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Observation on China's efficient mobilization and external dependencies in COVID-19 detection reagents, vaccines and drugs development

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Abstract: Respiratory infectious diseases had happened in China in recent years, and the outbreak of Corona Virus Disease 2019(COVID-19) had drawn worldwide attention. In order to control such high-mortality infectious diseases, the work of the Chinese government and the medical community in detection reagents, drugs, and vaccines had been speeded up. This research extensively searched the medical data of drugs, vaccines and kits development, the company's business report and the government's policy documents and conducted case analysis. We found some national mobilization measures had been put on the agenda and some special marketing authorization measures had been adopted. Due to the limitations of biotechnology research and the pharmaceutical industry, some key technologies and drugs still had a high external dependence. In the process of development, it was necessary to attach importance to scientific, ethical, and safety construction, and to strengthen international cooperation.

Keywords: Corona virus disease 2019, drug, authority, development; legal.

INTRODUCTION

The original epidemic time of the Corona Virus Disease 2019(COVID-19) had not yet been accurately traced. In China, according to the report by the Health Department of Wuhan Municipal, Hubei Province, the earliest onset of the patient was December 29, 2019. The epidemic was associated with a market-- "Wuhan South China Seafood City", animals were initially suspected of carrying the virus and transmitted to humans (Chinese Center for Disease Prevention and Control, 2020). By the end of January 2020, the COVID-19 had spread to all provinces in mainland China. The number of patients in China had reached 83537 and 4634 have died, the fatality rate in China was about 5%. (Chinese National Health Commission, 2020). In the process of medical treatment, China had solved the shortage of drugs and testing kits in a short time through independent development and introduction, and started to develop vaccines. This paper analyzed these R&D and production activities, trying to find some effective information that can help to deal with the epidemic

MATERIALS AND METHODS

This study first focused on the research progress of disease diagnosis, detection and drug use of COVID-19. This research extensively searched the medical data of drugs, vaccines and kits development, the company's business report and the government's policy documents, and conducted case analysis. This research also drew on the previous literature on the construction of China's public health system, the prevention and control of infectious diseases and the reform of drug approval system.

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RESULTS

Strong mobilization of COVID-19 detection kits and vaccines development

In the early days of the pandemic, medical activity faced some difficulties. The first was the challenge of reagent accuracy and detection capabilities. The COVID-19 had broken out during the winter in China. At the same period, the spread of influenza was at its peak. Both of them had common symptoms, such as cough and fever, and needed to take imaging tests. In terms of confirmatory diagnosis, the Chinese National Health Commission had integrated advice of laboratory test, imaging test and reagent test methods implemented from various hospitals and proposed two test standards. The first was the real-time fluorescent RT-PCR detection of nucleic acid expression in respiratory specimens, checked the result was positive or not. The second was blood specimen virus gene sequencing, checked the homologous to the COVID-19 virus. A diagnosis could be confirmed when either of the two tests meet (Chen, 2020).

The Chinese Center for Disease Prevention and Control had successively released two versions of the "Prevention and Control Plan for COVID-19" to explain laboratory testing technical guidelines, specimen collection and delivery, medical staff training. However, each hospital reported three concentrated problems during the implementation. First, in areas such as Wuhan where the epidemic was severe, there were not enough nucleic acid

kits, and suspected patients could not be tested in time and could not enter the next diagnosis and treatment process. Second, according to the requirements of the Chinese National Health Commission, the nucleic acid kit test must be performed by the Provincial Centre for Disease Prevention and Control, according to traditional testing methods, each sample test took at least 3 hours. However, the detection capacity of the Centers for Disease Prevention and Control had reached its limit. Until the end of January 2020, the Chinese National Health Commission authorized the 3A-level hospitals and third-party institutions to conduct inspections. Third, the accuracy of some nucleic acid tests was not high. Some patients were reported negative for all three tests, but then they suffered disease. It can be seen that the focus of the contradiction was the detection kit. (Huang, *et al* , 2020)

