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REVIEW

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Potential of live pathogen vaccines for defeating the COVID-19 pandemic: History and mechanism

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Abstract

The whole world has entered a terrible crisis with a huge and increasing number of human deaths and economic losses in fighting the pandemic of COVID-19 caused by the novel coronavirus termed SARS-CoV-2. The live pathogen vaccine (LPV) strategy, which originated in ancient China for fighting smallpox, has been applied successfully by US military recruits for decades to control acute respiratory diseases caused by types 4 and 7 adenoviruses. This strategy has also been widely employed in veterinary medicine. These facts suggest a fast way out of the current pandemic crisis, namely that SARS-CoV-2 could be directly used as a live vaccine. Beyond the two traditional mechanisms to guarantee the LPV's safety (the LPV seed strain is properly selected; the LPV is inoculated bypassing the respiratory sites of pathology), three novel mechanisms to further ensure the LPV's safety are available (the virus replication is inhibited with early use of an antiviral drug; symptomatic LPV recipients are cured with convalescent plasma; the LPV is inoculated in the hot season). This LPV strategy has multiple potential advantages over other options and could reduce morbidity and mortality greatly as well as the economic loss caused by the pandemic. The safety and efficacy of this strategy should be investigated strictly using animal experiments and clinical trials, and even if the experiments and trials all support the strategy, it should be implemented with enough caution.

KEYWORDS

antiviral, coronavirus, pandemic, safety, strategy, vaccine

1 | THE PANDEMIC CRISIS

The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus termed SARS-CoV-2 is spreading rapidly worldwide.[1] Over two million cases have been confirmed, and approximately 6% of them were fatal.[1]

Multiple types of vaccines are under urgent development, and some of them have entered clinical trial.[2-7] As no vaccine against coronavirus has been widely used in humans, experience is scant regarding the safety and efficacy of vaccination against COVID-19. Moreover, the development of vaccines against SARS CoV, which caused a deadly outbreak in the 2000s, encountered much difficulty.[3-7] The difficulty has also manifested in research on coronavirus vaccines in veterinary medicine.[8] First, coronaviruses can escape the immunity induced by inactivated vaccines or recombinant protein vaccines through rapid evolution.[8] Second, live attenuated vaccines of coronaviruses can regain their virulence through serial passages in cell culture or in vivo.[9] Third, sometimes vaccination in animals and humans may aid rather than inhibit pathogenesis of the targeted viruses. This phenomenon of vaccination enhancement may result from antibody-dependent enhancement, a process in which specific antibodies aid the infection of the targeted virus, or cell-based enhancement, a process involving allergic inflammation caused by immunopathology.[5] Vaccination enhancement has been observed in the research on SARS vaccines and may be a pitfall in the development of COVID-19 vaccines.[3-8]

Due to the difficulty in vaccine development, it is possible that no safe and effective vaccines will be marketed before 2022 when the pandemic will likely end worldwide, although various vaccines against COVID-19 are under development with unprecedented rapidity.[3,10] This possibility puts the whole world into a terrible crisis, and most countries have to maintain the blocking-and-curing strategy for months, which is very costly with too many deaths, too much uncertainty, and extensive chaos.

Bold strategies that are rational have been more effective than orthodox ones in multiple wars over history. Similarly, the live pathogen vaccine (LPV) strategy analyzed in this paper is bold and rational, and could be a fast way out of the pandemic crisis.

2 | THE LPV HISTORY

Infectious acute respiratory disease (ARD) is prevalent in US military recruits.[11] The disease persists for 3 to 10 days with fever, cough, sore throat, nasal discharge, headache, and fatigue. The majority of these ARD cases are caused by an adenovirus, usually types 4 and 7 and less frequently types 3, 14, and 21.[12] Historically, adenovirus has infected up to 80% of recruits, 20% of whom may be hospitalized; 90% of hospitalized cases of pneumonia in recruits have been attributed to adenovirus infections.[12]

Inactivated vaccines against adenoviruses were first investigated in the military, and they showed variable degrees of protection.[13] Concerns over the oncogenic potential of simian virus 40 contaminated in the cell lines used for growth of the adenoviruses have further hampered the application of the inactivated vaccines.[11] Recently, the oncogenic potential of simian virus 40 contaminated in cell lines was found to be unsubstantiated.[14]

