THE POTENTIAL APPLICATIONS OF US MRNA VACCINES IN CHINA AND IMPLICATIONS FOR A "UNIVERSAL" COVID VACCINE

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Abstract

The resurgence of Covid outbreak in China at the start of 2023 with the new XBB variants made people question the effectiveness of the Sinopharm vaccine. In this paper, I tried to investigate the applicability of the US mRNA vaccinations in the Chinese population, and the implication of the development of a universal Covid vaccine. I blasted the selected BA.2.12.1 strain's genome and spike protein sequences of China's, Japan's and the US's (NY, CA, WA and AZ) strains from the NCBI SARS-CoV-2 database. Blast results showed a high percentage (>0.95) of alignment among the complete genome and spike protein sequences from all the selected regions, which supported the ideas of the applications of one mRNA vaccine to target the dominant strain in different countries. On the other hand, the identification of certain point mutations (R343T, G679R) in the functional and structural part of the spike protein underlined the high mutability of the virus as it spreads across continents. These findings suggested that while mRNA vaccines could be more effective for the prevailing strain in China and potentially the rest of the world, in order to make a firm conclusion and medical plan for the implementation, it still required additional trials and research with more data.

Keywords

MRNA Vaccines, COVID-19, SARS-COV-2, NCBI

1. Introduction

1.1. History and Development of SARS-CoV-2

Coronavirus 19 (COVID-19) originating in Wuhan, China in 2019, is caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). The first ever Covid case identified was in Wuhan, China at a seafood market, and it was often proclaimed that the Covid-19 virus was brought to humans from consuming bats. SARS-CoV-2 virus is a single-stranded RNA virus with both structural (S, E, M, N) and nonstructural protein (nsp 1, nsp3, nsp 12, nsp13, nsp14, etc.) (Li et.al., 2020). S (surface or spike) protein that covers the surface of SARS-CoV-2 is responsible for the binding and infection of host cells. As a result, given the importance of the spike protein, many companies and academic institutions studied and created RNA vaccines based on the S glycoprotein, these newly developed vaccines have demonstrated their ability to generate neutralizing antibodies and have been deemed effective in fighting against the virus (Daniel Martínez-Flores et. al, 2021). During 2020, the highly infectious Alpha and Beta strains were the major strains. The Alpha strain (B.1.1.7) was the first of the highly publicized variants that appeared in Great Britain in November 2020 and spread worldwide that caused infections to surge in December of that year. The strain was identified as a Variant of Concern by CDC at the end of 2020 when it was 30% to 50% more contagious than the original covid strain identified in Wuhan, China.

Variant of Concern (VOC) is a level of classification by the CDC which helps them to monitor and classify different variants into different levels of alert and concern. Variants designated as VOC demonstrate characteristics such as high transmissibility, severe symptoms that lead to hospitalization or death, and reduction in the effectiveness of treatments or vaccines (CDC, 2023). The Beta strain was first identified in South Africa at the end of 2020, and it had a similar infectiousness compared to the contemporary Alpha strain (Yale Medicine). In 2021, the most severe variant was identified as the Delta Variant with unprecedented mutations. The Delta variant was more contagious than both the Alpha and Beta variants and caused a resurgence of covid cases worldwide from June to December 2021. According to a study from the Lancet, the number of hospitalization risks in England doubled over the summer of 2021 than the number of hospitalizations from the Alpha variants.

After the prevalence of the Delta variant worldwide, another new mutation-derived variant was found in the US, which was named the Omicron variant. The Omicron variant became predominant in 2022 and resulted in another resurgence of covid cases in multiple countries and regions such as the US, China and the UK. Compared to the previous mutated strains, the Omicron sub-variant was less lethal with a much lower

mortality rate. On the other hand, the omicron strain had a much higher infectious rate and a larger area of impact, which is shown by the large number of infected cases from almost every country worldwide (Catherine Hyams et. al, 2022). At the end of 2022, the covid cases had reached a peak with the on-going Omicron strain and a large range of regions were being affected with covid cases and death counts. In March 2023, regions like China, Singapore, and Indian experienced another resurgence of covid cases brought by the XBB recombinant strain, which was mutated from 2 other highly contagious Omicron sub-variants (Low De Wei, 2023). Due to the minimal harm done by the XBB variant and the relaxation of covid policy, most infected people in China underwent no covid test, which resulted in a lack of data in China for XBB.

