

Study of Vaccine Production Abroad and Scientific and Research Challenges of COVID-19 Vaccine Production in Iran

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ABSTRACT

Coronaviruses are enveloped viruses with single-stranded RNA that cause acute lung disease in a range of animal species, including humans. After the outbreak of the Coronavirus in 2019, the world economy entered a recession. Social and business relations became limited and the livelihoods of many people around the world were hampered. Meanwhile, in the absence of effective treatment against this disease, vaccine production is one of the major solutions to get out of the current critical situation. With the approval of COVID-19 vaccines for use in different parts of the world, the scale and complexity of their production, allocation, and distribution worldwide is unprecedented. However, vaccine production by both large foreign and domestic companies is fraught with challenges that have made public vaccination obscure in the short term. The risks of corruption, such as the entry of substandard and counterfeit vaccines into markets and the production budget leakage, may threaten the vital goals of vaccine production and public health. It is recommended that the general population not be tested by mistake until a safe domestic vaccine is obtained. As a result, any hasty action to provide the vaccine may induce irreparable consequences.

KEYWORDS

Covid 19, Vaccine, Production, Coronavirus, Corona, Vaccination.

Introduction

Coronaviruses are a diverse group of enveloped viruses that are highly resistant [1]. These viruses belong to the Coronaviridae family; this family includes α -coronavirus, β -coronavirus, γ -coronavirus, and delta-coronavirus [2]. In December 2019, a new coronavirus was discovered in China, and the resulting disease was called Covid 19 [3]. On March 11, 2020, the World Health Organization declared the outbreak of the COVID-19 virus as a “global pandemic”, and since then, the pandemic has continued and mortality is increasing worldwide. So far, more than 200 million people have been infected with the virus, of which about 4 million have died [4].

Clinical findings show that about 20 to 30 percent of infected people require intensive care due to severe respiratory problems [5-7]. This has led to the urgency of producing and ensuring access to cost-effective, safe and effective vaccines and their rapid and fair deployment. The positive outcomes announced by a number of vaccine candidates in November 2020 have led to the rapid distribution of vaccines in different parts of the world [8]. Due to the widespread prevalence of Covid 19 in the world, the present review study is conducted to investigate the production of Covid-19 vaccines worldwide, and the scientific and research challenges of producing Covid-19 vaccine in Iran.

Coronavirus

Coronaviruses cause respiratory, intestinal, liver, and neurological diseases of varying severity in a wide range of animal species, including humans. Over the past two decades, coronaviruses have caused three epidemics: Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and COVID-19 (Coronavirus Disease 2019) [9].

Covid 19 is caused by an enveloped virus, which has a helical capsid and their approximate genome size is 26-32 kb [10]. The virus genome has at least four major structural proteins, including the spike protein (S), the membrane (M), the envelope (E), and the nucleocapsid protein (N), and encodes other proteins that are required for the virus replication and entry to the cells [11]. Covid 19 is transmitted by sneezing and coughing through respiratory droplets. The incubation period of this disease is about 7 to 14 days [12]. The COVID-19 mortality rate (3%) has so far been much lower than the mortality rates of SARS (10%) or MERS (40%) [13].

Clinical Symptoms

The clinical symptoms of Covid 19, similar to influenza, are classified into four levels based on the severity of the symptoms: mild, moderate, severe, and critical. Mild patients have only mild symptoms and no radiographic features. Moderate patients have a fever, respiratory symptoms, and radiographic features. Severe patients meet one of these three criteria: a) shortness of breath and RR more than 30 beats per minute, b) oxygen saturation less than 93% in ambient air, c) PaO₂ / FiO₂ less than 300 mm Hg. Critical patients also have three criteria: a) respiratory failure, b) septic shock, c) multiple organ failure [6]. Although Covid-19 majorly affects the respiratory and cardiovascular systems, in patients with severe neurological symptoms (such as headache, dizziness, loss of olfactory and taste sensation, and neuropathic pain), complications such as encephalopathy, acute brain diseases, impaired consciousness, and Musculoskeletal damage are also observed [14].

