Review Article

SARS-CoV-2: An Overview of First Emerging Pandemic of 21st Century

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Abstract

The world has been greatly impacted by the first emerging pandemic of the 21st century. Huge pressure was built on medical and biological researchers to develop a vaccine/cure as soon as possible, but the novelty of the virus made it difficult. Three-step strategies were taken to tackle COVID-19, diagnosis, containment, and mitigation along with the production of vaccine or medicine. SARS CoV-2 has an 85% similarity with bat SARS-like beta coronaviruses but the less than 90% similarity of conserved replicase domains between the beta-coronaviruses and the samples indicates the novelty of the virus. Rate of transmission; Case fatality ratio (CFR) Secondary attack rate (SAR), reproductive number (Ro) and fatality rate of infection (FRI) helped to understand and estimate the dynamics of the pandemic, while genome surveillance helps track the VOCs emerging because of selection advantage. Now in 2021 multiple vaccines have been developed by different companies having efficacies ranging from 70% to 95%. With every passing day, the world is getting one step closer to better understand and possibly in a near future "close the book" of this infectious virus, but so far its continuous mutations are becoming a hurdle to find a panacea to cure this disease.

***Keywords**: SARS CoV-2, COVID-19, Rate of transmission, Vaccines, VOCs, Challenges*

Abbreviations

ACE2 receptor	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
APC	Antigen-presenting cell
CFR	Case fatality ratio
CD8 T cells	cytotoxic T lymphocytes
FRI	Fatality rate of infection
HCoV-229E	Human coronavirus 229E
HCoV-HKU1	Human coronavirus HKU1
HCoV-OC43	Human coronavirus OC43
HCoV-NL63	Human coronavirus NL63
MRC	Medical Research Council
MHC	Major histocompatibility complex
MERS	Middle East respiratory syndrome
PCR	Polymerase chain reaction
RBM	Receptor-binding motif
RBD	Receptor-binding domain
R_0	Reproduction number
Robs	Observed reproduction number
SARS	*Severe Acute Respiratory Syndrome*
SAR	Secondary attack rate
SGTF	*S-gene target failure*
TH17	T helper 17 cells
VOCs	Variants of concern
WHO	World Health Organization

Introduction

In December 2019 clusters of patients with unknown causes of pneumonia emerged in the city of Wuhan, China. Their samples were tested for known coronaviruses responsible for respiratory diseases but none of the samples detected positive for HCoV-HKU1, HCoV-229E, HCoV-OC43, and HCoV-NL63. RNA extracts from the bronchoalveolar fluid and airway epithelial cells of the patients were used as templates to get the sequence of viral reads by using sequencing techniques. The reads give 85% similarity with bat SARS-like *beta coronaviruses* but the less than 90% similarity of conserved replicase domains between the *beta coronaviruses* and the samples indicates the novelty of the virus (Zhu et al.). The new virus was named 2019-nCoV initially but WHO named it SARS-CoV-2 (considering the sentiments of people who were affected by the SARS outbreak of 2002) having the potential to cause COVID-19 (WHO, 2020).

Considering the severity, spread and inaction of containment for SARS-CoV-2 in more than 100 countries and cases up to 100,000 WHO on 11 March declared it as the pandemic of history with the positive message that it is the first pandemic of its type that can be controlled. Three-step strategies were taken to tackle COVID-19, diagnosis, containment, and mitigation to keep the curve flattened, along with the production of vaccine or medicine (Imai et al.).

Structure of SARS-CoV-2

The structure of SARS-COV-2 at the atomic level reveals that it is reminiscent of previous SARS-CoV, the RBD and RBM of novel coronavirus suggest that it also use ACE2 receptor for binding with human cells, Gln493 residue of SARS-CoV2 favors the binding. Asn501 residue shows less binding affinity with ACE2 but a single mutation at N501T can significantly enhance the affinity of binding with ACE2 so this needs to be monitored carefully in the patients. The structure also suggests the acquisition of three O-linked glycans adjacent to polybasic cleavage sites which are unique in SARS-CoV-2 (Wan et al.).