Under normal circumstances, the period from the development of the nucleic acid detection kit to the final marketing authorizations was 2-3 years, and some took 4-5 years. The R&D process included primer and probe design, template preparation, catalytic enzymes, probes, primer optimization, sensitivity test, repeatability test, stability test, minimum detection concentration, specificity and other interference substances, precision analysis, etc. Prior to this, the virus needed to be genetically sequenced. In order to speed up the R&D and production capacity of the detection kits, the Chinese Center for Disease Prevention and Control had disclosed the full sequence of the COVID-19 gene for free use by researchers and enterprises. The Ministry of Science and Technology of China had released a fund for the "R&D of COVID-19 rapid detection products" project, which can be applied by researchers, and some commercial companies had seized business opportunities. According to media reports, at least 80 institutions had announced the development of detection kits at the laboratory level. Some kit samples were being tested in hospitals, pending approval from the Chinese National Medical Products Administration. Some kits needed to cooperate with biotechnology product manufacturers to achieve commercialization. (Chinese National Medical Products Administration, 2020a).

There were two main types of detection kits currently being developed. The first was the RT-PCR (Polymerase Chain Reaction) method, which was the mainstream R&D method for detection kits. Through detecting three kinds of samples, including patient's nasopharyngeal swab, sputum, and alveolar lavage fluid, then reversing transcription specific RNA fragments into DNA and adding amplification detection reagent. If the reagent encountered the gene of the virus-, the reaction system in the reagent will exponentially amplify it, and the virus gene will be efficiently expressed, so as to verify the presence of the virus. At present, the types of detection kits being developed include multiplex PCR, fluorescent PCR (for N gene detection), fluorescent PCR (for ORF1ab gene detection), etc. Traditional methods required several hours of testing. Now the kits developed by some institutions can already realize the rapid detection of isothermal amplification the results can be automatically interpreted, and the detection time is shortened from several hours to 20 minutes (Zhang, 2020).

Recently, a comprehensive detection technology had appeared. It used the constant temperature amplification chip method, which can detect 6 kinds of common respiratory viruses in 1.5 hours, including COVID-19, influenza A virus, new influenza A H1N1 virus (2009), influenza A H3N2 virus, type B Influenza virus, respiratory syncytial virus (Shan, 2020).

Another method was the colloidal gold method. Because IgM was the earliest antibodies which appearing in the autoimmune process of virus infection, testing antibodies or antigens was also a method of kits development. The colloidal gold method was developed using immunocolloidal gold chromatography technology, using 1 drop of serum, plasma, or whole blood as the detection sample, using the specific binding of antigen or antibody, through serological detection, combined with marker coloration screening, which can quickly achieved qualitative detection of COVID-19 IgM / IgG antibodies in human body. Some kits used IgM/IgG antibody single card -, which can observe by naked eye. It can be used for on-site diagnosis and mainly used for early preliminary screening of communities, schools and homes, can be used as a supplement to nucleic acid detection. Now some institutions had claimed to complete the test within 3 minutes and some institutions were beginning to develop COVID-19 antigen detection kits (Wangand Li, 2020).

The virus detection kit belongs to the "NO.3 category of medical devices", before applying marketing authority approval, it must performed clinical trials, then must be tested by the Medical Device Quality Supervision and Inspection Center. The Chinese National Medical Products Administration has adopted two flexible measures. The first was to announce the implementation of the "Emergency Approval Procedures for Medical Devices". For safety, effectiveness and controllable quality, emergency approval was required. On January 26, 2020, the Chinese National Medical Products Administration approved the registration application for 4 COVID-19 detection products. The manufacturers were Shanghai Genuo Biotechnology Co., Shanghai Zhijiang Biotechnology Co., Shenzhen Huada Gene Co., and BGI Manufacturing Co., Three of these kits were RT-PCR nucleic acid detection kits, and one was viral nucleic acid sequencing system. At the same time, the Chinese National Medical Products Administration agreed that 7 other detection kits manufacturers can enter the fast-track approval channel. On January 28, 2020, the Chinese