Adenoviruses can also replicate in the intestinal tract.[13] This suggested that it might be possible to selectively infect the intestinal tract to bypass the respiratory tract where pathologic changes most often occur.[13] Subsequent attempts at intestinal infection with live wild pathogenic adenovirus were found to yield high rates of seroconversion with few adverse effects, leading to the birth of the LPV against human infectious diseases.[12] Initial application of the adenovirus LPV resulted in greatly reduced type 4 adenovirus infections and increased type 7 adenovirus infections.[12] Therefore, the bivalent LPV containing types 4 and 7 replaced the previous LPV only containing type 4 adenovirus.[12,13,15]

Routine vaccination with the bivalent LPV in US recruits began in 1971, and rates of adenovirus-associated ARD were reduced by up to 96%.[13] Despite their efficacy, the LPV vaccination was suspended in 1999 due to commercial reasons, and adenovirus-associated ARD in military recruits resurged. In October 2011, the bivalent LPV was universally administered to military recruits again, and adenovirus-associated ARD cases decreased by 99.66% among recruits.[15]

Hundreds of years ago, the LPV of smallpox virus was widely inoculated nasally in ancient China to prevent smallpox. The inoculation was effective although it caused a disease milder than the natural infection.[16] Later, this inoculation was replaced with the safer vaccine based on the cowpox virus. Like the fight against smallpox, the LPV strategy was widely used in veterinary medicine to reduce morbidity and mortality of rinderpest and swine fever at a time before live attenuated vaccines were developed.[17] In the 1980s, rotavirus caused diarrhea in pigs in China. The LPV of swine rotavirus was employed for years because the pigs did not show symptoms and yielded excellent immunity after they were intramuscularly injected with pathogenic swine rotavirus to bypass the intestine of pathology.[18] Currently, LPVs of moderate virulence continue to be used in poultry worldwide, to induce strong immunity against avian infectious laryngotracheitis, Newcastle disease, and infectious bursal disease.[19,20]

3 | THE SAFETY MECHANISMS

The safe and successful prevention of adenovirus-associated ARD in the US recruits suggests, not proves, that the LPV strategy could pave a way out of the terrible crisis of the coronavirus pandemic. In theory, five mechanisms can be employed to guarantee the safety of the LPV of SARS-CoV-2.

First, the seed strain of the LPV of SARS-CoV-2 is properly selected. In general, SARS-CoV-2 itself is not highly pathogenic as compared with the rabies virus, human immunodeficiency virus, Ebola virus, Nipah virus, and SARS CoV. Most natural infections of SARS-CoV-2 have no or mild symptoms, and the virus does not persist in most cases.[21,22] Moreover, SARS-CoV-2 is of distinct difference in pathogenesis and replication rate among strains, and the ideal seed strain of the LPV could be selected from those showing less pathogenesis and higher replication rate in cell culture.

Second, like the adenovirus LPV, the LPV of SARS-CoV-2 is intestinally inoculated through enteric-coated capsules, to move the battlefield from the lungs to the intestine. The outcome of the viral infection is determined by the battle between the immune system and the virus. The virus can kill immune cells and other cells through its replication or using its viruporins, and the immune system can kill the virus using chemokines, cytokines, complement factors, antibodies, macrophages, NK cells, and cytotoxic T lymphocytes.[9] The immunity of the intestine is likely stronger than that of respiratory organs, because the intestine has been successfully fighting against more pathogens in species and in amount during human evolution over millions of years. Although the virus can move from the intestine to other organs, this movement could be time-consuming, and thus could save time for the host to generate the acquired immunity to fight against the virus. Moreover, the intestine and the lungs are mainly responsible for providing nutrients and oxygen, respectively. As human bodies store nutrients for the needs of days and oxygen for a need of only seconds, infection and inflammation in the intestine is less fatal than in the lungs. Additionally, infection and inflammation in the lungs can affect the critical organ of the heart. Together, supported by the adenovirus LPV, the LPV strategy could reduce greatly morbidity and mortality.

Third, early use of antiviral drugs could substantially improve the LPV's safety. Successful treatment of COVID-19 patients involves three aspects: effectively inhibiting the virus replication which is the primary mechanism of viral pathogenesis, effectively repairing the damage in the lungs and other organs caused by the battle between the host and the virus, and effectively combating secondary mixed infections.[22-27] Obviously, few drugs have excellent efficacy in all these three aspects, and this is a challenge in judging the efficacy of medications for COVID-19. Nevertheless, some medications including remdesivir, chloroquine, and some traditional Chinese medicines like the one termed Lianhuaqingwen, have excellent efficacy in reducing virus replication in cell culture and inside patients.[24-27] Hence, early use of these medications following inoculation of the LPV could effectively inhibit virus replication in time. This could prevent damage in various organs and mixed infections subsequent to the LPV inoculation, and guarantee the safety of the LPV strategy thereby. Additionally, some antibiotics can be used to prevent secondary bacterial infection associated with the LPV vaccination.