Pathology of SARS-CoV-2

Initial symptoms entail cough, fever, and shortness of breath (WHO, 2020). Underlying pathology by histological examination indicated ARDS, inflammatory lesions due to lymphocytes in the lungs. Additionally, pneumocytes show viral cytopathic changes. Peripheral blood analysis implies that severe immune injuries are due to increased TH17 and higher cytotoxicity of CD8 T cells. Moreover, lymphopenia could be the crucial factor to affiliate mortality and severity of the case. Coronaviruses also possess immune evasion mechanisms; a long incubation period of SARS-CoV-2 favors the virus to evade immune detection. SARS-CoV and MERS-CoV also evade innate and adaptive immune responses, in severe and worst cases, lower type 1 interferon responses and downregulated antigen presentation to the MHC molecules are observed (Xu et al.).

Source and Rate of transmission

China to sustain and feed its population encourages the breeding and consumption of wildlife, Chinese wildlife life protection law 1984 also backs the Chinese wildlife farming industry (Bal et al.). In these circumstances zoonotic transmission was inevitable. The outbreak in the city of Wuhan was linked with the seafood market of Wuhan, indicating zoonotic transmission just like the previous epidemics of SARS AND MERS, but cases in multiple cities and outside of China also indicated human to human transmission (WHO, 2021).

While the Source of transmission is crucial to understand, the rate of transmission is also crucial to estimate the intervention, surveillance and quarantine measure a country needs. The rate of transmission is determined by estimating the number of people already infected and the basic reproductive number of virus R0 (average number of secondary infections in a susceptible population) these could be inferred from the volume of travel from infected countries. For an epidemic, R0 must be greater than one; a higher R0 indicates the infection is harder to control. Case fatality ratio (CFR) and fatality rate of infection (FRI) are also crucial to estimate the dynamics and cause of fatality during an epidemic. R0 values less than 1 and between 1.4 to 2.5 have been reported for SARS and MERS, respectively. With available data, mathematical models indicate an R0 value between 2.2 to 4 and in another study around 3.28; higher than the estimated value by WHO (Imai et al.; Xu et al.). In another study meta-analysis of 24 studies suggest a Ro value of 2.87 however, 99.5% heterogeneity among the reproductive number suggests variation of Ro in different countries and settings. In countries like, Japan, Germany, and Spain Ro of 6.32, 6.07 and 3.56 have been reported, respectively. Considering the trends in Ro exponential increase in infection is predicted (Billah et al.). These figures suggest that novel coronavirus is more deadly than the previous ones (Prompetchara et al.).

Imperial College of London in collaboration with WHO, MRC and other countries in its 38th report has conducted a meta-analysis to observe the observed reproduction number (Robs) and secondary attack rate (SAR) of SARS-CoV-2 in different settings. These parameters help in determining the symptom status, duration of exposure, age difference or dependency and household size of SARS-CoV-2, the observed data is than translated to devise control strategies such as isolation of cases, testing, tracing, and exploration of transmission patterns. By pooling the data of 45 studies, the household secondary attack rate (SAR) is significantly higher 21.1% compared with the observed reproduction rate (Robs) 0.96. The data suggested that the rate of transmission is higher in households and SAR is higher when the household exposure exceeds 5 days. Moreover, the risk of attack is higher in prolonged and familial contact 5.9% than the casual contacts 1.2%. For asymptomatic patients, the secondary attack rate is 3.5% than the symptomatic index of 12.8%. The factor of age with respect to the rate of transmission varies in a different setting. In a household setting transmission to and from individuals less than 20

years of age is only moderate (Thompson et al.).

