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Biotechnology and crisis management developments during the COVID-19 pandemic: Comprehensive analysis

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Abstract. Over the period from 2020 to 2023, a four-year non-military battle drew to a close, marking the end of the COVID-19 pandemic that will be etched into history. During this time frame, policies and technologies aimed at combating the virus were developed, ultimately saving numerous lives and enhancing people's efficacy in battling the virus while demonstrating unwavering determination. However, some less mature biological nucleic acid technologies and some controversial policy bases are still being improved. Through the development of biotechnology levels and policies, the research and development of three mRNA vaccines, health codes and RT-PCR nucleic acid detection methods have greatly improved the efficiency of epidemic prevention and control. The government's policy of controlling speech and behavior at the initial stage of the outbreak brought people together to fight against the virus. These technologies are being researched to reduce the number of casualties and minimize losses. For example, circRNA or saRNA vaccines are still in the research stage. If these more advanced techniques are put into use, it will undoubtedly greatly increase the means of fighting against the virus. This is also the direction and key for future research and development.

Keywords: mRNA Vaccines, crisis management, healthcare QR Code, RT-PCR techniques

1. Introduction

In late 2019 and early 2020, a pandemic broke out in Wuhan, which had a profound impact on the global situation in the next three years. After the initial cases and virus type were confirmed as SARS, the National Health Commission immediately took action, implementing measures similar to those taken during the SARS outbreak 17 years earlier [1]. COVID-19 not only triggered an unprecedented global health crisis but also led to a series of global recessions including economic and cultural impacts. The development of vaccines and active policies by countries at various stages have greatly alleviated pressure from patient overload and public demands on governments. Since the launch of COVID-19 vaccine and decline in hospital admissions, public health response measures have also evolved [2]. In summary, the global pandemic has precipitated a swift deterioration in cultural, economic, and other facets of numerous countries. Utilizing big data for pandemic-related research can facilitate a judicious approach to economic recuperation; efficient allocation of medical resources; exploration of viral structure and mutation mechanisms; development of targeted vaccines against mutated strains; and advancement in public health infrastructure culminating in the establishment of a global infectious disease control system. The profound impact left by the three-year pandemic on human history necessitates comprehensive analysis from physiological, psychological, policy, and other perspectives

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using specific case studies and global big data models to drive research and progress. The objective is to scrutinize the experiences and lessons derived from the COVID-19 pandemic with an aim to enhance global preparedness for future infectious diseases while averting recurrence of similar calamities. Moreover, the pandemic has underscored the importance of investing in healthcare systems, fostering international collaboration, and ensuring equitable access to healthcare resources. It has also highlighted the critical role of effective communication strategies in mitigating panic and ensuring the dissemination of accurate information.

2. mRNA vaccine mechanism, different types and effectiveness

2.1. Basic mechanism

The COVID-19 pandemic has swept the globe, causing massive loss of life and the disintegration of families, posing a serious threat to global public health. However, there are treatments or vaccines tailored to each virus or epidemic. Vaccines are the most effective and cost-effective intervention for controlling the spread of epidemics and building universal health protection systems. Among these, mRNA vaccines have emerged as standout candidates due to their distinct advantages, including rapid development cycles, facile industrialization, uncomplicated production processes, adaptability to new variants, and superior capacity to elicit immune responses [3]. The basic mechanism of mRNA vaccines relies on vectors to deliver the genetic information of each coronavirus variant, encoding the spike protein of the virus. Upon subcutaneous injection, the vaccine's mRNA is swiftly absorbed by muscle cells, triggering synthesis of the spike protein and activation of the body's immune system. Following absorption, ribosomes in muscle cells synthesize the spike protein targeting the virus as directed by the mRNA. This spike protein serves as a memory instruction recognized by the body's immune system as an "alien invader," prompting immediate activation of antibody secretion and T cell response against it. Subsequently, immunity is established against this spike protein or virus; if encountered again in future, rapid identification and attack can be mounted by the body. In summary, mRNA vaccines utilize carriers to transport nucleic acid molecules encoding antigens to host cells' target sites, inducing production and expression of target proteins to elicit an immune response [3]. This approach avoids active viral components and associated human infection risk while demonstrating high efficiency with broad applicability. Basically, three primary types of mRNA vaccines for COVID-19 could be categorized in: non-replicating mRNA vaccines, self-amplifying mRNA (saRNA), and circular mRNA (circ RNA). These distinct vaccine types exhibit significant variances in both structure and functionality (Figure 1).