1.2. Vaccine Development

Since the identification of the SARS-CoV-2 virus, countries and institutions have created various vaccines to target the major strains and reduce infection and mortality rate.

Table 1: *Summary of Covid-Vaccines Developed and Used by China and the USA*

Name	Types	Countries of Development	Efficacy	Source
Pfizer	RNA	USA	88%	(CDC, 2021)
Moderna	RNA	USA	93%	(CDC, 2021)
NovaVex	Subunit Protein Vaccine	USA	90%	(WHO, 2022)
Johnson & Johnson	Protein Vector	USA	72%	(WHO, 2022)
AstraZeneca	Viral Vector	USA	72%	(WHO, 2022)
CoronaVac	Inactivated virus vaccine	China	86.4%/92.9% for 2 doses	(Yuchen Wei et. al, 2023)
Sinopharm	Inactivated virus vaccine	China	67%	(Hafez Al-Momani et. al, 2022)

(Source: Self/Authors' Own Illustration)

China uses the inactivated virus vaccine, and the most dominant usage of vaccination is the Sinopharm vaccine, which is a type of Covid vaccination that injects dead or weak virus into the recipient's body in order to stimulate immune system response. Such vaccination is effective for specific variants such as the Delta or Omicron variant but won't be much more effective if encountered with mutated variants. The Sinopharm vaccine requires two dosages in order to become effective, which was recorded in a study that showed a 79%

efficacy against hospitalization. According to WHO, the vaccine efficacy in individuals aged 60 years and older against symptomatic disease after 213 days was 80% (95% CI: 5–98%), which proved to be effective in the population (WHO, 2022).

In the US, there were a variety of vaccinations that were created to combat the pandemic, which resulted in the different usage of vaccinations in different countries compared to China. The US developed a different type of covid-19 vaccination which is the mRNA vaccination that injects not viral bodies but mRNA sequences that may stimulate the development of antibodies in the patients. The mRNA vaccine provides instructions for the cells on how to make the spike proteins found on the surface of the Covid-19 virus, which causes the body to produce antibodies that target the covid-19 virus. The antibodies serve as a marker for the pathogens which once the patient is again exposed to such a virus, the immune system would recognize the pathogen and alert the body for immune responses. The mRNA vaccine was mainly provided by Pfizer and Moderna, and it has a higher efficacy (Pfizer-BioNTech: 88%; 95% CI = 85%–91%; Moderna: 93%, [CI] = 91%–95%) compared to the Sinopharm vaccine used in China (CDC, 2021). Another widely used covid-19 vaccine in the US is the vector vaccine made by the Johnson & Johnson and AstraZeneca company, which is a type of vaccine that places a modified version of the virus in order to trigger immune system responses. Similar to the mRNA vaccine, the viral vector vaccine triggers the immune system to create antibodies and defensive white blood cells, which are helpful when fighting the viral infection after exposure. The viral vector vaccine has an efficacy of 71% (95% CI = 56%–81%) with only 1 dosage and the efficacy can be improved to 94% after the application of 2 dosages (WHO, 2022).

The major difference between China and the US in terms of vaccination development is that the US was rapidly improving their medication and updating the currently existing vaccination for better protection against the newly mutated virus. In the US, approximately after the outbreak of the omicron variants in the country, the bivalent vaccine booster was developed and put into use by the general public. This vaccine specifically targets Omicron sub-variants BA.4 and BA.5 (FDA, 2023). The updated vaccine can more effectively combat the Omicron outbreak and provide a higher level of protection against exposure and infection. In contrast, in China, the Sinopharm vaccine was used for the entire population from the beginning of the Delta outbreak to the XBB outbreak in the beginning of 2023, which lasted in a span of 2 years without any improvement or target oriented developments. As shown in Figure 1, China experienced very few reported data based on the firstly developed "zero covid policy", which was an attempt to eliminate covid cases throughout the country and hospitalize the potential exposure population. Such policy was effective in terms of controlling the covid cases but with a huge amount of monetary cost and human effort, which eventually led to the fully "open-up" policy without any restriction to the covid exposure and vaccinations. However, the

inverting of the situation immediately caused spikes in covid cases throughout the entire country, which indicate the ineffectiveness of the previously designed vaccination against the latest mutated virus (Megha, 2023).

