Chapter

COVID-19 Response in Uzbekistan: From RT-PCR Test System to the Clinical Trial of Subunit Vaccine

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Abstract

The coronavirus pandemic showed the need for urgently improvement of different sectors in Uzbekistan, especially, the healthcare system and the biopharma industries. Uzbekistan government and private sectors have taken comprehensive measures to control the spread of infection in the country and tried to mitigate the impact of the pandemic. In this chapter, we discussed the primary measures taken to combat the coronavirus pandemic and the details of developing a local reverse transcription real-time PCR (RT-qPCR) detection kit as well as the experience of conducting the phase III clinical trials of the recombinant Uzbek-Chinese vaccine-ZF-UZ-Vac2001 against coronavirus infection. Finally, information is given on the mass vaccination campaign in the country, the difficulties encountered and the achievements made. The developed RT-qPCR detection kit was successfully implemented into production and have widely used for pathogen diagnosis. A total of 6965 volunteers over 18 years old participated in the clinical trials of ZF2001 and the vaccine had an efficacy level of 84.8%. More than 67.6 million doses were administered using seven types of anti-COVID vaccines in the country. The pandemics urged the country to establish a scientific and technical base that aimed at quickly responding to potential future challenges and emergencies.

Keywords: COVID-19, SARS-CoV-2, clinical trials, vaccination, vaccine, Uzbekistan

1. Introduction

The beginning of 2020 was alarming: the news of the impending coronavirus forced all countries to start preparing for the approaching infection. The wide spread of the COVID-19 pandemic has harmed the entire world showing the need for a more developed healthcare system to prevent such large-scale pandemics. A current advance in molecular diagnostic technology has enabled scientists to rapidly characterize the novel virus and deploy diagnostic tests [1]. The first

months of the pandemic resulted not only in absence of approved therapeutics and vaccines but also in rapid diagnostic tests, especially in developing countries. To fill the lack of diagnostic tests, some low- and middle-income countries including Uzbekistan were forced to develop and launch their own diagnostic kits [2–4]. In addition to diagnostic kits, for early diagnosis of the disease, leading countries for R&D-driven biotech have developed several vaccines against COVID-19 at once. The rapidly growing infection rate of COVID-19 worldwide during 2020 stimulated international alliances and government efforts to urgently organize resources to make multiple vaccine types and conduct clinical trials on shortened timelines.

One of the first vaccines to successfully pass the third phase of clinical trials was BNT162b2 (Pfizer-BioNTech) a nucleoside-modified RNA encoding the SARS-CoV-2 full-length spike. A total of 43,548 participants underwent randomized controlled trials resulted in 95% of efficacy in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Moreover, similar efficacy of BNT162b2 was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions [5]. This vaccine was widely used later against COVID-19. Another vaccine type, Ad26.COV2.S (Janssen; Johnson & Johnson) comprises a recombinant, replication-incompetent human adenovirus type 26 vector encoding a full-length, membrane-bound SARS-CoV-2 spike protein that was less efficient (66.9%; 95% CI 59.0 to 73.4) [6]. Subsequently, other vaccines successfully passed the 3-d phase of clinical trials worldwide, among them CoronaVac (Sinovac), an inactivated whole-virion SARS-CoV-2 vaccine yielding efficacy of 83.5% [7], mRNA-1273 (Moderna) a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes full-length spike protein yielding efficacy of 94.1% [8].

Uzbekistan, along with many other countries, has suffered in many ways due to the COVID-19 pandemic, but the country has used methods based on world experience to combat the pandemic and mitigate its consequences. At the beginning of the pandemic, there was a great need for testing systems for the detection of coronavirus in Uzbekistan, as well as in many countries. Due to the global shortage of these test systems, it took a relatively long time to get test results. To overcome this problem, a project to develop a local qPCR diagnostic kit was initiated [9]. Currently, two local companies produce and offer RT-qPCR kits for the detection of genomic RNA [10, 11]. The scientists also determined the variants of the SARS-CoV-2 that are circulating in the territory of Uzbekistan using Next Generation Sequencing which helped to elucidate the distribution of SARS-CoV-2 variants in the country [12, 13]. For the first time, under the China-Uzbekistan partnership program, large-scale phase III clinical trials of the recombinant protein vaccine, ZF-UZ-VAC2001 were conducted in Uzbekistan to provide the population with a safe, highly efficacious vaccine as it is one of the priorities to control the disease [14].