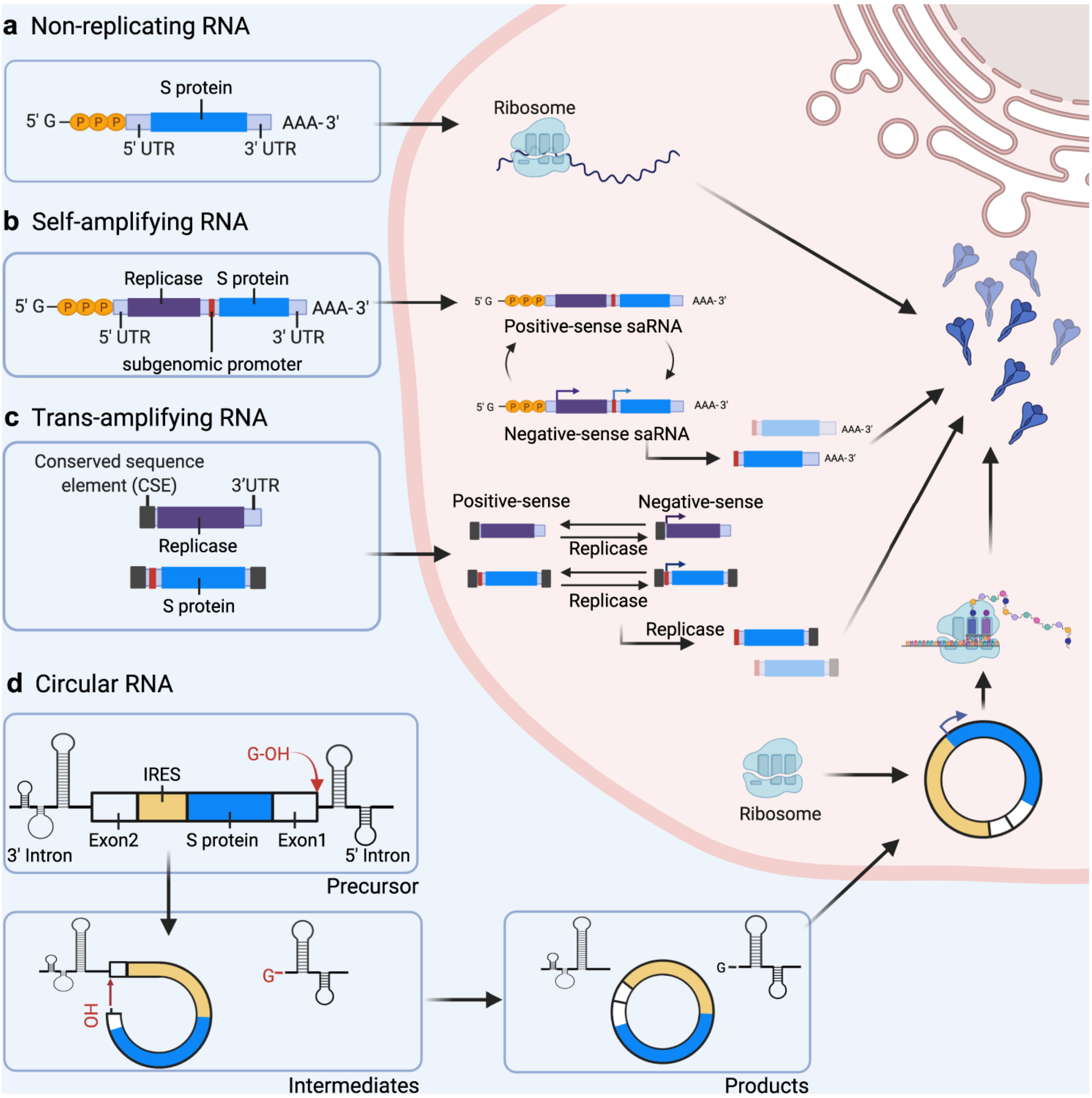

Figure 1. Antigen expression in different types of mRNA vaccines [4].

