri, L., & Holtzclaw, B. J. (2021). Assessing Vaccine Protection for Older Adults with Diabetes: A Systematic Review. *Western Journal of Nursing Research, 1939459211005710*. https://doi.org/10.1177/01939459211005710

Alwani, M., Yassin, A., Al-Zoubi, R. M., Aboumarzouk, O. M., Nettleship, J., Kelly, D., Al-Qudimat, A. R., & Shabsigh, R. (2021). Sex-based differences in severity and mortality in COVID-19. *Reviews in Medical Virology*. https://doi.org/10.1002/rmv.2223

Atarashi, K., Tanoue, T., Shima, T., Imaoka, A., Kuwahara, T., Momose, Y., Cheng, G., Yamasaki, S., Saito, T., Ohba, Y., Taniguchi, T., Takeda, K., Hori, S., Ivanov, I. I., Umesaki, Y., Itoh, K., & Honda, K. (2011). Induction of colonic regulatory T cells by indigenous Clostridium species. *Science, 331*(6015), 337–341. https://doi.org/10.1126/science:1198469

Au, L., Fendler, A., Shepherd, S. T. C., Rzeniewicz, K., Cerrone, M., Byrne, F., Carlyle, E., Edmonds, K., Del Rosario, L., Shon, J., Haynes, W. A., Ward, B., Shum, B., Gordon, W., Gerard, C. L., Xie, W., Joharatnam-Hogan, N., Young, K., Pickering, L., Furness, A. J. S., Larkin, J., Harvey, R., Kassiotis, G., Gandhi, S., Swanton, C., Fribbens, C., Wilkinson, K. A., Wilkinson, R. J., Lau, D. K., Banerjee, S., Starling, N., Chau, I., & Turajlic, S. (2021). Cytokine release syndrome in a patient with colorectal cancer after vaccination with BNT162b2. *Nature Medicine, 27*(8), 1362–1366. https://doi.org/10.1038/s41591-021-01387-6

Bachem, A., Makhlouf, C., Binger, K. J., de Souza, D. P., Tull, D., Hochheiser, K., Whitney, P. G., Fernandez-Ruiz, D., Dähling, S., Kastenmüller, W., Jönsson, J., Gressier, E., Lew, A. M., Perdomo, C., Kupz, A., Figgett, W., Mackay, F., Oleshansky, M., Russ, B. E., Parish, I. A., Kallies, A., McConville, M. J., Turner, S. J., Gebhardt, T., & Bedoui, S. (2019). Microbiota-derived short-chain fatty acids promote the memory potential of antigen-activated CD8(+) T cells. *Immunity, 51*(2), 285–297.e5. https://doi.org/10.1016/j.immuni.2019.06.002

Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S. A., Rouphael, N., Creech, C. B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., Janes, H., Follmann, D., Marovich, M., Mascola, J., Polakowski, L., Ledgerwood, J., Graham, B. S., Bennett, H., Pajon, R., Knightly, C., Leav, B., Deng, W., Zhou, H., Han, S., Ivarsson, M., Miller, J., & Zaks, T. (2021). Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England Journal of Medicine, 384*(5), 403–416. https://doi.org/10.1056/NEJMoa2035389

Banerji, A., Wickner, P. G., Saff, R., Stone, C. A., Robinson, L. B., Long, A. A., Wolfson, A. R., Williams, P., Khan, D. A., Phillips, E., & Blumenthal, K. G. (2021). mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: Current evidence and suggested approach. *Journal of Allergy and Clinical Immunology, 9*(4), 1423–1437. https://doi.org/10.1016/j.jaip.2020.12.047

Baradaran Ghavami, S., Pourhamzeh, M., Farmani, M., Raftar, S. K. A., Shahrokh, S., Shpichka, A., Asadzadeh Aghdaei, H., Hakemi-Vala, M., Hosein-Khannazer, N., Timashev, P., & Vosough, M. (2021). Cross-talk between immune system and microbiota in COVID-19. *Expert Review of Gastroenterology & Hepatology*, 1–14. https://doi.org/10.1080/17474124.2021.1991311

Barbosa, J. R., & de Carvalho Junior, R. N. (2021). Polysaccharides obtained from natural edible sources and their role in modulating the immune system: Biologically active potential that can be exploited against COVID-19. *Trends in Food Science & Technology, 108*, 223–235. https://doi.org/10.1016/j.tifs.2020.12.026

Beaudoin-Bussières, G., Laumaea, A., Anand, S. P., Prévost, J., Gasser, R., Goyette, G., Medjahed, H., Perreault, J., Tremblay, T., Lewin, A., Gokool, L., Morrisseau, C., Bégin, P., Tremblay, C., Martel-Laferrière, V., Kaufmann, D. E., Richard, J., Bazin, R., Finzi, A. (2020). Decline of Humoral Responses against SARS-CoV-2 Spike in Convalescent Individuals. *mBio, 11*(5). doi: 10.1128/mBio.02590-20.

Bhutia, Y. D., & Ganapathy, V. (2015). Short, but smart: SCFAs train T cells in the gut to fight autoimmunity in the brain. *Immunity, 43*(4), 629–631. https://doi.org/10.1016/j.immuni.2015.09.014

Biagi, E., Franceschi, C., Rampelli, S., Severgnini, M., Ostan, R., Turroni, S., Consolandi, C., Quercia, S., Scurti, M., Monti, D., Capri, M., Brigidi, P., & Candela, M. (2016). Gut microbiota and extreme longevity. *Current Biology, 26*(11), 1480–1485. https://doi.org/10.1016/j.cub.2016.04.016

Bos, R., Rutten, L., van der Lubbe, J. E. M., Bakkers, M. J. G., Hardenberg, G., Wegmann, F., Zuijdgeest, D., de Wilde, A. H., Koornneef, A., Verwilligen, A., van Manen, D., Kwaks, T., Vogels, R., Dalebout, T. J., Myeni, S. K., Kikkert, M., Snijder, E. J., Li, Z., Barouch, D. H., Vellinga, J., Langedijk, J. P. M., Zahn, R. C., Custers, J., & Schuitemaker, H. (2020). Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. *npj Vaccines, 5*(1). https://doi.org/10.1038/s41541-020-00243-x

Bosco, N., & Noti, M. (2021). The aging gut microbiome and its impact on host immunity. *Genes and Immunity, 22*(5-6), 289–303. https://doi.org/10.1038/s41435-021-00126-8

Brazal, A. M. (2021). Inoculation now or later? *Journal of Public Health (Oxf), 43*(3), e527–e528. https://doi.org/10.1093/pubmed/fdab179

Cagigi, A., & Loré, K. (2021). Immune responses induced by mRNA vaccination in mice, monkeys and humans. *Vaccines (Basel), 9*(1), 61. https://doi.org/10.3390/vaccines9010061

Campbell, C., McKenney, P. T., Konstantinovsky, D., Isaeva, O. I., Schizas, M., Verter, J., Mai, C., Jin, W. B., Guo, C. J., Violante, S., Ramos, R. J., Cross, J. R., Kadaveru, K., Hambor, J., & Rudensky, A. Y. (2020). Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells. *Nature, 581*(7809), 475–479. https://doi.org/10.1038/s41586-020-2193-0

Carli, G., Nichele, I., Ruggeri, M., Barra, S., & Tosetto, A. (2021). Deep vein thrombosis (DVT) occurring shortly after the second dose of mRNA SARS-CoV-2 vaccine. *Internal and Emergency Medicine, 16*(3), 803–804. https://doi.org/10.1007/s11739-021-02685-0

Longo, D. L., Castells, M. C., & Phillips, E. J. (2021). Maintaining safety with SARS-CoV-2 vaccines. *New England Journal of Medicine, 384*(7), 643–649. https://doi.org/10.1056/NEJMra2035343

Chang, M., Li, M., Li, M., Xie, Y., Li, Y., Yang, W., & Gao, Z. (2021). Changes of gut microbiota in pregnant sows induced by 5-Aminolevulinic acid. *Research in Veterinary Science, 136*, 57–65. https://doi.org/10.1016/j.rvsc.2021.01.021

Chaves, L. D., McSkimming, D. I., Bryniarski, M. A., Honan, A. M., Abyad, S., Thomas, S. A., Wells, S., Buck, M., Sun, Y., Genco, R. J., Quigg, R. J., & Yacoub, R. (2018). Chronic kidney disease, uremic milieu, and its effects on gut bacterial microbiota dysbiosis. *American Journal of Physiology-Renal Physiology, 315*(3), F487–F502. https://doi.org/10.1152/ajprenal.00092.2018

Chen, J., Hall, S., & Vitetta, L. (2021). Altered gut microbial metabolites could mediate the effects of risk factors in Covid-19. *Reviews in Medical Virology, 31*(5), 1–13. https://doi.org/10.1002/rmv.v31.510.1002/rmv.2211

Chen, J., & Vitetta, L. (2018). Inflammation-modulating effect of butyrate in the prevention of colon cancer by dietary fiber. *Clin Colorectal Cancer, 17*(3), e541–e544. https://doi.org/10.1016/j.clcc.2018.05.001

Chen, J., & Vitetta, L. (2020). The role of butyrate in attenuating pathobiont-induced hyperinflammation. *Immune Netw, 20*(2), Article e15. https://doi.org/10.4110/in.2020.20.e15

Chen, J., & Vitetta, L. (2021). Increased PD-L1 expression may be associated with the cytokine storm and CD8+ T-cell exhaustion in severe COVID-19. *Journal of Infectious Diseases, 223*(9), 1659–1660. https://doi.org/10.1093/infdis/jiab061

Chen, J., & Vitetta, L. (2021). Modulation of gut microbiota for the prevention and treatment of COVID-19. *Journal of Clinical Medicine, 10*(13), 2903. https://doi.org/10.3390/jcm10132903

Chen, R. E., Zhang, X., Case, J. B., Winkler, E. S., Liu, Y., VanBlargan, L. A., Liu, J., Errico, J. M., Xie, X., Suryadevara, N., Gilchuk, P., Zost, S. J., Tahan, S., Droit, L., Turner, J. S., Kim, W., Schmitz, A. J., Thapa, M., Wang, D., Boon, A. C. M., Presti, R. M., O'Halloran, J. A., Kim, A. H. J., Deepak, P., Pinto, D., Fremont, D. H., Crowe, J. E., Jr., Corti, D., Virgin, H. W., Ellebedy, A. H., Shi, P. Y., & Diamond, M. S. (2021). Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. *Nature Medicine, 27*(4), 717–726. https://doi.org/10.1038/s41591-021-01294-w

Chen, X., Chen, Z., Azman, A. S., Sun, R., Lu, W., Zheng, N., Zhou, J., Wu, Q., Deng, X., Zhao, Z., Chen, X., Ge, S., Yang, J., Leung, D. T., Yu, H. (2021). Comprehensive mapping of neutralizing antibodies against SARS-CoV-2 variants induced by natural infection or vaccination. medRxiv. doi: 10.1101/2021.05.03.21256506.