National Medical Products Administration approved 2 COVID-19 nucleic acid detection kits from 2 companies in accordance with the "Medical Device Emergency Approval Procedure". The producers were Da'an Gene Co., of Sun Yat-sen University and Shengxiang Biotechnology Co. On February 22, 2020, the Chinese National Medical Products Administration emergency approved 3 diagnostic reagent products, two of which were colloidal gold antibody detection reagents and one was a thermostatic amplification chip nucleic acid detection reagent. The producer was Wanfu Biological Co., and Chengdu Boao Biological Group. Second, in Hubei Province, where COVID-19 was most severe, the Chinese Government had adopted simpler measures allowing new kits listing in advance, then took marketing authorizations procedure after the pandemic was over. Through these mobilization methods, at the end of February, 2020, the production capacity of nucleic acid detection reagents reached 1.7 million copies per day, and the production capacity of antibody detection reagents reached 350,000 copies per day (State Council Information Office of China, 2020). However, only 9 products had been approved marketing authorization and other kits had not obtained the registration certificate. Once the diagnosis was missed, the risks were difficult to bear.

A similar strong mobilization had occurred in COVID-19 vaccines development. Vaccines had great significance to protect healthy people, block virus outbreaks and prevent the resurgence of COVID-19 in the future. They also had great development difficulties and strong safety requirements. Traditional vaccine R&D methods require screening, breeding of strains, attenuation of strains, researching on the stability of the strains in adapting to the cultured cell matrix and passage, establishment of animal models, clinical trials, and other steps, which spent a long time. The mRNA vaccine model simulated the process of natural virus infection, induced human cells to produce the same protein as the surface of the pathogen, and activated the immune response of the human body. It can quickly construct candidate vaccines and trial samples, but it also had defects in mass production and price. The Ministry of Science and Technology of China decided to fund the development of five types of vaccines, including inactivated vaccines, attenuated vaccines, nucleic acid vaccines, carrier vaccines and recombinant protein vaccines. With this incentive, more than 10 institutions and biotechnology companies in China had invested in it, Including Chinese Academy of Sciences, Chinese Centers for Disease Prevention and Control, Tsinghua University, Zhejiang University, Tianjin University, Tongji University, Kangxinuo Co., RuichengHaihui Pharmaceutical Co., WuXi Biotechnology Co., Sri Lanka Microbial Technology Co., Guanhao Biotechnology Co., Kangtai Biotechnology Co., Watson Biopharmaceutical Co., Liaoning Chengda Co., Hualan Biotechnology Co., Kangtai Biotechnology Co., Kangxinuo Biotechnology Co., Some institutions announced the establishment of vaccine seed batches, some institutions announced that the mRNA vaccine research has entered the animal experimental stage; some institutions confirmed the development of recombinant adenoviral vector vaccine, and some research teams produced wine Yeast-based oral vaccine. Although the vaccines were placed with great hopes, the Chinese National Medical Products Administration also opened a special review channel in the development of the COVID-19 vaccines, but China introduced the "Vaccine Management Law" in 2019 to strengthen the approval and supervision of vaccines. The vaccine needed at least a series of processes such as animal experiments and clinical trials before it can be listing (Yu and Li., 2019).

