# Beyond lockdowns, drugs and vaccines: Is there a smarter path to prepare our communities for novel pathogens?

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## Abstract

The coronavirus disease 2019 (COVID-19) spreading around the world has made a profound impact on emergency responding and policy-making in a public health crisis. Mandates on human activities for controlling the virus spread and classical cures for those infected, such as travel restrictions, lockdowns, repurposed drugs and vaccines, are unsatisfactory due to their negative impact or inherent limitations. A series of epidemics and pandemics endured by humans in the past two decades have set out a looming crisis of zoonotic pathogens frequently spilling over to humans, potentially caused by the radical expansion of anthropogenic activities disrupting ecological balances. This is exacerbated by the ever-increasing microbial resistance to therapeutic drugs and painfully slow process of vaccine research and development when facing lethal and fast spreading novel pathogens. Faced with these longstanding and emerging challenges, there is an imperative need for scientists and public health authorities to find a smarter path to prepare our communities for novel pathogens, beyond the current lockdowns, drugs and vaccines. Here we present a critical and updated assessment of the classical and emerging therapeutics for COVID-19, with a focus on the alternative treatments advocated in contemporary literature as well as long-term preventative strategies against human infections by pathogens. The strength and limitations of antibiotic and antiviral drugs, vaccines, and antibody-based therapeutics are discussed in the context of the current pandemic. Bacteriophages, probiotics, and proven methods of improving the functioning of the human immune system are highlighted as potential cures and preventive strategies which may gain more significant roles in our fights with novel pathogens in a future uncertain world.

***Keywords:*** Coronavirus; SARS-CoV-2; microbiota; immunotherapy; probiotics; immune system

## 1. Microbes and humans: Battles and cures

Microbes have lived and multiplied on earth for billions of years (Schopf et al. 2018). They have witnessed and, in some cases, facilitated the progress of human civilization. Bacteria, for instance, are nature's 'decomposers' which not only participate in natural energy flow and material circulation, but constitute an intrinsic part of the human metabolic system (Yatsunenko et al. 2012). As much as 8% of human genome consist of retroviral gene fragments. These 'gene fossils' are relics of human ancestors who survived viruses and epidemics (Wildschutte et al. 2016). Some microbes, called pathogens, are harmful and threaten human life and health. Indeed, millions of lives have been lost in epidemics caused by the infections and spread of pathogens in human history (Morens and Fauci 2020). With the ecological balance being disrupted by expanding social and industrial activities, more novel pathogens have spilled over to humans (Cui et al. 2019). In the past 20 years, humans endured a series of epidemics and pandemics including, most notably, 2002–04 Severe acute respiratory syndrome (SARS), 2009 swine flu (H1N1), 2012 Middle East respiratory syndrome (MERS), 2017–18 US seasonal influenza, 2013–16 Ebola virus and recently, the novel coronavirus disease (COVID-19), mostly caused by zoonotic pathogens (https://en.wikipedia.org/wiki/List_of_epidemics). At present, the global death toll has reached over 1.3 million, with more than 55 million people infected by the novel coronavirus (WHO, 2020a). While pathogens contribute to the evolution of living species on earth, the massive outbreaks of highly contagious and lethal pathogens may bring a devastating catastrophe to humans and some animals (Dyer 2020, O'Hanlon et al. 2018).

Centuries of scientific advancements have allowed humans to better understand microbes and even made use of them to fight against some pathogens (**Fig. 1**). In our long history of fight against

