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Understanding the Biological Basis, Spreading Patterns, and Treatments for Covid-19

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Abstract:

The COVID-19 pandemic is a serious global issue that requires effective control and prevention measures. Understanding how the virus spreads is crucial in implementing non-pharmaceutical measures. Previous studies have focused on the effects of urban socio-political measures on the contagion rate, but the fine-grained geographic urban spreading pattern remains an open question. To address this, we analyzed the trajectory data of 197,808 smartphone users (including 17,808 anonymous confirmed cases) in nine cities in China. Our analysis revealed that the spatial distribution of confirmed cases in all cities followed a power-law-like model and the spreading centroid human mobility remained constant over time. We also found that long average traveling distance resulted in a high growth rate of spreading radius and wide spatial diffusion of confirmed cases in the fine-grained geographic model. Using the Kendall model, we simulated the urban spreading of COVID-19, which matched the real spreading process well.

The COVID-19 vaccines have been associated with several side effects, including systemic events like fever, muscle pain, and headache, and injection site events like swelling, pain, and redness. This study focused on analyzing the side effects of three vaccines: BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), and JNJ-78436735 vaccines through both experimental and survey methods. By comparing the side effects of the vaccines during their design phase and after their release, we observed improvements in alleviating fever side effects. However, the results were inconclusive, and more research is needed to better understand and solve the long-term side effects of the COVID-19 vaccines.

This paper targets SARS-CoV-2 treatments by understanding viral replication. We examine viral entry and infection, develop monoclonal antibodies for COVID-19 treatment, and assess PVP-I mouthwash for inactivating the virus and lowering transmission risks. Both methods exhibit potential for COVID-19 treatment and prevention.

Introduction:

While being at the forefront of the community's mind when thinking of illness, COVID-19 is still one of the most prevalent viruses. Its general mechanism for replication is not unique. The viral strain is able to enter the body via two main methods but both require the ACE-2 receptor. The former involves the use of an endosome releasing the viral RNA into the cell while already being within the cell. The latter is able to release the viral RNA into the cell from the membrane. To treat COVID-19, multiple treatments have been developed involving inhibition of the viral RNA entering the cell at multiple steps, and almost all are administered in the form of vaccines.

When planning effective countermeasures and actions against large outbreaks of viruses such as the outbreak of COVID-19, the demographic spreading pattern of that specific virus must be taken into consideration. This pattern of spreading must be looked at in two different levels, both in terms of infection from individual to individual and infection within and among cities. To understand the spreading pattern of the virus from individual to individual, we compare the respiratory viral loads (rVL) from cases of COVID-19 with those of previous global outbreaks such as SARS and A(H1N1)pdm09. To look at the demographic spreading patterns of COVID-19, trajectory data of 197,808 smartphone users (including 17,808 anonymous confirmed cases) in 9 cities in China were analyzed. This information in conjunction with each other could provide more insight into the effective countermeasures against COVID-19 and viruses with similar spreading patterns.

The COVID vaccine has been remarkable in treating the virus in previous years, with the development of the first vaccine authorized for emergency use less than a year after the discovery of the virus. Currently, the COVID vaccines include mRNA vaccines, vector vaccines, and protein subunit vaccines. However, misinformation has skewed a portion of the public’s view on vaccines and has made them resistant to taking this precautionary step. While they are still urged to get vaccinated, there are alternatives that have proven effective in combating covid such as gargling virucidal solutions. This leads to the question: What are the biological mechanisms of COVID-19 and the COVID vaccine, and how do alternative treatments address the gap in vaccine efficacy?

In this paper, we will discuss the process of development and the potential side effects of most types of COVID vaccines in the market. In addition, due to these side effects and limitations of patients' physical situation, we highlight the need for alternative treatment options, such as monoclonal antibody therapy, and monitoring the effectiveness and safety of current vaccines.

Methodology: Demographic

We utilize a dataset of trajectory information sourced from unnamed smartphone users in China. This information comprises recorded activity locations and their corresponding timestamps, as reported by individuals while using location-based services. These data offer insights into the real-time movements of smartphone users, indicating the areas where they may have contracted or spread COVID-19. Our aim is to investigate the correlation between the spatial distribution of confirmed COVID-19 cases and their activity locations. To achieve this, the study employs a statistical metric called the activity centroid (σ) to characterize the activity locations. Specifically, the activity centroid of a given smartphone user is determined by calculating the average of the reported activity locations within a specified period (e.g., 1 month). This involves taking the set of Nj activity locations reported by user j, denoted as $Pj=\{Pj1,Pj2,\cdots,PjNj\}$, and computing the centroid $\sigma j=E(Pj)=\sum kPjk/Nj$. In order for the activity centroid to be an accurate representation of the underlying characteristic of activity locations, it is essential that it remains consistent over time for most smartphone users. To confirm this, we have randomly selected 20,000 smartphone users in Wuhan and calculated their activity centroids over different time periods (ranging from 1 to 6 months), resulting in 6 activity centroids $\sigma j(t)$, $t \in [1, 6]$ for each user j. Next, we computed the distances between these 6 activity centroids and the average centroid (i.e., $\sigma j\overline{\quad}=\sum 6t=1\sigma j(t)/6$) for each user j. We then determined the mean and standard variance of these distances for each user, and calculated the cumulative distributions of all smartphone users.

