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REVIEW

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Epidemic history and evolution of an emerging threat of international concern, the severe acute respiratory syndrome coronavirus 2

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Abstract

This comprehensive review focuses on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its impact as the cause of the COVID-19 pandemic. Its objective is to provide a cohesive overview of the epidemic history and

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evolutionary aspects of the virus, with a particular emphasis on its emergence, global spread, and implications for public health. The review delves into the timelines and key milestones of SARS-CoV-2's epidemiological progression, shedding light on the challenges encountered during early containment efforts and subsequent waves of transmission. Understanding the evolutionary dynamics of the virus is crucial in monitoring its potential for adaptation and future outbreaks. Genetic characterization of SARS-CoV-2 is discussed, with a focus on the emergence of new variants and their implications for transmissibility, severity, and immune evasion. The review highlights the important role of genomic surveillance in tracking viral mutations linked to establishing public health interventions. By analyzing the origins, global spread, and genetic evolution of SARS-CoV-2, valuable insights can be gained for the development of effective control measures, improvement of pandemic preparedness, and addressing future emerging infectious diseases of international concern.

KEYWORDS
COVID-19, emerging variants, evolution, genomic surveillance, SARS-CoV-2

1 | SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-CoV-2) A NOVEL THREAT OF INTERNATIONAL CONCERN

SARS-CoV-2, an emerging coronavirus, has given rise to a worldwide pandemic that has had significant repercussions on public health and the economy.[1] As a member of the coronavirus family, it can cause a spectrum of illnesses from common cold to severe respiratory syndromes like SARS and Middle East Respiratory Syndrome.[2] The virus is thought to have originated from bats and may have involved an intermediate host in its zoonotic emergence.[3] The initial epidemic in December 2019 in Wuhan, China, swiftly grew into a global pandemic, necessitating immediate and comprehensive control measures.[2] The primary mode of SARS-CoV-2 transmission is through respiratory droplets released when an infected person talks, coughs, or sneezes.[4] Although less common, the virus can also spread through contact with contaminated surfaces.[4] The incubation period is between 2 and 14 days, during which asymptomatic individuals can shed and transmit the virus to others.[4] COVID-19, the disease caused by SARS-CoV-2, exhibits a broad range of symptoms, varying from mild to severe. Common symptoms include fever, cough, fatigue, and difficulty breathing.[4] Some individuals may be asymptomatic, while others may require hospitalization or intensive care due to severe respiratory illness.[4] The pandemic has profoundly impacted society and the global economy, resulting in job losses, business closures, and disruptions to essential services and education.[5] To mitigate the spread, many countries have implemented stringent measures such as lockdowns, social distancing, and mask mandates.[5] Efforts to combat the pandemic have been multifaceted, including the development of effective vaccines, increased testing and contact tracing, and the use of therapeutic treatments for patients with COVID-19. Vaccines have been developed, approved, and are currently being distributed worldwide to mitigate the spread of the virus and the disease severity.

2 | STATISTIC AND EPIDEMIOLOGICAL DATA

On December 31, 2019, a cluster of pneumonia cases with an unknown cause was reported in Wuhan, Hubei Province, China (Figure 1). On January 9, 2020, the China CDC identified a new coronavirus as the causative agent, naming it coronavirus disease 2019 (COVID-19) (Figure 1).[6] This marked the beginning of the COVID-19 pandemic, which has seen over 766 million confirmed cases and more than 6.9 million reported deaths globally as of May 31, 2023.[7]

The COVID-19 outbreak was recognized as a global concern by the World Health Organization (WHO) on January 30, 2020, when it was declared a Public Health Emergency of International Concern.[1] This declaration emphasized the importance of international collaboration and coordination in responding to the rapidly spreading virus.[1] The situation escalated further on March 11, 2020, when the WHO officially declared COVID-19 as a global pandemic, underscoring the gravity and extensive reach of the disease (Figure 1).[1]

Within 10 months of the pandemic, the global death toll from COVID-19 surpassed one million (as reported on https://coronavirus.jhu.edu/map.html). In December 2020, emergency use authorization for COVID-19 vaccines was issued worldwide.[2] Around the same time, the United Kingdom announced the detection of a new and highly contagious SARS-CoV-2 variant known as Alpha variant (lineage B.1.1.7), the first classified Variant of Concern (VOC).[8] This discovery marked the beginning of a series of new variants being