pathogens, microbes have made tremendous contributions in saving human lives and maintaining public health (Newman and Cragg 2016). Along with synthetic chemical drugs (FDA 2018), many bio-derived drugs and biologics are potent cures and consist an essential part of modern medicines for treating human infections (Newman and Cragg 2020). Despite the impressive achievements, however, great challenges remain when tackling with a novel and rapidly spreading human pathogen. Now standing at the eleventh month since the onset of the current pandemic, there is still no vaccine or specific treatment available to the public for COVID-19 (Pan et al. 2020). Faced with this dilemma, refraining people from social activities, *i.e.*, travel restrictions and 'lockdowns', are mandated in many countries and regions as the best available approach to slow the spread of the virus in communities (Lau et al. 2020). Once put in place, however, these restrictions would cause severe disruptions to normal social, cultural, and economical activities in our societies. Moreover, new challenges continue to emerge from current persisting pandemic with re-emergent outbreaks (Han et al. 2020), novel viral strains (He et al. 2020), and reinfections that arise from the continuing spread and evolution of the virus (To et al. 2020), even with the current lockdowns in place. In light of these difficulties and uncertainties, one would ask the question by going back to square one: is there a smarter path to prepare our communities against novel pathogens beyond current lockdowns, drugs, and vaccines?

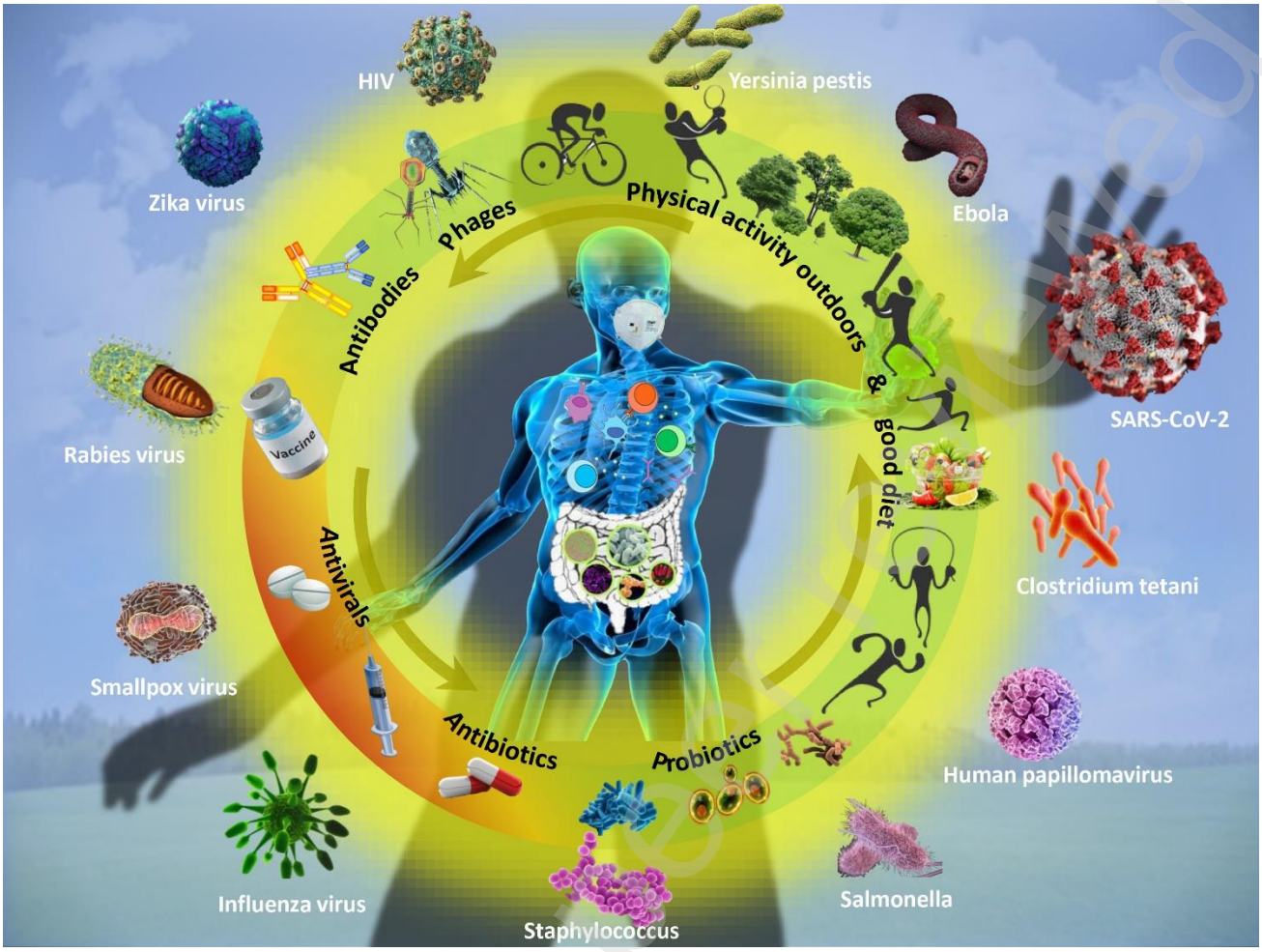


**Fig. 1** Human pathogens and various strategies available for fighting against them, including antibiotic and antiviral drugs, vaccines, antibodies, beneficial microbes, and methods to improve the functioning of human immune system (physical activities, maintaining a balanced diet, and spending time in natural environments)

## 2. Antibiotics and antivirals: A double-edged sword

Since the nineteenth century, major advancements in chemistry, microbiology and genetics have paved the way for a 'golden era' of drugs, with successful developments of pioneering drugs such as the aspirin in 1897 (Berk et al. 2013), insulin in 1922 (Forsham 1982), penicillin in 1929 (Mehnaz