Our results demonstrate that the mean values of 95.3% of smartphone users are less than 1.5 kilometers (Km) and the standard variance is relatively small. This suggests that the activity locations of smartphone users exhibit strong consistency over time, regardless of the selected period. The activity centroid is well-suited to capturing this intrinsic behavior. A statistical metric of interest is the most frequently visited location (MVL), which represents the activity

location that a smartphone user visits most often. We have calculated the percentage of top k ($k = 1, 2, \cdots, 5$) activity locations for each smartphone user and determined the average for all 20,000 users. Our analysis revealed that the MVL (i.e., top 1 activity location) only accounts for approximately 45% of all activity locations. In other words, more than half of the activity location information is not utilized by the MVL to characterize the activity behavior. Additionally, the performance of the top k activity locations metric approaches that of the activity centroid as k increases. Therefore, the activity centroid as the statistical metric is more reliable than the MVL.

In order to analyze the temporal spreading pattern, we partition the spreading duration in each city into L equal periods, and group the confirmed cases in set U into subset Ui based on their confirmation dates falling within the ith period, where $i \leq L$. By computing the average of their activity centroids, we obtain the overall spreading centroid (referred to as ρ) for the set U, which is represented as $\rho=E(\sigma)$, where $\sigma=\{\sigma j\}j \in U$. The cumulative spreading centroid is then computed as the average activity centroid of confirmed cases in the union of the first i subsets, denoted by $\cup ik=1$ Uk. Our focus now shifts to the spreading radius γ of set U, which is defined as the sum of Euclidean distances between the activity centroid of each confirmed case and the spreading centroid ρ of the set U, divided by the number of confirmed cases $|U|$. The spreading radius provides an estimate of the average distance between the activity centroids of confirmed cases and the spreading centroid. Through a collaboration with the Westlake Institute for Data Intelligence and local institutions for disease control and prevention, we acquired a dataset of confirmed COVID-19 cases who also use location-based services on their smartphones, which includes their activity centroids and confirmation dates (further information on the dataset can be found in the supplementary materials). The activity centroids allow us to measure the spatial and temporal patterns of COVID-19 transmission, as described in the following sections.

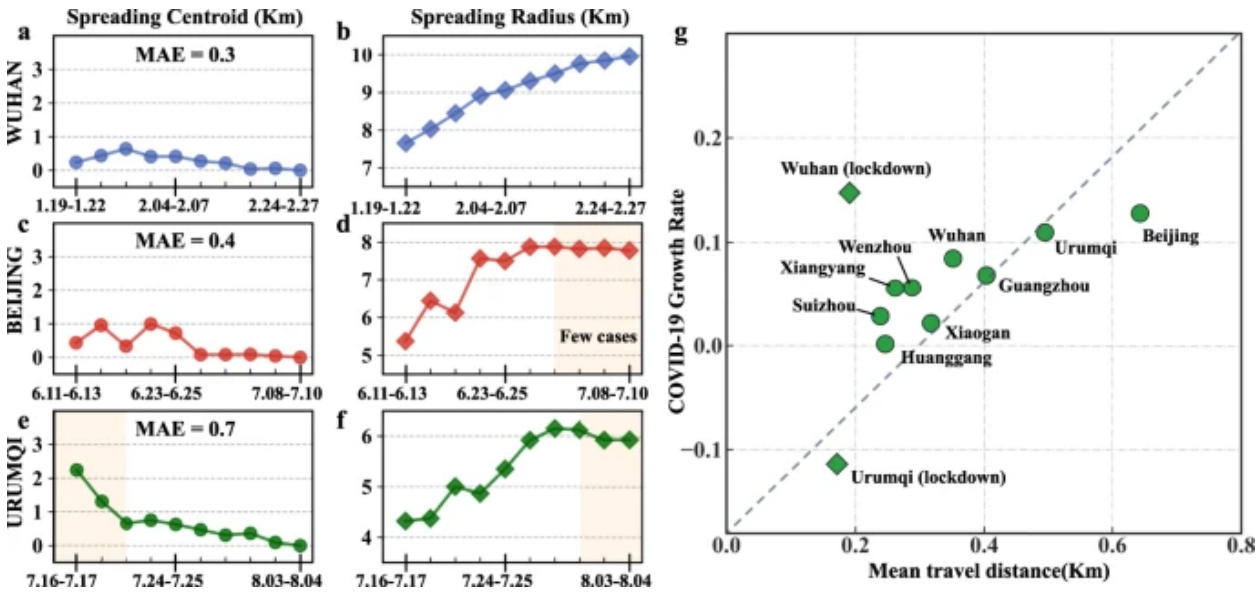

Figure 1: a–f The cumulative spreading centroid and spreading radius in Wuhan, Beijing, and Urumqi, respectively. g Relation between the mean travel distance of people in each city and the corresponding COVID-19 growth rate.