Chen, Z., & John Wherry, E. (2020). T cell responses in patients with COVID-19. *Nature Reviews Immunology, 20*(9), 529–536. https://doi.org/10.1038/s41577-020-0402-6

Chiang, B. L., Sheih, Y. H., Wang, L. H., Liao, C. K., & Gill, H. S. (2000). Enhancing immunity by dietary consumption of a probiotic lactic acid bacterium (Bifidobacterium lactis HN019): Optimization and definition of cellular immune responses. *European Journal of Clinical Nutrition, 54*(11), 849–855. https://doi.org/10.1038/sj.ejcn.1601093

Chung, Y. H., Beiss, V., Fiering, S. N., & Steinmetz, N. F. (2020). COVID-19 vaccine frontrunners and their nanotechnology design. *ACS Nano, 14*(10), 12522–12537. https://doi.org/10.1021/acsnano.0c0719710.1021/acsnano.0c07197.s001

Claesson, M. J., Cusack, S., O'Sullivan, O., Greene-Diniz, R., de Weerd, H., Flannery, E., Marchesi, J. R., Falush, D., Dinan, T., Fitzgerald, G., Stanton, C., van Sinderen, D., O'Connor, M., Harnedy, N., O'Connor, K., Henry, C., O'Mahony, D., Fitzgerald, A. P., Shanahan, F., Twomey, C., Hill, C., Ross, R. P., & O'Toole, P. W. (2011). Composition, variability, and temporal stability of the intestinal microbiota of the elderly. *Proceedings of the National Academy of Sciences of the United States of America, 108*(Supplement_1), 4586–4591. https://doi.org/10.1073/pnas.1000097107

Clinical-Trials-Org. (2020-2021). https://www.clinicaltrials.gov/ct2/results?cond=SARS-CoV-2&term=vaccine&cntry=&state=&city=&dist.

Connors, J., Bell, M. R., Marcy, J., Kutzler, M., & Haddad, E. K. (2021). The impact of immuno-aging on SARS-CoV-2 vaccine development. *Geroscience, 43*(1), 31–51. https://doi.org/10.1007/s11357-021-00323-3

Corbitt, N., Kimura, S., Isse, K., Specht, S., Chedwick, L., Rosborough, B. R., Lunz, J. G., Murase, N., Yokota, S., & Demetris, A. J. (2013). Gut bacteria drive Kupffer cell expansion via MAMP-mediated ICAM-1 induction on sinusoidal endothelium and influence preservation-reperfusion injury after orthotopic liver transplantation. *American Journal of Pathology, 182*(1), 180–191. https://doi.org/10.1016/j.ajpath.2012.09.010

Cornberg, M., & Eberhardt, C. S. (2021). Protected or not protected, that is the question - First data on COVID-19 vaccine responses in patients with NAFLD and liver transplant recipients. *Journal of Hepatology, 75*(2), 265–266. https://doi.org/10.1016/j.jhep.2021.05.007

COVID-19 Vaccine Breakthrough Infections Reported to CDC - United States, January 1-April 30, 2021. (2021). *MMWR Morb Mortal Wkly Rep, 70*(21), 792-793. doi: 10.15585/mmwr.mm7021e3.

Cox, R. J., & Brokstad, K. A. (2020). Not just antibodies: B cells and T cells mediate immunity to COVID-19. *Nature Reviews Immunology, 20*(10), 581–582. https://doi.org/10.1038/s41577-020-00436-4

Cryan, J. F., & Dinan, T. G. (2015). Gut microbiota: Microbiota and neuroimmune signalling-Metchnikoff to microglia. *Nature Reviews Gastroenterology & Hepatology, 12*(9), 494–496. https://doi.org/10.1038/nrgastro.2015.127

Dang, A. T., & Marsland, B. J. (2019). Microbes, metabolites, and the gut-lung axis. *Mucosal Immunology, 12*(4), 843–850. https://doi.org/10.1038/s41385-019-0160-6

Darwish A. (2020). Pilot study to evaluate the safety, tolerability, and efficacy of 5-ALA-phosphate + SFC as an immune system enhancer along with vaccination against COVID-19. https://clinicaltrials.gov/ct2/show/NCT04854876, accessed 2 July 2021.

de Jong, S. E., Olin, A., & Pulendran, B. (2020). The impact of the microbiome on immunity to vaccination in humans. *Cell Host & Microbe, 28*(2), 169–179. https://doi.org/10.1016/j.chom.2020.06.014

DeJong, E. N., Surette, M. G., & Bowdish, D. M. E. (2020). The gut microbiota and unhealthy aging: Disentangling cause from consequence. *Cell Host & Microbe, 28*(2), 180–189. https://doi.org/10.1016/j.chom.2020.07.013

Derikvand, N., Hatami, M., Chiniforush, N., & Ghasemi, S. S. (2020). The use of antimicrobial photodynamic therapy to maintain a hopeless tooth with a periodonticendodontic lesion: A case report. *Journal of Lasers in Medical Sciences, 11*(3), 355–360. https://doi.org/10.34172/jlms.2020.57

Dickson, R. P., Erb-Downward, J. R., Martinez, F. J., & Huffnagle, G. B. (2016). The microbiome and the respiratory tract. *Annual Review of Physiology, 78*(1), 481–504. https://doi.org/10.1146/physiol.2016.78.issue-110.1146/annurev-physiol-021115-105238

Edara, V. V., Lai, L., Sahoo, M. K., Floyd, K., Sibai, M., Solis, D., Flowers, M. W., Hussaini, L., Ciric, C. R., Bechnack, S., Stephens, K., Mokhtari, E. B., Mudvari, P., Creanga, A., Pegu, A., Derrien-Colemyn, A., Henry, A. R., Gagne, M., Graham, B. S., Wrammert, J., Douek, D. C., Boritz, E., Pinsky, B. A., Suthar, M. S. (2021). Infection and vaccine-induced neutralizing antibody responses to the SARS-CoV-2 B.1.617.1 variant. *bioRxiv*. doi: 10.1101/2021.05.09.443299.

Erny, D., Hrabě de Angelis, A. L., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., Keren-Shaul, H., Mahlakoiv, T., Jakobshagen, K., Buch, T., Schwierzeck, V., Utermöhlen, O., Chun, E., Garrett, W. S., McCoy, K. D., Diefenbach, A., Staeheli, P., Stecher, B., Amit, I., & Prinz, M. (2015). Host microbiota constantly control maturation and function of microglia in the CNS. *Nature Neuroscience, 18*(7), 965–977. https://doi.org/10.1038/nn.4030

Feng, L., Wang, Q., Shan, C., Yang, C., Feng, Y., Wu, J., Liu, X., Zhou, Y., Jiang, R., Hu, P., Liu, X., Zhang, F., Li, P., Niu, X., Liu, Y., Zheng, X., Luo, J., Sun, J., Gu, Y., Liu, B., Xu, Y., Li, C., Pan, W., Zhao, J., Ke, C., Chen, X., Xu, T., Zhong, N., Guan, S., Yuan, Z., & Chen, L. (2020). An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques. *Nature Communications, 11*(1). https://doi.org/10.1038/s41467-020-18077-5

Ferreira, C., Viana, S. D., & Reis, F. (2020a). Gut microbiota dysbiosis-immune hyperresponse-inflammation triad in coronavirus disease 2019 (COVID-19): Impact of pharmacological and nutraceutical approaches. *Microorganisms, 8*(10), 1514. https://doi.org/10.3390/microorganisms8101514

Ferreira, C., Viana, S. D., & Reis, F. (2020b). Is gut microbiota dysbiosis a predictor of increased susceptibility to poor outcome of COVID-19 patients? An update. *Microorganisms, 9*(1), 53. https://doi.org/10.3390/microorganisms9010053

Fourati, S., Cristescu, R., Loboda, A., Talla, A., Filali, A., Railkar, R., Schaeffer, A. K., Favre, D., Gagnon, D., Peretz, Y., Wang, I. M., Beals, C. R., Casimiro, D. R., Carayannopoulos, L. N., & Sékaly, R.-P. (2016). Pre-vaccination inflammation and B-cell signalling predict age-related hyporesponse to hepatitis B vaccination. *Nature Communications, 7*(1). https://doi.org/10.1038/ncomms10369

Frenck, R. W., Klein, N. P., Kitchin, N., Gurtman, A., Absalon, J., Lockhart, S., Perez, J. L., Walter, E. B., Senders, S., Bailey, R., Swanson, K. A., Ma, H., Xu, X., Koury, K., Kalina, W. V., Cooper, D., Jennings, T., Brandon, D. M., Thomas, S. J., Türeci, Ö., Tresnan, D. B., Mather, S., Dormitzer, P. R., Şahin, U., Jansen, K. U., & Gruber, W. C. (2021). Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. *New England Journal of Medicine, 385*(3), 239–250. https://doi.org/10.1056/NEJMoa2107456

Furusawa, Y., Obata, Y., Fukuda, S., Endo, T. A., Nakato, G., Takahashi, D., Nakanishi, Y., Uetake, C., Kato, K., Kato, T., Takahashi, M., Fukuda, N. N., Murakami, S., Miyauchi, E., Hino, S., Atarashi, K., Onawa, S., Fujimura, Y., Lockett, T., Clarke, J. M., Topping, D. L., Tomita, M., Hori, S., Ohara, O., Morita, T., Koseki, H., Kikuchi, J., Honda, K., Hase, K., & Ohno, H. (2013). Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature, 504*(7480), 446–450. https://doi.org/10.1038/nature12721

Gaebler, C., Wang, Z., Lorenzi, J. C. C., Muecksch, F., Finkin, S., Tokuyama, M., Cho, A., Jankovic, M., Schaefer-Babajew, D., Oliveira, T. Y., Cipolla, M., Viant, C., Barnes, C. O., Bram, Y., Breton, G., Hägglöf, T., Mendoza, P., Hurley, A., Turroja, M., Gordon, K., Millard, K. G., Ramos, V., Schmidt, F., Weisblum, Y., Jha, D., Tankelevich, M., Martinez-Delgado, G., Yee, J., Patel, R., Dizon, J., Unson-O'Brien, C., Shimeliovich, I., Robbiani, D. F., Zhao, Z., Gazumyan, A., Schwartz, R. E., Hatziioannou, T., Bjorkman, P. J., Mehandru, S., Bieniasz, P. D., Caskey, M., & Nussenzweig, M. C. (2021). Evolution of antibody immunity to SARS-CoV-2. *Nature, 591*(7851), 639–644. https://doi.org/10.1038/s41586-021-03207-w

Gallagher, K. M. E., Leick, M. B., Larson, R. C., Berger, T. R., Katsis, K., Yam, J. Y., Brini, G., Grauwet, K., Maus, M. V., . (2021). SARS -CoV-2 T-cell immunity to variants of concern following vaccination. *bioRxiv*. doi: 10.1101/2021.05.03.442455.

Gao, Q., Bao, L., Mao, H., Wang, L., Xu, K., Yang, M., Li, Y., Zhu, L., Wang, N., Lv, Z., Gao, H., Ge, X., Kan, B., Hu, Y., Liu, J., Cai, F., Jiang, D., Yin, Y., Qin, C., Li, J., Gong, X., Lou, X., Shi, W., Wu, D., Zhang, H., Zhu, L., Deng, W., Li, Y., Lu, J., Li, C., Wang, X., Yin, W., Zhang, Y., & Qin, C. (2020). Development of an inactivated vaccine candidate for SARS-CoV-2. *Science, 369*(6499), 77–81. https://doi.org/10.1126/science:abc1932

Garcia C. (2020). Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines (Vero Cell) to Prevent COVID-19 in Healthy Adult Population In Peru Healthy Adult Population In Peru (Covid-Peru). *https://clinicaltrials.gov/ct2/show/NCT04612972, accessed 2 July 2021*.