The Outbreak of the Coronavirus Disease

The WHO has released information on the Covid-19 virus since January 22, 2020, which is updated daily. On March 11, the WHO announced that COVID-19 could be described as a "global pandemic" that underscores the importance of global research on morbidity and mortality of the disease. Overall results from the mortality rates of the disease around the world show that although some risk factors, such as regional characteristics, can affect the incidence, mortality-related risk factors are not regional and genetic parameters may also affect mortality [15-17].

In order to study the prevalence and mortality of Covid-19, in a study, the whole world was divided into five regions. Then, the incidence and mortality rates were compared among these five regions. The lowest and highest mortality rates were observed in Europe and the western Pacific, respectively. In addition, the lowest and highest incidence rates of Covid-19 have been reported in Africa and Europe (Table 1). Comparisons showed that in terms of incidence of the disease, there was a statistically significant difference between the study areas. Accordingly, in a "two-on-two" comparison, the incidence rates in the European region versus the African region, the European region versus the United States, and the European region versus the Southeast Asian region were statistically different [15].

Table 1. Global overview of morbidity and mortality. Findings show significant differences between different parts of the world in terms of incidence of Covid-19 [15].

Region	Morbidity rate per 1 million		Mortality rate per 1 million	
	CI	mean	CI	Mean
Africa	(0-0.58)	0.25		0.00
Eastern Mediterranean	(0-40.76)	11.06	(0-2.68)	1.24
Europe	(0-101.46)	44.17	(0.06-0.84)	0.45
Part of America	(0-1.19)	0.67	(0-3.05)	1.03
Southeast Asia	(0-3.55)	1.36	(0-1.48)	0.50
Western Pacific	(0-95.69)	35.21	(0-6.1)	2.53

Vaccination and the Hypotheses under Consideration

In general, vaccines protect against infection and disease when exposed to certain pathogens, especially in vulnerable populations. In the current outbreak of the new coronavirus, vaccines help control and reduce disease transmission by providing general immunity in addition to protecting healthy people from infection. However, there are social, clinical, and economic barriers to vaccination programs that can be attributed to the general population willingness to be vaccinated with a new vaccine, the side effects and severe side effects of vaccination, the potential differences between vaccines, the low efficacy of the vaccine in different populations, and availability of the vaccine for a given population [13].

Prompt diagnosis, vaccination, and treatment are important factors in managing the spread of Covid-19 [13]. Given the threat of this epidemic to public health, scientists and physicians are discovering possible treatments and effective vaccines; this is because the disease can pose major challenges for global health systems and if its prevalence is not controlled, it would induce immense negative consequences for the world economy [18]. To date, many vaccines have been studied that have successfully passed the laboratory stage and reached mass production. In this regard, the United States, Russia, Australia, and Canada have provided vaccines with reasonable immunization.

Developing vaccines include viral vector-based vaccines, DNA vaccines, Virus-Like Particles (VLPs), and Inactivated Whole-Virus (IWV) vaccines [13]. Some vaccines are also made based on the S protein of these viruses, because the coronavirus genome encodes several structural proteins, including the spike protein (S), which acts as a major factor in the immune response of the host. This protein, which is responsible for the entry of the virus into host cells and replication, plays the most important role in the virus fusion and entry into the host cell. Therefore, this substance can be used as a target for the production of antibodies, inhibitors of virus entry, and vaccines [19].

SARS-CoV-2 enters the host cell by binding to a receptor protein called Angiotensin-Converting Enzyme 2 (ACE2) on the surface of the host cell membrane [18, 20]. The S protein mediates virus entry into host cells by binding to the host receptor through binding to the Receptor-Binding Domain (RBD) and then fusion of the virus and host membrane [21]. The RBD protein binds strongly to human ACE2 receptors. Therefore, studies show that by limiting the binding of RBD to ACE2-expressing cells by the vaccine, the virus can be prevented from entering host cells. Covid-19 specific RBD antibodies can interact with the immune system and be neutralized by the immune system. This presents the potential for the development of SARS-CoV RBD-based vaccines to prevent SARS-CoV-2 and SARS-CoV infection [19].