2.2. *Non-replicating mRNA vaccines*

The first type of non-replicating mRNA solely conveys the coding sequence to generate antibodies against the virus, encompassing the 5′-cap, 5′ UTR, 3′ UTR, and 3′-poly(A) tail regions [3]. This particular mRNA vaccine is currently prevalent due to its advanced technology and rapid development. Its fundamental composition includes an Open Reading Frame for the target antigen protein flanked by 5′ and 3′ UTR. Moreover, it features a 7-methylguanosine cap structure (7-mG cap) at the 5' end and a poly(A) tail structure at the 3' end. The coding sequence formed by the gene for the target antigen at both ends enhances mRNA stability while improving efficiency and precision, and can be ensured that it will not undergo rapid dissolution upon entry into the cell. After immunization, mRNA is injected into human cells using lipid nanoparticles (LNPs) or alternative delivery methods. After being absorbed by cells, ribosomes identify the mRNA and start translation. As was previously mentioned for the spike protein, ribosomes travel along the mRNA track in order to decode and translate the target antigen protein according to its coding sequence. Similar to a computer saving fingerprints, the spike protein's subsequent activation of the immune system results in the establishment of immunological memory

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against the genetic or structural characteristics of the pathogen. The moment the virus re-invades, the body mounts an instant defense.

2.3. circRNA vaccines

CircRNA is a non-terminating RNA that is characterized by a very stable single-stranded structure. circRNA is different from non-replicating RNA in that it does not have both 3' and 5' ends. One of its primary benefits is that, compared to other mRNA forms, it is far less susceptible to nucleic acid exonuclease degradation due to its circular shape. Ribosomes recognize circRNAs as having properties similar to viral spike proteins when they enter human cells. When the cell recognizes it, it allows a number of immune cells such as macrophages, or dendritic cells, to respond by responding to the spike protein and processing the antigen. These steps are like a chain, and B cells and T cells respond in kind. This recognition process is similar to the non-replicating RNAs discussed earlier. When B cells are activated, they form antibodies to specific variants of the novel coronavirus, and eventually the human body will respond with corresponding humoral reactions such as sneezing, runny nose, sweating and other symptoms. While these attributes are considered potential advantages in nature's context; currently only circRNAs based on type I ribozyme self-catalytic strategy are under development and study due to their relatively subtle advantages that have not yet progressed into clinical trials. Furthermore, circRNA has challenges in the production process and requires additional study and improvement before it can be employed extensively, even with its stable structure and persistent antigenicity. However, the science of biological genetics is still unsure about how well the vaccine delivers circRNA to target cells, therefore the delivery mechanism needs to be improved. In contrast, as technology advances, circRNA vaccines may prove to be a critical field of research for the development of vaccines of the next generation.

2.4. saRNA vaccines

The third mRNA vaccine for COVID-19 is called self-amplifying mRNA, in short name of saRNA. Just like the two mRNA vaccines mentioned earlier, sa RNA also has great potential for development. Compared to other mRNA vaccines, the self-replicating characteristic of saRNA allows it to produce multiple antigen-encoding RNA copies. This advantage lies in the fact that it requires less energy to perform the same level of spike protein analysis. Currently, saRNA vaccines are widely studied in clinical trials for their effectiveness and efficiency. One of the clinical trials mainly tested a Venezuelan equine encephalitis virus (VEEV)-derived replicase in one RNA molecule with the antigen coding sequence predominantly full-length S protein [5]. However, the results were not as expected, due to the large size of chain of the RNA. The required sequence encoding for the alphavirus genome is included in it, and the sub-protein sequence encoding is essential, so it cannot be shortened. As we all know, the length of RNA has a considerable impact on the stability and rate of delivery. Therefore, saRNA is still in the clinical research stage.

In conclusion, the above mentioned research and development of three mRNA vaccines against the novel coronavirus. The three different vaccines target different directions and are used to different degrees. The non-replicating mRNA vaccine, widely used at present, has the advantages of being low cost, easy to produce and highly effective, but it does not deal with different strains of the virus, meaning it was developed against a specific viral strain. Both circRNA and saRNA vaccines are under development. The effect is better due to the high cyclic stability of the former and the shorter RNA chains of the latter. However, due to the lack of practice, or their own defects, these two vaccines are still in the development stage and have not been put into use in society. There have been major breakthroughs in the research and development of biotechnology such as vaccines, and on the other side, the implementation of public health policies such as speech control and health codes have also been of great help to the control of the new coronavirus epidemic.

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3. Risk management, healthcare applications and techniques

3.1. Crisis managements policies

The first issue pertains to the disclosure and regulation of sensitive information. The predicament is that exposure to sensitive data can influence individuals' emotional responses to a crisis. When an unforeseen crisis abruptly occurs, people frequently exhibit a range of negative psychological traits, including anxiety, tension, and depression. If individuals are unable to manage these adverse emotions effectively, it may significantly hinder the management and control of the crisis. Consequently, the government is faced with two options: disclosure and control. Regulating information necessitates reducing outdoor activities and media attention, akin to censoring news. On the other hand, disclosing information encourages the public to actively engage and harness all available resources. In fact, when a crisis cannot be quelled in the short term, controlling information normally causes even greater panic [6].