This study investigated the necessity for China to acquire new vaccines such as Pfizer, Moderna, or the bivalent vaccine due to the low efficacy of its own vaccines. In the paper, I chose to analyze the data retrieved from the Omicron outbreak in both the US and China, from June 2021 to December 2022 because of the availability of large amounts of data and studies regarding the massive outbreak. By identifying and analyzing the dominant strains in the US and China, I wanted to infer the applicability of US vaccines to Chinese citizens based on the effectiveness and the similarities between the covid strains identified in both regions. In the paper, I chose to analyze the sequencing data retrieved from the Omicron outbreak in both the US and China, from June 2021 to December 2022 because of the availability of large amounts of data and studies regarding the massive outbreak. In addition, I decided to compare the data and sequence of the latest covid samples recorded in China in 2023 with BA.4 and BA.5 to see the applicability of bivalent vaccines for the current outbreak.

2. Method

In order to investigate the applicability of US produced vaccines (Pfizer, Moderna and Bivalent booster) in regions like China where it previously used its own vaccine, I wanted to compare the genome and protein sequence of the dominant strains found in these regions, which would be targeted by the vaccines. I wanted to investigate if the same covid strain would mutate as it spread in different regions, which would potentially affect the vaccine usage. I utilized the NCBI SARS-COV-2 database and blasting software to identify and compare the selected covid strains in our regions of interest. For the graphical representations, they were done by python Jupyter Notebook with the instruction and help from my mentor. Based on the public data on covid strains and the time of outbreak, in the span from April 2021 to December 2022, one of the most prevailing strains was the BA.2.12.1 covid strain, which is a sub-variant of the Omicron virus. For the purpose of the study, I selected nucleotide sequences from China, Japan, and 4 states in the US (NY, CA, WA, AZ), and blasted them with each other to compare their similarities and differences.

Only 2 complete sequences from China and 4 complete sequences from Japan were selected due to the lack of data. In comparison, due to the large sequencing efforts of covid strains, there were many available sequences from the US. I was able to select 10 complete sequences of the BA.2.12.1 covid strain in the span of 2022 in each selected state. The four states were chosen based on the availability of the sequencing data,

their large populations and regional variations in the US. Japan, which had been using US produced vaccines, was included in the analysis as another potential region of covid mutation. In addition, I cross blasted the spike proteins amino acid (AA) sequence. Point mutations were identified by looking at the blasting results. For each region, multiple complete sequences of BA.2.12.1 were selected for blasting to eliminate the random mutations. Only mutations that occur for over 90% of the results were identified.

For investigating the latest outbreak in China, I first looked at the newest reported case of BF.7.14 strain in the US which is the OQ978950 strain reported on May 14, 2023, and compared the specific strain with the previously found strains to see if any mutations or changes have occurred to the virus. Then, I used the NCBI website to find ten different BA.5 samples and ten different BA.4 samples of nucleotide sequences, blasted with the OQ978950 sample, and recorded the percentage of similarities and their standard deviation. After comparing the nucleotide sequences of the viral genome, I specifically targeted the spike protein (surface glycoprotein) sequences using FY.3.1 sample WKL08853 and BF.7.14 sample WHA34978 on NCBI website. The two protein sequences were blasted against 10 different BA.4 and BA.5 surface glycoprotein sequences separately. The percentages of alignment were recorded in the table, and after all, the average percentage of alignment with standard deviation was calculated as representation of the data strains.

