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Review Article

Genetic Evolution and Mutation Mechanisms in SARS-CoV-2 and Their Impact on Vaccine Efficacy

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Abstract: The coronavirus responsible for COVID-19, SARS-CoV-2, was first identified in late 2019 and quickly spread globally, bringing about a severe public health emergency of international concern. This review summarizes genetic evolution, mutation mechanisms, epidemiology trends and the impact of virus on vaccine induced immunity. With RNA replication error, recombination, and selective pressures, these have resulted in the emergence of several variants of concern such as Delta and Omicron with increased transmissibility with partial immune escape. The millions of new cases and hundreds of thousands of deaths are well documented in global and Iraqi epidemiological data; Iraq claims more than two million confirmed COVID cases. Viral mutations, most notably in the spike protein, have affected vaccine effectiveness, but booster doses and updated vaccines have helped protect against severe disease. Integrating genomic, epidemiological and immunological data is needed to inform ongoing public health responses, adapt the vaccine for evolving variants and ensure preparedness for other viral threats in the future.

Keywords: SARS-CoV-2, COVID-19, Mutations, Epidemiology, Vaccine Efficacy.

1. INTRODUCTION

In late 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the pathogen responsible for Coronavirus Disease 2019 (COVID-19), was first identified and has since become a global pandemic impacting health care systems and economies around the world [1]. SARS-CoV-2 is an RNA virus that displays genetic diversity mainly caused by replication error [3], even though the existence of a proofreading exonuclease (nsp14) reduces its mutation rate compared to several other RNA viruses [2, 3]. Following the original virus outbreak at the end of 2019, genetic variations were observed, resulting in new lineages with multiple shared mutations and more than 100 single-marker changes that contributed to improved transmission capacity or receptor affinity, pathogenicity alterations, or immunity penetration [4, 5], leading to classification as Variants of Concern (VOCs): Alpha (α), Beta(β), Gamma(γ), Deltaκ) and Omicron(o) [7].

As a result, the spike (S) glycoprotein has been described as playing a pivotal role in viral entry owing to its attachment to the human angiotensin-converting enzyme 2 (ACE2) receptor and is considered the most important target antigen toward neutralizing antibodies and vaccine development [6]. Mutations in key regions of the spike protein—especially the receptor-binding domain (RBD)—can also increase affinity for ACE2, enhance viral fitness, or decrease antibody neutralization and thereby influence vaccine-mediated protection [5-7]. Consequently, ongoing genomic surveillance has been critical for tracking viral evolution and characterizing the epidemiological and immunological relevance of newly emerging variants [8].

Vaccination is still the best public health intervention against COVID-19. Variants with the ability to evade immunity, however, have heightened concern for waning effectiveness of vaccines [9]. The evolution of virulent strains likely also is related to natural and vaccine-induced immune pressure; if so, such escape mutations could provide a selective advantage under certain conditions [10, 11]. Therefore, knowledge of the mechanisms driving genetic evolution of SARS-

CoV-2 and the consequences for vaccine performance are essential to inform vaccine update and booster strategies as well as pandemic preparedness at large.

2. Genomic Structure of SARS-CoV-2

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus within the Betacoronavirus genus of the Coronaviridae family [12]. Its genome is about 29.9 kb long, one of the largest genomes of all RNA viruses [13]. The viral genome is also arranged in a 5′ untranslated region (UTR), followed by two major open reading frames (ORF1a and ORF1b) that make up nearly two-thirds of the genome and are responsible for coding 16 non-structural proteins (nsps) related to viral replication and transcription [14].

2.1 Non-Structural Proteins and Replication Machinery

ORF1a and ORF1b are translated into two polyproteins (pp1a and pp1ab) that are processively cleaved by viral proteases to yield functional non-structural proteins [15]. These include nsp12, which encodes the essential RNA-dependent RNA polymerase (RdRp) responsible for viral RNA synthesis [16]. Importantly, nsp14 has 3′–5′-exonuclease (ExoN) proofreading activity — unusually among RNA viruses — that enhances replication fidelity and influences mutation dynamics [17]. The nsps forms a replication-transcription complex (RTC) that coordinates genomic replication and subgenomic mRNA production of the virus which ensures proper production of viral proteins [18].

2.2 Structural Proteins

According to Figure 1, the SARS-CoV-2 virion includes four major structural proteins as spike (S), membrane (M), envelope (E), and nucleocapsid (N) with the RNA genome packaged in a nucleocapsid. Spike glycoproteins facilitate interaction with host cells, as well as membrane fusion through binding to angiotensin-converting enzyme 2 (ACE2) receptors [6]. It is a heterotrimeric protein that contains two active subunits: S1 (containing the receptor-binding domain) and S2 (responsible for membrane fusion) [19]. The S protein is the main determinant of host range, tissue tropism and immunogenicity.