Fourth, if only a few people vaccinated with the LPV of SARS-CoV-2 become ill, even though they have taken an effective drug in time to inhibit the virus replication, they could be cured in time with convalescent plasma (CP). Passive immunotherapy using CP has showed excellent efficacy in curing severe patients with COVID-19.[28-31] In theory, its efficacy should be better in curing mild patients upon onset of symptoms.[32] Importantly, many recipients of the LPV vaccine or CP are potential candidates for donating CP, and this could ensure the supply of CP for the LPV strategy.

Fifth, mass vaccination of the LPV is conducted in the hot season when other respiratory infections are much rarer than in the cold season. This could reduce mixed infections and thus further safeguard the safety of the LPV strategy.

Importantly, inoculation of the LPV does not increase the risk to the world, because otherwise the virus will also spread to every corner of the world, and almost everyone will contact it one or more times.

4 | THE REQUIRED TESTS

The safety and efficacy of the LPV strategy theoretically analyzed above should be carefully confirmed using robust animal experiments and clinical trials.

First, animal experiments should be conducted to answer the following questions: What are the differences in pathology of the infection initiated at the small intestine, rectum, subcutaneous sites, muscles, and the respiratory tract? What are the differences in reducing virus replication by antiviral drugs administered at different time points after virus inoculation? What are the differences in immune responses induced by the virus inoculated at different sites followed by administration of antiviral drugs at different time points? Are the vaccinated animals immune to the challenge of SARS-CoV-2? Is boost immunization needed to secure solid immunity against the virus? Some of these experiments can be conducted rapidly using golden Syrian hamsters or ferrets rather than rhesus monkeys.[33,34]

Second, clinical trials could be conducted by a special approach involving two parts. The first part is to investigate whether early use of an antiviral medication upon infection confirmation and early use of CP upon symptom onset could reduce greatly the morbidity and mortality of COVID-19. The second part is to examine whether inoculation of the LPV bypassing the respiratory sites could also reduce morbidity and mortality greatly.

The current prevalent natural infections of the virus make clinical trials relatively readily available to implement the first part of the clinical trials. With informed consent, high-risk uninfected persons should be monitored twice a day to determine when they will be infected by SARS-CoV-2. A clinically approved antiviral medication is administered to some of these uninfected people once they are found to be infected with SARS-CoV-2, and 50 mL CP is administered to some of these infected people once they show mild symptoms, all with informed consent. Subsequent clinical symptoms and indexes of these people, including virological and immunological data, are recorded. Those naturally infected people carrying only the symptom of diarrhea are highly valuable for clinical trial, and their data should be analyzed separately. As this part reduces the risk of all participants without inoculation of the LPV of SARS-CoV-2, over 500 naturally infected people could be recruited to integrate the three phases of the clinical trials for this part into one big trial.

If the first part of the clinical trials and the relevant animal experiments yield supportive results, the LPV strategy requires three phases of clinical trials as per official requirements, to further confirm its safety and efficacy. Optimization of the manufacturing process could be started simultaneously, and some novel technologies could be employed, particularly regarding storage and distribution of live vaccines at ambient temperature.[35] Similarly, the people involved in phase two and phase three clinical trials could be selected from those at great risk to be infected naturally. Under the current severe pandemic situation, it is moral and ethical to recruit enough people to participate in the trials.[36]

If the animal experiments or the first part of the clinical trials do not support the LPV strategy, the efforts toward this strategy should be terminated. No matter what the results of the animal experiments and the clinical trials, they all have substantial significance in science and for treatment of COVID-19 patients, particularly regarding the efficacy of early use of some medications and CP.

5 | THE EXPECTED ADVANTAGES

The LPV, if supported by animal experiments and clinical trials, could be marketed earlier than other types of vaccines. This is because the animal experiments and the first part of the clinical trials could be conducted simultaneously and completed within 2 months, and the second part of the clinical trials could be completed in the following 2 months. Global collaboration could further ensure that these experiments could be completed within 4 months.

The LPV strategy has multiple advantages over the current "blocking and curing" strategy, as it could dramatically reduce the morbidity and mortality and reduce the time for establishing herd immunity against the pandemic virus. It could provide safety for society to lift various quarantine restrictions, restore social order, production, consumption, and freedom in various aspects. Therefore, the LPV strategy could have great significance in public health, social order and economy.