Despite the fact that many measures have been taken to eliminate the coronavirus pandemic in our country, this pandemic showed that there is an urgent need for the development and production of national vaccines. Thus and because of the success in the development of local test systems, the government provided funding for research proposals on vaccine development from several scientific research institutes. The government also has initiated the construction of pilot and full-scale plants for the production of vaccines, which is not only critical to control the COVID-19 pandemic but also to increase our preparedness for the next possible emergencies [15].

2. Primary COVID-19 response in Uzbekistan

On January 29, 2020, a Special Republican Commission has formed to develop a program of measures to prevent the penetration and spread of coronavirus in the Republic of Uzbekistan [16]. In order to ensure epidemiological stability and protect public health, in the early stages of the pandemic, enhanced quarantine restrictions were imposed throughout the country. Pupils and students studied remotely. Air traffic and railroads were suspended. The work of sanitary and quarantine facilities was strengthened, and the regions' adapted quarantine zones were created. Our citizens from abroad were brought home on charter flights and placed in quarantine zones [17]. In Uzbekistan, since March 24, 2020, the wearing of medical masks had been mandatory, while in many countries of the world this issue had only just been discussed [18]. To provide sufficient masks to the whole 34 million population, the government decided to mobilize the textile enterprises to produce protective masks. For example, as the date of May 18, 2020, 275 businesses produced over 6 million masks and 45 thousand pieces of protective gowns per day [19].

Quarantine facilities for 20,000 beds were built in the Tashkent region, 7085 beds in Namangan, Samarkand, and Surkhandarya regions, and the Republic of Karakalpakstan, special hospitals for 4000 beds in the Zangiata district of the Tashkent region. Such special hospitals were also created in Nukus, Samarkand, Termes, and Pap districts [20, 21]. The state fully assumed the costs of fighting the infection, its detection, and treatment of citizens from coronavirus. A progressive package of economic measures was adopted to mitigate the impact of the crisis on relatively vulnerable sectors of the economy. An Anti-Crisis Fund had been created under the Ministry of Finance with an initial amount of 10 trillion UZS ($1 billion). Firms and entrepreneurs were provided with tax "holidays," a number of other benefits, and deferrals of loan payments. Social assistance had been organized for the most vulnerable groups of the population [22, 23].

At the expense of the allocated funds, it was possible to significantly strengthen the potential of healthcare: personal protective equipment, artificial lung ventilators, and other medical equipment were purchased in large quantities, including 878 thousand protective overalls, which allowed to maintain the health of medical personnel, avoiding mass infection of doctors as in some countries, the number of medical staff in clinics had fallen to a critically low level.

3. PCR test development

In the early beginning of 2020, there were only 15 PCR laboratories in the country in the Service for Sanitary and Epidemiological Welfare and Public Health, nowadays, there are 106 such laboratories, including 5 mobile ones [24]. In March 2020, the Special Commission instructed the Centre for Advanced Technologies under the Ministry of Innovative Development to develop and set up mass production of SARS-CoV-2 qPCR detection kits. During that period, a widespread lockdown was announced: all public and private institutions were closed, the movement of any type of transport was prohibited, and a regime of complete isolation of citizens was imposed. The R&D staff of the Centre involved in the project was mobilized to work in laboratories with permanent residence due to the lack of the ability to move around the city. The diagnostic kit "Biotest-SARS-CoV-2" for the detection of SARS-CoV-2 RNA by the real-time reverse transcription polymerase chain reaction was successfully developed in a very short time.

The kit is designed to specifically detect RdRp and N genes of SARS-CoV-2 in clinical specimens in accordance with protocols developed by Universitätsmedizin Berlin Institute of Virology (Charité, Germany) [25] and National Institute For Viral Disease Control and Prevention under the Chinese Center For Disease Control and Prevention (CCDC) [26].