The second factor involves effective evaluation. These fundamental assessments are based on accurate data, as information biases may directly contribute to the exacerbation of the crisis. In the early stages, the government conducts investigations to gather information and meticulously verifies the accuracy of all data. Concurrently, real-time monitoring of potential crises is executed to ensure the timeliness of the information. In the context of epidemiology, after accumulating a substantial amount of data, experts and academics assess the contagiousness, susceptible population, and mortality rate.

The third factor primarily involves the establishment of crisis information communication channels and health education platforms, which encompass the dissemination of risk information, evacuation notices, risk prevention measures, and available support from public institutions. By utilizing these communication channels and platforms, the public can independently respond to crises, thereby assisting the government in managing them. When the public possesses a clear understanding of the epidemic, knows how to protect itself, and engages in adequate persuasion and communication with those around it, unnecessary troubles can be minimized.

The fourth factor pertains to the development and execution of a strategic crisis response plan. For the government, the key to managing a crisis lies in buying time. The longer it takes for a government to make a decision, the more likely it is to incite political criticism and rumors, factors that often contribute to the collapse of policy responses. The dilemma for governments, however, is that it often takes quite a long time to develop good policies, leading to a vicious circle.

The fifth element is the comprehensive mobilization of key resources. During the SARS and bird flu outbreaks, there was a severe shortage of resources, leading to shortages in medical and food supplies. Timely and effective transportation of emergency resources can greatly reduce the losses caused by public crises. While ensuring the quality of food and medical supplies, the rational allocation of resources and time safety have become the top priorities. Therefore, managers must determine the best time and method for resource allocation, and a reasonable public health crisis response system must ensure the determination of medical space, medical supplies, and medical personnel reserves. Effective censorship of speech not only increased the efficiency of fighting the epidemic, but also improved the allocation of supplies and the process of treating the sick. In addition, in terms of nucleic acid testing and health codes, it made the fight against the epidemic more uniform

3.2. Health QR code application

With the passage of time to 2021, the epidemic "battle" in China's mainland is breaking out sporadically in different cities. However, the emergence of a Health QR Code at the end of 2020 has brought the outbreak under apparent control, especially the cities include Chengdu, ZhengZhou, Beijing, Tianjin.etc.

Chengdu, a bustling metropolis, has achieved "victory" in the epidemic battle in the past few years. The appearance of the health code is undoubtedly a nice addition to the epidemic control. The government conducted targeted checks in the summer against the Delta variant, with pregnant women and children as the background, and the experience accumulated in the application of the health code in these cases was subsequently evaluated. The basic mechanism of the health code is a built-in module called the "entry code," which must be shown when entering communities and public places, and can record and upload the user's history of accessing public places or communities [7]. Circle management is an epidemic management method based on the core circle expanding outwards, with surrounding areas cooperating, similar to the ripples of water. The health code of those returning from middle-risk areas will change from green to yellow, and they will be required to undergo RT-PCR testing for 1, 7, and 14 days respectively. Close contacts and people returning from high-risk areas will have their health code turned red and RT-PCR, and will need to be negative for at least 14 days and stay at home.

As shown in Figure 2, between July 20 and August 13, the Health Commission confirmed six infection cases, and the circle management strategy proved effective. Close contacts were isolated and communities were sealed off based on the contacts. About 1,200 citizens were identified as high-risk individuals. It was as if the source had been monopolized, and the epidemic wave subsided around August 9, when people resumed their normal lives again.

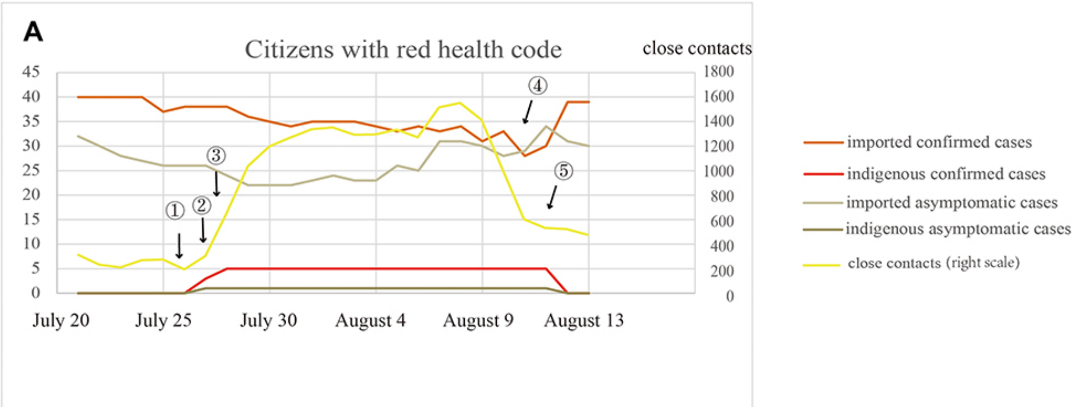

Figure 2. Citizens with Red Health Code [8].