Viral assembly is centered on the most abundant structural protein, the M protein (100), whereas the E protein also has roles in budding and pathogenesis (101). The N protein interacts with viral RNA, forming a ribonucleoprotein complex and regulating replication and immune modulation (22).

2.3 Accessory Proteins

SARS-CoV-2 also encodes a number of accessory proteins (e.g., ORF3a, ORF6, ORF7a, ORF8) that are not critical for replication but play a role in immune evasion and pathogenicity in addition to structural and nonstructural proteins [23]. This also occurs as some accessory proteins inhibit interferon signaling pathways, thereby facilitating the survival of the virus inside the host [24].

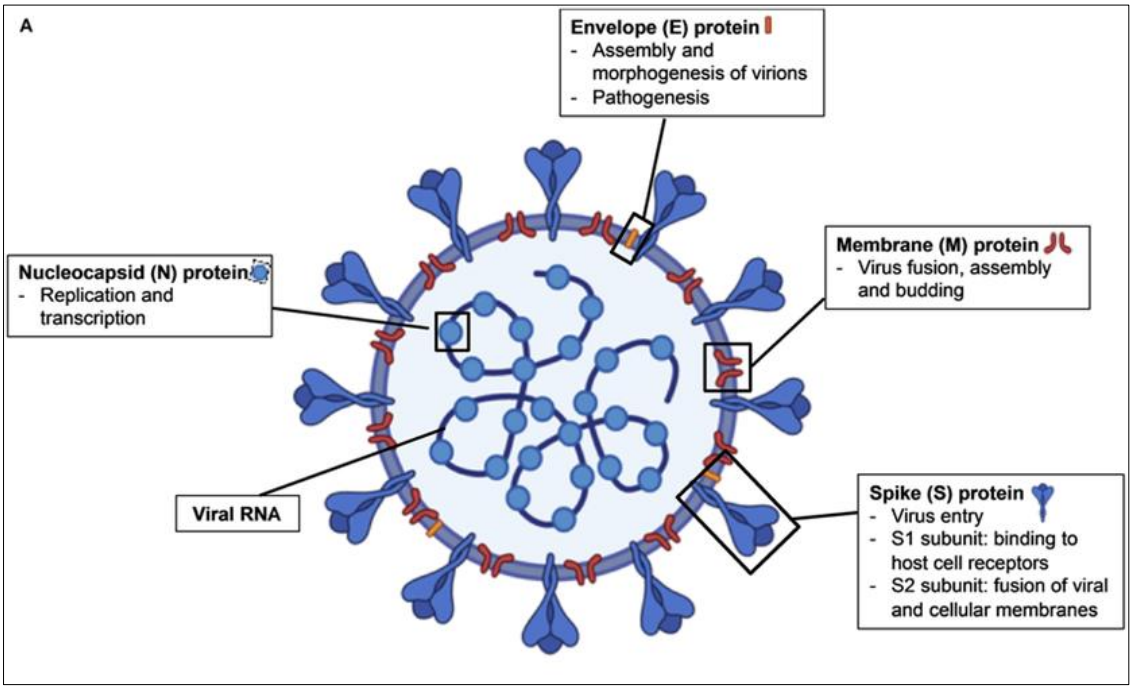

Figure 1: Schematic structure of SARS-CoV-2 showing structural proteins and genomic RNA (25)

3. Genetic Evolution and Mutation Mechanisms

3.1 Mechanisms of Mutation in RNA Viruses

Mutations are mainly generated from errors during genome replication, especially for RNA viruses because they do not have robust proofreading machinery. Despite encoding a proofreading exonuclease (NSP14), SARS-CoV-2 can still replicate with errors that drive genetic diversity [26, 27]. This replication-transcription complex (including RdRp and accessory factors) next is responsible for the replication and transcription but not to perfection so that the misincorporation of nucleotides occurs [26, 28]. Besides replication errors, mechanisms like host-mediated editing systems such as cytokine deamination catalyzed by APOBEC enzymes can generate c→u transitions and contribute to mutagenesis across the genome [29].

In fact, shuffling of different segments of the genome could cause genetic diversity in replication via template switching [30], which are evident at least in genes such as spike protein gene exhibit enough flexibility and evolution.