Limit of detection (LoD) studies determined the lowest detectable viral concentration of SARS-CoV-2 (Genomic Copy Equivalents or GCE) that can be detected by the "Biotest-SARS-CoV-2" RT-PCR kit in a particular specimen type at least 95% of the time (95% of all true positive replicates test positive). The LoD was determined by serial dilution studies of the synthetic target gene of known concentration available from Molecular Cloud and produced by GeneScript [27]. For each concentration, qPCR was performed in four replicates per setup, the total number of setups was 3. The amplification was scored by threshold cycles (Ct) on a DT Light instrument (DNA Technology, Moscow, Russia) and Rotor-Gene Q (Qiagen, Hilden, Germany) according to the instructions for the kit.

The highest and the lowest concentration that was used in the reaction was 90,000 and 2 copies, respectively. According to experimental results, on DT Light instrument the detection rate of 2 copies in the reaction (or about 67 copies/ml) is 62.5%, whereas on the Rotor-Gene Q instrument the lowest detectable concentration is 5 copies per reaction. The LoD of viral RNA in a sample depends on the instrument, sampling, storage and extraction method, and dilution ratio. It was determined that the lowest concentration of viral RNA in a sample that can be detected on both Instruments (DT Light and Rotor-Gene) by the "Biotest-SARS-CoV-2" RT-PCR kit with the confidence of ≥95% is 10 copies per reaction or 330 copies per milliliter (0.33/μl). Thus, this concentration is the LoD that is detected in 100% of the tests.

The accuracy of coronavirus RNA detection using the "Biotest-SARS-CoV-2" RT-PCR kit was performed on clinical samples (37 positives and 45 negatives) in three independent laboratories of the Agency for Sanitary and Epidemiological Welfare of the Population (National analog of CDC) under the Ministry of Health of the Republic of Uzbekistan. The primers and probes included in the Biotest-SARS-CoV-2 real-time PCR kit were designed to detect specifically the SARS-CoV-2 coronavirus RNA genes based on the publicly available nucleotide sequences of its strains on NCBI and GISAID databases (https://www.ncbi.nlm.nih.gov/; https://www.gisaid.org/). Search through databases showed their 100% homology with all currently known strains of SARS-CoV-2. This was assessed with in silico sequence comparison analyses. Upon in silico analysis of the Biotest-SARS-CoV-2 real-time PCR kit, the assay design was found to detect all SARS-CoV-2 virus strains and it was found that the oligonucleotide design does not have homology and cross-activity with respect to other types of coronaviruses and non-SARS-CoV-2 species.

The Diagnostic kit was registered with the Agency for the Development of the Pharmaceutical Industry of the Ministry of Health (registration certificate No. № TB/IVI 00395/05/2CIO dated May 7, 2020), and on May 9, an initial batch of 50,000 tests was released. On April 19, 2022, the intellectual property right for the diagnostic kit has been obtained (Patent # FAP02010). The first wave of COVID-19 in Uzbekistan had been started in July 2020, and lasted 3 months, at that time the production of qPCR kits reached 1 million per month and covered the needs of most state laboratories. In the context of a total shortage and the rising cost of diagnostic kits worldwide, only effective measures made possible to satisfy the need of Uzbekistan for COVID-19 diagnostic kits and overcome challenges with no bulk import. Currently, two companies are already producing COVID-19 diagnostic kits in the country [11].

4. Vaccine clinical trials, vaccination, and local vaccines

The next important step in the global fight against the pandemic was vaccine development and mass vaccination. As part of a partnership between the Ministry of Innovative Development and the Chinese Academy of Sciences, in July 2020, the question was raised about the need to create a vaccine and its further use. The Centre for Advanced Technologies under the Ministry of Innovative Development began cooperation with the Institute of Microbiology of the Chinese Academy of Sciences, and the pharmaceutical company Zhifei Longcom Biopharmaceutical Co. Ltd. on conducting phase III of clinical trials in Uzbekistan [28]. Noteworthy, none of the national medical institutions had previous experience in multicentre clinical trials for new drugs. Discussions involving scientists and leading doctors of the republic showed that there were doubts about conducting clinical trials at such a scale. Meanwhile, conducting the clinical trials would allow for analyzing the safety and efficacy of vaccines prior implementing to mass vaccination.