Gautier, T., David-Le Gall, S., Sweidan, A., Tamanai-Shacoori, Z., Jolivet-Gougeon, A., Loréal, O., & Bousarghin, L. (2021). Next-Generation Probiotics and Their Metabolites in COVID-19. *Microorganisms, 9*(5), 941. https://doi.org/10.3390/microorganisms9050941

Gill, H. S., Rutherfurd, K. J., Cross, M. L., & Gopal, P. K. (2001). Enhancement of immunity in the elderly by dietary supplementation with the probiotic Bifidobacterium lactis HN019. *American Journal of Clinical Nutrition, 74*(6), 833–839. https://doi.org/10.1093/ajcn/74.6.833

Golonka, R. M., & Vijay-Kumar, M. (2021). Atypical immunometabolism and metabolic reprogramming in liver cancer: Deciphering the role of gut microbiome. *Advances in Cancer Research, 149*, 171–255. https://doi.org/10.1016/bs.acr.2020.10.004

Graham, D. Y. (2020). Defined Fecal Microbiota Transplantation for Clostridium Difficile Diarrhea accessed 2 July 2021 https://clinicaltrials.gov/ct2/show/NCT01868373.

Grau, E., & Félez, J. (1987). Thrombotic thrombocytopenic purpura. *Med Clin (Barc), 88*(16), 628–630.

Gupta, A., Sardar, P., Cash, M. E., Milani, R. V., & Lavie, C. J. (2021). Covid-19 vaccine-induced thrombosis and thrombocytopenia-a commentary on an important and practical clinical dilemma. *Progress in Cardiovascular Diseases, 67*, 105–107. https://doi.org/10.1016/j.pcad.2021.05.001

Haghikia, A., Jörg, S., Duscha, A., Berg, J., Manzel, A., Waschbisch, A., Hammer, A., Lee, D. H., May, C., Wilck, N., Balogh, A., Ostermann, A. I., Schebb, N. H., Akkad, D. A., Grohme, D. A., Kleinewietfeld, M., Kempa, S., Thöne, J., Demir, S., Müller, D. N., Gold, R., & Linker, R. (2015). Dietary fatty acids directly impact central nervous system autoimmunity via the small intestine. *Immunity, 43*(4), 817–829. https://doi.org/10.1016/j.immuni.2015.09.007

Hang, S., Paik, D., Yao, L., Kim, E., Trinath, J., Lu, J., Ha, S., Nelson, B. N., Kelly, S. P., Wu, L., Zheng, Y., Longman, R. S., Rastinejad, F., Devlin, A. S., Krout, M. R., Fischbach, M. A., Littman, D. R., & Huh, J. R. (2019). Bile acid metabolites control T (H)17 and T(reg) cell differentiation. *Nature, 576*(7785), 143–148. https://doi.org/10.1038/s41586-019-1785-z

Haque, R., Snider, C., Liu, Y., Ma, J. Z., Liu, L., Nayak, U., Mychaleckyj, J. C., Korpe, P., Mondal, D., Kabir, M., Alam, M., Pallansch, M., Oberste, M. S., Weldon, W., Kirkpatrick, B. D., & Petri, W. A. (2014). Oral polio vaccine response in breast fed infants with malnutrition and diarrhea. *Vaccine, 32*(4), 478–482. https://doi.org/10.1016/j.vaccine.2013.11.056

Hatziantoniou, S., Maltezou, H. C., Tsakris, A., Poland, G. A., & Anastassopoulou, C. (2021). Anaphylactic reactions to mRNA COVID-19 vaccines: A call for further study. *Vaccine, 39*(19), 2605–2607. https://doi.org/10.1016/j.vaccine.2021.03.073

Hilty, M., Burke, C., Pedro, H., Cardenas, P., Bush, A., Bossley, C., Davies, J., Ervine, A., Poulter, L., Pachter, L., Moffatt, M. F., & Neyrolles, O. (2010). Disordered microbial communities in asthmatic airways. *PLoS ONE, 5*(1), e8578. https://doi.org/10.1371/journal.pone.0008578

Hoffmann, M., Arora, P., Groß, R., Seidel, A., Hörnich, B. F., Hahn, A. S., Krüger, N., Graichen, L., Hofmann-Winkler, H., Kempf, A., Winkler, M. S., Schulz, S., Jäck, H. M., Jahrsdörfer, B., Schrezenmeier, H., Müller, M., Kleger, A., Münch, J., & Pöhlmann, S. (2021). SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies. *Cell, 184*(9), 2384–2393.e12. https://doi.org/10.1016/j.cell.2021.03.036

Holscher, H. D. (2017). Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes, 8*(2), 172–184. https://doi.org/10.1080/19490976.2017.1290756

Hong, S., Seo, S. H., Woo, S.-J., Kwon, Y., Song, M., & Ha, N.-C. (2021). Epigallocatechin gallate inhibits the uridylate-specific endoribonuclease Nsp15 and efficiently neutralizes the SARS-CoV-2 strain. *Journal of Agriculture and Food Chemistry, 69*(21), 5948–5954. https://doi.org/10.1021/acs.jafc.1c0205010.1021/acs.jafc.1c02050.s001

Hou, Y.-C., Lu, K.-C., & Kuo, K.-L. (2021). The efficacy of COVID-19 vaccines in chronic kidney disease and kidney transplantation patients: A narrative review. *Vaccines (Basel), 9*(8), 885. https://doi.org/10.3390/vaccines9080885

Huda, M. N., Lewis, Z., Kalanetra, K. M., Rashid, M., Ahmad, S. M., Raqib, R., Qadri, F., Underwood, M. A., Mills, D. A., & Stephensen, C. B. (2014). Stool microbiota and vaccine responses of infants. *Pediatrics, 134*(2), e362–e372. https://doi.org/10.1542/peds.2013-3937

Ichinohe, T., Pang, I. K., Kumamoto, Y., Peaper, D. R., Ho, J. H., Murray, T. S., & Iwasaki, A. (2011). Microbiota regulates immune defense against respiratory tract influenza A virus infection. *Proceedings of the National Academy of Sciences of the United States of America, 108*(13), 5354–5359. https://doi.org/10.1073/pnas.1019378108

Isobe, J., Maeda, S., Obata, Y., Iizuka, K., Nakamura, Y., Fujimura, Y., Kimizuka, T., Hattori, K., Kim, Y. G., Morita, T., Kimura, I., Offermanns, S., Adachi, T., Nakao, A., Kiyono, H., Takahashi, D., & Hase, K. (2020). Commensal-bacteria-derived butyrate promotes the T-cell-independent IgA response in the colon. *International Immunology, 32*(4), 243–258. https://doi.org/10.1093/intimm/dxz078

Iwasaki, M., Saito, J., Zhao, H., Sakamoto, A., Hirota, K., & Ma, D. (2021). Inflammation triggered by SARS-CoV-2 and ACE2 augment drives multiple organ failure of severe COVID-19: Molecular mechanisms and implications. *Inflammation, 44*(1), 13–34. https://doi.org/10.1007/s10753-020-01337-3

Ji, L., & Hu, X. (2019). Sweet memories of 8 empowered by butyrate. *Immunity, 51*(2), 201–203. https://doi.org/10.1016/j.immuni.2019.07.005

Jia, Z., & Gong, W. (2021). Will mutations in the spike protein of SARS-CoV-2 lead to the failure of COVID-19 vaccines? *Journal of Korean Medical Science, 36*(18), Article e124. https://doi.org/10.3346/jkms.2021.36.e124

Jiang, N., He, J., Weinstein, J. A., Penland, L., Sasaki, S., He, X.-S., Dekker, C. L., Zheng, N. Y., Huang, M., Sullivan, M., Wilson, P. C., Greenberg, H. B., Davis, M. M., Fisher, D. S., & Quake, S. R. (2013). Lineage structure of the human antibody repertoire in response to influenza vaccination. *Science Translational Medicine, 5*(171). https://doi.org/10.1126/scitranslmed.3004794

Jing, W., Liu, Q., & Wang, W. (2020). Bifidobacterium bifidum TMC3115 ameliorates milk protein allergy in by affecting gut microbiota: A randomized double-blind control trial. *Journal of Food Biochemistry, 44*(11), Article e13489. https://doi.org/10.1111/jfbc.13489

Kang, Y. W., Park, S., Lee, K. J., Moon, D., Kim, Y. M., & Lee, S. W. (2021). Understanding the host innate immune responses against SARS-CoV-2 infection and COVID-19 pathogenesis. *Immune Network, 21*(1), Article e1. https://doi.org/10.4110/in.2021.21.e1

Khoury, D. S., Cromer, D., Reynaldi, A., Schlub, T. E., Wheatley, A. K., Juno, J. A., Subbarao, K., Kent, S. J., Triccas, J. A., & Davenport, M. P. (2021). Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nature Medicine, 27*(7), 1205–1211. https://doi.org/10.1038/s41591-021-01377-8

Kim, A. H., Hogarty, M. P., Harris, V. C., & Baldridge, M. T. (2020). The complex interactions between rotavirus and the gut microbiota. *Frontiers in Cellular and Infection Microbiology, 10*, Article 586751. https://doi.org/10.3389/fcimb.2020.586751

Kim, D., Kim, Y.-G., Seo, S.-U., Kim, D.-J., Kamada, N., Prescott, D., Chamaillard, M., Philpott, D. J., Rosenstiel, P., Inohara, N., & Núñez, G. (2016). Nod2-mediated recognition of the microbiota is critical for mucosal adjuvant activity of cholera toxin. *Nature Medicine, 22*(5), 524–530. https://doi.org/10.1038/nm.4075

Kim, D., Kim, Y.-M., Kim, W.-U., Park, J.-H., Núñez, G., & Seo, S.-U. (2019). Recognition of the microbiota by Nod2 contributes to the oral adjuvant activity of cholera toxin through the induction of interleukin-1β. *Immunology, 158*(3), 219–229. https://doi.org/10.1111/imm.v158.310.1111/imm.13105

Kim, E., Weisel, F. J., Balmert, S. C., Khan, M. S., Huang, S., Erdos, G., Kenniston, T. W., Carey, C. D., Joachim, S. M., Conter, L. J., Weisel, N. M., Okba, N. M. A., Haagmans, B. L., Percivalle, E., Cassaniti, I., Baldanti, F., Korkmaz, E., Shlomchik, M. J., Falo, L. D., & Gambotto, A. (2021). A single subcutaneous or intranasal immunization with adenovirus-based SARS-CoV-2 vaccine induces robust humoral and cellular immune responses in mice. *European Journal of Immunology, 51*(7), 1774–1784. https://doi.org/10.1002/eji.v51.710.1002/eji.202149167

Kim, M. J., Lee, D. K., Park, J. E., Park, I. H., Seo, J. G., & Ha, N. J. (2014). Antiviral activity of Bifidobacterium adolescentis SPM1605 against Coxsackievirus B3. *Biotechnology and Biotechnological Equipment, 28*(4), 681–688. https://doi.org/10.1080/13102818.2014.945237

Kim, S., & Jazwinski, S. M. (2018). The gut microbiota and healthy aging: A mini-review. *Gerontology, 64*(6), 513–520. https://doi.org/10.1159/000490615