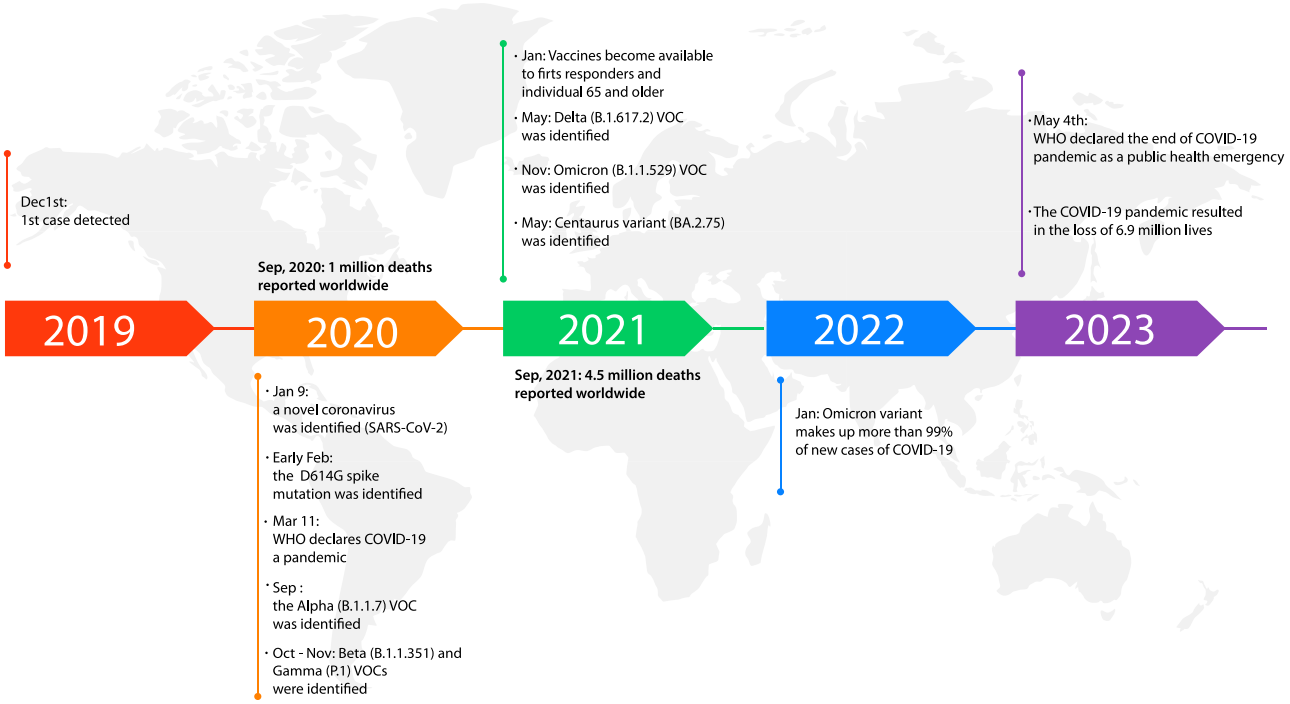

FIGURE 1 Timeline illustrating the evolution of the COVID-19 pandemic from December 2019 to May 2023. Each color represents a specific year or time point. Key milestones and significant events are emphasized.

identified, including the Gamma (lineage P.1) and Beta (lineage B.1.351).[9,10] The impact of new variants raised concerns about increased transmissibility and potential resistance to existing treatments. Efforts were intensified to monitor and study these variants, including their impact on vaccine efficacy and the need for updated immunization strategies. By February 2021, global COVID-19 cases had exceeded 100 million, with the death toll reaching two million.[7] As the year progressed, vaccination campaigns gained momentum in many countries. Several vaccines were administered to priority groups.[11] Vaccination programs aimed to protect vulnerable populations and reduce the severity of illness. However, access to vaccines remained a significant challenge, particularly in low-income countries, leading to concerns about global vaccine equity.[11] Throughout the year, governments and health authorities continued to navigate a delicate balance between controlling the spread of the virus and mitigating the socioeconomic impact of restrictions. Strategies such as testing, contact tracing, mask mandates, and targeted lockdowns were implemented to manage outbreaks and prevent overwhelming healthcare systems. These measures varied across countries, reflecting the diverse approaches taken in response to local epidemiological conditions and societal contexts. By the end of 2021, the global impact of the pandemic was far from over. The emergence of new variants, ongoing vaccination efforts, and the need for ongoing vigilance highlighted the need for continued public health measures and international collaboration. The path to recovery remained uncertain, with the SARS-CoV-2 virus continuing to evolve and pose challenges, emphasizing the importance of sustained efforts to control the pandemic and protect global health. 2022 began with a significant number of reported cases and deaths, reflecting the ongoing spread of the virus. The cumulative global case count surpassed hundreds of millions, highlighting the scale and magnitude of the pandemic's impact. The Omicron variant, first identified in late 2021 (Figure 1), demonstrated increased transmissibility and raised concerns about potential immune evasion.[12] In June 2022, the United States recorded over 84 million COVID-19 cases, making it the country with the highest number of cases worldwide. This significant milestone highlighted the ongoing impact of the pandemic on a global scale. On May 4, 2023, more than 3 years after its initial declaration, the WHO concluded the global emergency status for COVID-19 (Figure 1).[7] The WHO emphasized that countries should now focus on managing the virus, which has resulted in the loss of over 6.9 million lives, alongside other infectious diseases (Figure 1).[7]

3 | DIAGNOSTIC ASSAYS

The early diagnosis of SARS-CoV-2 infection is of utmost importance in monitoring and preventing the viral spread. Nucleic acid-based tests, such as real-time reverse transcription polymerase chain reaction (RT-qPCR), are considered the gold standard for SARS-CoV-2 testing.[13] These tests involve identification and amplification of viral genetic material and are commonly performed on nasopharyngeal or oropharyngeal swabs.[13] However, false positive or negative results can occur due to factors such as sample quality, timing of sampling, specimen handling, and reduced amplification sensitivity due to the presence of viral mutations.

