


## REVIEW

# Potential for elimination of SAR-CoV-2 through vaccination as inspired by elimination of multiple influenza viruses through natural pandemics or mass vaccination

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**Abstract**

The ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by the novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed many lives worldwide. To combat the pandemic, multiple types of vaccines are under development with unprecedented rapidity. Theoretically, future vaccination against COVID-19 may fall into long-term costly guerrilla warfare between SARS-CoV-2 and humans. Elimination of SARS-CoV-2 through vaccination to avoid the potential long-term costly guerrilla warfare, if possible, is highly desired and worth intensive consideration. Human influenza pandemics emerging in 1957, 1968, and 2009 established strong global herd immunity and led to the elimination of three human influenza viruses, which circulated worldwide for years before the pandemics. Moreover, both clade 7.2 of subtype H5 highly pathogenic avian influenza virus and subtype H7N9 avian influenza virus circulated in poultry in China for years, and they have been virtually eliminated through mass vaccination in recent years. These facts suggest that the rapid establishment of global herd immunity through mass vaccination using an appropriate vaccine could eliminate SARS-CoV-2. The coming 2 years are a golden time for elimination through vaccination, which requires tremendous national and international collaboration. This review also prioritizes the efficacy of vaccines for COVID-19 and elucidates the importance of the development of more live vaccines for COVID-19.

**KEYWORDS**

COVID-19, elimination, herd immunity, influenza, pandemic, SARS-CoV-2, vaccination, vaccine

## 1 | BACKGROUND

The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed many lives worldwide. To combat the pandemic, multiple types of vaccines are under development with unprecedented rapidity.<sup>1</sup> However, scientists have cautioned that possibly multiple years are needed to develop a safe and effective vaccine for COVID-19.<sup>2</sup>

Even if a safe and effective vaccine can be marketed in months, vaccination against COVID-19 may fall into long-term guerrilla

warfare between SARS-CoV-2 and humans. First, after the pandemic, COVID-19 could be as mild as human diseases caused by other human coronaviruses, or as severe as the coronavirus diseases in swine, chicken, feline, and murine, which are all more burdensome than influenza.<sup>3</sup> Second, SARS-CoV-2 could escape vaccination through its rapid mutation including site substitutions, genomic recombination, and open reading frame shift.<sup>4</sup> Third, SARS-CoV-2 could move swiftly through the movement of infected people, and hide in some people for weeks without symptoms.<sup>5</sup> Fourth, the hidden SARS-CoV-2 could unpredictably attack susceptible humans who have not been infected or vaccinated, or have

no sustainable immunity induced by the infection or vaccination, or have innate or acquired immunodeficiency.

Vaccination could accelerate the mutation of viruses through natural selection, and SARS-CoV-2 could diverge into distinct lineages through its rapid mutation, both of which could escalate the guerrilla warfare between SARS-CoV-2 and humans. Accordingly, the vaccine should be updated promptly to match the mutated virus, and multiple vaccine strains or antigens should be used to match the major diversified lineages of the virus. Vaccination, update of the vaccine, and addition of vaccine strains or antigens could be all highly burdensome. Difficulty in vaccine development, rapid mutation of coronaviruses, long-term guerrilla warfare between viruses and humans, and heavy disease burden have been demonstrated in animal coronavirus diseases.<sup>3</sup>

The above information suggests that elimination of SARS-CoV-2 through vaccination to avoid potential long-term costly guerrilla warfare, if possible, is highly desired and worth extensive discussion and intensive consideration. Moreover, the elimination initiative is inspired by the interesting history, wherein multiple influenza viruses have been eliminated through natural pandemics or mass vaccination, as explained below.