The vaccine formulated of protein subunit consisting of antigens with two SARS-CoV-2 spike RBD (HB-01 strain, residues 319–537, accession number: YP_009724390) connected in tandem (RBD-dimer), manufactured in the CHO ZN CHO K1 cell line. The advantages of this vaccine are included but are not limited to (1) the safety of this type of vaccine in comparison with other technologies and (2) storage conditions +4°C, which is important for Uzbekistan in terms of cold chain of storage and transportation [29]. A comprehensive study of the technology for obtaining a new vaccine, safety, and immunogenicity reports on phase I and phase II of trials made it possible to decide on our country's participation in clinical trials [30].

In October 2020, a tripartite memorandum was signed between the Ministry of Innovative Development, the Institute of Virology under the Ministry of Health of the Republic of Uzbekistan, and Zhifei Longcom Biopharmaceutical Co., Ltd. Thus, an agreement was reached to conduct the phase III of testing a vaccine against coronavirus in Uzbekistan. Prior to the start of clinical trials in Uzbekistan, the Pharmacological Committee of Uzbekistan conducted specification tests to analyze the effectiveness of antibody production and most importantly, evaluated the safety of the vaccine. In November, a group of Chinese researchers and specialists arrived in Tashkent. On our part, the Institute of Virology prepared a large group of doctors and nurses who were to work on the project that year, and more than 30 employees of the Centre for Advanced Technologies were allocated to the management and monitoring group. In total, more than a 100 medical workers were involved in the process, and later 36 more people were recruited to the Call Centre for daily monitoring of the health of volunteers.

At a meeting of the Ethical committee on December 10, 2020, an international, multicentre, double-blind, randomized, placebo-controlled III-phase clinical trial was approved in the Republic of Uzbekistan. The clinical trials were conducted according to the requirements of the international GCP standards and relevant regulations. Four vaccination sites were opened. Each volunteer was given a written consent form that contained the relevant details of the vaccine, the clinical trial, and the risks, and benefits associated with participation in the clinical trial. All volunteers were recruited based on voluntary principles after only signing a consent form and could suspend their participation at any time according to their will. To find eligibility the main health indicators were determined, and blood and swab samples were taken to determine previous COVID-19 and/or ongoing infection. Some of the subjects were not recruited for medical reasons, and others either had COVID-19 or refused to participate.

In Uzbekistan, between December 12, 2020, and Jun 30, 2021, a total of 13,855 volunteers underwent health screening, and 6965 people enrolled in clinical trials. Participants were stratified on the basis of age in two groups 18 ~ 59 years (6758 people) and ≥ 60 years (207 people) and randomly assigned into two groups to receive an investigational vaccine or placebo at a 1:1 ratio. A total of 6958 people (99.9%) were vaccinated with the first dose, 6717 people (96.4%) were vaccinated with the second dose, and 6395 people (91.8%) were vaccinated with the third dose. At least 7 days after the 3rd vaccination, a total of 53 COVID-19 cases were confirmed of which 46 were in the placebo group the vaccine showed an efficacy level of 84.8% (95% confidence interval, 66.2–94.2; **Table 1**).

Among the safety analysis set, 1301 (20.4%) participants reported at least one adverse event, with 709 (24.81%) participants in the vaccine group and 592 (23.36%) in the placebo group. Most of the reported adverse events 644 (20.22%) in the vaccine group and 517 (16.26%) in the placebo group were grade 1; 31 (0.86%) and 29 (0.83%), respectively, were grade 2; and 34 (1.07%) and 46 (1.44%) were grade 3 (**Table 1**).

During July–September, 2021 increase in COVID-19 incidence was observed in Tashkent with 84% of Delta strain detected by sequencing and PCR analysis. A total of 35 cases (1.08%) occurred among 3226 ZF-UZVAC-2001 group and 156 (4.84%) cases were confirmed in the 3221-placebo group. Vaccine efficacy for Uzbekistan trial group dropped from 84.8% to 80.2% (95% CI, 71.3–86.7). Other studies also reported a decrease in the effectiveness of the vaccine candidates against variants of concern including the Delta variant [31].