To confirm SARS-CoV-2 infection, RT-PCR assays should be well optimized and complemented with other tests, including serum-based testing. Innovative diagnostic approaches are necessary to improve outbreak control, enable early-stage diagnosis, and reduce transmission, morbidity, and mortality (Table 1). Another molecular technique, the reverse-transcription loop-mediated isothermal amplification (RT-LAMP), has emerged as an alternative testing approach in regard to RT-PCR.[14] RT-LAMP is a one-step DNA amplification method that operates at isothermal conditions and provides results in a shorter time.[14] While RT-LAMP shows promise, it is crucial to validate its results against the gold standard RT-PCR.[14] The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas technology has also demonstrated the ability to rapidly, simply, and accurately detect SARS-CoV-2 gene sequences. Various endonucleases, such as Cas9, Cas12, and Cas13, are used in targeting SARS-CoV-2 genes.[15] Different CRISPR/Cas-based systems have been developed, including a kit that targets specific genes using Cas13 endonucleases and a technique that combines CRISPR-Cas12 and RT-LAMP for viral genes detection. The sensitivity of CRISPR/Cas-based systems is comparable to conventional i.e., RT-PCR.[9] Additionally, biosensors are devices that detect nucleic acids and proteins in specimens and provide an analytical signal for precise detection.[16] They utilize electrochemical, and optical methodologies. An ultrasensitive electrochemical detection technology based on graphene oxide functionalized with calixarene has been reported for targeting SARS-CoV-2 RNA. Biosensors offer high sensitivity and ease of use, making them valuable as screening tools.[16] Alternatively, serological assays, such as enzyme-linked immunosorbent assay (ELISA) and chemiluminescence assay (CLIA), present the ability to detect anti-SARS-CoV-2 antibodies.[16] These assays can be qualitative or quantitative and exhibit varying sensitivity and specificity. IgM and IgG antibodies serve as indicators of SARS-CoV-2 exposure, with IgG demonstrating higher sensitivity and reproducibility. ELISA and CLIA are commonly employed for antibody detection.[16]

Lateral flow assays (LFAs) are rapid qualitative tests that do not require laboratory equipment but may have lower sensitivity. LFAs are designed to analyze various sample types, including blood, swabs, or saliva, making them versatile and adaptable to different testing scenarios. In the case of antibody-based LFAs, they detect the presence of specific antibodies generated by the immune system in response to SARS-CoV-2 infection.[17] This information is valuable in determining if an individual has previously been exposed to the virus. LFAs enable efficient screening of large populations, aiding in epidemiological studies and monitoring the spread of the virus. It's important to note that LFAs may have lower sensitivity compared to laboratory-based tests, which means they may not detect antibodies in individuals with low antibody levels, particularly those who have recently been infected or vaccinated.[17] On the other hand, antigen-based LFAs directly target viral antigens associated with SARS-CoV-2. These LFAs detect the presence of viral proteins in patient samples, indicating an ongoing infection at the time of testing. The advantage of antigen based LFAs is their ability to provide real-time information about active infections, enabling prompt isolation and appropriate management of cases. LFAs designed for SARS-CoV-2 antigen detection have demonstrated good sensitivity and specificity, making them effective tools for rapid diagnosis in settings where laboratory infrastructure is limited. It's important to consider the role of cycle threshold (C_t) values in interpreting the results of LFAs. C_t values indicate the number of cycles needed for the amplification of viral genetic material in polymerase chain reaction (PCR) testing. Although LFAs do not directly provide C_t values, they offer a qualitative assessment of the presence or absence of viral antigens or antibodies. C_t values are typically used in PCR-based tests to estimate the viral load and assess infectivity. While LFAs do not provide quantitative information like C_t values, they are

TABLE 1 Diagnostic methods utilized for the SARS-CoV-2 pandemic.

Method	Specimens	Specificity	Main features
RT-qPCR	Nasopharyngeal and oropharyngeal swab	98–100%	Gold Standard. Highly specific. Very low limit of detection. Time duration of 60–90 min.
RT-LAMP	Nasopharyngeal and oropharyngeal swab, saliva	95–99%	Highly specific. Low cost. Time duration of 30 min
ELISA	Blood/serum.	95.7–100%	The sensitivity and specificity depend on test/kit used for assay. Time duration of 60–120 min
LFA	Nasopharyngeal and Oropharyngeal swab	88–98%	Sensitivity and specificity depend on the test/kit used. Gives false-negative results in samples with low viral load. Time duration of 15–30 min
CLIA	Serum, Plasma, Whole Blood	97–100%	Highly specific. Time duration of 15–40 min
CRISPR technology	Nasopharyngeal swab	90–97	Highly specific detection of SARS-CoV-2. Time duration of 50 min
Biosensors	Nasopharyngeal swab	99%	Low-cost and rapid detecting time duration of 10 min

Abbreviations: CLIA, chemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; LFA, Lateral flow assays; RT-LAMP, reverse-transcription loop-mediated isothermal amplification; RT-qPCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

valuable in quickly identifying infected individuals and supporting timely public health interventions.

Finally, artificial intelligence (AI) has also played a crucial role in combating the viral pandemic.[18] AI algorithms have been developed to enable early and rapid virus detection and transmission tracking using data from large-scale screenings, such as patients' thoracic CT images. Automated diagnostic systems based on AI can provide quick and reliable diagnoses, assess lung impairment, and monitor the progression of COVID-19 patients.