## 2 | HISTORY

During the past seven decades, three human influenza viruses (HuIVs) disappeared coincidentally with the emergence of three influenza pandemics.<sup>7</sup> First, the H1N1 subtype HuIV, which circulated in humans for many years before 1957, disappeared during the pandemic of H2N2 subtype HuIVs emerging in 1957. Second, the above H2N2 subtype HuIV, which circulated for approximately 10 years after 1957, disappeared during the pandemic of H3N2 subtype HuIV emerging in 1968. Third, the H1N1 subtype HuIV, which circulated after its re-emergence in 1977, disappeared during the pandemic of swine-origin H1N1 subtype HuIV emerging in 2009.

The disappearance of the above three HuIVs can be explained only by the broad and strong herd immunity induced by the relevant pandemic viruses, in statistics and in biology.<sup>7</sup> This means that the pandemics provided natural, rapid, global, and highly effective vaccination, which eliminated three HuIVs having circulated in humans for years. The pandemic viruses harbored multiple genes from the

eliminated viruses, or shared the same HA and NA subtypes with the eliminated viruses (Table 1).<sup>8</sup> They, thus, shared various T and/or B cell epitopes with the eliminated viruses, and so the immunity induced by the pandemic viruses exerted the elimination effect.

The above elimination events demonstrated that the pandemic viruses, although disastrous, induced broader and stronger herd immunity rather than commercial influenza vaccines, which could reduce infections caused by limited clades of HuIVs within the same HA subtype.

The pandemic of swine-origin H1N1 HuIV in 2009 did not eliminate the H3N2 subtype HuIV, which has circulated since 1968, possibly because these two viruses did not harbor any genomic segments (Table 1), although the PB1 gene of the pandemic virus was from H3N2 subtype HuIVs circulating approximately 10 years before 2009,<sup>8</sup> and they thus shared less T and/or B cell epitopes. In 1977, the H1N1 HuIV which circulated in the 1950s re-emerged worldwide possibly due to a laboratory incident, and most infected people were under 23 and had not encountered the H1N1 HuIV before 1977.<sup>9</sup> Therefore, re-emergence of the H1N1 HuIV induced lower herd immunity than the above pandemics, and thus did not eliminate the above H3N2 HuIV either.

Deliberate vaccination has also eliminated an avian influenza virus (AIV).<sup>10</sup> H5 subtype highly pathogenic AIV (HPAIV) emerged in China in the early 2000s, and the virus was well controlled in 2005 with the inactivated vaccine termed Re-1. A variant of the virus escaping from the Re-1 vaccination emerged in 2006 in northern China, and diverged into the distinct clade 7.2 of H5 HPAIVs in China.<sup>11</sup> Therefore, during the years from 2006 to 2013, two or more vaccine strains were used to control H5 HPAIVs in China. Clade 7.2 was well controlled through vaccination until 2013, when a distinct vaccine-escaping variant of this clade caused multiple outbreaks in chickens in northern China.<sup>12</sup> This clade has not been identified for 6 years after the relevant vaccine strain was updated and widely used in chickens in northern China in 2014, as suggested through multiple times of mass surveillance.<sup>10</sup> The elimination of Clade 7.2 is relatively easy because it circulated exclusively in northern China in chickens without reservoirs in ducks and other birds.<sup>10</sup>

The H7N9 subtype AIV emerging in China in 2013 has been virtually eliminated through vaccination.<sup>10</sup> This low pathogenic AIV caused much more human cases than H5 HPAIVs. During the period from October 2016 to May 2017, human H7N9 cases increased by

Year	Pandemic virus	Cocirculating virus	Shared genomic segments	Shared subtype	Outcome
1957	Hybrid H2N2	H1N1 HuIV	PB2, PA, NP, MP, NS	None	Eliminated
1968	Hybrid H3N2	H2N2 HuIV	PB2, PB1, PA, NP, MP, NS	NA	Eliminated
2009	Swine H1N1	H1N1 HuIV	None	HA, NA	Eliminated
2009	Swine H1N1	H3N2 HuIV	None	None	Survived

**TABLE 1** Genomic segments shared by pandemic virus and cocirculating HuIVs

Abbreviation: HuIV, human influenza virus.