Genome surveillance and VOCs

However the parameters of the rate of transmission are dynamic rather than static for instance, rate of transmission varies with variant f concern (VOCs) and reproductive number directly correlates with the lockdown as sharp decrease and flattening of the curve is observed in Rt during rigid and partial lockdown (Santamaría and Hortal). Strick genome surveillance of SARS-CoV-2 has resulted in diagnosing a new variant B.1.1.7 of SARS-CoV-2 Between November 2020 and January 2021. A number of nonsynonymous mutations resulted in the replacement of N501Y in the spike region favored the binding of spike protein with ACE2 receptor (Chan et al.) and replacement of P618H favors the transmission (Peacock et al.). Moreover, deletion at 69-70 region of spike protein renders the PCR testing to detect the s region also known as S-gene target failure (Bal et al.). These mutations provide this variant of concern more potential to evade the immune system of the host. The data of SGTF indicate the VOC is prevalent in age group less than 20 years with not only a higher transmission rate but also 50- 100% higher Ro (Volz et al.). Another variant of concern P.1 has also emerged in late 2020 with 17 mutations majorly a trio E484K, K417T and N501Y in the S-region. This VOC also confers immunological favors to the virus and has enhanced the binding of the virus with ACE2 receptor with 1.7-2.4 fold increased transmission rate (Faria et al.). Genome surveillance has led to the detection of VOCs, emerged as a result of mutations and selection advantage but improving global surveillance can detect other linages which are circulating undetected.

Vaccines

With the identification of the SARS-CoV-2 complete genetic sequence on January 11, 2020, several researchers around the globe started to make vaccines. Now vaccine companies are collaborating with researchers from different backgrounds i.e., biotechnology, bioinformatics, and pharmacists, and their efforts have been fruitful in developing vaccines to reduce the burden of pandemics and avoid future causalities (Corey et al.). These vaccines are produced by traditional methods in combination with advanced technologies while keeping geographical diversity in mind. As of February 18th, 2021, 7 different vaccines are in the process of being administered to vulnerable populations across the countries. 200 vaccine candidates are being developed while more than 60 vaccines already in the process of clinical development (WHO, 2021)

Numerous Vaccine developing platforms such as CureVac, Moderna and Pfizer-BioNTech are developing mRNA-based vaccines while Inovio is using DNA-based vaccine development techniques (Crommelin et al.; Mahalingam et al.). Whereas Gamaleya and AstraZeneca (partnered with Oxford University), are using adenovirus vectors for vaccine development (Kim et al.). Up till now, both Pfizer and Gamaleya

vaccines have shown the efficacy of 95 and 92%, respectively while Moderna vaccine has 94.5% efficacy and AstraZeneca has 70% vaccine efficacy (Polack et al.). The table below is highlighting a comparison of vaccines, their recent efficacy, and properties.

Table 1: Comparison of vaccines, their recent efficacy, and properties

Vaccine Companies	Type of Vaccine	No of Doses Days	Current clinical stage	Clinical trial results	Current efficiency rate
Sinovac	Inactivated vaccines	20 and 14 days	Phase 3	6 µg/0.5 mL or 3 µg/0.5 mL doses of phase 2 trial showed efficient results with 91% efficiency in adults.	50.38%
Sinopharm (Wuhan Institute of Biological Products)	Inactivated vaccines	20 and 21 days	Phase 3	Phase 2 tiral results showed contrary reactions observed in 6.0% and 19.0% of vaccinated individuals	72.51%
Pfizer	RNA vaccines (BNT162b1)	20 and 28 days	Phase 3	Up to phase 2, vaccine showed moderate symptoms after 10 and 30 µg dose	95%
Moderna	RNA vaccines (mRNA-1273)	20 and 28 days	Phase 3	Phase 1 trial results were satisfactory, does not showede serious illness.	94.5%
CanSino Biological Inc	Non-replicating vector vaccines	1	Phase 3	Phase 2 trial showed better immune response	65.28%
AstraZeneca	Non-replicating vector vaccines	1	Phase 3	Ist and 2nd phase trials With mild symptoms showed 91% efficiency in participants.	81.3%
Gamaleya	Non-replicating vector vaccines	20 and 22 days	Phase 3	At day 28 better cellular immune response was observed in participants	91.6%

Future Prospects

Challenges to control COVID-19 disease transmission and combat its disastrous effects have been increased with the emergence of new mutated strains of SARS-CoV-2, the culprit of COVID-19. The new strains include UK strain B.1.1.7, South African strain 501Y.V2 and Brazilian strain B.1.1.28 (van Oosterhout et al.). In England recently a variant of SARS-CoV-2 termed B.1.1.7 has been designated as a variant of concern 202012/1. Reports have revealed its higher rate of transmission as compared to other variants with teenagers and children as its main targets, while the infection rate for elderly people has not been greatly affected (Volz et al.).