4 | OUTBREAK RESPONSE

Effective outbreak response relies on rapid and reliable data sharing. However, COVID-19 presented a challenge to governments and companies worldwide, as they sought real-time answers but faced a lack of adequate data or evidence to guide public health decision-making. Consequently, diverse, and fragmented policies and responses emerged. Initially, many countries reported cases through written press releases. As the situation evolved, reporting agencies transitioned to dedicated web pages or interactive dashboards.[19] The increasing number of data sources has posed a significant challenge. For instance, the White House and leading research groups collaborated to create the COVID-19 Open Research Data set (CORD-19).[20] This data set comprises over 1 000 000 scholarly articles, including more than 400 000 with full text, focusing on COVID-19, SARS-CoV-2, and related coronaviruses. It has been made freely available to the global research community, allowing the application of recent advances in natural language processing and AI techniques to generate new knowledge in support of the fight against the disease. In the face of diverse data types across different regions, global efforts in data curation and standardization are crucial to ensure rapid integration and dissemination of data during a pandemic. The scientific community has responded rapidly to the COVID-19 pandemic, releasing over 125 000 COVID-19-related scientific articles within 10 months of the first confirmed case, of which more than 30 000 were hosted by preprint servers. In particular, bioRxiv and medRxiv were the most used preprint servers for biomedical research.[21] Notable examples include the COVID-19 data portal,[22] as well as Nextstrain,[23] and CoV-Spectrum,[21] which monitor the genomic diversity and distribution of SARS-CoV-2 lineages. These initiatives enable the connection of disparate data streams and the development of tools for downstream analysis, providing public health-relevant information for research and decision-making. Optimal decision-making during a pandemic requires navigating uncertainty while responding promptly to avoid serious consequences. Data-driven tools play a crucial role in this context by fulfilling three key functions:

1. Monitoring and assessing the impact: In the early stages of an outbreak, fundamental knowledge about the new infection's characteristics is necessary, including transmission potential and natural history. Diagnostic tests, genomic sequencing, and rapid sharing of early results are essential. As outbreaks progress, predicting disease dynamics, estimating burdens, and evaluating intervention effectiveness become vital. Long-term data sets, such as cohort studies, can provide insights into epidemic processes over extended periods.[24]
2. Managing the epidemic: Various types of data are critical for epidemic management. Pathogen genomic data helps to identify causative agents, track mutations, and study transmission networks and geographic spread. Clinical data aids in understanding disease severity, developing case definitions, and evaluating possible pharmaceutical interventions. Serological data characterizes individual immunity and antibody responses. Epidemiological data, ranging from case counts to contact tracing, is crucial for estimating key parameters like the reproduction number (R0) and time distributions.[25]
3. Modeling and predicting the epidemic: Predictive modeling has regained importance in global responses to pandemics. Mathematical models alerted about the potential for a global pandemic and emphasized the need for drastic measures. Statistical modeling and computer simulations accurately projected epidemic dispersion and assessed the impact of measures like physical distancing and reduced travel. Targeted interventions rely on accurate estimates of transmission parameters. Mortality rates and changes in human mobility, measured through aggregate data, aided modeling efforts.[26]

To enable evidence-based responses, efficient and secure data sharing is essential, supporting tasks from monitoring variants to vaccine strain selection.[27] To achieve these goals, collaboration among diverse partners, is crucial for a multidisciplinary, multisectoral network that embraces a “One Health” perspective. Open-source platforms can facilitate integration among research groups and national governments, overcoming barriers and promoting accountability and democratization of public health. Several lessons have been recognized in regard to data systems, processes, and analysis.

1. Standardization. Obtaining reliable and synthesized information is a challenge, especially at a global scale. Therefore, a key step to facilitate data sharing among different countries is to define a standard format that is common to all the different health reporting systems.
2. Quality. Data quality can vary substantially among different data streams, especially in the early stages of an epidemic, when they are often less structured. Therefore, while researchers need to independently assess the feasibility of specific data to support the results of their studies, there is a need for a decentralized model in which volunteers and team members from different regions perform information validation, as demonstrated by the COVID Tracking Project (https://covidtracking.com/).
3. Sustainability. The volume and diversity of information generated during the COVID-19 pandemic was unprecedented. To process and analyze these data sets, scientists implemented new tools and

updated existing software. However, the health emergency has highlighted the need for a broader view of resource development and maintenance, as successful data and open-source software need continuous monitoring to respond quickly to the changing needs of user communities.

4. Equity. Recent historical events have reminded the world how fragile yet interconnected it is. What threatens some may soon threaten the entire community. The timely collection, integration, and dissemination of data will need to follow guidelines that prevent the information from being used to reinforce existing biases or discriminate against specific populations based on gender, age, or geographic location. It is also critical that data and software code be open source in the future to enable rapid integration among multiple research groups and national governments.

5 | GENOME SEQUENCING AND COVID-19: THE REAL-TIME GENOMIC REVOLUTION

Since its emergence in 2019, the SARS-CoV-2 virus responsible for the global pandemic, has undergone constant evolution and adaptation.[28] This ongoing evolution has led to the emergence of different viral lineages carrying mutations that can enhance transmission, infection, or evade neutralizing antibodies.[29] The generation and sharing of SARS-CoV-2 genomic sequences have reached unprecedented levels, with over 15 million sequences available via the Global Initiative on Sharing All Influenza Data (GISAID),[30] enabling near real-time surveillance. The importance of genomic surveillance in tracking the SARS-CoV-2 virus was demonstrated early on. By January 12, 2020, just a few weeks after the initial outbreak, the first four SARS-CoV-2 genomes were already uploaded to GISAID. This rapid sharing of genomic information has been instrumental in understanding the genetic diversity of the virus and its global spread. Genomic monitoring plays a critical role in tracking the virus's evolution, detecting new variants, and implementing effective public health measures. By sequencing the virus's genetic material, scientists can identify changes in its genome caused by mutations. These mutations can lead to the emergence of new variants with distinct characteristics, such as increased transmissibility, virulence, or resistance to vaccines.[2] Monitoring these changes enables a better understanding of the virus's evolution and supports the implementation of appropriate control strategies (Figure 2).