3.2. Different Mutation Types in SARS-CoV-2

Mutations in SARS-CoV 2 are grouped into different categories:

- Point mutations: single nucleotide substitutions which may be synonymous (no change in amino acid) or non-synonymous (amino acid changed). Recommended non-synonymous "super" mutations are common such as the D614G in the S protein associated with higher infectivity [31, 32].
- Insertions like ins214EPE seen in some Omicron sublineages — could alter antigenic properties [33].
- Deletion mutations seen in multiple variants (eg del69-70) are linked to a conformational change in the spike protein that is likely to reduce immune recognition [34].

All together these types of mutations determine structural and non-structural genes so that they serve to evolutionary mechanisms of the virus itself, but also contribute to variants emergence.

3.3. Selective Pressure and Virus Evolution

There are thus several selective pressures on SARS-CoV-2, such as host immunity, antiviral therapies and population-level vaccination. Positive selection results in the over-representation of non-synonymous mutations that confer a transmission or an immune escape benefit [35]. RBD binding regions are co-mutated members of a family of RBDs (L452R, T478K, N501Y) that are frequently linked to high fitness and immune escape such that variants with higher transmissibility or lower susceptibility to vaccines arise [36].

Table 1: Types of Mutations and Their Mechanisms in SARS-CoV-2

Mutation Type	Mechanism	Example Mutation	Observed Effect	Ref.
Synonymous	Replication errors	Silent C→T	No AA change	26
Non-synonymous	Replication errors	*D614G*	Increased infectivity	31,32
Deletion	Recombination/template switching	*del69-70*	Changes in antigenicity	34
Insertion	Recombination	*ins214EPE*	Alter altered antigenic loop	33

4. Classes of Mutations and Their Functional Effects

Genomic mutations in SARS-CoV-2 can have multiple effects on the biology of the virus, with changes to infectivity, antigenicity, transmission dynamics and ability to evade the immune response. While the vast majority of mutations are neutral or have minor phenotypic effects, more particularized spike protein mutations can carry significant functional consequences.

4.1 Mutations in the Spike and Receptor Binding

The spike (S) glycoprotein is responsible for the entry of virus to host cell, through receptor binding of S1 domain to ACE2 and fusion of viral membrane with host's membrane mediated by S2 domain. In this case, changes in important areas of the receptor-binding domain (RBD) can interfere with binding affinity and cleavage of neutralize by antibodies [5-32]. For example, D614G has been associated with increased infectivity and spike incorporation into virions, thereby making the virus more transmissible [31, 32]. Additional mutations, such as N501Y and L452R which reside in or near the receptor-binding motif, have also been linked to increased binding affinity for ACE2 and decreased neutralisation by certain monoclonal antibodies [36, 37].

4.2 Antigenic Drift and Immune Escape

Antigenic drift is defined as the progressive accumulation of mutations that change viral epitopes recognized by host immune responses. Reduced binding together with mutations in the receptor–binding domain (RBD) other than those that recognized the structural variants also give rise to immune escape phenotypes and challenge vaccine-induced protection [34-38]. The Omicron variant harbors a constellation of mutations within the spike protein domain that significantly reduce neutralization by sera from vaccinated or previously infected individuals [36-39].

4.3 Mutations in Non-Spike Proteins

Despite most attention focussing on the spike protein, mutations elsewhere—such as ORF1a, ORF1b and N protein—may have impact on viral replication efficiency [26], immune modulation [40], or pathogenicity. Some changes can affect replication fidelity, eventually affecting variant emergence [26-41], for instance, some non-synonymous polymorphisms that modify the nsp12 encoded protein (RdRp) [2].

4.4. Consequences of Fitness and Viral Evolution

In general, mutations that result in a selective advantage (i.e., provide upregulated transmission, improved fitness within host populations or immune evasion) will dominate in circulating viral pools [35]. In contrast, harmful mutations can be removed by negative selection. Mutation, selection, and genetic drift balance SARS-CoV-2 evolution trajectory [35-42].

Table 2: Selected SARS-CoV-2 Mutations and their Functional Consequences

Mutation	Location	Functional Effect	Observations / Consequences	Reference
D614G	Spike (S1)	Increased infectivity	Enhanced viral transmission	31,32
N501Y	Spike RBD	Increased ACE2 affinity	Higher transmissibility	36
L452R	Spike RBD	Reduced neutralization	Immune escape patterns	37
Δ69-70	Spike NTD	Conformational change	Affects detection & immune response	34
E484K	Spike RBD	Immune escape	Reduced vaccine sera neutralization	38
P323L	nsp12	RdRp alteration	Potential replication effects	41

5. Epidemiological Trends of SARS-CoV-2

SARS-CoV-2 emerged in late 2019 and rapidly circulated around the world, leading to a declaration by the World Health Organization (WHO) in March 2020 that COVID-19 was a pandemic [43]. By early 2024, global data showed >704 million confirmed cases and >7 million deaths worldwide [43, 44]. The fast pace of the spread has been shaped by several factors, including population density and international travel [30], public health measures [37], 1 and vaccine coverage [45].