Worldwide Production of Vaccine

Vaccines keep communities healthy and save millions of lives. The vaccine prepares the immune system of the body against the virus. When people are vaccinated against the Coronavirus disease (COVID-19), the virus cannot be easily transmitted from person to person, and the community is less likely to spread COVID-19, which is called "community immunity" or "herd immunity." [22].

Since the advent of SARS-CoV in 2002, several vaccines had been studied, but none of them have been approved by the FDA. On the other hand, unprecedented efforts have been made to develop vaccines during the SARS-CoV-2 epidemic. Just six months after the epidemic, more than 100 potential vaccines are in different stages of clinical trials. The designed vaccines mainly use the spike protein of the virus for inducing antiviral immunity. Also, other types of vaccines are being evaluated, such as complete viruses (weak or inactivated), viral antigens encoded by viral plasmids, and viral proteins [23].

In general, four main models have been used in the development of the Covid-19 vaccine, which are described below [13, 24]:

1. The first type, which is the old model, is based on the complete virus, and weak or inactive virus is used. Eight vaccines, including the vaccines of Iran (COV-Iran Barekat), India (Bharat), and China (Sinopharm), have been developed on this basis.
2. The second type is based on viral vectors, and 16 vaccines such as the British vaccine (Oxford–AstraZeneca), Russian vaccine (Sputnik), and another vaccine from China are made according to this model.
3. The third type, which is a new and controversial technology, is based on nucleic acids (DNA / RNA). About 16 vaccines are designed based on this model, and the most important of which are "Moderna" and "Pfizer" vaccines that are produced in the United States.
4. The fourth type is inactivated vaccine, which is based on viral proteins (subunit/recombinant), and the vaccines of France, the Pasteur Institute of Iran-Cuba (Sanofi), and Novavax (United States) are designed on this basis.

In addition, CoronaVac is a vaccine against Covid-19 developed by the Chinese company 'Sinovac' and uses an old model. It is currently produced separately in China, Brazil, Indonesia, and Egypt [25]. AD5-nCOV, under the brand name Convidecia, is a single-dose viral vector vaccine for COVID-19 developed by CanSino Biologics. Since late 2020, these trials have been conducted in the third phase in Argentina, Chile, Mexico, Pakistan, Russia, and Saudi Arabia with 40,000 participants [26]. Johnson & Johnson's covid-19 vaccine is another single-dose adenovirus vaccine that is 66% effective but has many side effects. Convidecia is similar to other viral vaccines such as AZD1222, Gam-COVID-Vac, and Ad26.COV2.S; since it is a single-dose vaccine and can be refrigerated at 2° C to 8° C, this vaccine can also be the preferred vaccine option for many countries [26]. Studies show that nucleic acid-based vaccines have been effective in preventing Covid-19. Moderna has designed and produced mRNA-based vaccines by encoding viral S protein, which is about 94% effective [24]. Given the above, the production of

recombinant vaccines based on nucleic acids can be a major step in preventing this disease, and it is highly important for the Ministry of Health to pay attention to this issue.

Since February 18, 2021, at least seven different vaccines have been distributed in various countries, and vulnerable populations are the highest priority for vaccination in all countries. At the same time, more than 200 additional vaccine candidates are being developed, more than 60 of which are in the clinical stage. COVAX is part of the ACT-Accelerator partnership (Access to Covid-19 Tools Accelerator) launched by WHO and its partners in 2020 with the aim of ending the acute phase of COVID-19; the goals of this partnership include accelerating the production of safe and effective vaccines against COVID-19, supporting the development of production capabilities, and collaboration with governments and manufacturers to ensure that vaccines are distributed fairly to all countries [22].