Each country has implemented its own response to the pandemic, taking into account the difficulties that some countries have encountered in establishing a PCR testing system and subsequent sequencing.

For the purpose of identifying as early as possible the new minority variants of SARS-CoV-2 circulating in a geographical area, a minimum level of genomes to be characterized has been set at around 0.5% in a time interval of around 21 days.[29] Generally, the highest sequencing levels were observed in Europe (mean 3.4% of characterized cases), the Western Pacific (2.7%) and the Americas (2.0%).

Several consortium and networks were established between universities, public health and private entities, such as:

1. COVID-19 Genomics UK Consortium (named COG-UK) in the United Kingdom, it was able to provide more than 800 000 SARS-CoV-2 genomes across UK between April 2020 and July 2021[30];
2. CDC has kicked off the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology and Surveillance (SPHERES) consortium in the United States IN 2021. Its purpose was to strengthen covid-19 mitigation strategies and incorporate genomic surveillance;
3. In 2020, The Africa Pathogen Genomics Initiative (Africa PGI), launched by the Africa Centers for Disease Control and Prevention (CDC), aims to integrate pathogen genomics and bioinformatics into public health surveillance, outbreak investigations, and disease control in Africa through collaboration with various partners. In South Africa, the Network for Genomic Surveillance in South Africa (NGS-SA) was established in March 2020, and within weeks, genomic analysis was helping to characterize outbreaks and community transmission;
4. COVID-19 Genomic Surveillance Regional Network created by PAHO-WHO in 2020 to establish a routine SARS-CoV-2 genomic sequencing in the Americas. It resulted in more than 850,000 SARS-CoV-2 genomes sequenced from Latin America and the Caribbean Member States of the Pan American Health Organization

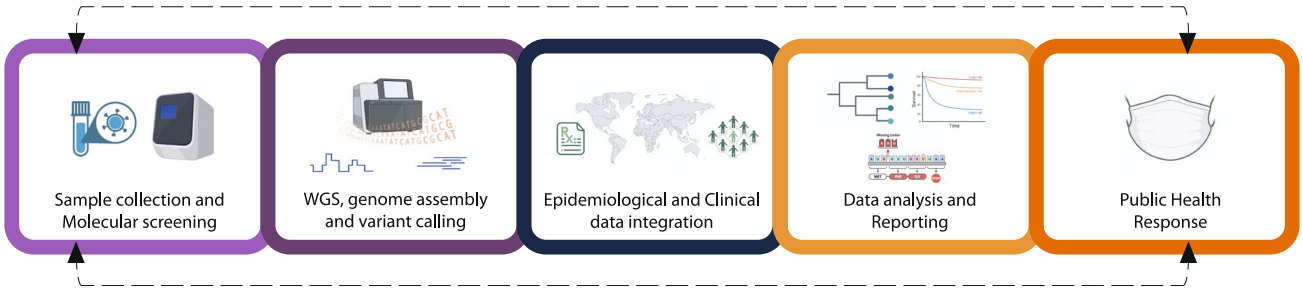

FIGURE 2 Genomic surveillance framework for the real-time monitoring of viral pathogens. The framework consists of five essential steps.

5. In Australia, it was built a pathogen genomics platform (AusTrakka) to enabled rapid data sharing, expanded access to computational and bioinformatic resources and expertize, and established nationwide real-time genomic surveillance.

This collaborative approach has facilitated rapid and widespread analysis of the virus's genetic makeup, contributing to global pandemic response strategies and the development of targeted interventions.

Notably, genomic monitoring has been pivotal in identifying and tracking the global spread of new SARS-CoV-2 variants, including VOCs, Variants of Interest and Variants Under Monitoring.[2] By sequencing the genomes of these variants, scientists can compare them to the original strain, assess their differences, and determine their global distribution.[2] This knowledge informs public health policies, such as travel restrictions and vaccine distribution prioritization. Additionally, genomic monitoring is crucial for vaccine development, as it helps determine the efficacy of existing vaccines against new variants and guides the development of updated vaccines or booster shots if needed.[2] Moreover, genomic monitoring provides valuable insights into the origin of the virus and its transmission from animals to humans. By comparing SARS-CoV-2 genetic sequences with other animal coronaviruses, scientists gain a better understanding of the virus's evolution and potential sources of transmission. This understanding contributes to efforts aimed at preventing future zoonotic disease outbreaks.