2013), and Chemotherapeutic agents (Wang et al. 2017). While antibiotics and antivirals are highly effective in treating human infections and have made tremendous contributions to public health, they are generally less effective in treating infections caused by novel pathogens (De Clercq and Li 2016). So far, none of the antiviral drugs can effectively fight against rabies, Ebola, and emerging coronaviruses such as MERs-CoV and SARS-CoV-2. One the other hand, the abuse of antibiotics destroys the balanced state between antibacterial drugs and bacterial resistance (Li et al. 2016). Through constant evolution and mutation, bacteria with single-drug resistance gradually evolve to become multi-drug or even pan-drug resistant, and eventually becoming 'superbugs' that are extremely difficult to treat with existing medicines (Rusu et al. 2015, Shin 2017). *Staphylococcus aureus* is a known drug-infective bacterium with high clinical importance, as it is almost resistant to all antibiotics (Antunes et al. 2020). *Pseudomonas aeruginosa* is resistant to multiple antibiotics and consequently joined the ranks of 'superbugs' due to its enormous capacity to engender resistance (Breidenstein et al. 2011). Indeed, the overuse and misuse of antibiotics and antivirals has been recognized as one of the grand challenges in human health care (Feigman and Pires 2018). One study reported that over 80% of outpatients with upper respiratory tract infections (URTIs) were prescribed with antibiotics (Li et al. 2016), although etiological studies show that the main cause of URTIs is viral infection, and only less than 10% of URTI cases are caused by bacteria and require antibiotic treatment (Costelloe et al. 2010). In a recent report, the World Health Organization (WHO) highlighted a staggering surge of resistance to two key antiviral drugs for treating human immunodeficiency virus (HIV), Efavirenz and Nevirapine (WHO 2019). The report further noted that combating antimicrobial resistance, including the emerging threat posed by drug-resistant HIV, is a major task of the research community. Further, excessive use of these drugs can severely disrupt

the microorganism communities in human bodies, causing massive elimination of beneficial microbes and aggressive selection of drug-resistant species (Croswell et al. 2009, Lawley et al. 2009, SanMiguel et al. 2017). Infections by drug-resistant pathogens lead to higher morbidity and mortality in patients, and impose additional burden and costs on our society (Wojewodzic 2020). In the U.S. alone, at least 2.8 million people are infected with antibiotic-resistant bacteria each year, and more than 35,000 people eventually die from these infections (CDC 2019). According the U.S. Centers for Disease Control and Prevention (CDC), antibiotic-resistant infections cost $20–$35 billion in direct healthcare costs annually in the United States (CDC 2014).