Kipshidze, N., Kipshidze, N., & Fried, M. (2021). COVID-19 vaccines: Special considerations for the obese population. *Obesity Surgery, 31*(8), 3854–3856. https://doi.org/10.1007/s11695-021-05404-y

Klimek, L., Novak, N., Hamelmann, E., Werfel, T., Wagenmann, M., Taube, C., Bauer, A., Merk, H., Rabe, U., Jung, K., Schlenter, W., Ring, J., Chaker, A., Wehrmann, W., Becker, S., Mülleneisen, N., Nemat, K., Czech, W., Wrede, H., Brehler, R., Fuchs, T., Jakob, T., Ankermann, T., Schmidt, S. M., Gerstlauer, M., Vogelberg, C., Zuberbier, T., Hartmann, K., & Worm, M. (2021). Severe allergic reactions after COVID-19 vaccination with the Pfizer/BioNTech vaccine in Great Britain and USA: Position statement of the German Allergy Societies: Medical Association of German Allergologists (AeDA), German Society for Allergology and Clinical Immunology (DGAKI) and Society for Pediatric Allergology and Environmental Medicine (GPA). *Allergo Journal International, 30*(2), 51–55. https://doi.org/10.1007/s40629-020-00160-4

Koff, W. C., Schenkelberg, T., Williams, T., Baric, R. S., McDermott, A., Cameron, C. M., Friemann, M. B., Neumann, G., Kawaoka, Y., Kelvin, A. A., Ross, T. M., Schultz-Cherry, S., Mastro, T. D., Priddy, F. H., Moore, K. A., Ostrowsky, J. T., Osterholm, M. T., & Goudsmit, J. (2021). Development and deployment of COVID-19 vaccines for those most vulnerable. *Science Translational Medicine, 13*(579). https://doi.org/10.1126/scitranslmed.abd1525

Kotowicz, N., Bhardwaj, R. K., Ferreira, W. T., Hong, H. A., Olender, A., Ramirez, J., & Cutting, S. M. (2019). Safety and probiotic evaluation of two Bacillus strains producing antioxidant compounds. *Benef Microbes, 10*(7), 759–771. https://doi.org/10.3920/bm2019.0040

Kowalczyk, A., Doener, F., Zanzinger, K., Noth, J., Baumhof, P., Fotin-Mleczek, M., & Heidenreich, R. (2016). Self-adjuvanted mRNA vaccines induce local innate immune responses that lead to a potent and boostable adaptive immunity. *Vaccine, 34*(33), 3882–3893. https://doi.org/10.1016/j.vaccine.2016.05.046

Kumar, A., Dowling, W. E., Román, R. G., Chaudhari, A., Gurry, C., Le, T. T., Tollefson, S., Clark, C. E., Bernasconi, V., & Kristiansen, P. A. (2021). Status report on COVID-19 vaccines development. *Current Infectious Disease Reports, 23*(6). https://doi.org/10.1007/s11908-021-00752-3

Kumar, V. M., Pandi-Perumal, S. R., Trakht, I., & Thyagarajan, S. P. (2021). Strategy for COVID-19 vaccination in India: The country with the second highest population and number of cases. *npj Vaccines, 6*(1), 60. https://doi.org/10.1038/s41541-021-00327-2

Laforge, M., Elbim, C., Frère, C., Hémadi, M., Massaad, C., Nuss, P., Benoliel, J. J., & Becker, C. (2020). Tissue damage from neutrophil-induced oxidative stress in COVID-19. *Nature Reviews Immunology, 20*(9), 515–516. https://doi.org/10.1038/s41577-020-0407-1

Laparra, J. M., Olivares, M., Gallina, O., Sanz, Y., & Leulier, F. (2012). Bifidobacterium longum CECT 7347 modulates immune responses in a gliadin-induced enteropathy animal model. *PLoS ONE, 7*(2), e30744. https://doi.org/10.1371/journal.pone.0030744

Larsen, J. M., Musavian, H. S., Butt, T. M., Ingvorsen, C., Thysen, A. H., & Brix, S. (2015). Chronic obstructive pulmonary disease and asthma-associated Proteobacteria, but not commensal Prevotella spp., promote Toll-like receptor 2-independent lung inflammation and pathology. *Immunology, 144*(2), 333–342. https://doi.org/10.1111/imm.2015.144.issue-210.1111/imm.12376

Ledford, H. (2020). How obesity could create problems for a COVID vaccine. *Nature, 586*(7830), 488–489. https://doi.org/10.1038/d41586-020-02946-6

Lee, J. H., & Lee, J. (2010). Indole as an intercellular signal in microbial communities. *FEMS Microbiology Review, 34*(4), 426–444. https://doi.org/10.1111/j.1574-6976.2009.00204.x

Lee, K. H., Song, Y., Wu, W., Yu, K., & Zhang, G. (2020). The gut microbiota, environmental factors, and links to the development of food allergy. *Clinical and Molecular Allergy, 18*, 5. https://doi.org/10.1186/s12948-020-00120-x

Lei, W.-T., Shih, P.-C., Liu, S.-J., Lin, C.-Y., & Yeh, T.-L. (2017). Effect of probiotics and prebiotics on immune response to influenza vaccination in adults: A systematic review and meta-analysis of randomized controlled trials. *Nutrients, 9*(11), 1175. https://doi.org/10.3390/nu9111175

Leong, D. P., Banerjee, A., & Yusuf, S. (2021). COVID-19 vaccination prioritization on the basis of cardiovascular risk factors and number needed to vaccinate to prevent death. *Canadian Journal of Cardiology, 37*(7), 1112–1116. https://doi.org/10.1016/j.cjca.2021.04.012

Leslie, M. (2020). T cells found in coronavirus patients 'bode well' for long-term immunity. *Science, 368*(6493), 809–810. https://doi.org/10.1126/science.368.6493.809

Levi, R., Azzolini, E., Pozzi, C., Ubaldi, L., Lagioia, M., Mantovani, A., & Rescigno, M. (2021). One dose of SARS-CoV-2 vaccine exponentially increases antibodies in individuals who have recovered from symptomatic COVID-19. *Journal of Clinical Investigation, 131*(12). https://doi.org/10.1172/JCI14915410.1172/JCI149154DS110.1172/JCI149154DS2

Leylabadlo, H. E., Ghotaslou, R., Feizabadi, M. M., Farajnia, S., Moaddab, S. Y., Ganbarov, K., Khodadadi, E., Tanomand, A., Sheykhsaran, E., Yousefi, B., & Kafil, H. S. (2020). The critical role of Faecalibacterium prausnitzii in human health: An overview. *Microbial Pathogenesis, 149*, 104344. https://doi.org/10.1016/j.micpath.2020.104344

Li, D., Breiman, A., le Pendu, J., & Uyttendaele, M. (2016). Anti-viral effect of bifidobacterium adolescentis against noroviruses. *Frontiers in Microbiology, 7*, 864. https://doi.org/10.3389/fmicb.2016.00864

Liao, M., Liu, Y., Yuan, J., Wen, Y., Xu, G., Zhao, J., Cheng, L., Li, J., Wang, X., Wang, F., Liu, L., Amit, I., Zhang, S., & Zhang, Z. (2020). Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nature Medicine, 26*(6), 842–844. https://doi.org/10.1038/s41591-020-0901-9

Lingblom, C. M. D., Kowli, S., Swaminathan, N., Maecker, H. T., & Lambert, S. L. (2018). Baseline immune profile by CyTOF can predict response to an investigational adjuvanted vaccine in elderly adults. *Journal of Translational Medicine, 16*(1), 153. https://doi.org/10.1186/s12967-018-1528-1

Logunov, D. Y., Dolzhikova, I. V., Shcheblyakov, D. V., Tukhvatulin, A. I., Zubkova, O. V., Dzharullaeva, A. S., Kovyrshina, A. V., Lubenets, N. L., Grousova, D. M., Erokhova, A. S., Botikov, A. G., Izhaeva, F. M., Popova, O., Ozharovskaya, T. A., Esmagambetov, I. B., Favorskaya, I. A., Zrelkin, D. I., Voronina, D. V., Shcherbinin, D. N., Semikhin, A. S., Simakova, Y. V., Tokarskaya, E. A., Egorova, D. A., Shmarov, M. M., Nikitenko, N. A., Gushchin, V. A., Smolyarchuk, E. A., Zyryanov, S. K., Borisevich, S. V., Naroditsky, B. S., & Gintsburg, A. L. (2021). Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: An interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet, 397*(10275), 671–681. https://doi.org/10.1016/S0140-6736(21)00234-8

Logunov, D. Y., Dolzhikova, I. V., Zubkova, O. V., Tukhvatulin, A. I., Shcheblyakov, D. V., Dzharullaeva, A. S., Grousova, D. M., Erokhova, A. S., Kovyrshina, A. V., Botikov, A. G., Izhaeva, F. M., Popova, O., Ozharovskaya, T. A., Esmagambetov, I. B., Favorskaya, I. A., Zrelkin, D. I., Voronina, D. V., Shcherbinin, D. N., Semikhin, A. S., Simakova, Y. V., Tokarskaya, E. A., Lubenets, N. L., Egorova, D. A., Shmarov, M. M., Nikitenko, N. A., Morozova, L. F., Smolyarchuk, E. A., Kryukov, E. V., Babira, V. F., Borisevich, S. V., Naroditsky, B. S., & Gintsburg, A. L. (2020). Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: Two open, non-randomised phase 1/2 studies from Russia. *Lancet, 396*(10255), 887–897. https://doi.org/10.1016/S0140-6736(20)31866-3

Lorenzon, M. (2020). Tolerability and Risk of Adverse Events With a Probiotic Supplement accessed 2 July 2021 https://clinicaltrials.gov/ct2/show/NCT03728868.

Lynn, D. J., Benson, S. C., Lynn, M. A., & Pulendran, B. (2021). Modulation of immune responses to vaccination by the microbiota: Implications and potential mechanisms. *Nature Reviews Immunology, 1–14*. https://doi.org/10.1038/s41577-021-00554-7

Ma, C., Han, M., Heinrich, B., Fu, Q., Zhang, Q., Sandhu, M., Agdashian, D., Terabe, M., Berzofsky, J. A., Fako, V., Ritz, T., Longerich, T., Theriot, C. M., McCulloch, J. A., Roy, S., Yuan, W., Thovarai, V., Sen, S. K., Ruchirawat, M., Korangy, F., Wang, X. W., Trinchieri, G., & Greten, T. F. (2018). Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science, 360*(6391). https://doi.org/10.1126/science:aan5931

Maecker, H. T. (2021). Immune profiling of COVID-19: Preliminary findings and implications for the pandemic. *Journal for ImmunoTherapy of Cancer, 9*(5), e002550. https://doi.org/10.1136/jitc-2021-002550

Maffei, V. J., Kim, S., Blanchard, E., Luo, M., Jazwinski, S. M., Taylor, C. M., & Welsh, D. A. (2017). Biological aging and the human gut microbiota. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 72*(11), 1474–1482. https://doi.org/10.1093/gerona/glx042

Mak, J. W. Y. (2020). Modulation of Gut Microbiota to Enhance Health and Immunity accessed 2 July 2021 https://clinicaltrials.gov/ct2/show/NCT04884776.