4. RT-PCR test for SARS-CoV-2

4.1. RT-PCR mechanism

RT-PCR is a method used to detect the SARS-CoV-2 RNA molecule in patients. There are many testing methods, such as nasal swabs, pharyngeal swabs, urine, and blood. The most popular testing methods during the epidemic are the first two. The basic mechanism is to extract RNA from body fluids, amplify the number of nucleic acids, and then detect it using gel electrophoresis or biosensors. Finally, the results are analyzed to determine the concentration and quantification of nucleic acids to determine whether the result is negative or positive.

4.2. Digital RT-PCR

The principle of Digital-PCR is to partition the reaction mixture into many sub-reactions before amplification; the original numbers are determined by counting the partition showing negative and positive reactions [9]. Its quantitative results are based on Poisson distribution analysis, and can be used for precise analysis of low concentration samples. It is also used for data analysis of low viral load, environmental detection of virus presence, and prediction and detection of possible subsequent mutations of the virus. According to the comparison data of pharyngeal swabs, the detection results of dRT-PCR are more accurate than those of ordinary RT-PCR, with higher detection efficiency and lower error rate. However, dRT-PCR also faces some challenges, such as the high price of detection equipment, the complexity of the steps that makes it difficult to match real-time cases, etc., which makes dRT-PCR only suitable for measurement of complex cases rather than being widely used for detection of all novel coronavirus in the market.

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4.3. Electrochemical RT-PCT

As nucleic acid sequencing technology has gradually developed, the extraction of pathogens from RNA and the combination with biological fluorescence reaction products has become a focus of research. Currently, quantitative real time-polymerase chain reaction (qPCR) is a standard method where a fluorescent signal is coupled with DNA polymerase chain reaction for quantification of DNA [10].

However, this technology is still conservative and is limited to research and use in laboratories. More often, electrochemical methods are used instead. Electrochemical methods not only can precisely measure the concentration of nucleic acids, helping RT-PCR improve its sensitivity; but also have a higher working efficiency. One of the most obvious advantages is that only a very small amount of sample is needed for precise detection. Another advantage is that it can measure multiple targets simultaneously, greatly improving sensitivity and specificity.

5. Conclusion

Generally speaking, The sudden outbreak of the epidemic made everyone feel uneasy and unprepared, but everyone came together to fight against the epidemic in various ways. First, the development of three mRNA vaccines against the novel coronavirus. These three vaccines have different basic structures, durability, and development directions. The non-replicating mRNA Vaccines currently on the market have lower costs and larger production volumes. Although it does not have the stability created by the circular RNA vaccine's ring-shaped structure, and the targeted and stronger effect of the saRNA vaccine, complex research results and high costs have led them to remain in the research and development stage. On the government side, especially the Chinese government, strict control was exercised over the initial statements regarding the epidemic. Timely filtering of statements that caused panic was carried out in this case, which greatly improved the efficiency of fighting the epidemic and soothed people's fearful minds, making them more united. On the other hand, the appearance of health codes and the use of RT-PCR nucleic acid testing undoubtedly added to the fight against the epidemic and control. Firstly, the appearance of health codes rationally divided safe groups, suspected contactors, close contacts, etc. RT-PCR nucleic acid testing was carried out for each group separately, and infected persons, non-infected persons, and suspected infected persons were divided. It's like a complete chain that effectively kills the pandemic at its roots. When faced with a natural disaster, people come together to fight against it, with various policies and technologies being employed. Each person takes responsibility for their own part, and the pandemic era officially comes to an end in 2023. When people face such natural disasters again in the future, enough experience and wisdom can help them win the battle with the highest efficiency and lowest cost. Due to the limitations of technology and some policy restrictions, many people may feel dissatisfied, such as China's epidemic risk control and isolation being lacking in humanitarianism, but on the contrary, due to the large population, some policies are also forced to be implemented to minimize the loss. On a future day, when a global natural disaster sweeps the world again, people should learn enough lessons from this to fight against it, including the progress of technology driving the popularization of circRNA and saRNA vaccines, which will reduce the risks and losses brought by unknown viruses to a greater extent.

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