## 3. Vaccines: An intelligent but lagging approach

The discovery of vaccines seemed to remind us that our body's immune system is the most intelligent weapon against invading pathogens. A preventive approach, the efficacy of vaccination has been proven on numerous human pathogens, such as smallpox, rabies, and tetanus (Ozawa et al. 2011). Subunit vaccines, non-replicating whole-virus or whole-bacteria vaccines, and attenuated live vaccines have all been shown to be highly effective in vaccinated populations, saving millions of lives today (Amanna and Slifka 2020, Yang et al. 2016). There are, however, inherent challenges and limitations on the development and use of vaccines (Dai et al. 2020). The research on any prospective vaccine requires stringent laboratory and clinical trials, a process that often takes years to complete to ensure its safety and efficacy (Wang et al. 2020b). Due to the long course of development and high specificity, vaccines are generally not considered as the first choices when responding to public health emergencies caused by novel pathogens (Lachenbruch 1998). Also, the

inability to adapt to new variants of pathogens may become the Achilles's heel of a vaccine. Rapidly evolving and frequently mutating pathogens, such as the HIV and *Helicobacter Pylori*, can make it prohibitively difficult to develop effective vaccines against them (Pavlakis and Felber 2018, Sutton and Boag 2019). For those which spread by selective routes (*e.g.*, HIV), we could perhaps wait for the eventual success of vaccine development while implementing effective measures by promoting public awareness and limiting their spread in the population. When dealing with a fast spreading and lethal novel pathogen, such as the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we simply do not have enough time to cross one failure after another.

## 4. Antibodies: Promising cure with low yields

Since the purpose of vaccination is to create specific antibodies, a natural question is that can we produce antibodies from other living organisms and supplement them to the human body? The discovery of passive immunotherapy in the late nineteenth century already answered this question, which also marked the beginning of a new type of therapeutic treatment (Rosenberg and Terry 1977). Since then, significant progress has been made in the field of immunotherapy, from murine monoclonal antibodies to the development of humanized antibodies (Manohar et al. 2015). The application of genetic engineering also brought new opportunities for the development of antibody drugs in recent years (Karagiannis et al. 2012). As COVID-19 sweeps across the world, antibody-based therapeutics has once again attracted wide attention for its ability to protect the host from being infected by the novel coronavirus. One of the antibodies was able to identify and bind to a particular protein on SARS-CoV-2 and subsequently render the virus incapable of infecting human

cells. The type of antibody, called 'neutralizing antibody', is regarded as one of the most promising treatment for COVID-19 (Shi et al. 2020). In a recent study, researchers selected a monoclonal antibody from transgenic mice and combined it with antibody-containing plasma of recovered patients, formulating a therapeutic cocktail for treating the novel coronavirus disease (Harrison 2020). This type of treatment, which received wide media coverage in the recent high-profile case of treating Donald J. Trump, the 45$^{th}$ President of the United States, can be highly effective and is well suited for treating individual patients. In a pandemic with widespread infections, however, it is difficult to adopt it for treating a large population due to the inherently low yield and long preparation cycle of antibodies. Further, since neutralizing antibodies only provide short-term prevention, patients would need replenishing of antibodies every 1–2 months after receiving the initial treatment (Ferner and Aronson 2020, Harrison 2020)

## 5. Phages: Picky predators for bacterial pathogens

Phagocyte is a type of cell in the human immune system that has the ability to ingest – and sometimes digest – foreign substances and pathogens. It is one of the body's natural defense mechanisms (Carlos and Harlan 1990). Interestingly, there is also a type of virus in nature – called 'bacteriophages' – which can 'munch on' bacteria. Bacteriophages have been used for treating people with bacterial infections in Russia and surrounding countries since the 1920s (Lammens et al. 2020), although the antibiotics that emerged later gradually took away their halo. In recent years, with the advent of 'super bacteria', phage research has returned in sight. In 2019, the U.S. Food and Drug Administration (FDA) approved the first clinical trial of intravenously administered bacteriophage