Interestingly, we observed that the cumulative spreading centroids in Wuhan, Beijing, and Urumqi were closely aligned with the overall spreading centroid, indicating a time-invariant feature of the temporal spreading centroid of COVID-19. The mean absolute errors (MAE) between cumulative and overall spreading centroids were found to be 0.3 Km, 0.4 Km, and 0.7 Km for Wuhan, Beijing, and Urumqi, respectively. Similar observations were made in the other six Chinese cities with a high number of confirmed cases, where the cases were mainly imported. Sensitivity analysis was conducted by varying the number of spreading periods L, but it was found to have minimal impact on the observed temporal pattern. Therefore, the temporal spreading pattern of COVID-19 in China is characterized by a time-invariant spreading centroid and slow growth of the spreading radius. There were significant differences in the growth rate of spreading radius observed in different cities and time periods.

To investigate the intrinsic mechanisms underlying these disparities, we divided the spreading period T of each city into two periods, L1 and L2, and calculated two spreading radii (R1 and R2) based on the activity centroids of confirmed cases reported in the spreading periods L1 and L2, respectively. The growth rate of spreading radius was defined as $2(R2-R1)/|T|$, where $|T|$ denotes the number of days in spreading period T. We computed the mean travel distance of 20,000 randomly selected smartphone users during the COVID-19 outbreak in each city to

approximate the mean travel distance of all citizens in that city. A larger value of mean travel distance indicated a stronger willingness of people for long-distance traveling. We observed a positive correlation between mean travel distance and growth rate of spreading radius, indicating that mobility patterns accelerated the urban spreading of COVID-19. We also considered the different control measures implemented in Wuhan and Urumqi since the outbreak of COVID-19, which significantly affected the corresponding mobility pattern and spreading of the pandemic. We divided the spreading period of these two cities into two sub-periods: before and after the implementation of travel restrictions and calculated the mean travel distance and growth rate of spreading radius in each sub-period. To analyze the spatial spreading pattern of COVID-19, we first divide the geographical area into grids of 1 Km × 1 Km and set the overall spreading centroid as the original point of grids. Confirmed cases are then projected into grids according to their activity centroids, and three-dimensional histograms are used to describe their spatial distributions in Wuhan, Beijing, and Urumqi.

To investigate the spatial distribution function F(d) driven by human mobility pattern, we apply logarithm to the actual distribution of human mobility pattern, confirmed cases, and the distance from the overall spreading centroid in all cities. The human mobility distributions and spatial distributions F(d) of several cities exhibit a prominent linear pattern, but Wuhan and Urumqi show a power-law-like spatial distribution. Thus, we use $F(d) = d\alpha$ for linear regression with $\alpha = -1.80$ for Beijing and $\alpha = -2.15$ for Urumqi. The spatial distribution of confirmed cases in Wuhan is also power-law-like, but it deviates slightly from the power-law model when d is small due to the influence of human mobility patterns during the lockdown period. Cases around the spreading centroid have a higher probability of infecting susceptible individuals, resulting in a higher risk of infection in the vicinity of the centroid. Thus, we divide the area into two parts by distance to the spreading centroid and fit the data with two different models. Specifically, the spatial distribution of cases around the spreading centroid ($d \leq 18$) is fitted by an exponential model $F(d) = \alpha d$, while when $d > 18$, it is fitted by a power-law model. F(d), $d \leq 18$ is well-fitted by an exponential model with a Pearson correlation of −0.99, and F(d), $d > 18$ is well-fitted by a power-law model with a Pearson correlation of −0.96. This indicates that the spatial distribution of confirmed cases in Wuhan has different characteristics depending on the distance to the spreading centroid, which is also observed in Xiangyang.

The phenomenon is mainly determined by human mobility patterns, which will be explained further in the next section. It has been observed that in cities like Guangzhou and Wenzhou, where imported cases are spread out, the pattern of spatial spreading is not as prominent. This is due to the presence of multiple clusters of confirmed cases in these cities, which affects the power-law-like spatial spreading. As a result, the observed spreading pattern is not applicable to cases with multiple infection sources. The Kendall model, which introduces the spatial dimension to the SIR model, has been widely used to understand the transmission characteristics of infectious diseases. The differential equations for this model can be expressed as equations (1)–(3) of supplementary materials. The confirmed cases in China are isolated for medical treatment once confirmed and considered recovered individuals in the Kendall model. The differential equation for the proportion of recovered individuals is given by $\partial R\partial t=-\lambda R(x,t)+\lambda I0(x)+\lambda[1-\exp(-1\lambda\int\infty-\infty R(y,t)K(x-y)dy)]$, where λ represents the inverse of the basic regeneration number R0 in the model, and $K(x-y)$ represents the kernel function that quantifies the probability of an infected individual at location y visiting location x.