FDA-approved vaccines and most Covid-19 vaccines target SARS-CoV-2 glycoproteins [27, 28]. Some FDA-approved COVID-19 vaccines require precise temperature control, and immunization failure may be caused by partial destruction of the vaccine due to insufficient cold chain or other issues during transport, storage, or administration. Since the FDA-approved COVID-19 vaccines are more widely administered, successful monitoring will be critical for detecting unexpected or clustering issues in patients, the vaccine prescribed, or the viral infection. While some studies have shown that neutralizing antibodies persist for months after normal infection with SARS-CoV-2, other studies have detected declining immunity over time [29-31].

The Importance of Vaccination

Vaccination has many benefits for society, the simplest of which is reducing mortality and complications of viruses [32]. Vaccination is the most important measure in reducing human sensitivity to coronavirus disease. The results show that with the increase of vaccination, the incidence of Covid-19 has significantly decreased in various communities. A review of 10 studies found that most Covid 19 vaccines were effective and safe, and vaccination with two doses demonstrated a better response; therefore, attention to the administered dosage of the vaccine is recommended. However, the researchers stated that further research is needed to evaluate the long-term efficacy and safety of vaccines, and the effect of dose, age, and production process on the efficacy of vaccines [33]. According to other reports, a very small percentage of vaccinated individuals have experienced severe complications [34]. Recent reports indicate that many centers in Europe lifted the Covid restrictions for the vaccinated population in June. In Germany, from 9 May 2021, vaccinated individuals can easily use recreational and welfare facilities [35].

The efficacy of the studied vaccines has been reported from 70 to 95%. This means that a small percentage of vaccinated people may suffer from the complications of the disease, and in cases of 90% effectiveness, the mortality rate is reduced by up to 10 times [34, 35]. These findings underscore the importance of vaccination.

Scientific and Research Challenges of Covid-19 Vaccine Production in Iran

In Iran, a total of 9 vaccination projects with different patterns are being pursued. The Shifa-Pharmed covid vaccine (in collaboration with Imam Khomeini's executive staff) is in phase one of clinical trials, and the Institute Pasteur's SARS-CoV-2 vaccine, prepared in collaboration with Cuba, is on the verge of entering phase three. Other vaccines are in the preclinical or animal trials phase [36]. According to the forecasts of the officials of the Executive Headquarters of Imam Khomeini, it is predicted that by the end of the spring of 2021, the supply of Shifa-Pharmed vaccine with a capacity of more than 10 million doses would begin. Regarding the Institute Pasteur vaccine, it is worth mentioning that this vaccine is being produced in cooperation with Cuba and is in phase 3 of human trials. Since, according to the agreement between the two countries, Iranian scientists must monitor the production process, and provided that this condition is met, this vaccine can be a more reliable international vaccine [36].

In the field of medicine, Iran and Cuba have been cooperating constructively for nearly two decades in the production of hepatitis B vaccine, which has led to the transfer of knowledge on the production of this vaccine to Iran. With the arrival of hepatitis B vaccine technology from Cuba to Iran, the biotechnology industry would also develop in our country. Little information is currently available about other Iranian vaccines [36]. Given the history of hepatitis B vaccination, the use of the Iranian-Cuban Covid-19 vaccine is likely to be useful in the future, but it is highly important to pay attention to providing the most effective vaccine and obtaining approval from the World Health Organization.

In our country, considering that the condition of the Ministry of Health for testing the foreign corona vaccine is the transfer of production technology, and since no country except Cuba has accepted this condition, the supply and injection process is slow and it is one of the main challenges of vaccination. However, there has been a cooperation with a company from Cuba, which is a developed country in the field of medicine [36].

Production, Allocation and Distribution of Covid-19 Vaccines

The fact that COVID-19 vaccines were rapidly produced during 2020 was a source of hope after a dark year. The approval of several vaccines at the end of last year is seen by many as a turning point in the global response to the epidemic, raising expectations that public health threats will soon be addressed through national vaccination strategies, and the limitations of everyday life can finally be lifted [37].

With the approval of COVID-19 vaccines for use in different parts of the world, the scale and complexity of their production, allocation, and distribution worldwide is unprecedented. However, the risks of corruption, such as the entry of substandard and counterfeit vaccines into markets and the production budget leakage, may threaten the vital goals of vaccine production and public health [8]. Studies have shown that there are risks of corruption in all parts of the world [38-40], and this is one of the challenges of production that should be considered by the country's officials.