over 300% compared with previous years, and the virus mutated into HPAIV,<sup>13</sup> which is one of multiple events where a virus increases its pathogenesis greatly after it has become prevalent in the host population. To control the dangerous changes of the H7N9 AIVs, the dual-value vaccine containing one strain against H5 HPAIVs and one strain against H7N9 AIVs was employed from October 2017 throughout China targeting all species of domestic birds including ducks. Although ducks infected with the H7N9 AIV did not show clinical symptoms, they could support asymptomatic circulation of the virus.<sup>10</sup> Therefore, ducks were also vaccinated with the bivalent vaccine for eliminating the H7N9 virus. The relevant mass vaccination started in the middle of 2017, and the prevalence of H7N9 almost declined to zero thereafter as indicated through mass surveillance of poultry. Also, human cases of H7N9 declined dramatically from 713 during the period from October 2016 to May 2017, to three after October 2017 (two in 2018 and one in 2019).<sup>13</sup> These data indicate that the virus has been virtually eliminated, and the virus has the possibility of being eliminated completely with the vaccine strain updated in 2019. Theoretically, this virus could not be eliminated if the elimination had not been considered from the beginning and ducks had not been covered in the mass vaccination because ducks support the asymptomatic circulation of the virus. Therefore, this example showed the importance for the world to consider now elimination of COVID-19, so that more efforts and resources could be given toward this highest goal of mass vaccination.

### 3 | APPLICATION

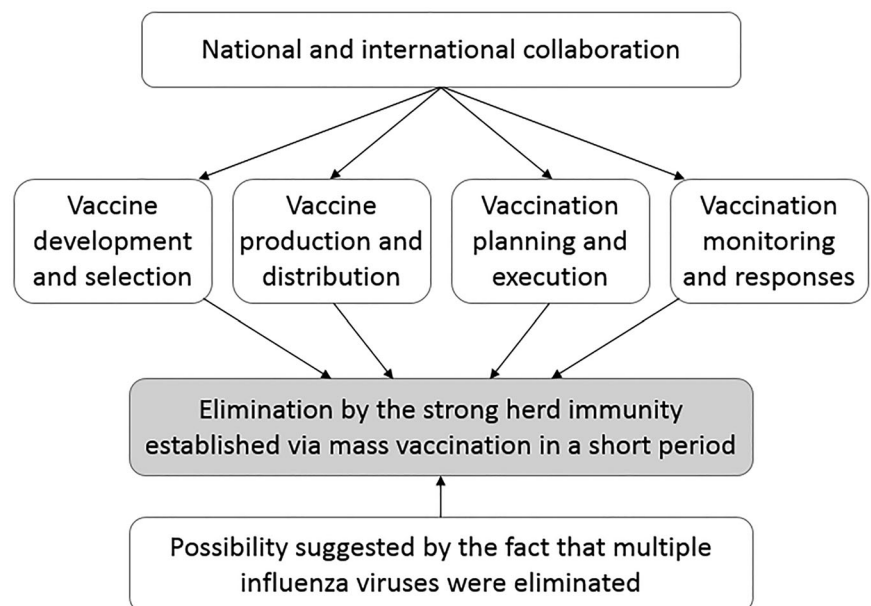
The mechanism of elimination of the three HuIVs and two AIVs was that strong immunity was induced in almost all susceptible hosts

in the affected areas against the targeted virus through natural or deliberate vaccination in a relatively short time,<sup>14</sup> and the established herd immunity blocked the circulation of a targeted virus completely. These events indicate that elimination of COVID-19, which is also a respiratory infectious disease caused by an RNA virus, is possible and should be based on the rapid establishment of global herd immunity through mass vaccination.

Theoretically, the coming 2 years are a golden time for elimination of SARS-CoV-2 through vaccination, because SARS-CoV-2 will likely have not diversified into distinct lineages during this period, and thus one vaccine strain or antigen could match all lineages of SARS-CoV-2 circulating worldwide.<sup>6</sup> Moreover, many people will have been infected in the coming months by SARS-CoV-2, which aids in establishing strong herd immunity for elimination.