External dependencies on COVID-19 drugs selection and development

As a new disease, there was no specific drug for COVID-19. Most of patients who infected with COVID-19 belonged to mild symptoms patients, and the lungs would not suffer permanent damage after cure, similar to the annual flu. However, the mortality rate of severe patients was high. -.. The task of finding effective drugs was very urgent and very difficult. There were many drugs and therapies used clinically, including anti-AIDS drugs, cold and flu drugs, interferons, glucocorticoids, various Chinese medicines, Chinese medicine injections, umbilical cord blood, stem cells, antibody-containing plasma, and so on. In order to guide clinical treatment, Chinese National Health Commission had revised and published six versions of the "COVID-19 Diagnosis and Treatment Program", which specified the etiology and epidemiological characteristics, clinical symptoms, diagnostic criteria and clinical characteristics of this disease. Some drugs were recommended in the plan, including IFN-α interferon, lopinavir, ritonavir, ribavirin, abidol, chloroquine phosphate, glucocorticoids, and plasma of recovered patients. These drugs can be divided into two broad categories. The first category was antiviral drugs, which have been clinically proven to have certain effects in the past. For example, in vitro studies on MERS and SARS had found that interferon had inhibitory effect on coronavirus (Chinese National Medical Products Administration, 2020b).

Ribavirin was a synthetic nucleoside drug. During SARS in 2003, it had experience using ribavirin combined with antibiotics and glucocorticoids to treat pneumonia (Pfefferle *et al*., 2011).

The second category was old medicines that had been on the market for many years and may be used for new indications, including lopinavir and ritonavir, which were previously used to treat AIDS. They were used by doctors in Hong Kong to treat SARS (Chan and Xu, 2003).

Chloroquine phosphate had been used in malaria treatment. In 2004, experiments showed that chloroquine phosphate had a therapeutic effect on coronavirus (Morgenstern *et al*., 2005).

Abidol, which was used to the influenza, had destructive effect on the COVID-19 virus when the effective concentration reaching 10-30 micromoles (Xu, *et al*., 2020).

For second category drugs, clinical trials were usually required to confirm their effectiveness and their new uses. t To this end, the Chinese National Medical Products Administration adopted the practice of promoting clinical use and emergency clinical trials, and approved clinical trials of five drugs including abidol, chloroquine phosphate and lopinavir (Lu, 2020).

Other than that, the Chinese National Medical Products Administration had approved special review channels for several innovative drugs One of the most interesting drugs was the new nucleoside analog antiviral drug "remdesivir", developed by the American Gilead Company It had a good inhibitory effect on Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome Coronavirus (MERS) (Chu *et al*., 2004), and had completed Phase I and Phase II clinical trials in the United States.(Sheahan, *et al*., 2017). American doctors took a "sympathetic medication" on a COVID-19 patient in January 2020 and received the effect. France also announced that one COVID-19 patient was cured. After the epidemic breakout, Gilead announced that it will provide free samples of remdesivir to China. On February 2, the Chinese Drug Evaluation Center opened a green channel to accept clinical trials of remdesivir. The drug would undergo phase III, randomized, double-blind, placebo-controlled trials in China.. A total of 761 patients would participate in the trial to determine the safety and effectiveness.. In addition, according to Article 26 of China's "Drug Administration Law", drugs conditional approval can be granted for the treatment of severely life-threatening diseases without effective treatment methods urgently needed in public health (Yu and Li, 2018).

Favipiravir, an anti-flu drug developed by Japan, had beenapproval for clinical trials, too (Coomes and Haghbayan, 2020) The Chinese National Medical Products Administration also approved a multicenter, randomized controlled clinical study of the efficacy and safety of "tocilizumab" produced by Roche Pharmaceuticals for the treatment of cytokine storms caused by COVID-19 (Luo *et al*., 2020).