3. Result

For BA.2.12.1, the blast results showed almost identical (0.99) similarities between the sequence of the entire genome of the strains from different regions. On the other hand, there were slight regional differences between the sequence of the spike protein. The results were displayed in Table 2 and visualized in the heatmap (figure 2). In general, all of the comparison data showed a higher than 0.90 similarity between the spike protein. For regions like China, Japan, and CA, they demonstrated almost identical spike protein sequences (0.99-1). The lowest blast alignment (0.93) was between the WA and AZ with NY strains respectively. For WA, it has a 0.93 similarity compared to AZ which is also relatively low. Consequently, I analyzed point mutations that repeatedly occurred in the blast results between strains (Table 3). The identified mutations were N161K and G679R for China and Japan's strains. The differences among the spike protein sequences among the US's strains were mostly due to incomplete sequencing. In addition, other mutations such as deletions and additions that cause large frame shifts were not considered for the study.

For the latest outbreak in China, BF.7.14 had an average 0.95±0.06 alignment with BA.5 and 0.99±0.028 alignment with BA.4. Furthermore, the blasting of spike protein sequences showed potential differences between these strains. The latest FY.3.1 sample (WKL08853) showed 0.95±0.013 alignment with

BA.4 spike proteins and 0.985±0.005 with BA.5 spike proteins. Meanwhile, the latest BF.7.14 sample collected on January 2, 2023, showed 0.955±0.01 with BA.4 spike proteins and 0.96±0.003 with BA.5 spike proteins. The low standard deviation in the data underlined the consistency of the blast results.

4. Discussion

From the beginning of the pandemic to the latest covid-19 outbreak in China in the beginning of 2023, the variants of concern had always been changing and rapidly mutating as result of the promptly developed vaccination and differences in between situation and circumstances of countries. Starting from the Alpha and Beta variants in China and the UK to the Omicron spikes in the US, the variants all present differences in their genetic expression and viral protein, which led to variation in their infection and mortality rates in different regions. In this study, for the period of interest, the most commonly found and infectious sub-variant BA.2.12.1 (Omicron) was put into comparison in between the strains and samples found in the US, China, and Japan.

The blast results showed a high percentage of alignment in between the local strains. The average spike protein sequence alignment exceeded 0.92. The high alignment of the protein and genetic sequences provided evidence for the argument of the utilization of US-produced vaccination in other regions like China and Japan, these vaccines would be beneficial to people when fighting against the newly mutated strains, since the lack of improved vaccination left the Chinese citizens with a much higher risk of exposure and danger after infection.

Spike protein sequences were studied across different local strains to compare similarities and differences. In SAR-CoV-2, spike protein is around the size of 180-200kDA with an extracellular N-terminus, a transmembrane domain, and an intracellular C-terminus (Bosch et.al., 2003). The extracellular domain binded to the surface receptor, angiotensin-converting enzyme 2 (ACE2) in human cells for viral entry (Huang, et.al 2020). The blast results between the protein sequences of BA.2.12.1 spike protein from China, Japan and the US showed a high percentage of similarity (Table 2), with certain point mutations (N161K, G679R) unique to the Asian strains.

Based on the spike protein model, the protein is composed of 1273 amino acids. There are 2 large subunits in the protein: S1 (14-685 residues) for receptor binding and S2 (686-1273 residues) for membrane fusion. Both N161K and G679R were in the S1 subunit of spike proteins for receptor binding but not in the functional domain (Table 5). Some other mutations were also identified (F2X, R343T, A876V), but none of the mutations were found consistently in the protein. The lack of regional mutations of the strain, especially in the RBD, would support the use of US mRNA vaccines in China and Japan. Nonetheless, the effects of the

mutations in the structural part of the protein shouldn't be overlooked that they could potentially affect the receptor binding ability and decrease the vaccine effectiveness. Moreover, these mutations highlight the high mutability of the virus as it spreads across continents. For example, R343T was a mutation in the RBD of the protein and might contribute to changes in the RBD with other mutations.

Consequently, when comparing BF.7.14 and FY.3.1 strains with BA.5 and BA.4 strains, the spike protein alignment all exceeded 0.95, even higher than some of the alignment between regional BA.2.12.1 strains. While this similarity cannot guarantee the certainty of the effectiveness of bivalent vaccine on the current outbreak in China, such high uniformity would be great indications for the likelihood of applications of the vaccine. Nonetheless, further studies would be required for consolidating the results.