6 | GENOMIC COMPOSITION AND MOLECULAR EVOLUTION OF SARS-CoV-2

The limited proofreading capacity of the coronavirus polymerase enzyme initially suggested a slow evolution for SARS-CoV-2. However, the high transmission rates and widespread global infection numbers have contributed to a higher mutation rate.[31] This, combined with the circulation of different variants in the same timeframe, creates opportunities for viral recombination, and the emergence of new recombinant viruses.[31] As a result, several variants with higher transmissibility and advantages in transmission, infectivity, and antigenicity have emerged. Efficient human-to-human transmission of SARS-CoV-2 relies on spike protein binding to human ACE2 and furin cleavage at the S1-S2 junction.[32] Mutations throughout the pandemic have allowed certain variants, such as Alpha and Delta, to enhance their interaction with ACE2 and optimize furin cleavage, leading to increased transmissibility compared to the previous variants.[32,33]

The Omicron variant stands in contrast to other variants with its increased transmissibility, characterized by a distinct entry phenotype involving both cell-surface fusion and cathepsin-mediated endosomal fusion. This enables the Omicron variant to infect a broader range of cell types. The alternative entry mechanism through the endosomal pathway is believed to contribute to the reduced severity of the Omicron variant, as it exhibits lower fusogenicity and a preference for infecting the upper respiratory tract rather than the lower respiratory tract.[34,35] The D614G mutation, first discovered in early 2020, was the first notable mutation in the spike protein of SARS-CoV-2. Since then, several variants with different mutations in the spike protein, particularly in the receptor-binding domain (RBD), have emerged periodically (Figure 1).[36] The D614G mutation has been reported to enhance "viral fitness" by increasing in vitro protease-induced S protein cleavage and affinity binding to ACE-2. Since the initial expansion, several variants have been identified based on mutations in the spike protein, particularly in the receptor-binding domain (RBD). The B.1.1.7 (α) variant, also known as the UK variant, was identified in September 2020, and quickly spread globally (Figure 1).[37] It carries various mutations and deletions in the spike protein, including Δ69/70 and Δ144 in the N-terminal domain (NTD), N501Y in the RBD, and P681H, T716I, S982A, and D1118H mutations. These mutations affect virus infectivity, spike protein incorporation into virions, and affinity for ACE2, contributing to increased transmissibility.[38] The full impact of each mutation on survival or vaccine efficacy is still not completely understood (Table 2).

Subsequent variant, Beta, was first identified in October 2020 in South Africa (Figure 1).[39] It carries eight mutations in the spike protein, including N501Y, K417N, and E484K mutations in the RBD regions. These mutations are associated with the escape of neutralizing antibodies and reduced vaccine effectiveness against infection.[40] Additionally, the triple deletion in the NTD (Δ241/4, Δ242, Δ243) results in a shift of nearby N3 and N5 loops, which form part of the NTD neutralizing epitope. The E484K mutation leads to increased electrostatic interactions at the RBD-ACE2 interface, suggesting its contribution to a higher rate of transmission compared to previous variants. The Gamma variant (P1 lineage), was first reported in Brazil in November 2020 (Figure 1).[39] It carries 12 mutations in the spike protein, including N501Y, K417T/N, and E484K mutations in the RBD regions. However, it is less resistant to naturally acquired or vaccine-induced antibodies compared to the Beta variant, possibly due to the presence of other spike protein mutations impacting neutralization.[39] The B.1.617.2 (δ) variant, initially identified in India in October 2020 (Figure 1) had two amino acid changes in the spike protein sequence (L452R and P681R), which raised concerns as they are critical sites for binding with the ACE2 receptor (Table 2).[2] This variant showed an increased positive electrostatic potential due to amino acid changes, potentially enhancing its affinity for the ACE2 receptor. The B.1.617 lineage includes three sublineages: B.1.617.1 (also known as Kappa), B.1.617.2 (the most transmissible in humans), and B.1.617.3. The Delta variant exhibits higher transmissibility than the Alpha, Beta, and Gamma variants, likely due to its higher replicating rate and fourfold higher viral loads compared to the wild strain virus. The evolutionary rate of this variant started to slow down as it became endemic and had "exhausted its capacity to adapt." The Omicron variant of SARS-CoV-2, which emerged in South Africa in November 2021 (Figure 1), marked a significant genomic shift in the virus (Table 2).[18]

TABLE 2 Lineage-Specific Mutations in SARS-CoV-2 Variants of Concern (VOCs).

Variants	Spike	NTD	RBD	Pathological effects
Alpha (B.1.1.7)	ΔH69, ΔV70, ΔY144, N501Y, A570D, D614G, E484K, T716I, S982A, P681H, D1118H	ΔH69, ΔV70, ΔY144	E484K, S494P, N501Y	Increased transmissibility; increased binding affinity between RBD and ACE-2.
Beta (B.1.351)	L18F, D80A, E84K, D215G, Δ241/4, Δ242, Δ243, R246I, N501Y, D614G, K417N, A701V	L18F, D80A, E84K, D215G, R246I, Δ241/4, Δ242, Δ243	K417N, E484K, N501Y	Increased transmissibility; resistance to neutralization by NTD/RBD specific mAbs, convalescent plasma and vaccine sera.
Gamma (P1)	L18F, T20N, P26S, D138Y, R190S, D614G, E484K, N501Y, K417T, H655Y, T1027I	L18F, T20N, P26S, D138Y, R190S,	K417N, E484K, N501Y	Reduction of neutralizing antibody effectiveness in convalescent plasma and vaccine sera; enhanced viral entry through endosomal pathways.
Delta (B.1.617.2)	T19R, G142D, Δ156, Δ157, R158G, L452R, T478K, E484Q, D614G, P681R, D950N	T19R, G142D, Δ156, Δ157, R158G	L452R, E484Q	High transmissibility and pathogenicity alongside enhanced immune escape; increase in hospitalization.
Omicron BA.1 (B.1.1.529)	A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211-212, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F	A67V, Δ69-70, T95I, G142D Δ143-145, Δ211-212	G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H	Higher infectivity (by strengthening the binding with host ACE2 receptors); reduced neutralization by antibodies (mAb, T-cell, or convalescent or vaccine plasma).