Mallapaty, S. (2021). WHO approval of Chinese CoronaVac COVID vaccine will be crucial to curbing pandemic. *Nature, 594*(7862), 161–162. https://doi.org/10.1038/d41586-021-01497-8

Man, A. L., Bertelli, E., Rentini, S., Regoli, M., Briars, G., Marini, M., Watson, A. J., & Nicoletti, C. (2015). Age-associated modifications of intestinal permeability and innate immunity in human small intestine. *Clinical Science (London), 129*(7), 515–527. https://doi.org/10.1042/cs20150046

Manosso, L. M., Lin, J., Carlessi, A. S., Recco, K. C. C., Quevedo, J., Gonçalves, C. L., & Réus, G. Z. (2021). Sex-related patterns of the gut-microbiota-brain axis in the neuropsychiatric conditions. *Brain Research Bulletin, 171*, 196–208. https://doi.org/10.1016/j.brainresbull.2021.04.001

Mantus, G., Nyhoff, L. E., Kauffman, R. C., Edara, V. V., Lai, L., Floyd, K., Shi, P. Y., Menachery, V. D., Edupuganti, S., Scherer, E. M., Kay, A., McNair, N., Anderson, E. J., Rouphael, N., Ahmed, R., Suthar, M. S., & Wrammert, J. (2021). Evaluation of cellular and serological responses to acute SARS-CoV-2 infection demonstrates the functional importance of the receptor-binding domain. *Journal of Immunology, 206*(11), 2605–2613. https://doi.org/10.4049/jimmunol.2001420

Marjot, T., Webb, G. J., Barritt, A. S., Ginès, P., Lohse, A. W., Moon, A. M., Pose, E., Trivedi, P., & Barnes, E. (2021). SARS-CoV-2 vaccination in patients with liver disease: Responding to the next big question. *Lancet Gastroenterol Hepatol, 6*(3), 156–158. https://doi.org/10.1016/S2468-1253(21)00008-X

Mateus, D., Sebastião, A. I., Carrascal, M. A., Carmo, A. D., Matos, A. M., & Cruz, M. T. (2021). Crosstalk between estrogen, dendritic cells, and SARS-CoV-2 infection. *Reviews in Medical Virology, e2290*. https://doi.org/10.1002/rmv.2290

Mateus Rodríguez, J. A. (2020). Efficacy and Tolerability of ABBC1 in Volunteers Receiving the Influenza or Covid-19 Vaccine accessed 2 July 2021 https://clinicaltrials.gov/ct2/show/NCT04798677.

Mathieu, E., Escribano-Vazquez, U., Descamps, D., Cherbuy, C., Langella, P., Riffault, S., Remot, A., & Thomas, M. (2018). Paradigms of Lung microbiota functions in health and disease, particularly, in asthma. *Frontiers in Physiology, 9*, 1168. https://doi.org/10.3389/fphys.2018.01168

Mazzoni, A., Di Lauria, N., Maggi, L., Salvati, L., Vanni, A., Capone, M., Lamacchia, G., Mantengoli, E., Spinicci, M., Zammarchi, L., Kiros, S. T., Rocca, A., Lagi, F., Colao, M. G., Parronchi, P., Scaletti, C., Turco, L., Liotta, F., Rossolini, G. M., Cosmi, L., Bartoloni, A., & Annunziato, F. (2021). First-dose mRNA vaccination is sufficient to reactivate immunological memory to SARS-CoV-2 in subjects who have recovered from COVID-19. *J Clin Invest, 131*(12). https://doi.org/10.1172/JCI14915010.1172/JCI149150DS1

Mercado, N. B., Zahn, R., Wegmann, F., Loos, C., Chandrashekar, A., Yu, J., Liu, J., Peter, L., McMahan, K., Tostanoski, L. H., He, X., Martinez, D. R., Rutten, L., Bos, R., van Manen, D., Vellinga, J., Custers, J., Langedijk, J. P., Kwaks, T., Bakkers, M. J. G., Zuijdgeest, D., Rosendahl Huber, S. K., Atyeo, C., Fischinger, S., Burke, J. S., Feldman, J., Hauser, B. M., Caradonna, T. M., Bondzie, E. A., Dagotto, G., Gebre, M. S., Hoffman, E., Jacob-Dolan, C., Kirilova, M., Li, Z., Lin, Z., Mahrokhian, S. H., Maxfield, L. F., Nampanya, F., Nityanandam, R., Nkolola, J. P., Patel, S., Ventura, J. D., Verrington, K., Wan, H., Pessaint, L., Van Ry, A., Blade, K., Strasbaugh, A., Cabus, M., & Barouch, D. H. (2020). Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. *Nature, 586*(7830), 583–588. https://doi.org/10.1038/s41586-020-2607-z

Mezouar, S., Chantran, Y., Michel, J., Fabre, A., Dubus, J.-C., Leone, M., Sereme, Y., Mège, J., Ranque, S., Desnues, B., Chanez, P., & Vitte, J. (2018). Microbiome and the immune system: From a healthy steady-state to allergy associated disruption. *Human Microbiome Journal, 10*, 11–20.

Michael, H., Langel, S. N., Miyazaki, A., Paim, F. C., Chepngeno, J., Alhamo, M. A., Fischer, D. D., Srivastava, V., Kathayat, D., Deblais, L., Rajashekara, G., Saif, L. J., & Vlasova, A. N. (2020). Malnutrition decreases antibody secreting cell numbers induced by an oral attenuated human rotavirus vaccine in a human infant fecal microbiota transplanted gnotobiotic pig model. *Frontiers in Immunology, 11*. https://doi.org/10.3389/fimmu.2020.0019610.3389/fimmu.2020.00196.s001

Milani, C., Duranti, S., Bottacini, F., Casey, E., Turroni, F., Mahony, J., Belzer, C., Delgado Palacio, S., Arboleya Montes, S., Mancabelli, L., Lugli, G. A., Rodriguez, J. M., Bode, L., de Vos, W., Gueimonde, M., Margolles, A., van Sinderen, D., & Ventura, M. (2017). The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. *Microbiology and Molecular Biology Reviews, 81*(4). https://doi.org/10.1128/MMBR.00036-17

Miller, L., Lehtoranta, L., & Lehtinen, M. (2017). The effect of bifidobacterium animalis ssp. lactis HN019 on cellular immune function in healthy elderly subjects: Systematic review and meta-analysis. *Nutrients, 9*(3), 191. https://doi.org/10.3390/nu9030191

Min, L., & Sun, Q. (2021). Antibodies and vaccines target RBD of SARS-CoV-2. *Front Mol Biosci, 8*, Article 671633. https://doi.org/10.3389/fmolb.2021.671633

Miyazaki, A., Kandasamy, S., Michael, H., Langel, S. N., Paim, F. C., Chepngeno, J., Alhamo, M. A., Fischer, D. D., Huang, H. C., Srivastava, V., Kathayat, D., Deblais, L., Rajashekara, G., Saif, L. J., & Vlasova, A. N. (2018). Protein deficiency reduces efficacy of oral attenuated human rotavirus vaccine in a human infant fecal microbiota transplanted gnotobiotic pig model. *Vaccine, 36*(42), 6270–6281. https://doi.org/10.1016/j.vaccine.2018.09.008

Moradi-kalbolandi, S., Majidzadeh-A, K., Abdolvahab, M. H., Jalili, N., & Farahmand, L. (2021). The role of mucosal immunity and recombinant probiotics in SARS-CoV2 vaccine development. *Probiotics and Antimicrobial Proteins, 13*(5), 1239–1253. https://doi.org/10.1007/s12602-021-09773-9

Mossad, S. B. (2021). Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus: No cause for alarm. *American Journal of Transplantation, 21*(8), 2908. https://doi.org/10.1111/ajt.v21.810.1111/ajt.16687

Müller, L., Andrée, M., Moskorz, W., Drexler, I., Walotka, L., Grothmann, R., Ptok, J., Hillebrandt, J., Ritchie, A., Rabl, D., Ostermann, P. N., Robitzsch, R., Hauka, S., Walker, A., Menne, C., Grutza, R., Timm, J., Adams, O., & Schaal, H. (2021). Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciab381

Nakamoto, N., Sasaki, N., Aoki, R., Miyamoto, K., Suda, W., Teratani, T., Suzuki, T., Koda, Y., Chu, P. S., Taniki, N., Yamaguchi, A., Kanamori, M., Kamada, N., Hattori, M., Ashida, H., Sakamoto, M., Atarashi, K., Narushima, S., Yoshimura, A., Honda, K., Sato, T., & Kanai, T. (2019). Gut pathobionts underlie intestinal barrier dysfunction and liver T helper 17 cell immune response in primary sclerosing cholangitis. *Nature Microbiology, 4*(3), 492–503. https://doi.org/10.1038/s41564-018-0333-1

Noor, R. (2021). Developmental status of the potential vaccines for the mitigation of the COVID-19 pandemic and a focus on the effectiveness of the pfizer-BioNTech and moderna mRNA vaccines. *Curr Clin Microbiol Rep, 8*(3), 178–185. https://doi.org/10.1007/s40588-021-00162-y

O'Toole, P. W., Marchesi, J. R., & Hill, C. (2017). Next-generation probiotics: The spectrum from probiotics to live biotherapeutics. *Nature Microbiology, 2*, 17057. https://doi.org/10.1038/nmicrobiol.2017.57

Oh, J., Ravindran, R., Chassaing, B., Carvalho, F., Maddur, M., Bower, M., Hakimpour, P., Gill, K. P., Nakaya, H. I., Yarovinsky, F., Sartor, R. B., Gewirtz, A. T., & Pulendran, B. (2014). TLR5-mediated sensing of gut microbiota is necessary for antibody responses to seasonal influenza vaccination. *Immunity, 41*(3), 478–492. https://doi.org/10.1016/j.immuni.2014.08.009

Osterholm, M. T., Kelley, N. S., Sommer, A., & Belongia, E. A. (2012). Efficacy and effectiveness of influenza vaccines: A systematic review and meta-analysis. *Lancet Infectious Diseases, 12*(1), 36–44. https://doi.org/10.1016/s1473-3099(11)70295-x

Pabst, O., & Hornef, M. (2014). Gut microbiota: A natural adjuvant for vaccination. *Immunity, 41*(3), 349–351. https://doi.org/10.1016/j.immuni.2014.09.002

Paik, Y. H., Schwabe, R. F., Bataller, R., Russo, M. P., Jobin, C., & Brenner, D. A. (2003). Toll-like receptor 4 mediates inflammatory signaling by bacterial lipopolysaccharide

in human hepatic stellate cells. *Hepatology, 37*(5), 1043–1055. https://doi.org/10.1053/jhep.2003.50182

Pattaroni, C., Watzenboeck, M. L., Schneidegger, S., Kieser, S., Wong, N. C., Bernasconi, E., Pernot, J., Mercier, L., Knapp, S., Nicod, L. P., Marsland, C. P., Roth-Kleiner, M., & Marsland, B. J. (2018). Early-life formation of the microbial and immunological environment of the human airways. *Cell Host & Microbe, 24*(6), 857–865.e4. https://doi.org/10.1016/j.chom.2018.10.019

Pellini R, Venuti A, & Pimpinelli F. (2021). Obesity may hamper SARS-CoV-2 vaccine immunogenicity. *medRxiv*. doi: https://doi.org/10.1101/2021.02.24.21251664.