Overall, the close alignment of China and the US provides good evidence and possibility of the applicability of the US vaccines in China. In addition, Japan had always been using US RNA vaccines for combating covid. Given the similarities between China and Japan's strains, the implementation of US vaccinations such as the Pfizer and Moderna mRNA vaccine and the bivalent boosters would possess high likelihood of success and effectiveness in the Chinese citizens. On the other hand, the study had revealed that local strains could develop mutations in the structural and potentially the functional part of spike protein. As a result, a decrease in vaccine efficacy of USA vaccines would be expected when used in China or other countries even when all regions share the same dominant strain.

5. Conclusion

After combating the pandemics for over two and a half years, most of the world have called for the end of the pandemic by reopening countries' borders and removing covid-19 regulations. Nonetheless, the virus is still in the air. With the reduction of lethality but high transmission rate and mutability, SARS-Cov-2 is still a major public health concern. In addition, the potential overlapping of influenza and covid outbreak in the future may further burden the public health care system. As a result, the need for vaccine and treatment development is still high for new strains. Global efforts and cooperation are necessary in dealing with highly transmissible diseases. Scientists have been trying to develop the so-called "universal" influenza vaccine (Nachbagauer & Krammer, 2017). This concept shall also be considered for covid vaccine development due to the fast transmission of virus from one country to another and not all countries have the ability to manufacture their own vaccines in time to combat the virus. This study supported this idea by showing the low regional variability of dominant strain as it spread across continents. Nonetheless, potential mutations may still

undermine the effectiveness of vaccines. Therefore, necessary sanitary actions like wearing masks and frequent hand washing during the covid and influenza seasons are still highly encouraged.

Introducing foreign vaccinations would need to go through a series of trial and error in order to establish the most fundamental safety issues, but these vaccinations would provide a strengthened baseline for the global population against the pandemic. In addition, the mRNA vaccine has proven to be effective and efficient for all age groups to combat highly mutable SARS-Cov-2 viruses when compared to more traditional vaccines. Countries such as China should be more active towards the development of the mRNA vaccines. Meanwhile, this study also highlighted the need for more sequencing and public health data, such as the number of infections and vaccinations, to fully examine the mutations in the virus genome and the corresponding phenotypical changes. For example, there is a lack of sequencing data from China for the recent covid outbreak, which hinders the scientific community from analyzing the major strain. These data, which should be made more transparent and accessible, are important for developing future vaccines, especially mRNA vaccines.

6. Tables

Table 2: *Percent Similarity Between Regional BA.2.12.1 Strains with Standard Deviation*
The cross-blasting results of (BA 2.12.1) spike protein amino acid (AA) sequence from the indicated regions (two countries China and Japan, and 4 different states in the US). The results were shown in the average of all the strains plus and minus the standard deviation.

Regions	China	Japan	USA NY	USA CA	USA WA	USA AZ
# of strains	2	4	10	10	10	10
China	-	1	0.98±0.014	0.99	0.97 ±0.033	0.98 ±0.017
Japan	1	-	0.98±0.014	0.99	0.97 ±0.033	0.98 ±0.017
USA NY	0.98±0.014	0.98±0.014	-	0.98±0.014	0.93 ±0.036	0.94 ±0.021
USA CA	0.99	0.99	0.98±0.014	-	0.97 ±0.033	0.98 ±0.017
USA WA	0.97 ±0.033	0.97 ±0.033	0.93 ±0.036	0.97 ±0.03	-	0.93 ±0.034
USA AZ	0.98 ±0.017	0.98 ±0.017	0.94 ±0.021	0.98 ±0.017	0.93 ±0.034	-

(Source: Self/Authors' Own Illustration)

Table 3: *Position of Point Mutations. Point mutations in the spike protein regions identified from the cross blasting between different strains. Only point mutations, appearing in 90% of the results, were shown.*

Regions	China	Japan	USA NY	USA CA	USA WA	USA AZ
# of strains	2	4	10	10	10	10
China	-	-	N161K, G679R	N161K, G679R	N161K, G679R	N161K, G679R
Japan	-	-	N161K, G679R	N161K, G679R	N161K, G679R,	N161K, G679R
USA NY	N161K, G679R	N161K, G679R	-	-	-	-
USA CA	N161K, G679R	N161K, G679R	-	-	-	-
USA WA	N161K, G679R,	N161K, G679R,	-	-	-	-
USA AZ	N161K, G679R	N161K, G679R	-	-	-	-