The power-law distribution is used to describe the city-level movement behaviors, with η representing the power-law exponential that denotes the travel willingness and strongly correlates with the mean traveling distance. To fit the model for recovered individuals, the parameter η in the power-law distribution is first calculated using the mobility data of anonymous smartphone users. The diagnosed date for each confirmed case and corresponding activity centroid is also calculated as input of the model. The model is then fitted based on these precalculated parameters and Least Squares algorithm to obtain optimal parameters (λ and $I0(x)$). The RMSE values for Wuhan, Beijing, and Urumqi during the whole spreading period indicate that the evolution of recovered individuals $R(x, t)$ can be well captured by the proposed Kendall model. The impact of parameter η on spatial dispersion of confirmed cases, the number of daily new confirmed cases, and the growth rate of spreading radius during the whole spreading period are then studied. The concept of Simpson Divergence is introduced to characterize the spatial dispersion of confirmed cases. Two scenarios are considered under different basic regeneration number R0: $R0 < 1$ and $R0 > 1$. It is found that with the decrease of η, Simpson Divergence decreases to 1, indicating high clustering of confirmed cases. The growth rate of the spreading

radius also decreases with the decrease of η. A large η results in quick spreading of COVID-19, with the peak of daily reported cases arriving early, while travel restriction policies will delay the peak arrival. The impact of η on the growth rate of spreading radius is also studied, with spreading radii under different η increasing with time and converging to a fix value when $R0 > 1$. When $R0 < 1$ and the mean traveling distance is low, the pandemic will not spread spatially. Therefore, η in the mobility model drives the temporal-spatial spreading process, and can be optimized by implementing a specific travel restriction policy to achieve the desired control and prevention performance. A detailed discussion of the Kendall model and the parameter fitting process is provided in supplementary materials.

Discussion: Demographic

Prior research has examined the link between human mobility and the spread of infectious diseases. These studies have shown that the number of infected individuals at a destination is strongly correlated with the total population and the distance from the source to the destination, which is influenced by population flow. By combining population flow data and epidemic simulation models, researchers have accurately characterized the spatial-temporal spread of epidemics and predicted future trends. As human mobility patterns often follow a power-law distribution model, it is expected that the spread of diseases also follows a similar distribution. Prior research has explored the impact of human mobility on the spread of diseases and provided insights on mitigating transmission through travel restrictions.

This article presents a model based on trajectory data of anonymous confirmed cases to study the fine-grained spatial-temporal spread of COVID-19 in China. The model assumes homogeneity of individuals in the downtown area with constant infection rates and similar mobility patterns before and after the lockdown policy. The results of the model provide information on the most likely infection center, growth rate, and infection risk of different communities in a new outbreak. However, the model does not consider the impact of other social factors on city size and population heterogeneity in certain areas. Despite this limitation, the model's results are consistent with real trajectory data of anonymous confirmed cases in nine Chinese cities, providing a good approximation of the fine-grained spreading process.

Methodology: Covid Vaccine

For COVID-19 RNA Vaccine Candidate (BNT162b1), BioNTech/Pfizer conducted a phase 1/2 trial on 45 healthy volunteers between the ages of 18 and 55 with available safety, tolerability, and immunogenicity data from an ongoing placebo-controlled, observer-blinded dose escalation study. Participants were divided into groups receiving different doses (10, 30, and 100 μg) of the BNT162b1 mRNA vaccine or a placebo. The participants who received the vaccine were given two doses, 21 days apart, except for the group receiving 100 μg, which only received one dose.

Similar to vaccine mRNA-1273 from Moderna, the phase 1 trials involved 45 healthy participants aged 18-55 years old, who were divided into 3 groups to receive different doses (25, 100, and 250 μg). Two doses were given at 28-day intervals. Two participants missed their second dose due to suspected COVID-19 exposure but later tested negative.

Results: Covid Vaccine

Interim data from the phase 1/2 trial of the BNT162 mRNA vaccine showed that the vaccine elicited an immune response, with increased levels of IgG (the most common type of antibody found in the bloodstream) and neutralizing antibodies observed in participants who received the vaccine. The immune response was more pronounced in the 10 and 30 μg groups, and no data was available for the 100 μg group as they did not receive a second booster dose. Researchers grouped the symptoms after injection mainly into 4 groups: mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization.

Systemic and local reactions were mostly mild to moderate and dose-dependent, with pain at the injection site being the most common event. Frequently happening systemic occurrences were fatigue, headache, chills, muscle, and joint aches. Fever and other symptoms escalated with the dosage but were resolved within a day. No Grade 4 adverse events were reported, but a few participants complained of Grade 3 pyrexia and sleep disturbance. Laboratory values did not change much for most individuals, but a few had decreased lymphocyte and neutrophil count, which returned to normal within 6-8 days post-vaccination. Based on these findings, the 10 and 30 μg doses are considered better candidates and are more likely to proceed through future trials.

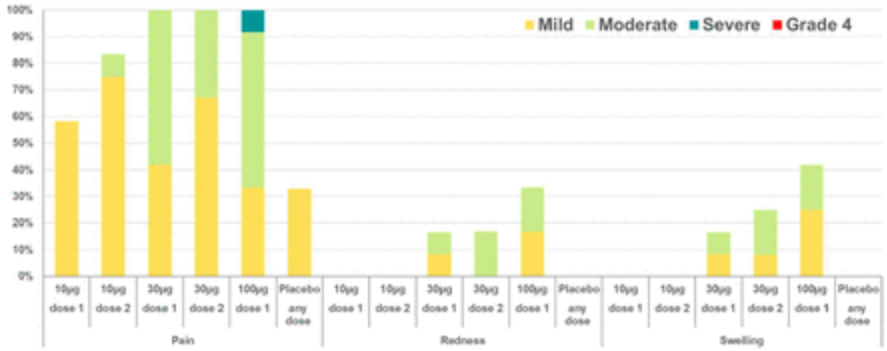

Figure 2: Local reactions reported within 7 days of vaccination, all dose levels.