Philippe, D., Heupel, E., Blum-Sperisen, S., & Riedel, C. U. (2011). Treatment with Bifidobacterium bifidum 17 partially protects mice from Th1-driven inflammation in a chemically induced model of colitis. *International Journal of Food Microbiology, 149*(1), 45–49. https://doi.org/10.1016/j.ijfoodmicro.2010.12.020

Philley, J. V., Kannan, A., Olusola, P., McGaha, P., Singh, K. P., Samten, B., Griffith, D. E., & Dasgupta, S. (2019). Microbiome diversity in sputum of nontuberculous mycobacteria infected women with a history of breast cancer. *Cellular Physiology and Biochemistry, 52*(2), 263–279. https://doi.org/10.33594/000000020

Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., Pérez Marc, G., Moreira, E. D., Zerbini, C., Bailey, R., Swanson, K. A., Roychoudhury, S., Koury, K., Li, P., Kalina, W. V., Cooper, D., Frenck, R. W., Jr., Hammitt, L. L., Türeci, Ö., Nell, H., Schaefer, A., Ünal, S., Tresnan, D. B., Mather, S., Dormitzer, P. R., Şahin, U., Jansen, K. U., & Gruber, W. C. (2020). Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *New England Journal of Medicine, 383*(27), 2603–2615. https://doi.org/10.1056/NEJMoa2034577

Prasad, R., Patton, M. J., Floyd, J. L., Vieira, C. P., Fortmann, S., DuPont, M., Harbour, A., Jeremy, C. S., Wright, J., Lamendella, R., Stevens, B. R., Grant, M. B., . (2021). Plasma microbiome in COVID-19 subjects: an indicator of gut barrier defects and dysbiosis. *bioRxiv*. doi: 10.1101/2021.04.06.438634.

Rabinowich, L., Grupper, A., Baruch, R., Ben-Yehoyada, M., Halperin, T., Turner, D., Katchman, E., Levi, S., Houri, I., Lubezky, N., Shibolet, O., & Katchman, H. (2021). Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *Journal of Hepatology, 75*(2), 435–438. https://doi.org/10.1016/j.jhep.2021.04.020

Ragonnaud, E., & Biragyn, A. (2021). Gut microbiota as the key controllers of "healthy" aging of elderly people. *Immun Ageing, 18*(1), 2. https://doi.org/10.1186/s12979-020-00213-w

Ramasamy, M. N., Minassian, A. M., Ewer, K. J., Flaxman, A. L., Folegatti, P. M., Owens, D. R., Voysey, M., Aley, P. K., Angus, B., Babbage, G., Belij-Rammerstorfer, S., Berry, L., Bibi, S., Bittaye, M., Cathie, K., Chappell, H., Charlton, S., Cicconi, P., Clutterbuck, E. A., Colin-Jones, R., Dold, C., Emary, K. R. W., Fedosyuk, S., Fuskova, M., Gbesemete, D., Green, C., Hallis, B., Hou, M. M., Jenkin, D., Joe, C. C. D., Kelly, E. J., Kerridge, S., Lawrie, A. M., Lelliott, A., Lwin, M. N., Makinson, R., Marchevsky, N. G., Mujadidi, Y., Munro, A. P. S., Pacurar, M., Plested, E., Rand, J., Rawlinson, T., Rhead, S., Robinson, H., Ritchie, A. J., Ross-Russell, A. L., Saich, S., Singh, N., Smith, C. C., & Zizi, D. (2020). Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): A single-blind, randomised, controlled, phase 2/3 trial. *Lancet, 396*(10267), 1979–1993. https://doi.org/10.1016/S0140-6736(20)32466-1

Rampelli, S., Soverini, M., D'Amico, F., Barone, M., Tavella, T., Monti, D., Capri, M., Astolfi, A., Brigidi, P., Biagi, E., Franceschi, C., Turroni, S., Candela, M., . (2020). Shotgun metagenomics of gut microbiota in humans with up to extreme longevity and the increasing role of xenobiotic degradation. *mSystems, 5*(2). doi: 10.1128/mSystems.00124-20.

Rodda, L. B., Netland, J., Shehata, L., Pruner, K. B., Morawski, P. A., Thouvenel, C. D., Takehara, K. K., Eggenberger, J., Hemann, E. A., Waterman, H. R., Fahning, M. L., Chen, Y., Hale, M., Rathe, J., Stokes, C., Wrenn, S., Fiala, B., Carter, L., Hamerman, J. A., King, N. P., Gale, M., Jr., Campbell, D. J., Rawlings, D. J., & Pepper, M. (2021). Functional SARS-CoV-2-specific immune memory persists after mild COVID-19. *Cell, 184*(1), 169–183.e17. https://doi.org/10.1016/j.cell.2020.11.029

Röltgen, K., Nielsen, S. C. A., Arunachalam, P. S., Yang, F., Hoh, R. A., Wirz, O. F., Lee, A. S., Gao, F., Mallajosyula, V., Li, C., Haraguchi, E., Shoura, M. J., Wilbur, J. L., Wohlstadter, J. N., Davis, M. M., Pinsky, B. A., Sigal, G. B., Pulendran, B., Nadeau, K. C., Boyd, S. D., . (2021). mRNA vaccination compared to infection elicits an IgG-predominant response with greater SARS-CoV-2 specificity and similar decrease in variant spike recognition. *medRxiv*. doi: 10.1101/2021.04.05.21254952.

Rothhammer, V., Mascanfroni, I. D., Bunse, L., Takenaka, M. C., Kenison, J. E., Mayo, L., Chao, C. C., Patel, B., Yan, R., Blain, M., Alvarez, J. I., Kébir, H., Anandasabapathy, N., Izquierdo, G., Jung, S., Obholzer, N., Pochet, N., Clish, C. B., Prinz, M., Prat, A., Antel, J., & Quintana, F. J. (2016). Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nature Medicine, 22*(6), 586–597. https://doi.org/10.1038/nm.4106

Russo, A. G., Decarli, A., & Valsecchi, M. G. (2021). Strategy to identify priority groups for COVID-19 vaccination: A population based cohort study. *Vaccine, 39*(18), 2517–2525. https://doi.org/10.1016/j.vaccine.2021.03.076

Sadoff, J., Gray, G., Vandebosch, A.n., Cárdenas, V., Shukarev, G., Grinsztejn, B., Goepfert, P. A., Truyers, C., Fennema, H., Spiessens, B., Offergeld, K., Scheper, G., Taylor, K. L., Robb, M. L., Treanor, J., Barouch, D. H., Stoddard, J., Ryser, M. F., Marovich, M. A., Neuzil, K. M., Corey, L., Cauwenberghs, N., Tanner, T., Hardt, K., Ruiz-Guiñazú, J., Le Gars, M., Schuitemaker, H., Van Hoof, J., Struyf, F., & Douoguih, M. (2021). Safety and efficacy of single-dose Ad26.COV2.S vaccine against covid-19. *New England Journal of Medicine, 384*(23), 2187–2201. https://doi.org/10.1056/NEJMoa2101544

Sasikala, M., Shashidhar, J., Deepika, G., Ravikanth, V., Krishna, V. V., Sadhana, Y., Pragathi, K., Reddy, D. N., . (2021). Immunological memory and neutralizing activity to a single dose of COVID-19 vaccine in previously infected individuals. *Int J Infect Dis, 108*, 183-186. doi: 10.1016/j.ijid.2021.05.034.

See, I., Su, J. R., Lale, A., Woo, E. J., Guh, A. Y., Shimabukuro, T. T., Streiff, M. B., Rao, A. K., Wheeler, A. P., Beavers, S. F., Durbin, A. P., Edwards, K., Miller, E., Harrington, T. A., Mba-Jonas, A., Nair, N., Nguyen, D. T., Talaat, K. R., Urrutia, V. C., Walker, S. C., Creech, C. B., Clark, T. A., DeStefano, F., Broder, K. R., . (2021). US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. *Jama, 325*(24), 2448-2456. doi: 10.1001/jama.2021.7517.

Segal, L. N., Clemente, J. C., Tsay, J.-C., Koralov, S. B., Keller, B. C., Wu, B. G., Li, Y., Shen, N., Ghedin, E., Morris, A., Diaz, P., Huang, L., Wikoff, W. R., Ubeda, C., Artacho, A., Rom, W. N., Sterman, D. H., Collman, R. G., Blaser, M. J., & Weiden, M. D. (2016). Enrichment of the lung microbiome with oral taxa is associated with lung inflammation of a Th17 phenotype. *Nature Microbiology, 1*(5). https://doi.org/10.1038/nmicrobiol.2016.31

Selvaraj, G., Kaliamurthi, S., Peslherbe, G. H., & Wei, D. Q. (2021). Are the allergic reactions of COVID-19 vaccines caused by mRNA constructs or nanocarriers? *Immunological Insights. Interdiscip Sci, 13*(2), 344–347. https://doi.org/10.1007/s12539-021-00438-3

Shu, S.-A., Yuen, A. W. T., Woo, E., Chu, K.-H., Kwan, H.-S., Yang, G.-X., Yang, Y., & Leung, P. S. C. (2019). Microbiota and food allergy. *Clinical Reviews in Allergy and Immunology, 57*(1), 83–97. https://doi.org/10.1007/s12016-018-8723-y

Smith, R. M., Goldberg, R. I., & Jarett, L. (1988). Preparation and characterization of a colloidal gold-insulin complex with binding and biological activities identical to native insulin. *Journal of Histochemistry and Cytochemistry, 36*(4), 359–365. https://doi.org/10.1177/36.4.3279110

So, S. Y., & Savidge, T. C. (2021). Sex-bias in irritable bowel syndrome: linking steroids to the gut-brain axis. *Front Endocrinol (Lausanne), 12*, Article 684096. https://doi.org/10.3389/fendo.2021.684096

Soiza, R. L., Scicluna, C., & Thomson, E. C. (2021). Efficacy and safety of COVID-19 vaccines in older people. *Age and Ageing, 50*(2), 279–283. https://doi.org/10.1093/ageing/afaa274

Sokal, A., Chappert, P., Barba-Spaeth, G., Roeser, A., Fourati, S., Azzaoui, I., Vandenberghe, A., Fernandez, I., Meola, A., Bouvier-Alias, M., Crickx, E., Beldi-Ferchiou, A., Hue, S., Languille, L., Michel, M., Baloul, S., Noizat-Pirenne, F., Luka, M., Mégret, J., Ménager, M., Pawlotsky, J. M., Fillatreau, S., Rey, F. A., Weill, J. C., Reynaud, C. A., & Mahévas, M. (2021). Maturation and persistence of the anti-SARS-CoV-2 memory B cell response. *Cell, 184*(5), 1201–1213.e14. https://doi.org/10.1016/j.cell.2021.01.050

Solforosi, L., Kuipers, H., Jongeneelen, M., Rosendahl Huber, S. K., van der Lubbe, J. E. M., Dekking, L., Veldman, D., Huizingh, J., Kaszas, K., Dalebout, T. J., Myeni, S. K., Kikkert, M., Snijder, E. J., Barouch, D. H., Böszörményi, K. P., Stammes, M. A., Kondova, I., Verschoor, E. J., Verstrepen, B. E., Koopman, G., Mooij, P., Bogers, W., van Heerden, M., Muchene, L., Tolboom, J., Roozendaal, R., Brandenburg, B., Schuitemaker, H., Wegmann, F., & Zahn, R. C. (2021). Immunogenicity and efficacy of one and two doses of Ad26.COV2.S COVID vaccine in adult and aged NHP. *J Exp Med, 218*(7). https://doi.org/10.1084/jem.20202756