(Source: Self/Authors' Own Illustration)

Table 4: *Percent Comparison of BA.4 and BA.5 protein sequence with the Latest FY.3.1 and BF.7.14 spike protein in China. Blasting results of the 2 different spike protein sequences of the latest prevalent FY.3.1 and BF.7.14 strain found in China to BA.4 and BA.5 in the US. Individual blasting results were listed with the average and standard deviation at the last row.*

BA.4 Sample of spike protein	% Similarity with sample WKL08853	% Similarity with sample WHA34978	BA.5 Sample of spike protein	% Similarity with sample WKL08853	% Similarity with sample WHA34978
WKT27639	0.99	0.99	WHS89080	0.96	0.95
WJP81058	0.99	0.98	WKF16943	0.96	0.96
WJJ47712	0.98	0.98	WJP60339	0.96	0.96
WII99904	0.98	0.99	WIJ09769	0.96	0.96
WIJ04758	0.99	0.98	WJP34028	0.96	0.96
WGO72935	0.98	0.99	WII99796	0.96	0.96
WGS90790	0.99	0.99	WIJ30834	0.96	0.96
WGV36408	0.95	0.98	WID10437	0.93	0.96
WHL52108	0.97	0.98	WAN07672	0.95	0.96
WGH55563	0.98	0.99	WGL13173	0.95	0.96
Average	0.95±0.013	0.985±0.005	Average	0.955±0.017	0.96±0.003

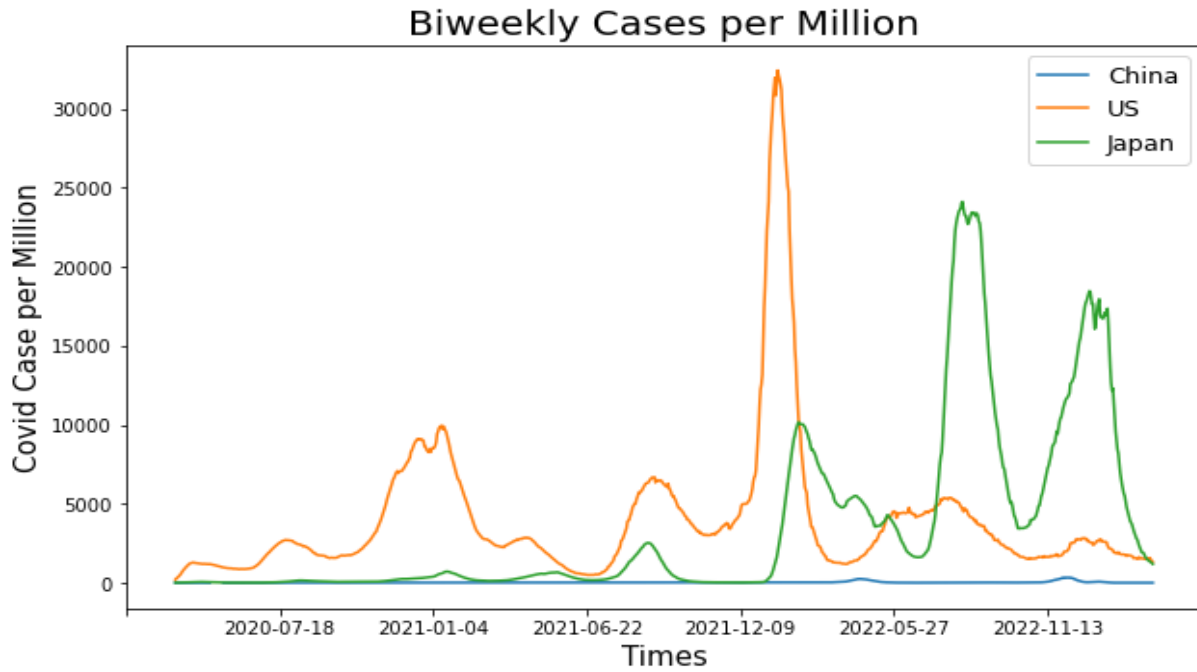*(Source: Self/Authors' Own Illustration)*