According to the preliminary report of mRNA-1273, the interim results of a vaccine trial showed no serious adverse events, but some participants experienced mild to moderate side effects such as hives, fever, pain at the injection site, myalgia, headaches, fatigue, and chills. The vaccine produced a specific antibody response depending on the dose, with higher doses producing a higher response. CD4+ T cell responses were also detected. The trial found that two doses were needed for NAbs to be detected in all participants. Results for older participants are still pending, and it will be important to see the dosage used and any resulting side effects.

Methodology: Survey

The survey study of side effects of COVID-19 is given the name of COVID-19 Citizen Science (CCS), performed on the Eureka Research Platform (University of California, San Francisco), a digital platform for clinical research studies including a mobile application (app) and web-based software. Participants are recruited through email invitations, word of mouth, partner organizations, and press releases. Participants are required to be older than 18 years old, register an Eureka Research Platform account, and have an IOS or Android smartphone with the app, or enroll in the web-based study. After consenting to the study, participants need to complete baseline surveys daily, weekly, and monthly regarding COVID-19 vaccines, including time, brand, dose, place, side effects, and additional shots after months. The survey provides participants options for side effects they experienced, which include fever, chills, fatigue, sore/scratchy throat, muscle pain, joint pain, headache, other pain, redness/swelling at the injection site, rash other than at the injection site, allergic reaction/anaphylaxis, other, none of the above, and duration and self-rated adverse effect severity.

Results: Survey

Because of the time taking the survey, the result only contains three brands of vaccine: BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), or JNJ-78436735. 65,921 people participated in the US trial, and as of May 19, 2021, 19,586 of those people said they had received at least one dose of vaccination. Fatigue, muscle soreness, headaches, chills, redness/swelling at the injection site, joint pain, and fever were the most frequent side effects. The most important component that contributed to bad reactions was vaccine dose, with two doses of BNT162b2 or mRNA-1273 or one dose of JNJ-78436735 being linked to a threefold increase in the likelihood of adverse reactions as compared to one dose of BNT162b2 or mRNA-1273. The likelihood of subjects reporting unpleasant effects increased twofold after receiving mRNA-1273 compared to BNT162b2 vaccination, and adverse effects and their intensity varied across vaccine brands.

According to this study, evidence from clinical trials and government-sponsored surveillance is consistent with the low incidence of major side effects following COVID-19 vaccination. More people who were younger, female, Asian, pregnant, marijuana users, or who had previously taken COVID-19 experienced adverse effects. Asthmatic people were less likely to experience negative consequences. Future research should make targeted recruitment attempts to include representative communities because the study gives crucial information to the public about the safety of vaccines.

Discussion: Covid Vaccines

The study found that as more people were tested and recorded, the range and severity of side effects were expanded. The experimental method used in the study failed to account for a wide range of factors such as race, drug history, pregnancy, and age, among others, and this may be a possible reason to limit the diversity of the study participants and the inconclusion of our experimental result. In addition, we failed to find the trail experimental results for JNJ-78436735, so we are unable to conclude the relationship between JNJ-78436735 in trial and in the market, which may be accounted for our wide range of side effects detected in the survey.

Despite these limitations, the side effects of the vaccines remained manageable within the scope of the study. The study found that as the doses of the vaccines increased, the severity of the symptoms worsened. This underscores the importance of administering the correct dosage of vaccines to minimize the risk of adverse side effects.

For future studies, it is crucial to include a more diverse range of subjects in vaccine studies to ensure that the results are representative and inclusive. The study highlights the need for a more inclusive vaccine that can reduce side effects for everyone, even as the COVID-19 pandemic comes to an end. As such, ongoing research and development are critical to finding effective vaccines that are safe and accessible to everyone.

Conclusion: Covid Vaccines

The two studies analyzed the side effects of COVID-19 vaccines, specifically BNT162b2, mRNA-1273, and JNJ-78436735, through experimental and survey methods. The first study of BNT162b2 found that the immune response was more pronounced in the 10 and 30 μg groups, and the side effects were mostly mild to moderate and dose-dependent. The second study of mRNA-1273 had shown good safety and a specific antibody response with higher doses resulting in a higher response. Two doses were necessary for full efficacy. Mild to moderate side effects were reported, and further results for older participants are pending. The third survey study found that fatigue, muscle soreness, headaches, chills, redness/swelling at the injection site, joint pain, and fever were the most frequent side effects, and adverse effects and their intensity varied across vaccine brands. All three studies concluded that adverse effects were generally manageable, but future research should target more representative communities for a better understanding of vaccine safety.

Methodology: Alternative treatments

The aim of this study is to develop targeted treatments for SARS-CoV-2, the virus responsible for COVID-19, through a comprehensive understanding of the viral replication process. To achieve this, a thorough review of the literature was conducted to explore the stepwise process of viral entry and infection. The process begins with the attachment of the virus to specific receptors (ACE-2 receptors) on the surface of the host cell, triggering conformational changes in

the viral spike proteins. This enables the virus to fuse with the cell membrane and release its genetic material into the host cell cytoplasm. Once inside, the viral RNA is translated into viral proteins, which replicate the viral genome and assemble new virions. Understanding the intricacies of this process is essential for developing targeted treatments that can disrupt specific steps of the viral replication cycle.