Elimination of COVID-19 through vaccination should be a great project requiring tremendous national and international collaboration (Figure 1), and the elimination project is of the vital interest for all countries as it saves much money and lives. Moreover, most people in the world have known the risk of COVID-19 and could actively aid or involve in the elimination. The Chinese government has pledged to donate two billion USD to the world to fight COVID-19, and such donations could support strongly this elimination project. We assessed preliminarily that the benefit/cost ratio of the elimination could be over 10, because elimination through vaccination requires about threefold efforts for common vaccination in a year, and elimination could remove over 30 years of heavy burden caused by COVID-19. Even if the disease has not been eliminated through tremendous efforts, the elimination efforts should remain highly valuable because it could be beneficial for better control of the disease.

The relevant international cooperation mechanism should be established for the global elimination project. All countries should



**FIGURE 1** The framework for the elimination of severe acute respiratory syndrome coronavirus 2 through mass vaccination

collaborate with unprecedented solidarity to fully discuss this issue, rationally design the route map, and actively deploy resources to implement the project. Lessons and experiences of the past in vaccination against other viral infectious diseases should be well considered in the project design.

The vaccine for the elimination project should be carefully selected. The vaccine should be safe, effective, inexpensive, rapid in production, easy for storage, and convenient for vaccination, but few vaccines meet all these requirements.<sup>2</sup> Table 2 shows the presumed advantages and disadvantages of major types of vaccines with exceptions (eg, some live attenuated vaccines [LAVs] including those for poliomyelitis and mumps are safe for use).<sup>15</sup>

Critically, sometimes a higher vaccine efficacy means lower safety risk due to lower morbidity. For example, vaccine B should be superior to vaccine A, if vaccine A is 100% safe and reduces symptomatic COVID-19 cases by 60% from 5.0% to 2.0% of the vaccinated population, and vaccine B reduces symptomatic cases caused by natural infection by 100%, although 0.2% of the people inoculated with vaccine B become symptomatic COVID-19 cases caused by the vaccine. Moreover, almost all the few vaccine-associated cases can be cured, like that of 99.84% of the cases in China beyond the province Hubei, who were treated in time, successfully recovered.<sup>16</sup> Therefore, unlike the vaccines for rabies and polio, the efficacy of COVID-19 vaccines could be prioritized.

LAVs have been used successfully in control of various infectious diseases and are suitable for the elimination project, due to their high efficacy, high production efficiency, and potential simple inoculation (eg, oral administration),<sup>2</sup> all of which are important for the elimination project. For these reasons, LAVs have replaced inactivated vaccines and become the predominant vaccines for multiple viral infectious diseases including measles, mumps, poliomyelitis, and yellow fever. Of the 15 human viral infectious diseases controlled with vaccines in the United States, 11 are controlled with LAVs and one is controlled with a live pathogen vaccine (LPV).<sup>17</sup> However, the development of safe and effective LAVs is usually time-consuming. The current LAV under research for COVID-19 based on codon-modification could reduce the pathogenesis rapidly, but whether the

LAV can be generated and propagate efficiently in cells is of concern because it employs many rare codons.<sup>2</sup> Considering that LAVs have multiple potential advantages and various successful applications, more types of LAVs should be developed for COVID-19.