Table 5: *The Domain and Functions Are Residues of Spike Protein*

| Subunit	Residue	Domain and functions
S1	1-13	N -terminus signal peptide
	14-305	N-terminal domain
	319-541	Receptor-binding domain (RBD)
S2	788-806	Fusion peptide (FP)
	912-984	Heptapeptide repeat sequence 1 (HR1)
	1163-1213	Heptapeptide repeat sequence 2 (HR2)
	1213-1237	Transmembrane domain (TM)
	1237-1273	Cytoplasm domain

(Source: Huang et.al, 2020)

7. Figures

Figure 1: *A line plot of the biweekly cases by million in each country from April 2021 to December 2022. The blue line was China, the orange line was the US, and the green line was Japan. The number on the y-axis is the recorded average number of covid cases in every one million people per two weeks.*

(Source: Self/Authors' Own Illustration)

Figure 2: *A heat map representation of the blast results of the BA.2.12.1 omicron subvariant strains in different countries and regions (Table 1). The blast result shows the percentage of similarity in the protein sequence of the spike protein. All the results recorded in the heat map are the average taken from blasting 10 different strains in one region with the other 10 different strains in the other region. Except for China, there are only two strains recorded so they are used as the target sequence and blasted with the others. A result of 1 represents no difference between the sequence in both regions such as Japan and California.*
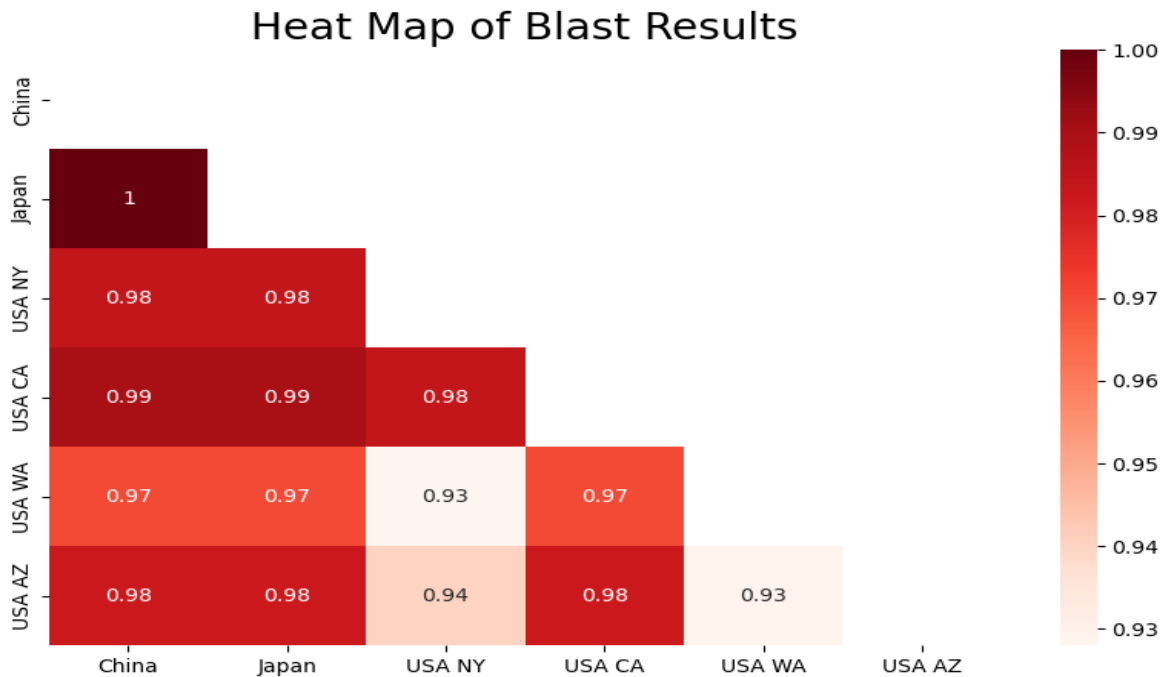
(Source: Self/Authors' Own Illustration)

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