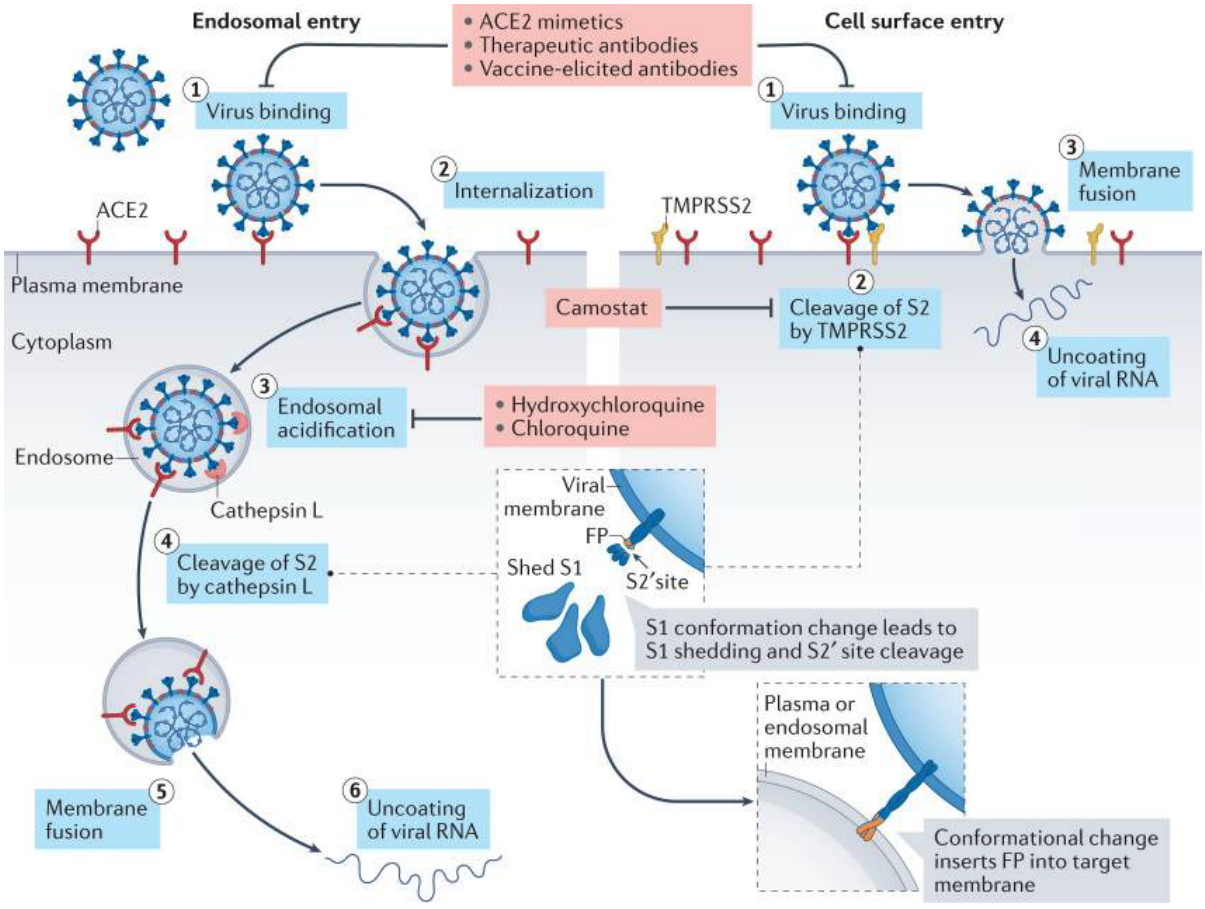

Figure 3. Mechanism of viral infection. This image illustrates two mechanisms for how the SARS-CoV-2 virus can enter and infect a host cell.

Expanding on their previous research, a new approach to isolating monoclonal antibodies for treating COVID-19 is described in the second paper of this study. In this study, a library of antibodies was generated by isolating B cells from the blood of individuals who had recovered from COVID-19, extracting their RNA to create a library of antibody sequences. The antibodies were then screened for their ability to bind to the SARS-CoV-2 spike protein using phage display. From the thousands of antibodies screened, two highly effective monoclonal antibodies, B38 and H4, were identified that bound tightly to the spike protein and could block the virus

from infecting cells in vitro. These two antibodies were further characterized to understand how they interact with the spike protein, and it was found that both could neutralize SARS-CoV-2 and related coronaviruses. In animal models, both B38 and H4 were shown to prevent and treat SARS-CoV-2 infection in mice and hamsters, demonstrating the potential of monoclonal antibodies as a therapeutic option for COVID-19.