A variant of SARS-CoV-2 termed 50Y.V2 has been found predominantly in the South African population. It is high transmission rate is worrisome, as the strain appeared to be resistant to vaccines that are currently available, though studies are performed to confirm this aspect further (Duong; Tang et al.). Brazilian B.1.1.28 clade are also spreading rapidly and are the reason of concern for its being highly infectious and response to vaccines, for which various studies are being performed (Toovey et al.). Mutations are the cause for increased transmission, establishment, and propagation of these all strains, due to the variant enhanced interactions with host cell receptors i.e., ACE2 receptors of epithelial cells (Tegally et al.).

Herd immunity has been recently the topic with respect to COVID-19, at population level achieving threshold immunity which leads to interruption of the chain of infectious disease transmission naturally or by the help of vaccination (*Vaccine Glossary of Terms | CDC*).

But we probably will not be able to achieve herd immunity in recent years, as COVID-19 basic reproduction is between 2-6 (Li et al.; Sanche et al.). Reproduction Number (R0) is estimated/expected infected individuals due to entrance of infection in an immunologically naïve population, whereas expected/estimated infected individuals due to entrance of infection in population which is not immunologically naive is effective reproduction number (R) (Anderson et al.). R is influenced by susceptible individuals; its value dwindles by the increase in the number of survivors of infection. Need is to bring the value of R below 1 for the prevention of disease transmission, but it is wishful as vaccine efficacy should be 100% and its immunity long term even with R-value as low as 0.99 and herd immunity 60-70% (Kadkhoda, “Herd Immunity to COVID-19”). An estimation by epidemiologists has revealed that to achieve the threshold necessary for herd immunity at least 70% of the whole population should become resistant to disease (Clemente-Suárez et al.).

Currently, the vaccines that are being developed are targeting the healthy population age from 18 to 55, but to safely cut the route of disease transmission, there is a necessity for vaccine development that

targets infants, children and immunocompromised people including pregnant women (Kashte et al.). Animals are also infected by the virus and act as a reservoir for continuously mutating the virus and its spillback into humans that are susceptible to disease. The need is to develop vaccines that target animals to eliminate the routes for disease transmission (Mahdy et al.).

A proteomic study hypothesizes that the ancestors of this novel virus after infecting the host used them as natural selection platforms to better adapt themselves. 3D folding of ORF1ab of non-structural proteins of SARS CoV-2 was generated to elucidate its characteristics. Phyre2 fold tool was used to analyze the amino acid sequence of the selected protein and then compare these sequences with fold library to overview structural variation, sequence alignment, conserved domain and evolutionary routes. Secondary structures of the selected proteins were obtained by using PAIRED. Two proteins identified one share the conserved domain with MERS and SARS while the other corresponds with proteins of very distinct species of different kingdoms. If minor variation occurs in this protein which is possible because of RNA which is more prone to the mutations, the virus can form a large pool of minor variants with high replication and transmissibility rates in a diverse range of organisms. Hence, an effective vaccine against ORF1ab can evert the worse outcome in the form of an even severe pandemic in the future (Kadkhoda, “Herd Immunity to COVID-19”).

Conclusion

The dynamic nature of SARS-CoV-2 has brought challenges for the scientific community. Rate of transmission are strictly monitored to the device and revise the containment strategies while genome surveillance has led to the detection of VOCs, emerged as a result of mutations and selection advantage but, improving global surveillance can detect other linages which are circulating undetected. Currently available vaccines are unable to stop the virus transmission cycle hence; we can only view current vaccines as a helper to eliminate the threat of COVID-19, instead of considering it a panacea. Proper hygiene and social distancing are still important factors for preventing infection by the virus.

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