It carries the highest number of mutations seen in any strain to date.[41] The spike protein of the Omicron variant exhibit over 30 mutations, with approximately 15 of them occurring in the RBD. Notable mutations such as Q498R and N501Y strengthen the binding to ACE2, while H655Y, N679K, and P681H enhance cleavage of the S1/S2 site.[42] Additionally, modifications in the NTD and RBD hinder infectivity, contribute to immune evasion and reduced neutralization by vaccine-induced antibodies.[43] Currently, Omicron seems to cause milder symptoms compared to other variants, and although vaccination significantly increases protection, it provides limited defense against symptomatic disease. The specific amino acid changes in the spike (S) gene of SARS-CoV-2 variants are summarized in Table 2. The modifications in the electrostatic potential altered interactions with other molecules, including antibodies. The variant presented several subvariants and sublineages (including BA.1-5) with varying expansion capabilities over the years. Therefore, the virus prevailing evolutionary mechanisms changed in the last times. In fact, while in the early pandemic the phenomenon of recombination was relatively rare being the antigenic drift prevalent,[43] in the post-Omicron era recombination events have increased significantly, becoming an important mechanism of viral evolution capable of improve the virus ability to escape convalescent or postvaccination immunity.[44]

Concerns arose in mid-2022 regarding the Centaurus variant (BA.2.75), which caused a temporary increase in infections (Figure 1). However, Centaurus evolved even more slowly than previous variants and did not become dominant. Similarly, other subsequent variants, such as Cerberus (BQ.1), Gryphon (XBB), Kraken (XBB.1.5), and BF.7, displayed fluctuations in population size but did not exhibit significant expansion capabilities.[4] These variants showed varying evolutionary rates and remained confined to specific regions, raising concerns but not causing widespread outbreaks. The evolutionary rates reflected the low level of genetic variability and limited capacity for significant demographic expansion. In early 2023, the BF.7 lineage caused concerns in the Asian region due to a resurgence in COVID-19 cases.[4] However, it also exhibited limited capacity for significant expansion, reflected in its evolutionary rate. Overall, the subsequent variants that raised concerns followed a pattern of vicariance, taking turns without becoming truly worrisome in terms of global impact.

7 | SARS-CoV-2 VACCINES DEVELOPMENT: A RACE AGAINST TIME

The development of COVID-19 vaccines has been a remarkable feat, with significant progress achieved in a relatively short period. The genetic sequence of SARS-CoV-2 was obtained in January 2020, initiating vaccine research. By spring 2020, vaccination studies were already in progress. Surprisingly, within less than 12 months, the European Medicines Agency granted the first conditional authorization for a COVID-19 vaccine in December 2020.[44] Just a month later, in January 2021, another COVID-19 vaccine received a second recommendation.[45] This rapid development, accomplished within a year of identifying the virus, is unprecedented in the history of

TABLE 3 Type of vaccines against SARS-CoV-2.

Vaccine	COVID-19 Vaccine Name	Vaccine component	Antibody induction mechanism
RNA based platform	BNT162b2 (Comirnaty, Pfizer-BioNTech) mRNA-1273 (Spikevax, Moderna)	mRNA that encodes for the viral spike is encapsulated in lipid nanoparticles	Induction of strong Th1 cell response, B cell response. Induction of neutralizing antibodies
Adenoviral Vector	Astra- Zeneca/Oxford vaccine (Covishield or ChAdOx1, Vaxzevria) Gamelaya-Sputnik Janssen vaccine	Replication-deficient viruses express the gene sequence of a target antigen inside the host cells	Induction of Th1 cell responses and strong protective effects
Inactivated virus	BBIBP-CorV (Sinopharm) CoronaVac (Sinovac Biotech) COVAXIN (Bharat Biotech International)	Viruses cultured in vitro and inactivated by chemical reagents	Wide range of antibodies against different epitopes of the entire virus
Protein-Based	Novavax/Covovax (NVX-CoV2373)	Delivering the recombinant viral spike protein or peptides through the cellular-based systems	Induce Th1 cell responses

vaccinology.[46] Various types of vaccines have been developed and tested for their efficacy against SARS-CoV-2, including mRNA-based vaccines, viral-vector vaccines, inactivated virus-based vaccines, and protein-subunit vaccines (Table 3).