Finally, in the third paper the experiments evaluate the effectiveness of PVP-I gargle/mouthwash in inactivating SARS-CoV-2 and reducing the risk of transmission were performed in various ways. In vitro experiments were conducted to assess the virucidal activity of PVP-I against SARS-CoV-2. These experiments involved exposing the virus to different concentrations of PVP-I for varying periods of time and then measuring the virus's ability to infect host cells. The in vitro experiments mentioned in the article were conducted to determine the virucidal activity of PVP-I against SARS-CoV-2. To do this, the researchers first prepared a stock solution of the SARS-CoV-2 virus by growing the virus in Vero E6 cells, a type of kidney epithelial cell. The virus was then harvested from the cell culture medium and diluted to a specific concentration for use in the experiments. Next, different concentrations of PVP-I were prepared by diluting the commercial solution in distilled water. The concentration of PVP-I used ranged from 0.23% to 7.5%. The virus was then exposed to each of the PVP-I concentrations for varying periods of time, ranging from 5 seconds to 5 minutes. A control group was also included, which involved exposing the virus to distilled water without PVP-I. After the virus was exposed to the PVP-I or control solution, the researchers measured the virus's ability to infect host cells. This was done by adding the virus to a monolayer of Vero E6 cells and incubating the cells for 48 hours. The cells were then fixed with formaldehyde and stained with crystal violet, and the virus-induced cytopathic effect was observed under a microscope. The experiments were performed in triplicate (3 identical samples that are prepared and tested the same to further validate results) and the data was analyzed using statistical software.

The results showed that a PVP-I gargle/mouthwash at a concentration of 1% or higher was effective in inactivating SARS-CoV-2 within 15 seconds of exposure in vitro. The experiments provided evidence that PVP-I may be an effective tool in reducing the transmission of SARS-CoV-2. Clinical studies were also conducted to evaluate the effectiveness of PVP-I in reducing the viral load in COVID-19 patients and the incidence of COVID-19 in healthcare

workers. In these studies, participants were asked to use PVP-I gargle/mouthwash for a specific period, and the outcomes were measured by analyzing the viral load in saliva samples or through regular COVID-19 testing. In the systematic review and meta-analysis cited in the article, the effect of PVP-I mouthwash on COVID-19 transmission in dental settings was examined. The review included studies that investigated the use of PVP-I mouthwash in dental clinics for patients and healthcare workers. The studies included in the review used different protocols for PVP-I mouthwash administration. Some studies used a pre-procedural rinse with PVP-I mouthwash, while others used a rinse during and/or after the procedure. The concentration of PVP-I mouthwash used also varied between studies, ranging from 0.23% to 5%. The duration of the rinse ranged from 15 seconds to 3 minutes.

Results: Alternative Treatments

The monoclonal antibodies B38 and H4 were found to be highly effective against SARS-CoV-2, the virus that causes COVID-19, in both in vitro and animal studies. In animal models, both antibodies were able to prevent and treat SARS-CoV-2 infection. In a study with hamsters, treatment with B38 or H4 reduced the viral load in the lungs and nasal turbinates by over 99%, and the animals showed no signs of disease. In another study with mice, treatment with B38 or H4 reduced the viral load in the lungs by over 99.9%, and the mice survived the infection without any signs of weight loss or illness. In addition, the researchers found that both antibodies can neutralize not only SARS-CoV-2 but also related coronaviruses, such as the virus that caused the SARS outbreak in 2003. This suggests that the antibodies may have potential for use in future outbreaks of related coronaviruses. Overall, the results suggest that monoclonal antibodies like B38 and H4 have the potential to be effective treatments for COVID-19. However, further studies are needed to evaluate the safety and efficacy of these antibodies in human clinical trials.

The article discusses several studies that have investigated the effectiveness of povidone-iodine (PVP-I) gargle/mouthwash in inactivating SARS-CoV-2 and reducing the risk of transmission. One study showed that a PVP-I gargle/mouthwash at a concentration of 1% or higher was effective in inactivating SARS-CoV-2 within 15 seconds of exposure in vitro. Another study found that a 0.23% PVP-I mouthwash reduced the viral load in the saliva of COVID-19 patients by 75% after using it for 30 seconds. The article also discussed a randomized controlled trial involving healthcare workers in Japan who used a PVP-I gargle/mouthwash three times a day.

The results showed that the use of mouthwash was associated with a significant reduction in the incidence of COVID-19 compared to the control group. Furthermore, the article cited a systematic review and meta-analysis that examined the effect of PVP-I on COVID-19 transmission in dental settings. The review found that the use of PVP-I mouthwash significantly reduced the risk of COVID-19 transmission during dental procedures. Overall, the article suggests that PVP-I gargle/mouthwash may be an effective and affordable tool in reducing the risk of transmission of SARS-CoV-2 in both healthcare and community settings. However, further studies are needed to confirm these findings and to determine the optimal concentration and frequency of use of PVP-I gargle/mouthwash.

Table 2

Evidence confirming the efficacy of Povidone-Iodine (PVP-I) against SARS-CoV-2.