The research and organizational work of scientists from the Centre for Advanced Technologies and the Institute of Virology were highly appreciated by Chinese specialists and independent experts. The Chinese side announced the acceptance of Uzbekistan as a coauthor, and the vaccine was given the brand name ZF-UZ-VAC2001. Phase III of the research was carried out in five countries (China, Uzbekistan, Indonesia, Pakistan,

	Total cases	**ZF2001**	**Placebo**	**Vaccine efficacy, % (95% CI)**
Symptomatic COVID-19	53/6365 (0.8%)	7/3185 (0.2%)	46/3180 (1.4%)	84.8% (66.2 to 94.2)
Severe symptomatic COVID-19 and beyond	3/6365 (0.09%)	0/3185 (0%)	3/3180 (0.09%)	92.9% (52.4 to 99.8)
Death by COVID-19	0/6365 (0%)	0/3185 (0%)	0/3180 (<0.0%)	100% (−8.4 to 100)
Stratification by age				
Aged 18–59 years	52/6365 (0.8%)	7/3185 (0.2%)	45/3180 (1.4%)	81.2% (72.8 to 87.3)
Aged ≥60 years	1/207 (0.5%)			87.6% (2.5 to 99.7)
Adverse effects				
Total adverse effects	1301/6365	709/3185 (24.81%)	592/3180 (23.36%)	
Grade 1	1161/6365	644/3185 (20.22%)	517/3180 (16.26%)	
Grade 2	60/6365	31/3185 (0.86%)	29/3180 (0.83%)	
Grade 3	80/6365	34/3185 (1.07%)	46/3180 (1.44%)	

Table 1.
ZF2001 vaccine efficacy against COVID-19 with onset at least 7 days post-vaccination.

and Ecuador) with the involvement of 28,500 volunteers. The results of phase III clinical trial of the ZF-UZ-Vac2001 vaccine were published recently [32]. Vaccine efficacy after the third dose was 87.6% (95% CI, 70.6 to 95.7) in preventing moderate to severe forms of COVID-19. In total, out of 28,500 volunteers, 14,249 received the vaccine and 14,251 received a placebo, 647 of the volunteers were diagnosed with coronavirus, 221 of them—7 days after the third dose of the vaccine, 35 of those infected received the vaccine, and 186—placebo. These results demonstrate vaccine efficacy of 81.76% [32].

On March 1, 2021, the ZF-UZ-VAC2001 vaccine was registered with the Pharmaceutical Industry Development Agency of the Ministry of Health and approved for mass use in Uzbekistan. Thus, Uzbekistan became the first country in the world to approve and begin the mass use of a recombinant protein vaccine against coronavirus. On March 15, the vaccine was approved for use in China [33]. In April 2021, a mass vaccination campaign for adults over 65 and people at risk began, and a month later, vaccination of all populations was initiated [34]. All vaccination costs were made free for the population. The purchase of vaccines and the costs related to the vaccination program was covered by the state budget [35, 36]. To increase the vaccination coverage of the population, extensive explanatory work was conducted on the importance of vaccination and how they work. In addition, the introduction of various benefits to vaccinated people significantly increased the coverage of vaccination [37]. As the date of September 15, 2022, seven types of 44.2 million doses of vaccines were imported and 27.5 million doses of vaccines were produced in Uzbekistan from which 26.6 million doses of ZF-UZ-VAC2001 and 881.8 thousand doses of two-component Sputnik V vaccine.

Up to date, 71.9 million doses of vaccines have been used of which the majority share (48.2 million doses) of the vaccines belonged to of ZF-UZ-VAC2001 vaccine. In addition to the protein vaccine, the following vaccines were used in the country: Astra Zeneca 2.6 M doses (4%), (2%), Moderna 10.7 M doses (16%), Pfizer-BioNTech 6.8 M doses (9%), Sinovac 2.0 M doses (3%), and Sputnik-V and Light 1.645 M doses (2%) (**Figure 1**).