Steed, A. L., Christophi, G. P., Kaiko, G. E., Sun, L., Goodwin, V. M., Jain, U., Esaulova, E., Artyomov, M. N., Morales, D. J., Holtzman, M. J., Boon, A. C. M., Lenschow, D. J., & Stappenbeck, T. S. (2017). The microbial metabolite desaminotyrosine protects from influenza through type I interferon. *Science, 357*(6350), 498–502. https://doi.org/10.1126/science:aam5336

Stefan, N., Birkenfeld, A. L., & Schulze, M. B. (2021). Global pandemics interconnected - obesity, impaired metabolic health and COVID-19. *Nature Reviews Endrocrinology, 17*(3), 135–149. https://doi.org/10.1038/s41574-020-00462-1

Sterlin, D., Mathian, A., Miyara, M., Mohr, A., Anna, F., Claër, L., Quentric, P., Fadlallah, J., Devilliers, H., Ghillani, P., Gunn, C., Hockett, R., Mudumba, S., Guihot, A., Luyt, C. E., Mayaux, J., Beurton, A., Fourati, S., Bruel, T., Schwartz, O., Lacorte, J. M., Yssel, H., Parizot, C., Dorgham, K., Charneau, P., Amoura, Z., & Gorochov, G. (2021). IgA dominates the early neutralizing antibody response to SARS-CoV-2. *Science Translational Medicine, 13*(577). https://doi.org/10.1126/scitranslmed.abd2223

Sui, Z., Dai, X., Lu, Q., Zhang, Y., Huang, M., Li, S., Peng, T., Xie, J., Zhang, Y., Wu, C., Xia, J., Dong, L., Yang, J., Huang, W., Liu, S., Wang, Z., Li, K., Yang, Q., Zhou, X., Wu, Y., Liu, W., Fang, X., & Peng, K.e. (2021). Viral dynamics and antibody responses in people with asymptomatic SARS-CoV-2 infection. *Signal Transduct Target Ther, 6*(1). https://doi.org/10.1038/s41392-021-00596-2

Tan, H.-X., Lee, W. S., Wragg, K. M., Nelson, C., Esterbauer, R., Kelly, H. G., Amarasena, T., Jones, R., Starkey, G., Wang, B. Z., Yoshino, O., Tiang, T., Grayson, M. L., Opdam, H., D'Costa, R., Vago, A., Mackay, L. K., Gordon, C. L., Wheatley, A. K., Kent, S. J., & Batac, R. (2021). Adaptive immunity to human coronaviruses is widespread but low in magnitude. *Clin Transl Immunology, 10*(3). https://doi.org/10.1002/cti2.v10.310.1002/cti2.1264

Tan, T. G., Sefik, E., Geva-Zatorsky, N., Kua, L., Naskar, D., Teng, F., Pasman, L., Ortiz-Lopez, A., Jupp, R., Wu, H. J., Kasper, D. L., Benoist, C., & Mathis, D. (2016). Identifying species of symbiont bacteria from the human gut that, alone, can induce intestinal Th17 cells in mice. *Proceedings of the National Academy of Sciences of the United States of America, 113*(50), E8141–E8150. https://doi.org/10.1073/pnas.1617460113

Tavukcuoglu, E., Horzum, U., Cagkan Inkaya, A., Unal, S., & Esendagli, G. (2021). Functional responsiveness of memory T cells from COVID-19 patients. *Cellular Immunology, 365*, 104363. https://doi.org/10.1016/j.cellimm.2021.104363

Thevarajan, I., Nguyen, T. H. O., Koutsakos, M., Druce, J., Caly, L., van de Sandt, C. E., Jia, X., Nicholson, S., Catton, M., Cowie, B., Tong, S. Y. C., Lewin, S. R., & Kedzierska, K. (2020). Breadth of concomitant immune responses prior to patient