therapy (Voelker 2019). Systems biologist Marcin Wojewodzic recently commented that phages could be used to help COVID-19 patients by suppressing bacterial co-infections and producing antibodies (Wojewodzic 2020). Some phages are known to prey on bacterial pathogens that can cause human respiratory failure. By further modifying their genomes, phages can also be used as mini production factories for making protective antibodies against the virus. Compared with vaccines and antibodies, the development cycle for phage treatment is often shorter and the yield can be considerable (Lammens et al. 2020). Since phages are 'picky predators' and only act on specific types of bacteria (Sulakvelidze et al. 2001), the high specificity to target bacterium species gives the benefit of causing minimal damages to beneficial microbes in patient's body (Wojewodzic 2020). Provided that such treatment is successful in clinical trials, it has the potential to become an augmented therapy for treating bacterial co-infections in COVID-19 patients.

## 6. Probiotics: A strong foundation for developing novel therapeutics

There are about 9–10 times as many microbes as there are cells in the human body. Many of them are beneficial to human metabolic activities, which are often referred to as beneficial microbes, or 'probiotics' (Mandel et al. 2019). Over the past two decades, we have witnessed a surge in research on beneficial microbial communities with robust developments in the application of immunobiotics to combat human infections (Bhushan et al. 2019, Mandel et al. 2019). As the dominant organisms in human microbiome, probiotics play an indispensable role in the functioning of the human immune system. For instance, probiotics strengthen the gastrointestinal barrier by regulating tight junctions between intestinal epithelial cells (Zhang et al. 2018). One study showed

that *Bacillus subtilis* strain 29784 enhanced the expression of tight junction proteins including zonula-1, occludin, and claudin-1 to reinforce the intestinal barrier integrity (Rhayat et al. 2019). Some probiotics could inhibit the invasion or overgrowth of pathogens (O'Callaghan and Corr 2019). Such effects have been demonstrated by the facts that intestinal microbiota can provide colonization resistance to infected *Citrobacter rodentium* (Lawley et al. 2009), and the cecal colonization of *enterohemorrhagic E. coli*, an enteric pathogen, could be reduced by commensal *E. coli* strains that compete for proline, a proteinogenic amino acid (Sassone-Corsi and Raffatellu 2015). The inhibition activity of *Lactobacillus* strains has also been proven on several pathogenic bacteria such as *Salmonella*, *Shigella*, *Escherichia coli*, *Enterobacter*, where *Lactobacillus* strains produced bioactive soluble molecules to inhibit the growth of invading pathogens (Iordache et al. 2008). In a more recent study, probiotics *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a were found to inhibit the colonization of upper-airway pathogens and reduced the inflammation on human respiratory mucosa by interfering with the biofilm formation of pathogens and dispersing their pre-formed biofilms (Bidossi et al. 2018). Probiotics can also boost human immune functions by secreting bio-enzymes and bioactive peptides to promote the multiplication of immune cells and to participate in the repair of organs and tissues (Kasahara et al. 2018, Lai et al. 2010, Mandel et al. 2019). One study showed that probiotics in HIV-infected patients exhibited therapeutic effects by restoring the functions of the epithelial barrier, facilitating the secretion of cluster differentiation $(CD4)^+$ T-cells, and promoting immune activation (D'Angelo et al. 2017). Evidence was also found that various human skin resident microbes controlled the expression of antimicrobial peptides (Gallo and Hooper 2012) and augmented cutaneous IL-1 signaling to promote T-cells effector functions (Naik et al. 2012). Meisel et al. (2018) further confirmed these findings at the transcriptome level

and revealed that skin microbiome mediated the immune response and epidermal development and differentiation through modulating gene expression.