A total of 21.5 million of population was included in target group for the mass vaccination according to their age. No people under 18 were included for the national vaccination program against coronavirus infection. A total of 21.1 million people received the first dose, 17.8 million received the second dose, and finally, 10.6 million

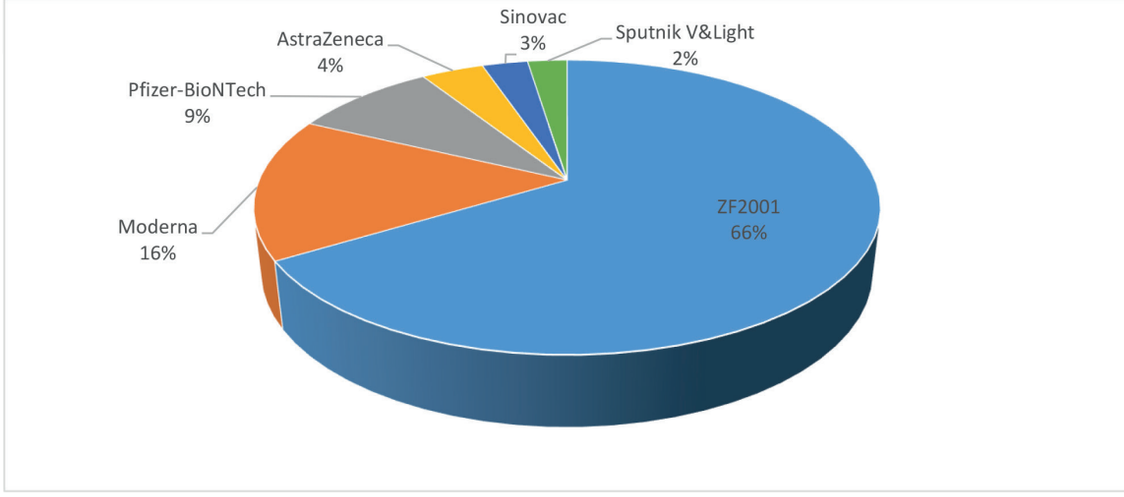

Figure 1.
The proportion of anti-COVID-19 vaccines used in Uzbekistan.

people received the third dose. From those 16.4 million people (76.6% of the target population) received a full vaccination course. Uzbekistan has become one of the countries where seven types of vaccines obtained using different technologies were simultaneously used. All vaccines showed good protection against severe forms of coronavirus: in persons who completed the full course of vaccination, there were practically no deaths, as well as no need for resuscitation [38].

In addition, scientists in Uzbekistan are conducting research on the development of vaccines against coronavirus. There are three vaccines listed by the WHO that are currently undergoing preclinical studies: the Renovac recombinant protein vaccine (developed by the Centre for Advanced Technologies), the Genovac DNA vaccine, and the Tomovac edible vaccine obtained by genetically modifying tomatoes (developed by the Centre of Genomics and bioinformatics, Academy of Sciences of Uzbekistan) [39].

5. Conclusions

The establishment of a special commission to fight against the coronavirus pandemic in Uzbekistan and the involvement of employees of state bodies with various backgrounds made it possible to consistently discuss the issues and make decisions in a short period. Multilateral cooperation in order to cover the need for vaccines became an important factor in the implementation of vaccination campaigns. The scientific and technical base created for the detection of the coronavirus also helped in the identification of new variants of the coronavirus. qPCR-based kits have already been developed that allow the detection of variants of concern such as Alpha, Delta, and Omicron. From a further perspective, the production of local kits for the detection of other important diseases may be implemented. In fact, there is already ongoing work to introduce new local test systems into the market. Uzbekistan's experience in conducting large-scale clinical trials stimulates local companies to conduct research on novel drugs. In addition, research teams are working on several vaccine platforms that may, in turn, enhance Uzbekistan's capacity for the development of national vaccines. Finally, these all initiatives including vaccine production capability can pave the way for increased resilience to combat infectious diseases and threats in the country.

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Conflict of interest

The authors declare no conflict of interest.

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