recovery: A case report of non-severe COVID-19. *Nature Medicine, 26*(4), 453–455. https://doi.org/10.1038/s41591-020-0819-2
Thiagarajan, K. (2021). What do we know about India's Covaxin vaccine? *BMJ, 373*, Article n997. https://doi.org/10.1136/bmj.n997
Thiele, T., Ulm, L., Holtfreter, S., Schönborn, L., Kuhn, S. O., Scheer, C., Warkentin, T. E., Bröker, B., Becker, K., Aurich, K., Selleng, K., Hübner, N. O., & Greinacher, A. (2021). Frequency of positive anti-PF4/polyanion antibody tests after COVID-19 vaccination with ChAdOx1 nCoV-19 and BNT162b2. *Blood, 138*(4), 299–303. https://doi.org/10.1182/blood.2021012217
Thuluvath, P. J., Robarts, P., & Chauhan, M. (2021). Analysis of antibody responses after COVID-19 vaccination in liver transplant recipients and those with chronic liver diseases. *Journal of Hepatology*. https://doi.org/10.1016/j.jhep.2021.08.008
Torjesen, I. (2021). Covid-19: Norway investigates 23 deaths in frail elderly patients after vaccination. *BMJ, 372*, Article n149. https://doi.org/10.1136/bmj.n149
Townsend, M. J., Kyle, T. K., & Stanford, F. C. (2021). COVID-19 vaccination and obesity: Optimism and challenges. *Obesity (Silver Spring), 29*(4), 634–635. https://doi.org/10.1002/oby.v29.410.1002/oby.23131
Troelnikov, A., Perkins, G., Yuson, C., Ahamdie, A., Balouch, S., Plinio, R. H., & Hissaria, P. (2021). Basophil reactivity to BNT162b2 is mediated by PEGylated lipid nanoparticles in PEG allergic patients. *The Journal of Allergy and Clinical Immunology*. https://doi.org/10.1016/j.jaci.2021.04.032
Trompette, A., Gollwitzer, E. S., Pattaroni, C., Lopez-Mejia, I. C., Riva, E., Pernot, J., Ubags, N., Fajas, L., Nicod, L. P., & Marsland, B. J. (2018). Dietary fiber confers protection against flu by shaping Ly6c(-) patrolling monocyte hematopoiesis and CD8(+) T cell metabolism. *Immunity, 48*(5), 992–1005.e8. https://doi.org/10.1016/j.immuni.2018.04.022
Tunney, M. M., Einarsson, G. G., Wei, L., Drain, M., Klem, E. R., Cardwell, C., Ennis, M., Boucher, R. C., Wolfgang, M. C., & Elborn, J. S. (2013). Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation. *American Journal of Respiratory and Critical Care Medicine, 187*(10), 1118–1126. https://doi.org/10.1164/rccm.201210-1937OC
Turroni, F., Foroni, E., Pizzetti, P., Giubellini, V., Ribbera, A., Merusi, P., Cagnasso, P., Bizzarri, B., de'Angelis, G. L., Shanahan, F., van Sinderen, D., & Ventura, M. (2009). Exploring the diversity of the bifidobacterial population in the human intestinal tract. *Applied and Environment Microbiology, 75*(6), 1534–1545. https://doi.org/10.1128/AEM.02216-08
Tvede, M., & Rask-Madsen, J. (1989). Bacteriotherapy for chronic relapsing Clostridium difficile diarrhoea in six patients. *Lancet, 1*(8648), 1156–1160. https://doi.org/10.1016/s0140-6736(89)92749-9
Vasireddy, D., Atluri, P., Malayala, S. V., Vanaparthy, R., & Mohan, G. (2021). Review of COVID-19 vaccines approved in the united states of america for emergency use. *Journal of Clinical Medicine Research, 13*(4), 204–213. https://doi.org/10.14740/jocmr4490
Vitetta, L., Saltzman, E., Thomsen, M., Nikov, T., & Hall, S. (2017). Adjuvant probiotics and the intestinal microbiome: enhancing vaccines and immunotherapy outcomes. *Vaccines (Basel), 5*(4), 50. https://doi.org/10.3390/vaccines5040050
Vitte, J., Diallo, A. B., Boumaza, A., Lopez, A., Michel, M., Allardet-Servent, J., Mezouar, S., Sereme, Y., Busnel, J. M., Miloud, T., Malergue, F., Morange, P. E., Halfon, P., Olive, D., Leone, M., & Mege, J.-L. (2020). A granulocytic signature identifies COVID-19 and its severity. *J Infect Dis, 222*(12), 1985–1996. https://doi.org/10.1093/infdis/jiaa591
Vlasova, A. N., Chattha, K. S., Kandasamy, S., Liu, Z., Esseili, M., Shao, L., Rajashekara, G., Saif, L. J., & Subbiah, E. (2013). Lactobacilli and bifidobacteria promote immune homeostasis by modulating innate immune responses to human rotavirus in neonatal gnotobiotic pigs. *PLoS ONE, 8*(10), e76962. https://doi.org/10.1371/journal.pone.0076962
Voysey, M., Clemens, S. A. C., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Aley, P. K., Angus, B., Baillie, V. L., Barnabas, S. L., Bhorat, Q. E., Bibi, S., Briner, C., Cicconi, P., Collins, A. M., Colin-Jones, R., Cutland, C. L., Darton, T. C., Dheda, K., Duncan, C. J. A., Emary, K. R. W., Ewer, K. J., Fairlie, L., Faust, S. N., Feng, S., Ferreira, D. M., Finn, A., Goodman, A. L., Green, C. M., Green, C. A., Heath, P. T., Hill, C., Hill, H., Hirsch, I., Hodgson, S. H. C., Izu, A., Jackson, S., Jenkin, D., Joe, C. C. D., Kerridge, S., Koen, A., Kwatra, G., Lazarus, R., Lawrie, A. M., Lelliott, A., Libri, V., Lillie, P. J., Mallory, R., Mendes, A. V. A., Milan, E. P., Minassian, A. M., Pollard, A. J., & Zuidewind, P. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet, 397*(10269), 99–111. https://doi.org/10.1016/S0140-6736(20)32661-1
Walton, G. E., Gibson, G. R., & Hunter, K. A. (2021). Mechanisms linking the human gut microbiome to prophylactic and treatment strategies for COVID-19. *British Journal of Nutrition, 126*(2), 219–227. https://doi.org/10.1017/s0007114520003980
Wang, J., Hou, Z., Liu, J., Gu, Y.e., Wu, Y., Chen, Z., Ji, J., Diao, S., Qiu, Y., Zou, S., Zhang, A., Zhang, N., Wang, F., Li, X., Wang, Y., Liu, X., Lv, C., Chen, S., Liu, D., Ji, X., Liu, C., Ren, T., Sun, J., Zhao, Z., Wu, F., Li, F., Wang, R., Yan, Y., Zhang, S., Ge, G., Shao, J., Yang, S., Liu, C., Huang, Y., Xu, D., Li, X., Ai, J., He, Q., Zheng, M. H., Zhang, L., Xie, Q., Rockey, D. C., Fallowfield, J. A., Zhang, W., & Qi, X. (2021). Safety and immunogenicity of COVID-19 vaccination in patients with non-alcoholic fatty liver disease (CHESS2101): A multicenter study. *Journal of Hepatology, 75*(2), 439–441. https://doi.org/10.1016/j.jhep.2021.04.026
Wang, X., Ba, T., Cheng, Y., Zhang, P., & Chang, X. (2021). Probiotics alleviate adipose inflammation in high-fat diet-induced obesity by restoring adipose invariant natural killer T cells. *Nutrition, 89*, 111285. https://doi.org/10.1016/j.nut.2021.111285
Wang, Z., Schmidt, F., Weisblum, Y., Muecksch, F., Barnes, C. O., Finkin, S., Schaefer-Babajew, D., Cipolla, M., Gaebler, C., Lieberman, J. A., Oliveira, T. Y., Yang, Z., Abernathy, M. E., Huey-Tubman, K. E., Hurley, A., Turroja, M., West, K. A., Gordon, K., Millard, K. G., Ramos, V., Da Silva, J., Xu, J., Colbert, R. A., Patel, R., Dizon, J., Unson-O'Brien, C., Shimeliovich, I., Gazumyan, A., Caskey, M., Bjorkman, P. J., Casellas, R., Hatziioannou, T., Bieniasz, P. D., & Nussenzweig, M. C. (2021). mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. *Nature, 592*(7855), 616–622. https://doi.org/10.1038/s41586-021-03324-6
Weiskopf, D., Weinberger, B., & Grubeck-Loebenstein, B. (2009). The aging of the immune system. *Transplant International, 22*(11), 1041–1050. https://doi.org/10.1111/j.1432-2277.2009.00927.x
Wingert, A., Pillay, J., Gates, M., Guitard, S., Rahman, S., Beck, A., Vandermeer, B., & Hartling, L. (2021). Risk factors for severity of COVID-19: A rapid review to inform vaccine prioritisation in Canada. *BMJ Open, 11*(5), e044684. https://doi.org/10.1136/bmjopen-2020-044684
Wu, L., Zeng, T., Zinellu, A., Rubino, S., Kelvin, D. J., & Carru, C. (2019). A Cross-Sectional Study of Compositional and Functional Profiles of Gut Microbiota in Sardinian Centenarians. *mSystems, 4*(4). doi: 10.1128/mSystems.00325-19.
Wu, S., Zhong, G., Zhang, J., Shuai, L., Zhang, Z., Wen, Z., Wang, B., Zhao, Z., Song, X., Chen, Y., Liu, R., Fu, L., Zhang, J., Guo, Q., Wang, C., Yang, Y., Fang, T., Lv, P., Wang, J., Xu, J., Li, J., Yu, C., Hou, L., Bu, Z., & Chen, W. (2020). A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. *Nature Communications, 11*(1). https://doi.org/10.1038/s41467-020-17972-1
Wu, Z., Hu, Y., Xu, M., Chen, Z., Yang, W., Jiang, Z., Li, M., Jin, H., Cui, G., Chen, P., Wang, L., Zhao, G., Ding, Y., Zhao, Y., & Yin, W. (2021). Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: A randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infectious Diseases, 21*(6), 803–812. https://doi.org/10.1016/S1473-3099(20)30987-7
Xia, S., Duan, K., Zhang, Y., Zhao, D., Zhang, H., Xie, Z., Li, X., Peng, C., Zhang, Y., Zhang, W., Yang, Y., Chen, W., Gao, X., You, W., Wang, X., Wang, Z., Shi, Z., Wang, Y., Yang, X., Zhang, L., Huang, L., Wang, Q., Lu, J., Yang, Y., Guo, J., Zhou, W., Wan, X., Wu, C., Wang, W., Huang, S., Du, J., Meng, Z., Pan, A., Yuan, Z., Shen, S., Guo, W., & Yang, X. (2020). Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. *JAMA, 324*(10), 951. https://doi.org/10.1001/jama.2020.15543
Xia, S., Zhang, Y., Wang, Y., Wang, H., Yang, Y., Gao, G. F., Tan, W., Wu, G., Xu, M., Lou, Z., Huang, W., Xu, W., Huang, B., Wang, H., Wang, W., Zhang, W., Li, N., Xie, Z., Ding, L., You, W., Zhao, Y., Yang, X., Liu, Y., Wang, Q., Huang, L., Yang, Y., Xu, G., Luo, B., Wang, W., Liu, P., Guo, W., & Yang, X. (2021). Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: A randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infectious Diseases, 21*(1), 39–51. https://doi.org/10.1016/S1473-3099(20)30831-8
Xie, X., Liu, Y., Liu, J., Zhang, X., Zou, J., Fontes-Garfias, C. R., Xia, H., Swanson, K. A., Cutler, M., Cooper, D., Menachery, V. D., Weaver, S. C., Dormitzer, P. R., & Shi, P.-Y. (2021). Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. *Nature Medicine, 27*(4), 620–621. https://doi.org/10.1038/s41591-021-01270-4
Yadava, K., Pattaroni, C., Sichelstiel, A. K., Trompette, A., Gollwitzer, E. S., Salami, O., von Garnier, C., Nicod, L. P., & Marsland, B. J. (2016). Microbiota promotes chronic pulmonary inflammation by enhancing IL-17A and autoantibodies. *American Journal of Respiratory and Critical Care Medicine, 193*(9), 975–987. https://doi.org/10.1164/rccm.201504-0779OC
Yagi, K., Huffnagle, G. B., Lukacs, N. W., & Asai, N. (2021). The lung microbiome during health and disease. *International Journal of Molecular Sciences, 22*(19), 10872. https://doi.org/10.3390/ijms221910872
Yakabe, K., Uchiyama, J., Akiyama, M., & Kim, Y.-G. (2021). Understanding Host immunity and the gut microbiota inspires the new development of vaccines and adjuvants. *Pharmaceutics, 13*(2), 163. https://doi.org/10.3390/pharmaceutics13020163
Yan, L., Cai, B., Li, Y.i., Wang, M.-J., An, Y.-F., Deng, R., Li, D. D., Wang, L. C., Xu, H., Gao, X. D., & Wang, L.-L. (2020). Dynamics of NK, CD8 and Tfh cell mediated the production of cytokines and antiviral antibodies in Chinese patients with moderate COVID-19. *Journal of Cellular and Molecular Medicine, 24*(24), 14270–14279. https://doi.org/10.1111/jcmm.v24.2410.1111/jcmm.16044
Yang, Y. (2020). A Study to Evaluate The Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines (Vero Cell) in Healthy Population Aged 18 Years Old and Above (COVID-19) accessed 2 July 2021 https://clinicaltrials.gov/ct2/show/NCT04510207.
Yu, G., Gail, M. H., Consonni, D., Carugno, M., Humphrys, M., Pesatori, A. C., Caporaso, N. E., Goedert, J. J., Ravel, J., & Landi, M. T. (2016). Characterizing human lung tissue microbiota and its relationship to epidemiological and clinical features. *Genome Biology, 17*(1). https://doi.org/10.1186/s13059-016-1021-1
Zhang, J., Wu, Q., Liu, Z., Wang, Q., Wu, J., Hu, Y., Bai, T., Xie, T., Huang, M., Wu, T., Peng, D., Huang, W., Jin, K., Niu, L., Guo, W., Luo, D., Lei, D., Wu, Z., Li, G., Huang, R., Lin, Y., Xie, X., He, S., Deng, Y., Liu, J., Li, W., Lu, Z., Chen, H., Zeng, T., Luo, Q., Li, Y. P., Wang, Y., Liu, W., & Qu, X. (2021). Spike-specific circulating T follicular helper cell and cross-neutralizing antibody responses in COVID-19-convalescent individuals. *Nature Microbiology, 6*(1), 51–58. https://doi.org/10.1038/s41564-020-00824-5
Zhang, S., Zeng, B.o., Chen, Y., Yang, M., Kong, F., Wei, L., Li, F., Zhao, J., & Li, Y. (2021). Gut microbiota in healthy and unhealthy long-living people. *Gene, 779*, 145510. https://doi.org/10.1016/j.gene.2021.145510
Zhao, Y. (2020). Safety and Immunogenicity Study of Inactivated Vaccine for Prevention of SARS-CoV-2 Infection(COVID-19) accessed 2 July 2021 https://clinicaltrials.gov/ct2/show/NCT04383574.
Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. *Cell Research, 30*(6), 492–506. https://doi.org/10.1038/s41422-020-0332-7

Zhou, R., To, K.-W., Wong, Y.-C., Liu, L.i., Zhou, B., Li, X., Huang, H., Mo, Y., Luk, T. Y., Lau, T. T., Yeung, P., Chan, W. M., Wu, A. K., Lung, K. C., Tsang, O. T., Leung, W. S., Hung, I. F., Yuen, K. Y., & Chen, Z. (2020). Acute SARS-CoV-2 infection impairs dendritic cell and T cell responses. *Immunity, 53*(4), 864–877.e5. https://doi.org/10.1016/j.immuni.2020.07.026

Zhou, Z., Ren, L., Zhang, L.i., Zhong, J., Xiao, Y., Jia, Z., Guo, L., Yang, J., Wang, C., Jiang, S., Yang, D., Zhang, G., Li, H., Chen, F., Xu, Y., Chen, M., Gao, Z., Yang, J., Dong, J., Liu, B., Zhang, X., Wang, W., He, K., Jin, Q., Li, M., & Wang, J. (2020). Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell Host & Microbe, 27*(6), 883–890.e2. https://doi.org/10.1016/j.chom.2020.04.017

Zhu, F.-C., Guan, X.-H., Li, Y.-H., Huang, J.-Y., Jiang, T., Hou, L.-H., Li, J. X., Yang, B. F., Wang, L., Wang, W. J., Wu, S. P., Wang, Z., Wu, X. H., Xu, J. J., Zhang, Z., Jia, S. Y., Wang, B. S., Hu, Y., Liu, J. J., Zhang, J., Qian, X. A., Li, Q., Pan, H. X., Jiang, H. D., Deng, P., Gou, J. B., Wang, X. W., Wang, X. H., & Chen, W. (2020). Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: A randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet, 396*(10249), 479–488. https://doi.org/10.1016/S0140-6736(20)31605-6

Zhu, F.-C., Li, Y.-H., Guan, X.-H., Hou, L.-H., Wang, W.-J., Li, J.-X., Wu, S. P., Wang, B. S., Wang, Z., Wang, L., Jia, S. Y., Jiang, H. D., Wang, L., Jiang, T., Hu, Y., Gou, J. B., Xu, S. B., Xu, J. J., Wang, X. W., Wang, W., & Chen, W. (2020). Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: A dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet, 395*(10240), 1845–1854. https://doi.org/10.1016/S0140-6736(20)31208-3

Zou, J., Xie, X., Fontes-Garfias, C. R., Swanson, K. A., Kanevsky, I., Tompkins, K., Cutler, M., Cooper, D., Dormitzer, P. R., & Shi, P.-Y. (2021). The effect of SARS-CoV-2 D614G mutation on BNT162b2 vaccine-elicited neutralization. *npj Vaccines, 6*(1). https://doi.org/10.1038/s41541-021-00313-8

Zuo, W., & Zhao, X. (2021). Natural killer cells play an important role in virus infection control: Antiviral mechanism, subset expansion and clinical application. *Clinical Immunology, 227*, 108727. https://doi.org/10.1016/j.clim.2021.108727