The COVID-19 epidemic exposed China's strong external dependence on drug development. The currently recommended therapeutic drugs were all from abroad, and there was no Chinese self-developed drug, which indicated that China's new drug development capabilities need to be improved. The more important issue was China's pharmaceutical development planning and sustainability. After the end of the SARS epidemic in 2003, China's pathological research on respiratory infectious diseases had become an upset, and government funding had decreased. Many researchers had not continued their research. Similarly, Chinese pharmaceutical manufacturers were not strong in drug development. They believed that if there were no patients with disease, there was no market for the new drugs. The COVID-19 epidemic also showed the utilitarian approach of some institutions in China. According to media reports, there have been more than 200 clinical studies or clinical trials of COVID-19 drugs in China (Rosa and Santos, 2020). If strict and standardized implementation of clinical research were required, not only the informed consent and cooperation of the participants, but also a sufficient sample size can not meet the requirements of these researches. Except in Hubei Province, China, where the epidemic was most concentrated, it was difficult to find more than 500 patients to support clinical trials in other provinces. Therefore, the sample size of some clinical studies were only tens of cases, and some were only less than 10 patients (Keyaerts *et al*., 2004). This was likely leading to bias results. If there was no high-quality clinical trial design, or the selection of the control group was unreasonable, or the randomization and masking of the group were not strictly enforced, or the evaluation criteria of the efficacy indicators were not objective, or the data integrity and authenticity were insufficient, then these clinical studies were difficult to provide high-quality evidence of effectiveness and safety, and China's drug development and efficacy evaluation was difficult to be recognized by the world.

DISCUSSION

COVID had become the largest and most difficult infectious disease in China since 1949. detection kits, drugs, and vaccines were all urgently needed weapons to combat the disease, but based on medical, biotechnology, legal constraints and history lessons learned from China, the development work for COVID-19 medical products needed to consider the following:

First, it must be alert to anti-science and anti-ethical phenomena in development. Some countries have reported that the accuracy of new coronavirus nucleic acid detection kits exported from China were unstable. As of March 2020, the Chinese National Medical Products Administration approved a total of 19 new coronavirus detection kits, including 10 nucleic acid detection kits and 9 antibody detection reagents, other kits had not obtained the registration certificate. This also indicated that the development of nucleic acid detection kits must improve the selection and preparation of positive reference

materials and negative reference materials, improve the selection and preparation of minimum detection limit of reference material. The positive detection rate, negative detection rate, precision, and repeatability of the kits must be stable. The same hidden dangers also existed in COVID-19 drug development. In the early time of pandemic, some doctors chose drugs based on their experience that against SARS and flu every year; some selected drugs based on reports from famous medical literature; some researchers used case and toxicology tests to verify whether certain drugs were effective in human body. In some places, the method of combining Chinese medicine and Western medicine was adopted. For the sake of emergency management, these options were understandable, but there are some drug proposals that still needed to be scientifically verified. For example, abidol, which was used for the treatment of influenza, was found that it had destructive effect on the COVID-19 virus when the effective concentration reached 10-30 micromoles. However, this concentration was higher in vitro, patients cannot reach this concentration in the body after taking the drug and other side effects had not been confirmed. During the development process, experiments and testing work must meet the requirements of clinical applications. if clinical trials were reduced, or the data effects that can be produced by different drugs were attributed to a certain drug, it was not in line with the requirements of evidence-based medicine.

Second, security needed to be strengthened. According to regulations, the COVID-19 classified as serious infectious diseases. Relevant reagent testing must be carried out in a laboratory that has achieved biosafety level 2 (P2) (Sheahan *et al*., 2020). There must be negative pressure equipment in the testing laboratory, air can only enter and cannot go out. The laboratory cleanliness, ventilation system, and disinfection all had requirements (Expert Group on Prevention and Control of New Coronavirus Pneumonia of Chinese Preventive Medicine Association, 2020). Prevent cross-infection was even important when laboratory's security level is up.

Third, we must strengthen international cooperation. When more and more countries are involved in the COVID-19 epidemic, successful drug development meant huge market value. Researchers around the world were also researching corona viruses. Some public databases and research literature had shared, and some drug development ideas can be used for reference. But there was also technology and business competition.. Although, there was also technology and business competition, there were still some controversies on the source of the pandemic, but cooperation was inevitable. For example, China may consider moving clinical trials of some drugs to other countries which can accommodate more COVID-19 patients, Chinese pharmaceutical companies can provide more high-purity APIs.

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