As of April 2023, apart from inactivated vaccines, most vaccine candidates have been developed using antigen fragments or the full-length spike protein. Globally, 50 vaccines have been approved in at least one country, while 183 vaccines are in clinical development and 199 are in preclinical development. Among the vaccine candidates in the clinical phase, 32% (59/183) are protein subunits, 14% (25/183) are viral vectored vaccines, 9% (17/183) are DNA vaccines, 24% (43/183) are RNA vaccines, 12% (22/183) are inactivated virus vaccines, and 10% (17/183) belong to other types of vaccine candidates.[11] Two mRNA vaccines, BNT162b2 from Pfizer-BioNTech and mRNA-1273 from Moderna, have gained considerable attention as relatively new technologies that had not been previously approved for any use. mRNA vaccines carry the genetic information for triggering the production of the antigen by the cells of the vaccine recipients. They consist of viral spike-encoding messenger RNA stabilized by lipid nanoparticles. BNT162b2 and mRNA-1273 have shown efficacy rates of 95% and 94%, respectively, in preventing COVID-19 illness. They have also been found to induce both humoral and cellular immunity with high efficiency, which plays a critical role in defending against virus infection.[47] Viral-vector vaccines use non-replicating viral vectors as vaccine vectors to deliver antigen-coding genes into host cells, stimulating an immune response. Vaccines such as Sputnik V, Oxford-AstraZeneca, Johnson & Johnson, and Convidicea, developed on recombinant adenovirus platforms, have shown an overall efficacy range of 60–90%.[48] Inactivated vaccines are the most traditional and time-tested vaccination strategy. They contain killed SARS-CoV-2 virus, which is recognized by the immune system to trigger a response without causing COVID-19 illness. Examples of inactivated vaccines include CoronaVac, Covaxin, BBIBP-CorV, and CoviVac. Inactivated vaccines have shown effective protection ranging from 80% to 90% against COVID-19.[49,50] Protein subunit vaccines contain viral proteins such as the spike protein or its segments as antigens, which are assumed to elicit both humoral and cellular immunity and provide good protective effects. The Novavax vaccine (NVX-CoV2373) contains the full-length spike protein formulated into nanoparticles with the Matrix-Madjuvant and has demonstrated 90% efficacy.[51] ZF2001 (RBD-Dimer) was developed using the receptor binding domain (RBD) from the spike protein in aluminum adjuvant and showed efficacy rates of 90–96%.[52]

The effectiveness of COVID-19 vaccines is a significant concern due to the potential immune evasion resulting from newly emerging variants. In fact, a decline in vaccine effectiveness against different degrees of COVID-19 variants has been observed. While booster vaccinations offer improved protection, repeated boosting with current vaccines based on the ancestral SARS-CoV-2 virus is not sustainable.

One advantage of mRNA vaccines is their ability to easily and rapidly modify the mRNA sequence to target new emerging variants. mRNA-based vaccines, such as Pfizer and Moderna, have been developed against variants like Beta, Delta, Omicron, and bivalent boosters, which include combinations like the original vaccine plus Beta, Beta plus Delta, and original plus Omicron. Some studies have reported that the effectiveness of mRNA-based vaccines against variants is similar to that against the ancestral SARS-CoV-2, but lower against Omicron variants.[47] However, an overall marked reduction in efficacy against Omicron has been observed, as indicated by the reduced neutralization capacity of immune sera from vaccinated individuals against Omicron variants, even after receiving a booster. Specifically, the newly circulating Omicron sublineages BQ.1, BQ.1.1, XBB, and XBB.1 have shown resistance to all clinical monoclonal antibodies, and the effectiveness of both parental and bivalent mRNA vaccines has been significantly reduced against these sublineages.[53–55] The reduced neutralizing antibody titer and vaccine effectiveness against BQ.1.1 and XBB.1 sublineages can possibly be attributed to the R346T substitution,

which leads to higher humoral immune evasion in these new sublineages compared to BA.5 and BA.2.[53–55]

A recent meta-analysis by Wu and colleagues assessed the long-term vaccine efficacy of COVID-19 vaccines, including BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (Oxford-AstraZeneca), and Ad26. COV2.S (Janssen), against infection, hospitalizations, and mortality. The study also examined vaccine efficacy against emerging Omicron variants.[56] The findings indicated that mRNA-based vaccines had greater efficacy after primary vaccinations compared to adenovirus-carried vaccines.[57,58] The efficacy levels for mRNA-based vaccines were 87% against infection, 93% against hospitalization, and 94% against mortality, while adenovirus vaccines showed lower efficacy at 69% against infection, 90% against hospitalization, and 84% against mortality. However, overall vaccine efficacy was lower against the Omicron variant compared to other variants. Booster doses, especially against Omicron infection, showed reduced efficacy over time. The study recommends carefully considering the initial choice of a vaccine platform, as it may influence an individual's long-term immunologic response to SARS-CoV-2. Future research should focus on understanding how repeated COVID-19 booster vaccinations, including variant-specific recalls, can address the lower vaccine efficacy observed after a primary series of adenovirus vaccinations compared to mRNA-based priming.[57] The development of vaccine formulations that provide broader protection against all SARS-CoV-2 variants is needed. Next-generation vaccine platforms that elicit a combination of long-lasting humoral and cellular immunity against antigenically diverse viruses may be the most effective strategy.

8 | CONCLUSION

The SARS-CoV-2 pandemic has underscored the urgent need for a comprehensive and integrated approach to epidemic preparedness. Lessons learned from this global health crisis emphasize the importance of implementing a One Health monitoring system. This concept recognizes the interconnectedness of human, animal, and environmental health and emphasizes a holistic approach for disease surveillance and control. By establishing a One Health monitoring system, we can better detect and respond to emerging infectious diseases. This requires collaboration between human, animal health, and environmental sectors, sharing data, information, and expertize. Additionally, the pandemic has highlighted the significance of global and state-specific pandemic plans. A global plan would enable coordinated responses, information sharing, and joint research efforts, while state-specific plans would address local challenges. These plans should include strategies for early detection, surveillance, risk assessment, resource allocation, and healthcare system preparedness. They should also consider social, economic, and psychological impacts and ensure equitable access to healthcare services. In conclusion, a One Health monitoring system and pandemic plans are essential for epidemic preparedness, enabling proactive and comprehensive responses to future pandemics, safeguarding global health and well-being.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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