The elimination history of the three HuIVs suggests that LPV can induce broad and strong immunity, because the relevant pandemic influenza viruses could be considered as LPVs which eliminate the relevant HuIVs. The LPV strategy has been applied successfully in US military recruits for nearly 40 years to control acute respiratory diseases caused by types 4 and 7 adenoviruses, and reduced morbidity by over 99%.<sup>18</sup> It avoids causing disease through oral administration of enteric-coated capsules containing the LPV to bypass the pathogenic site of the fragile lungs.<sup>19</sup> Beyond inducing broad and strong immunity, LPVs have no concerns regarding pathogenic reversion and inhibits indirectly the mutation and diversification of the targeted virus through replacing various virus mutants circulating in vaccinated regions.<sup>20</sup> Although the safety of the LPV strategy is a big public concern, safety has been well guaranteed in the LPV of adenovirus used in US military recruits, and can be further guaranteed with novel measures.<sup>20</sup> As all the vaccines under development for COVID-19 have known or unknown disadvantages,<sup>2</sup> the efficacy of COVID-19 vaccines could be prioritized, as elucidated above, the LPV strategy for COVID-19 deserves investigation as early as possible, to enhance the possibility to curb and eliminate the pandemic earlier. If COVID-19 was caused by a novel adenovirus, the LPV strategy would have been under investigation.

Detailed plans should be formulated to guide the global elimination project. Over half the people worldwide should be vaccinated in a relatively short time to establish strong herd immunity. Considering the rate of the vaccine production and risk factors of COVID-19, elderly people and healthcare workers should be vaccinated first.<sup>21</sup> Mass vaccination is favorably conducted in warm or hot seasons when the prevalence of many infectious viruses including COVID-19 is lower and the human immunity is higher than in the cold season.<sup>22</sup> Moreover, an epidemiological monitoring system should be well designed and established to identify potential problems associated with the global elimination project, and scientific solutions to these problems should be prepared in advance.

**TABLE 2** Presumed advantages/disadvantages of major types of vaccines with exceptions

Vaccines	Success history	Safety assurance	Efficacy	Low cost	Production efficiency	Storage simplicity	Inoculation simplicity
Live attenuated	+++++	+++	+++++	++++	++++	++	++++
Inactivated	+++++	++++	+++	++	++	++++	+++
Protein-based	+++	++++	+++	++	++	++++	+++
DNA-based	+	++++	++	++	++	++++	+++
mRNA-based	-	?	?	?	?	?	?
Nonreplicating vector	-	++++	++	+++	++++	++++	+++
Replicating vector	+	+++	+++	++++	++++	++	+++

Note: -, nil; +, rare; ++, mild; +++, moderate; +++++, strong; ?, unknown. Abbreviation: mRNA, messenger RNA.

If successful, this global elimination project could pave the road for the elimination of other viral infectious diseases. It will also greatly enhance global solidarity, which is the core welfare and challenge for mankind.

## ACKNOWLEDGMENTS

We thank Meng Yang for her helpful advice and assistance.

## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

J-MC, Y-XC, and J-WC designed and wrote this article, and J-MC 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 contain the participation of animals and humans other than the authors.