The COVID-19 vaccine should be considered a universal commodity. For this reason, public institutions must identify and address potential gaps and barriers, such as the risk of corruption in distribution and allocation processes, to ensure that the population has fair access to the vaccine. The concept of corruption in the allocation and distribution of COVID-19 vaccines was also emphasized in a statement issued by the Secretary-General of the United Nations António Guterres in October 2020. The statement said that corruption is far more damaging in times of crisis, as the world is now facing. He also noted that the Covid-19 pandemic is creating new opportunities for corruption [41].

The urgency of vaccine production, as well as treatment and diagnosis of COVID-19, has led to significant public and private investment in related research and development. A large number of these activities have been in the direction of discovering a COVID-19 vaccine that would be globally safe and effective. The World Health Organization is considering vaccine candidates, which are in the clinical trials phase or preclinical and animal trial phase, for the future [42].

Various factors are effective in accelerating the process of Covid-19 vaccine injection. One way to speed up the process of vaccination is to allow other countries to conduct clinical trials of the vaccine in their country. In other words, the vaccine would be tested on the people of that country. Israel, the UAE, and Bahrain are the countries that injected large numbers of vaccines during the clinical trials and before final approval and seem to have made a risky decision. Regarding Israel, it should be noted that despite the widespread vaccination, this country faced the third wave of Covid-19 in early January, which, according to health principals, was heavier than the first and second waves; so that, 7,000 new patients were identified daily and the capacity of hospitals was almost full. This has raised many concerns and questions about the effectiveness of vaccines purchased by this country [43]. Providing vaccines with high efficacy and minimal side effects by Iranian experts can solve many problems related to the efficacy and safety of the vaccine. However, with 275 million injected doses (81% of the population), the United States tops the list of countries with the highest number of Covid-19 vaccinations in the world [44, 45]. In the UK, 80% of people have been vaccinated and this rate is more than 50% in many developed countries, but due to the importance of vaccination, the process of biological research in Europe and providing the best vaccine is still of interest to molecular biologists [34, 45, 46]. Unfortunately, in developing countries, biologists, who play an important role in the initial process of vaccine production, have a low place in the healthcare community, which should be considered by officials.

Another important issue was the side effects of some vaccines, such as Indian Covaxin and American Johnson & Johnson; these vaccines demonstrated high side effects compared to other vaccines, but the vaccination results were still acceptable [44], and this shows that in the first stage vaccine production should be considered and then attention should be paid to increasing the effectiveness and quality of the vaccine.

Conclusion

The production of the Covid-19 vaccine is a time-consuming process, and all currently available vaccines have been approved for the present emergency situation, and the side effects of none of these vaccines have been identified. There are also risks of corruption in between, and they may threaten vital public health goals. These risks include the entry of substandard and counterfeit vaccines into the markets, theft of vaccines in distribution systems, leaks in the emergency budget set for the production and distribution of vaccines, etc. However, vaccination is actually the most important measure in reducing complications and mortality of Coronavirus disease. The results show that with the increase of vaccination, the incidence of this disease in the community would decrease and according to reports, a very small percentage of people have experienced severe complications of vaccination so far. It is therefore recommended that the general public be vaccinated as soon as possible. Presently, 2 billion of the world's 6.8 billion people have been vaccinated and recombinant vaccines have been shown to be most effective; thus, in our country, more attention should be paid to the production of effective recombinant vaccines. The vaccination rate in some countries is more than 80 percent, while in developing countries and many poor parts of the world this rate is around one to two percent. In Iran, the vaccination process is slow, and increasing the speed of vaccination should be considered. Also, the use of vaccines with low effectiveness can cause many side effects for individuals, so providing approved vaccines in terms of quality and low side effects can ensure the health of the community. In general, findings indicate that vaccination is the major solution for terminating this disease and should be given serious consideration.

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