If the world retains the present blocking-and-curing strategy until 2022, almost all people worldwide will catch the virus, and approximately 20% of them will manifest moderate or severe symptoms, and the case fatality rate (CFR) will be approximately 4%. Therefore, the morbidity and mortality of the total population due to COVID-19 will be approximately 20% and 0.8%, respectively.[21,22] As the adenovirus LPV with a single safety guarantee reduced adenovirus-associated ARD cases by 99.66% among the US recruits,[15] we presume that the LPV strategy of SASR-CoV-2 with five safety mechanisms could reduce the morbidity by 90% to 2% and the CFR by 90% to 0.4%, and thus the mortality could decline by 99% to 0.008%, as compared with natural infections.

As compared with other types of vaccines, the LPV of SARS-CoV-2 could also havedistinct advantages, beyond its potential rapid evaluation and earlier marketing. First, the LPV could be rapidly supplied to many people because the virus grows rapidly in cell culture, and less viruses are needed for the LPV to vaccinate a person, as compared to the inactivated vaccine which also employs cell culture of the pathogen virus. Second, if the LPV is administered with enteric-coated capsules, the vaccination process is simpler than vaccination of other vaccines, because no syringe, needle, or other adjunct equipment is needed. Third, usually the LPV could induce stronger acquired immunity against SARS-CoV-2 than other vaccines, especially in mucosal immunity which is paramount for prevention of respiratory viruses. Fourth, some live vector virus vaccines have the potential of carcinogenicity and mutagenicity,[37] and these potentials have not been identified in live coronaviruses. Fifth, some live attenuated coronaviruses can regain their virulence,[9] and this is not a concern with the LPV strategy. Sixth and importantly, other types of vaccines have the potential to accelerate mutation and diversification of the targeted virus to escape the induced immunity,[38] while mass inoculation of the single strain of the LPV, the immunity induced by the LPV, and the medications to inhibit the replication of the LPV, all have the potential to inhibit the replication of diversified SARS-CoV-2 circulating in different regions of the world.

Taken together, the LPV could induce stronger immunity, establish herd immunity more rapidly, and inhibit indirectly viral mutation and diversification. These advantages further suggest that the LPV could eliminate SARS-CoV-2 from the world.

6 | THE APPLICATION PLANNING

Even if animal experiments and clinical trials all support the LPV strategy, this strategy should be widely discussed with public scrutiny before mass application. Moreover, a comprehensive plan should be well designed and implemented. The plan should cover the following recommendations. First, as explained above, mass vaccination of the LPV should be conducted in the hot season to reduce mixed infections. Second, mass vaccination of the LPV could be initiated in the army, prisons, and countryside due to their good isolation facilities. Third, mass vaccination of the LPV should be conducted community by community and simultaneously for the same community. All recipients should stay at home for a few days. If most people in the world could be vaccinated in a few months, the virus will have fewer people to sustain its circulation worldwide. In this sense, global collaboration is required to make enough vaccine for everyone.[39]

The LPV vaccination could be mandatory to all people to build up adequate herd immunity against COVID-19. However, pregnant women and persons with immunodeficiency or other illness should be excluded. These excluded persons should be isolated for weeks to prevent infection caused by the virus from LPV recipients. This does not mean that the LPV increases the infection risk in these people because they otherwise will catch the pandemic virus sooner or later. Additionally, if the herd immunity of a community, city, or region is established and so the coronavirus cannot circulate, pregnant women and people with illness could be protected thereby.

As the feces of the vaccine recipients likely contain the virus, the feces should be well managed at least for a few days. Moreover, domestic animals including cats and dogs should be isolated for certain days during the vaccination period. Similarly, this does not mean that the LPV increases the infection risk in domestic animals because they otherwise also have possibilities of contacting the pandemic virus.

7 | CONCLUSIONS

The whole world has entered a terrible crisis due to the pandemic of COVID-19. The LPV strategy could be a fast way out of the crisis, as supported by its successful application in the control of human and animal diseases. Five mechanisms could be employed to guarantee the safety of the LPV strategy which could reduce morbidity and mortality dramatically. Collectively, the LPV strategy deserves global collaboration and financial support to conduct the relevant animal experiments and clinical trials, which themselves are highly valuable for science and for treatment of COVID-19 patients. Even if the LPV strategy is supported by animal experiments and clinical trials, it should be implemented with cautioun.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

JwC and JmC designed and wrote this article, and JmC made the major conclusions.

DATA AVAILABILITY STATEMENT

The data supporting the views of this article are available from the corresponding author on request.

ETHICS STATEMENT

The article does not include the participation of animals and humans other than the authors.

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