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## REFERENCES

- Thanh LeT, Andreadakis Z, Kumar A, et al. The COVID-19 vaccine development landscape. *Nat Rev Drug Discov*. 2020;19(5):305-306. <https://doi.org/10.1038/d41573-020-00073-5>
- Callaway E. The race for coronavirus vaccines: a graphical guide. *Nature*. 2020;580(7805):576-577. <https://doi.org/10.1038/d41586-020-01221-y>
- Decaro N, Martella V, Saif LJ, Buonavoglia C. COVID-19 from veterinary medicine and one health perspectives: what animal coronaviruses have taught us. *Res Vet Sci*. 2020;131:21-23. <https://doi.org/10.1016/j.rvsc.2020.04.009>
- Jimenez-Guardeño JM, Regla-Nava JA, Nieto-Torres JL, et al. Identification of the mechanisms causing reversion to virulence in an attenuated SARS-CoV for the design of a genetically stable vaccine. *PLOS Pathog*. 2015;11(10):e1005215. <https://doi.org/10.1371/journal.ppat.1005215>
- Gao Q, Bao L, Mao H, et al. Rapid development of an inactivated vaccine candidate for SARS-CoV-2. *Science*. 2020;368. <https://doi.org/10.1126/science.abc1932>
- Zhou X, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-CoV-2 infection. *Clin Microbiol Infect*. 2020;26. <https://doi.org/10.1016/j.cmi.2020.03.024>
- Palese P, Wang TT. Why do influenza virus subtypes die out? A hypothesis. *mBio*. 2011;2(5):e00150-11. <https://doi.org/10.1128/mBio.00150-11>
- Zhuang Q, Wang S, Liu S, et al. Diversity and distribution of type A influenza viruses: an updated panorama analysis based on protein sequences. *Virology*. 2019;16(1):85. <https://doi.org/10.1186/s12985-019-1188-7>
- Wertheim JO. The re-emergence of H1N1 influenza virus in 1977: a cautionary tale for estimating divergence times using biologically unrealistic sampling dates. *PLoS One*. 2010;5(6):e11184. <https://doi.org/10.1371/journal.pone.0011184>
- Liu S, Zhuang Q, Wang S, et al. Control of avian influenza in China: strategies and lessons. *Transbound Emerg Dis*. 2020;67. <https://doi.org/10.1111/tbed.13515>
- Liu L, Zeng X, Chen P, et al. Characterization of clade 7.2 H5 avian influenza viruses that continue to circulate in chickens in China. *J Virol*. 2016;90(21):9797-9805. <https://doi.org/10.1128/JVI.00855-16>
- Ma QX, Jiang WM, Liu S, et al. Subclinical highly pathogenic avian influenza virus infection among vaccinated chickens, China. *Emerg Infect Dis*. 2014;20(12):2152-2154. <https://doi.org/10.3201/eid2012.140733>
- Zeng X, Tian G, Shi J, Deng G, Li C, Chen H. Vaccination of poultry successfully eliminated human infection with H7N9 virus in China. *Sci China: Life Sci*. 2018;61(12):1465-1473. <https://doi.org/10.1007/s11427-018-9420-1>
- Lim W, Zhang P. Herd immunity and a vaccination game: an experimental study. *PLoS One*. 2020;15(5):e0232652. <https://doi.org/10.1371/journal.pone.0232652>
- Bloom BR, Lambert PH. *The Vaccine Book*. San Diego: Academic Press; 2003. <https://doi.org/10.1016/B978-0-12-107258-2.X5000-8>
- Worldometer. Coronavirus (COVID-19) mortality rate. <https://www.worldometers.info/coronavirus/coronavirus-death-rate/#nhc>
- Centers for Disease Control and Prevention. Vaccines and preventable diseases. <https://www.cdc.gov/vaccines/vpd/index.html>
- Choudhry A, Mathena J, Albano JD, et al. Safety evaluation of adenovirus type 4 and type 7 vaccine live, oral in military recruits. *Vaccine*. 2016;34(38):4558-4564. <https://doi.org/10.1016/j.vaccine.2016.07.033>
- Couch RB, Chanock RM, Cate TR, et al. Immunization with types 4 and 7 adenovirus by selective infection of the intestinal tract. *Am Rev Respir Dis*. 1963;88(Suppl):394-403. <https://doi.org/10.1164/arrd.1963.88.3P2.394>
- Chen JW, Chen JM. Potential of live pathogen vaccines for defeating the COVID-19 pandemic: history and mechanism. *J Med Virol*. 2020;92. <https://doi.org/10.1002/jmv.25920>
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
- Xu DL, Xu MM, Wang DH. Effect of temperature on antioxidant defense and innate immunity in Brandt's voles. *Zool Res*. 2019;40(4):305-316. <https://doi.org/10.24272/j.issn.2095-8137.2019.045>

**How to cite this article:** Chen J-M, Sun Y-X, Chen J-W. Potential for elimination of SAR-CoV-2 through vaccination as inspired by elimination of multiple influenza viruses through natural pandemics or mass vaccination. *J Med Virol*. 2020;92:2453-2457. <https://doi.org/10.1002/jmv.26162>