No	Study	Objective	Materials and methods	Results and conclusion	References
1.	In-vitro observational study	Virucidal activity of PVP-1 against SARS-CoV-2	Four products of PVP-I a. Antiseptic solution (PVP-I 10%) b. Skin cleanser (PVP-I 7.5%) c. Gargle and mouth wash (PVP-I 1%) d. Throat spray (PVP-I 0.45%) Tested for a contact time of 30 s for virucidal activity	All products of PVP-I inactivated the virus by ≥99.99% which corresponded to ≥4$\log_{10}$ reduction of virus titre, within 30 s of contact	Anderson et al., 2020 [6]
2.	In-vitro observational study	Optimal contact time and concentration of oral PVP-I against SARS-CoV-2	a. PVP-I at a concentration of 0.5%, 1% and 1.5% compared with b. Ethanol (70%) and water for 15 and 30 s Tested against SARS-CoV-2-USAWA1/2020 strain	PVP-I (0.5%, 1% and 1.5%) inactivated SARS-CoV-2 completely within 15 s of contact 70% ethanol group did not inactivate SARS-CoV-2 after 15 s of contact, but was able to inactivate the virus at 30 s of contact	Bidra et al. [60]
3.	In-vitro observational study	Compare hydrogen peroxide (H_2O_2) and PVP-I oral antiseptic rinses against SARS-CoV-2	a. PVP-I (0.5%, 1.25% and 1.5%) and b. H_2O_2 aqueous solutions (3% and 1.5% concentrations) at contact periods of 15 s and 30 s Was tested against SARS-CoV-2	PVP-I (0.5%, 1% and 1.5%) inactivated SARS-CoV-2 completely at 15 s The H_2O_2 solutions (1.5% and 3.0%) showed minimal virucidal activity after 15 s and 30 s of contact time	Bidra et al. [61]
4.	Systematic review	To evaluate the specific efficacy of PVP-I against SARS-CoV-2	All protocols for nasal and oral PVP-I against COVID-19 were systematically reviewed	PVP-I can be safely administered for up to 5 months in the nasal cavity and 6 months in the oral cavity	Frank et al. [62]
5.	Short communication	The impact of PVP-I mouthwash on the salivary viral load of SARS-CoV-2	a. Nasopharyngeal swabs and salivary samples were tested for SARS-CoV-2 in patients before and after rinsing with 15 mL of 1% PVP-I for 1 min	PVP-I resulted in a significant drop in viral load, which remained for at least 3 h	Lamas et al. [53]

Figure 4. Reported results of the efficacy of PVP-I against SARS-CoV-2. These results summarize various studies done to illustrate PVP-I as a way to prevent SARS-CoV-2 infection.

Discussion: Alternative Treatments

The discovery that the monoclonal antibodies B38 and H4 are highly effective against SARS-CoV-2, the virus that causes COVID-19, is a significant breakthrough in the fight against the pandemic. The results from animal studies show that these antibodies can prevent and treat SARS-CoV-2 infection, reducing the viral load in the lungs and nasal turbinates by over 99%. This means that patients who are infected with COVID-19 may be able to recover more quickly and with fewer complications if they are treated with these antibodies. Moreover, the ability of these antibodies to neutralize related coronaviruses suggests that they may have the potential for use in future outbreaks of similar viruses. This could provide a more rapid response to outbreaks and could potentially save lives. Monoclonal antibodies like B38 and H4 represent a promising new avenue of treatment that could potentially be used in combination with other therapies to

improve outcomes for patients. However, it is important to note that further studies are needed to evaluate the safety and efficacy of these antibodies in human clinical trials. Overall, the review provides strong evidence that COVID-19 vaccines are among the most effective ways to prevent and control the spread of COVID-19. Vaccination not only protects individuals from severe disease and death but also helps to reduce transmission of the virus and prevent new outbreaks.

The article also discusses the use of virucidal solutions to combat COVID-19, particularly for those who may be resistant to getting vaccinated. Virucidal solutions can be an effective tool to prevent the spread of the virus in situations where vaccination is not possible or for those who may be resistant to vaccination, The article suggests that virucidal solutions, such as hydrogen peroxide, sodium hypochlorite, and ethanol, can effectively inactivate the virus on surfaces, reducing the risk of transmission from contact with contaminated surfaces. This can be particularly beneficial in settings such as hospitals, schools, and public transportation, where large numbers of people may encounter high-touch surfaces. The use of virucidal solutions can also be beneficial for individuals who may be resistant to getting vaccinated. While vaccines are highly effective in preventing COVID-19 infection and reducing the severity of the disease, some individuals may be hesitant to get vaccinated due to various reasons. In these cases, the use of virucidal solutions can help to reduce the risk of transmission and protect individuals who may be vulnerable to the disease. However, it is important to note that the use of virucidal solutions alone may not be sufficient to prevent the spread of COVID-19 and should be used in combination with other preventive measures such as wearing masks, practicing social distancing, and maintaining good hand hygiene. In conclusion, virucidal solutions can provide an additional layer of protection against COVID-19, particularly for individuals who may be resistant to getting vaccinated, while vaccines remain the most effective way to prevent the spread of the virus.

Conclusion: Alternative Treatments

This study aimed to develop targeted treatments for SARS-CoV-2 by understanding the viral replication process. Monoclonal antibodies B38 and H4 were identified as highly effective against SARS-CoV-2 in both in vitro and animal studies, while PVP-I gargle/mouthwash showed promising results in reducing the transmission of the virus. These findings provide a foundation for further research and the development of effective therapies for COVID-19.

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