Some researchers have explored the possibility of developing probiotic-based therapies for COVID-19 treatment. A recent investigation on changes in intestinal bacteria during COVID-19 patients' hospitalization highlighted the concept that novel and targeted modulation of gut microbiota may present a therapeutic avenue for COVID-19 and comorbidities (Zuo et al. 2020). In a recent review focusing on the use of beneficial microbes to protect the public in the ongoing pandemic, Antunes et al. (2020) presented evidence supporting the use of probiotics and prebiotics to promote gut and lung immunity. With new knowledge and insights into the functions of beneficial microbiota, the discovery of new probiotics and further understanding of their mechanisms of actions could provide a strong foundation for developing novel therapeutics against human infections by novel pathogens.

## 7. Our immune system: An evolving arsenal in future battles with pathogens

While the COVID-19 pandemic has caused over 1.3 million deaths and a greater number of hospitalizations, there has been a significant portion of asymptomatic and self-recovering individuals among those infected (Oran and Topol 2020). It is believed that after infected with COVID-19, symptom aggravation not only depends on the viral loads and strains from the initial transmission, but closely related to the functioning of the individual's immune system. If COVID-19 becomes an endemic like influenza and malaria (WHO 2020b), as many have suggested (WHO 2020c), then probably the best preventive strategy is to increase the immunity of the general population,

particularly those who are at elevated risks or more vulnerable to infections. Without public access to effective vaccines or specific treatment, a properly functioning immune system could be our most reliable and last line of defense for COVID-19 and its variants, and novel pathogens that will emerge in the future.

There are viable methods, many of which have been proven to increase the immunity of the human body, if practiced routinely (Lichtfouse 2020). To begin with, it has been long recognized that maintaining an adequate level of physical activities has profound effects on the functioning of the human immune system. Regular exercising improves immune regulation by affecting leucocytes, red blood cells, and cytokines while it also contributes to preventing infections and curing diseases (Wang et al. 2020a). Yoga, which originated in ancient India and is often recommended for people with depression or eating disorders, is an easy-to-practice exercise for promoting one's physical and mental health (Greenlee et al. 2017). A recent study found that yoga practitioners overall enjoyed better health and had healthier lifestyles compared with the wider population (Cramer et al. 2019). Other alternatives such as Tai Chi, a traditional internal Chinese martial art, improves the well-being of a person and helps prevent or alleviate chronic conditions (Guo et al. 2014). Secondly, maintaining a healthy diet is an essential step for keeping the proper functioning of the intestinal immune system (Molendijk et al. 2019). A good, balanced diet rich in vitamins, probiotics, and other nutrients preserves the balance of gut microbiota and the body's metabolism (Schmidt et al. 2018, Shoaie et al. 2015). Last but not the least, being close to nature by spending time in natural outdoor environments can do wonders for one's health. There is a lot of hidden knowledge in these ecological medicines and treatments. The green and park prescriptions Swinburn et al. (1998) told many stories about the health benefits of spending time in nature. Seltenrich (2015) suggested using parks to

improve children's health after reviewing ample documented evidence that children have much to gain from their activities in natural environments, which enhance their emotional well-being and amplify the benefits of physical exercise. In a review focused on how living and interacting with nature promote human health, Kuo (2015) discussed over twenty mechanisms in the nature-health connection. By dividing those into three groups, namely, active ingredients or environmental conditions including volatile organic chemicals emitted by plants, sights and sounds of nature, and protection from air pollutants and heat, Kuo concluded that improved immune functions is a common outcome of health benefits acquired from such practices. There is also emerging evidence that evergreen Mediterranean forests and shrubland plants may have alleviated the infections and symptom aggravation of COVID-19 in southern Italy (Roviello and Roviello 2020). With a growing global population, urbanization, and industrialization, it can be anticipated that more novel pathogens, including zoonotic agents will emerge in the future (Zhong et al. 2020). While modern medicine and treatments are essential building blocks of the public health systems, a smarter path could be pursued to provide long-term protection for people to live well in the future world. Studies on probiotics and the human immune system, maintaining a healthy lifestyle, learning to live and evolve with microbial flora in nature may provide the ultimate answers for humans to adapt to the future uncertain world.

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## Conflict of Interest

The authors declare that they have no conflict of interest in this work.

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