The countries with some of the highest absolute numbers of infections have those that are heavily populated. For example, the US had more than 111 million confirmed cases and over 1.2 million deaths, India reported about 45 million cases and 533,000 deaths, while Brazil had nearly 38.7 million cases and 711,000 deaths. In France, there were >40 million confirmed cases and deaths of >167K [44, 45].

In the Middle East, Iraq confirmed its first case in February 2020, and later hata reported several epidemic waves. By the beginning of 2024, approximately 2,465,545 cumulative confirmed cases had been reported in Iraq (total deaths: 25,375; total recovery: ~2,439,497) [46, 47]. Differences between countries in case counts and mortality reflect differences in health-care infrastructure, testing capacity, demographics, and implementation of preventive measures [46, 47].

Although Iraq's real-time case-fatality ratio (CFR) is 1.0%, which appears very close to global estimates of 0.9% and can be meaningfully analyzed as a metric, comparison across other countries highlights differences in health system capacity and population structure. CFRs are lower and reporting is more complete in high-income countries with strong healthcare infrastructure [44-46].

Over the course of the pandemic COVID-19 has shown an ability to spread rapidly around the world, with successive waves throughout global populations led by new variants of concern. Surveillance and high-quality epidemiological data are still needed for public health planning and pandemic preparedness [43–47].

Table 3: COVID-19 Epidemiological Data: Global and Selected Countries

Region / Country	Confirmed Cases	Total Deaths	Ref.
Global	~704,753,890	~7,010,681	43,44
United States	~111,820,082	~1,219,487	44
India	~45,035,393	~533,570	44
Brazil	~38,743,918	~711,380	44
France	~40,138,560	~167,642	44
Germany	~38,828,995	~183,027	44
Iraq	~2,465,545	~25,375	46,47

6. Influence of Viral Mutations on Vaccine-Mediated Immunity

Mutations in SARS-CoV-2, particularly those affecting the spike (S) protein, can substantially impact virus sensitivity to neutralizing antibodies raised by vaccines. Mutations in the receptor-binding domain (RBD) and the N-terminal domain (NTD) have been linked to diminished binding of antibodies that were elicited through vaccination, a mutation pattern referred to as immune escape [31-38].

The D614G amino acid substitution, which subsequently attained wide global dominance in 2020, conferred increased viral infectivity but no substantive impact on vaccine-induced immunity [31, 32]. In contrast, mutations in variants of concern like Delta (B.1. 617. 2) and Omicron (B.1. 1. 529) associated with reduced neutralization by sera from vaccinated individuals and breakthrough infections despite full vaccination [36-48]. The omissions of K417N, E484A and N501Y in Omicron's many spike mutations appear to paradoxically correlate with both higher transmissibility and partial vaccine escape, but protection against severe illness and hospitalization still comes from the vaccines [39-49].

Such mutations influence different vaccine platforms differently. Low neutralizing titers against Omicron, but lots of T-cell mediated immunity with mRNA vaccines (Pfizer-BioNTech, Moderna). However, there is a variable reduction for viral vector (AstraZeneca, Johnson and Johnson) and inactivated vaccine depending on variant/dosing schedule49 50 Boosting doses restore neutralizing antibody titers and enhance protection against newly emerged variants [50, 51].

Table 4: Effect of Key SARS-CoV-2 Mutations on Vaccine-Induced Immunity

Mutation / Variant	Vaccine Type	Effect on Neutralization	Observed Consequence	Reference
D614G	mRNA, viral vector	Minimal reduction	No significant impact on vaccine efficacy	31,32
Delta (B.1.617.2)	mRNA, viral vector	Moderate reduction	Increased breakthrough infections	36,48
Omicron (B.1.1.529)	mRNA, viral vector, inactivated	Significant reduction	Partial immune escape; breakthrough infections	39,48,49
E484K	mRNA, viral vector	Reduced neutralization	Vaccine escape in some studies	38,49

7. CONCLUSIONS

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), has emerged as a global threat with hundreds of millions of cases and millions of deaths reported globally. Iraq went through several rounds of infection, a cycle repeated across the globe but one adapted to differences in health care capacity, demographics and measures taken to limit the spread of disease. Changes in the viral genome, particularly relating to mutations in the spike protein—were major drivers of transmissibility and immune escape. Variants including Delta and Omicron have managed to evade neutralization by the vaccine − at least in some, though not all cases − making more compelling the case for booster doses and up to date vaccination strategies.

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